PHARMACEUTICAL CHEMISTRY

Fundamentals of Organic Chemistry including Reaction Mechanisms

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CONTENTS

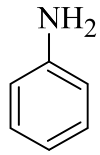
Keywords
Benzene, arenes, amines, phenols arylhalides, malonic ester, acetoacetic ester, alpha-beta- unsaturated carbonyl compounds, aromaticity, electrophilic aromatic substitution, nucleophilic aromatic substitution, conjugate addition, non-classical ions, molicular orbitals symmetry, chemical reaction

Benzene

Benzene was first isolated by Michael Faraday in 1825 from the oily residue that collected in the illuminating gas lines of London. It was found in coal tar by Hofmann in 1845, and this is still a source of benzene and its derivatives. It is a colourless compound with a melting point of 5.5^0c and a boiling point of 80^0c. The molecular formula of benzene is C_6H_6, which suggests a high degree of unsaturation. So it might be expected to show many of the reactions characteristic of alkenes and alkynes. Yet, benzene is remarkably uncreative. It does not undergo addition, oxidation, and reduction reaction characteristic of alkenes and alkynes. For example benzene does not react with bromine, hydrogen chloride, or other reagents that usually add to carbon-carbon double and triple bonds.

The term aromatic was originally used to classify benzene and its derivatives because many of them have distinctive odors. The term "aromatic" as it is now used, refers instead to the fact that these compounds are highly unsaturated and unexpectedly stable towards reagents that attack alkenes and alkynes.

Nomenclature: Aromatic compounds acquired a larger number of non-systematic names than the any other class of organic compounds. Although the use of such names is discouraged, IUPAC rules allow for some of the more widely used names to be retained. For examples



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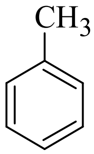
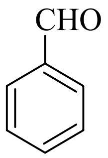
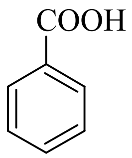


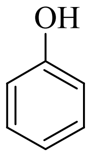
toluene



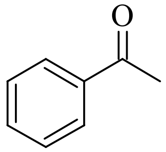
benzaldehyde



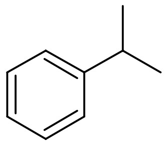
benzoic acid



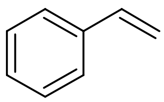
phenol



acetophenone

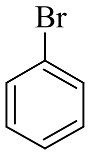


cumene

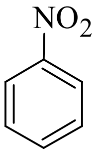


styrene

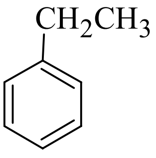
1. Monosubstituted benzene derivatives are systematically named in the same manner as other hydrocarbon, with *benzene* as the parent name. For example C_6H_5Br is bromobenzene, $C_6H_5NO_2$ is nitrobenzene and $C_6H_5C_2H_5$ is ethylbenzene.



bromobenzene



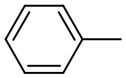
nitrobenzene



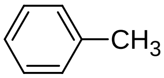
ethylbenzene

2. Benzene, other aromatic hydrocarbons and their alkyl derivatives as a class are known as **arenes**. The substituent group derived by loss of an H-atom from benzene is a **phenyl group,** abbreviated Ph-; that derived by loss of an H atom from the methyl group of toluene is a **benzyl group** abbreviated Bn-.

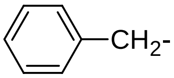
benzene



phenyl gorup, Ph

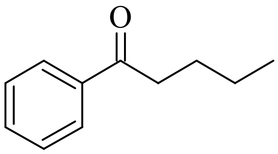


toluene

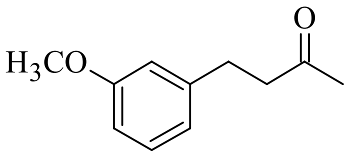


Benzyl group, Bn

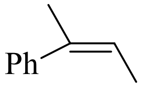
In a molecule containing other functional groups, the phenyl group and its derivatives are named as substituents.



1-phenylpentan-1-one

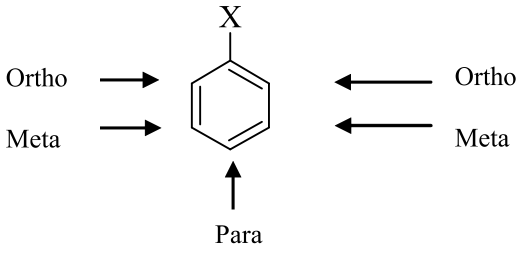


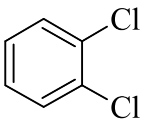
4-(3-methoxyphenyl)butan-2-one



(Z)-2-Phenyl-2-butene

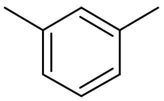
3. When two substituents occur on a benzene ring, three constitutional isomers are possible. The substituents may be located by numbering the atoms of the ring or by using the locator ortho, meta and para; 1,2 is equivalent to ortho (Greek, straight or correct), 1,3- is equivalent to meta (Greek, in the middle, between), and 1,4 is equivalent to para (Greek, beyond).
4. Benzene with three or more substituents are named by numbering the position of each substituents so that the lowest possible numbers are used. The substituents are listed alphabetically when writing the name.





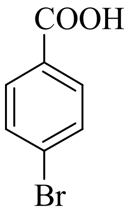
ortho-Dichlorobenzene

1,2-disubstituted



meta-Xylene

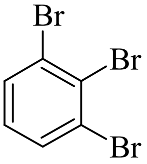
1,3-disubstituted

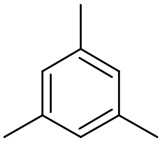


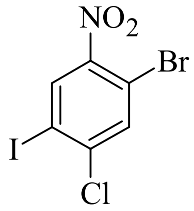
para-bromobenzoic acid

1,4-disubstituted

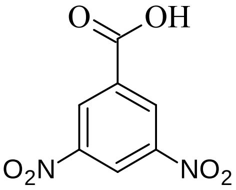
For examples: -

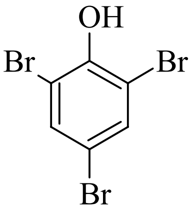

1,2,3-tribromobenzene

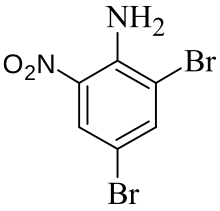

1,2,3-trimethylbenzene
(mesitylene)

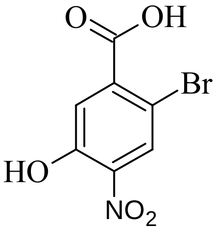

2-bromo-4-chloro-5-iodonitrobenzene

5. If one the substituents in a polysubstituted benzene derivative is that which gives a common name to the molecule, the numbering of carbon atoms in the benzene is so done that the group responsible for giving it a common names gets position 1.
   For example:

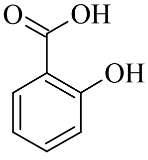

3,5-dinitrobenzoic acid

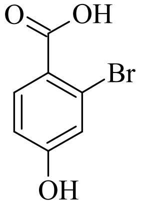

2,4,6-tribromophenol

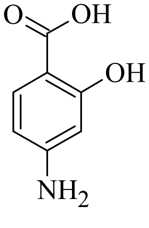

2,4-dibromo-6-nitroaniline


2-bromo-5-hydroxy-4-nitrobenzoic acid

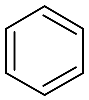
6. When two or more functional groups are present, the principal functional group gets number. The usual order for choosing the principal functional group is;
   Carboxylic acid, sulphonic acid acyl halide amide, aldehyde, cyanide, isocyanide, ketone, alcohol, phenol, thioalcohol, amine, imine and ether.


2-hydroxybenzoic acid
or
salicylic acid


2-bromo-4-hydroxybenzoic acid

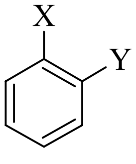

4-amino-2-hydroxybenzoic acid

Structure of Benzene: The first structure for benzene was proposed by the German chemist Friedrich Kekule in 1866. It was believed that a double bond in a ring somehow behaved differently from a double bond in a open chain.

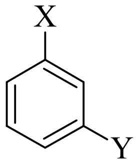


I
benzene

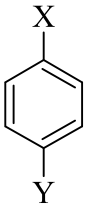
However, structure I could not explain the formation of three and only three substitution products of benzene. Structure I would give four, rather than three disubstitution products as shown below.



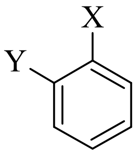
1,2-disubstituted product



1,3-disubstituted product

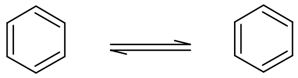


1,4-disubstituted product



1,6-disubstituted product

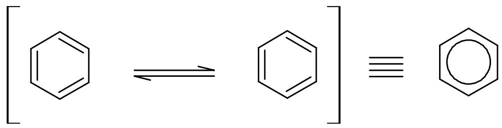
To explain this anomaly Kekule suggested in 1872 that the ring contains three double bonds that shift back and forth so rapidly that the two forms cannot be separated.



Consequently, the 1,2 and 1,6-disubstituted products were in rapid equilibrium and precluded separation.

Resonance Representation: In Kekule structure, the single bonds would be longer than the double bonds. Spectroscopic methods have shown that the benzene ring is planar, and all the bonds are of the same length (1.397 Å).

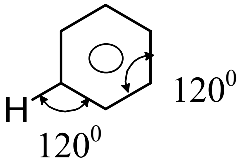
Benzene is actually a resonance hybridization of two Kekule structures. This representation implies that the pi electrons are delocalised with a bond order of 1½ between adjacent carbon atoms. The carbon carbon bond lengths in benzene are shorter than typical single bond lengths, yet longer than typical double bond lengths.



Bond order= 1½
All carbon carbon bond length 1.397Å

Because the pi bonds are delocalised over the ring, we often inscribe a circle in hexagon rather than drawing three localized double bonds.

Benzene is a ring of sp^2 hybridised carbon atoms, each bonded to one hydrogen atom. All the carbon carbon bonds are the same length and all the bond angles are exactly 120^0. Each sp^2 carbon atom has an unhybridised p-orbital perpendicular to the plane of ring, and six electrons occupy this circle of p orbital.



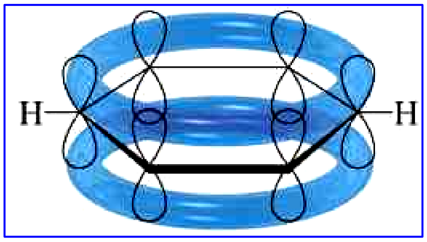
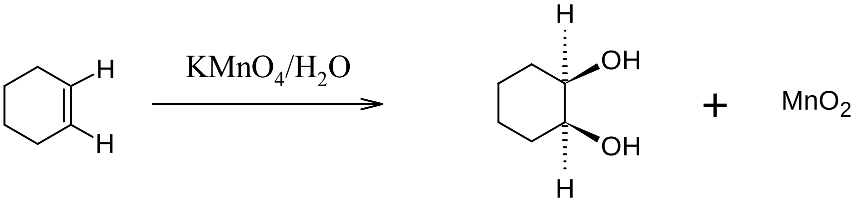
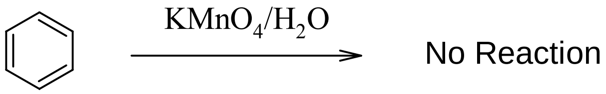


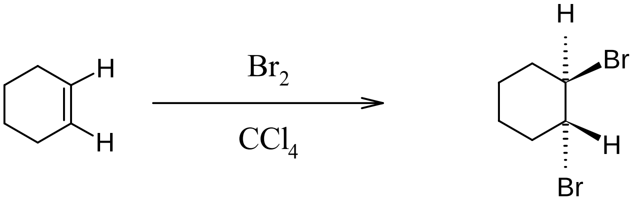
Fig. Orbital picture of the benzene showing the pi electron clouds

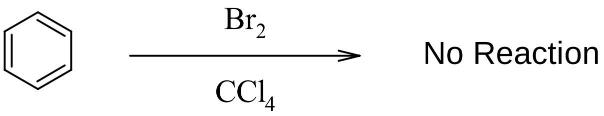
Unusual Structure of Benzene: Both the Kekule structure and the resonance delocalized picture show that benzene is cyclic conjugated triene. However it shows quite unusual reaction in contrast to typical reactions of polyenes. For example, an alkene reacts with potassium permanganate to form a glycol, however no reaction occurs when permanganate is added to benzene.



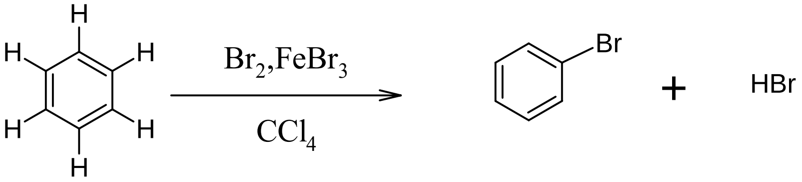


Generally alkenes add a molecule of bromine across the double bond in presence of carbon tetrachloride. But no reactions occur when bromine is added to benzene.





In presence of a catalyst such as ferric bromide, benzene undergoes substitution reaction with bromine instead of addition.



Unusual Stability of Benzene:

Heat of Hydrogenation of Benzene : Each carbon carbon double bond contributes about 121KJ mol^{-1} towards the overall heat of hydrogenation of an unsaturated compound. On this basis benzene with the above structure (cyclohexatriene) should have heat of hydrogenation of about (3 x 121) 363 KJ mol^{-1}. Actually, the heat of hydrogenation of benzene is only 209 KJ mol^{-1} and this is less than the value calculated for cyclohexatriene by about 154 KJ mol^{-1}. It means that benzene contains about 154 KJ mol^{-1} less energy than that predicted for the cyclohexatriene structure for benzene. In other words *actual benzene molecule is more stable than cyclohexatriene by about 154 KJ mol*$^{-1}$

Heat of Combustion on Benzene: Heat of combustion of benzene molecule, as determined experimentally, is -3301.6 KJ mol^{-1}. The calculated value for cyclohexatriene structure for benzene comes to be –3446.8 KJ mol^{-1}. Thus the actual benzene molecule is more stable than cyclohexatrine by (3446.8-3301.6) 145.2 KJ mol^{-1}.

Visualising benzene as a resonance hybrid of two Kekule structures cannot explain the unusual stability of the aromatic ring.

Molecular Orbital Model of Benzene: Benzene is a planar molecule with the shape of a regular hexagon. All carbon carbon bond angles are 120^0, all six-carbon atoms are sp^2 hybridised and each carbon has a p-orbital perpendicular to the plane of the six-membered ring.

Since all six carbon atoms and all six p-orbitals in benzene are equivalent, it is impossible to define three localized pi-bonds in which the given p-orbital overlaps only one neighboring p orbital. Rather each p orbital overlaps equally well with both neighboring p orbitals, leading to a picture of benzene in which the six electrons are completely delocalised around the ring.

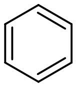
In the orbital picture of benzene the p orbitals overlap in both directions and each electron participates in several bonds. This ability of pi electrons to participate in several bonds, known as delocalization of electrons, results in stronger bonds and more stable molecule. This electronic configuration explains the unusual stability of benzene.

Aromaticity: Aromatic compounds are those that meet the following criteria:

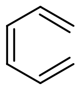
1. The structure must be cyclic, containing conjugated pi bonds.
2. Each atom in the ring must have an unhybridised p orbital.
3. The unhybridised p orbitals must overlap to form a continuous ring of parallel orbitals. In most cases, the structure must be planar (or nearly planar) for effective overlap.
4. Delocalisation of pi electrons over the ring must result in a *lowering* of the electronic energy.

An **antiaromatic** compound is one that meets the first three criteria but delocalisation of the pi electrons over the ring results in an *increase* in the electronic energy.

Aromatic structures are more stable than their open chain counterparts. For examples, benzene is more stable than 1,3,5 –hexatriene.



More stable
(Aromatic)



Less stable

A cyclic compound that does not have a continuous, overlapping ring of p orbitals cannot be aromatic or antiaromatic. It is said to be nonaromatic, or aliphatic. Its electronic energy is similar to that of its open chain counterpart. For example, 1,3-cyclohexadiene is about as stable as cis, cis- 2,2-hexadiene.

Non-aromatic
similar stabilities

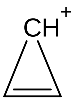
Huckel's Rule:

According to a theory devised by the German physicist Erich Huckel in 1931, a molecule is aromatic only if it has a planar, monocyclic system of conjugation with a total 4*n*+2 pi electrons, where *n* is an integer (*n* = 0,1,2,3…). In other words only molecules with 2,6,10,14,18 pi electrons can be aromatic.

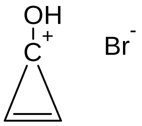
System with 4*n* pi electrons (4,8,12,16…) cannot be aromatic, even though they may be cyclic and apparently conjugated. In fact, planar, conjugated molecules with 4n pi electrons are even said to be **antiaromatic**, because they are **destabilised** by delocalisation of their pi electrons.

Examples of aromatic and antiaromatic compound under the Huckel theory:-

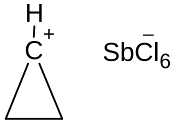
1. Benzene is a planar monocyclic compound with a pi cloud of six electrons. There are six pi electrons, so it is a 4n+2 system, with n=1. Huckel's rule predicts benzene to be aromatic.
2. Cyclopropenyl cation. This cation is a closed shell (4n+2) pi electron molecule with n=0. Therefore it should be a stable aromatic system. Actually several cyclopropenium salts have been prepared. For example



Cyclopropenyl cation
(2pi electrons)

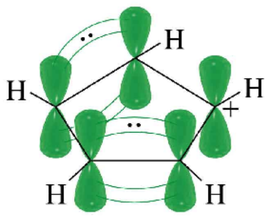


Hydroxy
cyclopropenylbromide
(Stable)

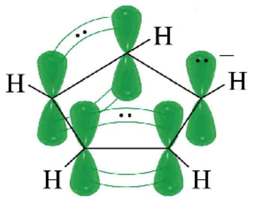


Cyclopropenyl hexachloroantimonate
(Stable)

3. Cyclopentadienyl ions: The five sp^2 hybridised carbon atoms with unhybridised p orbitals form a continuous ring. Huckel's rule predicts the cation with 4pi electrons to be antiaromatic while anion with 6pi electrons is aromatic.

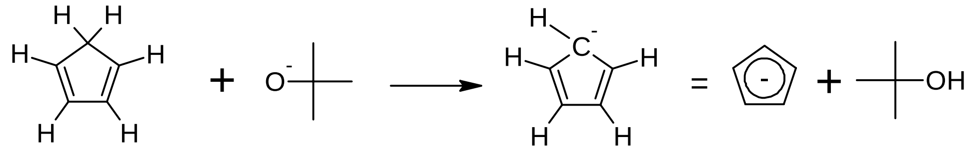


4-pi electrons
cyclopentadienyl cation



6-pi electrons
cyclopentadienyl anion

Because the cyclopentadienyl anion (6pi electrons) is aromatic, it is unusually stable compared to other carbanions. It can be formed by abstracting a proton from cyclopentadiene, which is unusually acidic for an alkene. It is entirely deprotonated by potassium t-butoxide.

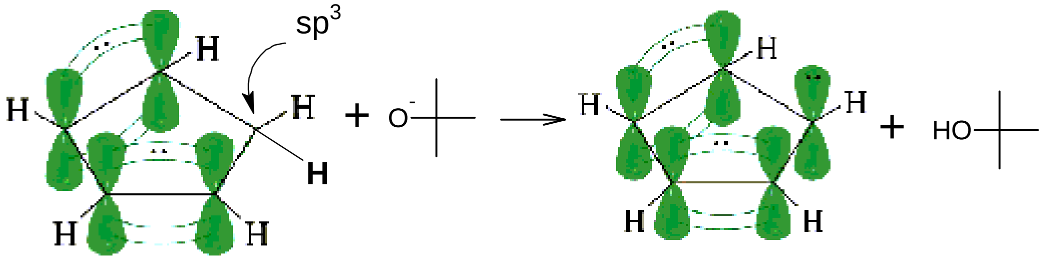


cyclopentadiene

cyclopentadienyl anion

6-pi electrons

The loss of a proton converts the nonaromatic diene to aromatic cycopentadienyl anion. Cyclopentadiene contains an sp^3 hybrid (CH_2) carbon atom without an unhybridised p orbital, so there can be no continuous ring of p orbitals. Deprotonation of the $-CH_2$-group leaves an orbital occupied by a pair of electrons. These orbitals can rehybridise to a p orbital, completing a ring of p orbitals containing six-pi electron; the two electrons on the deprotonated carbon, plus the 4 electrons in the original double bonds.

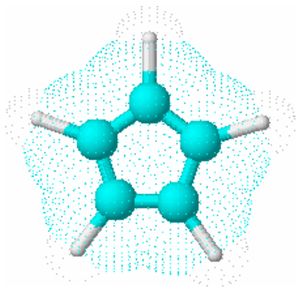


cyclopentadiene

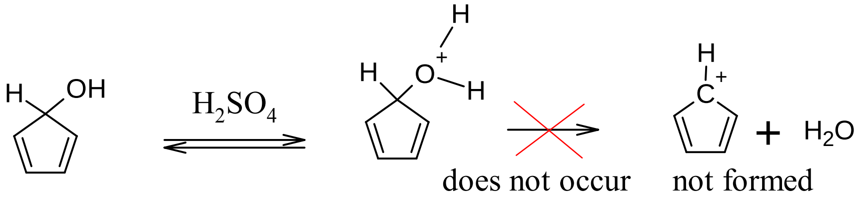
Non-aromatic

cyclopentadienyl anion

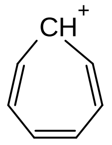
Aromatic



Huckel’s rule predicts that the cyclopentadienyl cation, with four pi electrons is antiaromatic. In an agreement with this prediction, the cyclopentadienyl cation is not easily formed. 2,4-cyclopentadienes do not protonate and lose water (to give the cyclopentadienyl cation), even in concentrated sulfuric acid. The antiaromatic cation is simply too unstable.

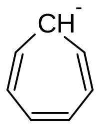


4. Cycloheptatrienyl ions: The cation has six pi electrons, and the anion has eight pi electrons. Huckel’s rule predicts that the cycloheptatrienyl cation which contains six pi electrons is aromatic and the corresponding anion which contains 8 pi electrons is antiaromatic (if it remains planar).



cycloheptatrienyl cation

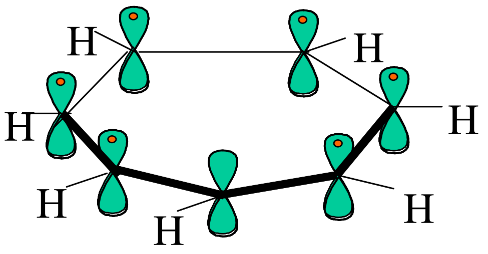
6-pi electrons (Aromatic)

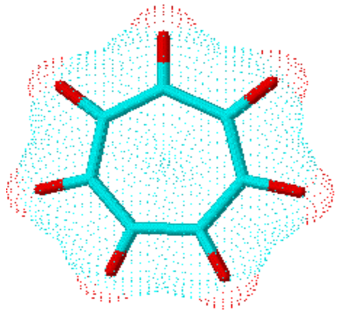


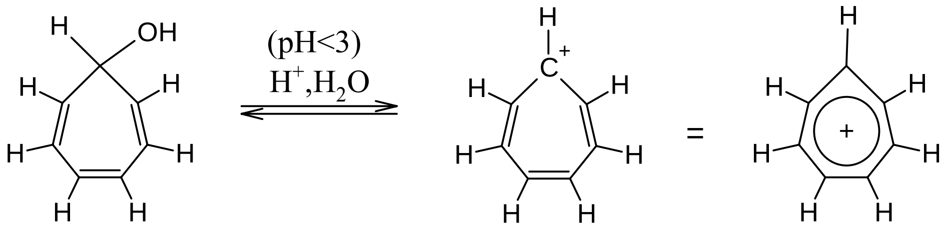
cycloheptatrienyl anion

8-pi electrons (Anti-aromatic)

The cycloheptatrienyl cation also called tropylium ion formed by treating the corresponding alcohol with dilute aqueous sulphuric acid.

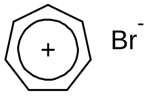




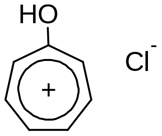


cyclopentadienyl cation
6-pi electrons

This aromatic ion is much less reactive than most carbocation. Some stable tropylium salts have actually been prepared. For example

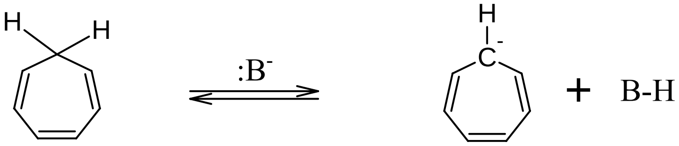


Tropylium bromide
(stable)

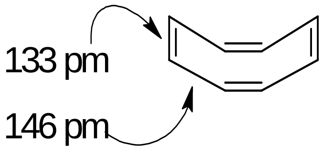


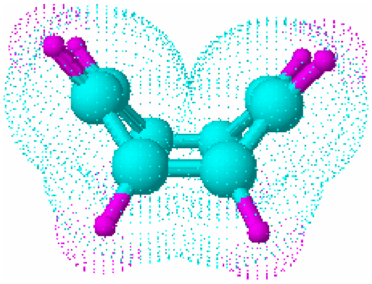
Hydroxy tropylium chloride
(stable)

In contrast to the easy formation of tropylium ion, preparation of the corresponding anion is difficult, because it is antiaromatic. Cycloheptatrienyl anion is unstable and very reactive. This result agrees with the prediction of Huckel's rule that the cycloheptarienyl anion is antiaromatic.



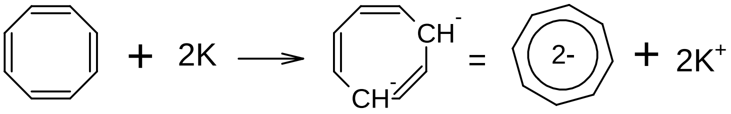
5. Cyclooctatetraene : Cyclooctratetraene with eight pi electrons is not aromatic for the following reasons: -
   X-ray studies show clearly that the most stable conformation of the molecule is a nonplanar "tub" conformation with two distinct types of carbon carbon bonds: Four longer carbon carbon single bonds and four shorter carbon carbon double bonds. The four single bonds are equal in length to the single bonds between sp^2 hybridised carbons (approximately 146pm), and the four double bonds are equal in length to double bonds in alkenes (approximately 133 pm) Cyclooctatetraene shows reactions typical of alkenes and is classified as nonaromatic.





1,3,5,7-Cyclooctatetraene
Tub conformation

6. Cyclooctatetraene dianion: Dianion of hydrocarbons are usually much more difficult to form. Cyclooctatetraene reacts with potassium metal, however, to form an aromatic dianion.

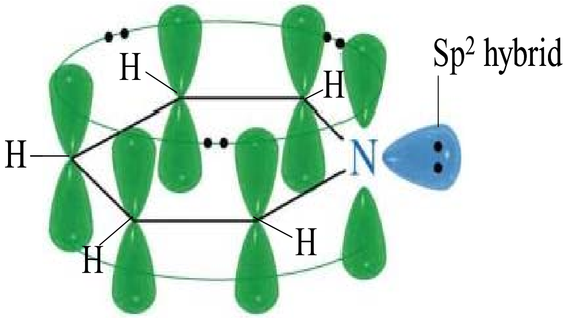


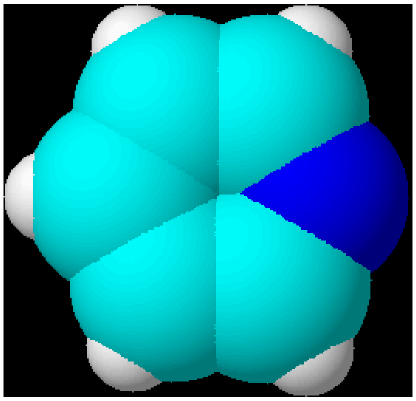
10-pi electrons

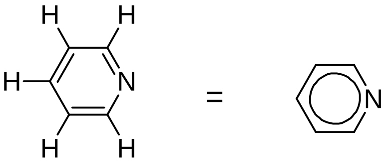
   The cyclooctatetraene dianion has a planar, regular octagonal structure with 10 pi electrons (4n+2, n=2). The cyclooctratetraene dianion is easily prepared because it is aromatic.

7. Heterocyclic compounds: Aromatic character is also found in heterocyclic compounds. Heterocyclic compound, with rings containing sp^2 hybridised atoms of element, can also be aromatic.

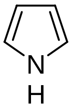
Pyridine: Pyridine is a heterocyclic analogue of benzene. Pyridine has a nitrogen atom in place of one of the six C-H units of benzene. In pyridine, nitrogen is sp^2 hybridised, and its unshared pair of electrons occupies an sp^2 orbital in the plane of the ring and perpendicular to the 2p orbitals of the pi system; thus it is not a part of the pi system.



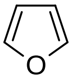




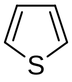
Pyrrole Furan and Thiophene: The five membered ring heterocyclic compounds are also aromatic



Pyrrole

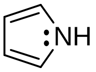


Furan

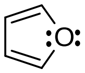


Thiophene

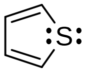
In furan and thiophene, one unshared pair of electrons of the heteroatom lies in the unhybridised 2p orbital and is a part of the pi system, the other unshared pair of electrons lies in an sp^2 hyhbrid orbital perpendicular to the 2p orbitals and is not a part of it. In pyrrole, the unshared pair of electrons on nitrogen is part of the aromatic sextet.



Pyrrole

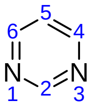


Furan

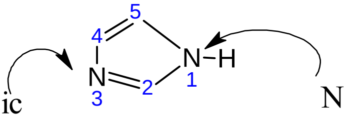


Thiophene

Pyrimidine and Imidazole : Pyrimidene is a six membered heterocycles with two nitrogen situated in a 1,3 arrangement. Both nitrogen atoms have their lone pair of electrons in the sp^2 hybrid orbital in the plane of the aromatic ring. Thus lone pairs are not needed for the aromatic sextet, and they are basic, like the lone pair of pyridine.



Pyrimidine



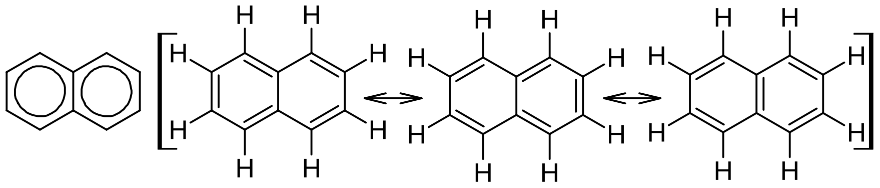
Basic

Not basic

Imidazole

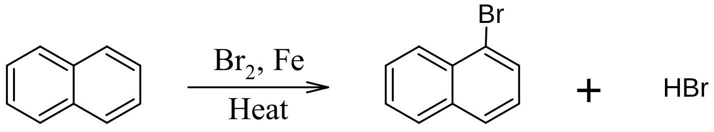
Imidazole is an aromatic five membered heterocyclic with two nitrogen atoms. One nitrogen atom (the one bonded to hydrogen) uses its third sp^2 orbital to bond to hydrogen, and its lone pair is part of the aromatic sextet. Like the pyrrole nitrogen atom, this imidazole N-H nitrogen is not very basic. The other nitrogen has its lone pair in a sp^2 orbital that is not involved in the aromatic system; this lone pair is basic.

8. **Polynuclear Aromatic Hydrocarbons:** All polycyclic aromatic hydrocarbons can be represented by a no. of different resonance forms. Naphthalene, for instance has three;



The true structure of naphthalene is a hybrid of the three resonance forms and the no of pi electrons correspond it the Huckel no 10.

Naphthalene and other polycyclic aromatic hydrocarbons show many of the chemical properties associated with aromaticity. Thus, naphthalene reacts slowly with electrophiles such as Br_2 to give substitution products rather than double bond addition products.



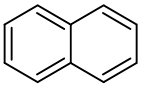
Naphthalene

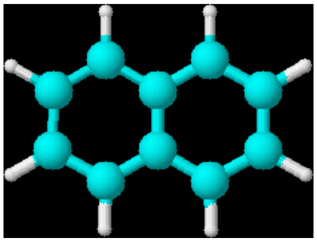
1-Bromonaphthalene

(75%)

Naphthalene has a cyclic, conjugated pi system, with p-orbital overlap bond around the ten-carbon periphery of the molecule and across the central bond.

Since ten pi electrons is a Huckel no. there is pi electron delocalisation and consequent aromaticity in naphthalene.

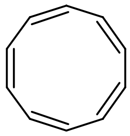




Annulenes: An annulene is a monocyclic hydrocarbon with continuous alternation of single and double bonds. They are generally named by prefixing the no. of carbon atoms in the ring in brackets followed by the word “annulene.”

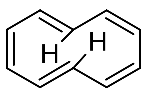
Aromaticity in the larger annulenes depend on whether the molecule can adopt the necessary planar conformation;

For example, in all cis-[10]annulene, the planar conformation requires an excessive amount of angle strain. The [10] annulene isomer with two trans double bonds cannot adopt a planar conformation either, because two hydrogen atoms interfere with each other.



All cis

not aromatic



two trans

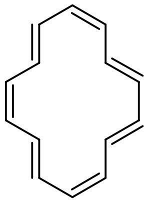
not aromatic

10 pi electrons

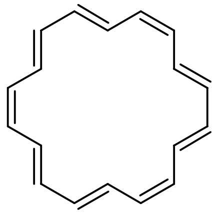
i.e. (4n+2)pi electrons, n=2

non-planar

Some of the lager annulenes with (4n+2) pi electrons can achieve planar conformations. For example the following [14] annulene and [18] annulene have aromatic properties.



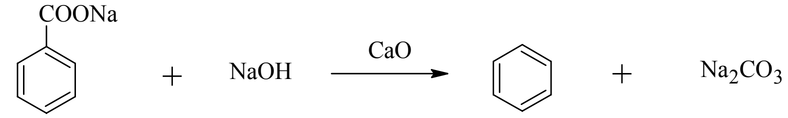
[14] Annulene
(aromatic)



[18] Annulene
(aromatic)

General Method of Preparation Of Benzene:

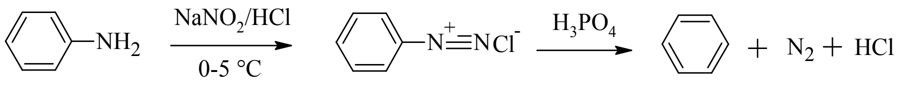
1. Decarboxylation: When a aromatic acids or their sodium salts are heated with soda lime, carbondioxide is eliminated to form hydrocarbon



Sodium benzoate

benzene

2. By reduction of aryl diazonium salt: Diazonium salts formed by the reaction of aromatic amine and nitrous acid, when heated with phosphorous acid undergo removal of diazo group forming aromatic hydrocarbons.



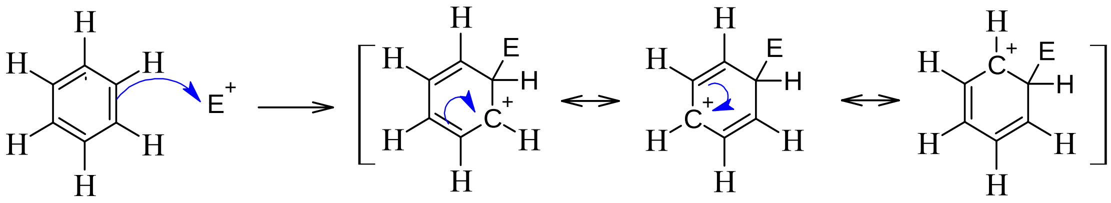
benzene

3. By polymerization of alkynes: Alkynes on polymerization at high temperature or in presence of catalyst yield benzene.

Physical Properties: Benzene is a colourless, highly refractive liquid having a characteristic aromatic odor melting point 55^0c, boiling point 80^0c and specific gravity 0.8790 at 20^0c. It is insoluble in water and soluble in organic solvents such as ethanol, ether etc. It is used as solvent in various reactions. However, the use of benzene has been banned in some countries due to its carcinogenic nature.

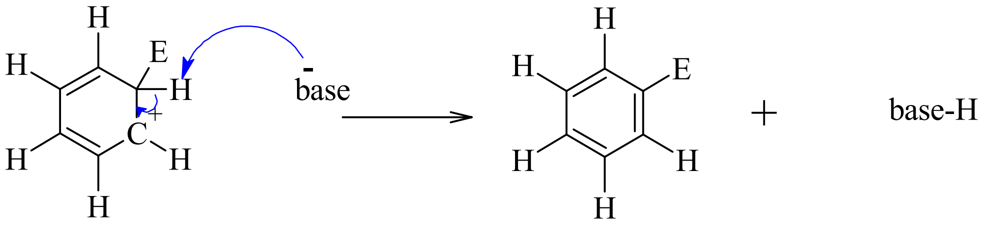
Chemical Properties: Benzene and related compound undergo substitution reaction under normal conditions.

(1). Electrophilic Aromatic Substitution Reactions : Like an alkene, benzene has clouds of pi electrons above and below its sigma bond frame work. Although pi electrons in benzene are in a stable aromatic system, they are unavailable to attack a strong electrophile to give carbocation. This resonance stablised carbocation is called a sigma complex, because the electrophile is joined to the benzene ring by a new sigma bond.



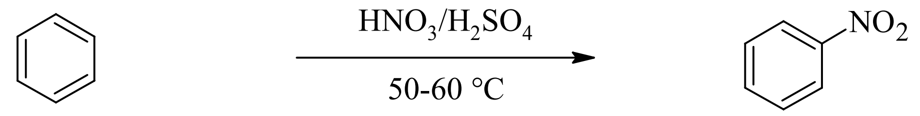
Sigma complex

The sigma complex loses a proton to a base to regenerate the aromatic ring. If the sigma complex were attacked by a nucleophile, the resulting addition product would not regain the aromatic stability of the star sting material. The overall reaction, then, is the substitution of an electrophile for a proton on the aromatic ring i.e. electrophilic aromatic substitution.



This class of reactions includes a wide variety of reactions such as nitration, halogenation, sulphonation, Friedel Craft alkylation and Friedel Craft acylation. These substitution reactions are given by almost all aromatic compounds, and they are better known as aromatic electrophilic substitutions reactions.

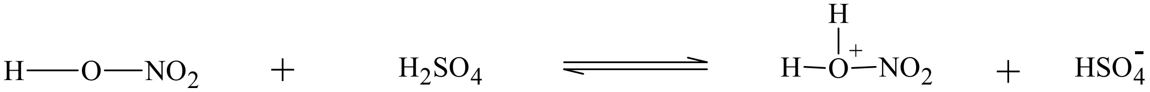
(i) Nitration : Substitution of a hydrogen by the nitro group in an aromatic ring is called nitration. It is usually brought about by the action of mixture of nitric acid and sulphuric acid, often called nitrating mixture.



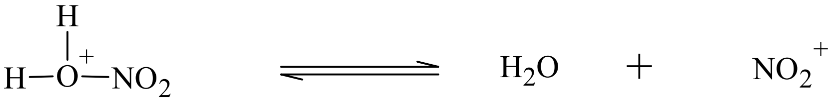
benzene

nitro benzene

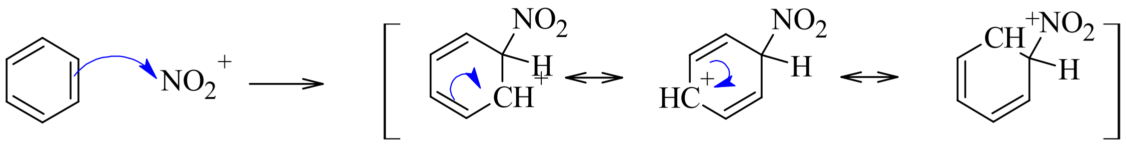
The mechanism of nitration can be outlined as follows.



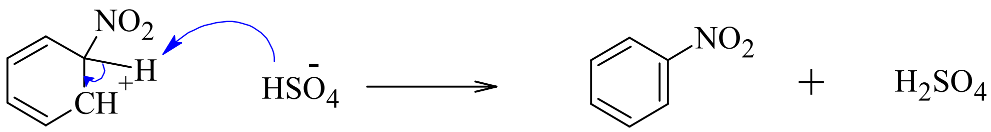
$$H-O-NO_2 + H_2SO_4 \rightleftharpoons H-\overset{\overset{H}{|}}{O}^{+}-NO_2 + HSO_4^-$$



$$H-\overset{\overset{H}{|}}{O}^{+}-NO_2 \rightleftharpoons H_2O + NO_2^+$$

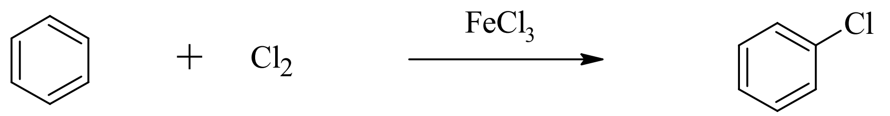


Sigma complex



The evidence for the participation of nitronium ion in nitration is given by the fact that other species furnishing nitronium ion such as $NO_2^+BF_4^-$, $NO_2^+NO_3^-$ and $NO_2^+ClO_4^-$ also form nitrated aromatic hydrocarbon.

(ii). Halogenation: Aromatic compound reacts with halogen in presence of Lewis acid catlyst such as ferric chloride or aluminium chloride to give halogen substituted products.

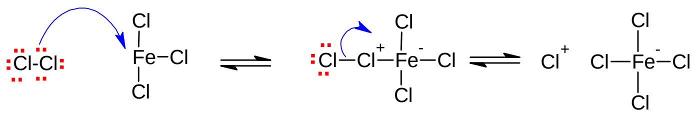


benzene

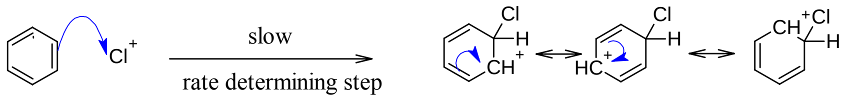
chloro benzene

Mechanism :

Step 1: Generation of an electrophile

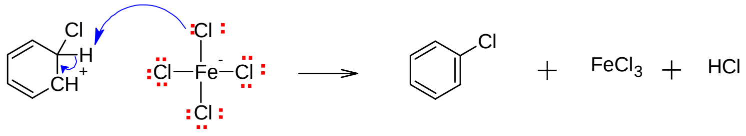


Step 2: Attack on an electrophile to the aromatic ring.



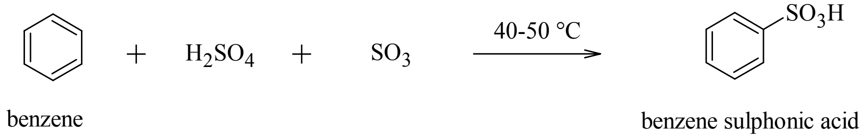
Resonance stabilised carbocation intermediate

Step 3: Removal of proton.



This reaction begins with interaction of chlorine and the Lewis acid catalyst to give a molecular complex with a positive charge on chlorine and negative charge on iron. Redistribution of electrons in this complex generates a chloronium ion, Cl^+, as part of the ion pair. Reaction of the Cl_2-$FeCl_3$ complex with pi electron cloud of the aromatic ring forms a resonance-stabilised cation intermediate, here represented as hybrid of three contributing structures. Proton transfer from the cation intermediate to $FeCl_4^-$ forms HCl, regenerates the Lewis acid catalyst and gives chlorobenzene.

(iii). Sulphonation: Sulphonation of benzene is carried out by heating aromatic hydrocarbons with concentrated sulphuric acid or fuming sulphuric acid containing dissolved sulpher trioxide.

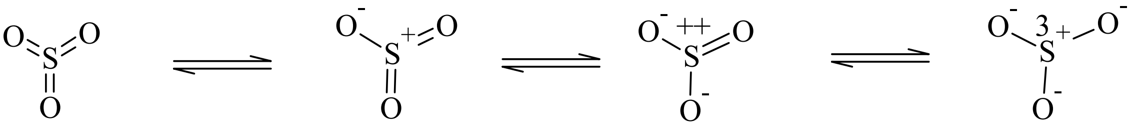


The reactive electrophile is neutral sulphertrioxide prosuced by the reaction of sulphuric acid.

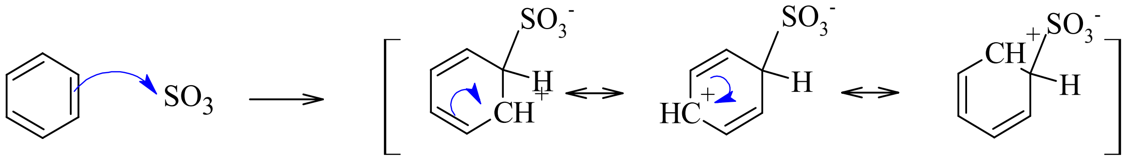
Mechanism

Step 1: Generation of an electrophile

$$H_2SO_4 \rightleftharpoons SO_3 + HSO_4^- + H_2O$$

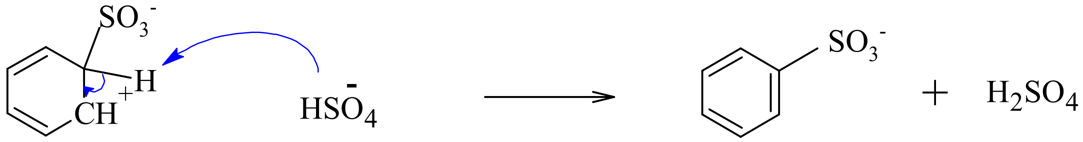


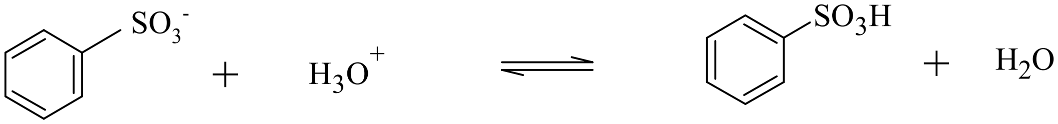
Step 2: Attack of an electrophile



Sigma complex

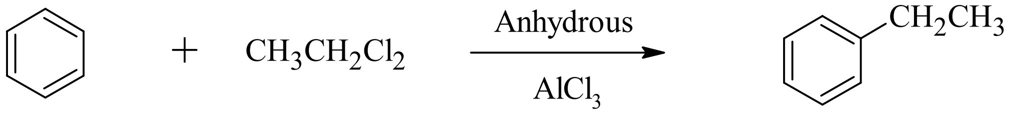
Step 3: Removal of proton





benzene sulphonic acid

(iv). Friedel Craft Alkylation: Replacement of Hydrogen atom in aromatic ring by an alkyl group in presence of Lewis acid like anhydrous aluminium chloride is termed as Friedel Craft alkylation.



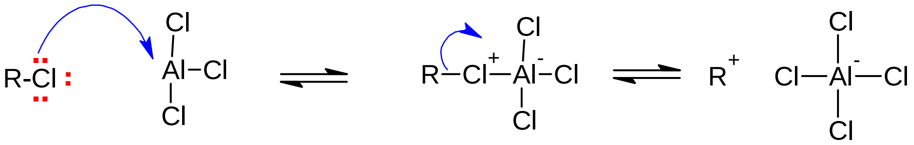
benzene

ethyl benzene

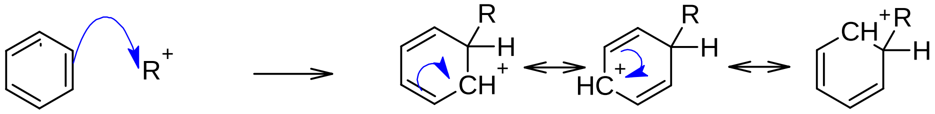
Friedel Craft alkylation is among the most important methods for forming new carbon-carbon bonds to aromatic rings. It begins with formation of a complex between the alkyl halide and aluminium chloride in which aluminium has a negative charge and the halogen of the alkyl halide has a positive charge. The alkyl group is very often written as carbocation to simplify the mechanism. Reaction of an alkyl carbocation with aromatic ring gives a resonance stablised cation intermediate, which then loses a hydrogen to give an alkyl benzene.

Mechanism:

Step-1: - Generation of an electrophile

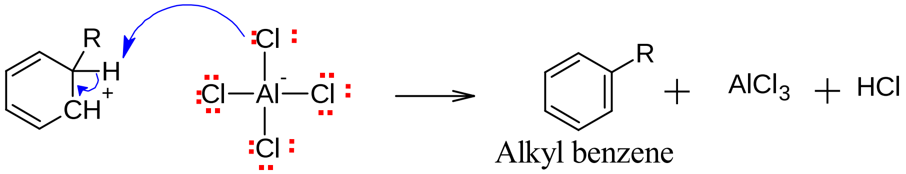


Step-2 : - Attack of an electrophile



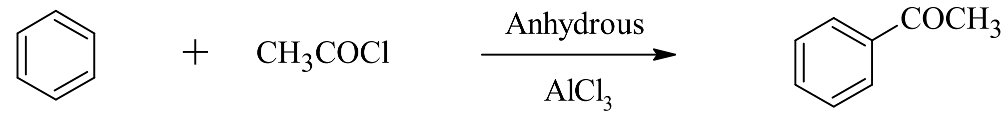
Delocalisation of positive charge

Step-3: - Removal of hydride ion



Alkyl benzene

(iv). Friedel Craft Acylation: The substitution of an acyl group into the aromaic ring in presence of Lewis acid catalyst such as anhydrous AlCl3 is known as Friedel Craft acylation.

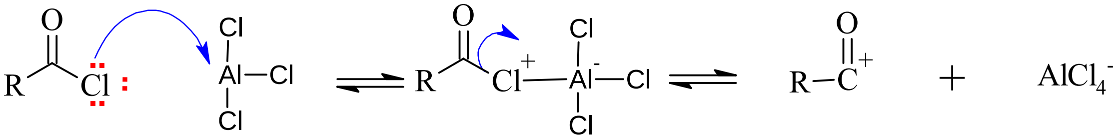


benzene

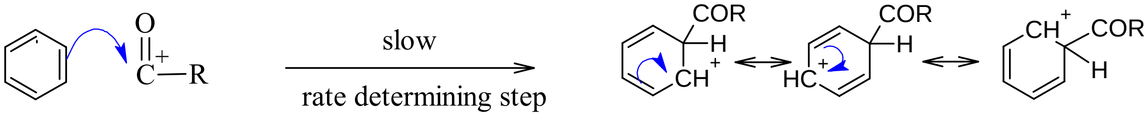
acetone

Mechanism:

Step-1: - Generation of an electrophile

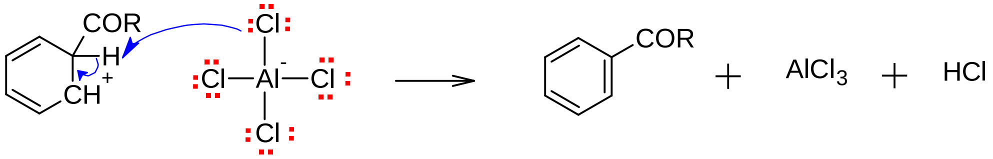


Step-2 : - Attack of an electrophile



Resonance stabilised carbocation intermediate

Step-3: - Removal of hydride ion

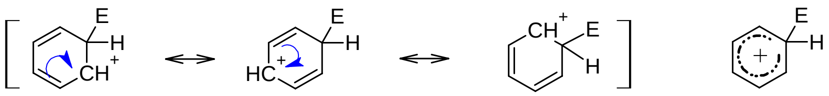


Theory of Reactivity and Orientation in Electrophilic Aromatic Substitution

The rate-determining step in the mechanism of an elctrophilic aromatic substitution reaction is the slow step involving the formation of a carbocation, irrespective of the nature of the attacking electrophile.

The difference in the rates of substitution in two closely related electrophilic aromatic substitution reaction will be determined essentially by the relative stabilities of the concerned carbocation, the greater the speed with which it will be formed (hence the rate of the over all reaction).

The above-mentioned carbocation is resonance hybrid of following structure.



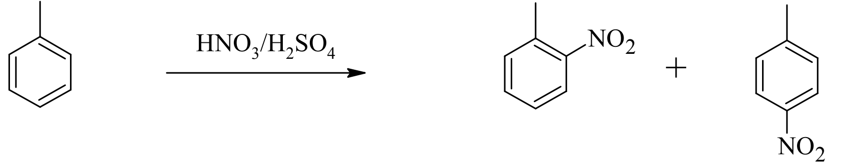
The positive charge is distributed all over the ring in the contributing structure, but it is strongest at positions ortho and para to the carbon under attack. A substituent already present on the benzene ring would, therefore, affect the stability of the carbocation, depending on its electron releasing or electron withdrawing character. So the reactivity and orientation in electrophilic substitution reaction is divided into three groups.

(I). Ortho and para directing activators: The substituents that relax electrons, activate the benzene ring and direct the incoming groups to ortho and para positions. For example –CH_3, -NH_2, -OCH_3, -OH, -$NHCOCH_3$, -C_6H_5 etc.

(II). Meta directing deactivators: The substituent that withdraw electrons deactivate the benzene ring for further substitution and direct the incoming groups to meta position. For examples, -NO_2, -CN, -COOH, -CHO, -SO_3H etc

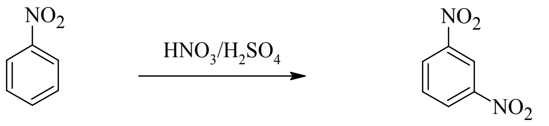
(III). Ortho and para directing deactivators: The substituent that withdraw electrons, deactivate the ring and direct the incoming group to ortho and para positions. For examples, -Cl, -Br, etc.

Effects of Substituents On Orientation: Nitration of toluene gives mainly the ortho and para products



o-nitro toluene o-nitro toluene

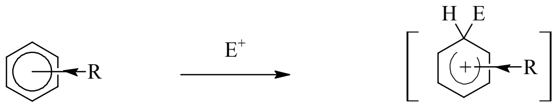
On the other hand nitration of nitrobenzene gives m-nitrobenzene as a major product.



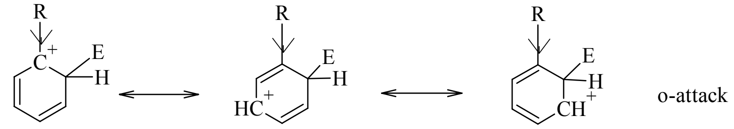
m-dinitro benzene

It is important to note that activating groups activates all the positions of the ring. They are ortho and para directing because they activate ortho and para positions much more than the meta position. Similarly deactivating groups deactivate ortho and para position much more than the meta position making them meta directors.

Ortho and Para Directing Activators: Let us understand the effect of substituent by taking some examples.
(a) Effect of alkyl group as substituent: Since alkyl group is an electron releasing group, it tends to stabilize the carbocation by dispersal of its positive charge.

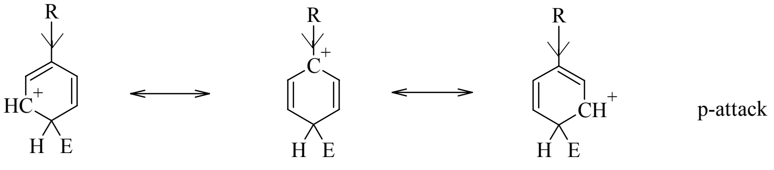


Let us now compare the carbocation formed by substitution at the ortho, para and meta positions.



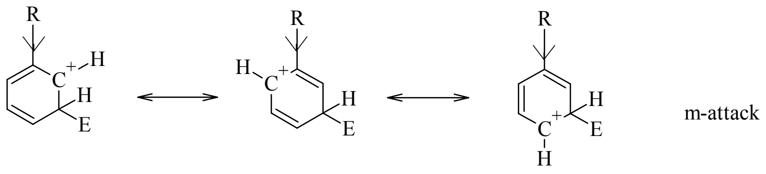
I II III

Particularly stable ; positive charge on carbon carrying R



IV V VI

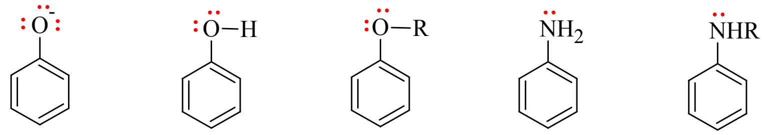
Particularly stable ; positive charge on carbon carrying R



VII VIII IX

The contributing structure I and IV are particularly stable because the electron releasing alkyl group is located on the carbon carrying the positive charge, and hence the charge dispersal is maximum in these structures. No contributing structure of the hybrid carbocation resulting from meta substitution, however, has comparable stability. Therefore, the hybrid carbocation resulting from ortho and para substitution would be more stable than those formed from meta substitution. Ortho and para substitution should, therefore, proceed faster than meta substitution in alkyl benzenes.

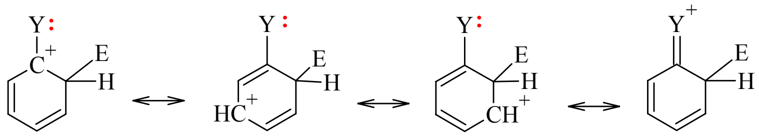
(a) **Effect of electron releasing substituents other then alkyl groups :** These substiuents contain one or more pairs of unshared electrons on atoms directly linked to the aromatic ring as shown below.



etc

These substituents can release electrons to the aromatic ring by resonance effect. Electron-release by these substituents should stabilize the carbocation and hence activate the aromatic ring for the electrophilic substitution.

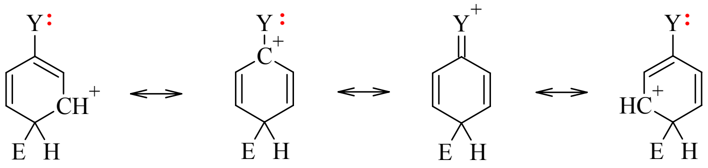
Let us now compare the carbocations resulting from the ortho, meta and para substitutions.



I II III IV

o-attack

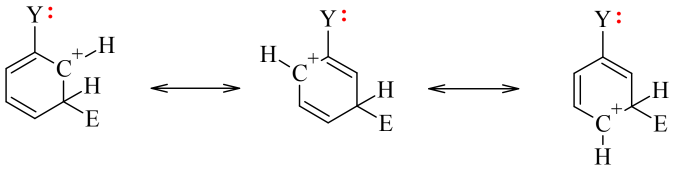
Particularly stable ; each atom has complete octet



V VI VII VIII

p-attack

Particularly stable ; each atom has complete octet



IX X XI

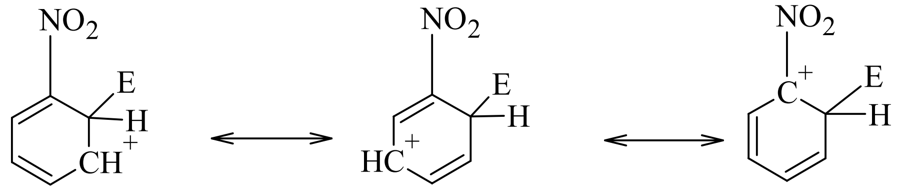
m-attack

Evidently the carbocations formed during ortho and para substitutions are resonance stabilised to greater extent than those formed during meta substitution. Further, the contributing structures IV and VII are particularly stable because each atom in them (except hydrogen), has a complete octet of electrons. Thus the carbocation formed during ortho and para substitutions are much more stable than the carbocation formed during meta substitution. Therefore substitution occurs predominantly at ortho and para position.

Meta Directing Deactivators: Substituents like $–NO_2$, -CN, -COOH, -COOR, -CHO, -COR, -SO_3H etc are deactivating groups when it is directly linked to the aromatic ring.

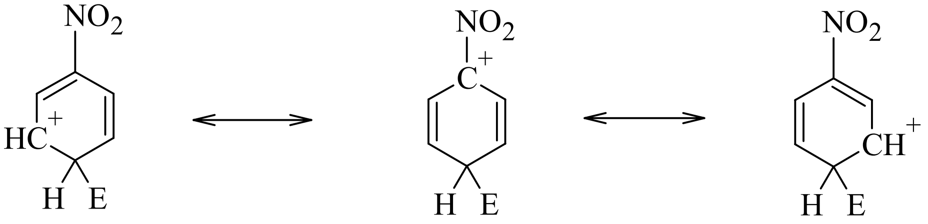
The inductive withdrawal of electrons makes aromatic ring a poorer electron source than benzene. Since the electron withdrawal intensifies the positive charge on the carbocation and hence destabilizes it, electrophilic substitution in compounds containing such electron withdrawing substituents take place much more slowly than in benzene.

Let us compare the resonance structures of carbocations formed during electrophilic substitution of nitrobenzene.



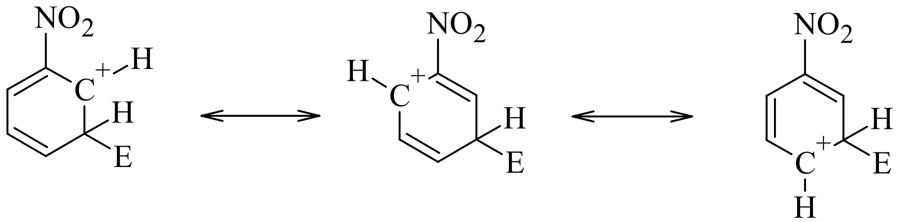
I II III

o-attack



IV V VI

p-attack

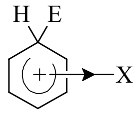


IX X XI

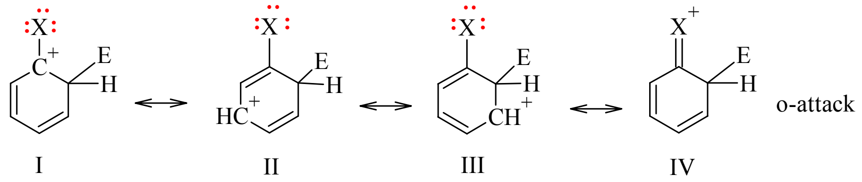
m-attack

Here the number of resonating structure due to otho, para and meta attack are equal i.e. three but structure III and V are unfavourable as the positive charge is present on the carbon having electron withdrawing group where as no such structure is possible with meta attack making it more favourable position for attack by an electrophile compared to ortho and para.

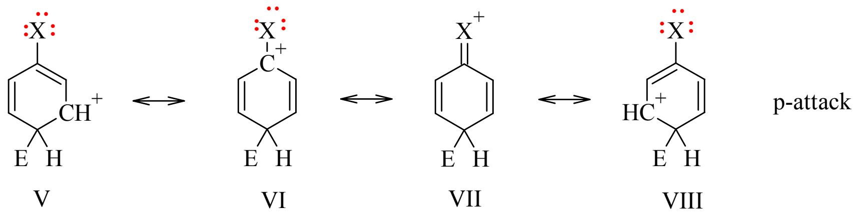
Ortho and Para Directing Deactivators: The strong electron withdrawing inductive effect of a halogen intensifies the positive charge on carbocation resulting from the electrophilic substitution of halobenzene.



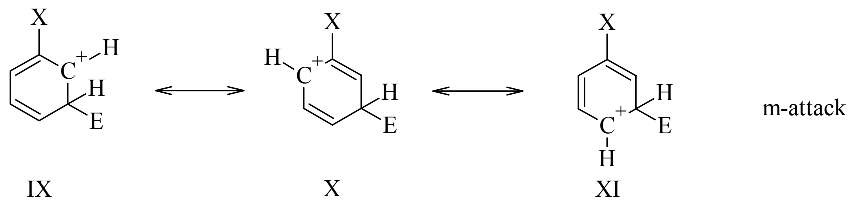
Let us compare the carbocation resulting from ortho, para and meta substitution in halobebzene.



Comparatively stable ; each atom has complete octet of electron



Comparatively stable ; each atom has complete octet of electron



Structures IV and VIII arising from ortho and para attack are more stable as every atom has its octet of electrons complete making halobenzene ortho and para directing and no such stabilisation is possible in meta attack. Structure I and VI are unfavourable because chlorine withdraws electrons through inductive effect, but the stabilisation by structure IV and VIII is more than the destabilisation by structure I and VI. Therefore halobenzene should undergo electrophilic substitution at ortho and para positions in preference to that at meta position.

Arenes

The aromatic hydrocarbons composed of both aliphatic and aromatic units are called arenes. The arenes can be of the following types.

Alkyl benzenes (e.g. toluene $C_6H_5CH_3$)

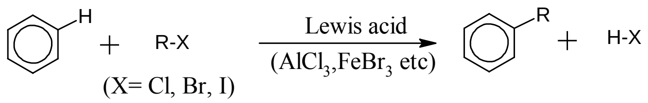
Alkenyl benzenes (e.g. syrene $C_6H_5\text{-}CH{=}CH_2$)

Alkynyl benzenes (phenyl acetylene $C_6H_5\text{-}C{\equiv}CH$)

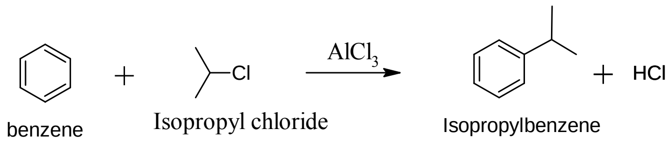
Alkyl Benzene:

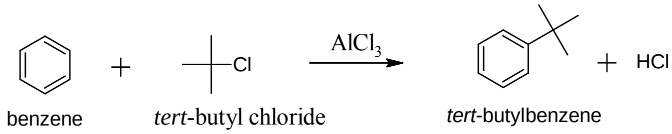
General Methods of Preparation:

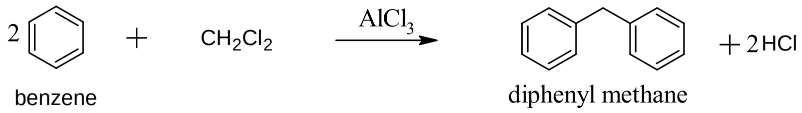
1. Friedel-Craft alkylation: The direct introduction of an alkyl group into the aromatic nucleus in the presence of lewis acid catalyst such as aluminium chloride or ferric chloride and an alkyl halide. This is the most important method for the preparation of alkyl benzenes.

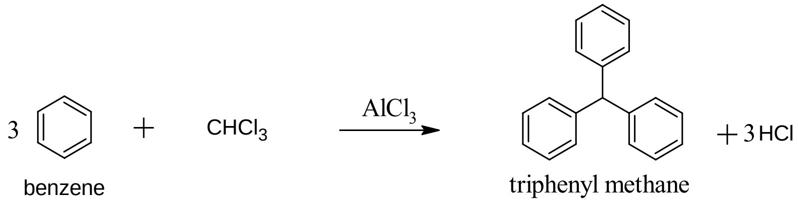


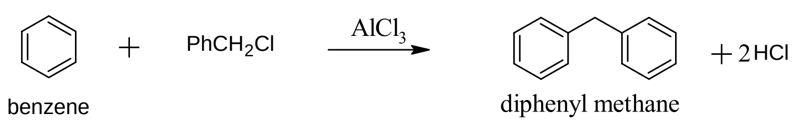
For examples;





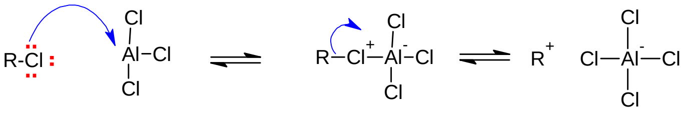




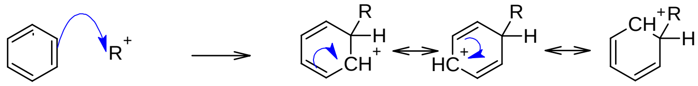


Mechanism: It follows the electrophilic substitution reaction mechanism

Step-1: - Generation of an electrophile

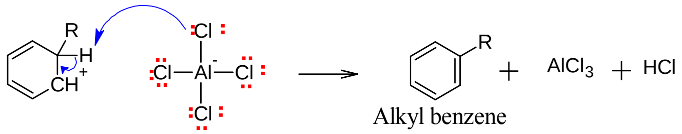


Step-2 : - Attack of an electrophile



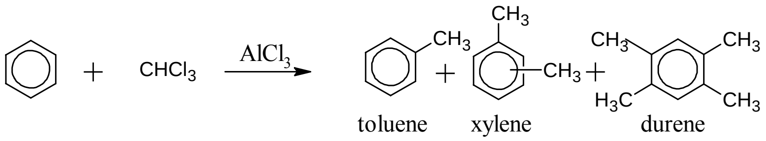
Delocalisation of positive charge

Step-3: - Removal of hydride ion

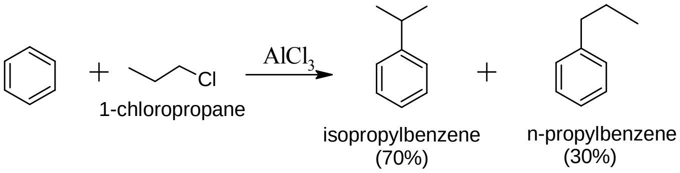


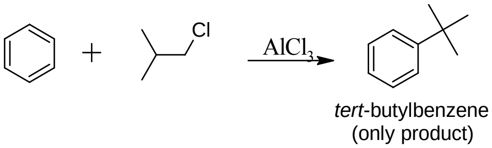
Limitations: It suffers from the following limitations.

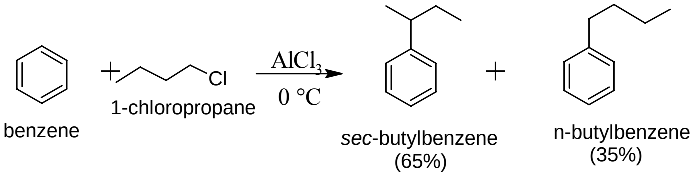
(i). Polyalkylation: It is very hard to stop this reaction at mono-alkylation because the product alkyl benzene is more reactive than the starting material.



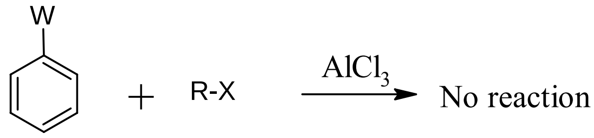
(ii). Rearrangement of alkyl group: Friedel Craft alkylation involve the generation of carbocation which may rearrange to more stable carbocations. For examples







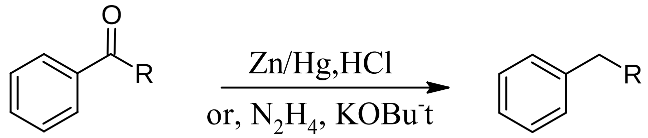
(iii). This reaction does not succeed on benzene ring bearing one or more strongly electron withdrawing groups.



W= any electron withdrawing group

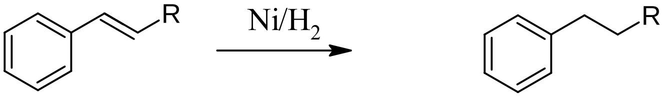
(e.g. NO_2, -CN, -CHO, -COOH etc.)

2. Reduction of acyl benzenes: Acylbenzene can be reduced to alkyl benzene by zinc amalgam and hydrochloric acid (Clemmensen reduction) of by hydrazine and a strong base (Wolf-Kishner reduction)



Unlike Friedel Craft alkylation it does not involve a rearrangement of alkyl group.

3. Hydrogenation of alkenyl benzene: Catalytic hydrogenation of alkenyl benzenes gives alkyl benzene in excellent yields.

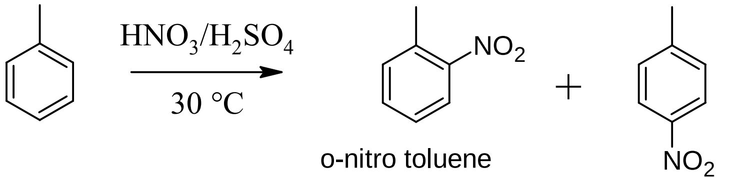


General Physical Properties: Alkyl benzene are generally colourless liquids with a charateristic odour. They are lighter than water. Being almost non-polar, they are insoluble in water but readily miscible with non-polar solvents like petroleum ether, carbontetrachloride and diethyl ether. They are flammable and burn with a highly sooty flame.

General Chemical Properties:

1. Reaction of benzene ring: Alkyl benzene undergoes the typical electrophilic substitution reactions. As the alkyl groups activate the ring, the reactions proceed more readily than in the case of benzene and the incoming substituent is usually directed to ortho and para positions.

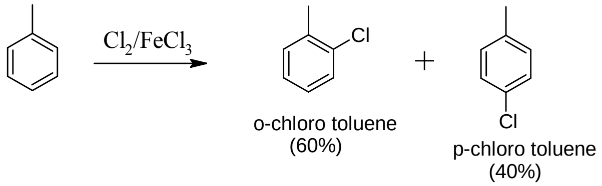
(i) Nitration: -



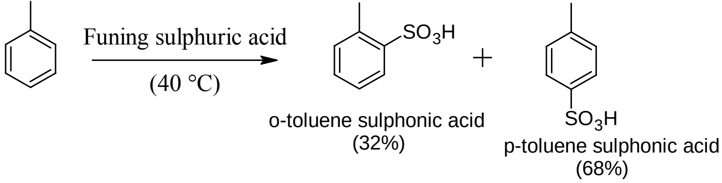
o-nitro toluene
(58%)

p-nitro toluene
(38%)

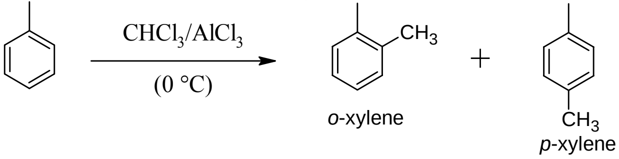
(ii) Halogenation: -



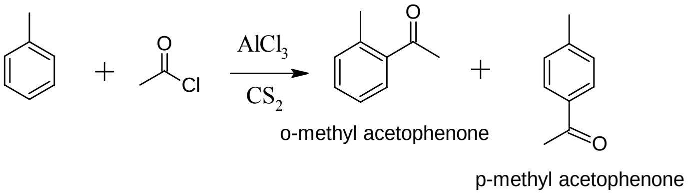
(iii) Sulphonation: -



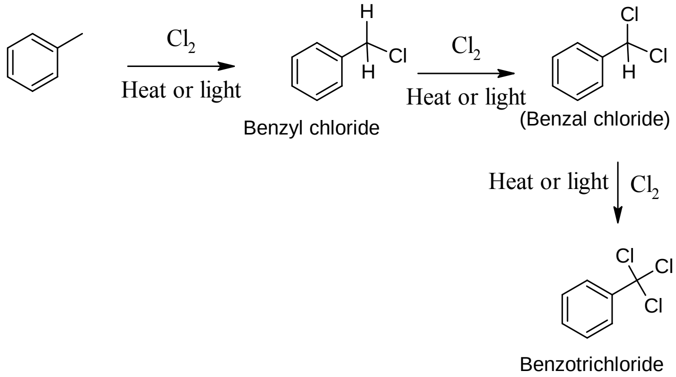
(iv) Friedal Craft alkylation: -



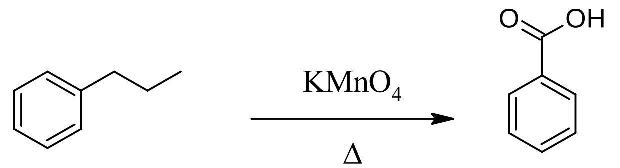
(v) Friedal Craft acylation: -



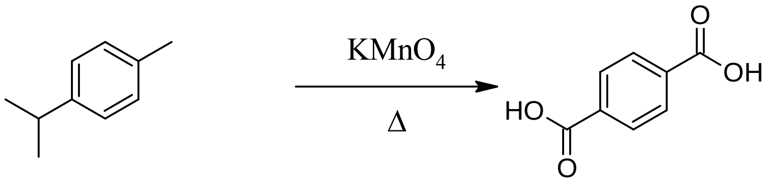
2. Reaction of the side chain: When alkyl benzenes are arylated with halogens at high temp or in the presence of UV-light, the halogenation of side chain occurs.



3. Oxidation: Oxidising agent like $KMNO_4$ and $K_2Cr_2O_7$ have no action on benzene ring but they oxidize the side chain in an alkyl benzene.

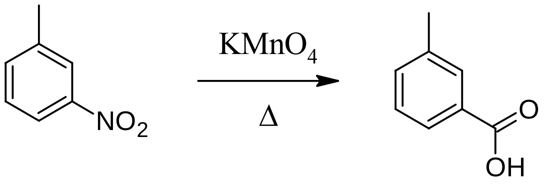


n-propylbenzene benzoic acid

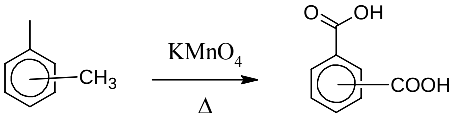


p-cymene terephthalic acid

It is useful rout for the synthesis of aromatic carboxylic acid.

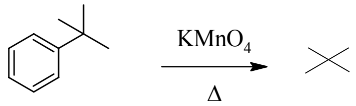


m-nitrotoluene m-nitrobenzoic acid



o,p or m-xylene o,p or m-benzene dicarboxylic acid

It must be noted that the side chain in arene must have at least one benzylic hydrogen to undergo oxidation.



tert-butylbenzene

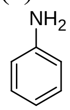
(No benzylic hydrogen in the side chain)

Aromatic Amines

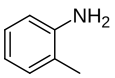
Aromatic amines can be of two types, nucleus substituted amines or arylamines and side chain substituted amines or arylalkyl amines. Amines are also classified as primary (or 10), secondary (20) or tertiary (30) amines, according to the number of groups attached to the nitrogen atom.

1. NUCLEUS SUBSTITUTED AMINES OR ARYL AMINES

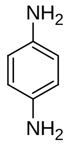
(a). Primary amines



aniline

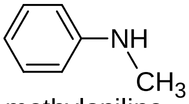


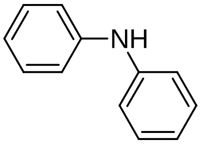
o-aminotoluene



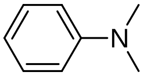
p-diaminobenzene

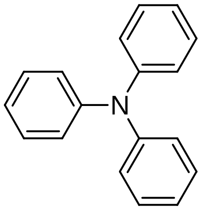
(b). Secondary amines


N-methylaniline

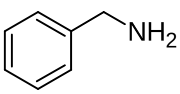

N-phenylaniline

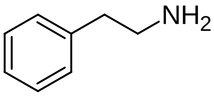
(c). Tertiary amines

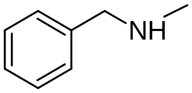

N,*N*-dimethylaniline

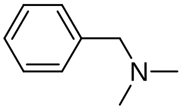

N,*N*-diphenylaniline

2. SIDE CHAIN SUBSTITUTED AMINES OR ARYLALKYL AMINES


1-phenylmethylamine (1^0)


2-phenylethylamine (1^0)


N-methylbenzylamine (2^0)


N,*N*-dimethylbenzylamine (3^0)

Aryl Amines

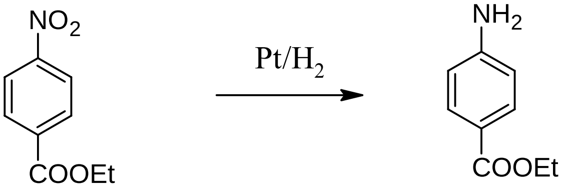
Preparation of Aryl Amines:

1.Reduction of nitro compounds: The reduction of aromatic nitro compounds can be carried out in many different ways, depending on the circumstances.

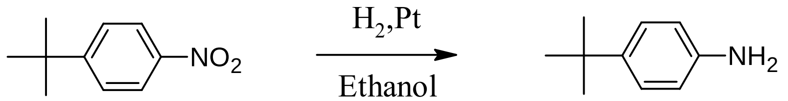
(i). Catalytic Method: Catalytic hydrogenation over platinum gives high yields but is incompatible with the presence elsewhere in the molecule of other reducible groups, such as carbon carnon double bonds or carbonyl groups

$$Ar—NO_2 \longrightarrow Ar—NH_2$$

excellent yield



ethyl p-aminobenzoate



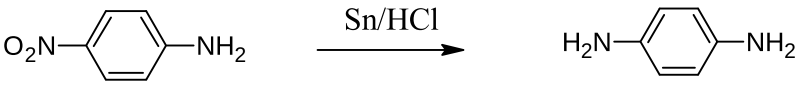
p-*tert*-butylnitrobenzene p-*tert*-butylaniline (100%)

(ii) *Complex metal hydrides* like lithium aluminium hydride reduce nitro compounds to primary amines very readily.

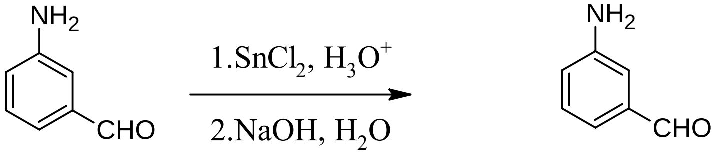
$$Ar{-}NO_2 \xrightarrow{LiAlH_4} Ar{-}NH_2$$

(iii) *Metal-acid combination* like Iron, zinc, tin and stannous chloride are effective when used acidic aqueous solution. stannous chloride is particularly mild and is often used when other reducible functional groups are present.

$$Ar{-}NO_2 \xrightarrow{Sn/HCl} Ar{-}NH_2$$

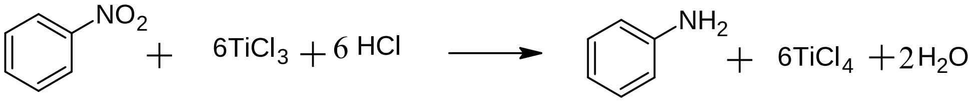


p-nitroaniline p-aminoaniline



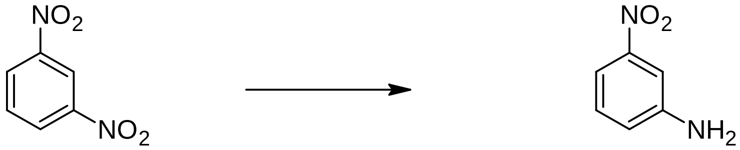
3-aminobenzaldehyde 3-aminobenzaldehyde

(iv).*Titanous chloride*, TiCl3 in hydrochloric acid is specially useful for the quantitative determination of the number of nitrogen groups in a compound.

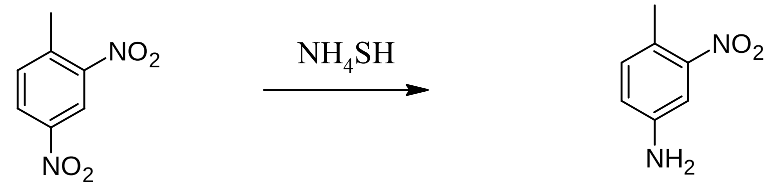


nitrobenzene aniline

(v). Ammonium hydrogen sulphide is useful for the selective reduction of polynitro compounds.



1,3-dinitrobenzene 3-nitroaniline



2,4-dinitrotoluene   4-methyl-3-nitroaniline

General physical properties: Pure arylamines are usually colourless, but they get discoloured due to great susceptibility to atmospheric oxidation. They are usually insoluble or sprangly soluble in water but fairly soluble in less polar solvents like benzene, ether etc.They are generally steam volatile and possess characteristic unpleasant odour.

General Chemical Properties:

1. Basicity : - Aryl amines are weak bases forming salts with acids

$$\underset{\text{Amine}}{Ph-NH_2} + H-X \rightleftharpoons \underset{\text{Salt}}{Ph-\overset{+}{N}H_3\,\overset{-}{X}}$$

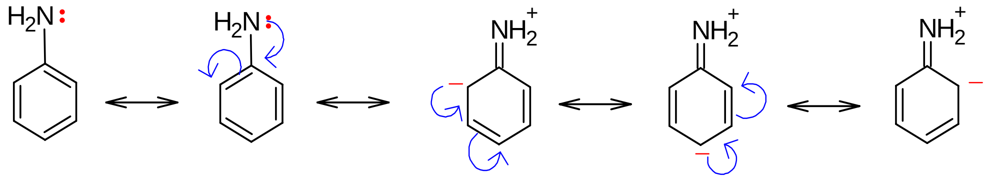
$$Ph-NH_2 + R-COOH \rightleftharpoons Ph-\overset{+}{N}H_3\,\overset{-}{O}OC-R$$

These salts, when treated with stronger bases like sodium hydroxide, liberate the “free” amines.

$$Ph-\overset{+}{N}H_3\,\overset{-}{X} + \underset{\text{Strong base}}{HO^-} \longrightarrow \underset{\text{Weak base}}{Ph-NH_2} + H_2O + X^-$$

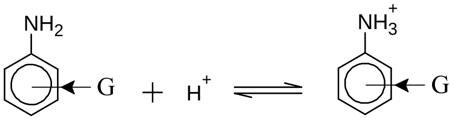
Structure and Basicity: Factors which increase the ability of nitrogen in an amine to share its electron pair increase the basicity of the amine, and vice versa.

(a) Simple aryl amine: Aryl amines are less basic than alkyl amines because the nitrogen lone-pair electrons are delocalised by interaction with the aromatic ring pi electron system and are less available for bonding to H^+.

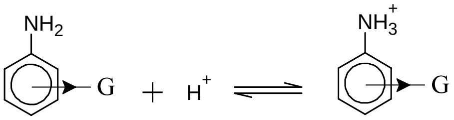


Resonance stabilisation of aniline

(b) Substituted aryl amines can be either more basic or less basic than aniline, depending on the substituent. Electron donating substituent, which increase the reactivity of an aromatic ring toward electrophilic substitution, also increase the basicity of the corresponding arylamine. Electron wihthdrawing substituents, which decrease reactivity toward electrophilic substitution, also decrease arylamine basicity.



(G = CH_3, NH_2, NHR, OR etc.) G-release electrons, stabilizes anilinium ion and increases basic strength.



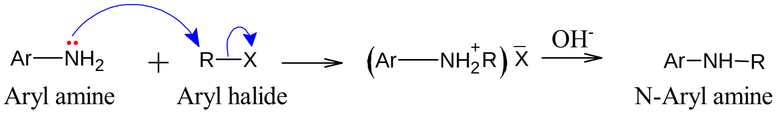
G-withdraw electrons, destabilizes anilinium ion and decreases basic strength.

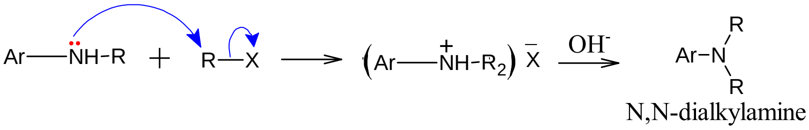
Table: Basic strength of some p-substituted aniline

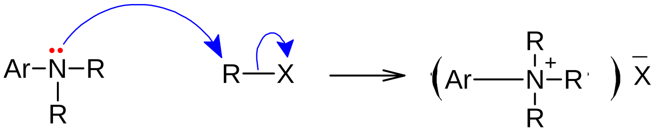
Substituent, Y	**p*K*$_a$**
-NH2	6.15
-OCH3	5.34
-CH3	5.08
-H	4.63
-Cl	3.98
-Br	3.86
-CN	1.74
-NO2	1.00

Similar trends are observed for ortho and meta derivatives.

2.Alkylation: Primary aromatic amines, undergoes reaction with alkyl halide to give successively secondary, tertiary amines and quaternary ammonium salts. These reactions are example of nucleophilic substitution reaction.

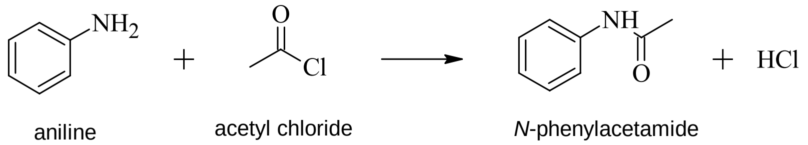


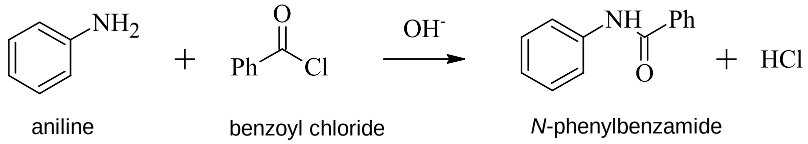




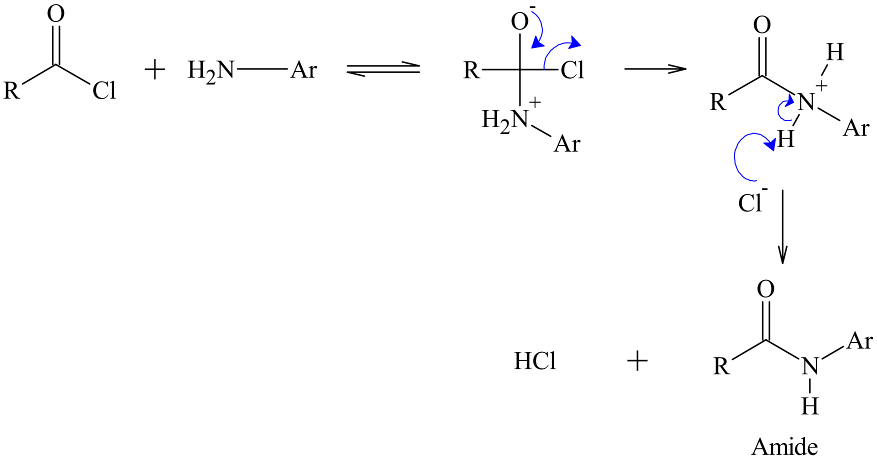
Quarternary salts

3. Acylation :The amino group of arylamines react with acid halide to form amides. This reaction is an example of *nucleophilic acyl substitution*

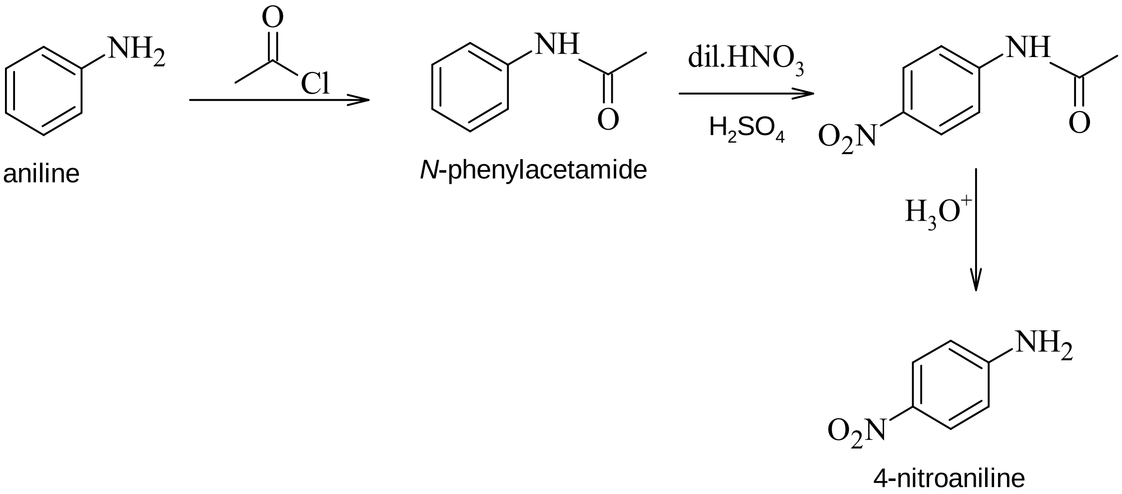




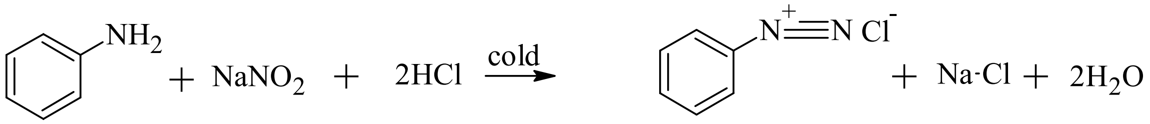
The acid chloride is more reactive than a ketone or an aldehyde because the electronegative chlorine atom draws electron density away from the carbonyl carbon, making it more nucleophilic. The chlorine atom is also a good leaving group.



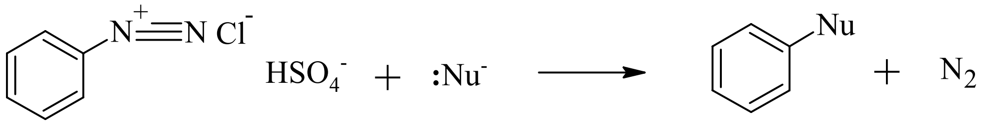
Acylation can ‘protect’ amino group in synthetic sequences. For example.



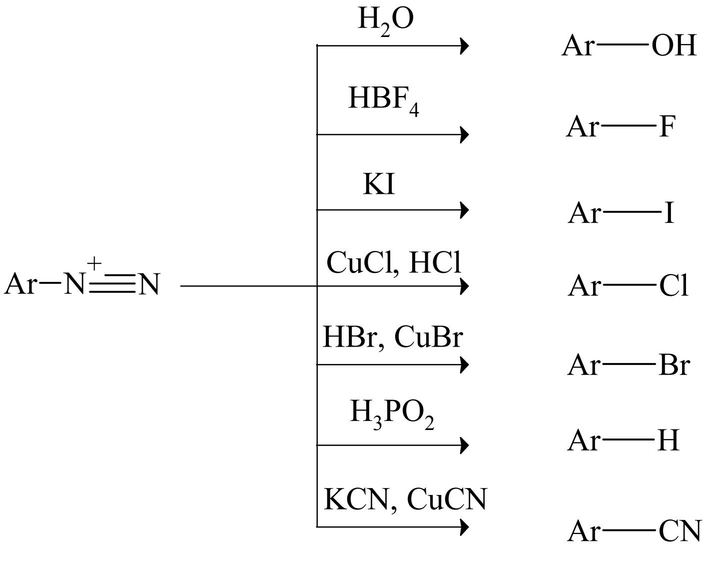
4. Reaction with nitrous acid:Primary (not secondary and tertiary) arylamines react with nitrous acid at low temperatures and in the presence of a strong mineral acid, to give relatively stable, water soluble compounds known as diazonium salts. This reaction, known as **diazotisation**, is an extremely important reaction for variety of organic compounds.



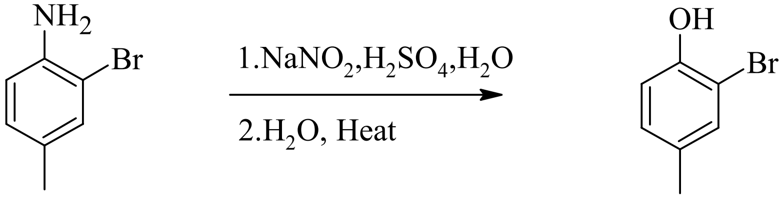
Arenediazoinum salts are extremely usrful because the diazonio group (N_2) can be replaced by a nucleophile in a radical substitution rection.



Many different functional groups can by introduced via arendiazounuim salts.



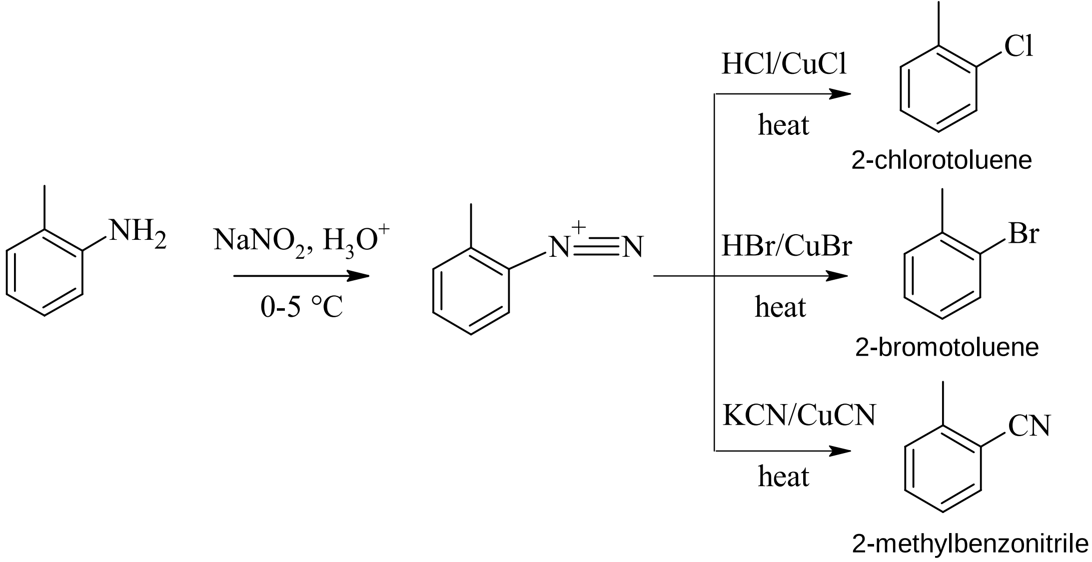
Replacement of Diazonium group by hydroxide: Aromatic amines can be converted to phenols by first forming the arenediazonium salt in aqueous sulphuric acid and then heating the solution.



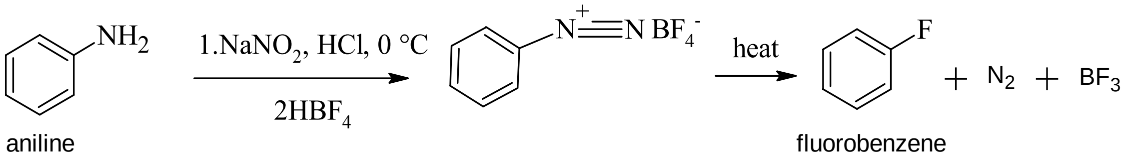
2-bromo-4-methylaniline

2-bromo-4-methylphenol

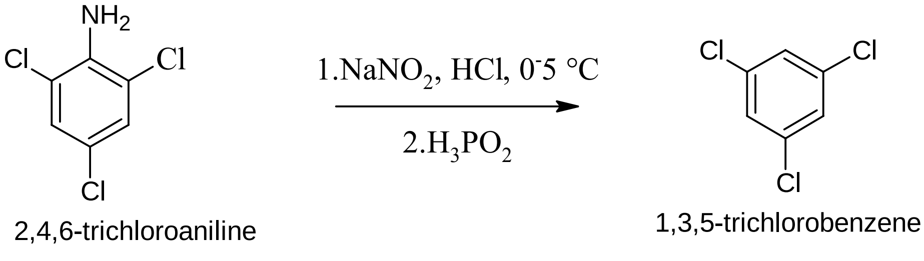
Replacement of Diazonium group by chloride, bromide, and cyanide: Treatment of primary aromatic amine with nitrous acid followed by heating with HCl/CuCl, HBr/CuBr or KCN/CuCN results in replacement of the diazonium group by –Cl, -Br, or –CN, respectively, and is known as *Sandmeyer reaction.*



Replacement of Diazonium group by floride and iodide: When primary aromatic amine is treated with sodium nitrite in aqueous HCl followed by addition of HBF_4 or $NaBF_4$, the diazonium fourobortate salt precipitates and is collected and dried. Heating the dry salt brings about its decomposition to an aryl fouoride, nitrogen and borontrifloride. This reaction is called *Schiemann reaction.*

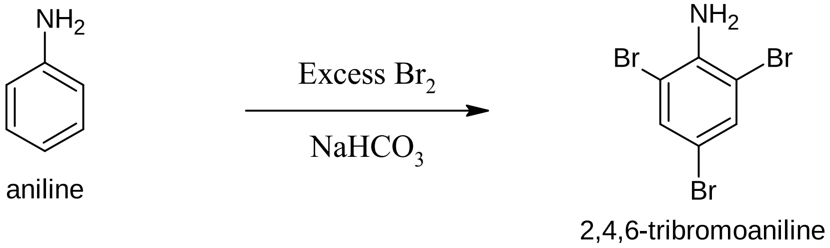


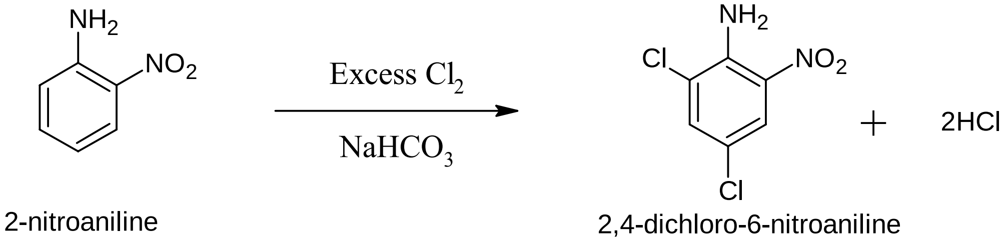
Replacement of Diazonium group by hydrogen: Treatment of arenediazonium salts with hypophosphorous acid, results in reduction of the diazonium group and its replacement by hydrogen.



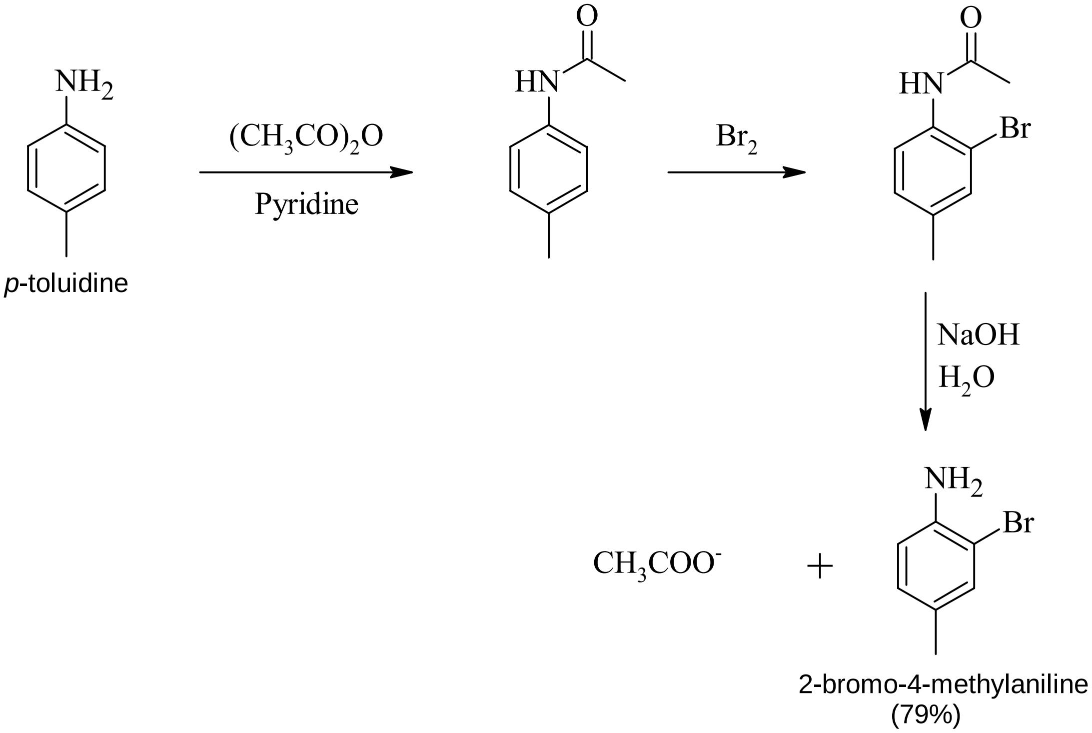
4. Electrophilic aromatic substitution : The amino group is an ortho, para directing and a powerful activating substituent, so that arylamines undergo the typical electrophilic substitution reaction very readily. In fact, the rate of these reaction is so great in certain cases that polysubstitution, rather monosubstitution, occurs even under mild conditions.

(i) Halogenation: - Halogention occur rapidily at the unsubstituted ortho and para postion without a catalyst.

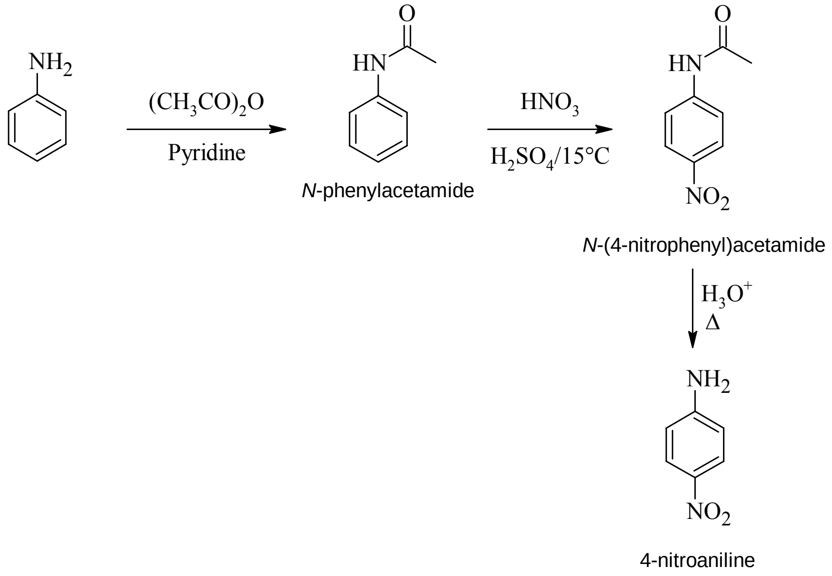




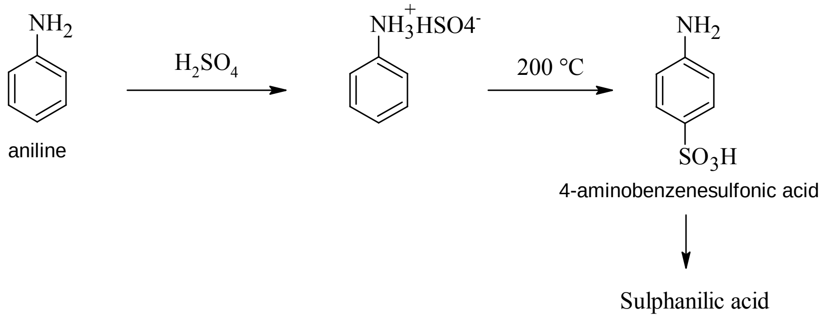
If it is desired that only monohalogention occurs, the free amino group is acetylated prior to halogention. Treatment of an amine with acidic anhydride yields an N-acetylated product which is less strongly activating and less basic than amino groups because their nitrogen lone pair electrons are delocalised by the neighboring carbonyl group. As a result, bromination of an N-arylamide occurs cleanly to give mono bromo product, and hydrolysis with aqueous base then gives the free amine.



(ii) Nitration : - The amino group is protected by acetylation prior to nitration so that the reaction proceeds according to the known principles of orientation and reactivity.

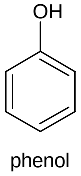


(iii) Sulphonation: -

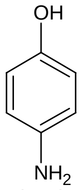


Phenols

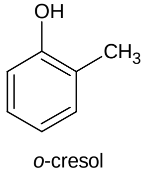
Phenols contain the hydroxyl group(s) attached directly to the aromatic nucleus. It occurs widely throughout nature and also serves as intermediates in the industrial synthesis of products as diverse as adhesive and antiseptics.



phenol



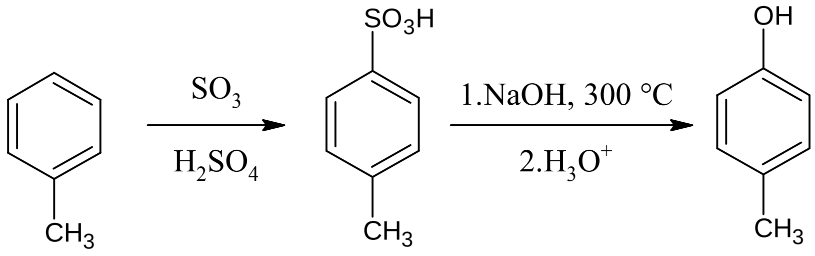
4-aminophenol



o-cresol

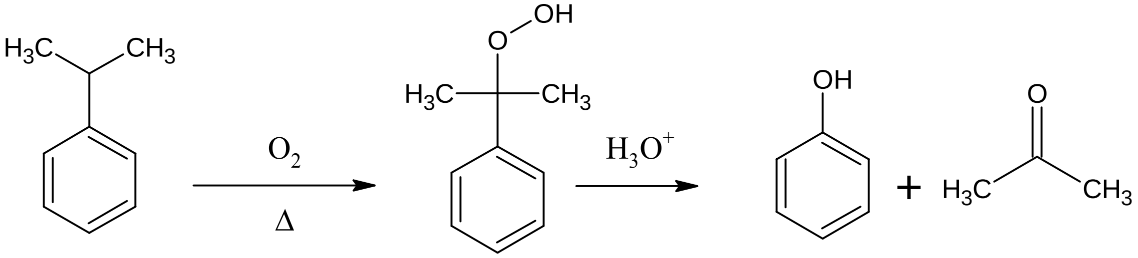
Preparation of Phenols

1. From Sulphonic acid: In the laboratory simple phenols can be prepared from aromatic sulphonic acids by melting with NaOH at high temperature.



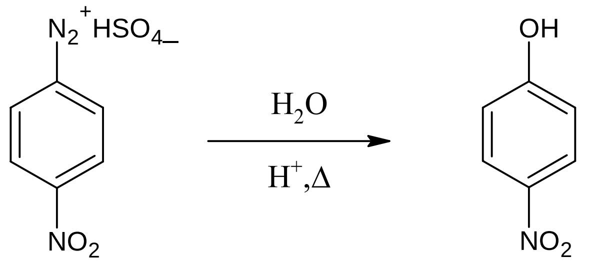
toluene 4-toluenesulfonic acid *p*-cresol (72%)

2. Industrial method (From Cumene): Cumene reacts with air at high temperature by a radical mechanism to form cumene hydroperoxide, which is converted into phenol and acetone by treatment with acid. This is particularly efficient process because two valuable chemicals are prepared at the same time.



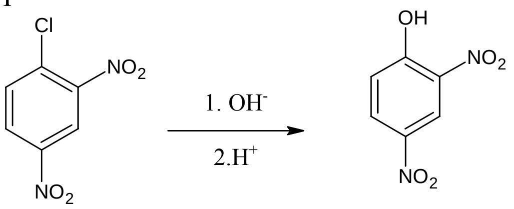
cumene cumene hydro hydroperoxide phenol acetone

3. From diazonium salts: The diazonium salt solution usually added to hot dilute acid. This method is quite popular especially for the preparation of phenols containing substituents like –Cl, -NO_2 etc.



p-nitrobenzenediazonium hydrogen sulphate p-nitrophenol

4. Hydrolysis of aryl halide:This method is quite useful for the hydrolysis of aryl halide containing electron-withdrawing substituents like NO_2 group in ortho and para position. For example

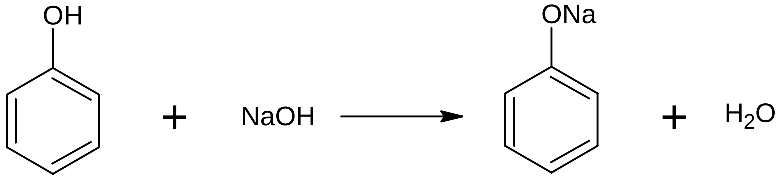


2,4-dinitrochlorobenzene 2,4-dinitrophenol

General Physical Properties: Pure phenols are generally colourless solids or liquids, but they turn reddish, due to atmospheric oxidation. Substituents like –NO_2 groups, however, impart yellow colour to phenols. They are generally insoluble in water, but phenol itself, and di, and tri-hydric phenols are fairly soluble. They usually have relatively high boiling points due to intermolecular hydrogen bonding. Phenol (molecular weight=94) boils at 182^{0}c whereas n-heptane (molecular weight=100) boils at 98^{0}c only. Intermolecular hydrogen bonding leading to special physical properties also occurs in substituted phenols, where structure permits. o-Nitrophenol, for example, has much lower boiling point and lower solubility in water than its m- and p- isomers.

General Chemical Properties:

1. Acidic Character: Phenols are fairly acidic compounds which form salts (phenoxides) on reaction with alkali metal hydroxides.

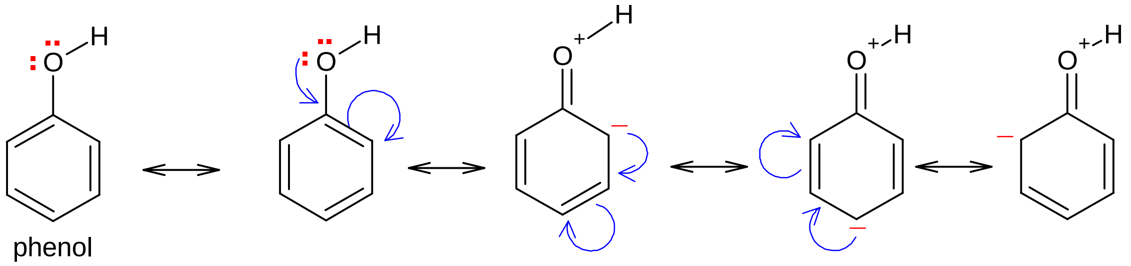


phenol

sodium phenoxide

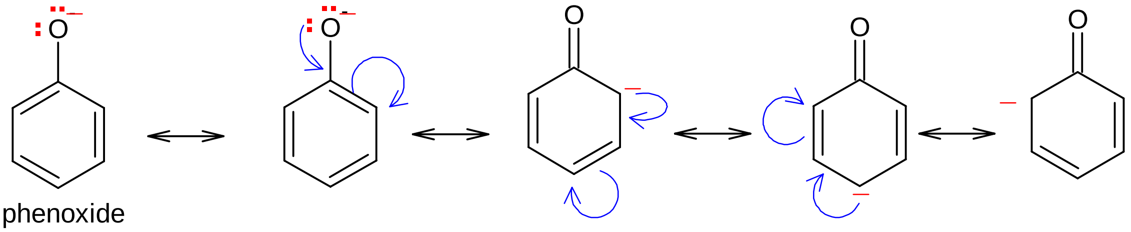
Phenol is such a weak acid that it cannot decompose metallic carbonates. The acidic nature is due to the existence of phenol as resonance hybrid. Due to resonance, the oxygen atom of –OH gets a positive charge and so a proton is easily released. All the three structure (I, II, and III) for phenol carry both positive and negative charges.

On the other hand, the resonating structures of phenoxide ion contain only negative charges.



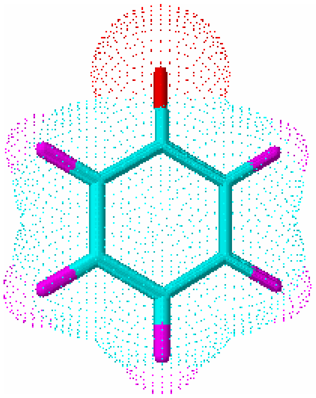
phenol

Resonance hybrid of phenol



phenoxide

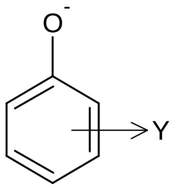
Resonance hybrid of phenoxide ion



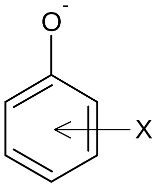
Phenoxide ion

It can be seen that more energy would be required to separate the positive and negative charges in phenol; consequently phenol has greater energy than phenoxide ion. In other words, phenoxide is more stable than the phenol.

Substituted phenols can either more acidic or less acidic than phenol itself. Phenols with an electron withdrawing substituent are generally more acidic because there substituents stabilize the phenoxide ion by delocalising the negative charge. Phenols with an electron donating substituent destabilize the phenoxide ion by localizing the charge.

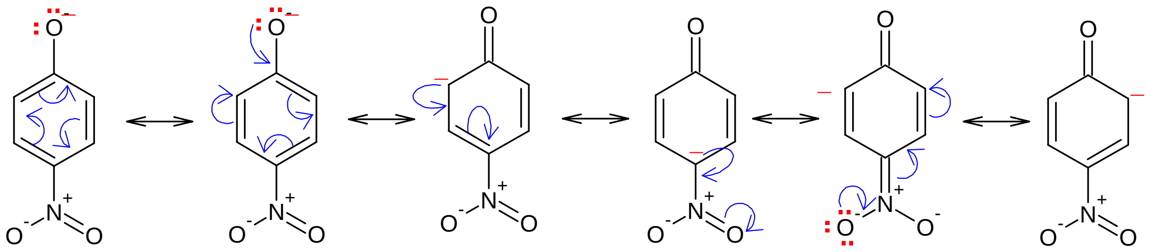


Y= electron withdrawing group.
stabilise phenoxide ion
acidity increases



X= electron donating group
destabilise phenoxide ion
acidity decreases

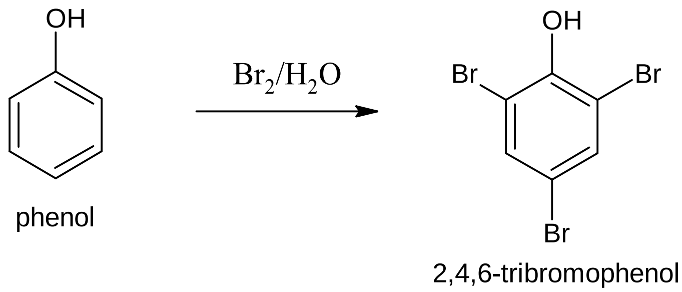
The acidifying effect of an electron-withdrawing substituent is particularly noticeable for phenols having a nitro group at the ortho or para position.

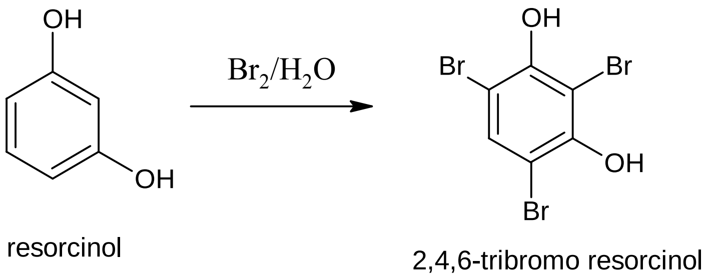


Dispersal of negative charge through resonance stabilization of p-nitrophenoxide ions

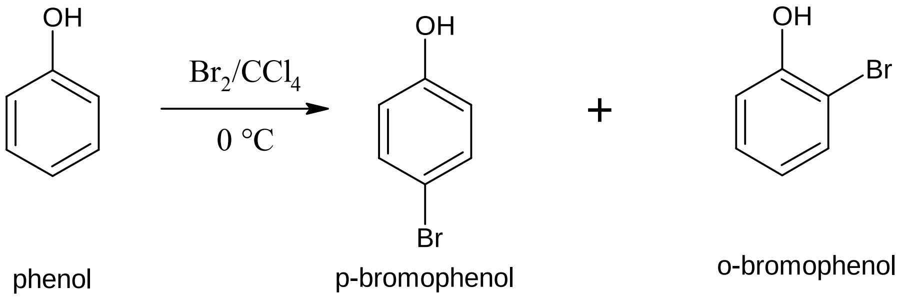
2. Electrophilic aromatic substitution:The hydroxy group is strongly activating ortho and para directing substituent in the electrophilic aromatic substitution reaction. As a result it is usually difficult to prevent polysubstitution and oxidation.

   (i) Halogenation: -

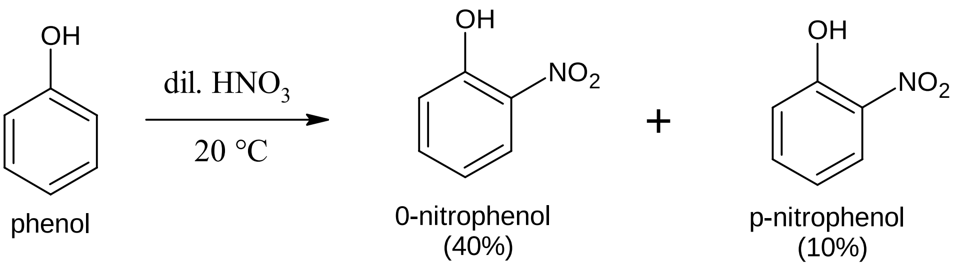




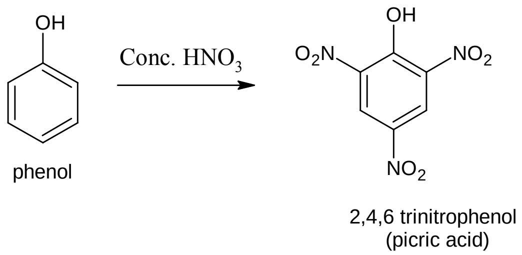
If it is desired to stop the reaction at monosubstitution stage, it should be carried out at low temperature and in non-polar solvent like carbon tetrachloride and carbondisulphide.



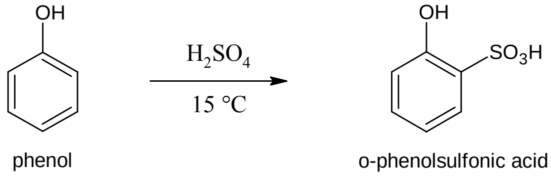
(ii) Nitration: -

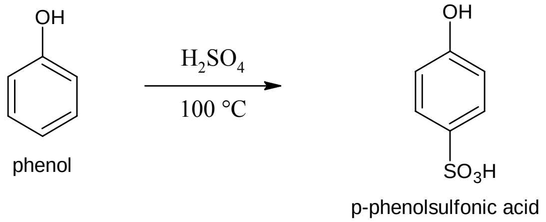


The relatively low yields of products are due to losses by oxidation of reactive phenols. Use of concentrated HNO_3 leads to the formation of picric acid.

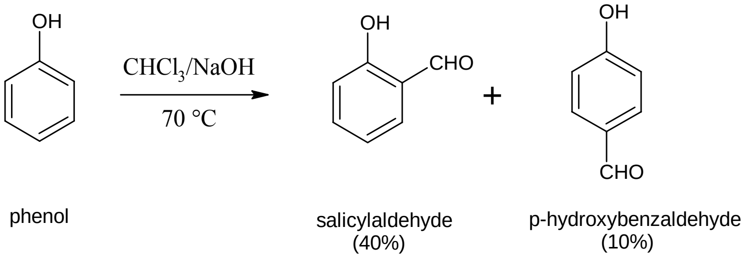


(iii)Sulphonation: Low temperature favours ortho isomer while high temperature favour para isomers.

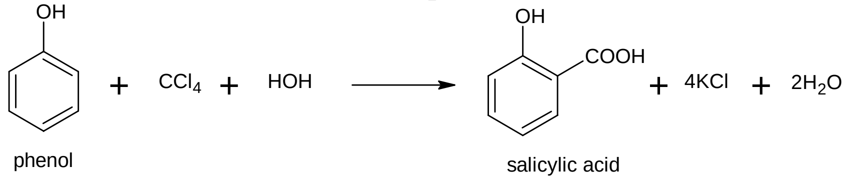




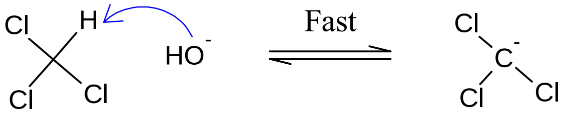
3. Reimer-Tiemann reaction: When a phenol is treated with chloroform and sodium hydroxide solution, an aldehyde group is introduced to the aromatic ring.

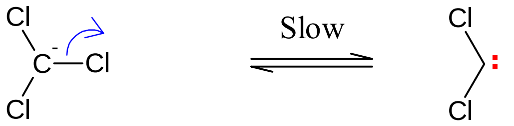


If CCl_4 is used instead of $CHCl_3$, phenolic acid is formed.

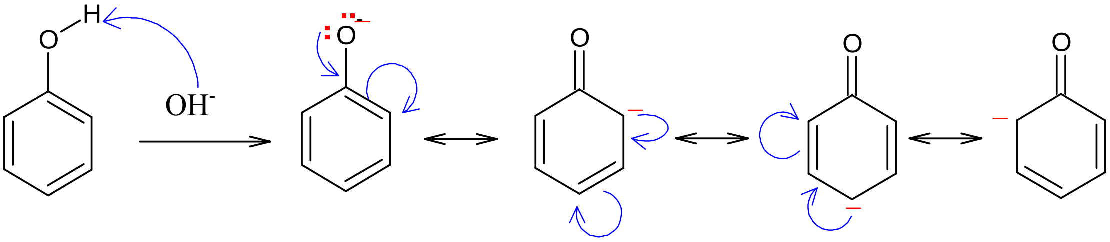


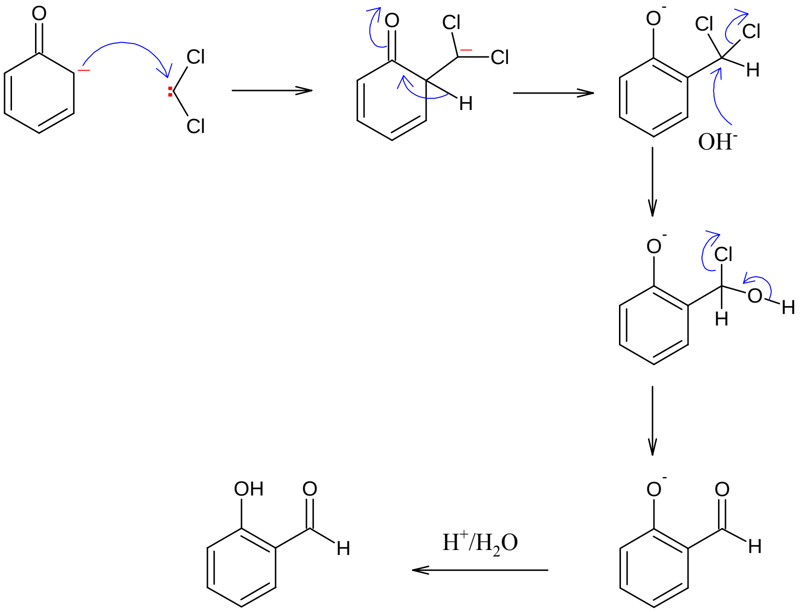
Mechanism: - This is a base catalysed reaction.





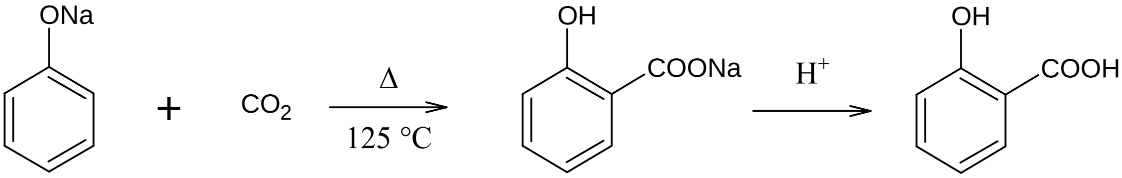
dichlorocarbene
(strong electrophile)





salicylaldehyde

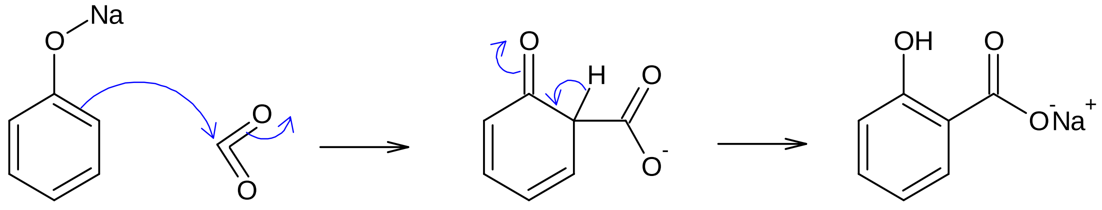
4. Kolbe Reaction: When sodium phenoxide is treated with carbon dioxide gas under pressure a carbonyl group is introduced, preferably in ortho position to the –OH group.



sodium salicilate

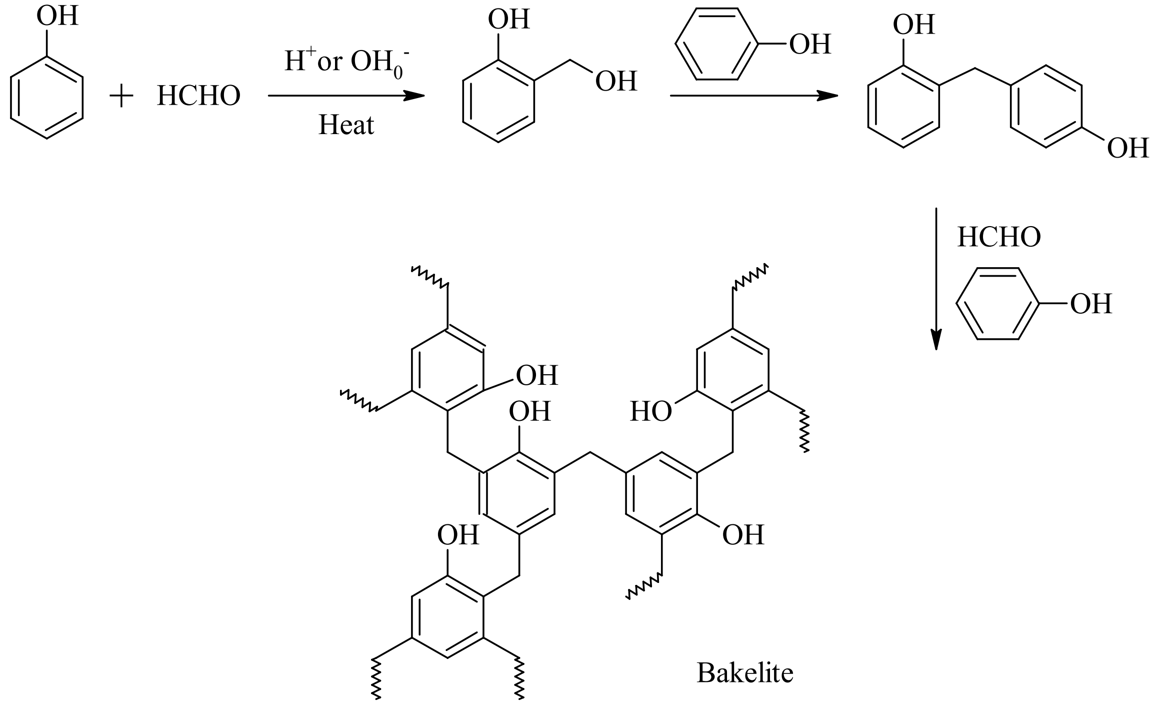
salicylic acid

Mechanism:



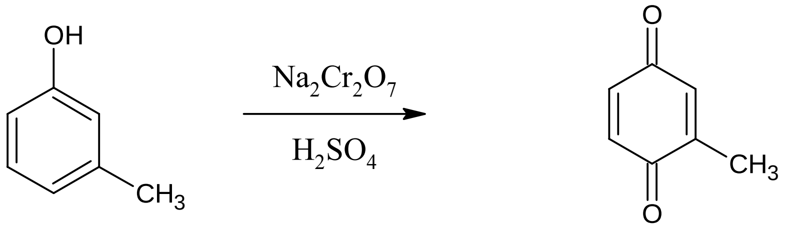
sodium salicylate

5. Reaction with formaldehyde: When a phenol is treated with formaldehyde in the presence of acids or alkali, a phenolic resin (Bakelite is produced.



Bakelite

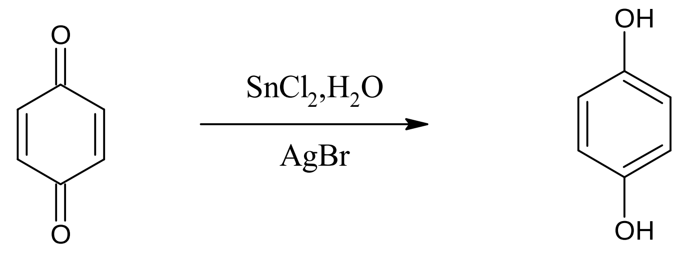
6.Oxidation of phenol: Chromic acid oxidation of phenol gives a conjugated 1,4-diketone called **quinone**. In the presence of air, many phenol slowly auto oxidise to dark mixture containing quinone.



m-cresol

2-methylbenzo-1,4-quinone

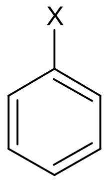
Quinines can be easily reduced to hydroquinones by reagents such as $NaBH_4$ and $SnCl_2$ and hydroquinones can be easily reoxidised back to quinines by AgBr.



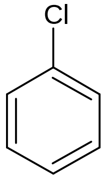
benzo-1,4-quinone hydroquinone

Aryl Halide

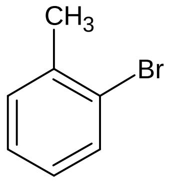
If halogen is bonded to the benzene ring, the compound belongs to a class called haloarene, often given the generic symbol Ar-X, where –X may be –F, -Cl, -Br or –I.



Aryl halide



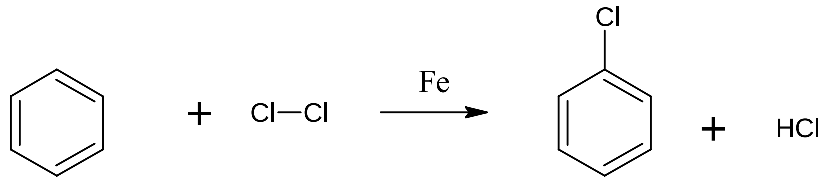
chlorobenzene



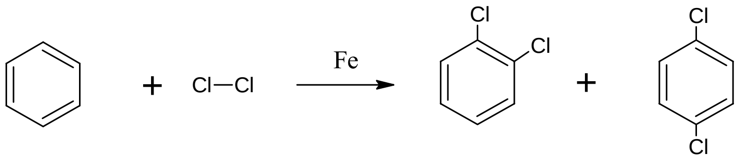
o-bromo-toluene

Methods of Preparation

1.Direct halogenation: Aryl chlorides and bromides can be prepared by treating the arene with chlorine or bromine at low temperature, in the absence of sunlight and in the presence of Lewis acid like $AlCl_3$, $FeCl_3$ etc.

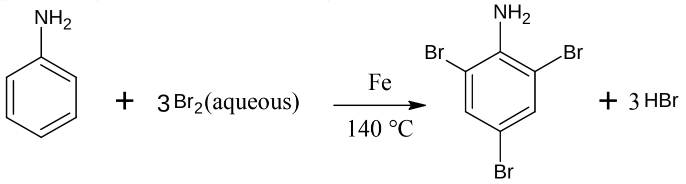


benzene one mole chlorobenzene



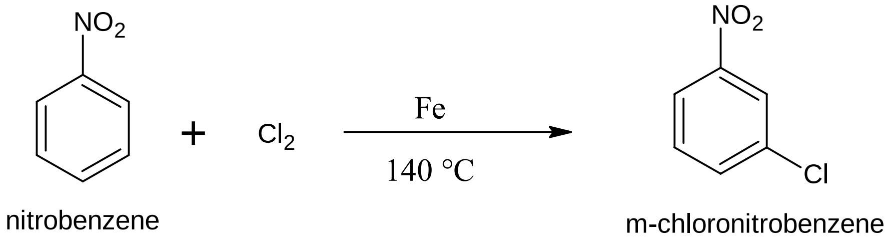
benzene two moles o-dichlorobenzene p--dichlorobenzene

Highly activated groups like amines and phenols undergo halogenation so easily that they do not require any Lewis acid catalyst.



aniline 2,4,6-tribromoaniline

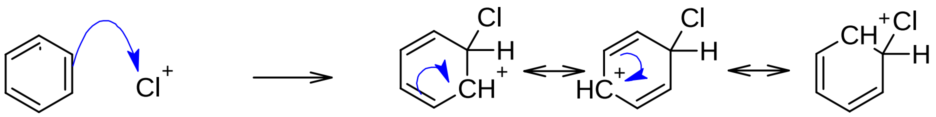
Deactivated compounds like nitrobenzene require high temperature as well as catalyst.



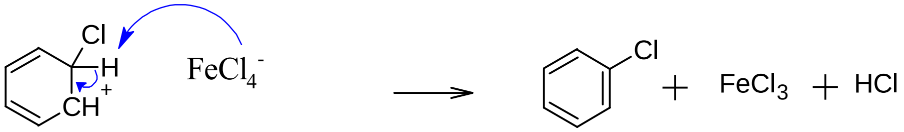
Mechanism: - It is an electrophilic substitution reactions

$$2Fe + 3Cl_2 \longrightarrow 2FeCl_3$$

$$Cl{-}Cl + FeCl_3 \longrightarrow \overset{\delta^+}{Cl}{-}\overset{\delta^-}{Cl}\cdots\cdots FeCl_3 \longrightarrow FeCl_4^- + Cl^+$$



Delocalisation of positive charge



chlorobenzene

2. From diazonium salts (Sandmeyer's reaction): This is the most convenient method for preparing aryl halides. The methodconsists in worming an aqueous solution of diazonium salt with cuprous halide.

$$C_6H_5\overset{+}{N_2}Cl^- \xrightarrow{CuCl/HCl} C_6H_5Cl + N_2$$

chlorobenzene

$$C_6H_5\overset{+}{N_2}Cl^- \xrightarrow{CuBr/HBr} C_6H_5Br + N_2$$

bromobenzene

3. Hansdiecker reaction: - It consists in treating the silver salts of aromatic carboxylic acid with bromine.

$$C_6H_5COOAg + Br{-}Br \longrightarrow C_6H_5Br + AgBr + CO_2\uparrow$$

General Physical Properties

1. Halogen derivatives are colourless liquids or crystalline solids, insoluble in water but soluble in organic solvents because of their low polarity.
2. Their boiling points and densities are greater than those of the parent arens. The boiling points and densities of monohalogen derivatives of benzene are in are:
   Iodo >Bromo >Chloro

3. The boiling points of *o*-, *m*-, and *p*-isomers have so close that these are difficult to separate by distillation. However, the melting point of *p*-isomer has been much higher than that of an *o*-or *m*- isomer because the more symmetrical *p*-isomer fits more easily into a crystal lattice and the stronger intra crystalline forces gives rise to a higher melting point.

General Chemical Properties

1. Nucleophilic aromatic substitution: Simple aryl halides, unlike alkyl halide do not undergo reaction with nucleophilic reagent under conditions.

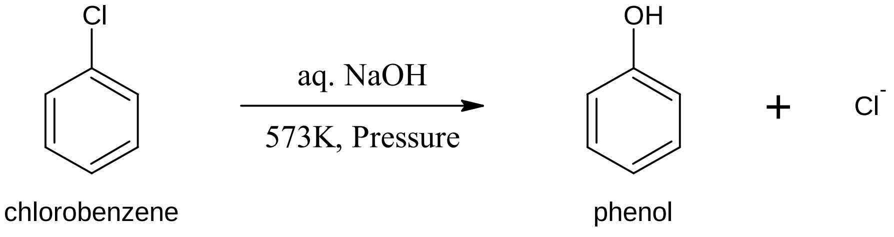
$$H_3C\text{—}Cl + {:}Nu \longrightarrow H_3C\text{—}Nu + Cl^-$$

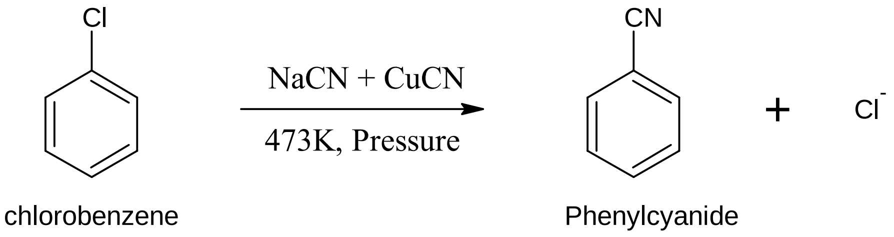
chloromethane

$$H_5C_6\text{—}Cl + {:}Nu \longrightarrow \text{No reaction}$$

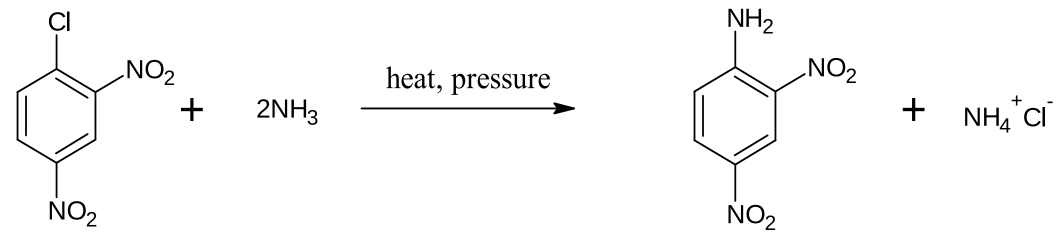
chlorobenzene

However, at sufficiently high temperature and pressure, many nucleophilic substitution can take place.



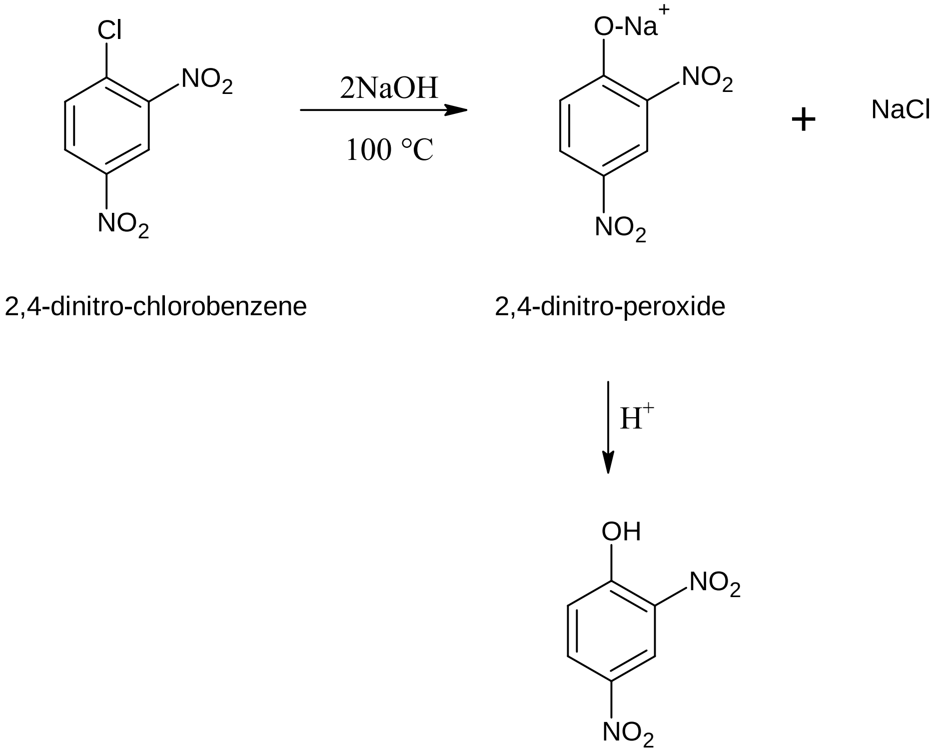


Nucleophile can displace halide ions from aryl halides, particularly if there are strong electron withdrawing group ortho or para to the halide.



2,4-dinitro-chlorobenzene

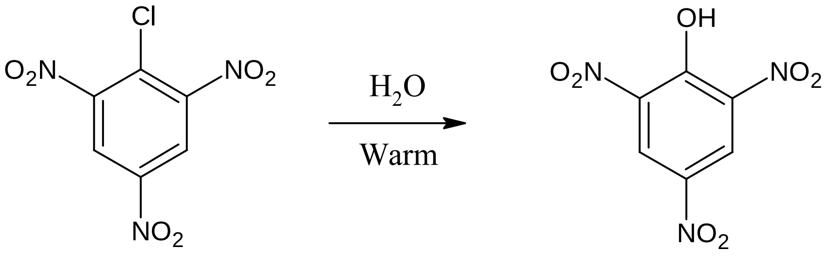
2,4-dinitroaniline



2,4-dinitro-chlorobenzene

2,4-dinitro-peroxide

2,4-dinitrophenol
(95%)



2-chloro-1,3,5-trinitrobenzene

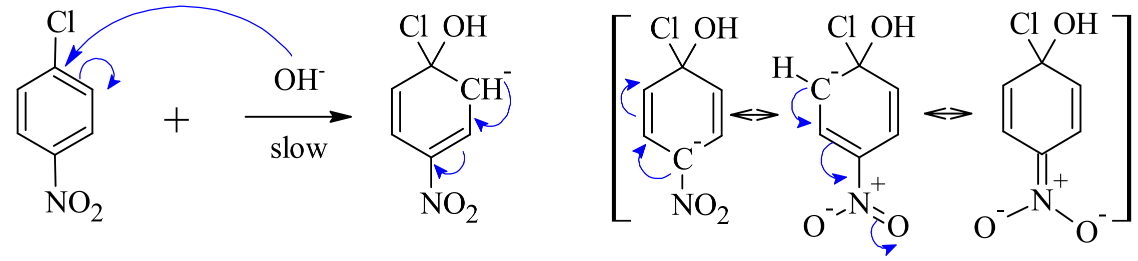
picric acid

In nucleophilic aromatic substitution a strong nucleophile replaces a leaving group, such as halide; but the mechanisms of the nucleophlic aromatic substitutions shown above are not immediately apparent. They cannot use SN^2 mechanism, because aryl halides cannot achieve the correct geometry for backside displacement. The aromatic ring blocks approach of the nucleophile to the back of the carbon bearing the halogen.

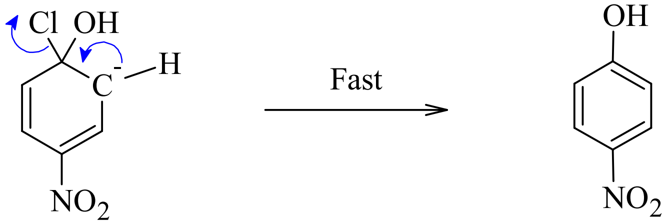
The SN^1 mechanism cannot be involved either; strong nucleophilic electrons are required, and the reaction rate is proportional to the concentration of the nucliophile. The nucleophile must be involved in the transition state

The two mechanisms, viz., bimolecular displacement mechanism and benzyne intermediate mechanism have been proposed for these substitution reactions.

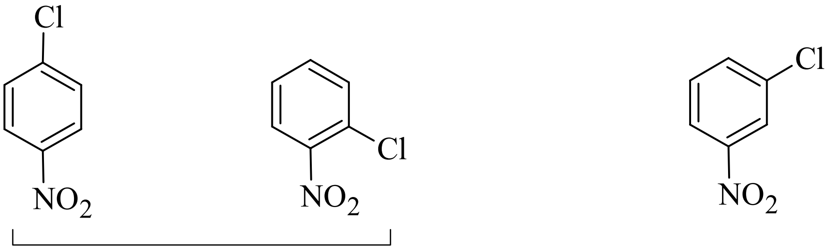
a. **Bimolecular displacement mechanism (The addition-elimination mechanism):** This mechanism operates in the case of substitution reactions involving relatively milder nucleophilic reagent and active aryl halides containing electron-withdrawing substituents in ortho and/or para position.



Resonance stabilised carbanion (sigma complex)



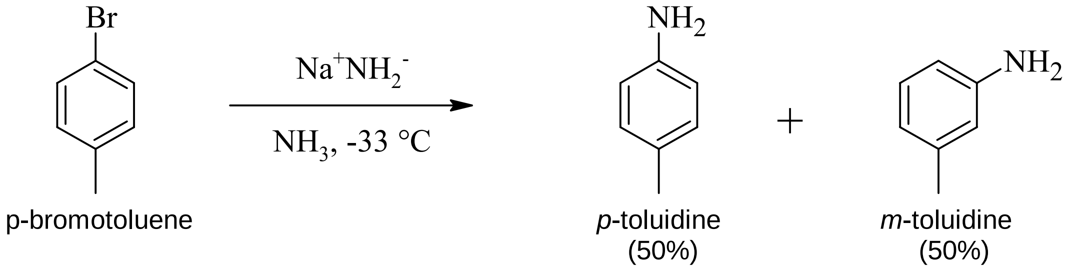
The greater the stability of carbanion, the greater the ease with which it will be formed. The resonance structures shown above illustrate how nitro groups ortho and para to the halogen help to stabilize the intermediate. Without strong electron with drawings in these positions, formation of the negatively charged sigma complex is unlikely.



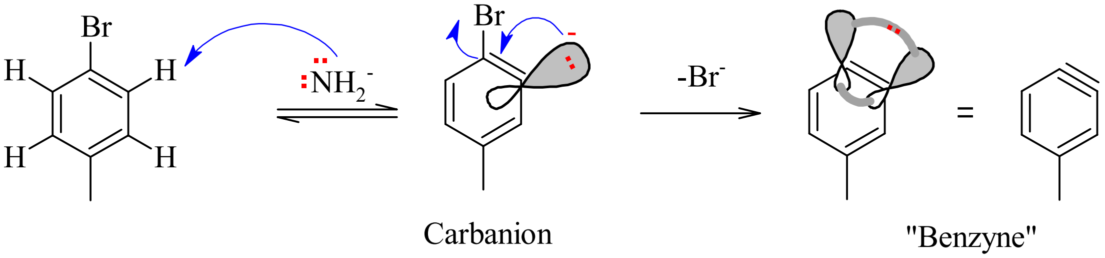
Activated

Not activated

b. **The benzyne intermediate mechanism (Elimination-Addition):** This mechanism operates for reactions involving rather strong nucleophilic reagents (e.g. amide ion or liquid ammonia) and relatively less reactive aryl halides (e.g. chlorobenzene) or aryl halide containing electron-releasing substituents in ortho and /or para position.



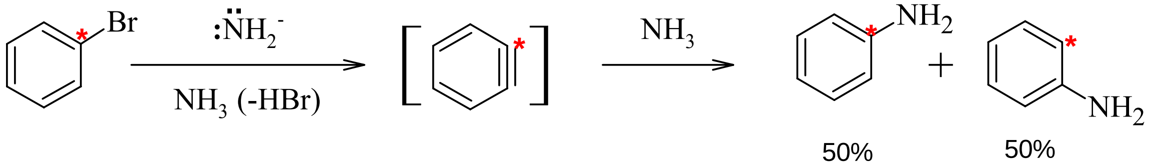
These two products are explained by an elimination-addition mechanism, called the benzyne mechanism, because of its unusual intermediate. Sodium amide reacts as a base, abstracting a proton. The product is a carbanion with a negative charge and a non-bonding pair of electrons localized in the sp^2 orbital that once formed the C-H bond.



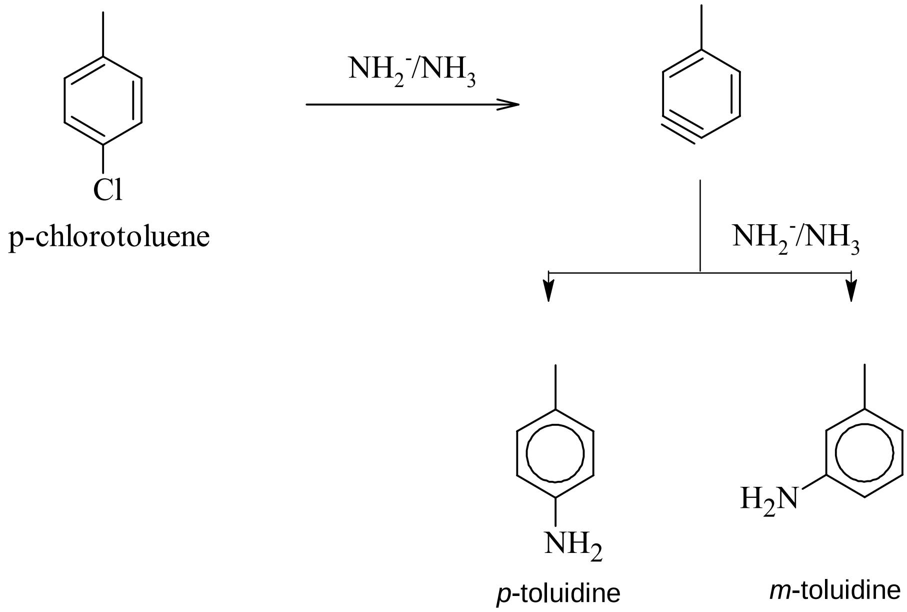
The novel benzyne intermediate with a carbon-carbon triple bond in the benzene ring involves the formation of a new carbon-carbon bond by side ways overlapping of sp^2 orbitals. The two sp^2 orbitals are directed 60^0 away from each other, so there overlap is not very effective. This triple bond is highly strained and is very reactive.

Evidence In Support of the Benzyne Intermediate Mechanism

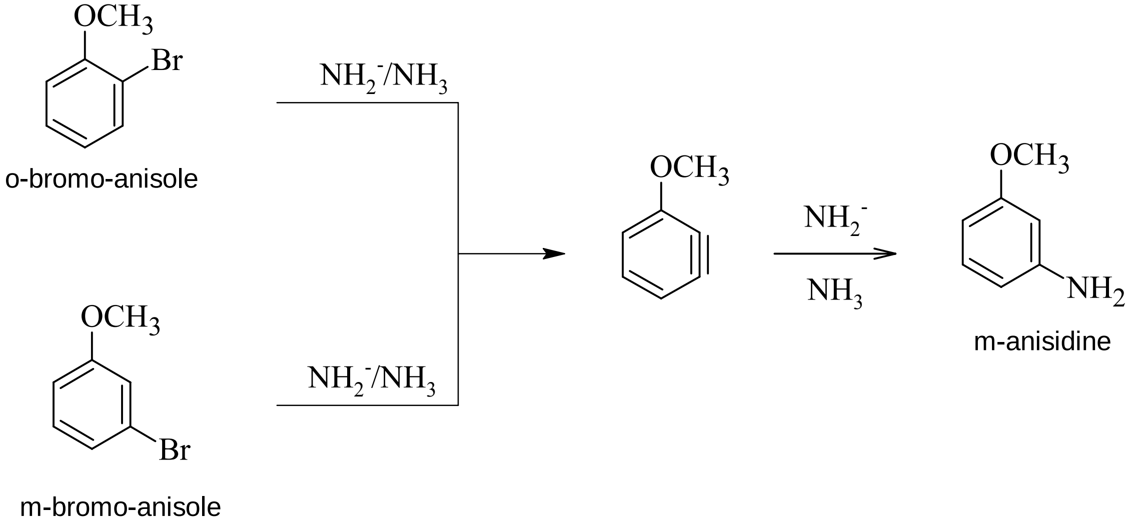
a. Labeling experiment: When bromobenzene labeled with radioactive ^{14}C at the C-1 position is used, the substitution product has the label scrambled between C-1 and C-2. The reaction must therefore proceed through a symmetrical intermediate in which C-1 and C-2 are equivalent- a requirement that only benzyne can meet.



b. When p-chlorotoluene is treated with sodamide in liquid ammonia, the product consists of a mixture of p- and m- toluidines.



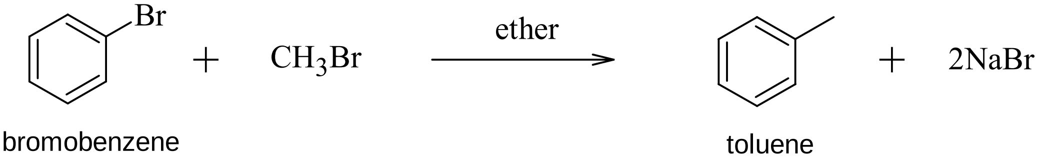
c. When m-bromoanisole and o-bromoanisole are treated with sodamide in liquid ammonia, the same product i.e. m-anisidine is formed.



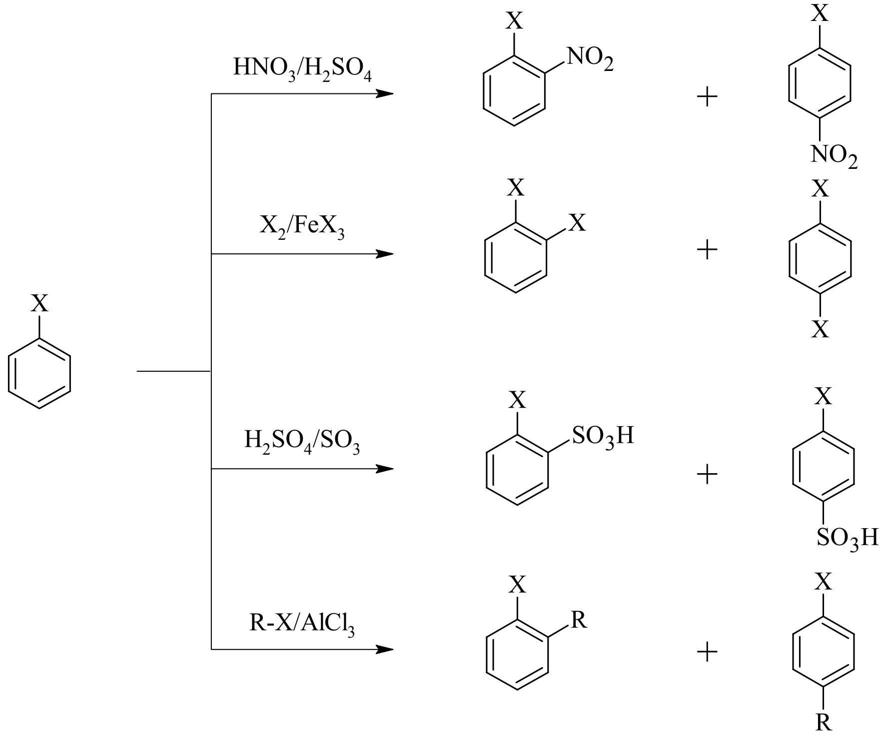
The amino group prefers the m-position to avoid steric hindrance, which it will have to face at o-position.

2. Formationof Grignard reagent: -

3. Wurtz-Fittig reaction: When an ethereal solution of an aryl halide is warmed with an alkyl halide, in the presence of sodamide an alkyl benzene is formed.



4. Electrophilic aromatic substitution reaction: Aryl halide undergo the typical electrophilic aromatic substitution reactions in the ortho and para-position, though less readily than benzene because halogens have a deactivating influence on the aromatic ring.

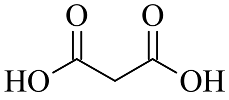


5. Reduction: Aryl halides can be converted into the corresponding hydrocarbons by reduction with nickel aluminium alloy in the presence of alkali.

$$C_6H_5Br + 2H \xrightarrow[NaOH]{Ni/Al} C_6H_6 + HCl$$

Malonic Ester

Malonic esters are the esters of malonic acid (systematic name: propanedioic acid)



malonic acid

The most common example of a malonic ester is diethyl malonate

Preparation: -

1. It is prepared by heating sodium chloroacetate and sodium cyanide. The sodium cyanoacetate thus formed is heated with absolute ethanol and concentrated hydrochloric acid.

$$Cl\text{-}CH_2\text{-}COONa \quad + \quad NaCN \longrightarrow NC\text{-}CH_2\text{-}COONa \quad + \quad NaCl$$

sodiumchloroacetate

$$NC\text{-}CH_2\text{-}COONa \quad + \quad C_2H_5OH \quad + \quad HCl \longrightarrow H_5C_2OOC\text{-}CH_2\text{-}COOC_2H_5 \quad + \quad 2NH_4Cl$$

diethyl malonate

2. Malonic ester may also be prepared by hydrolysis and esterification of methylene cyanide which in turn is prepared from the methylene chloride with sodium cyanide.

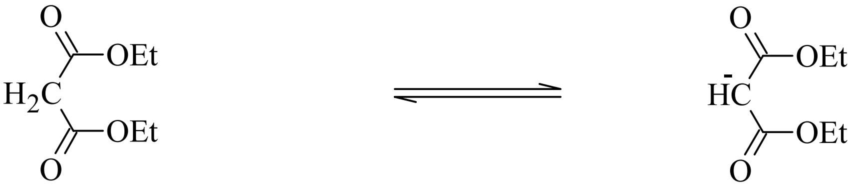
$$Cl\text{–}CH_2\text{-}Cl \quad + \quad NaCN \xrightarrow[\text{-NaCl}]{\Delta} NC\text{-}CH_2\text{-}CN \xrightarrow[C_2H_5OH]{H^+/H_2O} H_5C_2OOC\text{-}CH_2\text{-}COOC_2H_5 \quad + \quad 2NH_4Cl$$

diethyl malonate

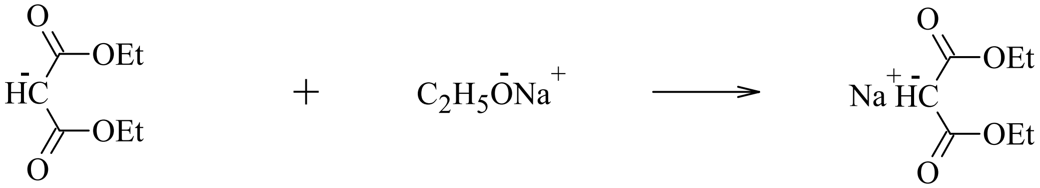
Physical Properties : It is colourless, pleasant smelling liquid (boiling point 198^0c). it is sparingly soluble in water but soluble in ethanol, benzene and chloroform.

Chemical Properties : -

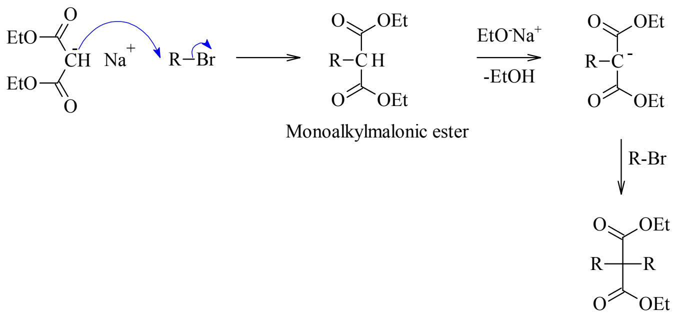
1. Acidic nature: The methylene group of diethyl malonate is flanked between two carbonyl groups. Since the carbonyl group is electron withdrawing, the hydrogen atoms of methylene group become quite acidic and mobile. The resulting carbanion is highly resonance-stabilised and provides the droving force for the dissociation of malonic ester as an acid.



In view of the acidic nature of methylene hydrogens, malonic ester forms the sodium salt of malonic ester when treated with a strong base like sodium ethoxide.



2. Sodium diethyl malonate serve as a strong nucleophile and replaces halogen from alkyl halides forming mono and dialkyl malonic ester.


Monoalkylmalonic ester

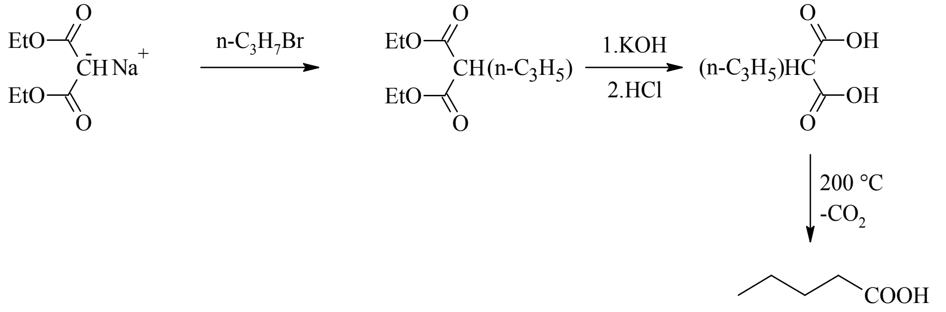
Dialkylmalonic ester

3. Malonic ester on hydrolysis with aqueous potassium hydroxide followed by acidification gives malonic acid which readily decarbosylates when heated to form acetic acid.

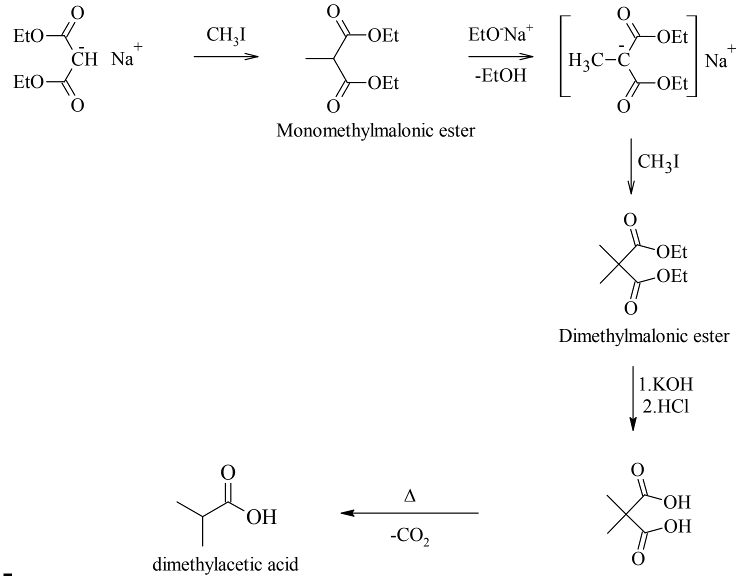
$$H_5C_2OOC\text{-}CH_2\text{-}COOC_2H_5 \xrightarrow[2.H_3O^+]{1.OH^-} HOOC\text{-}CH_2\text{-}COOH \xrightarrow[-CO_2]{\Delta} H_3C\,COOH + CO_2$$

Diethyl Malonate in Organic Synthesis

1. Synthesis of Carboxylic acid: The following examples show how malonic ester synthesis can enable us to prepare alkyl acetic acids.
   (a) n-Valeric acid (n-propyl acetic acids) : -


n-Valeric acid(pentanoic acid)

(b) Dimethyl acetic acid :


Monomethylmalonic ester

Dimethylmalonic ester

dimethylacetic acid

(c) Fatty acids: -

$$H_2C(COOEt)_2 \overset{EtONa}{\rightleftharpoons} H\overset{-}{C}(COOEt)_2 \xrightarrow{n\text{-}C_4H_9Br} n\text{-}C_4H_9CH(COOEt)_2$$

$$\Big\downarrow \begin{array}{l} KOH \\ H_2O \end{array}$$

$$n\text{-}C_4H_9CH(COOH)_2$$

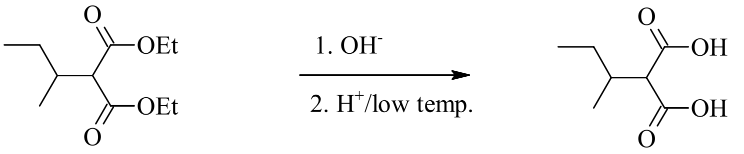
$$\Big\downarrow \begin{array}{l} \Delta \\ -CO_2 \end{array}$$

$$n\text{-}C_4H_9CH_2COOH$$

Caproic acid

2. Synthesis of Dicarboxylic acid

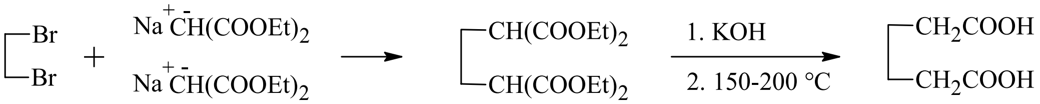
(a) Substituted malonic acids: Substituted malonic acids are thermally unstable and readily lose CO_2 on heating. However, if the substituted malonic esters are carefully hydroxysed in alkali, followed by acidification at low temperatures, substituted malonic acids can obtained.



Ethylmethyl malonic ester

1,3-dicarboxylic acid

(b) Adipic acid: -



adipic acid

Similarly, other higher dicarboxylic acids can be prepared using dihalides.

$$2\,Na^{+}\overset{-}{C}H(COOEt)_2 + Br\text{-}(CH_2)_n\text{-}Br \longrightarrow (H_5C_2OOC)_2CH(CH_2)_nCH(COOC_2H_5)$$

$$\Big\downarrow \begin{array}{l} \text{1. Hydrolysis} \\ \text{2. } \Delta, -CO_2 \end{array}$$

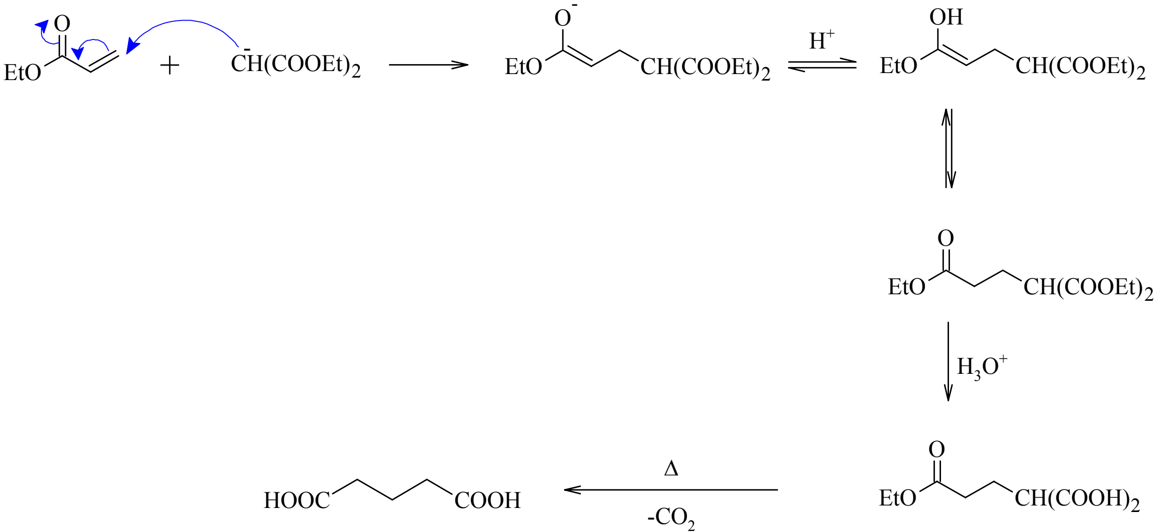
$$HOOCCH_2(CH_2)_nCH_2COOH$$

Dicarboxylic acid

These dicarboxylic acids may also be prepared by the treatment of malonic ester with appropriate chloro ester.

$$Na^{+}\overset{-}{C}H(COOEt)_2 + Cl{-}CH_2COOC_2H_5 \longrightarrow H_5C_2OOCCH_2CH(COOEt)_2 \xrightarrow[2.\ \Delta,\ -CO_2]{1.\ Hydrolysis} \underset{\text{Succinic acid}}{HOOCCH_2CH_2COOH}$$

(c) Synthesis of Glutaric acid : It can be obtained by the Michael addition of acrylic ester to malonic ester, followed by alkaline hydrolysis and subsequent decarboxylation as shown below.



Pentane-1,5-dioic acid
(glutaric acid)

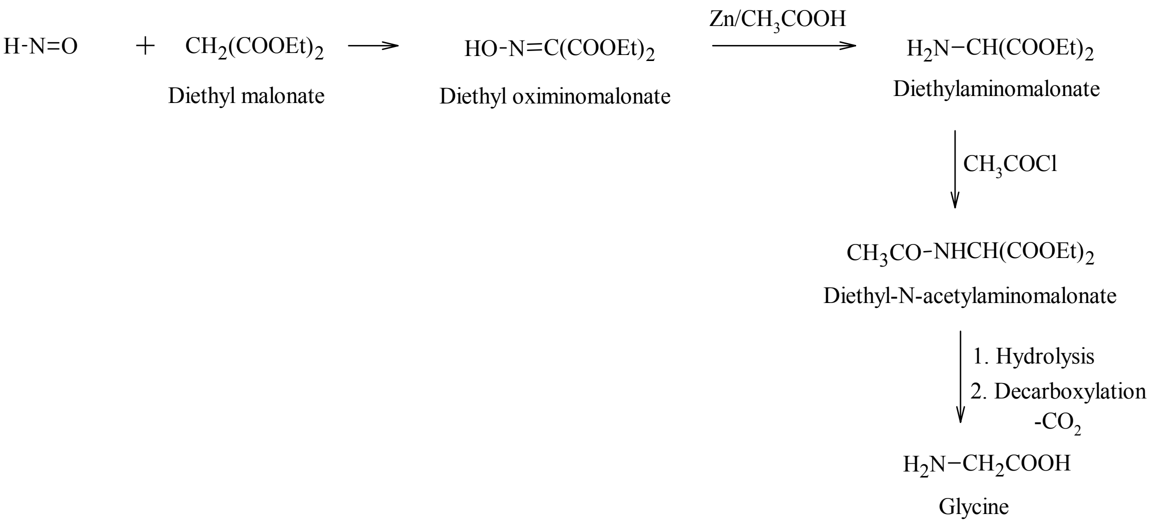
3. Synthesis of α,β-unsaturated acid: -When malonic ester is treated with aldehyde or ketone in presence of base such as pyridine or diethylamine, α,β-unsaturated esters are formed. These esters on hydrolysis and decarboxylation, yields α,β-unsaturated acids.

$$CH_3CHO + CH_2(COOEt)_2 \xrightarrow{\text{Pyridine}} H_3CCH{=}C(COOEt)_2 \xrightarrow[\text{2. Decarboxylation}\ -CO_2]{\text{1. Hydrolysis}} \underset{\text{Crotonic acid}}{CH_3CH{=}CHCOOH}$$

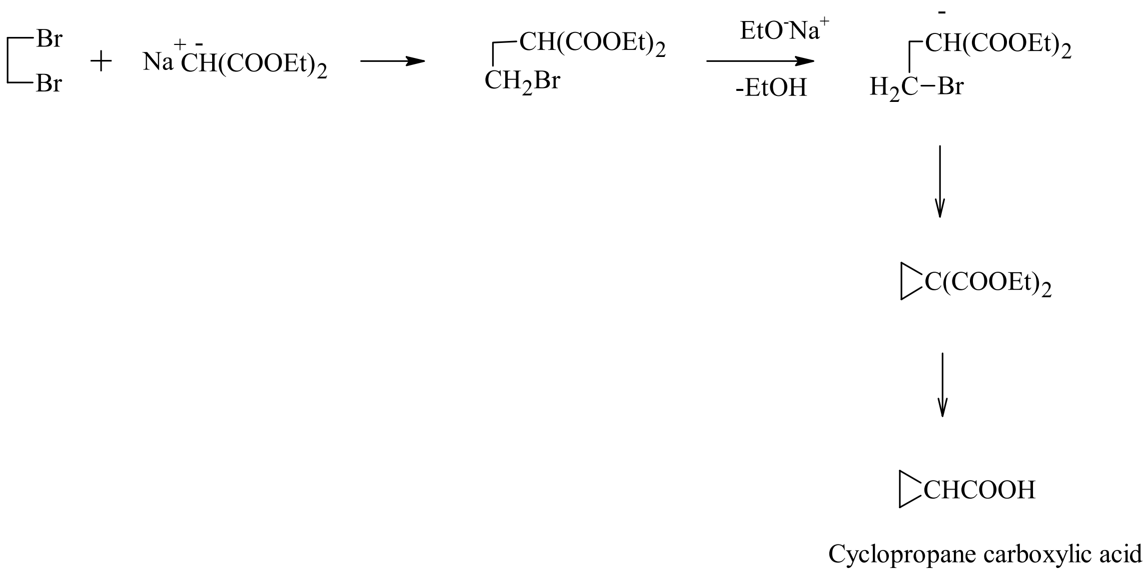
4. Synthesis of keto acid: Malonic ester on treatment with acid chloride followed hydrolysis and decarboxylation produces β-keto acids.

$$CH_3COCl + Na^{+}\overset{-}{C}H(COOEt)_2 \longrightarrow CH_3CO{-}CH(COOEt)_2 \xrightarrow[\text{2. Decarboxylation}\ -CO_2]{\text{1. Hydrolysis}} \underset{\text{-Acetoacetic acid}}{CH_3CO{-}CH_2COOH}$$

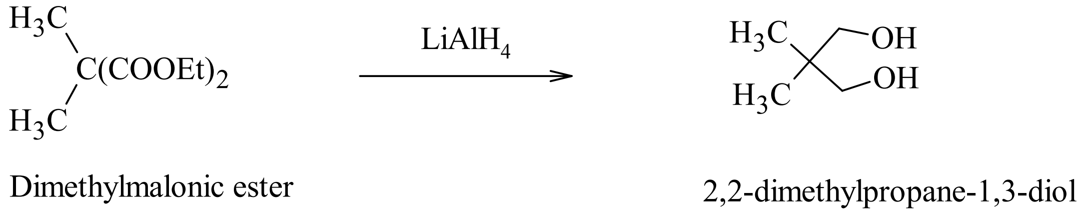
5. Synthesis of amino acids: When malonic ester is treated with nitrous acid followed by reduction amino malonic ester is obtained, which on usual hydrolysis and decarboxylation gives amino acids.



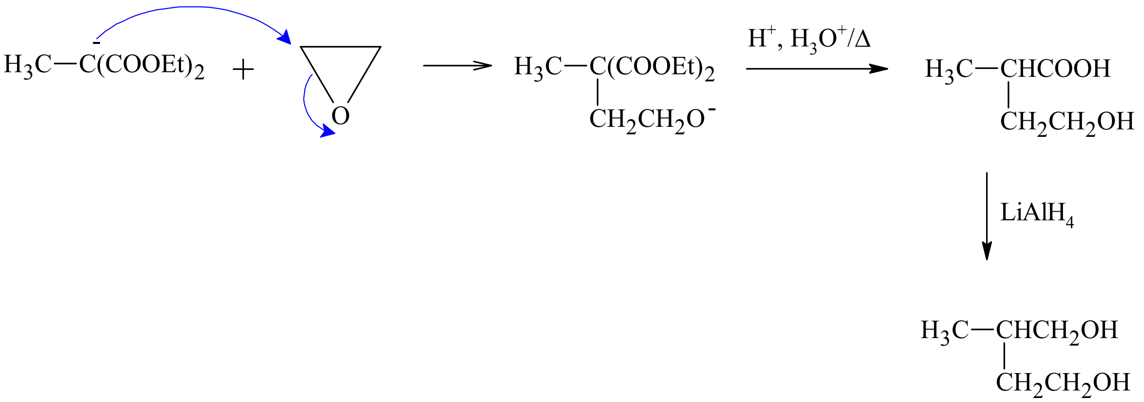
6. Synthesis of alicyclic compounds: Treatment of one mole of diethyl malonate with dihalides gives alicyclic compounds.



7. Synthesis of diols: Substituted malonic esters on reduction with lithium aluminium hydride yield 1,3-diols.

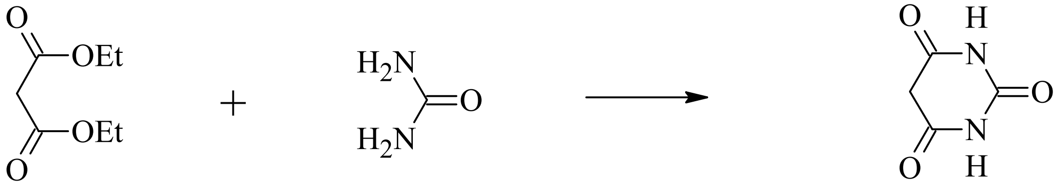


Reaction of sodiomalonic ester with ethylene oxide or substituted ethylene oxides (epoxide) gives 1,4-diols.



2-Methylbutane1,4-diol

8. Synthesis of barbiturates: Malonic ester condenses with urea to give barbiturates which have medicinal use as hypnotics (sleep inducers).

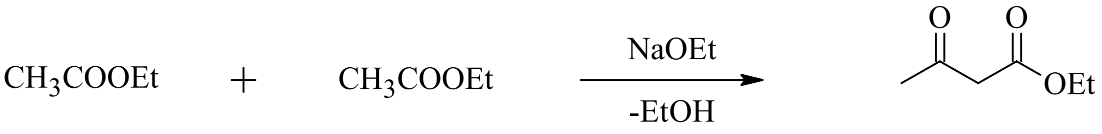


Barbituric acid

Ethyl Acetoacetate

Preparation: -

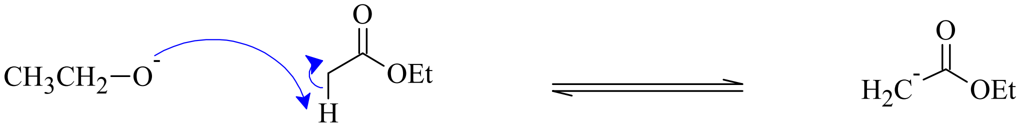
1. It is prepared by the condensation of two molecules of ethyl acetate in the presence of sodium ethoxide.

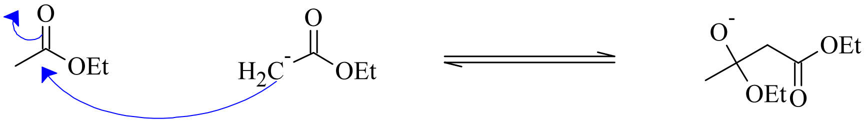


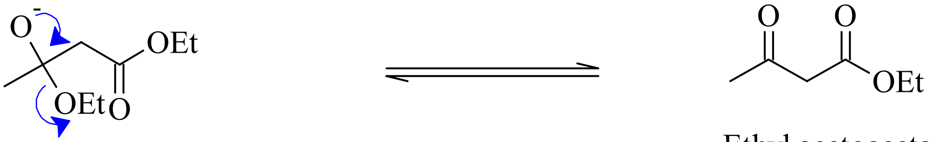
Ethyl acetoaetate

This is an example of Claisen condensation in which keto group is formed by reaction of two molecules of ester having α-hydrogen atoms.

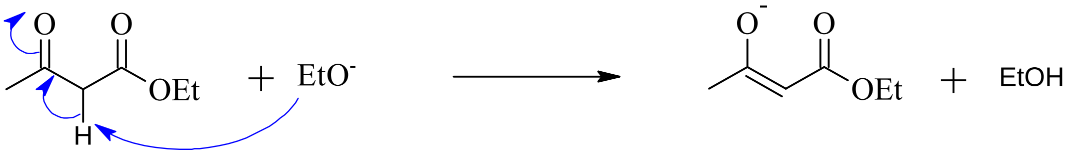
Mechanism: - The most widely accepted mechanism for Claisen condensation involves the formation of carbanion, which attacks the electropositive carbonyl carbon to give ethyl acetoacetate.

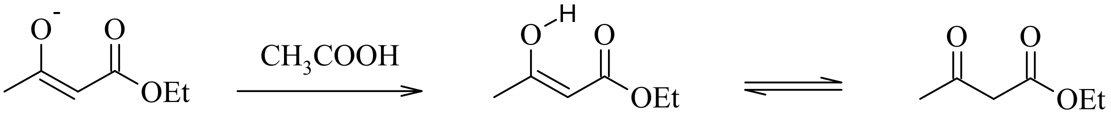






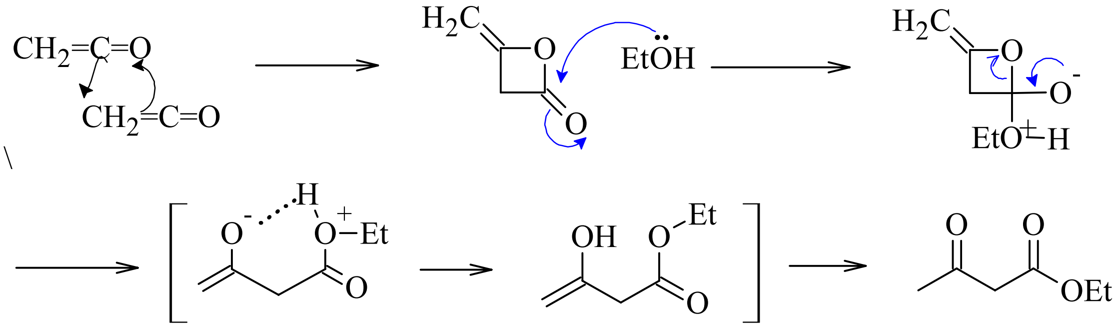
Ethyl acetoacetate



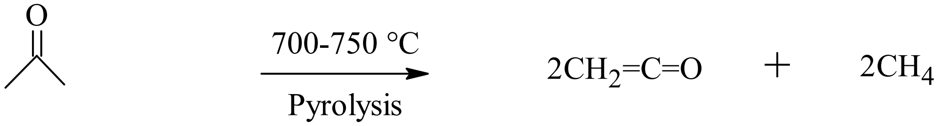


Ethyl acetoacetate

2. Industrial Preparation: - Acetoacetic ester is produced on endustrial scale by dimerisation of ketene in cold acetone. The diketene thus formed reacts with ethanol to form the ester.



The diketene is formed by the pyrolysis of acetone.



Keto-Enol Tautomerisim in Ethyl Acetoacetate: A carbonyl compound with hydrogen atom on its α-carbon rapidly equilibrates with its corresponding enol *(ene + ol)*. This rapid interconversion between two substances is a special kind of isomerism known as tautomerism; the individual isomers are called tautomers.

Keto tautomer

Enol tautomer

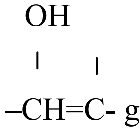
Keto-enol tautomerism in carbonyl compounds is catalysed by both acids and bases. In ethyl acetoacetate enol form is more volatile and change from enol to keto form is extremely sensitive to catalyst. The keto form was suggested by Franland and Duppa in 1863 whereas the enol form was independently proposed by Geuther in 1865, both the structure were srpported by various evidences.

Evidence In Favour Of Keto Form

1. It formcyanohydrin with hydrogencyanide.
2. It reacts with hydroxyl amine and phenylhydrazine to form oxime and phenylhydrazone respectively.
3. It forms a bisulphate compound with sodium hydrogen sulphite.
4. When reduced with amalgam, it yields a secondary alcohol.

Evidence In Favour Of Enol Form

1. The presence of hydroxyl group is indicated by the reaction of ester with sodium to give its sodium salt and hydrogen gas.
2. It gives the reddish-violet colour with ferric chloride indicating the presence of



$-\overset{\overset{OH}{|}}{C}H=\overset{|}{C}-$ group.

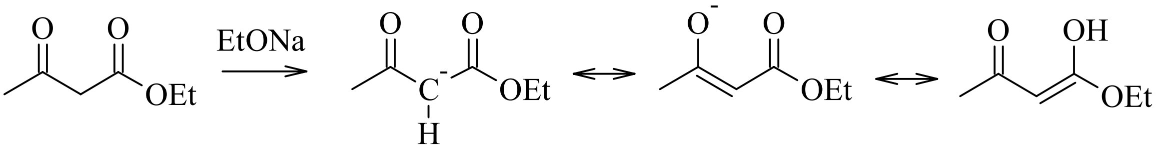
3. When it is treated with ethanolic solution of bromine, the colour of bromine immediately discharged showing the poresence of double bound or unsturation.
4. When treated with phosphorous pentachloride it gives a chloro derivative indicating presence of hydroxyl group.

Physical Properties:

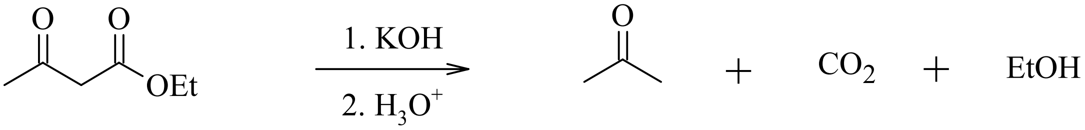
It is colourless, pleasant smelling liquid, sparingly soluble in water but freely soluble in organic solvents. It boils at 181^0c with tendency to decompose under ordinary atmospheric conditions.

Chemical Properties:

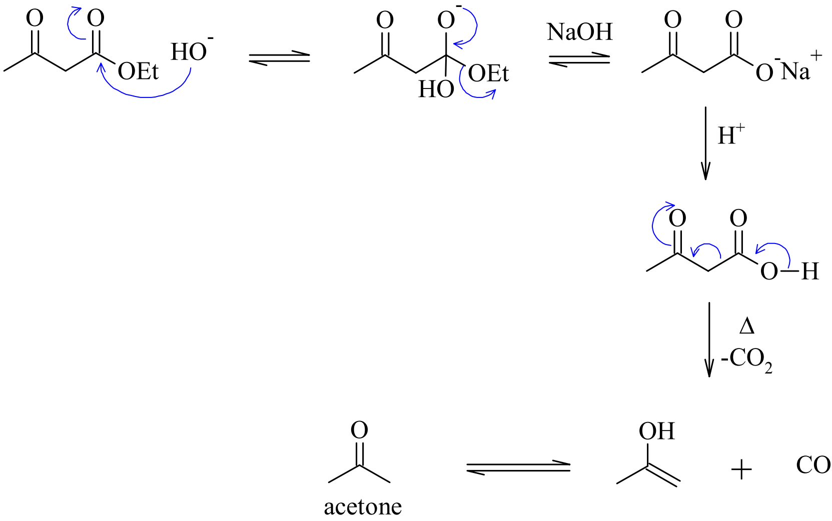
1. Acidic nature:The methylene group of ethyl acetoacetate is flanked on either side by electron withdrawing carbonyl groups. It can, therefore, behave as an acid and form salts when treated with bases like sodium ethoxide. The carbanion so formed is resonance stablised and provides the droving force for acidic nature.



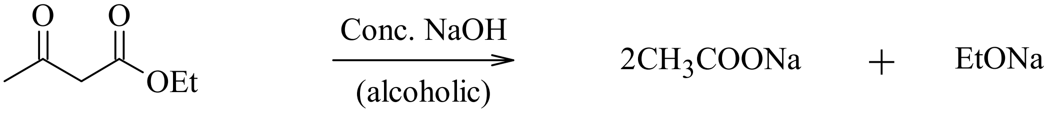
2. Ketonic hydrolysis:When ethyl acetoacetate is treated with dilute aqueous alkali followed by acidification it cleaves into acetone, and the reaction is known as ketonic hydrolysis.



Mechanism: -The first step is the nucleophilic attack at electron deficient carboxyl carbon followed by decarboxylation.



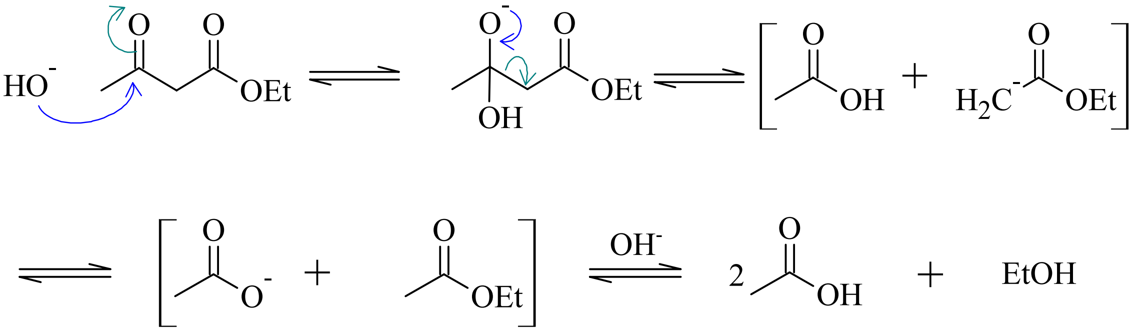
3. Acidic hydrolysis: When ethyl acetoacetate is heated with concentrated alcoholic alkali solution, it yields two molecule of acetic acid.



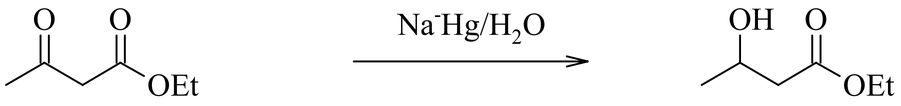
Ethyl acetoacetate

As the ultimate product of this reaction are acids, the reaction sequence is called acidic hydrolysis.

Mechanism: The key step is the reversal of Claisen condensation.

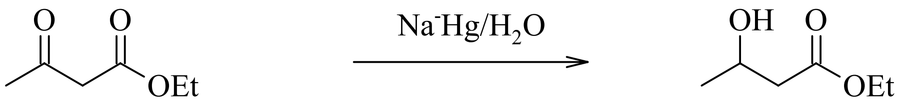


4. Reduction: Keto form of ethyl acetoacetate undergo reduction with sodium amalgam to form β-hydroxy compounds.



Ethyl acetoacetate Ethyl-β–hydroxybutyrate

5. Cyanohydrin formation: It reacts with hydrogen cyanide to give cyanohydrins.



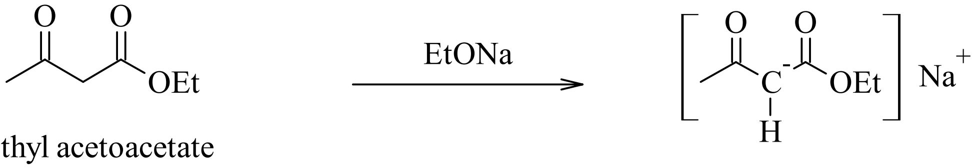
Ethyl acetoacetate Ethyl-β–hydroxybutyrate

Similarly it reacts with sodium hydrogen sulphate to give bisulphate compounds.

Ethyl acetoacetate Bisulphite compound

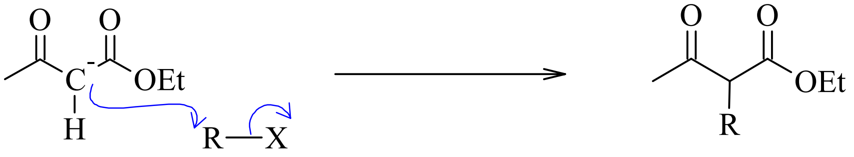
Synthetic Importance

1. Synthesis of alkyl substituted acetone/acetic acid: Due to acidic nature of methylene hydrogens in ethyl acetoacetate, it forms sodium salt with base.



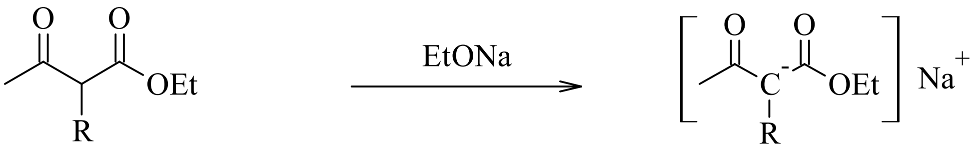
Ethyl acetoacetate

The sodium salt so formed is a typical nucleophile which can take part in the nucleophilic substitution reaction. For example

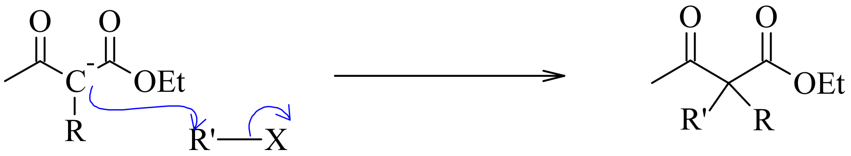


Monoalkylethyl acetoacetate

Monoalkyl ethyl acetoacetate still contains an acidic hydrogen and can, therefore form the sodium salt again when treated with base.

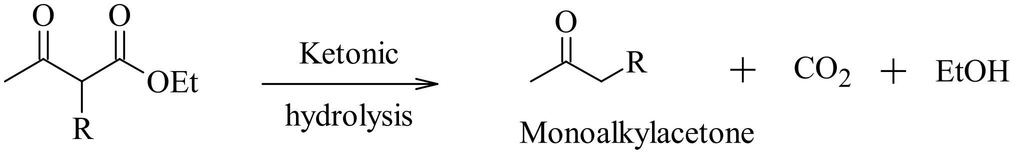


This carbanion can participate in yet another nucleophilic substitution reaction.

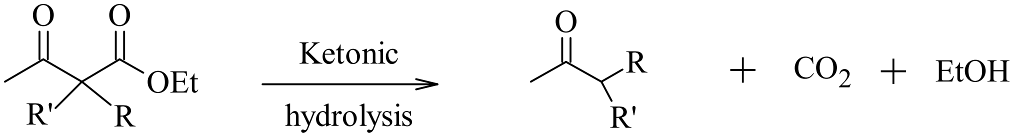


Dialkylethyl acetoacetate

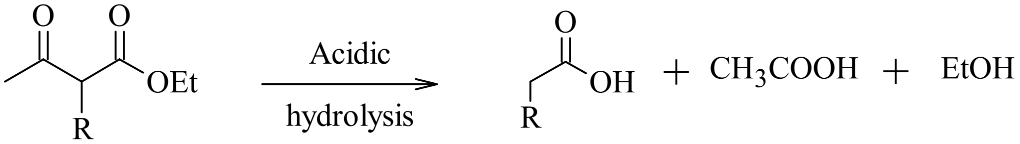
Then alkyl derivatives of ethyl acetoacetate can undergo ketonic and acidic hydrolysis to give alkyl substituted ketones and alkyl substituted acids.



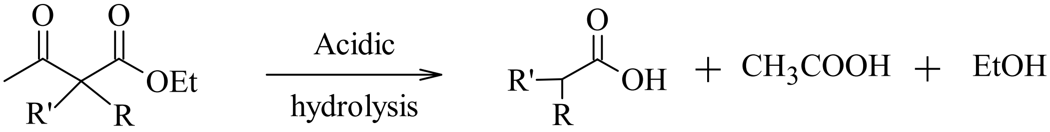
Monoalkylacetone



Dialkylacetone

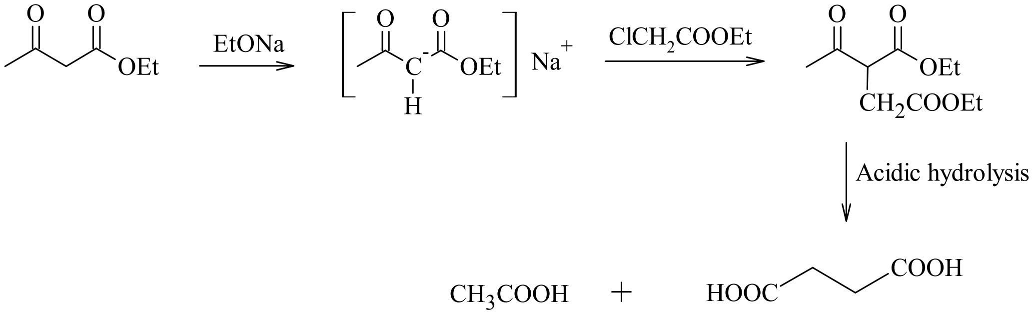


Monoalkylacetic acid



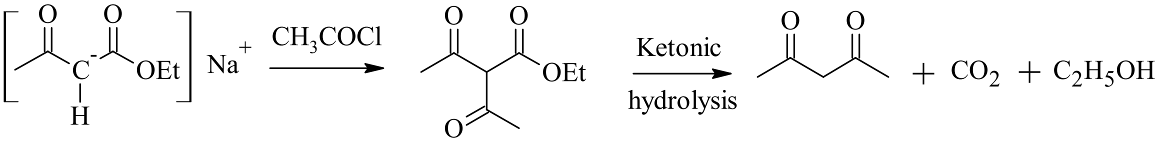
Dialkylacetic acid

2. Synthesis of Dicarboxylic acids: Sodium salt of ethyl acetoacetate is treated with appropriate halo ester followed by acid hydrolysis.



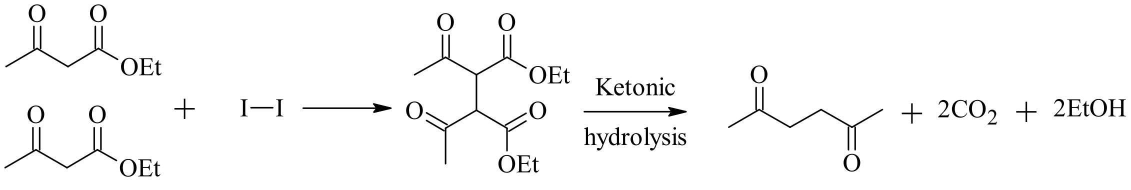
succinic acid

3. Synthesis of 1,3-dicarboxylic acid: Sodium salt of ethyl acetoacetate reacts with acetyl chloride followed by ketonic hydrolysis to give 1,3-diketone.



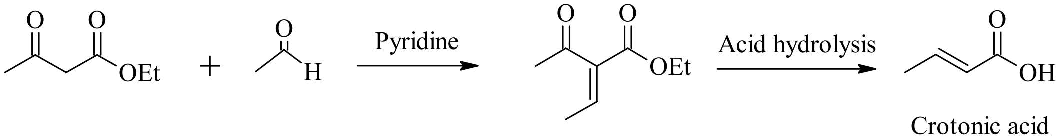
Acetyl acetoacetic ester Acetylacetone

Synthesis of 1,4-diketone: When sodium salt of ethyl acetoacetate is treated with iodine followed by ketonic hydrolysis, 1,4-diketones are formed.



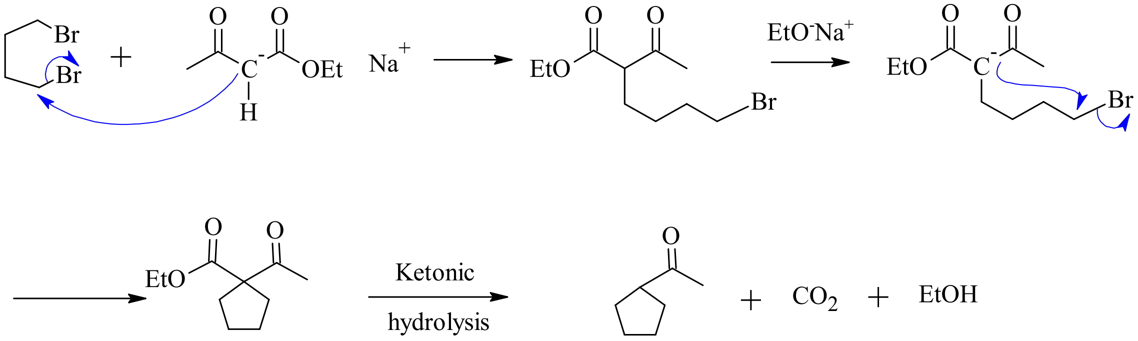
Acetonylacetone

4. Synthesis of α,β-unsaturated acid: Ethyl acetoacetate condense with aldehyde or ketone in the presence of a base like pyridineto form a product which on acid hydrolysis gives α,β-unsaturated acids.



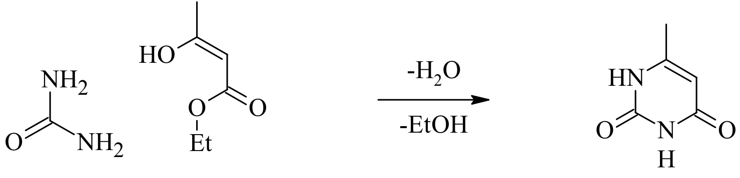
Crotonic acid

5. Synthesis of alicyclic compounds: Sodium salts of ethyl acetoacetate react with dihalogen compounds to form alicyclic compounds.

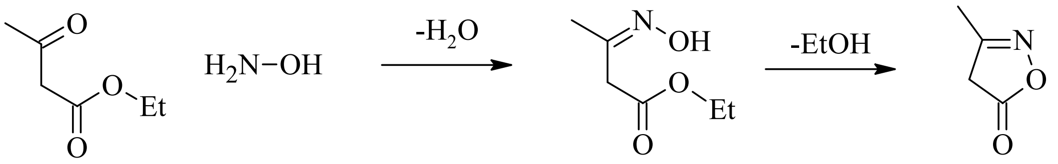


Acetylcyclopentane

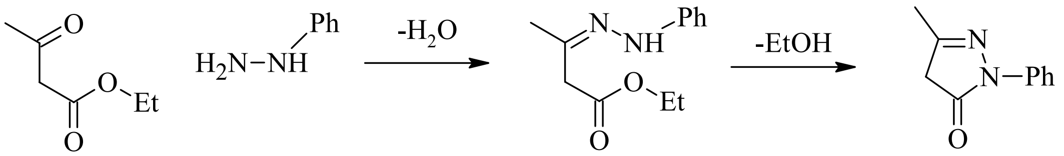
Synthesis of heterocyclic compounds: Ethyl acetoacetate condenses with compound such as urea, hydroxyl amine, hydrazine, phenyl hydrazine etc forming heterocyclic compounds.



4-Methyl uracil



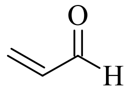
Methyl-isoxazolone



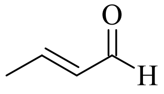
3-Methyl-1-phenylpyrazolone

α,β-Unsaturated Carbonyl Compound

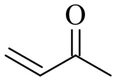
When carbonyl group and carbon-carbon double bond are separated by just one carbon-carbon single bond, the resulting carbonyl compound is referred to as α,β-unsaturated carbonyl compounds.



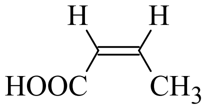
Acrolein
(Propenol)



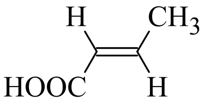
Crotonaldehyde
(2-Butenal)



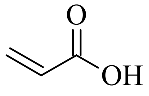
Methyl vinyl ketone



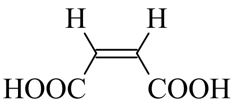
Isocrotonic acid
(Cis-but-2-enoic acid)



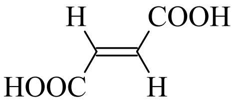
Crotonic acid
(Trans-but-2-enoic acid)



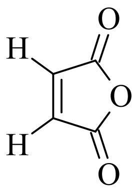
Acrylic acid



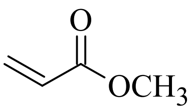
Maleic acid



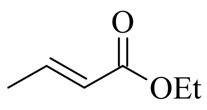
Fumeric acid



Maleic anhydride



Methyl acrylate

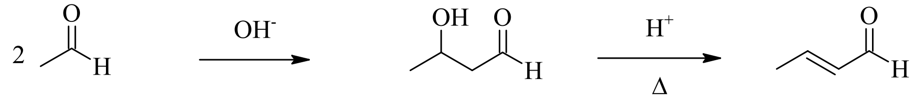


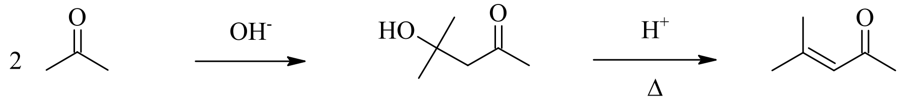
Ethyl crotonate

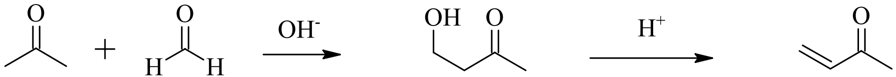
Preparation:

6. Aldol Condensation: Two molecules of an aldehyde or a ketone having α-hydrogen condense together in the presence of base or dilute acid to form β-hydroxy aldehyde or β-hydroxy ketone and the reaction is referred as Aldol condensation.

This β-hydroxy compound on heating loses a molecule of water to form an α,β-unsaturated carbonyl compound.


Crotonaldehyde

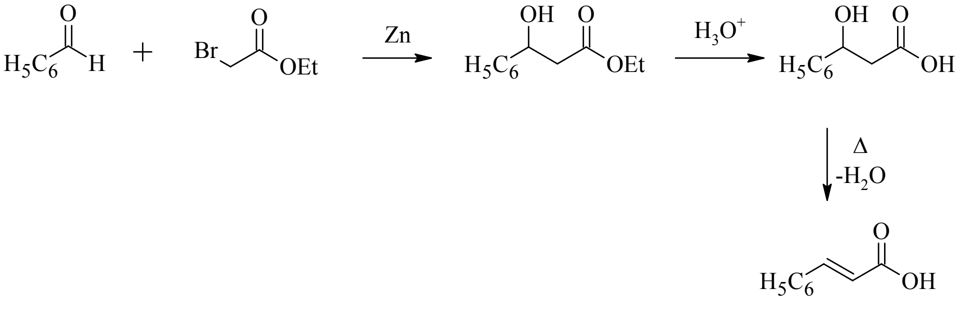

Mesityl oxide


Methyl vinyl ketone

α,β-unsaturated aldehydes can then be oxidized by Tollen's reagent to α,β-unsaturated carboxylic acids.

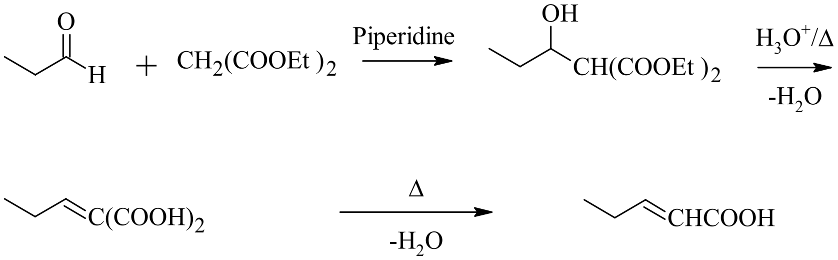
7. Reformatsky Reaction: Aldehydes or ketones react with α-halo ester in presence of zinc to form a product which on hydrolysis gives β-hydroxy compound

This β-hydroxy compound on heating eliminates a molecule of water to give α,β-unsaturated carbonyl compound.

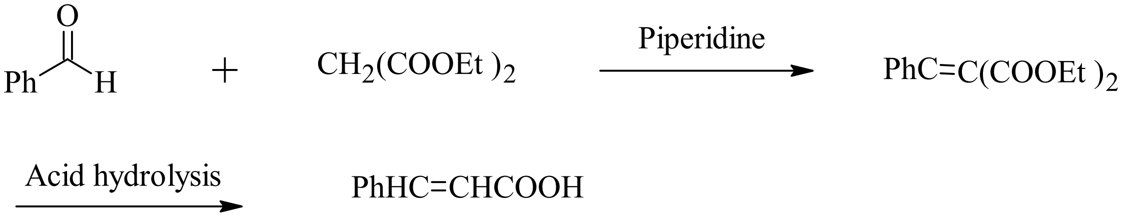

Cinnamic acid

8. Knoevengel Reaction: It involves condensation of a carbonyl compound with an active methylene compounds in the presence of base such as piperidine. For example,

(i)

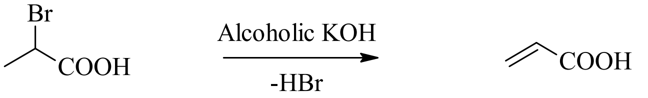

2-Pentenoic acid

(ii)



Cinnamic acid

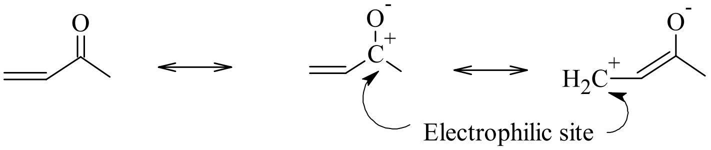
9. Dehydrohalogenation of α-halo acid: α-Halo acid when treated with alcoholic KOH, a mlecule of water is removed as a result α,β-unsaturated compound is formed



Acrylilc acid

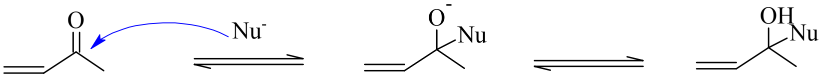
Conjugate Addition

α,β-unsaturated carbonyl compounds have unusually reactive double bonds. The β-carbon is electrophilic because it shares the partial positive charge of the carbonyl carbon through resonance.

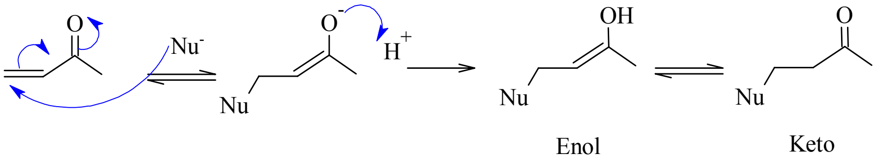


A nucleophile can attack an α,β-unsaturated carbonyl compound either at the carbonyl group itself or at the β-position. When attack occurs at the carbonyl group, protonation of oxygen leads to a **1,2 addition product** in which the nucleophile and the proton have added to adjacent atoms. When attack occurs at the β-position, the oxygen atom is the forth atom counting from the nucleophile and the addition is called **1,4-addition**. The net result of 1,4-addition is addition of the nucleophile and a hydrogen atom across the double bond that was conjugated with a carbonyl group. For this reason, 1,4-addition is often called conjugate addition

1,2-Addition

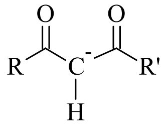
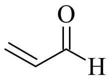
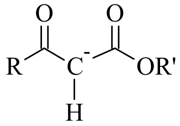
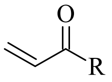
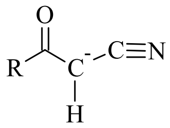
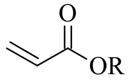
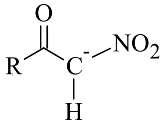
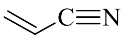


1,4-Addition

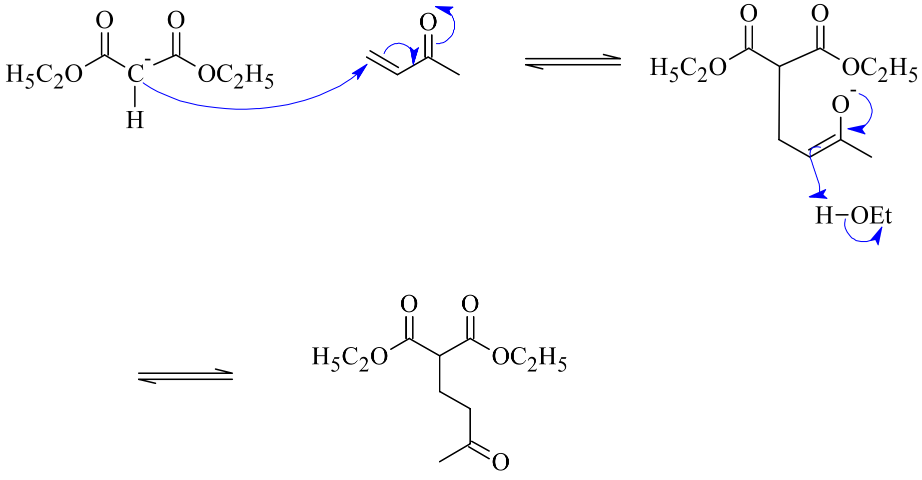


Addition of a stabilised enolate ion to the double bond of an α,β-unsaturated carbonyl compound is called Michael addition. The electrophile (the α,β-unsaturated carbonyl compound) accepts a pair of electrons; it is called the **Michael acceptor.** The attacking nucleophile donates a pair of electrons; it is called the **Michael donar**. Common donors are enolate ions that are stabilized by two strong electron-withdrawing groups such as carbonyl groups, cyano groups or nitro groups. Common acceptors contain a double bond conjugated with a carbonyl group, a cyano group, or a nitro group.

Example of Michael donar and Michael acceptor

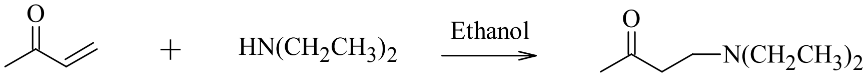
Michael donars		Michael acceptors	
	β–diketone		conjugated aldehyde
	β–ketoester		conjugated ketone
	β–keto nitrile		conjugated ester
	α-nitro ketone		conjugated nitrile

A typical Michael Addition

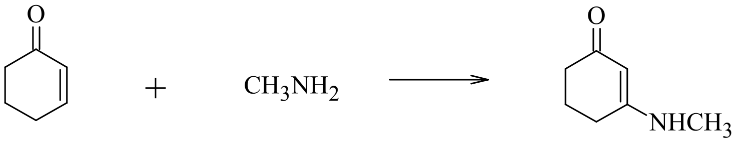


1,4-Addition product

Conjugate Addition of Amines: Primary and secondary amines add to α,β-unsaturated aldehydes and ketones to yield β-amino aldehydes and ketones. Reaction occurs rapidly under mild conditions with good yields.



4-N,N-Dimethyl amino-2-butanone

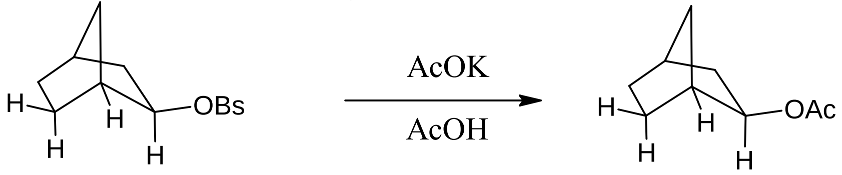


3-(N-Methylamino)cyclohexanone

Non-Classical Ion

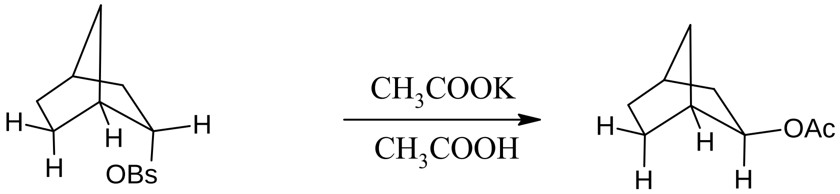
Non-classical ions in organic chemistry are a special type of carbonium ions displaying delocalization of sigma bonds in 3-center-2-electron bonds of bridged systems. The term *non-classical ion* was first used by J.D. Roberts in 1951 in relation to the properties of cyclobutyl cations but the actual ions were first described by S. Winstein in 1949 in order to explain the reactivity of certain norbornyl compounds.

The compounds exo-norbornyl brosylate and its endo isomer undergo solvolysis or acylation with the potassium salt of acetic acid in acetic acid. A key observation is that in this nucleophilic displacement both isomers give the same reaction product an exo-acetate.



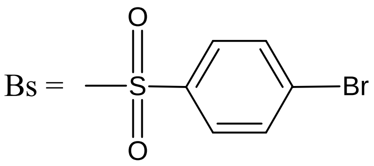
exo-norbornyl brosylate

exo-norbornyl acetate



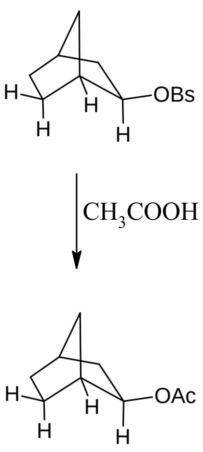
endo-norbornyl brosylate

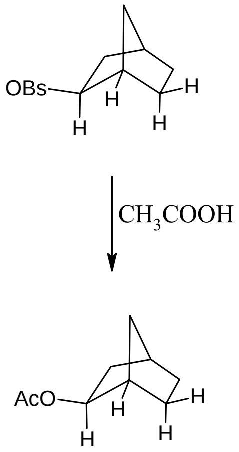
exo-norbornyl acetate



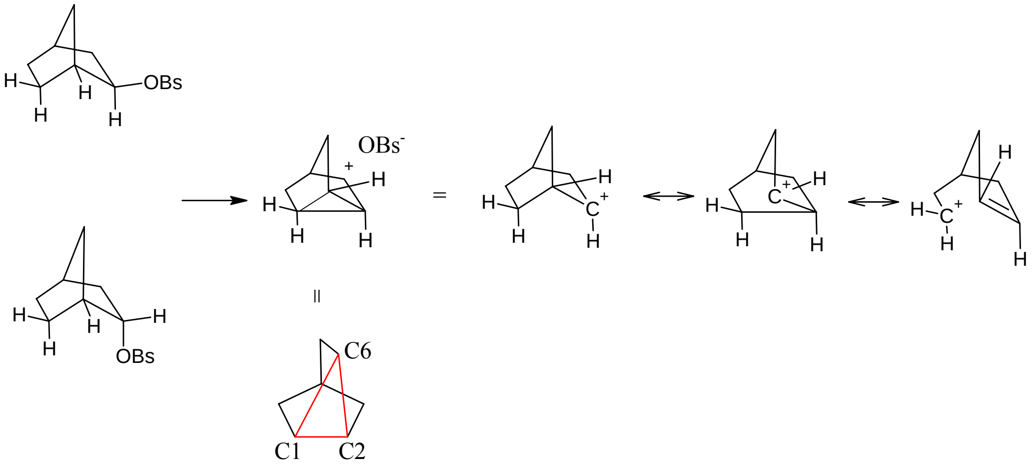
Also the reaction rate for the exo-reaction is 350 times the reaction rate for the endo reaction or a cyclohexyl control reaction

In a related experiment both enantiomers of the exo-brosylate on solvolysis give the same racemic reaction product. The optical activity of the reaction disappears at the same reaction rate as that of the solvolysis.





These observations are explained by invoking a non-classical ion as an reactive intermediate as the initial reaction product of both endo and exo isomer. This ion is formed when sigma electrons in the C1-C6 bond assist by neighbouring group participation with the expulsion of the leaving group and now the positive charge residing on C1 is delocalized on C2 as well. The formation of the carbocation is the slow rate determining step. In this reaction step the exo leaving group is better positioned in relation to C1 than the endo leaving group and this explains the markedly difference in reactivity. The C2 carbon atom in the intermediate is pentavalent and therefore a carbonium ion. The ion is also symmetrical which is more obvious in the equivalent structure.



This symmetry explains the observed racemization. In classical resonance treatment the carbocation can be regarded as a hybrid of resonance structures with a full positive charge on C2, C6 and C7.

Suggested Readings:

- Organic Chemistry by Clayden, Greeves, Wavren and Wothers, Oxford University Press, 2001.
- Organic Chemistry Structure and Reactivity by Seyhan Ege, 5th edition. 2004
- Organic Chemistry by I. L. Finar, vol. 1, 6thedition
- Organic Chemistry by Paula Yurkanis Bruice, 3rd edition.
- Organic Chemistry by Robert T. Morrison and Robert Neilson Boyd, 6th edition.
- Organic Chemistry by K. Peter C. Vollhardt and Neil E. Schore, 4th editeion.