UNIT – 1
STEREO ISOMERISM

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STEREOISOMERISM

INTRODUCTION

Many organic compounds have same molecular formula but are different in their physical and chemical properties. These compounds are known as isomers and this property is known as isomerism.

STRUCTURAL ISOMERISM

Structural isomers are compounds that have same molecular formula but different structural formulas.

- Types of Structural isomers: (i) Chain isomerism (ii) Position isomerism (iii) Functional isomerism (iv) Metamerism (v) Tautomerism

STEREOISOMERISM:

The isomers have the same structural formula but differ in relative arrangement of atoms or groups in space within the molecule are known as stereoisomers and the phenomenon as stereoisomerism. It can be further classified into three types: - 1. Geometrical isomerism 2. Optical isomerism 3. Conformational isomerism

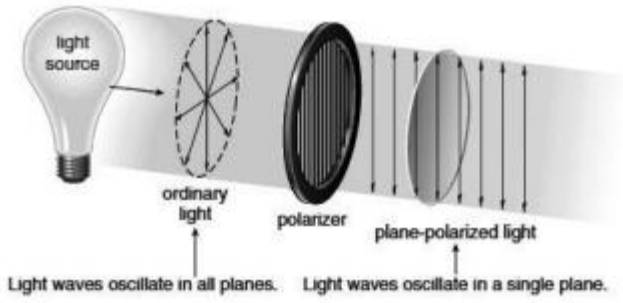
2. OPTICAL ISOMERISM:

Any substance that rotates the plane polarized light is optically active and the phenomenon related to it is called optical isomerism.

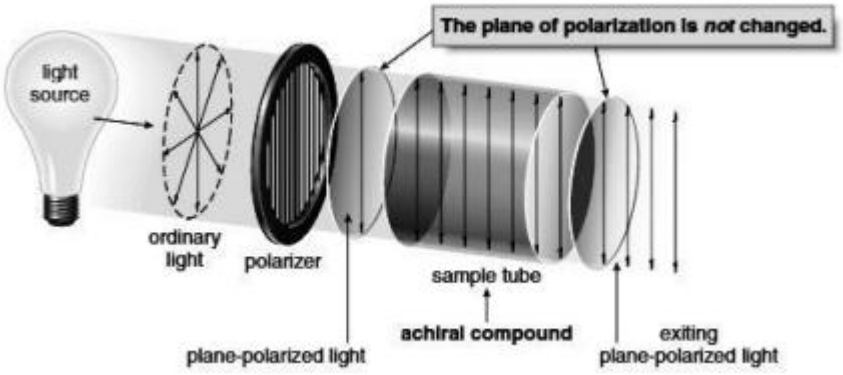
- the out standing feature of optical isomers is that they have the ability to rotate plane polarized lite.
- most compounds do not rotate the plane of polarized light.
- When a beam of polarized light passes through an individual molecule, in nearly every instance its plane is rotated a tiny amount by interaction with the charged particles of the molecule; the direction and extent of rotation varies with the orientation of the particular molecule in the beam.
- Optical activity in a compound is detected and measured by means of a polarimeter.
- When a solution of a known concentration of an optically active material is placed in the polarimeter, the beam of polarized light is rotated through a certain number of degrees, either to the right (clockwise) or to the left (anti-clockwise).
- The compound which rotates the plane of polarized light to the right (clockwise) is said to be dextrorotatory. It is indicated by the sign (+).
- The compound which rotates the plane of polarized light to the left (anticlockwise) is said to levorotatory. It is indicated by the sign (-).

Plane polarized light:

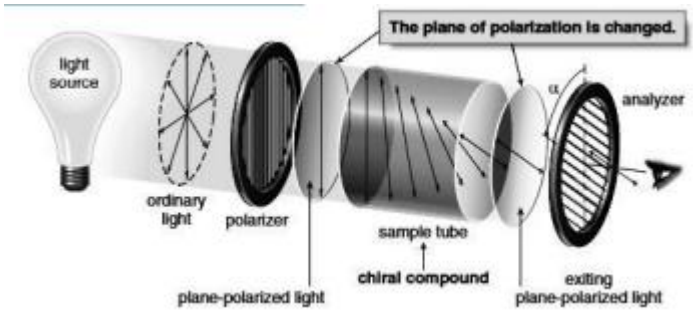
Ordinary light consists of electromagnetic waves that oscillate in all planes perpendicular to the direction in which the light travels. Passing light through a polarizer allows light in only one plane to come through. This is plane-polarized light (or simply polarized light), and it has an electric vector that oscillates in a single plane.



A polarimeter is an instrument that allows plane-polarized light to travel through a sample tube containing an organic compound. After the light exits the sample tube, an analyzer slit is rotated to determine the direction of the plane of the polarized light exiting the sample tube. There are two possible results. With achiral compounds, the light exits the sample tube unchanged, and the plane of the polarized light is in the same position it was before entering the sample tube. A compound that does not change the plane of polarized light is said to be optically inactive.



With chiral compounds, the plane of the polarized light is rotated through an angle α. The angle α, measured in degrees (°), is called the observed rotation. A compound that rotates the plane of polarized light is said to be optically active.



The rotation of polarized light can be in the clockwise or counter clockwise direction.

- if the rotation is clockwise the compound is called dextrorotatary. the rotation is labelled d or (+).

- if the rotation is counter clockwise, the compound is called levorotatary. The rotation is labelled as l or (-)

OPTICAL ACTIVITY:

Substances which can rotate the plane polarised light through a certain angle are called optically active substances and this property of a substance by virtue of which the organic substances rotate the plane polarised light is called as optical activity. If the plane polarised light shows no change in angle it means that the substance is optically inactive.

ANGLE OF ROTATION:

The angle through which the plane polarized light is rotated by an optically active substance is called as angle of rotation. It is denoted by α

SPECIFIC ROTATION:

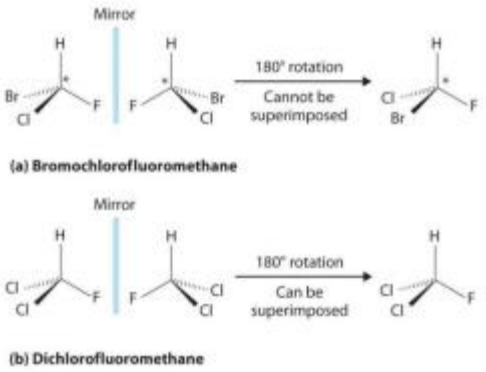
The observed rotation depends on the number of chiral molecules that interact with polarized light. This in turn depends on the concentration of the sample and the length of the sample tube. To standardize optical rotation data, the quantity specific rotation (*α+) is defined using a specific sample tube length (usually 1 dm), concentration, temperature (25 °C), and wavelength (589 nm, the D line emitted by a sodium lamp). - Specific rotations are physical constants just like melting points or boiling points, and are reported in chemical reference books for a wide variety of compounds.

$$c = \alpha \cdot \frac{1}{[\alpha]_{\lambda}^{T}} \cdot \frac{100}{l}$$

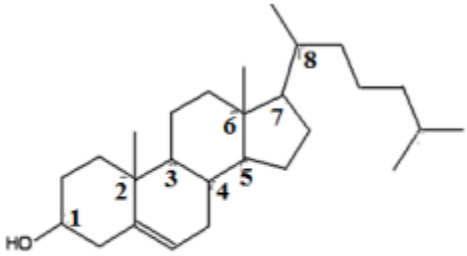
desired quantity — measured value — input values

chiral and achiral molecule:

- A molecule is said to be chiral or dis-symmentric, if it is not superimposable on its mirror image and the property of non-superimposability is called chirality.
- on the other hand, a molecule which is superimposable on its mirror image is called achiral.
- chiral carbon atom, carbon atom bounded to 4 different atoms or groups is called an asymmentric carbon atom or a chiral atom. A chiral atom is indicated by an asterisk(*)



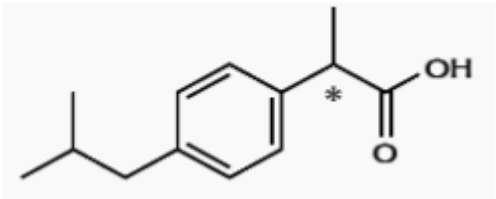
- If a molecule contains only one chiral Centre/atom, then the molecule has to be optically active (i.e. non superimposable on its mirror image) as it will not contain any element of symmetry. Molecules containing two or more chiral centers may or may not be chiral (optically active).
- it is necessary to distinguish chiral and chiral Centre. the word chiral is used for molecule as a whole which is optically active, where as chiral Centre is for an atom which is attached to form different atoms/groups.



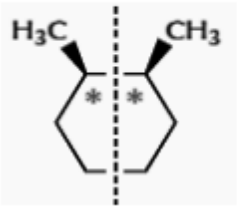
Cholesterol has eight chiral centres

- Relationships between Chiral Centers and Chiral Molecules
- The term chiral center refers to an atom in the molecular structure. The term chiral molecule refers to the entire molecule.
- The presence of one chiral center renders the entire molecule chiral. The presence of two or more chiral centers may or may not result in the molecule being chiral. In the examples given below the chiral centers are indicated with an asterisk. The vertical broken line represents a plane of symmetry.

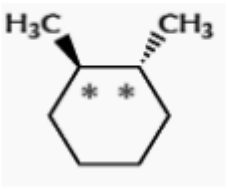
Ibuprofen: One chiral center renders the molecule chiral



cis-1,2 dimethylcyclohexane **is an achiral molecule**



***trans*-1,2- dimethylcyclohexane** is a chiral molecule



CHIRALITY: The property of non superimposability of an object on its mirror image is called chirality. Such molecule has no symmetry elements of the second kind. If the molecule is superposable on its mirror image, it is ACHIRAL.

ELEMENT OF SYMMETRY:

To exhibit optical activity molecule must not have the symmetry elements, (a) plane of symmetry (b) Centre of symmetry (c) n-fold alternating access of symmetry. If these three are absent then only the compounds exhibit optical activity.

A symmetry element is a point of reference about which symmetry can take place. In particular elements can be identities, mirror planes, axis of rotation and centres of inversion.

The Identity Symmetry

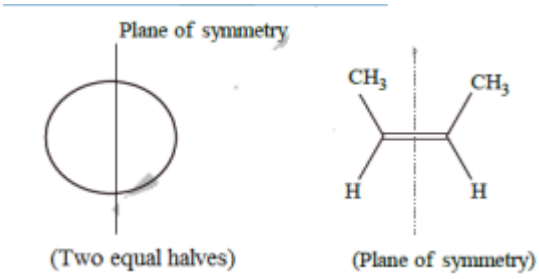
The identity operation consists of doing nothing, and the corresponding symmetry element is the entire molecule. Every molecule has at least this element.

For example, the CHFClBr molecule. The identify symmetry is not indicated since all molecule exhibit this symmetry

Plane of symmetry: A molecule is said to possess a plane of symmetry if the atoms or groups on one side of the plane forms the mirror image of those on the other side. In other words, a plane which bisects a molecule/object in two equal halves.

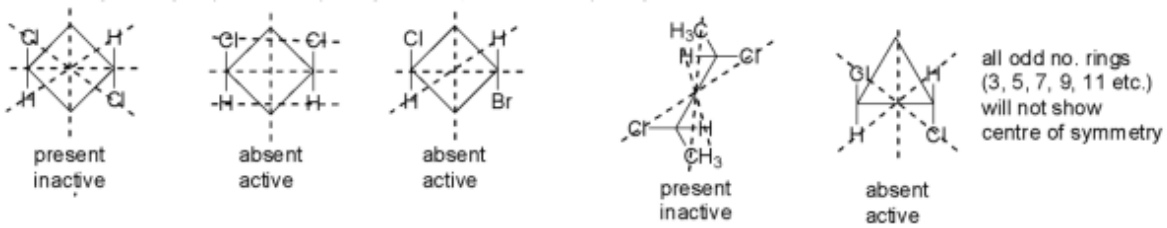
A plane which divides an object into two symmetrical halves, is said to be plane of symmetry.

For example, a person or a hat has a plane of symmetry. An object lacking a plane of symmetry is called Chiral (pronounced as Ki-ral) er Dyssymmetric. A symmetric object is referred to as Achiral. Achiral object cannot be superimposed on its mirror image. A left hand, for example, does not posses a plane of symmetry, and its mirror image is not another left hand but a right hand. The two are not identical, because they cannot be superimposed. If we were to lay one hand on top of the other the fingers and the thumbs would clash.



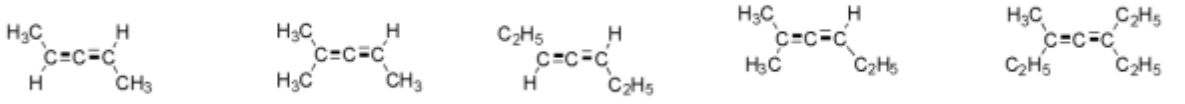
Centre of symmetry:

A Centre of symmetry in a molecule is said to exist if a line is drawn from any atom or group to this point and then extended to an equal distance beyond this point meets the identical atom or group. A Centre of symmetry is usually present only in an even membered ring.



n-Fold alternating access of symmetry: If a rotation by 360º/n degrees (n = 1, 2, 3, …) followed by reflection in plane perpendicular to the access taken results in identical molecule the compound said to be possess n-fold alternating access of symmetry. If plane of symmetry or Centre of symmetry is present then n-fold alternative access of symmetry is present. If plane of symmetry or centres of symmetry are absent then n-fold alternating access of symmetry will be absent. If the n-fold alternating access of symmetry present then the molecule is optically inactive, if absent then optically active.

Allenes are optically active because absence of plane of symmetry.
However, if on first or third carbon two same groups present it will be inactive.



ENANTIOMERS & DIASTEREOMER

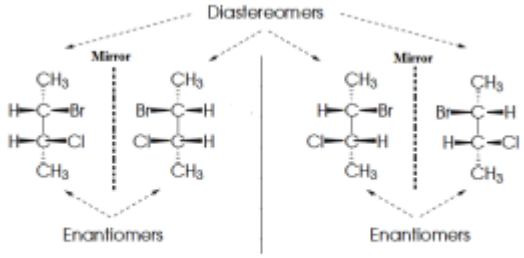
Enantiomers

- An enantiomer is one of two stereoisomers that are non-superimposable complete mirror images of each other.
- Molecules must contain at least one chiral centers
- Enantiomers have, when present in a symmetric environment, identical chemical and physical properties except for their ability to rotate plane polarized light by equal amounts but in opposite directions.
- A mixture of equal parts of an optically active isomer and its enantiomer is termed Racemic and has a net rotation of plane polarized light of zero.

Diastereomers

- Diastereomers (or diastereoisomers) are stereoisomers that are not enantiomers (nonsuperimposable mirror images of each other).
- Molecules must contain more than one chiral center
- Diastereomers can have different physical properties and different reactivity. In another definition diastereomers are pairs of isomers that have opposite configurations at one or more of the chiral centers but are not mirror images of each other.
- Each chiral carbon atom in a molecule doubles the number of theoretically pos isomers.

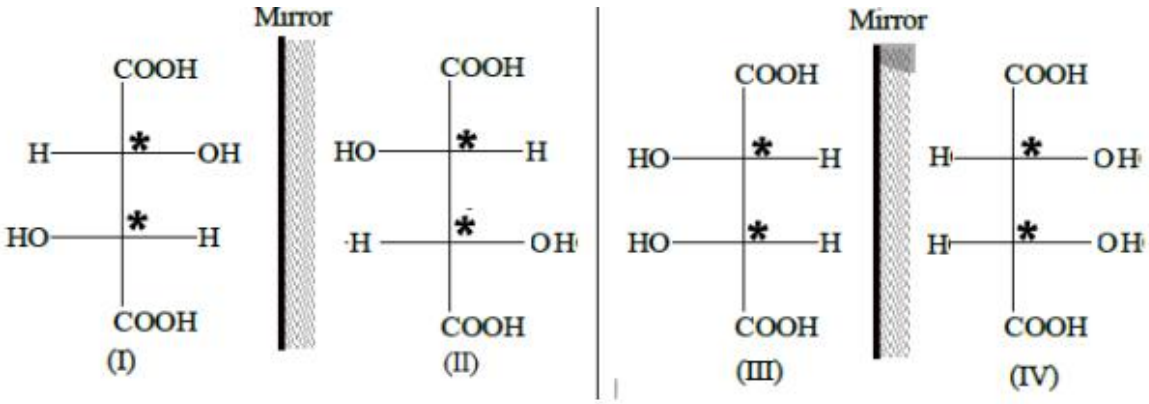
- Hence, molecule with n chiral carbon atoms should have 2 stereoisomers. Two diastereomers will have different melting points, boiling points, and solubilities. They will have different chemical reactivities toward most reagents
- Racemic mixture is not possible.



2-bromo-3-chlorobutane

MESO COMPOUND

- An optically inactive compound whose molecule is superimposable on its mirror image inspite of the presence of chiral carbon atoms is called a meso compound.
- If a molecule has two or more chiral centers, it is usually chiral. The exceptions are meso-molecules, which are not chiral. These are molecules that due to symmetry have chiral centers that 'cancel' each other out.
- Has two or more chiral centers
- Has a plane of symmetry.

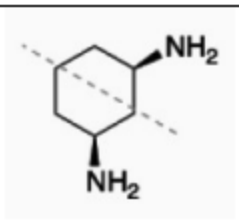
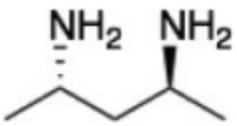
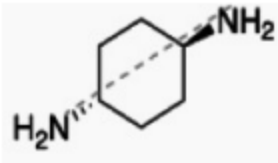


I and II are enantiomers (non-superimposable); III and IV are meso form (superimposable).

A compound with two or more chiral carbon atoms, but also having a plane of symmetry is called a meso compound.

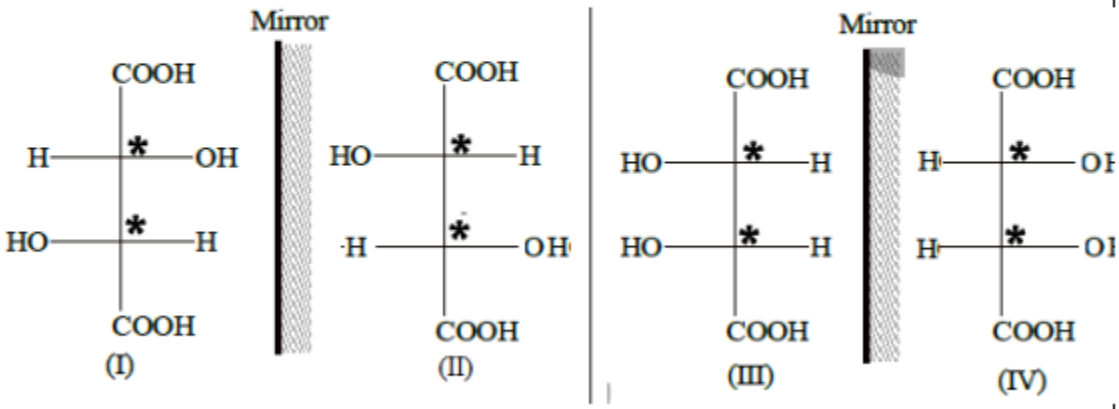
These molecule have planes of symmetry dividing them midway between the two chiral carbon atoms in each.

Notice that one half of the molecule is the mirror image of the other, both the molecules are optically inactive even though which have two chiral centres neither will rotate the plane polarized light.

	A person is meso (NOT CHIRAL) even though they have chiral elements (hands and feet). There is a plane of symmetry down the middle of a person, which makes a person the same as their mirror image.
	This molecule is meso (NOT CHIRAL). It has two chiral centers and a plane of symmetry.
	This molecule is not meso (CHIRAL). It has two chiral centers but no plane of symmetry.
	This molecule is not meso (NOT CHIRAL). It has a plane of symmetry but no chiral centers. The carbons attached to the NH_2 groups may look like chiral centers but they are not.

In Tartaric acid:

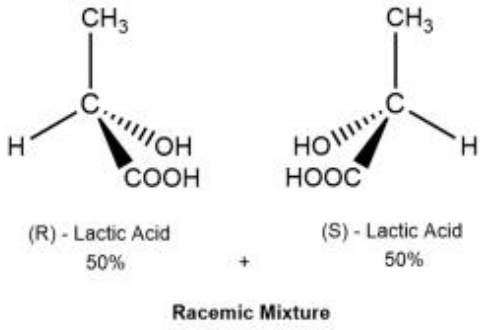
The molecule contains two chiral carbons and the number of optical isomers should be $2^n = 2^2 = 4$ but number of optical isomer is reduced to 3 because one molecule has a plane of symmetry. The stereoisomers of tartaric acid are,



I and II are enantiomers (non-superimposable); III and IV are meso form (superimposable).

8. RACEMIC MIXTURE

- A racemic mixture is a 1:1 mix of two enantiomers (Each of a pair of molecules that are mirror images of each other).
- No matter how many molecules are in a mixture, it is racemic if there are equal numbers of the two enantiomers.
- The racemic mixture produces a net optical rotation - of plane polarized light - of zero degrees. This is because the mixture contains equal amounts - equimolar mixture - of both enantiomers that have opposite rotations.
- A racemic mixture is a solution containing equal amounts of a pair of enantiomers.



A solution containing equal amounts of **(R)-2-butanol** and **(S)-2-butanol** is a **racemic mixture**.

RESOLUTION OF RACEMIC MIXTURES

- The separation of a racemic mixture into the individual enantiomerically pure enantiomers is called resolution.
- Since enantiomers have identical physical properties, such as solubility, boiling point and melting point, they cannot be resolved by common physical techniques such as direct crystallization, distillation or basic chromatography.
- The main difficulty in a process of resolution is that d or (+) and l or (–) forms have identical physical and chemical properties, so they cannot be separated by ordinary methods. However, the following methods can be used for this purpose.

(i) Mechanical separation:

- if the d or (+) and l or (-) forms of a substance exists in well-defined crystalline forms, the separation can be done by hand picking with the help of magnifying lens and a pair of tweezers.
- for example, the d and l forms of sodium ammonium tartarate can be separated by this method.
- the method has very limited appications and applies to only few crystalline constituents having different shape.

(ii)Biochemical separation:

- In this method the resolution done by the use of microorganisms.

- when certain bacteria or moulds are added to a solution of a racemic mixture, they decompose one of the optically active forms more rapidly than the other.
- For example, when the mould, racemic ammonium tartarate, the mould completely decompose the d and l forms is left practically unaffected. the main drawback of the method is that half of the material is destroyed during resolution. The process is very slow and only small amounts of the materials can be separated.

(iii)Chemical separation:

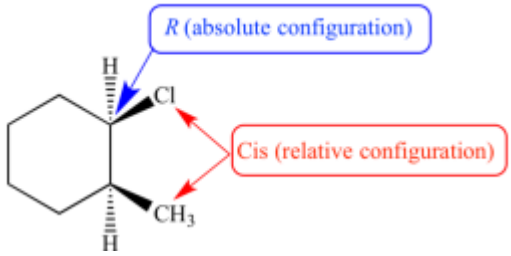
- this is probably the best method of resolution. The racemic mixture is made to combine with another optically active compound and the resulting solubility in various solvents.
- by fractional crystallization forms a suitable solvent, they can be separated.
- For example, the racemic mixture of lactic acid is allowed to combine with the optically active base (-) starchnine or (+) brucine

CONFIGURATION:

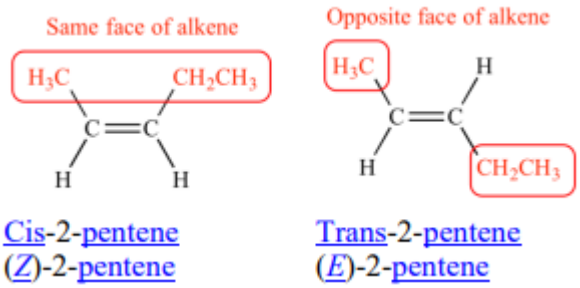
The arrangement of atoms that characterizes a particular stereoisomer is called its configuration.

Relative configuration:

The position of atoms or groups in space in relation to (i.e., relative to) something else in the molecule. Compare with absolute configuration, which is independent of atoms or groups else where in the molecule.



Relative to the position of the methyl group, the chlorine atom is on the same face of the cyclohexane ring. The stereocenter bearing the chlorine atom has an R absolute configuration (this configuration does not involve or depend on positions elsewhere in the molecule). Hence this molecule is cis-1-chloro-2-methylcyclohexane or (1R, 2S)-1-chloro-2- methylcyclohexane.

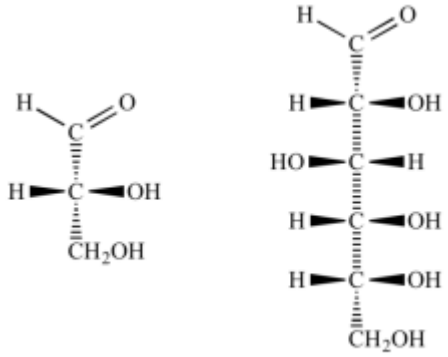


Cis-2-pentene
(Z)-2-pentene

Trans-2-pentene
(E)-2-pentene

In cis-2-pentene, the methyl and ethyl groups are on the same side of the alkene. The groups with highest Cahn-Ingold-Prelog priority are on the same face of the alkene, so this is also (Z)-2-

pentene. In trans-2-pentene, also named (E)-2-pentene, the methyl and ethyl groups are on opposite faces of the alkene. Cis, trans, E, and Z are all designations of relative configuration.



D-glyceraldehyde D-glucose

At the stereocenter next to the CH2OH carbon, both of these monosaccharides have the OH group pointing to the right, so they have the same relative configuration. This relative configuration is indicated with the prefix D. D and L are designations of relative configuration.

Absolute configuration:

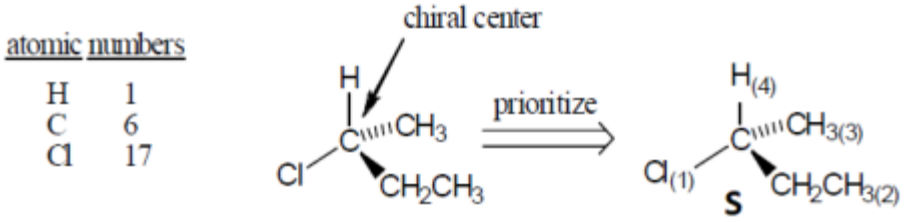
R, S-System

- An absolute configuration refers to the spatial arrangement of the atoms of a chiral molecular entity (or group) and its Stereochemical description e.g. R (Rectus) or S (Sinister).
- The arrangement of atoms in an optically active molecule, based on chemical interconversion from or to a known compound, is a relative configuration. Relative, because there is no way of knowing just by looking at a structure whether the assignment of (+) or (-) is correlated to a particular isomer, R or S.
- R and S notations are used only to describe asymmetric molecules following Cahn-Ingold Prelog (CIP) sequence rules.

(a) Rule I: first we assign the priority numbers to the four atoms/groups attached to chiral Centre according to CIP rules.

For example, in the case of CHClBrI, the four atoms attached to the chiral center are all different and priority will be given based on atomic weight, thus the priority follows as I, Br, Cl, H.

Rule 2: If two or more of the atoms that are bonded directly to the chiral center are the same, then prioritize these groups based on the next set of atoms (i.e., atoms adjacent to the directly bonded atoms). Continue until priorities can be assigned. Priority is assigned at the first point of difference.



Step 1. Following a set of sequence rules, we assign a sequence of priority to the four atoms or groups of atoms that is, the four ligands-attached to the chiral center. In the case of CHCIBrl, for example, the four atoms attached to the chiral center are all different and priority depends simply on atomic number, the atom of higher number having higher priority.

Thus I. Br, Cl, H.

Step 2. We visualize the molecule oriented so that the ligand of lowest priority is directed away from us, and observe the arrangement of the remaining ligands. It proceeding from the ligand of highest priority to the ligand of second priority and thence to the third, our eye travels in a clockwise direction, the configuration specified R (Latin: rectus, right); if counterclockwise, the configuration is specified S (Latin: sinister left).

Thus configurations I and II are viewed like this: and are specified R and S, respectively. A complete name for an optically active compound reveals-if they are known both configuration and direction of rotation, as, for example, (S)-(+)-sec butyl chloride.

A racemic modification can be specified by the prefix RS, as, for example, (RS)-sec-butyl chloride. We must not, of course, confuse the direction of optical rotation of a compound a physical property of a real substance, like melting point or boiling point-with the direction in which our eye happens to travel when we imagine a molecule held in an arbitrary manner. So far as we are concerned, unless we happen to know what has been established experimentally for a specific compound, we have no idea whether (+) or (-) rotation is associated with the R or the S configuration. To establish the group priorities. we use the following Sequence Rules:

Rule 1. Of the atoms attached directly to the chiral carbon atom, the one atomic number has the highest priority. For example, I > Br > C > F > 0 > N > C > H.

Highest---------->Lowest

Rule 2. Of the atoms attached to the chiral carbon atom are the same, we determine priority by going to the next atom away from the chiral carbon atom.

For example, Highest---------->Lowest

Ethyl has a higher priority than methyl because the ethyl group has (CHH attached to the fir carbon, whereas the methyl carbon has only hydrogens (HHH), and C has priority over, Isopropyl is of higher priority than ethyl because it has two carbons attached to the first carbon and ethyl has only one. If there is no difference at the second atom in the chain, we go to the next atom and so forth.

Rule 3. A double bond is treated as though each atom of the double bond were bonded to two atoms

UNIT – 2

GEOMETRICAL ISOMERISM

Dr.MARY GRACE PANDU
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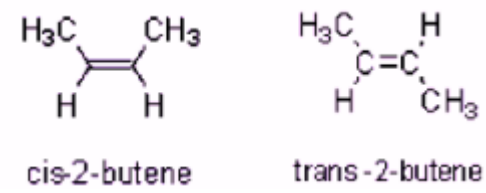
Geometrical isomerism

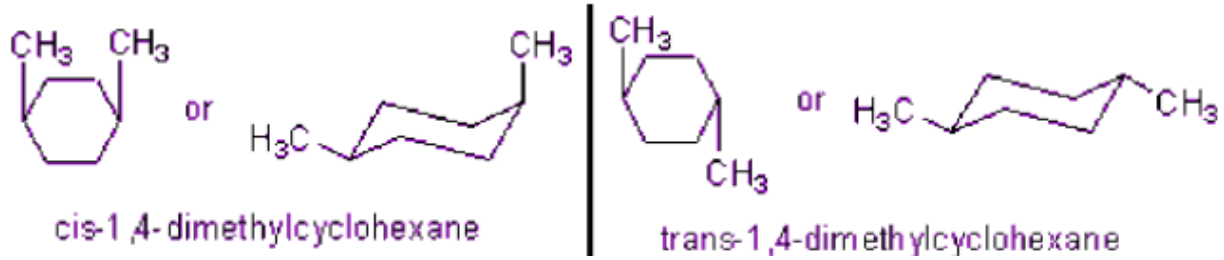
GEOMETRICAL ISOMERISM: The isomers which are having same structural formula but are differing in spatial arrangement of the groups or atoms around the double bond are termed as geometrical isomers and the phenomenon is termed as geometrical isomerism.

Example 1: - Two different spatial arrangements of methyl groups about a double bond in 2-butene give rise to the following geometrical isomers. - Two forms are not inter convertible due to restricted rotation of double bond. In the cis isomer, the two methyl groups are arranged on the same side of a double bond. Whereas in the Trans isomer, they are on the opposite side.



cis-2-butene trans-2-butene

Example 2: - There are two geometrical isomers (cis & trans) possible in case of 1,4–dimethyl cyclohexane. - Here the methyl groups are arranged differently about the plane of the cyclohexane ring. These isomers are not inter convertible since it is not possible to rotate the bonds

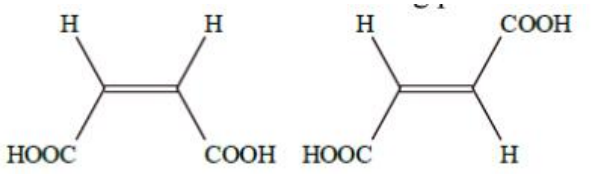


cis-1,4-dimethylcyclohexane trans-1,4-dimethylcyclohexane

Methods of determination of configuration of geometrical isomers:-

Melting point: - In general, the melting point of a trans isomer is higher than that of the corresponding cis isomer. This is due to the reason that the molecules of a trans isomer are more symmetrical and hence fit more closely in the crystal lattice as compared to the molecules of a cis isomer.

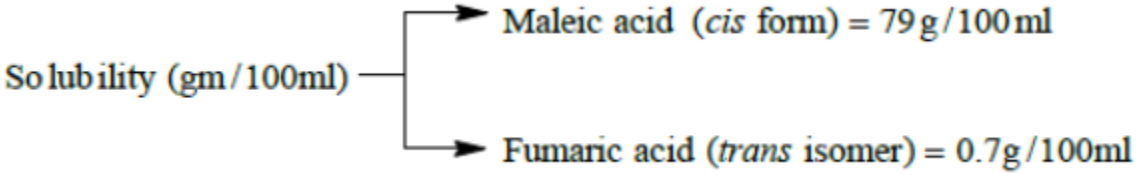
- In order for the intermolecular forces to work well, the molecules must be able to pack together efficiently in the solid. Trans isomers pack better than cis isomers. The "U" shape of the cis isomer doesn't pack as well as the straighter shape of the trans isomer. The poorer packing in the cis isomers means that the intermolecular forces aren't as effective as they should be and so less energy is needed to melt the molecule a lower melting point.



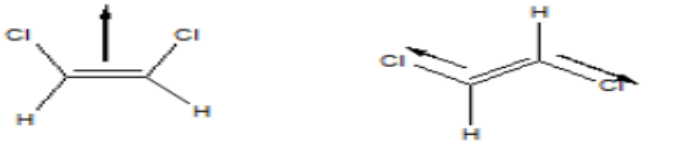
Maleic acid (*cis* isomer) m.p. = 403 K

Fumaric acid (*trans* isomer) m.p. = 575 K

Solubility: In general, solubility of a cis isomer is higher than that of the corresponding trans isomer. This is due to the reason that the molecules of a cis isomer are less tightly held in the crystal lattice.



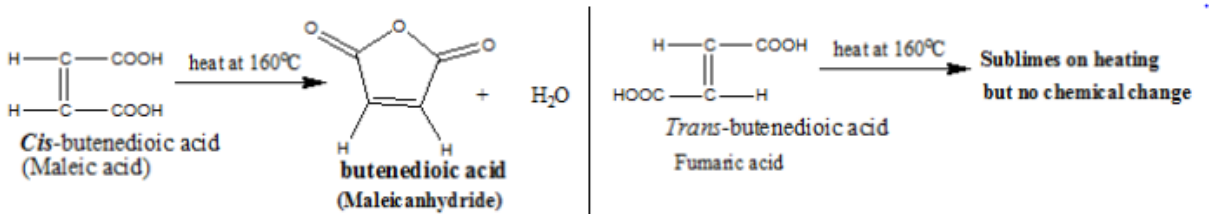
Dipole moment: The cis isomer has higher dipole moment than the corresponding trans isomer.



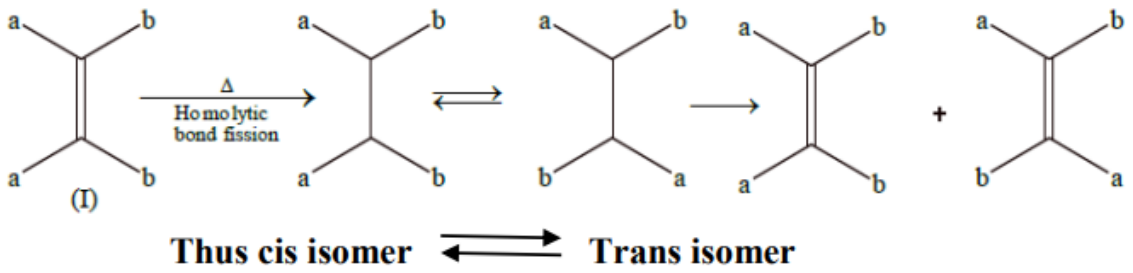
Cis-1,2 dichloro ethene $\mu = 1.85$

Trans-1,2 dichloro ethene $\mu = 0$

Stability: The trans isomer is more stable than cis isomer due to steric hindrance. Intermolecular reactions occur easily when reacting groups are close together. Hence, the cis isomer will form cyclic derivatives more readily as against trans derivatives. But this reaction will take place in only those cis isomers in which the substituent's on two double bonded carbons are capable of intramolecular reaction with each other.



Action of heat: On strong heating cis and trans isomers are interconvertible. This interconversion takes place as follows:



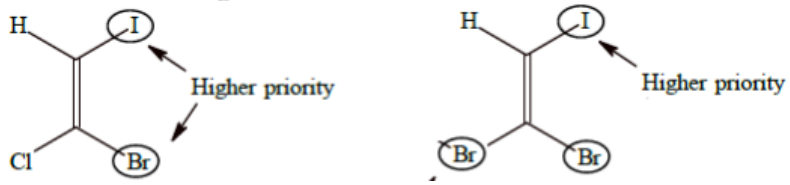
E & Z NOTATION FOR GEOMETRIC ISOMERISM

The simple convenction of denoting the geomertrical isomers by cis/trans descriptors is not sufficient when there are more than two different substituents on a double bond. To differentiate the stereochemistry in them, a new system of nomenclature known as the E & Z notation method is to be adopted.

According to this method, if the groups with higher priorities are present on the opposite sides of the double bond, that isomer is denoted by E. Where E = Entgegen (the German word for 'opposite0) or E = Enemy

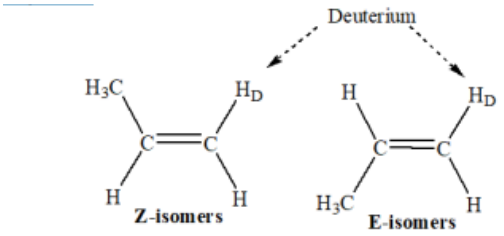
- However, if the groups with higher priorities are on the same side of the double bond, that isomer is denoted by **Z.** Where **Z = Zusammen** (the German word for '**together**')
- The letters **E** and **Z** are represented within parentheses and are separated from the rest of the name with a hyphen.
- Step by step procedure to determine the **E** and **Z configuration**: *The following procedure is to be adopted to denote the geometrical isomers by E & Z descriptors.*
- First determine the higher priority group on each end of the double bond.
- If the higher priority groups are on the opposite sides of double bond, the isomer is denoted by the **descriptor, E**.
- Otherwise if they are on the same side of double bond, the **Z descriptor** must be used.
- ***The priorities are assigned by following Cahn-Ingold-Prelog sequence rules***:

- **Rule 1:** Rank the atoms directly attached to the olefinic carbon according to their **atomic number**. **High priority** is given to the atom with **higher atomic number**.

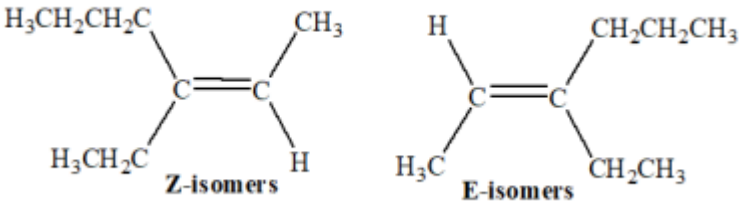


Rule 2: If isotopes of same element are present, the higher priority is given to the isotope with higher atomic mass. E.g. the Deuterium isotope (H2 or D) has more priority than protium (H1 or H). The C13 isotope has more priority than C12.

geometrical isomerism

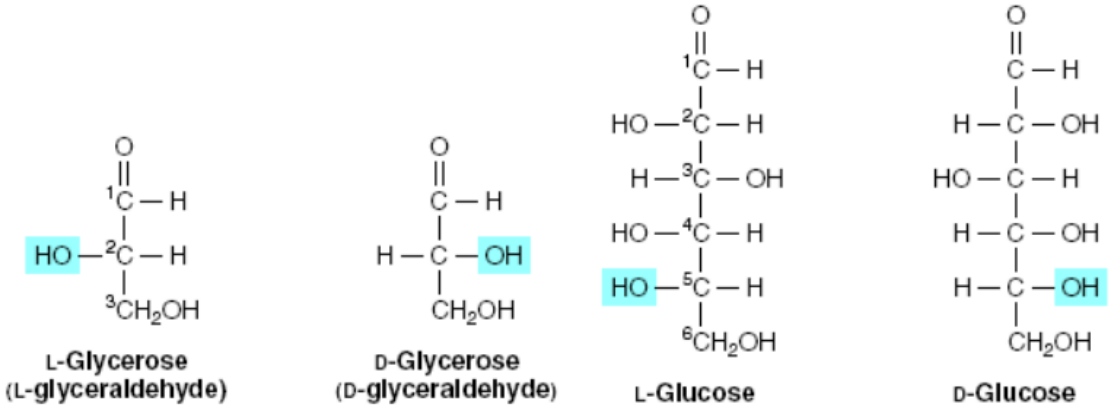


Rule 3: If the relative priority of two groups cannot be decided by Rule 1, it shall be determined by applying to the next atom or sequence of atoms in the group 'X'. e.g. for typing groupings in organic molecules where X is more than one atom .... X = -CH2CH2CH3 > -CH2CH3 > -CH3 > -H i.e. the longer the hydrocarbon carbon chain the higher its priority



D & L-System –

The D & L convention, not to be confused with the d (dextro) and l (levo) descriptors used to designate the direction of specific rotation of chiral compounds, is a convention used to distinguish between enantiomers of chiral monosaccharides and chiral alpha-amino acids, based on the molecule drawn as a Fischer projection in a specific orientation. - The L and D forms of the sugar depends on the orientation of the -H and -OH groups around the carbon atom adjacent to the terminal primary alcohol carbon (carbon 5 in glucose) determines whether the sugar belongs to the D or L series. - The D- and L- notation is based on glyceraldehyde. - When the -OH group on this carbon is on the right, then sugar is the D-isomer; when it is on the left, then it is the L-isomer.

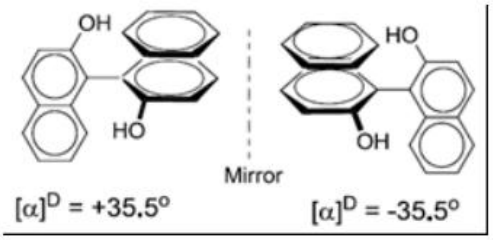


D- and L-isomerism of glycerose and glucose

ATROPISOMERISM –

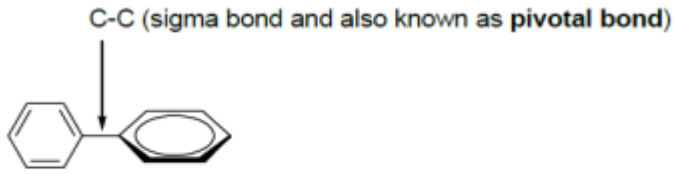
Biphenyls are compounds whereby a phenyl ring is connected to another through a central σ bond. In unsubstituted biphenyl, there is sufficient amount of freedom of rotation around the central single bond to allow for free interconversion between the various conformers or rotamers so that the various rotamers cannot exist independently.

However, biphenyls with large substituents at the ortho positions on either side of the central σ bond experience restricted rotation along this bond due to steric hindrance. If the substituents are different, a chiral molecule existing as a pair of enantiomers called atropisomers is obtained. - Polynuclear aromatic systems such as binol also exist as enantiomers.



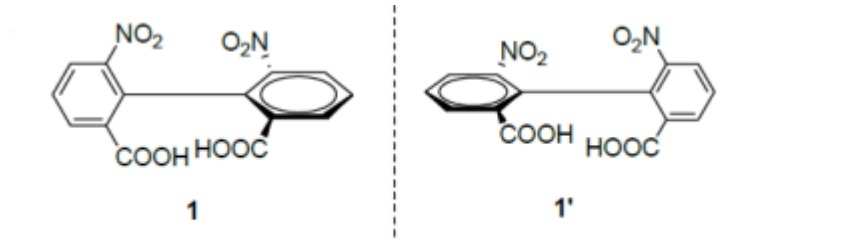
Atropisomerism are stereoisomers as a result of restricted rotation about a single bond. - Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers (from Greek, a = not and tropos = turn).

- If bulky group on ortho position of bi-phenyl or strained ring structural features. Bulky substituents or strained rings may enhance the barrier to rotation between two distinct conformations to such an extent as to allow observation of atropisomers.
- Atropisomerism is also called axial chirality and the chirality is not simply a centre or a plane but an axis.



Structure of biphenyl

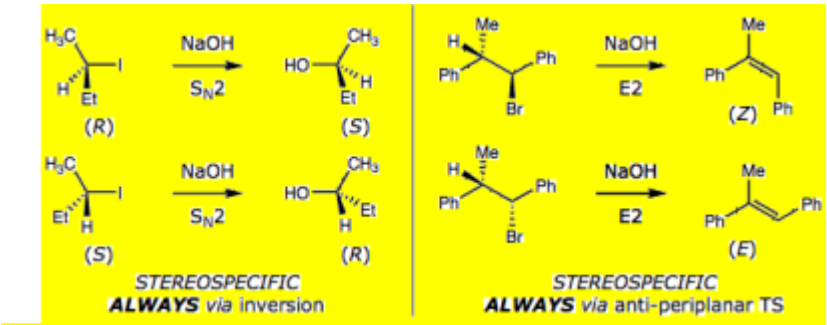
- Biphenyl substituted on ortho position, which contains a chiral axis along the biphenyl linkage. The biphenyl rings are perpendicular to each other in order to minimize steric clashes between the four ortho substituents meaning that rotation about the biphenyl bond through pivotal bond is restricted.



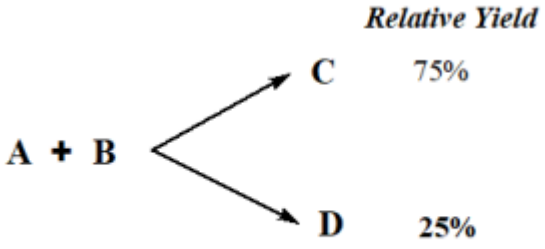
Enantiomers of the 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid

Stereospecific and Stereoselective Reactions

STEREOSPECIFIC REACTIONS - A stereospecific reaction is one which, when carried out with stereoisomeric starting materials, gives a product from one reactant that is a stereoisomer of the product from the other. - 'Stereospecific' relates to the mechanism of a reaction, the best-known example being the SN2 reaction, which always proceeds with inversion of stereochemistry at the reacting centre.

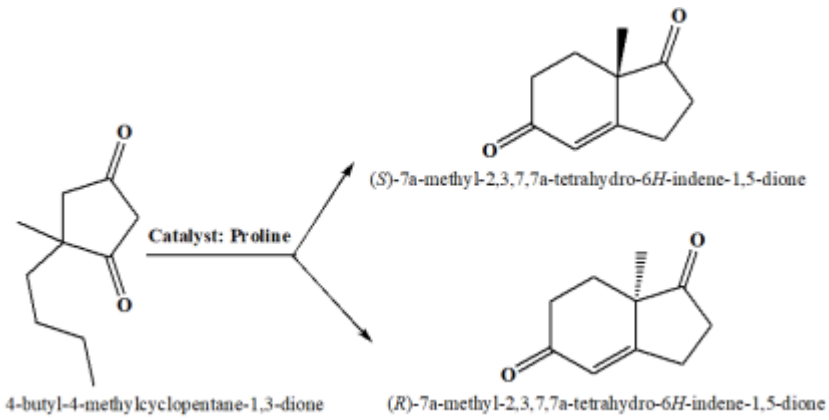


STEREOSELECTIVE REACTIONS - A stereoselective process is one in which one stereoisomer predominates over another when two or more may be formed. - If more than one reaction could occur between a set of reactants under the same conditions giving products that are stereoisomers and if one product forms in greater amounts than the others, the overall reaction is said to be stereoselective.

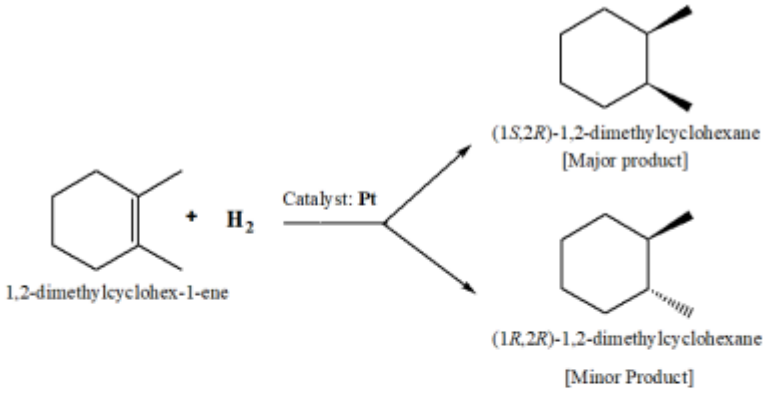


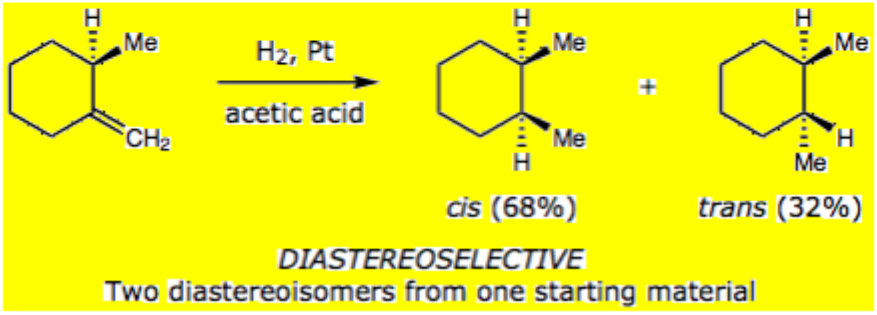
The overall reaction between A and B is stereoselective.

A stereoselective reaction in which the possible products are enantiomers is said to be Enantioselective.



A stereoselective reaction in which the possible products are diastereomers is said to be Diastereoselective.





	Stereospecific Reactions	***Stereoselective Reactions***
Definition	A stereospecific reaction is a reaction in which the stereochemistry of the reactant completely determines the stereochemistry of the product without any other option.	A stereoselective reaction is a reaction in which there is a choice of pathway, but the product stereoisomer is formed due to its reaction pathway being more favorable than the others available.
Number of Products	A stereospecific reaction gives a specific product from a certain reactant.	A stereoselective reaction can result in multiple products.
Effects	The final product of a stereospecific reaction depends on the stereochemistry of the reactant.	The selectivity of the reaction pathway depends on differences in steric effects (presence of bulky groups cause steric hindrance) and electronic effects.

Conformational Isomerism: The different arrangements of the atoms in space that result from the rotation of group about C-C bond axis called conformation. Conformations represent conforms which are readily interconvertible and thus nonseparatable.

Conformations of Ethane:

There is a 12 kJ/mol (2.9 kcal/mol) barrier to rotation in ethane. The most stable (low energy) conformation is the one in which all six C–H bonds are as far away from each other as possible (staggered when viewed end-on in a Newman projection).

The least stable (high energy) conformation is the one in which the six carbon–hydrogen bonds are as close as possible (eclipsed in a Newman projection).

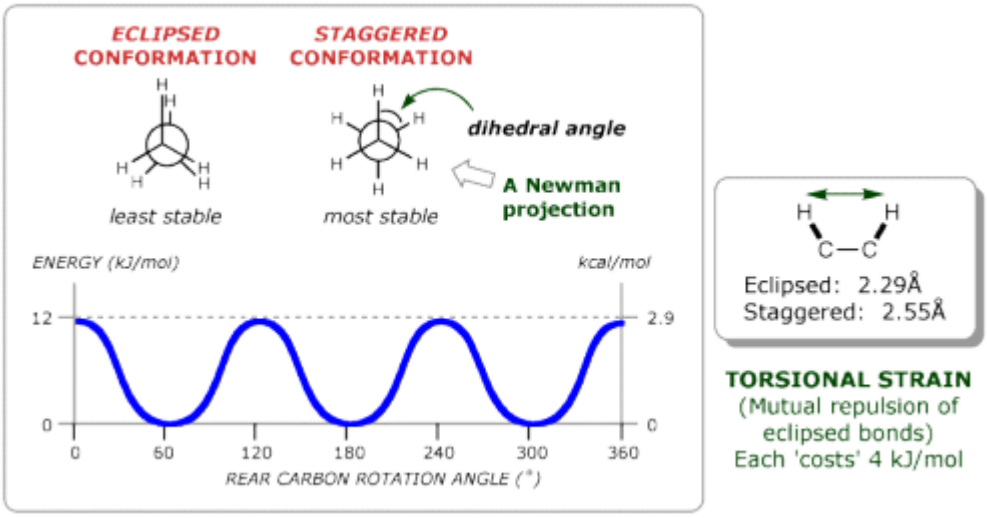
All other conformations lie between these two limits. The barrier to rotation is the result of three equal C–H bond-eclipsing interactions, so we can assign a value of about 4.0 kJ/mol (1.0 kcal/mol) to each of these interactions.

The corresponding energy in propane is 14 kJ/mol (3.4 kcal/mol). The 12 kJ/mol of extra energy in the eclipsed conformation of ethane is called torsional strain.

The barrier to rotation that results from this strain can be represented in a graph of potential energy versus degree of rotation in which the angle between C–H bonds on C-1 and C-2 (the dihedral angle) completes one revolution.

Energy minima occur at staggered conformations, and energy maxima occur at eclipsed conformations. The torsional strain

is thought to be due to the slight repulsion between electron clouds in the eclipsed bonde



We can represent conformational isomers in one of two ways.

Sawhorse representations view the carbon–carbon bond at an angle so as to show the spatial orientation of all C–H bonds.

In a Newman projection the carbon–carbon bond is viewed along its axis and the two carbon atoms are repesented by a circle.

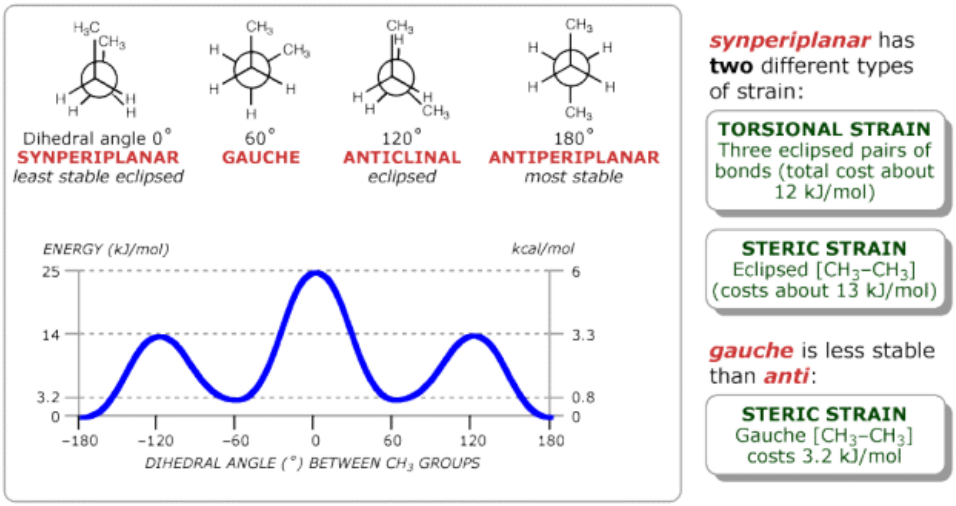
The bonds attached to the front carbon are represented by lines going to the centre of the circle, and bonds attached to the rear carbon are represented by lines going to the edge of the circle.

The advantages of Newman projections are that they are easy to draw and they clearly show the relationships among substituents on the different carbon atoms.

Conformation of n-butane: The conformational possibilities increase as alkanes become larger. A plot of potential energy against rotation about the C (2)–C (3) bond in butane.

The lowest-energy arrangement, called the antiperiplanar (or anti) conformation, is the one in which the two large methyl groups are as far apart as possible. As rotation around the C (2)–C (3) bond occurs, another eclipsed conformation (anticlinal) is reached in which there are two Me–H interactions and one H–H interaction.

If we assign the energy value (4 kJ/mol) for H–H eclipsing interactions that was previously derived from ethane, we can predict that each Me–H interaction in the anticlinal conformation costs about 5 kJ/mo



synperiplanar has **two** different types of strain:

TORSIONAL STRAIN
Three eclipsed pairs of bonds (total cost about 12 kJ/mol)

STERIC STRAIN
Eclipsed [CH_3–CH_3] (costs about 13 kJ/mol)

gauche is less stable than ***anti***:

STERIC STRAIN
Gauche [CH_3–CH_3] costs 3.2 kJ/mol

As bond rotation continues, an energy minimum is reached at the staggered conformation where the methyl groups are 60° apart (a gauche relationship).

This lies 3.2 kJ/mol higher in energy than the anti conformation even though it has no eclipsing interactions. This energy difference is due to the fact that the hydrogen atoms of the methyl groups are near each other in the gauche conformation, resulting in steric strain, which is the repulsive interaction that occurs when atoms would otherwise tend to occupy the same space.

As the dihedral angle between the methyl groups approaches 0°, an energy maximum is reached. The methyl groups are forced even closer together than in the gauche conformation, and both torsional strain and steric strain are present. A total strain energy of 25 kJ/mol has been estimated for this conformation, allowing us to calculate a value of 17 kJ/mol for the Me–Me eclipsing interaction.

Completing the 360° rotation after the synperiplanar point produces the mirror images of what we've already seen; another gauche conformation, another eclipsed conformation and finally a return to the anti conformation.

Cyclohexane is not planar but puckered into a 3-D conformation that relieves all strain. Its most stable arrangement is referred to as the chair conformation. The different chair conformations of cyclohexane can interconvert or 'flip' very easily: the activation barrier is 45 kJ/mol.

CHAIR

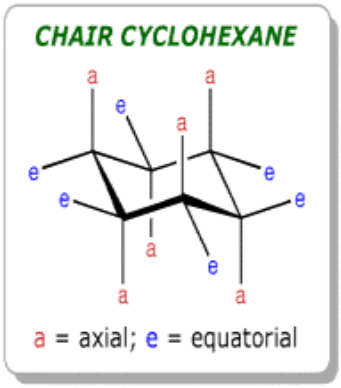
C—C—C angles 111° (no angle strain)
All bonds staggered (no torsional strain)
Predominant conformation (>99.8%)

BOAT

High steric strain (short 1,4 distance)
Torsional strain (eclipsing of C–H bonds)
27 kJ/mol less stable than chair

TWIST BOAT

Less steric strain than boat (1,4 distance larger)
Less torsional strain than boat (less eclipsing)
6 kJ/mol more stable than boat



UNIT – 3

HETERO CYCLIC COMPOUNDS

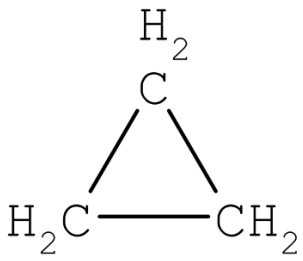
Dr.Mary Grace Pandu
Assistant.Professor

HETERO CYCLIC COMPOUNDS

Heterocyclic compounds are a class of organic compounds that contain a ring structure composed of at least one atom other than carbon (heteroatom) along with carbon atoms. These heteroatoms can include elements like nitrogen, oxygen, sulfur, and others.

The cyclic part from the Greek kyklos, meaning “circle” of heterocyclic indicates that at least one ring structure is present in such a compound, while the prefix hetero- from Greek heteros, meaning “other” or “different” refers to the noncarbon atoms, or heteroatoms, in the ring. In their general structure, heterocyclic compounds resemble cyclic organic compounds that incorporate only carbon atoms in the rings.

for example, cyclopropane (with a three-carbon-atom ring)



Heterocyclic compounds include many of the biochemical material essential to life. i.e. nucleic acids, the chemical substances that carry the genetic information controlling inheritance, consist of long chains of heterocyclic units held together by other types of materials. Many naturally occurring pigments, vitamins, and antibiotics are heterocyclic compounds, as are most hallucinogens. Modern society is dependent on synthetic heterocycles for use as drugs, pesticides, dyes, and plastics.

Nomenclature and classification

heterocyclic compounds obey IUPAC rule and obeys allows three nomenclatures i.e.

1.Common names

2.The replacement nomenclature

3.The hantzsch-widman nomenclature

1.COMMON NAMES OR TRIVIAL NAMES:

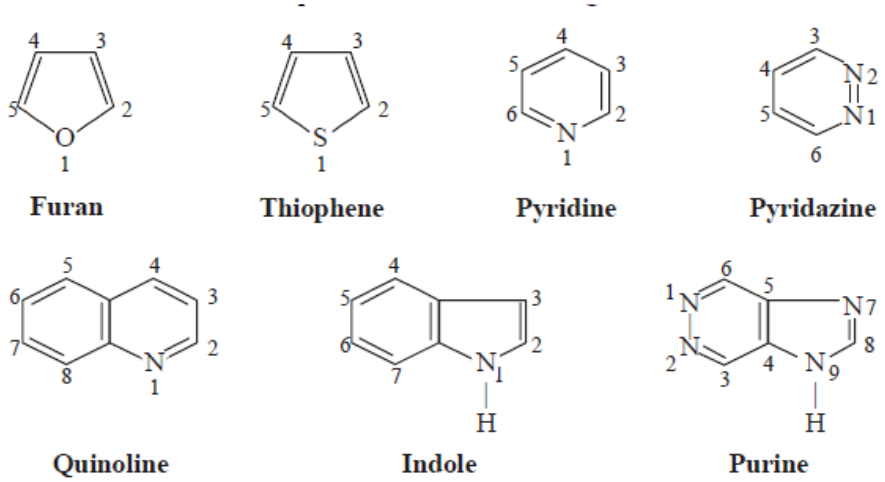
There are a large number of important ring system

-they no have structural information but widely used with their non systemic or common names.

-Each compound gives the corresponding trivival name., these are usually originates from the compounds occurrence in its first preparation or its special properties.

-if there is more than one hetero atom of the same type numbering starts at the saturated one.

E.g.

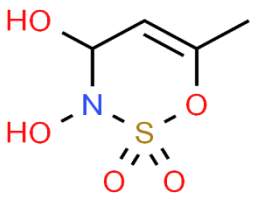


THE REPLACEMENT NOMENCLATURE:

In replacement nomenclature, the hetero cycles name is composed of the carbocycles's name and a prefix that denotes the hetero atom.

-The hetero atom is designated as number and the substituents around the ring are numbered.so as to have the lowest number for the substitution.

-In case of ring containing more than one hetero atom, the order of preference for numbering is O, S, N. the ring is numbered from the hetero atom of preference.in such away so as the give the smallest possible number to the heteroatom in the ring.



6-Methyl-1,2,3-oxathiazine

HANTZCH WIDMAN NOMENCLATURE

The hantzsch-widman nomenclature is based on the type(Z) of the hetero atom, the ring size and nature of the ring.

heterocycle compounds

-which are cyclic compound that contains atoms of at-least two different elements as number of their ring.

-this system provides a standardized method for naming these compounds based on their ring size, the type of the hetero atoms present, and saturation level of the ring.

The type of the hetero atom: The type of hetero atom is indicated by a prefix.

Heteroatom	prefix
O	Oxa
N	Aza
S	Thia
P	Phospha

The ring size:

The ring size is indicated by the suffix.

Ring size	Suffix
3	Ir
4	Et
5	Ol
6	In
7	Ep
8	Oc
9	On
10	Ec

The endings indicate the size and degree of unsaturation of the ring.

For example: the size of the ring indicates 3-if it is saturated indicates **irane,** and unsaturated indicates **irine**.

If it is saturated but contains nitrogen then it is **iridine.**

Classification of hetero cyclic compounds:

Heterocyclic compounds can be classified in to based on several criteria, including the size of the ring, the type and number of heteroatoms, and the ring structure (whether it is aromatic or non-aromatic)

Based on the aromaticity:

heterocycle compounds

These are further divided into**:** Aliphatic and Aromatic heterocyclic compounds**.**

Aliphatic heterocyclic compounds-which does not contain double bond

-These are also known as non-aromatic heterocycles.

-the properties of the aliphatic heterocyclic compounds are mainly affected due to ring stain.

ethylene oxide **tetra hydro furan** **pyrrolidine**

Aromatic heterocyclic compound: These compounds contains one or more hetero atoms with in a ring structure that exihibits aromaticity.

-Aromatic hetero cyclic compounds obeys hackle's rule i.e.

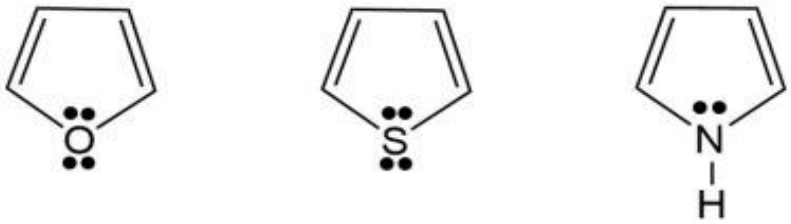
-it should be cyclic.

-it should be planner.

-it should not contain any sp3 hybridization atom.

-it must have (4n+2) pie electrons.

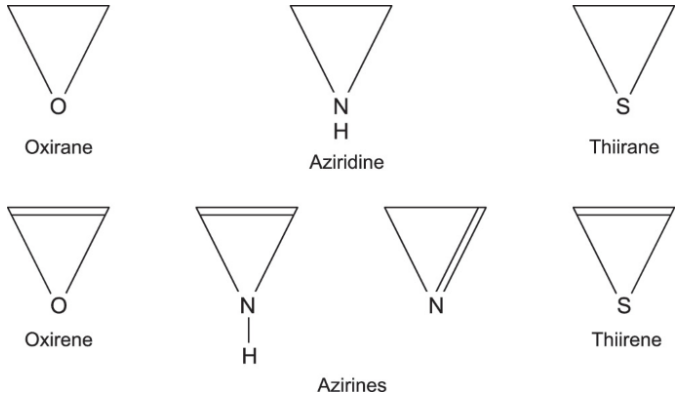
Furan **Thiophene** **Pyrrole**



heterocycle compounds

Based on ring Size:

1. **Three-Membered Rings**: contains three atoms which may be saturated or unsaturated
    - Aziridine (contains nitrogen)
    - Oxirane (epoxide, contains oxygen)
    - Thiirane (contains sulfur)



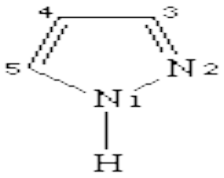
Four-Membered Rings: contains four hetero atoms

- Azetidine (contains nitrogen)
- Oxetane (contains oxygen)
- Thietane (contains sulfur)

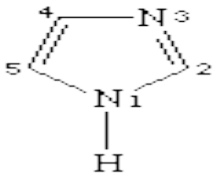
Five-Membered Rings:

- Pyrrole (contains nitrogen)
- Furan (contains oxygen)
- Thiophene (contains sulfur)
- Imidazole (contains two nitrogen atoms)

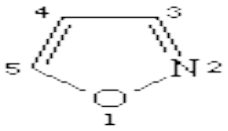
heterocycle compounds



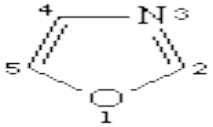
pyrazole



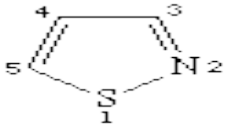
imidazole



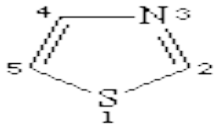
isoxazole



oxazole



isothiazole

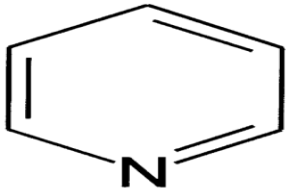


thiazole

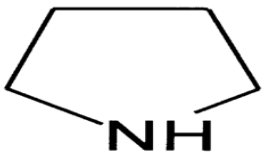
Six Membered Rings: contains one hetero atom

- Pyridine (contains nitrogen)
- Pyran (contains oxygen)
- Thiopyran (contains sulfur)
- Pyrimidine (contains two nitrogen atoms)

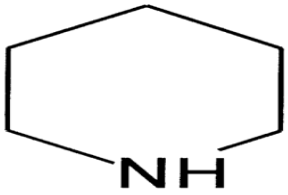
Pyrrole



Pyridine



Pyrrolidine



Piperidine

Based on Saturation:

1. **Fully Saturated Heterocycles**:
   - Contain only single bonds within the ring (e.g., piperidine, tetrahydrofuran).

2.**Partially Unsaturated Heterocycles**:

- Contain one or more double bonds within the ring but are not fully aromatic (e.g., pyrroline).

heterocycle compounds

Synthesis, reactions and medical use

Pyrrole : it is an aromatic heterocycle having week aniline i.e. odor.

Physical properties of pyrrole:

Colour – colourless

Boiling point - 129 to 131

Molecular formula - C4H4NH

Solubility - Slightly soluble in water,
Completely soluble in ether and
Alcohol.

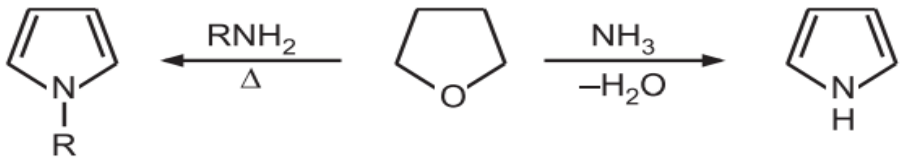
-it is highly sensitive to air, when pyrrole is exposed to air it turns to brown and gradually resinifies.

- pyrrole has three pair of delocalized π electrons, two of the pairs shows as the bond and the third pair shown as a lone pair of non-bonding electrons on the nitrogen atom.

Chemical synthesis

Synthesis from furan: pyrrole is prepared industrially from furan.

When furan passing it over the ammonia and heated at 400 c in the presence of strong catalyst.

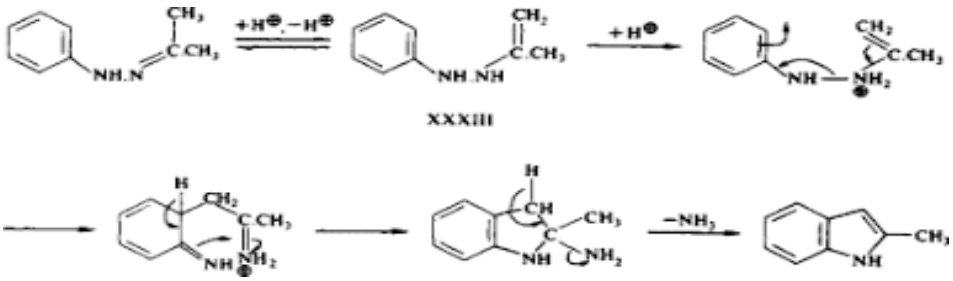


1-substituted pyrrole Furan Pyrrole

Hantzch -pyrrole synthesis: When α haloketones or aldehyde is reacted with a β keto ester or β chloroketones and base ammonia it gives pyrrole.

-the base functions both as a reactant and as a catalyst.

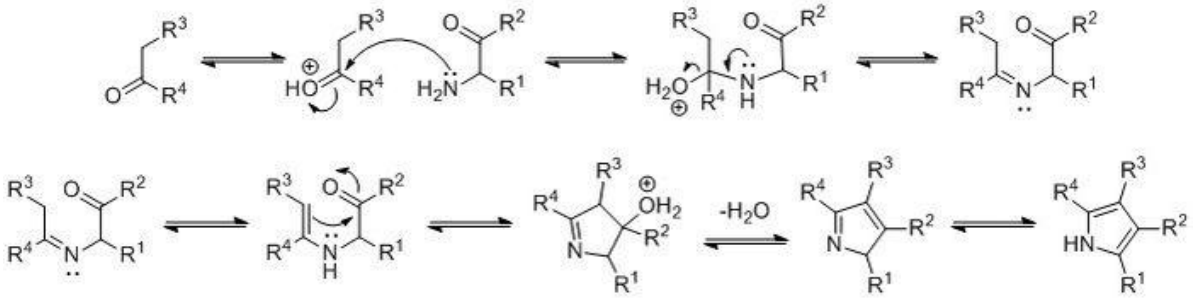
Reaction:



XXXIII

Knorr pyrrole synthesis:

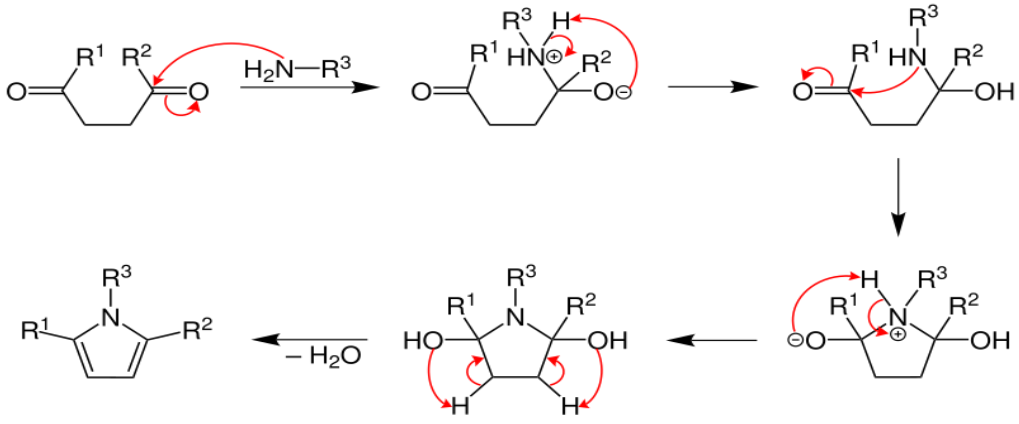
When α amino ketones condensed with another Di carbonyl compound containing an electron withdrawl group in the presence of acetic acid.



Paal knor pyrrole synthesis:

Condensation reaction between di carbonyl group with ammonia to form a substituted pyrrole.

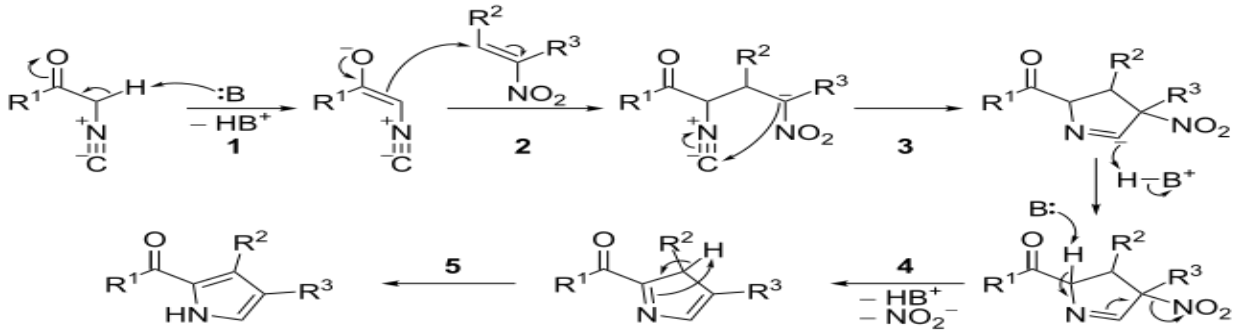
-pyrrole itself formed from the succinyl aldehyde and ammonia.



Barton -zard synthesis:

When an iso-cyano acetate reacts with a nitro alkene in a 1,4 -addition followed by a cyclization and elimination of nitro group

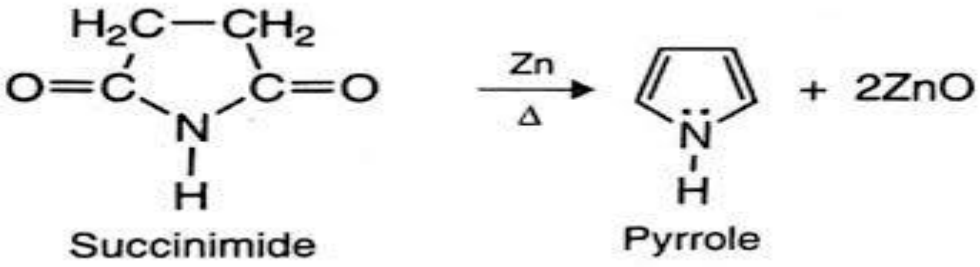
Reaction:



From distillation of succinimide:

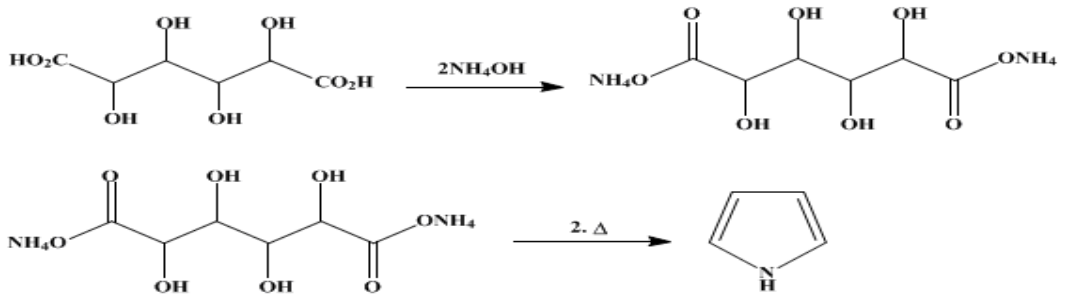
When succinimide undergoes distillation with the zinc dust then the pyrrole ring is obtained.

Reaction:



From acetylene and ammonia:

While by passing acetylene and ammonia through the red -hot tube pyrrole is obtained.



Chemical reactions:

-pyrrole, furan, and thiophene all are π excessive ring.

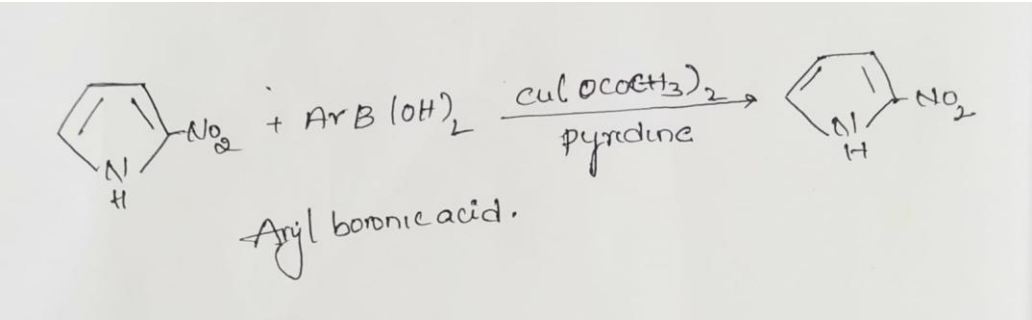
-all these rings are highly prone to electrophilic substitution reactions on the carbon.

-the greater reactivity of pyrrole towards the electrophilic due to the greater electron releasing ability of N atom than oxygen and sulfur atom, thiophene is least reactive.

Alkylation is a chemical process in which an alkyl group is transferred from one molecule to another.

-the sodium/ potassium salt of pyrrole reacts with alkyl halide to give corresponding N-acetyl pyrrole in presence of electron withdrawing substituent on pyrrole ring favor the rapid N-alkylation or N- arylation.

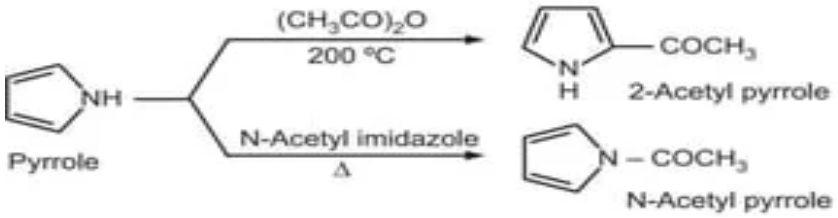
Reaction:



Acylation:

When pyrrole is heated with acetic anhydride at 200®c gives 2-actyl pyrrole.

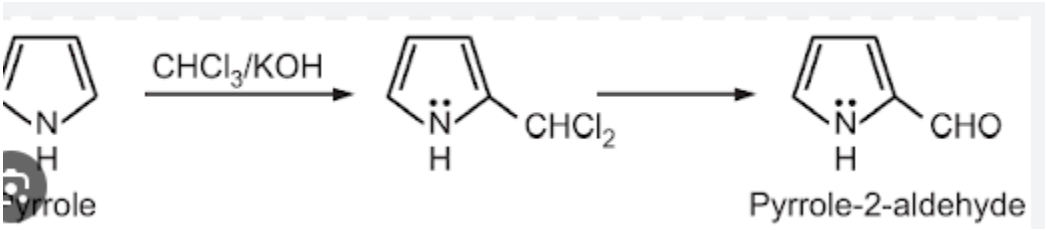
-while N-acetyl pyrrole can be obtained by the heating pyrrole with N-acetyl imidazole.



Reimer-tiemann reaction:

In the presence of strong base and chloroform, pyrrole undergoes reimer-tiemann reaction to form prrrole-2-aldehyde.

Reaction:

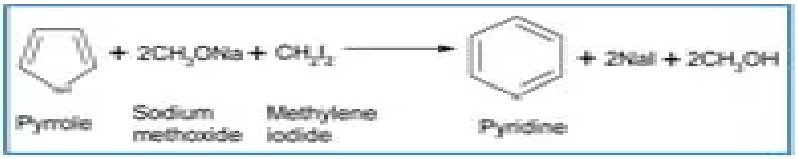


Ring expansion:

When potassium pyrrole is heated with chloroform and sodium ethoxide, the pyrrole ring expanded to pyridine.

-pyrrole-five membered ring expanded to pyridine-six membered ring.

Reactions:



furan

furan is a hetero cyclic compound, consisting of a five membered aromatic ring with four carbon atoms and one oxygen atom.

Physical properties:

Colour - colourless

Formula - C4H4O

Molar mass - 68.O7g/mol

Boiling point - 31.3

Melting point - 85.6

Solubility - slightly soluble in water

Completely soluble in alcohol

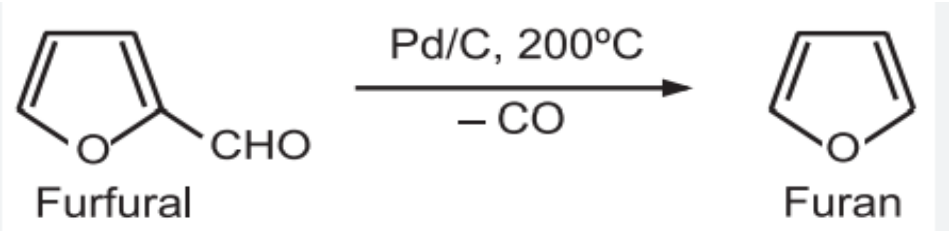
and acetone.

-these are toxic and may be carcinogenic.

Chemical synthesis:

Decarboxylation of furfural in the presence of palladium and charcoal gives furan.

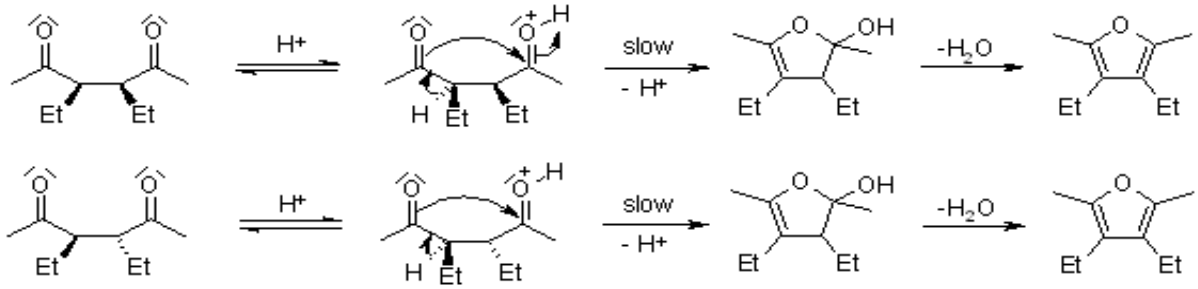
Reaction:



Paal knor synthesis:

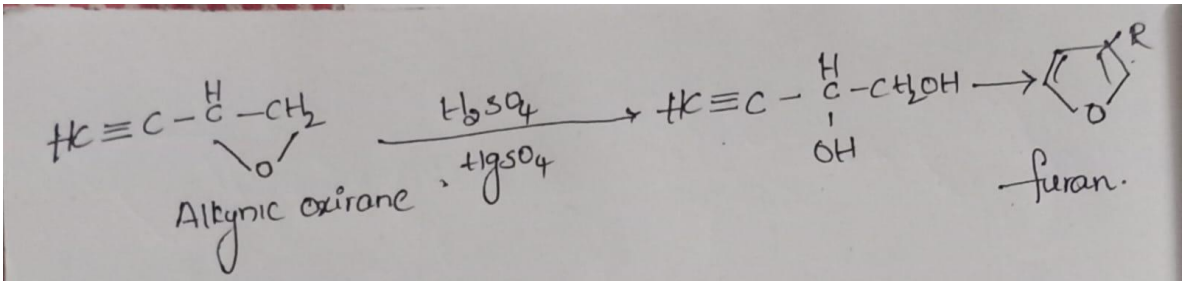
Under the non-aqueous acidic conditions 1,4-diketones undergoes cyclization followed by dehydratuion gives furan.

Reaction:

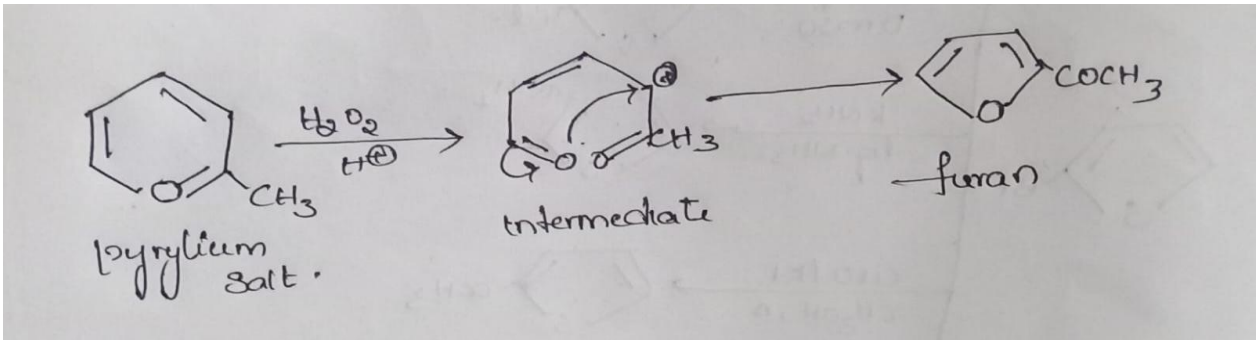


II. Allenyl ketone undergoes cyclaization in presence of silver nitrate in CH3CN to gives furan.

Ring expansion: Alkynic oxirans are treated with sulfuric acid and mercury sulfate it undergoes ring expansion to produce furan.



From ring contraction: contraction of oxidative ring of pyrylium salts with aqueous hydrogen peroxide and perchloric acid leads to the formation of 2-acyl furan.



CHEMICAL REACTIONS:

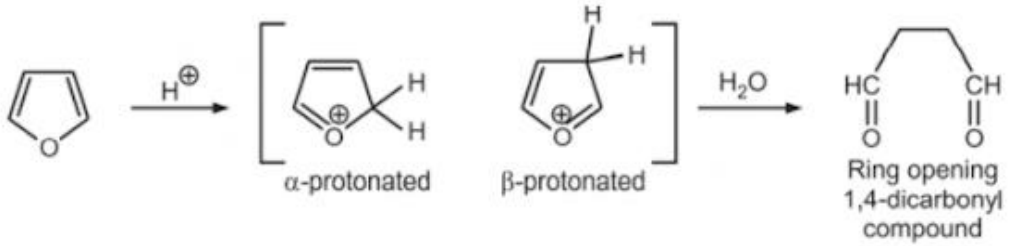
It prefers electrophilic substitution reaction.

-it behaves chemically as a typical diene and exhibits greater reactivity toward the addition reaction.

PROTONATION:

While electron withdrawing furan substitutions are more stable towards the acids.

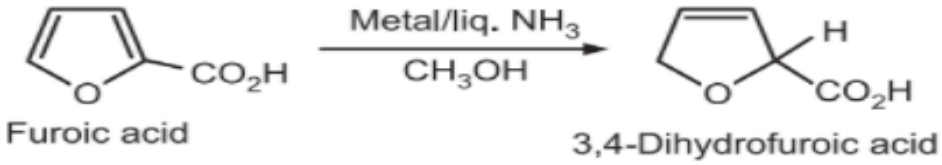
-presence of electron releasing substituents on furan leads to generation of reactive electrophiles during protonation which activate polymerization and the reaction which leads to ring opening



MERCURATION:

Furan undergoes mercuriation readily.

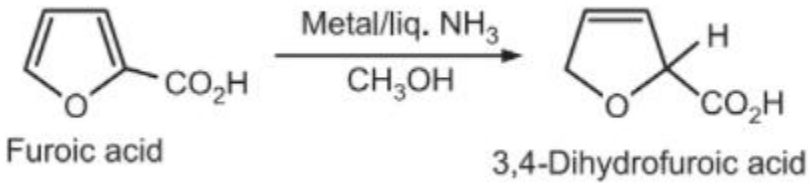
-it is an essay process for furan.



REDUCTION:

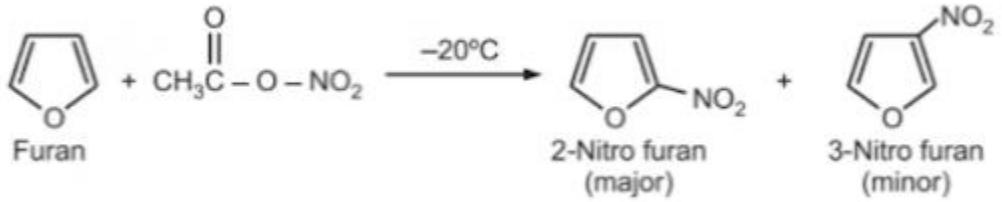
Simple furan is difficult to reduce a tetrahydro furan without ring opening, furoic acid can be reduced to de-hydro derivatives.

- it is possible to decompose furoic acid into dihydro furans

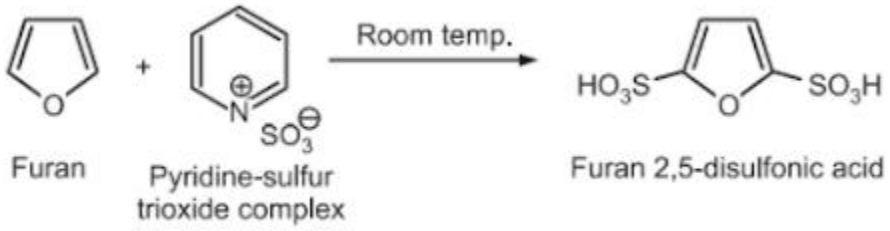


ELECTROPHILLIC SUBSTITUTION:

Nitration: furan is nitrated with acetyl nitrate which is mild nitrating agent at low temperature.

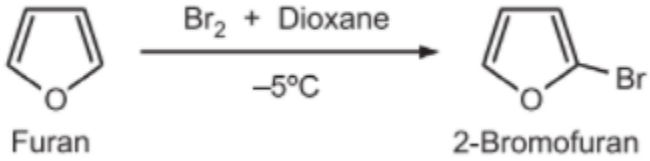


Sulfonation: furan is sulfonated with the complex of sulfur trioxide and pyridine at room temperature is give 2,5- disubstituted furan.



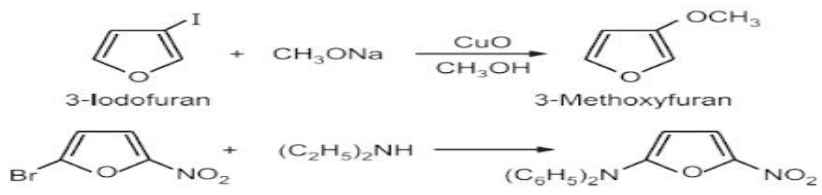
Halogenation: the high reactivity of furan with chlorine and bromine at room temperature results in poly halogenated product.

-milder conditions are required to yield mono chloro or mono bromo furans.

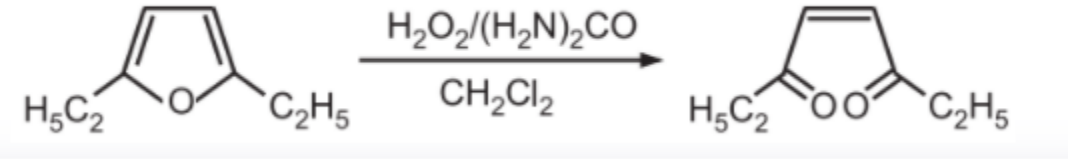


Reaction with nucleophilic reagents: the presence of electron withdrawing substituents i.e., nitro carboxy or carbo alkyl in halofurans further increase their reactivity.

-halofurans shows more reactivity towards nucleophilic than simple furan.

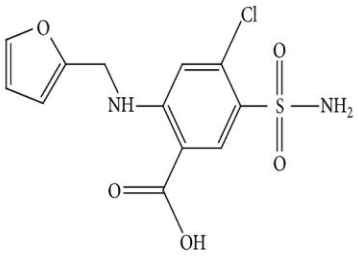


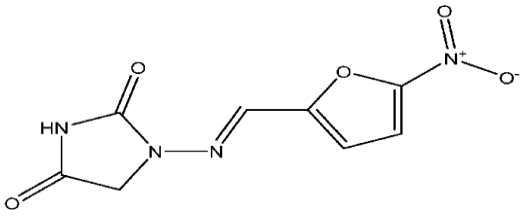
Oxidation: when furan is treated with sodium hypochlorite or hydrogen peroxide it results in the ring opening.



Applications of drug synthesis:

Furan is an important scaffold present in the drugs like ranitidine, nitro furazone, ascorbic acid and many natural terpinoids.





furosemide nitrofurantoin

-it is used to treat amoeba infections.

-it is used for treating urinary tract infections caused by several types of bacteria.

THIOPHENE

-The compound which containing a five membered ring made up of one sulfur as a hetero atom.

Physical properties:

Colour - colourless

Boiling point - 84®c

Solubility - insoluble in water but soluble in

organic solvents

Melting point - -38®c

Odour - benzene like odour.

-it is isolated as an impurity in commercial benzene in 1882 by victor meyer.

-it is π execessive aromatic heterocycle.

Chemical synthesis

Paal-knorr synthesis:

In this synthesis procedure involves cyclic condensation of 1,4-diketones-

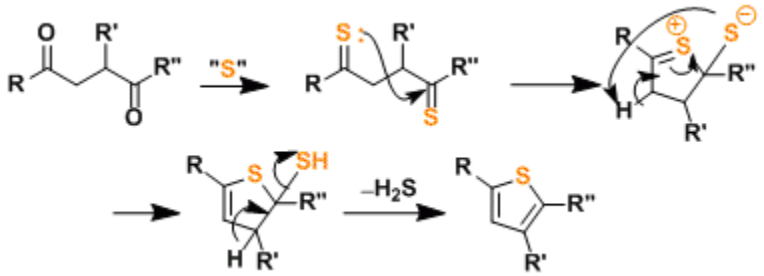
a. with primary amine.

b. with a sulfur source.

c. di hydration of di ketone.

-phosphorus pentasulfide or bis sulfide acts as sulfurizing agent as well as dehydrating agent.

-hydrogen sulfate in the presence of an acid catalyst is also effective.

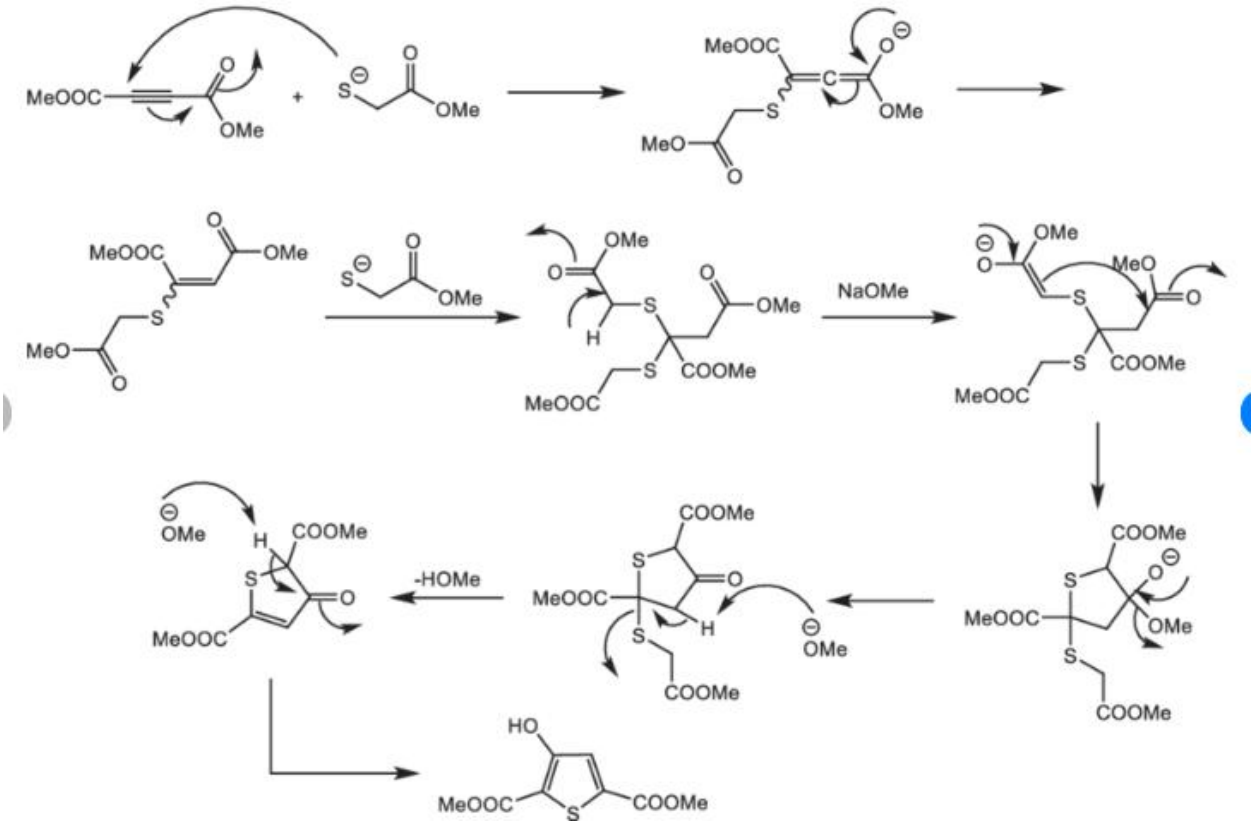


1,4-di carbonyl compounds can be heated with phosphorus penta sulfide i.e a source of sulfur to give thiophene.

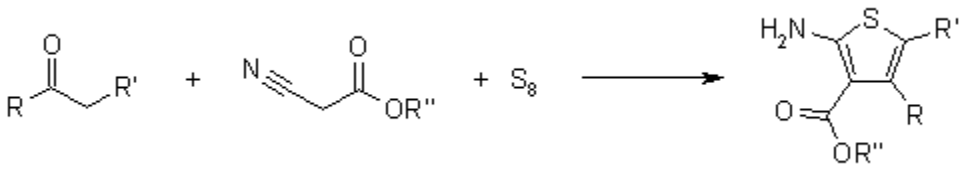
hinsberg synthesis:

condensation between 1,2-dicarbonyl compound and di- ethyl thio-diacetate in the presence of a strong base gives thiophene.

fiesselmann thiophene synthesis: condensation reaction of thioglycolic acid with α, β-acetylnic ester to give 3-hydroxy 2-thiophene carboxylic acid.



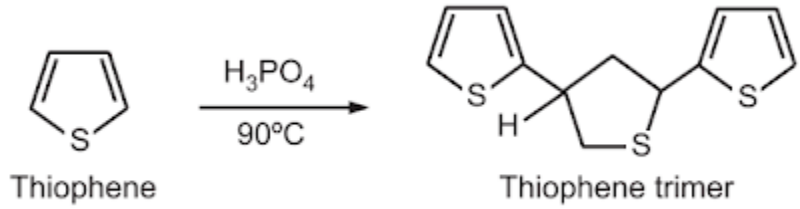
Gewald amino thiophene synthesis: it is base catalysed condessaton of a ketone with a β-keto-nitrile to form olefin, followed by cyclization with elemental sulfur to give 2-aminothiophenes.



Chemical reactions:

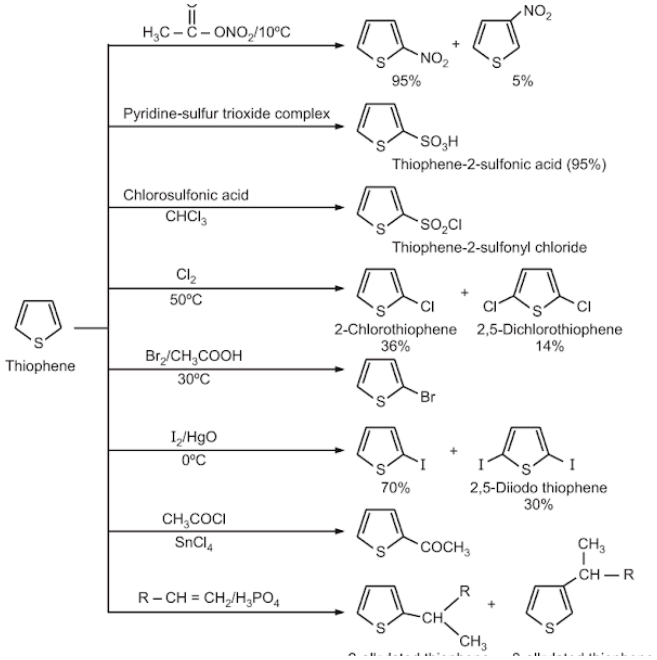
Protonation

Acids have little effects on thiophene. Hot phosphoric acid, for example, produce thiophene trimmer when exposed to very strong acid.



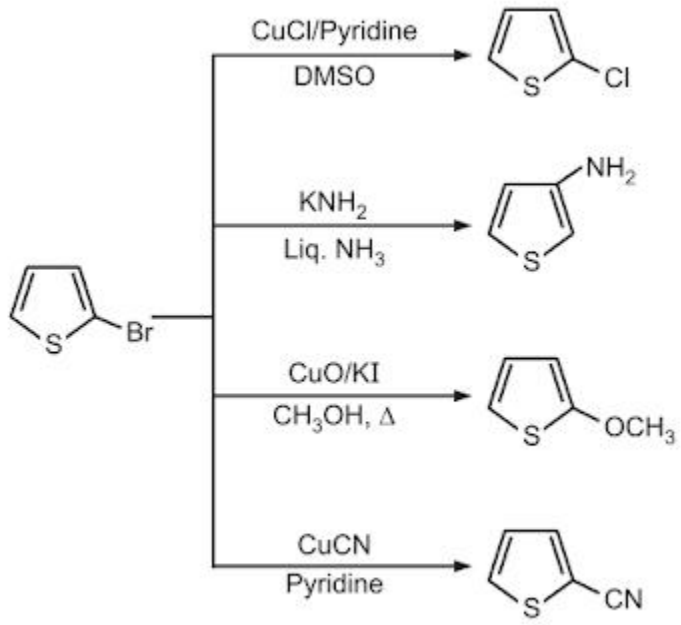
Electrophilic substitution:

The reactivity order for electrophilic substitution reaction is pyrrole>furan>thiophene>benzene. The preffered site of attack in thiophene is C2 position.

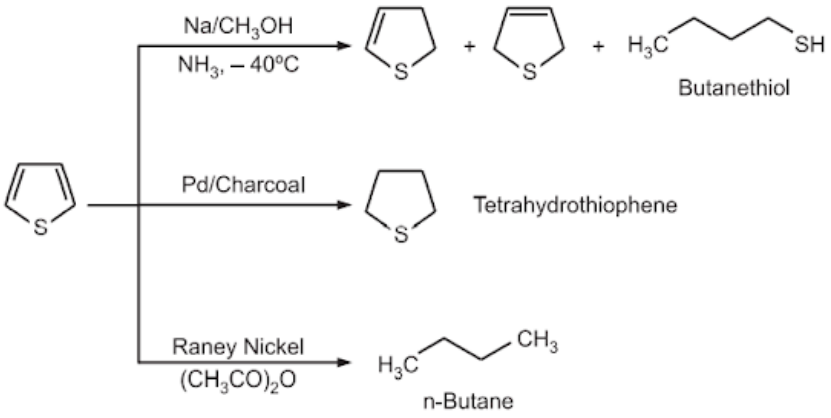


Nucleophilic substitution:

Thiophene substituted with electron withdrawing substituents are much more reactive to the nucleophilic substitution.



Reduction:

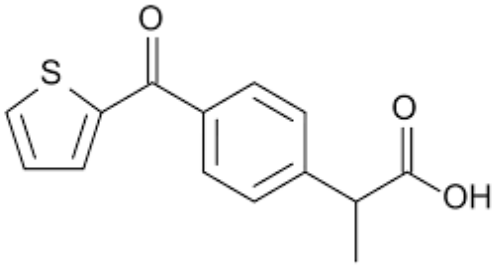


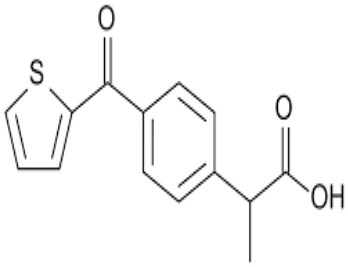
Applications in drug synthesis:

Thiophene derivatives possess remarkable activities like anti-bacterial, anti-inflammatory, anti- anxiety, anti -psychotic, anti-arrhythmic and anti -cancer.

Examples include lomoxicam, pyrantel, raltitrexed, cephalothin, suproprofen,

ticrynafen, clotiazepam, ticlopidine etc.…





Lomoxicam suproprofen

Relative aromaticity of Pyrrole, **Furan and Thiophene**

Furan, Pyrrole and thiophene each consists of a flat ring of four carbon atoms and a hetero atom with a cyclic electron cloud of six delocalized π-electrons. So according to Huckel rule, all these compound shows aromatic character.

All the three compounds have five contributing structure in which there is only one structure in each case which does not involve charge separation. The relative aromaticity of Pyrrole, Thiophene and Furan depends upon the electronegativities of the hetero atoms present in pyrrole, furan and thiophene and it is in the order as follows:

O> N> S

It means oxygen has very less tendency to release or donate its pair of electrons to the aromatic sextet. So number of ionic resonating structure should be least in case of Furan followed by Pyrrole and should be maximum in case of Thiophene. So the order of aromaticity will be

Furan<Pyrrole<Thiophene

All these heterocycles are less aromatic than benzene as all the resonating structures of benzene are uncharged and equally stable and involves no separation of +ve and –ve charges. The resonance energies of these

heterocycles is less than that of benzene. So the aromatic character of these heterocycles relatives to benzene decreases in order as

Benzene>Thiophene>Pyrrole>Furan

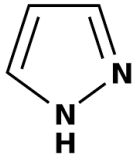
UNIT - 4

SYNTHISIS REACTIONS AND MEDICAL USES OF COMPOUNDS OR DERIVATIVES

Dr.P. MARY GRACE

PYRAZOLE

Pyrazoles are the derivatives of a five-membered heterocyclic ring system called pyrazole. Pyrazole consists of two nitrogen atoms at 1 and 2 positions of the cyclic system.



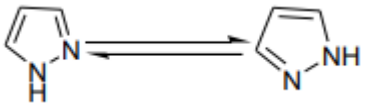
Physical Properties: 1. Pyrazole is a colourless solid.

2. It possesses a pleasant smell.

3. Pyrazole is soluble in water.

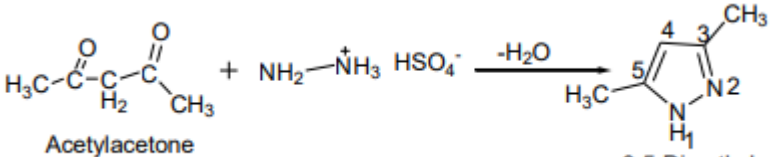
4. Pyrazole exhibits tautomerism.

5. Pyrazole has aromatic properties

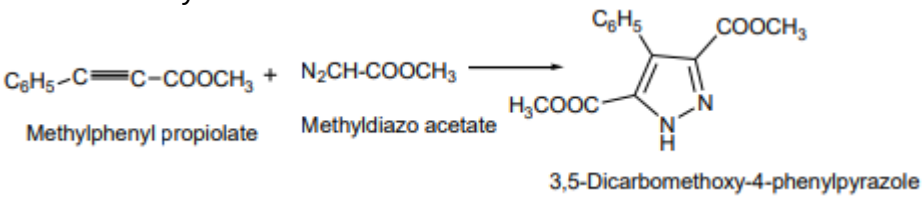


Synthesis

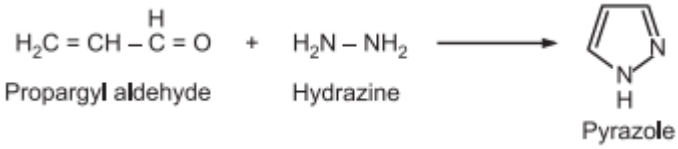
1. From 1,3-dicarbonyl compounds- 1,3-Dicarbonylcompounds react with hydrazine or hydroxylamine and gives pyrazole.



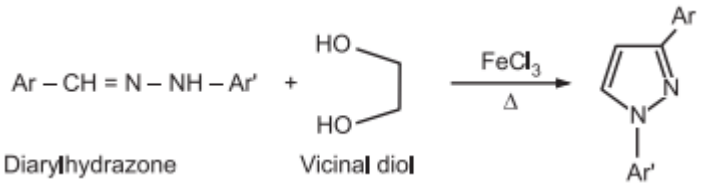
2. From 1,3-di polar compounds- Pyrazole derivatives can also be prepared by adding a diazo compound to an acetylenic derivative.



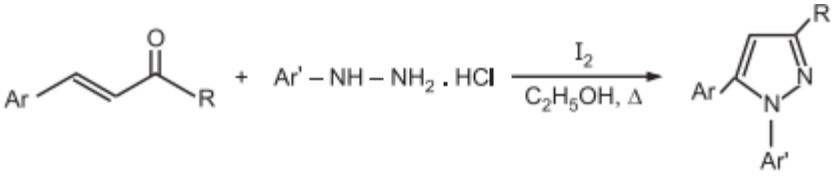
3. Pyrazole itself can be formed by the reaction of hydrazine with propargyl aldehyde.



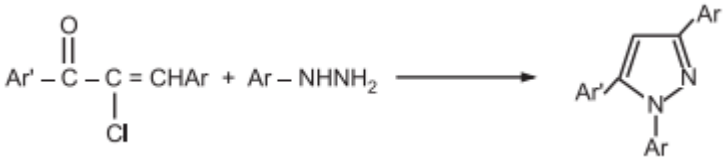
5.An iron catalyzed reaction of di arylhydrazones and vicinal diols give, 1, 3-substituted pyrazoles.



6.An α, β-unsaturated aldehydes/ketones readily react with hydrazine salts in an I2 – mediated reaction to give substituted pyrazole.

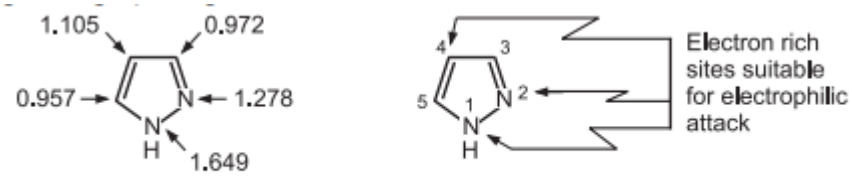


7.An α, β-ethylene carbonyl derivative reacts easily with hydrazine to give substituted pyrazole.



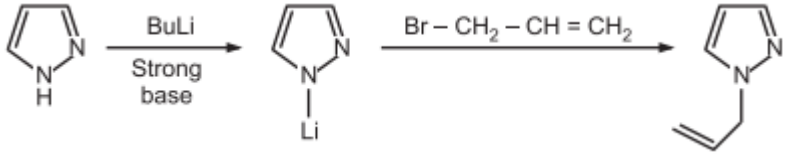
Chemical Reactions

The N-atom at position-1 is unreactive. It can lose its proton (H atom) easily in the presence of the base and offers the site of substitution reaction. The N-atom at position-2 with two electrons is basic and therefore reacts easily with electrophiles. The combined electron richness of both N-atoms reduce the charge density at C3 and C5, making C4 available for electrophilic attack. Deprotonation at C3 can occur in the presence of strong base, leading to ring opening.

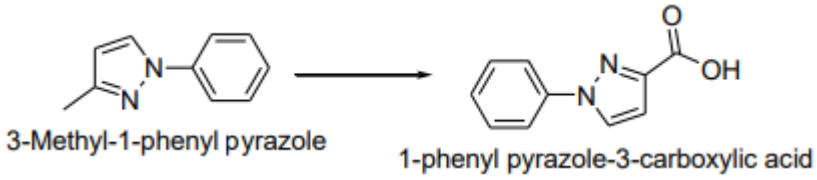


Electron density on Pyrazole

1.The N1 atom easily loses its proton with a strong base. The resulting nucleophile on nitrogen can afterwards react with an electrophile.

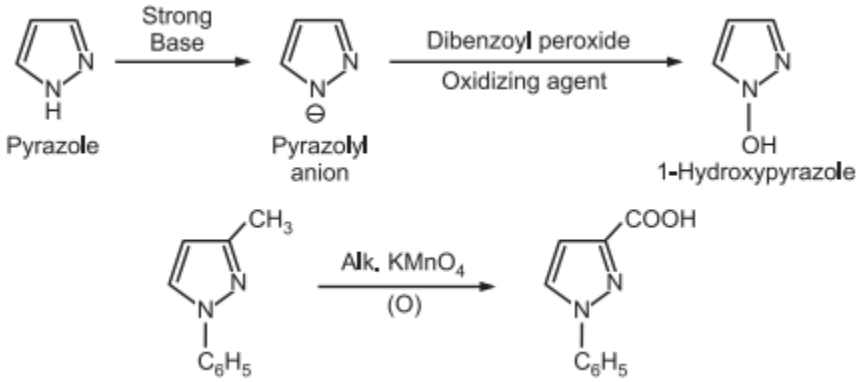


Oxidation: Pyrazole is resistant to oxidizing agents but the side chain may be oxidized to carboxylic acid group in presence of potassium permanganate.



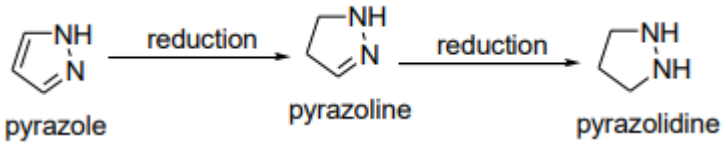
(Or)

Oxidation reaction: The pyrazole ring is remarkably stable to the action of oxidizing agent but the side chain may be oxidized

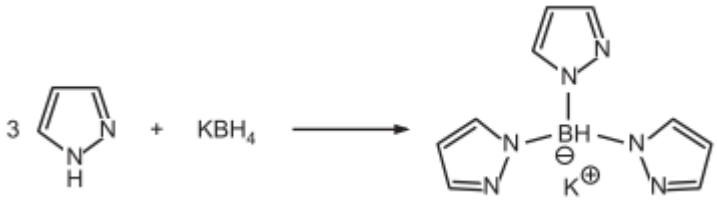


Reduction: Pyrazole ring system can be reduced with molecular hydrogen and metal catalyst.

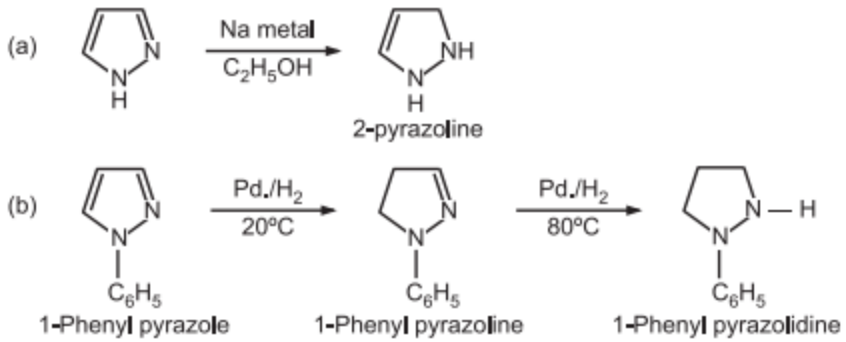
Pyrazolene and pyrazolidine are stronger bases than Pyrazole.



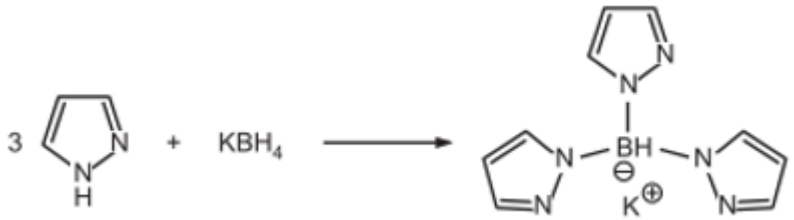
Scorpionate (**tridentate ligand**) **formation**: Pyrazole reacts with potassium borohydride to form a tridentate ligand known as scorpionate.



Reduction reaction: Unsubstituted pyrazole is relatively stable to catalytic and chemical reductive conditions. Pyrazole derivatives may undergo reduction under variety of conditions. e.g.,



Scorpionate (**tridentate ligand**) **formation**: Pyrazole reacts with potassium borohydride to form a tridentate ligand known as scorpionate.



Applications in Drug Synthesis

Pyrazole derivatives are used for their analgesic, antipyretic, anti-inflammatory (e.g., antipyrine, phenylbutazone, celecoxib), antibacterial, tranquilizing, anticancer and antidiabetic activities.

Imidazole

Imidazole are the derivatives of imidazole. Imidazole is a five-membered heterocyclic compound possessing of two nitrogen atoms at 1 and 3 positions. Imidazole is isomeric with Pyrazole and occurs in purine nucleus and in histidine.

Physical properties:

• Imidazole is colorless liquid

• Boiling point is 256 °C - High boiling point among all other five membered heterocyclic compounds

• Shows that hydrogen bonding exists in imidazole ring.

• More basic (pka 7.2) than pyridine (pka5.2).

Chemistry of Imidazole

• Imidazole exists in tautomeric forms, either of the nitrogen can bear the hydrogen atom and 2 nitrogen become indistinguishable

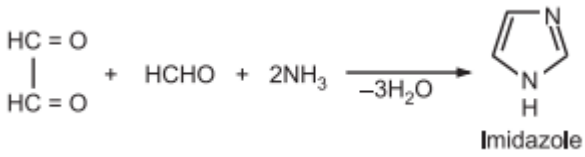
• Numbering becomes rather complex for mono substitution

• For example, 4-methylimidazole is identical with 5 methylimidazole and depending on the position of imino hydrogen

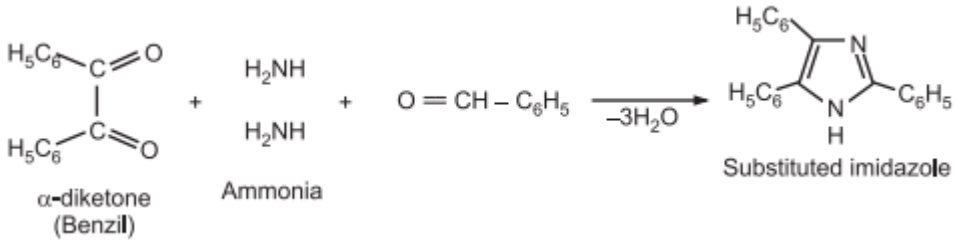
• Such compound is designated as 4(5)-methyl imidazole

Chemical Synthesis

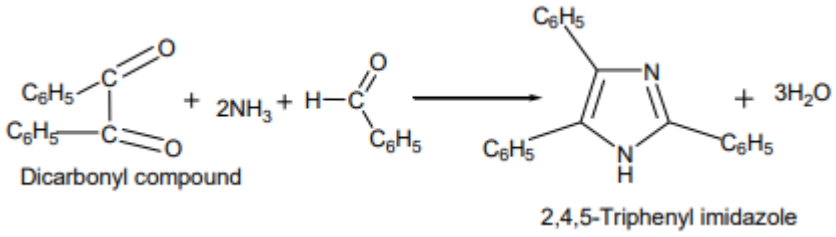
(i) **Debus Method:** Glyoxal, formaldehyde and ammonia condensed to form imidazole (glyoxaline) in Debus Method reported in 1858. It provides 2-monosubstituted and 2, (3, 4 homo) trisubstituted imidazoles



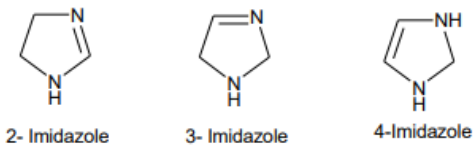
(ii) **Radiszewski synthesis:** It consists of condensing a glyoxal (e.g., benzil), an aldehyde (e.g., benzaldehyde) in the presence of ammonia. Formamide may be used in place of ammonia.



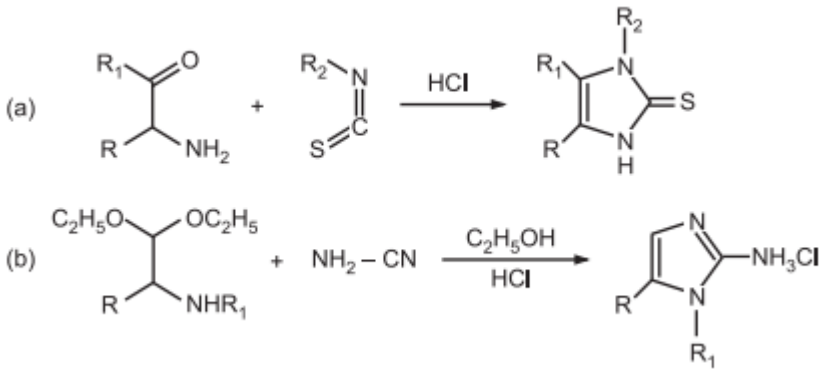
From dicarbonyl compounds: Imidazoles can be prepared by condensing a dicarbonyl compound with an aldehyde in presence of ammonia.



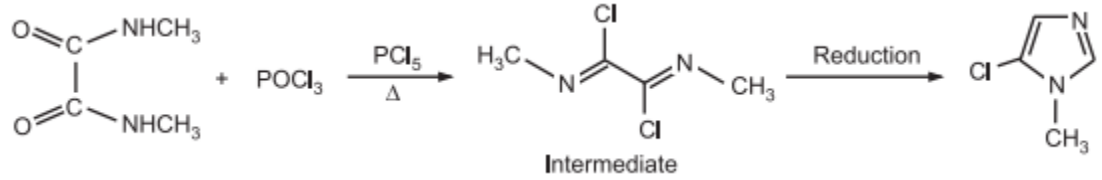
By dehydrogenation of Imidazolines: Imidazolines are the dihydrogenated derivatives of Imidazoles.These Imidazolines can be readily dehydrogenated to imidazoles in presence of sulphur.



(iii) Marckwald synthesis: It is the reaction between α-aminoketones with cyanates, thiocyanates or isothiocyanates producing 3 H-imidazoline-2-thiones (2-mercaptoimidazoles). The latter can be readily converted to imidazole by dehydrogenation.



(iv) Wallach Synthesis: The reaction of N, N'-disubstituted oxamide with phosphorus oxychloride gives chlorine containing intermediate which upon reduction with hydriodic acids, gets converted to 1-substituted imidazole. It provides 1, 2-disubstituted chloroimidazoles.

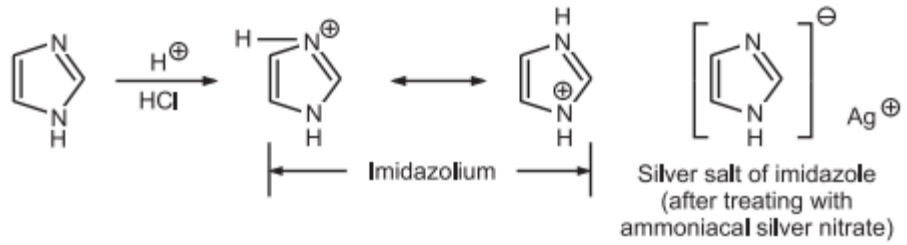


Chemical Reactions

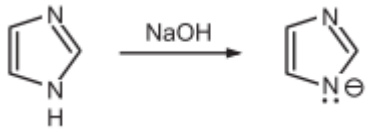
Imidazole is a base and an excellent nucleophile. It easily undergo electrophilic (alkylating, acylating) substitution reactions at the –NH nitrogen. However, the C4 and C5 atoms of imidazole are also susceptible for electrophilic attacks. Due to the resonance structures, the position most prone to nucleophilic attack is C-2.

Imidazole ring contains N1 atom (pyrrole like nitrogen) and N3 atom (pyridine like nitrogen). The pyrrole like nitrogen is acidic while the pyridine like nitrogen is basic and nucleophile. From the structure, it appears that both N-atoms have highest electron density followed by C4 and C5 atoms. The C2-atom is sandwitched between more electronegative Natoms and hence most electron deficient. Hence the C2 atom is most prone to the nucleophilic attack. While rest of the atoms (C4, C5, N1 and N3) are susceptible for electrophilic attack.

(i) Reaction with Acids: Imidazole forms stable crystalline salts with strong acids by protonation of N3-atom.

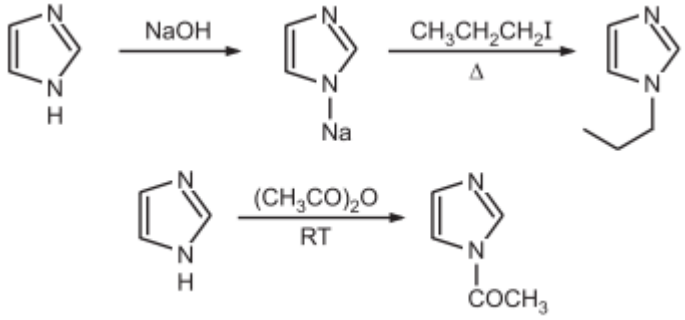


On the other side, imidozle can act as an acid and the proton on N1 atom can be removed by a strong base. Thus imidazole can act as acid and base. It is more acidic than pyrrole and more basic than pyridine.

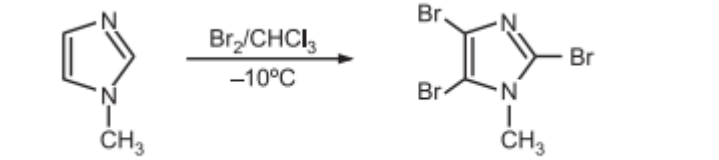


(ii) Electrophilic Substitution reaction:

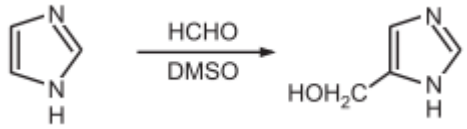
(a) N-alkylation and N-acylation:



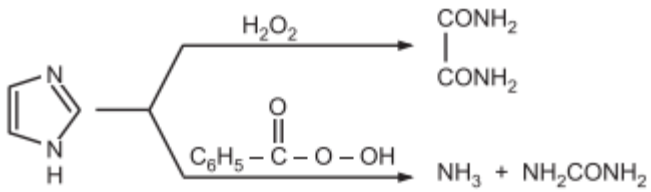
(b) Halogention:



Reaction with aldehydes and ketones: N-unsubstituted imidazole undergoes hydroxymethylation at C4-position when treated with HCHO (formaldehyde) in the presence of DMSO.



Action of oxidizing agents: Imidazole is stable to auto oxidation and to the action of chromic acid but is attacked by hydrogen peroxide or perbenzoic acid.

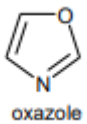


Applications in Drug Synthesis

Imidazole is a parent skeleton in amino acid, histidine and an autacoid, histamine. Important drugs containing imidazole ring include ketoconazole (antifungal), midazolam (sedative) and metronidazole (antibiotics). It is a main skeleton present in biotin (vitamin), nucleic acid and various alkaloids. Losartan (angiotensin receptor blocker), Eprosartan (angiotensin receptor blocker), azomycin (antibioitic) and clotrimazole (anticancer) also contain imidazole nucleus.

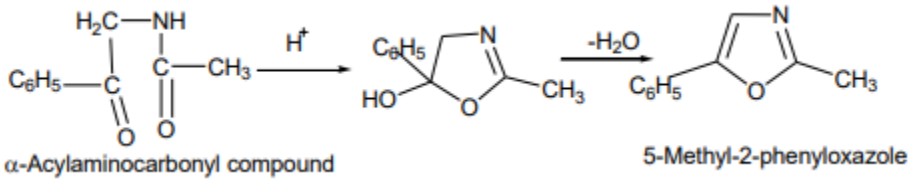
oxazole

Oxazole is a 1, 3-azole having an oxygen atom and a pyridine type nitrogen atom at the 3-position in a five membered ring. The scientist Hantzsch was first to introduce it in 1887. Oxazole is a liquid with a boiling point of 69°C. Unlike imidazole and thiazole, the oxazole is not naturally occurring. Oxazoles are weakly basic in nature. The lone pair of electrons on the pyridine type nitrogen is not involved in maintaining aromaticity but it is available for protonation. Thus, the lone pair of electrons imparts basicity to the molecule.


oxazole

Synthesis:-

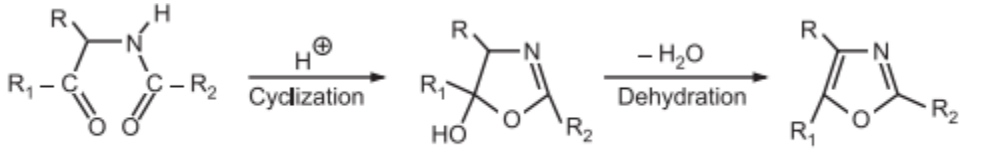
1. **From α-acylamino carbonyl compound:** Oxazole is prepared by refluxing αacylamino carbonyl compound with acid or phosphorous pentaoxide. This is the most common method to prepare oxazoles which involve cyclization and dehydration in presence of phosphorous pentaoxide or strong mineral acid.



α-Acylaminocarbonyl compound

5-Methyl-2-phenyloxazole

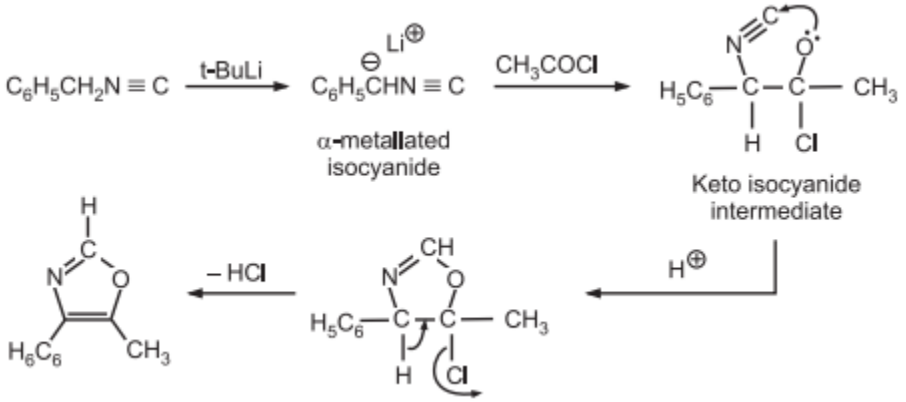
2. **Robinson-Gabriel Synthesis:** In this method, an α-acylamino ketone undergoes cyclization and dehydration to give 2, 5 –diaryloxazoles.



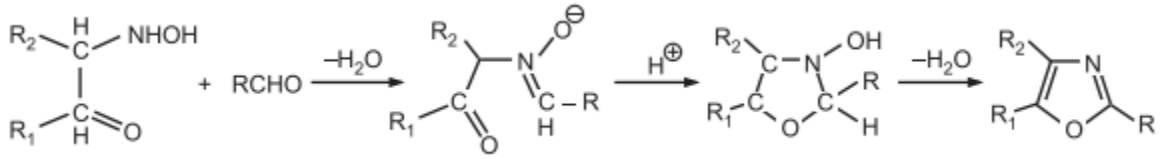
Substituted oxazole

Polyphosphoric acid, phosgene or anhydrous hydrogen fluoride are used to induce cyclization while H2SO4, PCl3, POCl3 or SOCl2 may be used as dehydrating agent in this reaction

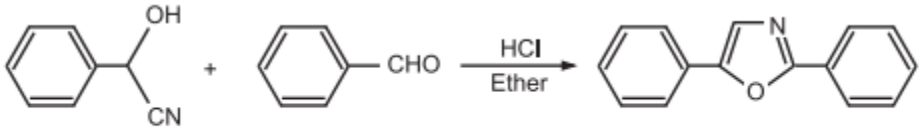
3. **From isocyanides with acid chlorides:** Isocyanides when treated with t-butyllithium gives α - metallated isocyanide. The latter when reacted with carboxylic acid derivatives (e.g., acid chloride, ester or amide) gives oxazole.



4. **Reaction of α-Hydroxyamino ketones with aldehyde:** The α-hydroxyamino ketone reacts with aldehyde in the presence of sulfuric acid and acetic anhydride to give oxazole. The C2 – atom in oxazole comes from the aldehyde.

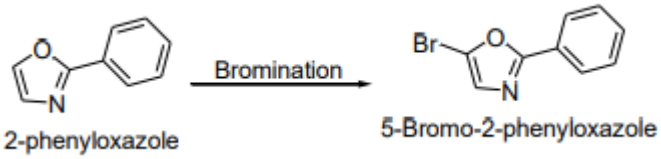


5. **Fischer Oxazole synthesis:** This synthesis was discovered by Emil Fischer in 1896. In this method, a cyanohydrin reacts with an aldehyde in the presence of anhydrous HCl to give substituted oxazole.

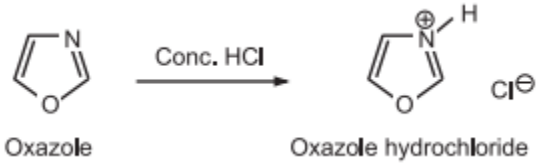


Chemical Reactions:

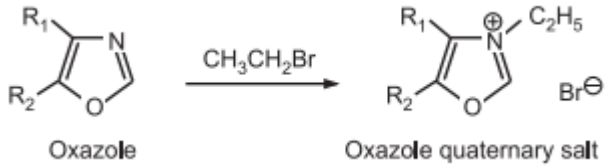
- **Electrophilic Substitution:** Oxazole undergoes electrophilic aromatic substitution reactions. The preferred attack is at position-5. These reactions occur more readily when the oxazole ring is activated by electron-donating group. Oxazole is more reactive with electrophiles than thiazole but less than imidazole.



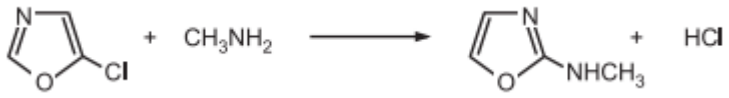
- **Protonation (Basicity):** Oxazole is a weak base. It reacts with acids to form unstable salts (hydrochloride/picrate salts).



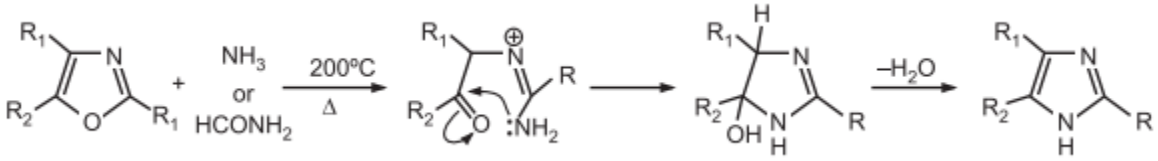
- **N-alkylation:** Oxazoles form quaternary salts, N-alkyloxazolium salts with alkylating agents.



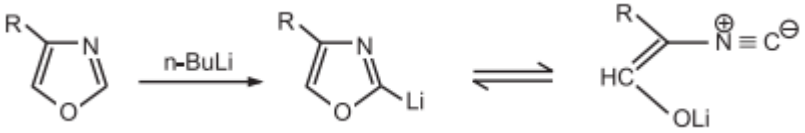
- Nucleophilic substitution reactions: Oxazole with unsubstituted 2-position get easily deprotonated at C2-position by a strong base. Otherwise oxazole rarely undergo nucelophilic substitution reactions. Electron withdrawing substituent at C4 facilitates nucleophilic attack at most electron deficient C2-position. For example, halogen atom at C2 of oxazole ring is easily replaced by nucleophile.



In most of the cases, nucleophile attack on oxazole ring rather result in the cleavage of oxazole ring than actual nucleophilic substitution reactions. For example, oxazoles get transformed into imidazoles via ring cleavage when treated with ammonia /formamide (nucleophile)

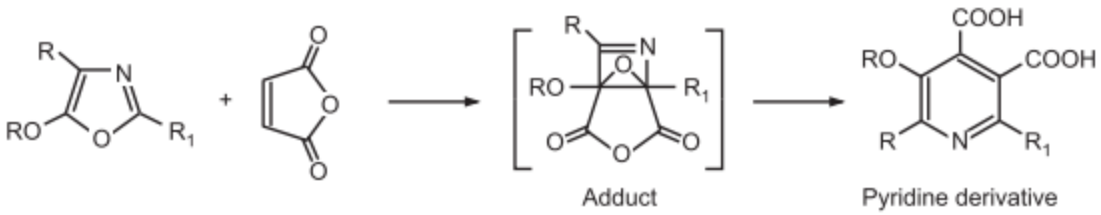


- **Metallation:** Lithium preferentially attack the most electron deficient C2-atom. The resulting 2-lithio-oxazoles are unstable and get cleaved to the open chain isocyanides

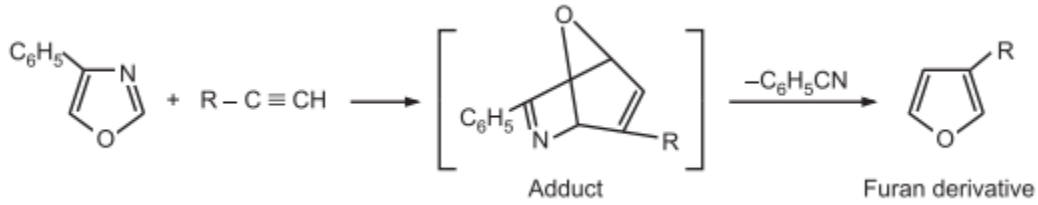


Cycloaddition reactions: Oxazoles easily undergo cycloaddition across 2, 5-positions. The presence of electron donating substituents on the oxazole ring facilitates the reactions with dienophiles. The adducts so obtained serve as important precursors for substituted pyridine or furan derivatives. Cycloadditions have been reported with alkene, alkyne and benzyne dienophiles.

- Alkene dienophile:



- Alkyne dienophile:



Applications in Drug Synthesis

Oxazole is one of the important components in penicillin (antibiotic) structure. Oxazole family includes oxazoles, isoxazoles, oxazolines, oxadiazoles, oxazolidones, benzoxazoles, etc. Oxazoles display versatile biological activities including antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, analgesic, antidiabetic, etc.

THIAZOLE:

Thiazoles are five membered heterocyclic compounds consisting of nitrogen and sulphur heteroatoms. The numbering in thiazole starts from the sulphur atom.

Thiazole

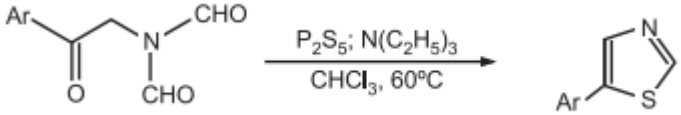
Physical Properties:

1. Thiazole is a colourless liquid.
2. It has the characteristic odour like pyridine and is miscible with water.
3. It is weakly basic and behaves as a tertiary base.

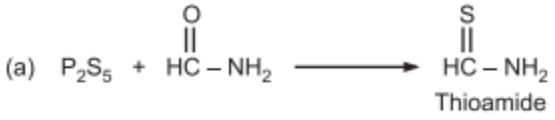
It is a pale yellow liquid having a boiling point of 116-118°C. It is an aromatic compound having odor similar to pyridine. It is a weaker base than pyridine. Thiazole was first described by Hantzsch and Weber in 1887. The partially reduced thiazoles are called thiazolines and completely reduced thiazole is called thiazolidine.

Chemical Synthesis

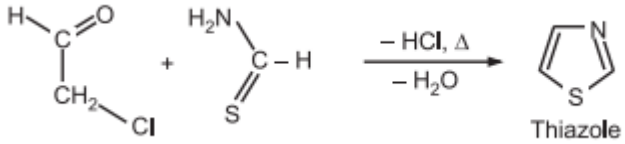
(i) Treatment of N, N-diformylaminomethyl aryl ketones with phosphorus pentasulfide and triethylamine in chloroform gives 5-arylthiazoles.



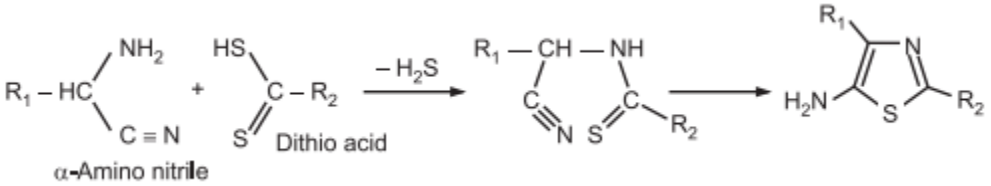
(ii) **Hantzsch's Synthesis**: It is a condensation reaction between α - halo carbonyl compound with an appropriate thiomide or thiourea. The thioamide can be obtained by reacting phosphorus pentasulfide and formamide at room temperature.



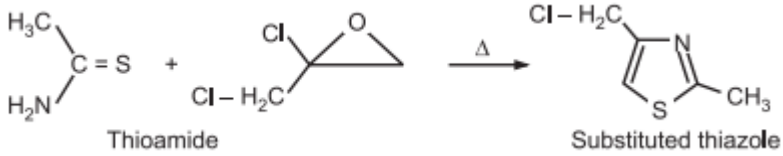
Chloroacetaldehyde on condensation with thioformamide yields unsubstituted thiazole.



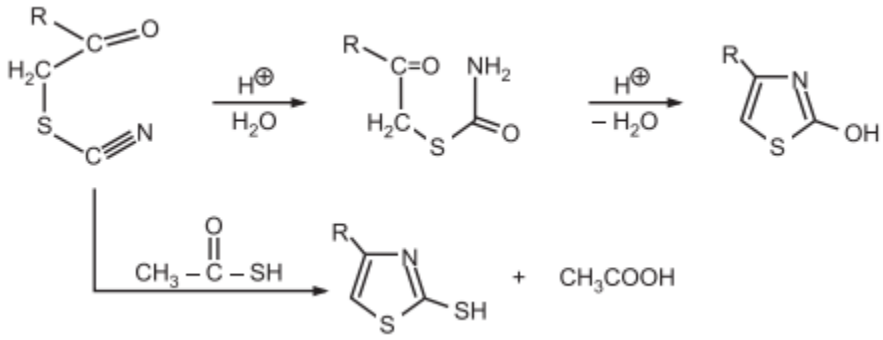
(iii) **Cook-Heilborn's synthesis**: Under mild conditions, α-aminonitriles are treated with dithioacids or esters, carbon disulfide, carbon oxysulfide or isothiocyanates to yield 5-aminothiazoles.



(iv) **From thioamides**: Thioamide is reacted with substituted 2-chloroxiranes to give thiazole derivatives



(v) **Tcherniac's Synthesis**: The 2-substituted thiazoles are obtained either from acidic hydrolysis of α-thiocyano ketones or its treatment with sulfur compounds.

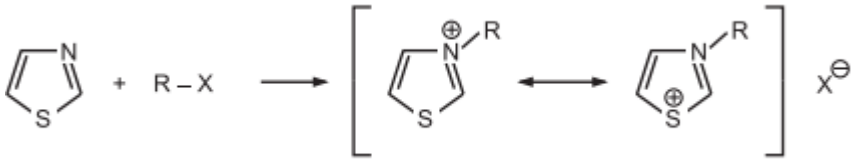


Thiazole contains thiophene type sulfer atom at the position-1 and pyridine type nitrogen at the position-3. It's chemical reactivity is similar to other 1, 3-azoels (i.e., imidazole and oxazole).

Protonation: Thiazoles get easily protonated at N3 position due to lone pair of electrons available with nitrogen. In thiazole ring, the position-2 is most electron deficient, position-4 almost neutral and position-5 is slightly electron rich.

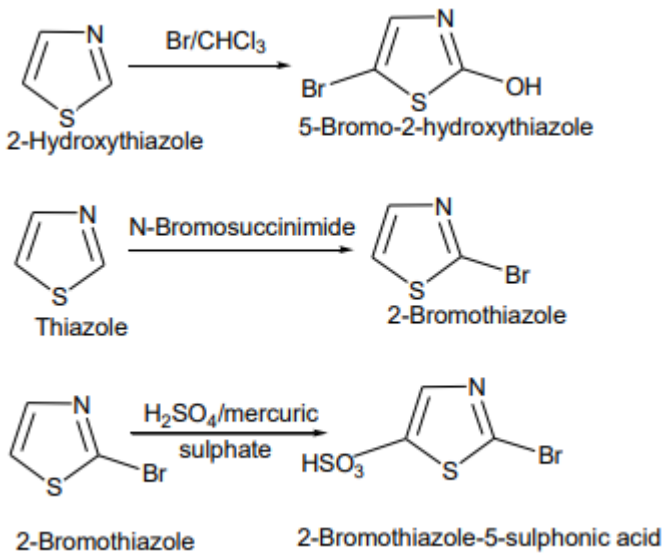
Deprotonation at C2: The organolithium compounds cause removal of proton at C2. The resulting nucteophilic site at C2 then reacts with a range of electrophiles such as aldehydes, akylhalides and ketones

N – Alkylation: Thiazoles react with alkyl halides to form thiazolium cations. This cation is resonance stabilized with the positive charge residing mostly on the sulfur atom



Electrophilic substitution reactions:

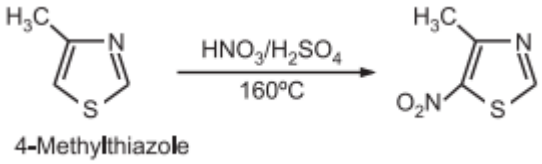
Thiazole undergoes electrophilic substitution reactions. The reactivity of thiazole is intermediate to pyridine and thiophene. It is resistant to substitution reactions but if an electron donating group is present at positions 2, thiazole readily undergoes the following substitution reactions.



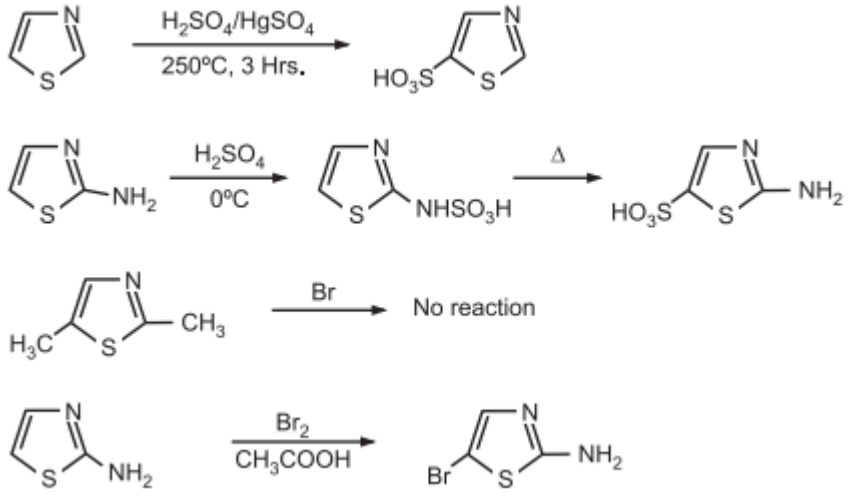
(a) At N3-atom: The loan pair of electrons on N3-atom is less reactive. Hence, N-alkylation occurs at slower rate in thiazole.

(b) Nitration: In acidic media, the attack usually takes place through the formation of thiazolium (N – protonated) cation. The positive charge on the protonated nitrogen of the thiazolium ion deactivates the ring considerably towards electrophilic attack. Nitration of thiazole is rather difficult and is not nitrated even in oleum at 160°C.

However, 4-methylthiazole is nitrated at position – 5 under relatively mild conditions.



Sulphonation and halogenation: In thiazole ring, C5 is the preferred position of attack for all electrophiles. It the C5 position is already substituted, electrophile does not attack on other positions. The presence of electron-donating substituent at C2-position makes easy the attack of electrophile at C5-position even under mild conditions. e.g.,



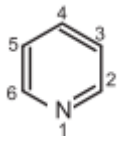
Applications in Drug Synthesis

Vitamin thiamine (B1) contains both pyrimidine and thiazole ring systems. The ring is also present in meloxicam (non-steroidal anit-inflammatory). It is also an important scaffold in antibacterial, antifungal, antidiabetic, anticancer and anticonvulsant drug design. These include nitazoxanide (anti-viral), thiabendazole, (anthelmintic), fanetizole (immunomodulator), fentiazac (NSAID), sulfathiazole (antibacterial), nizatidine (H2 – receptor blocker), thiamethoxam (systemic insecticide), etc Penicillins contain reduced thiazole ring (thiaozolidine)

Pyridine

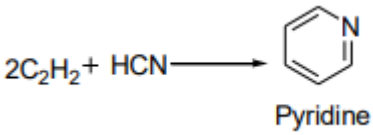
It is a colorless liquid with a boiling point of 115°C. It has a fishy odor. It was first obtained from bone oil in 1849 and coal tar. Pyridine is mainly used as a solvent and as a base. The lone pair

on N-atom is located in a sp2 hybridized orbital and is not involved to maintain aromaticity. The lone pair of electrons is available for protonation and explains the basicity of pyridine. Electron donating substituent at 2 – and 6 – positions enhances the basicity.

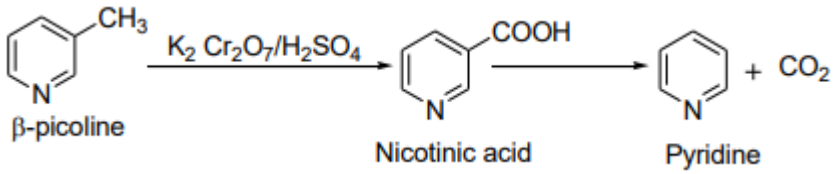


Preparation:- 1. Pyridine is present in light oil fraction of coal tar distillation. The light oil fraction is treated with dilute sulphuric acid. This dissolves basic substances including pyridine. The acid layer is isolated, neutralised and fractionated several times to get pure pyridine.

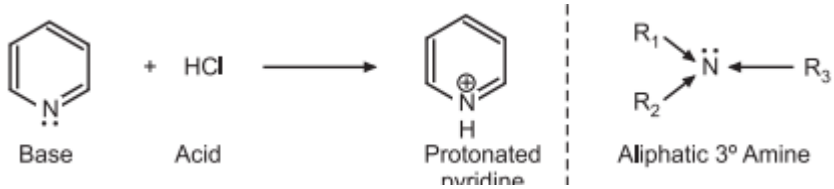
2. Pyridine is prepared by passing a mixture of acetylene and HCN through a red hot tube



3.From picoline: On oxidation with potassium dichromate and sulphuric acid β-picoline changes into nicotinic acid. This on decarboxylation with calcium oxide gives rise to pyridine.



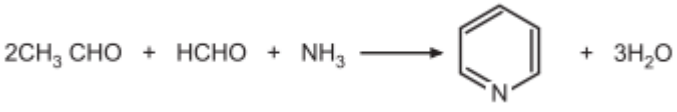
Pyridine is considerably more basic than pyrrole and less basic than aliphatic 3° amine.



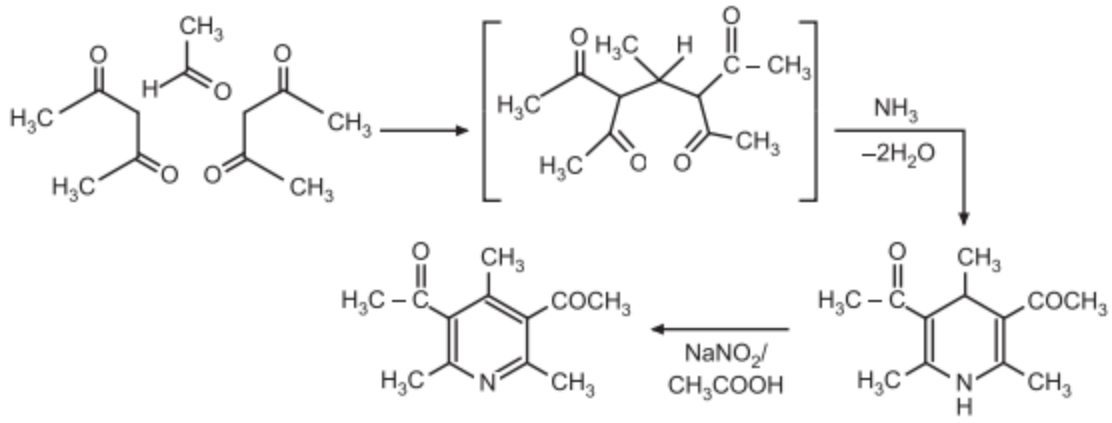
The alkyl group is an electron donating group. In aliphatic 3° amine, all the three alkyl groups donate electrons to the N-atom, thereby making lone pair of electrons on N-atom even more easily available for protonation. Hence, pyridine is less basic than aliphatic 3° amine.

Chemical Synthesis

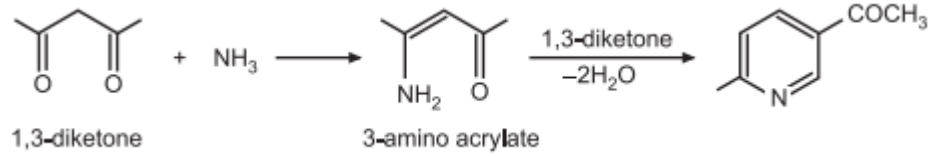
Pyridine is synthesized by reacting acetaldehyde with formaldehyde and ammonia.



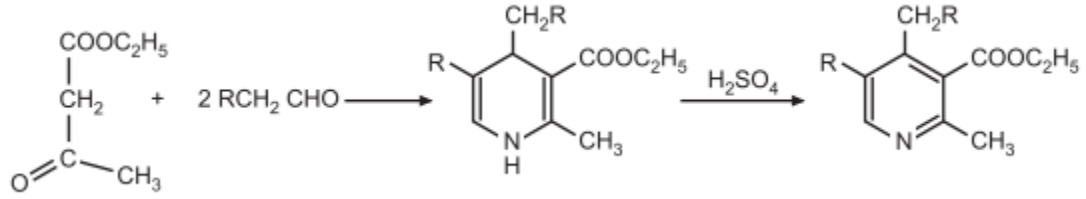
Hantzsch synthesis: It is a condensation reaction between an aldehyde, two equivalents of 1, 3-dicarbonyl compound and ammonia.



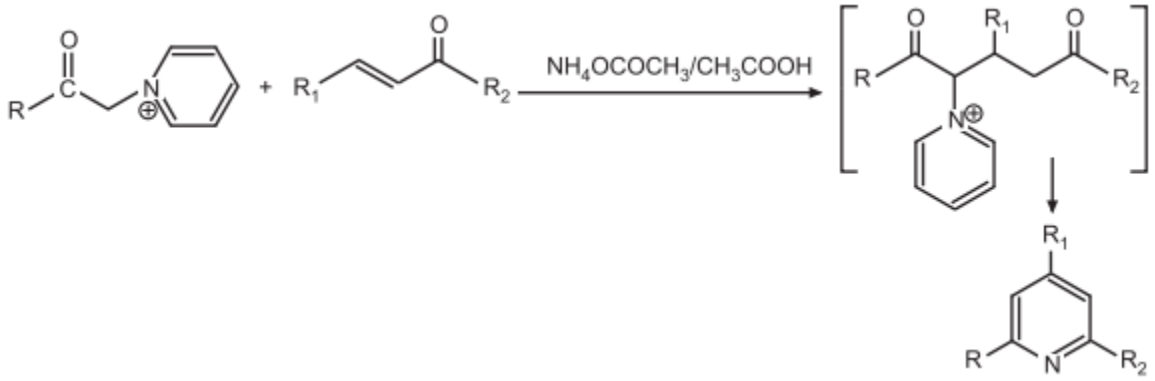
From 1,3-dicarbonyl compound and 3-aminoacrylate: Unsymmetrically substituted pyridine can be synthesized by reaction between a 1,3-dicarbonyl compound with 3-aminoacrylate.



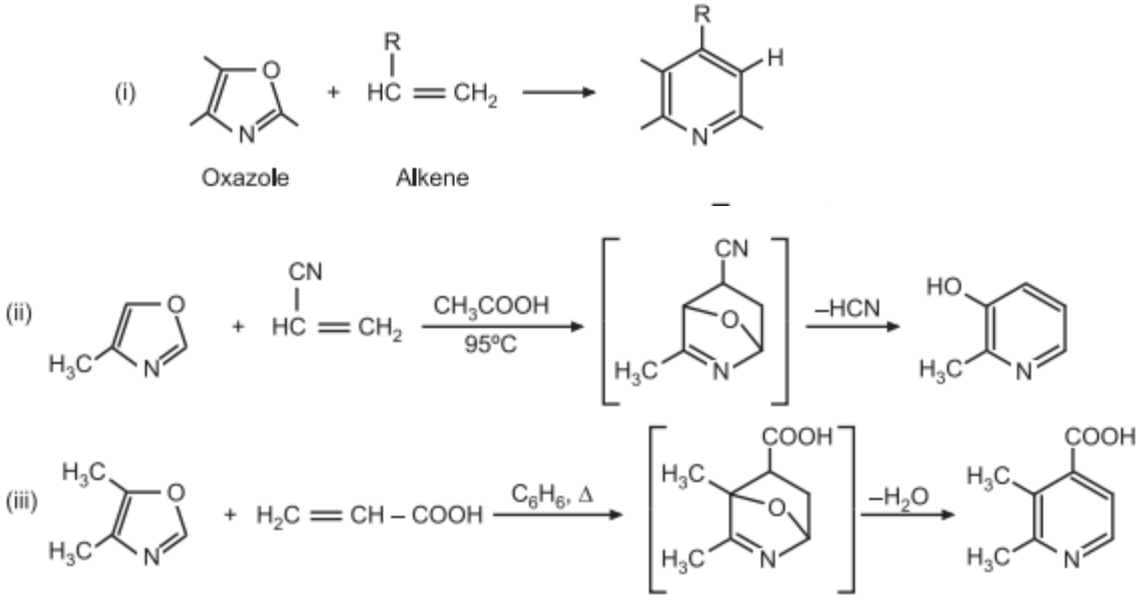
Guareschi Thorpe Synthesis: Two molecules of aldehydes condense with the keto ester to give substituted pyridine.



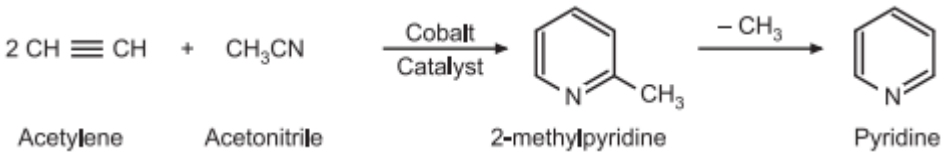
Krohnke pyridine synthesis: The α-pyridinium methyl ketone salts react with α, β-unsaturated carbonyl compounds to give 2, 4, 6-trisubstituted pyridines.



Cycloaddition reaction: Various electrocyclic additions have been used to give pyridines as the final products.

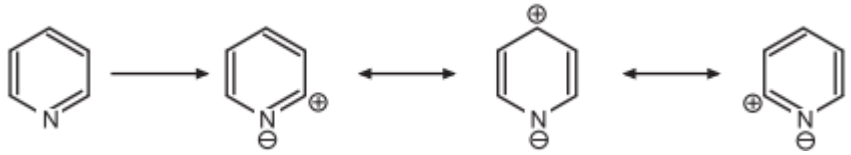


Bonnemann Cyclization: It involves trimerization of one part of a nitrile molecule and two parts of acetylene either by heat or by light.



Chemical Reactions

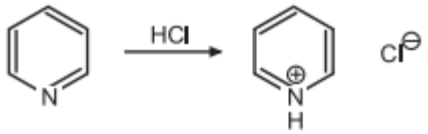
The electronegative nitrogen in the pyridine ring makes the pyridine molecule relatively electron deficient. Hence unlike benzene.



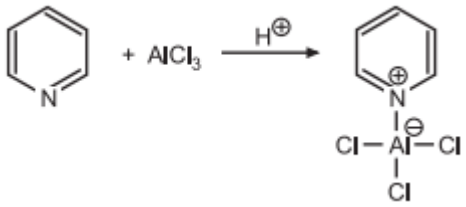
(i) Pyridine does not undergo electrophilic aromatic substitution readily.
(ii) Pyridine is more prone to nucleophilic substitution at positions 2 and 4 and metalation of the ring by strong organometallic bases, and
(iii) Like tertiary amine, pyridine undergoes N – protonation and undergoes oxidation to form N-oxide.

(a) N-Protonation: The lone pair of electrons on the nitrogen atom in pyridine is available for extra bonding. When a pyridine reacts with acids, metallic ions or acyl, sulfonyl, anhydrides, it forms quaternary salts.

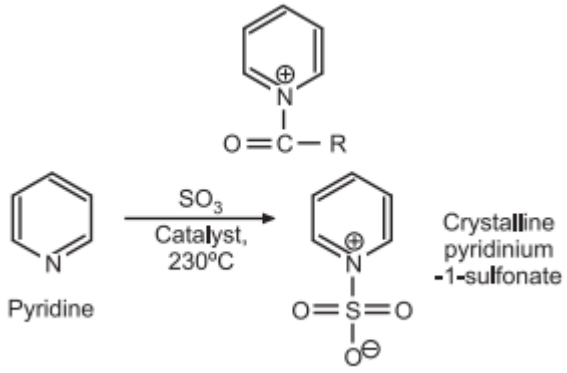
Pyridines form crystalline, hygroscopic salts with most protic acids.



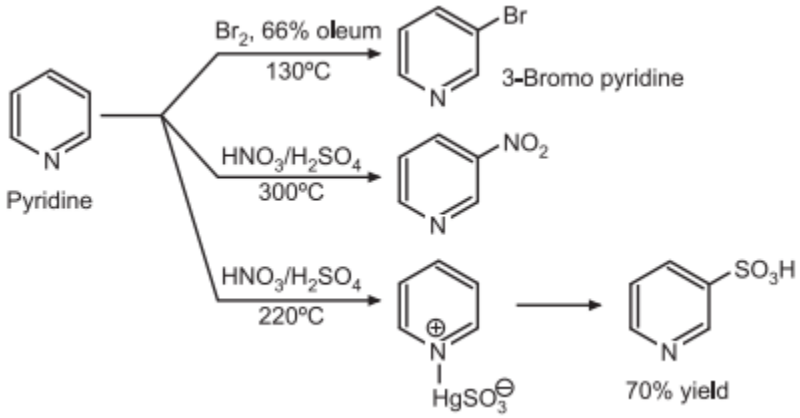
Metallic ions such as aluminium, boron, berrylium, etc. form complex with basic pyridine.



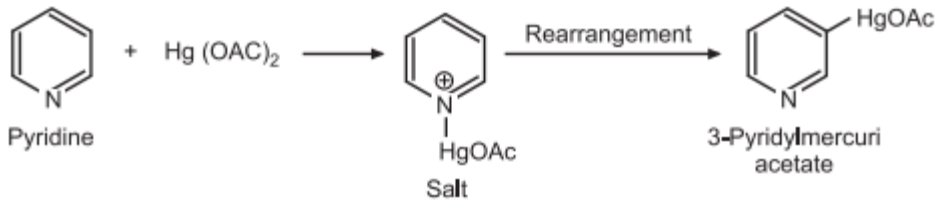
Acyl, sulfonyl or anhydrides readily react with pyridine to form quaternary salts which function as acylating and sulfonating agents



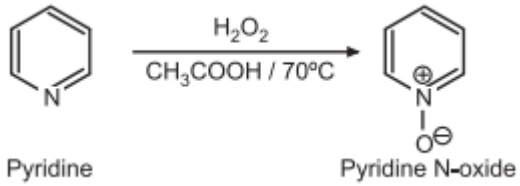
Halogenation and nitration:



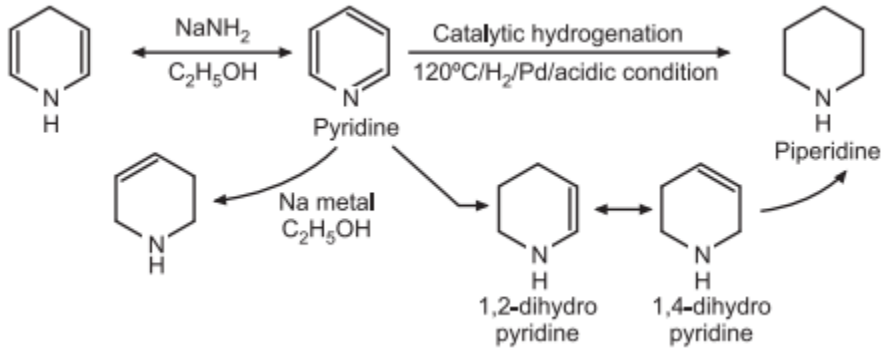
Mercuration: When pyridine is heated with mercuric acetate at 170-180°C, the salt initially formed undergoes rearrangement to give 3-pyridylmercuriacetate.



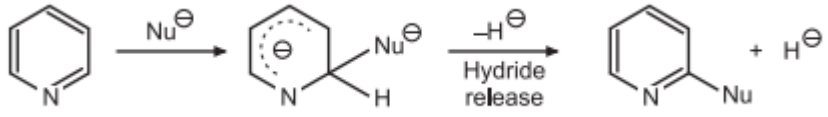
(c) Oxidation: Pyridine ring is resistant to oxidation, but the N-atom being highly electron rich, can easily be oxidized by hydrogen peroxide or various peracids to pyridine-Noxide.



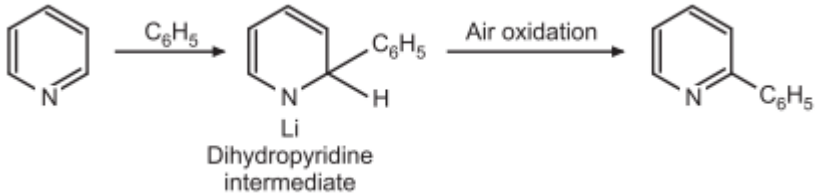
Reduction: Since pyridine easily reacts with nucleophiles, it may be reduced by nucleophilic reducing agents.



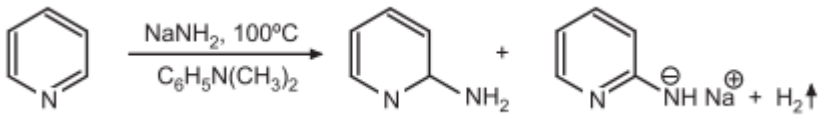
(e)Nucleophilic substitution: Electrophilic substitution is the characteristic reaction of benzene while nucleophilic substitution is the characteristic of pyridine. Nucleophilic substitution takes place at C2 and C4 positions.



(i)Alkylation and arylation: Pyridine reacts with alkyl or aryl lithiums to give a dihydropyridie intermediate which then gets converted into substituted peridine.



(ii)Amination: Pyridine reacts with sodamide to give 2-aminopyridine. It is called chichibabin reaction.

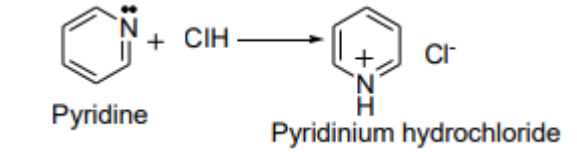


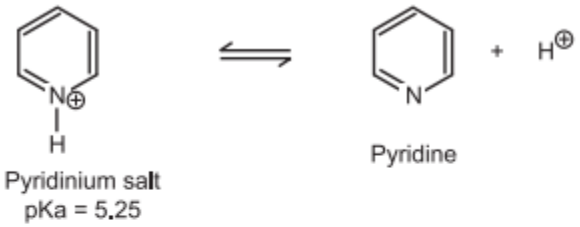
Applications in Drug Synthesis

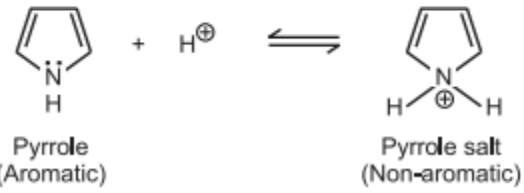
It is present as a core skeleton in sulfapyridine (antibacterial), tripelenamine, mepyramine (antihistaminic), nicacin, pyridoxine (vitamin), isoniazid (anti – T. B.), etc.normal functioning of skin, intestinal tract and nervous system.

1 BASICITY OF PYRIDINE Pyridine is a weakly basic compound. The nitrogen bears a basic lone pair of electrons than lies outside the ring on an sp2 hybrid orbital and is available for protonation. In pyrrole, the lone pair on the N-atom is already involved in the aromatic array of pi electrons. Protonation of pyrrole results in loss of aromaticity and is therefore unfavourable. Because the lone pair is not part of the aromatic ring, pyridine is a base. Pyridine can act as Lewis base by donating its lone pair of electrons to a Lewis acid, forming pyridinium salts.

Pyridine is basic in nature and reacts with acids to forms salts. The basicity of pyridine is due to the availability of lone pair of electrons on nitrogen atom. Pyridine is a much weaker base than alkylamines because the lone pair of electrons of nitrogen are present in sp2 hybrid orbital instead of sp3 hybrid orbital. Consequently, the lone pair is more tightly held and is less available for protonation due to more S character of pyridine nitrogen.

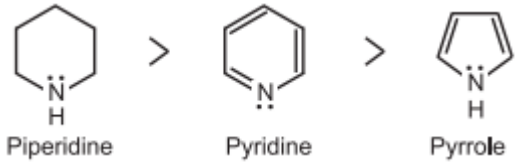




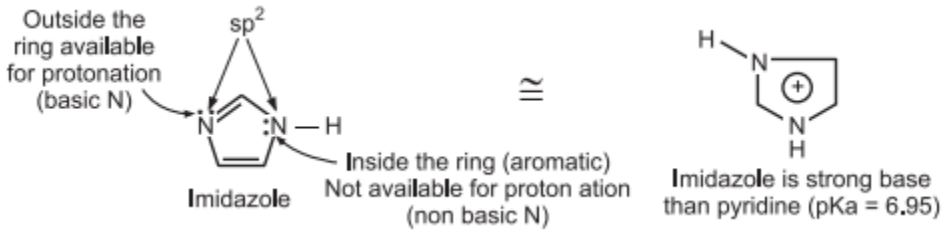


In pyridine, the lone pair is on sp2 hybridized nitrogen atom (more electronegative). The sp2 hybridized orbital contains (100/3) = 33.33% s-character while sp3 hybrid orbital contains only (100/4) = 25% s-character. More the s-character, smaller the hybrid orbital. Hence, sp2 is

smaller in size than sp3 hybrid orbital. The lone pair on nitrogen in sp2 hybrid orbital (pyridine) is much closer to the nitrogen nucleus than that of sp3 hybrid orbital (piperidine). The lone pair of electrons in sp2 hybridized orbital is thus held more tightly by the nucleus than in sp3 hybridized orbital and hence lone pair of electrons in pyridine is less readily available for protonation than aniline or other aliphatic amines.

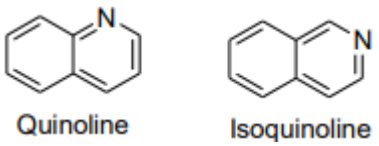


In aniline, the lone pair is on sp3 hybridized nitrogen (less electronegative). This makes pyridine less basic than aniline. Unlike pyridine, however in aniline the lone pair is in resonance with the pi electrons of the phenyl ring. This lowers the basicity of aniline and makes pyridine more basic than aniline. Imidazole is about 100 times more basic than pyridine. The increased basicity results from resonance stabilization of the positive charge to both nitrogen atoms present in imidazole.



QUINOLINE AND ISOQUINOLINE:

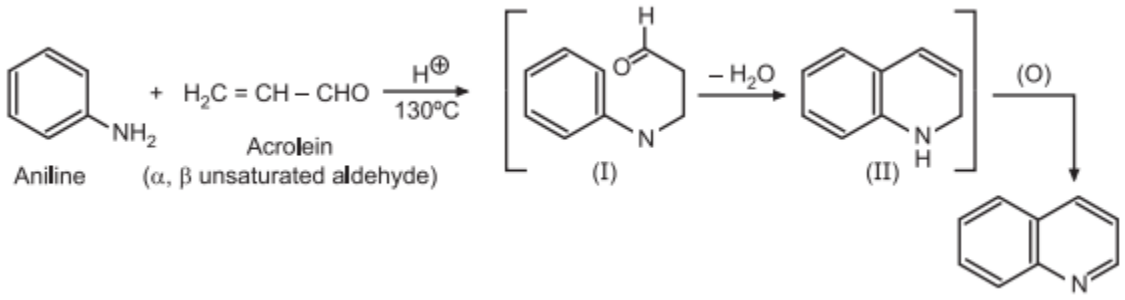
Quinoline and isoquinoline are condensed heterocyclic systems. They are also known as benzopyridines because they have fused benzene and pyridine rings. They are aromatic compounds.



Quinoline or 1-azanaphthalene is a colourless liquid with sweetish odour and has a high boiling point of 237°C. It was first isolated in 1834 from coal tar. Quinoline and isoquinoline are benzopyridines, which are composed of a benzene ring fused to a pyridine ring. Quinoline is a weakly basic compound. Electron releasing substituents at the 2 and 4 positions of quinoline increase the basicity. The electrophilic attack will take place at electron rich C5 and C8 positions. Due to presence of electronegative N-atom close to C2, the C2 and C4-positions are electron deficient. Hence, nucleophilic attack takes place preferentially at the C2 and C4 positions.

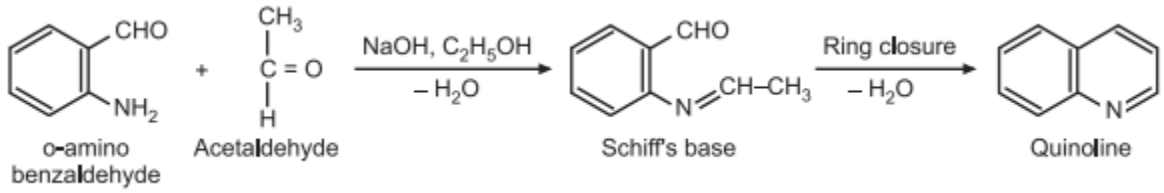
1 Chemical Synthesis (1) Skraup synthesis: When aniline, concentrated sulfuric acid, glycerol and a mild oxidizing agent are heated together, quinoline is formed. The reaction begins when

glycerol is first dehydrated by concentrated sulfuric acid to acrolein. Aniline is then added begins to it to produce 1, 2-dihydroquinoline.



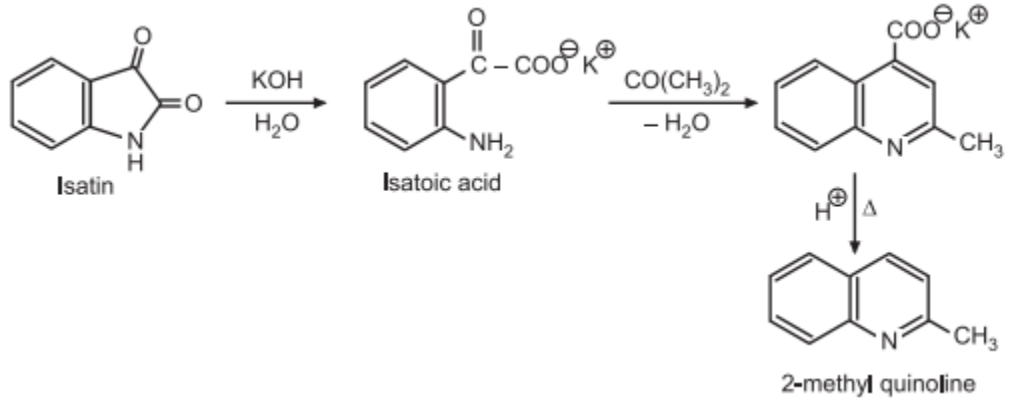
The 1, 2-dihydroquinoline is further oxidized to give quinoline. Aniline adds to acrolein through Michael addition to give aniline propanal (I). Substituted anilines give quinoline derivatives in which substituents appear in benzene ring portion.

(2) Friedlander synthesis: When o-aminobenzaldehyde or o-aminoacetophenone condenses with an aldehyde or ketone (which must contain an active α-methylene group) in alcoholic sodium hydroxide solution, it yields quinoline.

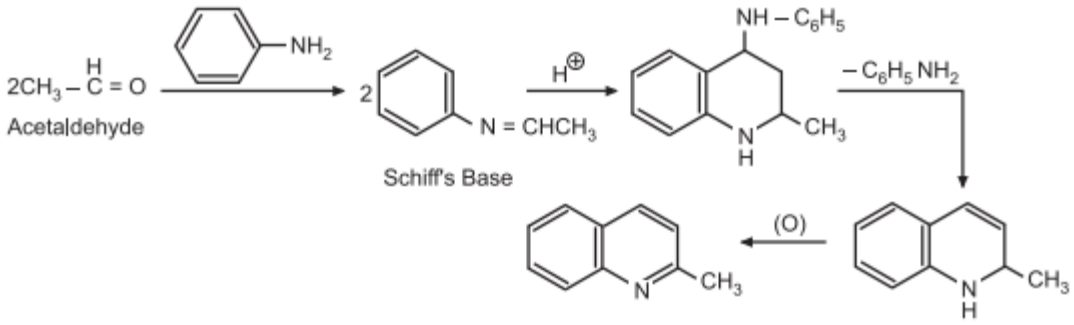


2- substituted quinoline derivatives are usually prepared by this method.

Pfitzinger synthesis: In this method, isatin in the presence of a base, is converted to isatoic acid which is condensed with a ketone to give quinoline-4-carboxylic acid. The carboxylic acid group can be removed by pyrolysis with calcium oxide to give substituted quinolines.



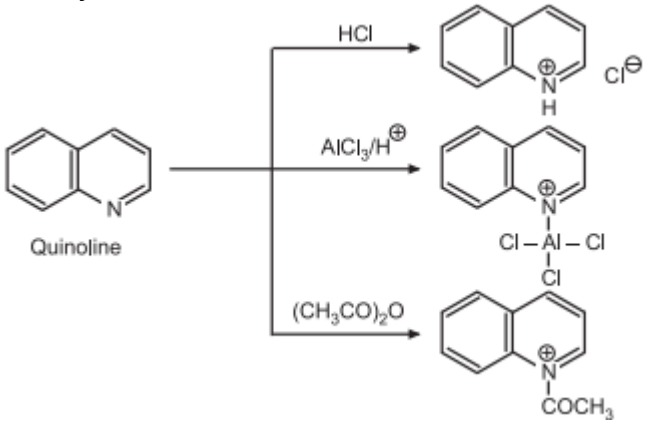
Doebner Miller Synthesis: An aniline and two moles of acetaldehyde are heated in the presence of HCl to form Schiff's base. Two molecules of this Schiff's base condense to form quinoline derivative.



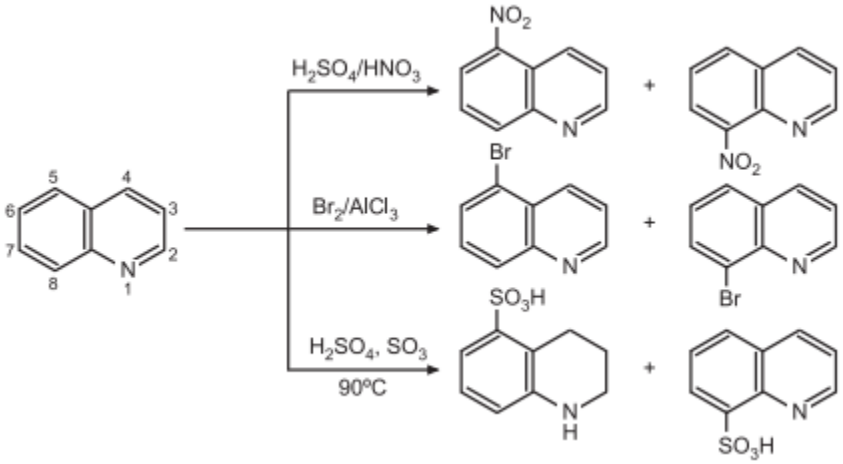
Chemical Reactions

Quinoline is a weak base. The electron rich N-atom of quinoline is the main site for attack by electrophile. This N-atom deactivates the ring towards electrophilic attack. Hence, electrophilic substitution on quinoline ring requires vigorous reaction condition. The electron rich N-atom makes the pyridine ring (hetero ring) more π-electron deficient. Hence, electrophilic attack occurs at the benzo rather than more resistant hetero ring. While nucleophilic attack occurs at hetero ring rather than benzo-ring.

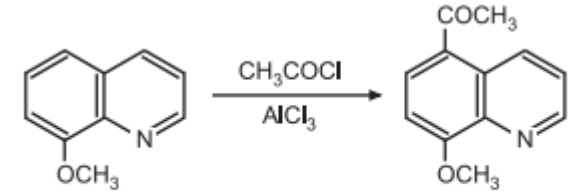
(1) Addition to nitrogen: The lone pair of electrons on the N-atom is available for extra bonding. When quinoline reacts with acids, metallic ions or acyl, sulfonyl, anhydrides, it forms quaternary salts.



(2) Electrophilic substitution: Electrophilic substitution preferably occurs at positions 5 and 8.

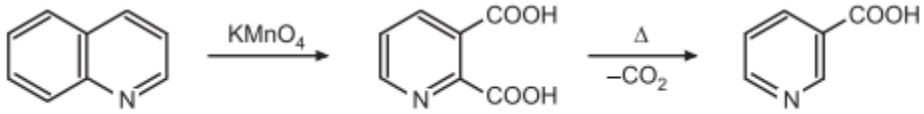


(b) Acylation and alkylation: The quinoline ring is already deactivated by the N-atom. Hence, alkylation and acylation occurs only in those rings which have a strong electron donating substituents.



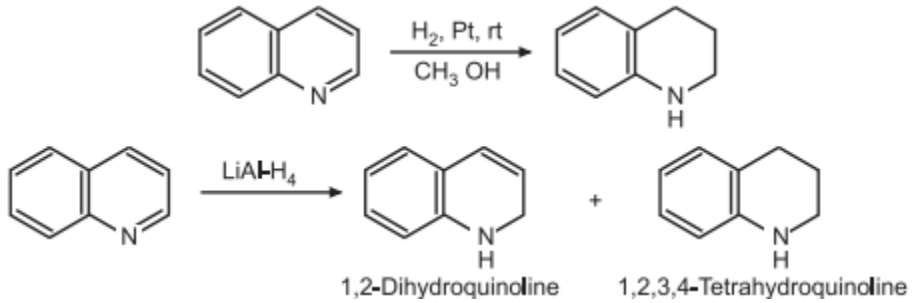
8-Methoxyquinoline 5-Acetoxy-8-methoxy quinoline

Oxidation: Quinoline is resistant to oxidation. Under vigorous condition, pyridine ring remains intact while the benzene ring is opened up on treatment with alkaline KMnO4.



Quinolinic acid Nicotinic acid (Niacin)

Reduction: Quinoline is reduced to 1, 2, 3, 4 – tetrahydroquinoline using catalytic hydrogenation in methanol.



1,2-Dihydroquinoline 1,2,3,4-Tetrahydroquinoline

Lithium in liquid ammonia can produce, 1, 4 – dihydroquinoline under certain conditions. In acid medium, the benzene ring can be selectively reduced.

Applications in Drug Synthesis

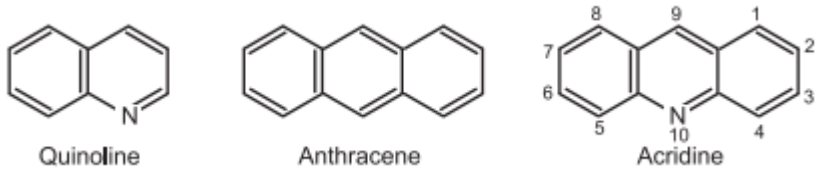
Quinoline is a core component in the structure of chloroquine (antimalarial), papaverine (smooth muscle relaxant), quinapril (antihypertensive), singulair (anti-asthma), hydroxychloroquine (antimalarial), narcotine (depressant), emetine (emetic: vomiting inducer), dimethisoquin (anaesthetic), etc.

It is used for the suppression and treatment of malaria by interfering with DNA. It is used as an anthelmintic drug. It is used as high boiling basic solvent in organic reaction. It is used in manufacturing of pharmaceutical dyes.

ACRIDINE:

Acridine is a condensed heterocyclic system. It is a tertiary base. Acridine is also known as benzoquinoline or dibenzpyridine.

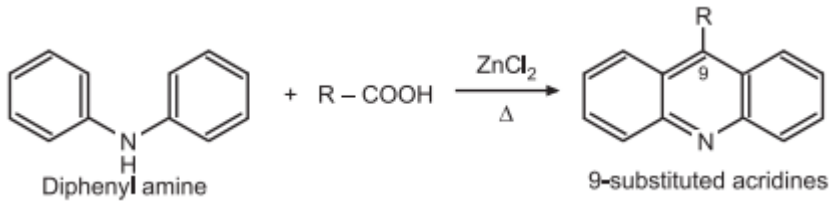
It is a colourless aromatic compound having a melting point of 106-110°C. It is structurally related to anthracene with one of the central atom replaced by nitrogen. It was first isolated from coal tar in 1870 by Carl Grabe and Heinrich Caro. Like pyridine, it is mildly basic



Quinoline Anthracene Acridine

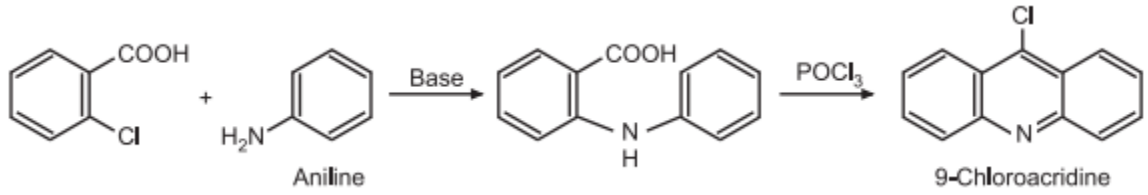
Chemical Synthesis

(1) Bernthsen acridine synthesis: When diphenyl amine is condensed with carboxylic acids in presence of zinc chloride, it provides acridines.



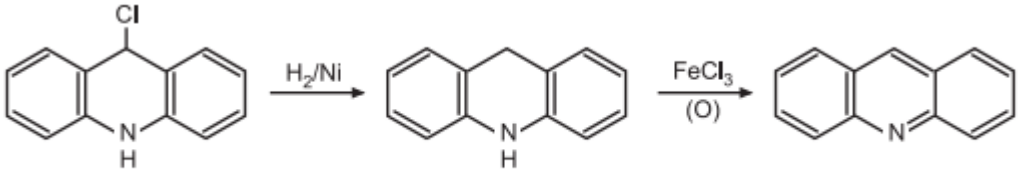
Diphenyl amine 9-substituted acridines

From o-chlorobenzoic acid (Ullmann synthesis): Aniline and o-chlorobenzoic acid are condensed to form diphenylamino-2-carboxylic acid. This acid is cyclized with POCl3 to give 9-chloroacridine.



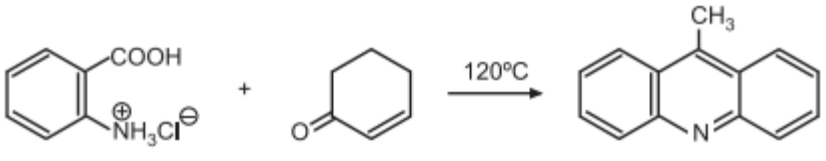
Aniline 9-Chloroacridine

The 9-chloroacridine is first reduced by catalytic hydrogenation followed by oxidation using ferric chloride to give acridine.



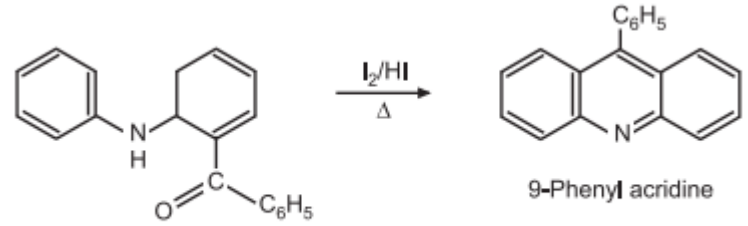
9-Chloroacridine 9,10-Dihydro acridine Acridine

Friedlander synthesis: The salt of anthranilic acid is treated with cyclohex-2-enone at 120°C to give 9-methyl acridine.



Anthranilic acid salt | Cyclohex-2-enone | 9-Methyl acridine

From C-acylated diphenylamines: The diphenylamine is first acylated. The acylated diphenylamine is heated in the presence of I2/HI to give 9-phenylacridine

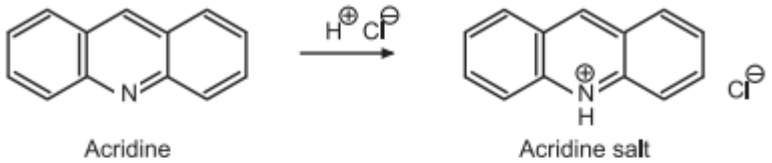


Phenyl-(6-phenylaminocyclohexa-1,3-dienyl) methanone | 9-Phenyl acridine

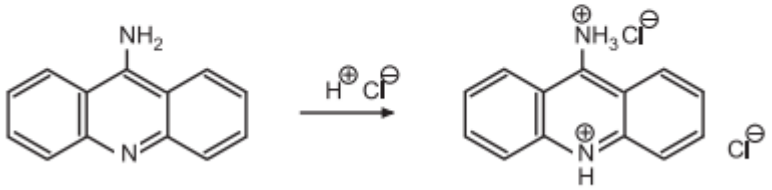
Chemical Reactions

Acridine is the aza derivative of anthracene. It is a weak base. The lone pair of electrons available on N-atom and aromatic nature of acridine compel it to behave chemically, similar to pyridine and quinoline.

(a)N-protonation: Acridine being a weak base, forms soluble salt by protonation at N-atom using its lone pair of electrons. Amino-acridine forms a double salt where the ring N-atom is first to get protonated.

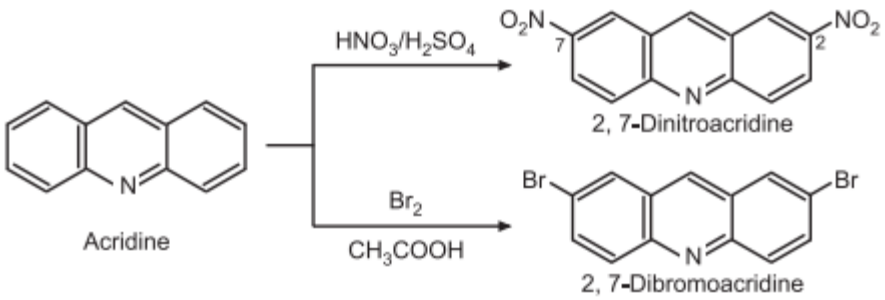


Acridine | Acridine salt

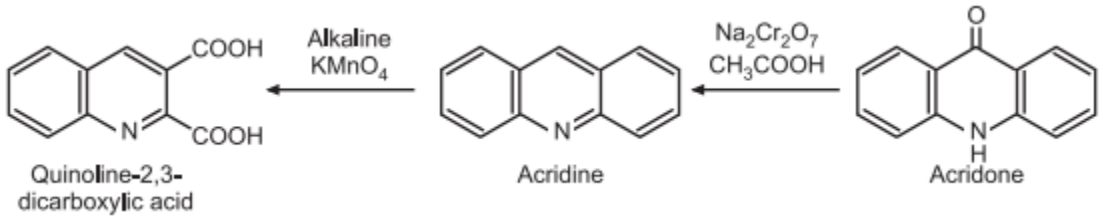


9-Amino acridine | Double salt of 9-aminoacridine

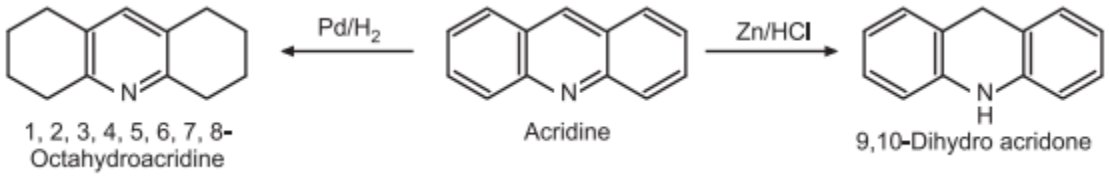
Electrophilic substitution: The electrophile attacks the benzenoid ring preferably at 2- and 7-positions resulting in di-substitution. e.g.,



Oxidation: Acridine is oxidized by dichromate in acetic acid to give acridone. The oxidative ring cleavage occurs by KMnO4 in alkaline medium forming quinoline -2, 3-dicarboxylic acid.



Reduction: The benzene rings of acridine can be selectively reduced by catalytic hydrogenation while the pyridine ring can be selectively reduced by Zn/HCl to give 9, 10-dihydroacridine.

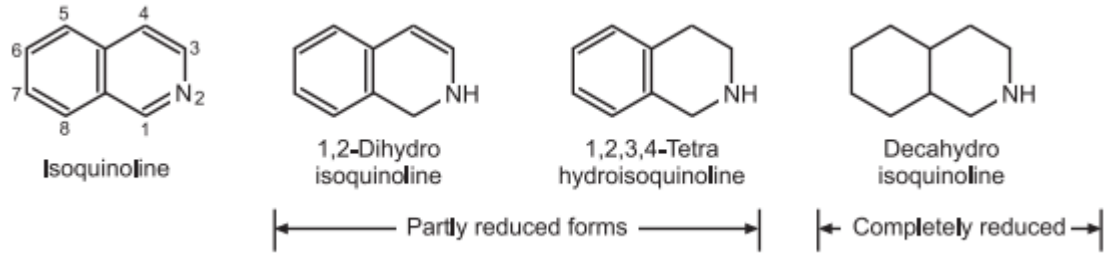


Applications in Drug Synthesis

Many drugs in the market have acridine as a core skeleton. These drugs include bucricaine (anaesthetic), quinacrine (or mepacrine: antimalarial), 9-ammoacridine (disinfectant), proflavin (antibacterial), nitracrine (anticancer), acriflavin (antiseptic), etc.

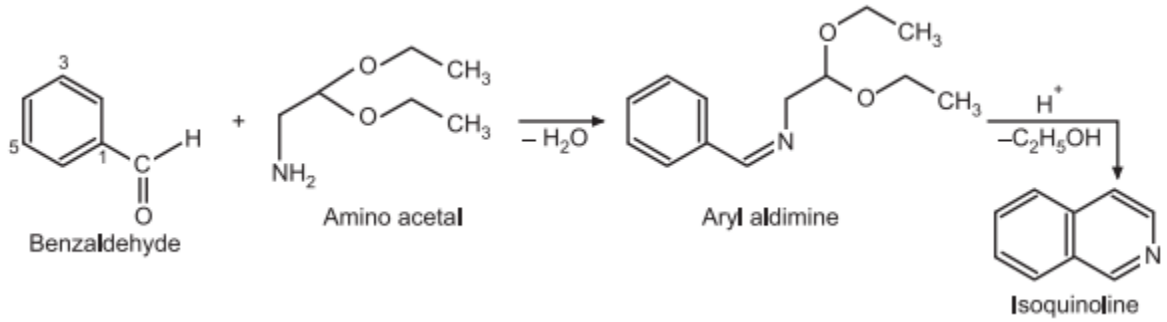
Isoquinoline

Isoquinoline is a colourless hygroscopic liquid having an unpleasant odour. Like quinoline, it is also a weak base. It was first isolated from coal tar by Hoogewerff and Dorp



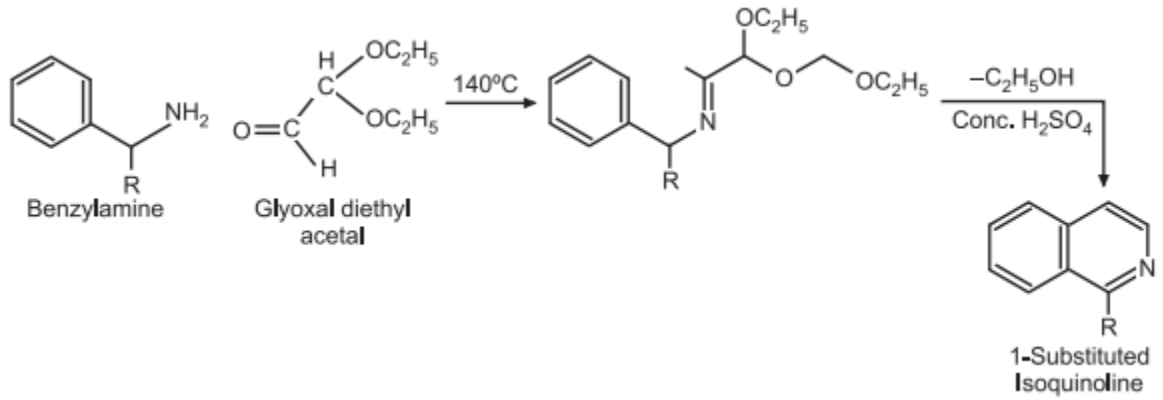
Chemical Synthesis

Pomeranz-Fritsch reaction: In this reaction, benzaldehyde is condensed with aminoacetal to form an aryl aldimine. The aldimine is cyclized using strong acid such as concentrated Sulfuric acid or phosphorous pentoxide.

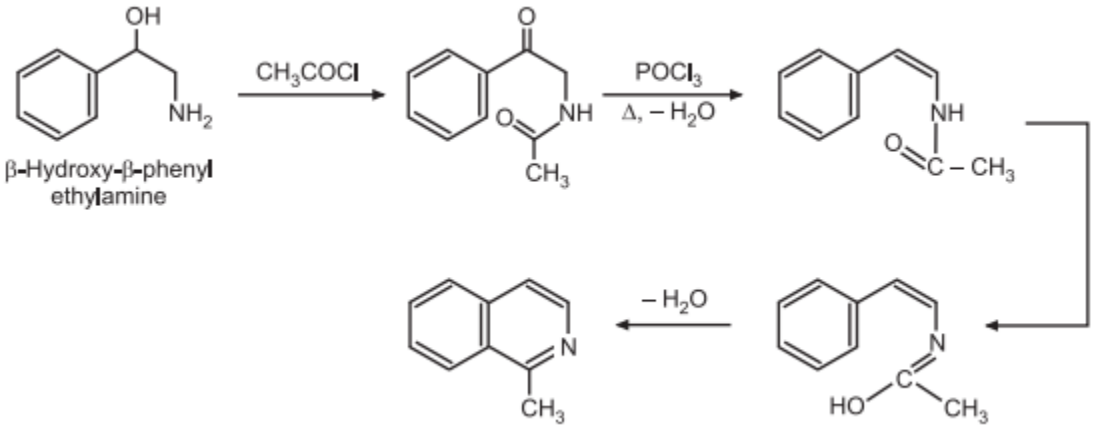


The electron donating groups (if present at 3 and/ or 5 position in benzaldhyde) increase the rate of reaction while electron withdrawing groups decrease the rate.

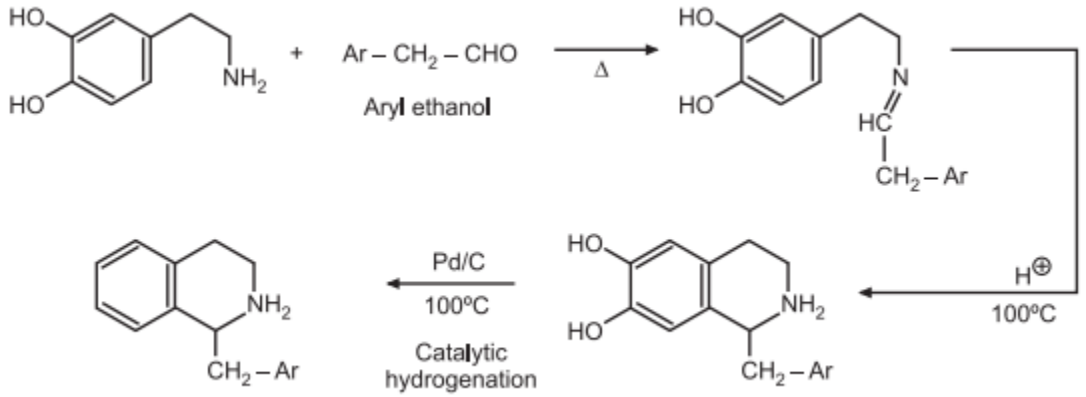
Schlitttler – Muller Modification: When benzylamine condenses with glyoxal diethyl acetal, the resulting imine can be cyclized with acid to give 1-substituted isoquinoline. It is a modification of Pomeranz-Fritsch reaction.



Pictet-Gams modification: In this method, β-phenylethylamine is replaced by β-hydroxy-β-phenylethylamine which is heated with cyclization catalyst, POCl3.



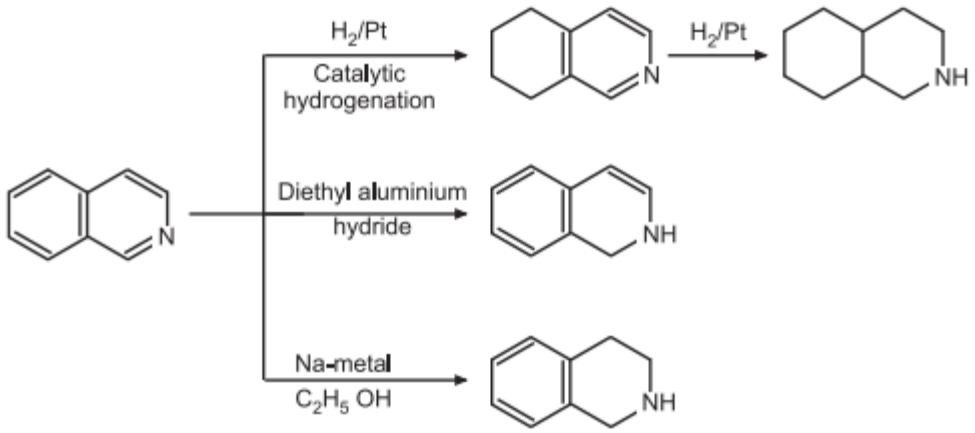
Pictet-Spengler synthesis: When arylethanamines react with aldehyde, it gives imines. Under acid catalysed cyclization, the imine gets converted to 1, 2, 3, 4 – tetrahydroisoquinoline. If electron donating substituents are present on phenyl ring, ring closure (i.e., cyclization) occurs under very mild conditions. e.g.,



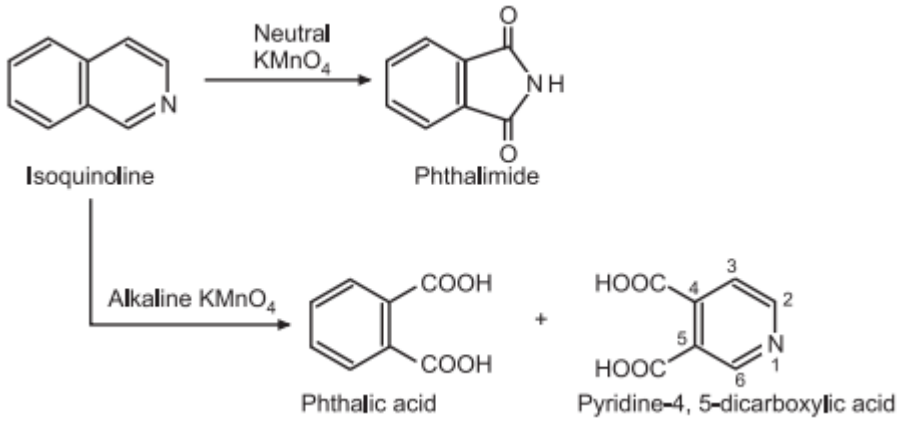
Chemical Reaction

As like pyridine, isoquinoline is a weak base. It protonates to form salts upon treatment with strong acids. The lone pair of electrons available on N-atom and aromatic nature of isoquinoline compel it to behave similar to quinoline in its chemical reactions. For example, like quinoline, 5- and 8-positions of isoquinoline are most susceptible to electrophile attack while the nucleophile attacks preferably at 1-position or at 3-position if position-1 is already occupied.

(a) Reduction: Isoquinoline gives rise to different reduced products under the attack of different reducing agents.



) Oxidation: Isoquinoline is resistant to oxidation. If vigorous conditions employed, isoquinoline undergoes ring cleavage to give degradation products.

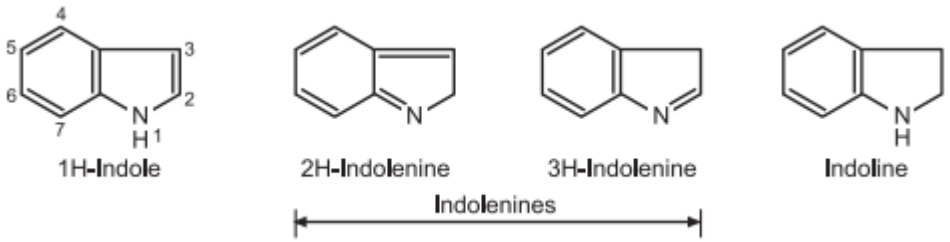


Applications in Drug Synthesis

Isoquinoline is a core part of structure of many drugs. These drugs include dimethisoquin (anesthetic), debrisoquine, quinapril (antihypertensive), papaverine (vasodilator) and many therapeutically active alkaloids like berberine, emetine, etc.

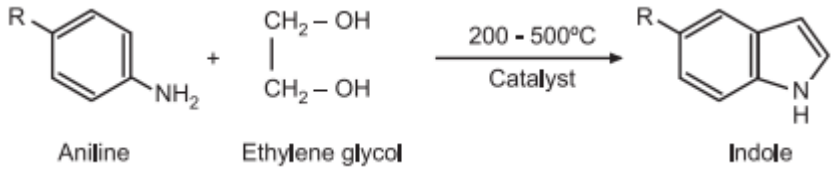
indole

It is an aromatic heterocyclic compound consisting of a benzene ring fused to a pyrrole ring. it is a white solid having the melting point 52-54°C. Indole was first obtained in 1866 by zinc dust distillation of oxindole. The tautomeric forms of indole are known as indolenines.

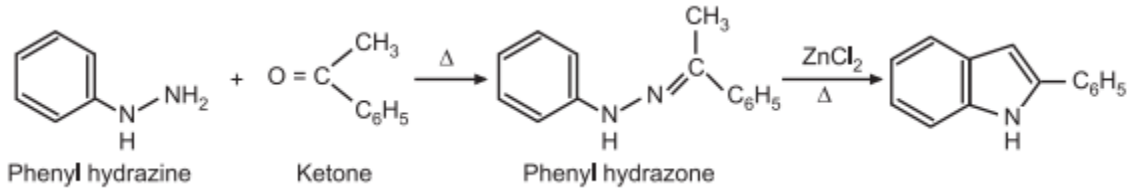


Chemical Synthesis

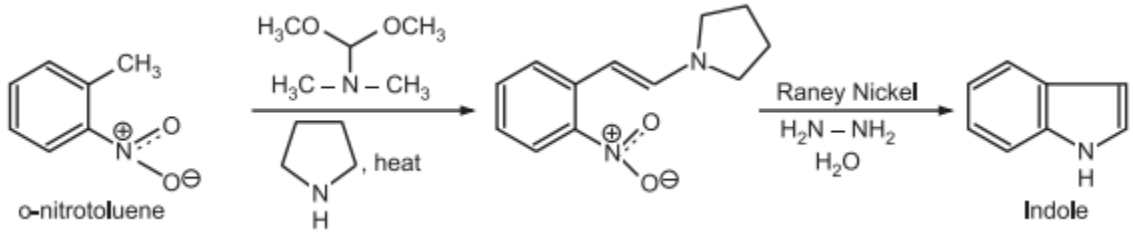
(1)Aniline via vapour-phase reaction with ethylene glycol in the presence of catalyst gives indoles.



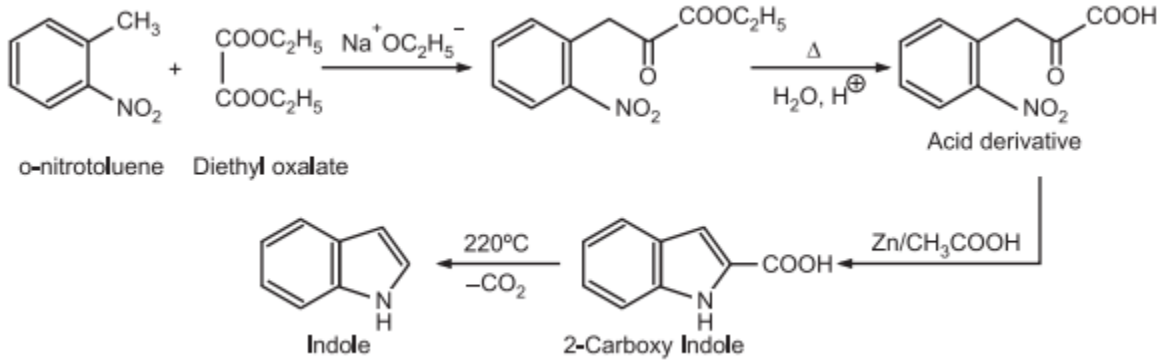
Fischer-Indole synthesis: This method was developed in 1883 by Emil Fischer. It is used to synthesize 2- and/or 3-substituted indoles. It consists of heating an arylhydrazine with an aldehyde or ketone, followed by acid catalyzed rearrangement of resulting arylhydrazone with a loss of ammonia give an indole.



Leimgruber-Batcho indole synthesis: In this reaction, o-nitrotoluence reacts with pyrrolidine in the presence of N, N-dimethyl formamide dimethyl acetal (DMFDMA) to give an enamine. This enamine undergoes reductive cyclization to give an indole.

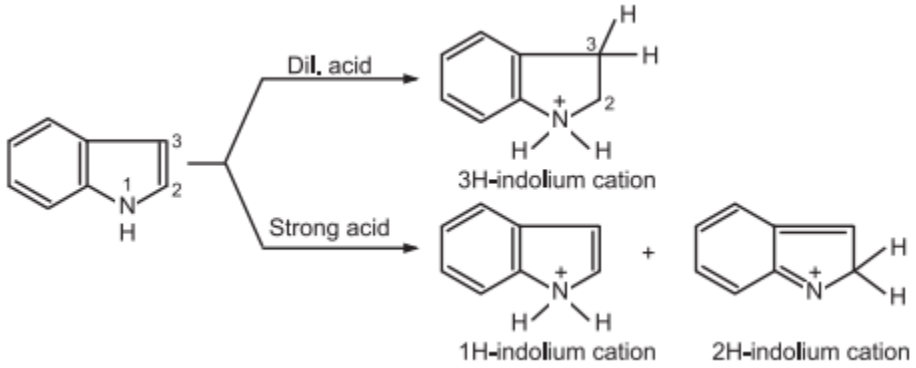


Reissert synthesis: The methyl group ortho to nitro on a benzene ring is acidic enough to get condensed with diethyl oxalate in the presence of sodium ethoxide. After hydrolysis the resulting acid undergoes reductive cyclization to give an indole.

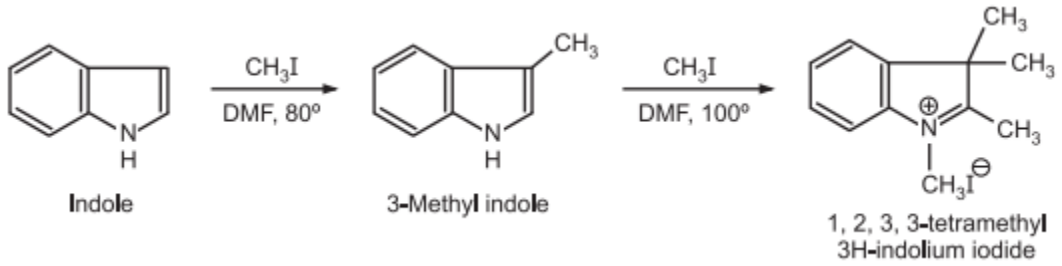


Chemical Reactions

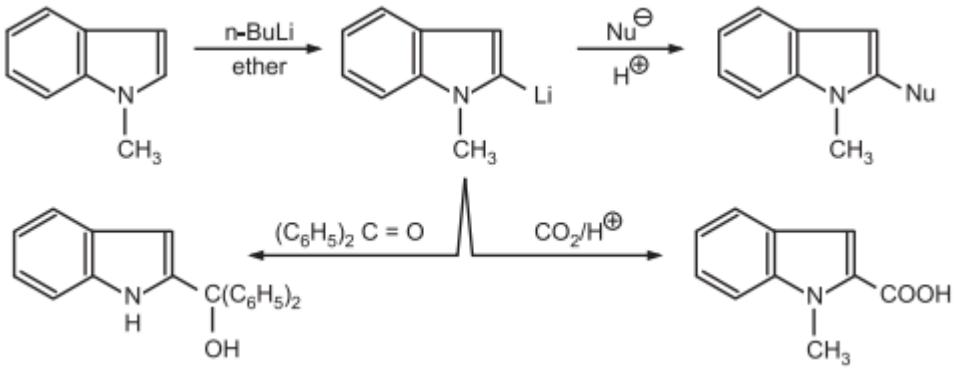
Indoles are aromatic heterocyclic compounds where the ring nitrogen atom is not basic. Indoles are very weak bases.



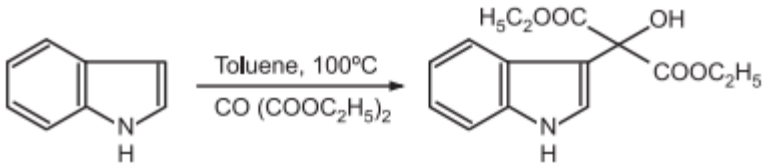
Alkylation: The lone pair of electrons on ring N-atom is a part of aromatic sextet and not available free and exclusively at nitrogen atom. Hence, indoles do not react with alkyl halides at room temperature. However indole reacts with methyliodide in DMF at about 80°C to give 3-methyl indole. As temperature is gradually raised above 100°C, 1, 2, 3, 3-tetramethyl-3H-indolium iodide is formed



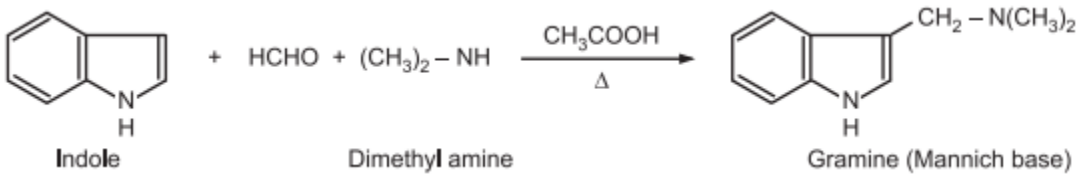
Nucleophilic substitution: Indoles undergo very few nucleophilic substitution reactions. These reactions do not occur in indoles by direct displacement of ring bound substituent. Initially the indole is deprotonated by readily displacable nucleophilic reagent such as n-BuLi. The nucleophile then attacks at C-2 position by displacing the Li-atom.



Reaction with aldehydes and ketones: Under acid catalysed conditions, indoles react with aldehydes and ketones to give indol-3-ylcarbinols.



Mannich reaction: Indole reacts with a mixture of formaldehyde and dimethylamine in acetic acid to give Mannich base at C3-position



Application in Drug Synthesis

Indole is a core part of the structure of serotonin (neurotransmitter, autacoid), vinblastine (anti-cancer), indomethacin (NSAIDs), besipirdine (effective in treatment of Alzheimer's disease), fendosal (NSAIDs), Ondasetron (antiemetic in cancer chemotherapy) brassinin (anticancer), melatonin (hormone), etc.

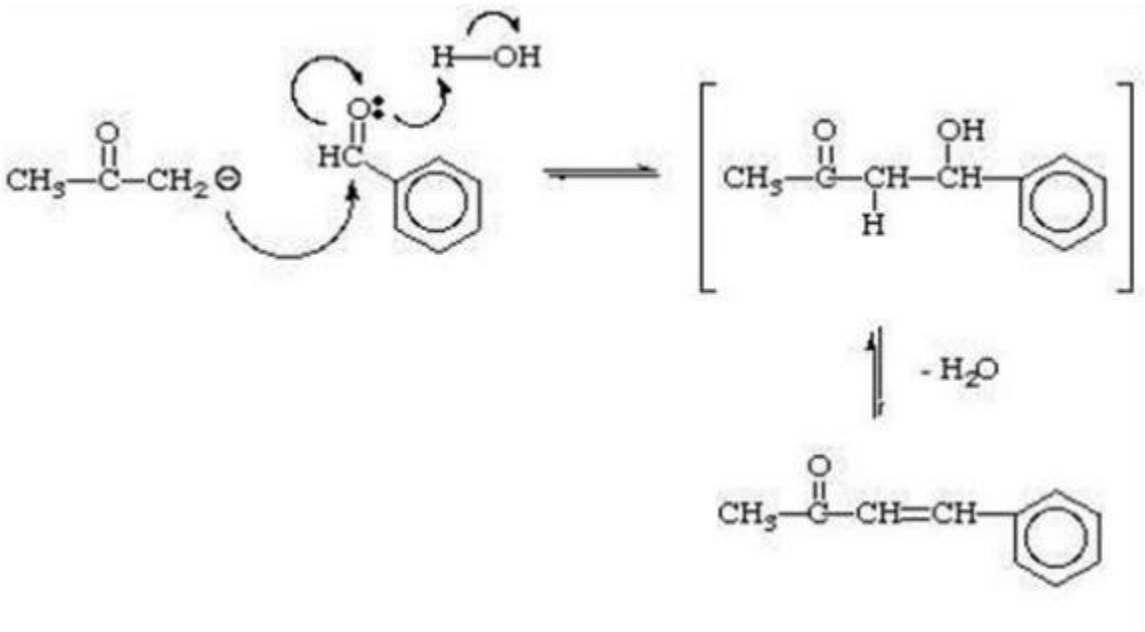
UNIT – 5
REACTION OF SYNTHETIC IMPORTANCE

Dr.Mary Grace Pandu
Assistant .professor

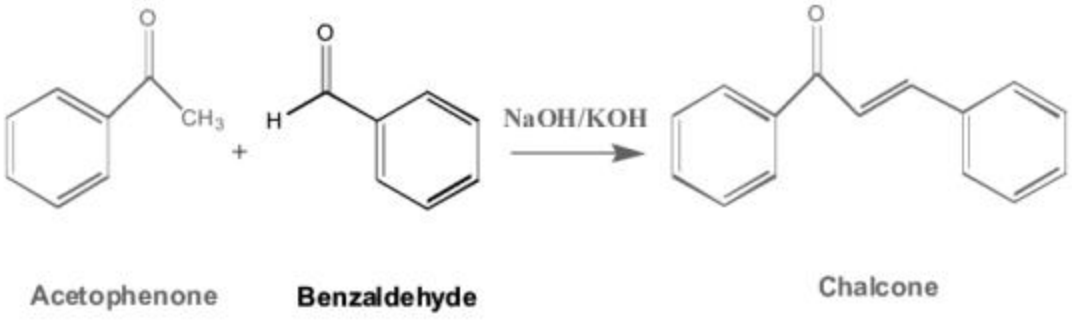
Claisen–Schmidt Condensation Reaction

The reaction between an aldehyde or ketone having an alpha-hydrogen with an aromatic carbonyl compound lacking an alpha hydrogen is called the Claisen–Schmidt condensation.

In cases where the product formed still has reactive alpha hydrogen and a hydroxide adjacent to an aromatic ring, the reaction will quickly undergo dehydration leading to the condensation product.



Enolate ions are formed when molecules with hydrogens alpha to a carbonyl group are treated with a base like sodium hydroxide. For example, acetone reacts with base to give an enolate.

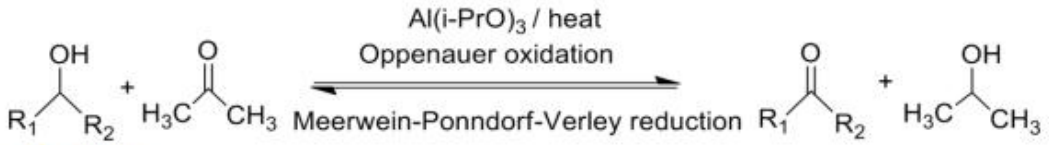


Claisen-Schmidt condensation reaction

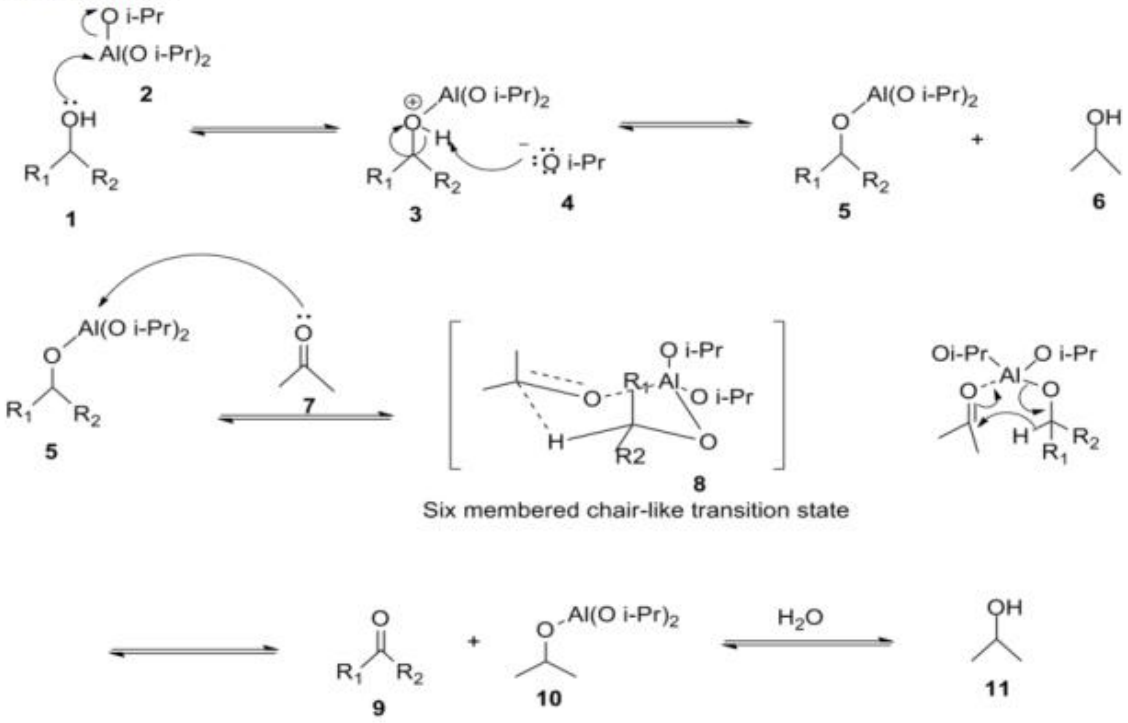
Oppenauer Oxidation Reaction

- The Oppenauer oxidation is an organic reaction used to convert a primary or secondary alcohol to a ketone using another excess ketone reagent (such as acetone) and an aluminium triisopropoxide catalyst.

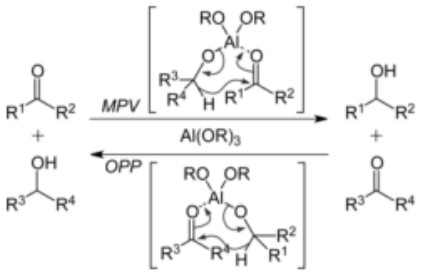
- Oppenauer oxidation, named after Sir Rupert Viktor Oppenauer

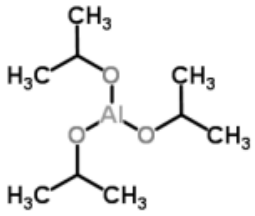


- ***Reaction Mechanism:***



(1)	Coordinates to the aluminium to form a complex.
(3)	Which then, in the second step, gets deprotonated by an alkoxide ion
(4)	To generate an alkoxide intermediate
(5)	In the third step, both the oxidant acetone
(7)	The substrate alcohol are bound to the aluminium. The acetone is coordinated to the aluminium which activates it for the hydride transfer from the alkoxide. The aluminium-catalyzed hydride shift from the α-carbon of the alcohol to the carbonyl carbon of acetone proceeds over a six-membered transition state
(8)	The desired ketone
(9)	is formed after the hydride transfer

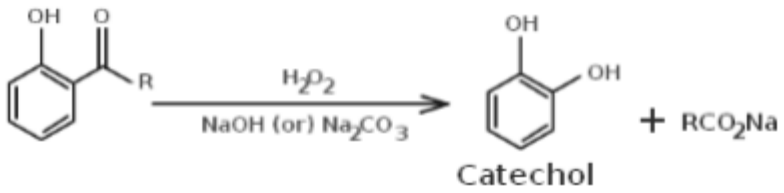


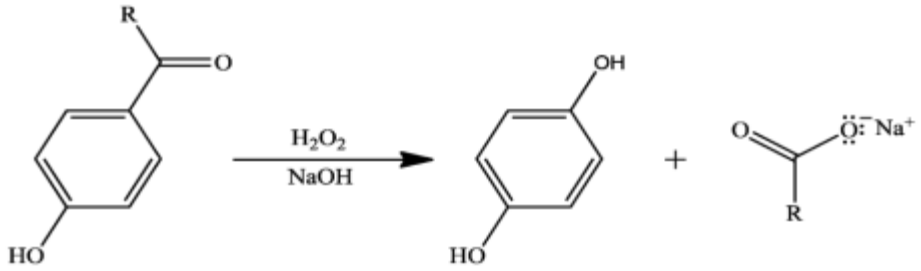


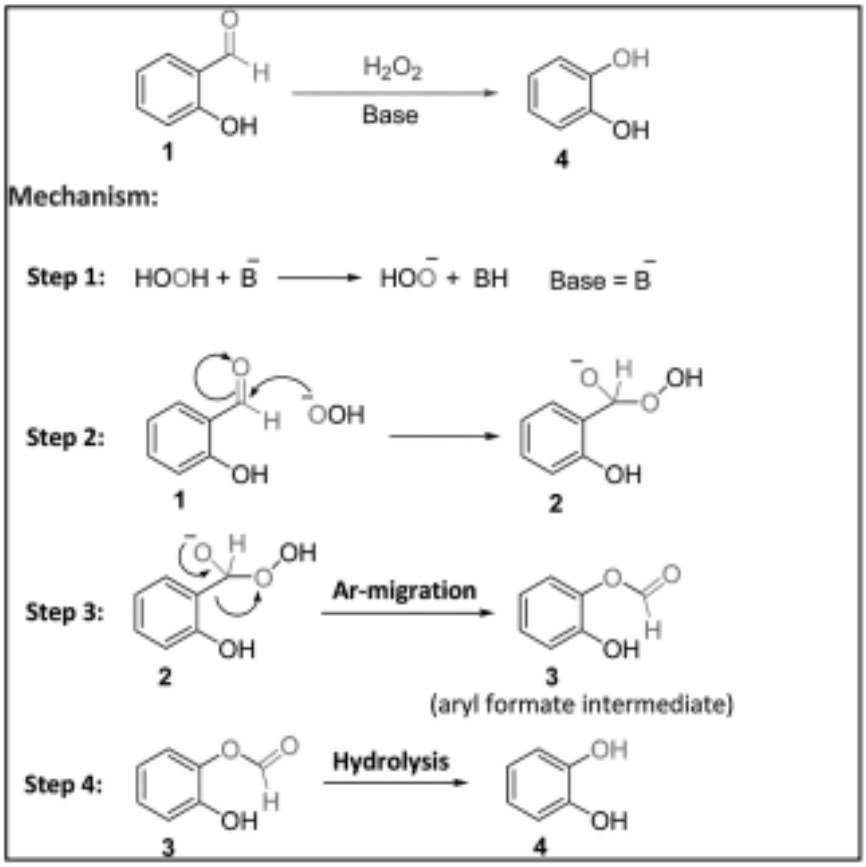
Aluminium isopropoxide

Dakin Reaction - Dakin Reaction is the replacement of the aldehyde group of ortho and para hydroxy and ortho aminobenzaldehyde (or ketone) by a hydroxyl group on reaction with alkaline hydrogen peroxide.

Reaction of synthetic importance

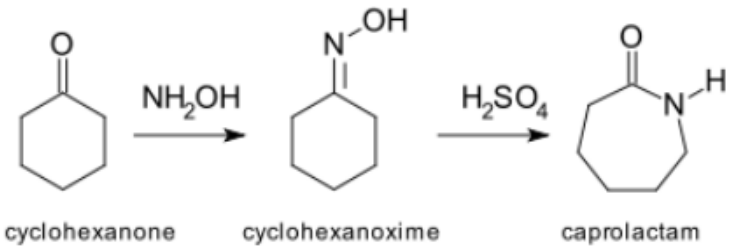






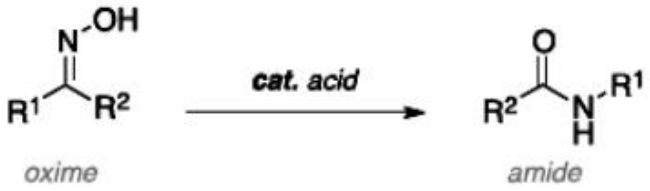
Beckmann Rearrangement Reaction

- The Beckmann rearrangement is an organic reaction used to convert an oxime to an amide under acidic conditions

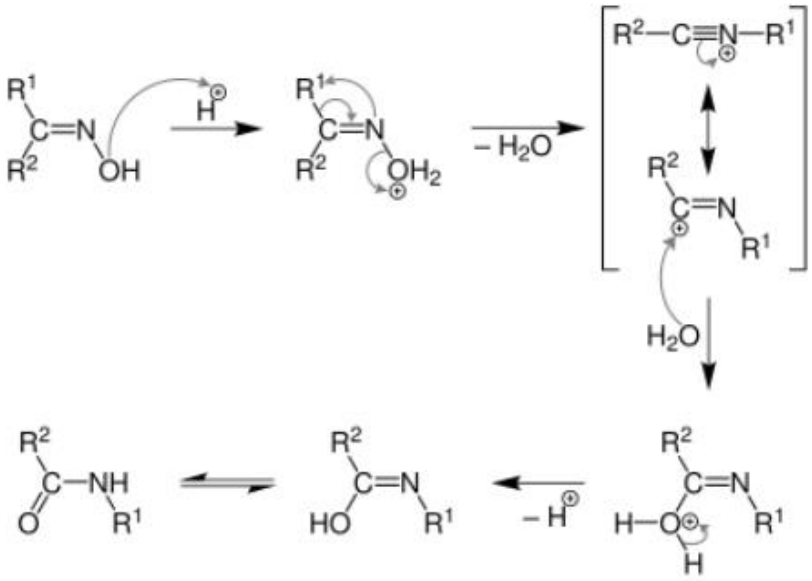


cyclohexanone cyclohexanoxime caprolactam

- ***Reaction mechanism***

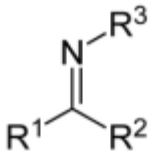


oxime *amide*



IMINE

An imine is a functional group or chemical compound containing a carbon–nitrogen double bond.

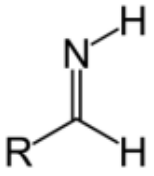
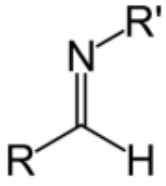
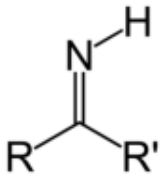
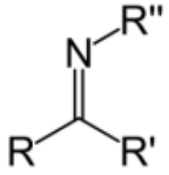


Imine

A primary imine in which C is attached to both a hydrocarbyl and a H is called a primary aldimine.

A secondary imine with such groups is called a secondary aldimine.

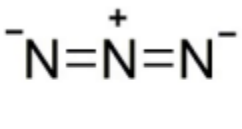
A primary imine in which C is attached to two hydrocarbyls is called a primary ketamine; a secondary imine with such groups is called a secondary ketamine.

			
Primary aldimine	*Secondary aldimine*	*Primary ketimine*	*Secondary ketimine*

AZIDE

Azide is the anion with the formula N 3−. It is the conjugate base of hydrazoic acid (HN3). N 3− is a linear anion.

The dominant application of azides is as a propellant in air bags.

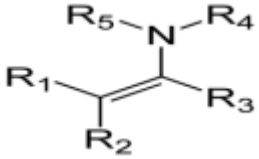


The azide anion

The azide functional group can be shown by two resonance structures

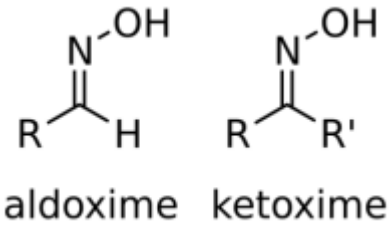
ENAMINE

- An ENAMINE is an unsaturated compound derived by the condensation of an aldehyde or ketone with a secondary amine



OXIME

- An oxime is a chemical compound belonging to the imines, with the general formula RR'C=NOH, where R is an organic side-chain and R' may be hydrogen, forming an aldoxime, or another organic group, forming a ketoxime.

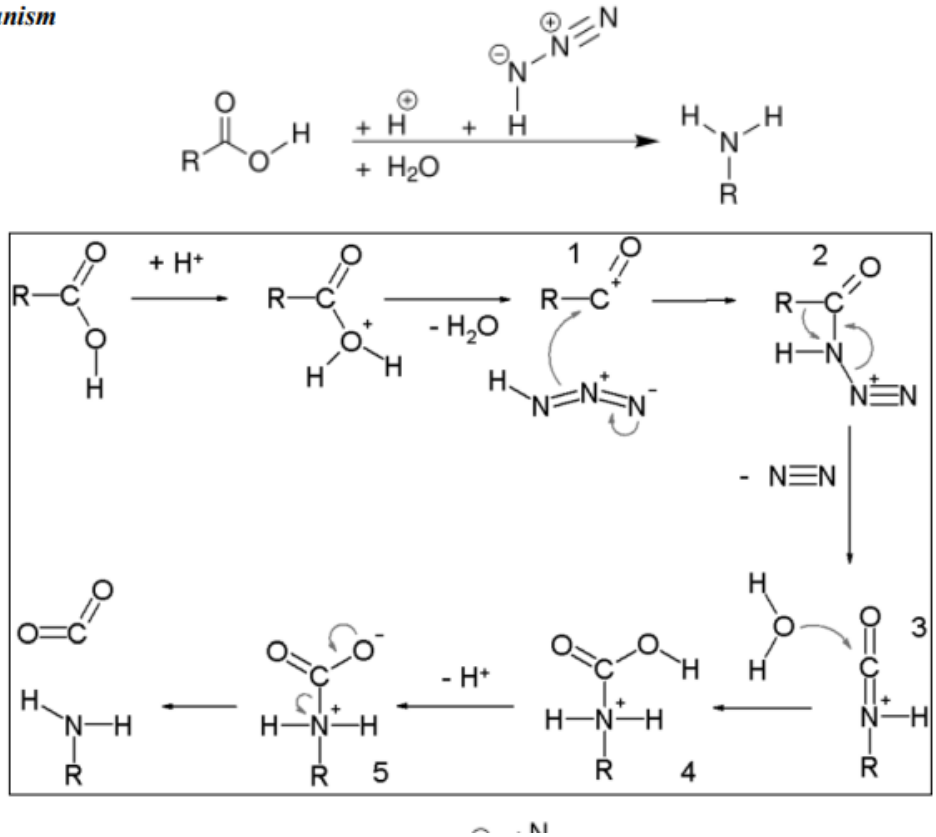


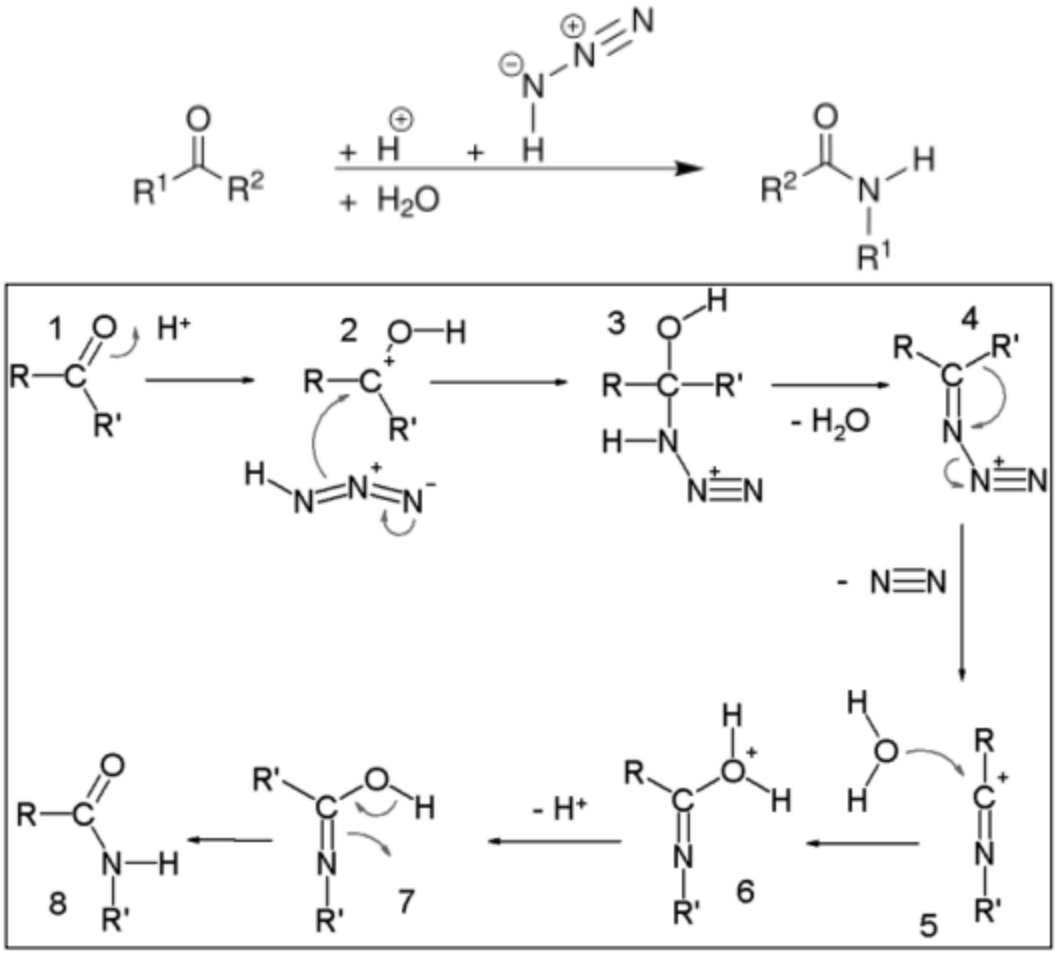
Schmidt Rearrangement

- The Schmidt reaction is an organic reaction in which an azide reacts with a carbonyl group to give an amine or amide, with expulsion of nitrogen.

- It is named after Sir Karl Friedrich Schmidt.

- ***Reaction Mechanism***





Birch Reduction

- The reduction of aromatic substrates with alkali metals, alcohol in liquid ammonia is known as "Birch reduction".

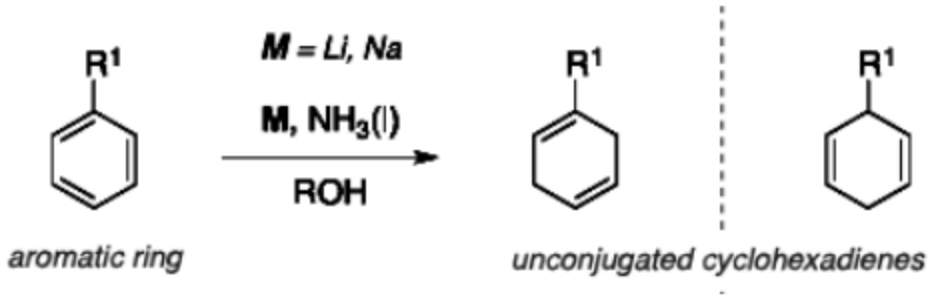
- This reaction is named after a Australian chemist Sir Arthur John Birch.

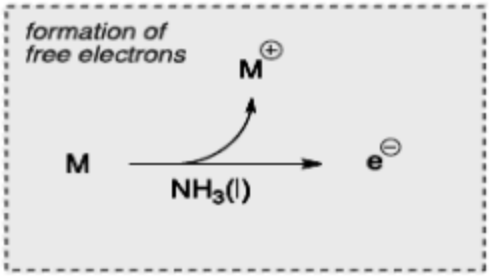
- The Birch reduction is an organic reaction where aromatic rings undergo a 1,4-reduction to provide unconjugated cyclohexadienes.

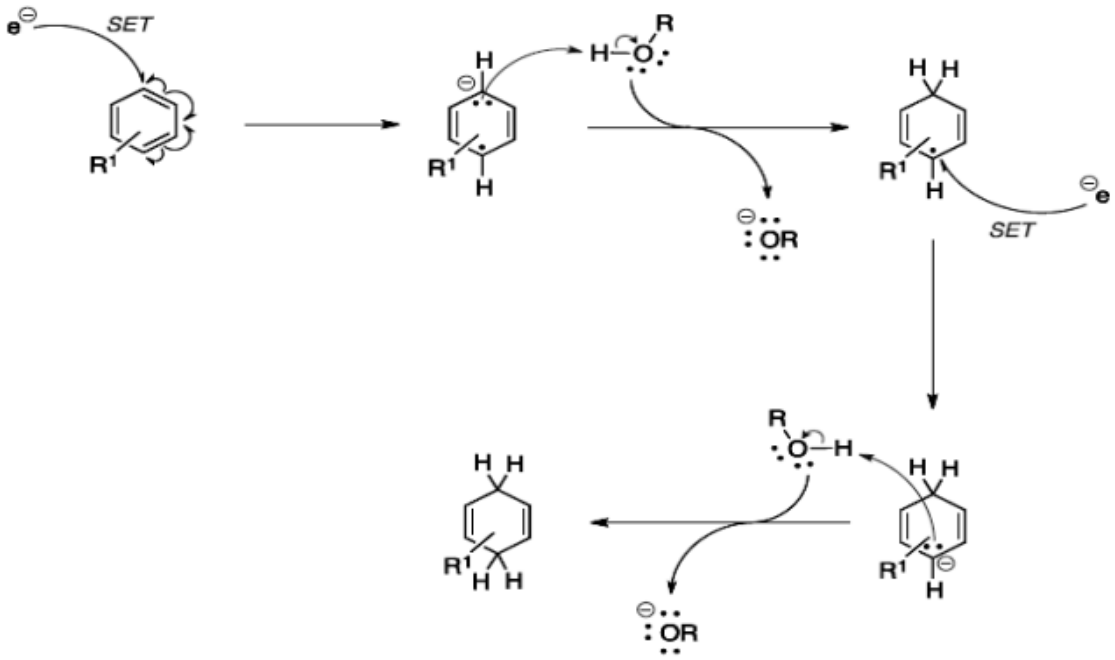
- The reduction is conducted by sodium or lithium metal in liquid ammonia and in the presence of an alcohol.

- The mechanism begins with a Single Electron Transfer (SET) from the metal to the aromatic ring, forming a radical anion.

- The anion then picks up a proton from the alcohol which results in a neutral radical intermediate. Another SET, and abstraction of a proton from the alcohol results in the final cyclohexadiene product and two equivalents of metal alkoxide salt as a by-product.







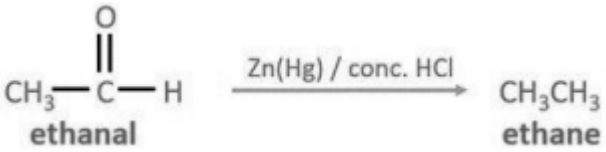
Clemmensen Reduction Reaction

- Clemmensen reduction is a chemical reaction described as a reduction of ketones (or aldehydes) to alkanes using zinc amalgam and hydrochloric acid.

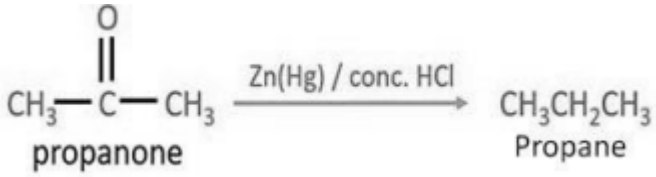
- Clemmensen reduction is an organic reduction reaction shown by both aldehydes and ketones, But Carboxylic acid (-COOH) group can't be reduced by this method (but the -COOH group can be reduced by treating it with soda lime [NaOH+ CaO] and then heating).

- Here, C=O group of aldehydes and ketones is reduced to -CH2- by clemmensen reduction. Zinc amalgam and concentrated hydrochloric acid (Zn (Hg)/conc. HCl) is used as the reagent for Clemmensen reduction. (Note By: alkenes and alkynes don't react with clemmensen reagent.)

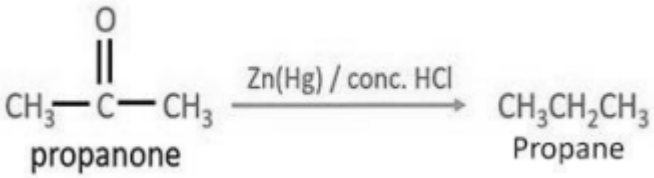
Clemmensen reduction of ethanal: Ethanal is an aldehyde. Ethanal is reduced to ethane by Clemmensen reduction. Zinc amalgam and concentrated HCl is used as the Clemmensen reducing reagent. Ethane is an alkane compound



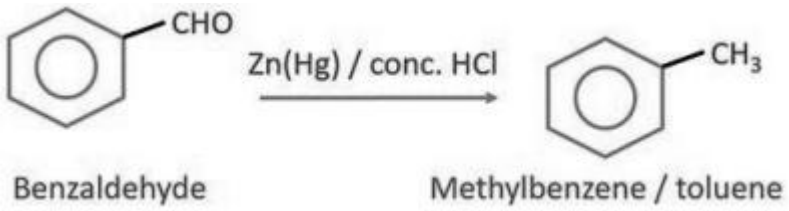
Clemmensen reduction of Propanal: When propanal and Zn(Hg)/conc. HCl react, propane is given as the product. Propane also an alkane.



Clemmensen reduction of propanone: Propanone gives propane as the product with Zn (Hg)/conc. HCl. Propane is an alkane compound.

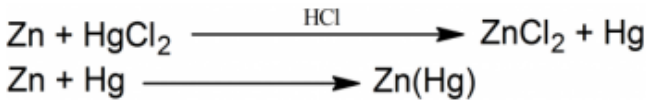


Benzaldehyde and Clemmensen reduction: Methylbenzene (toluene) is given when benzaldehyde is reacted with Zn (Hg) / concentrated HCl.



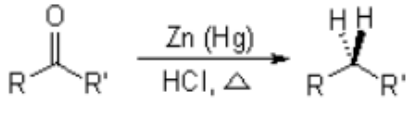
An AMALGAM is an alloy of mercury with another metal, which may be a liquid, a soft paste or a solid, depending upon the proportion of mercury. These alloys are formed through metallic

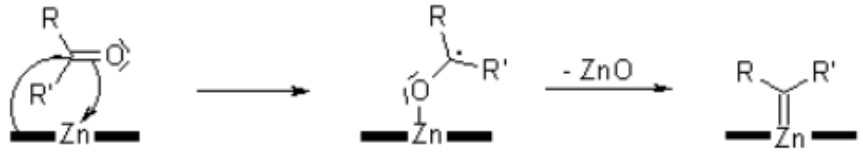
bonding, with the electrostatic attractive force of the conduction electrons working to bind all the positively charged metal ions together into a crystal lattice structure. Almost all metals can form amalgams with mercury, the notable exceptions being iron, platinum, tungsten, and tantalum. Silver-mercury amalgams are important in dentistry, and gold, mercury amalgam is used in the extraction of gold from ore.

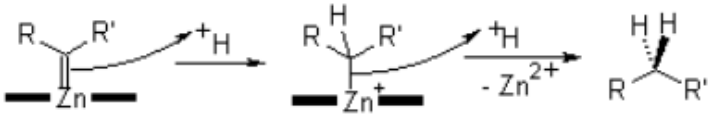


Preparation of zinc amalgam

- ***Reaction Mechanism***



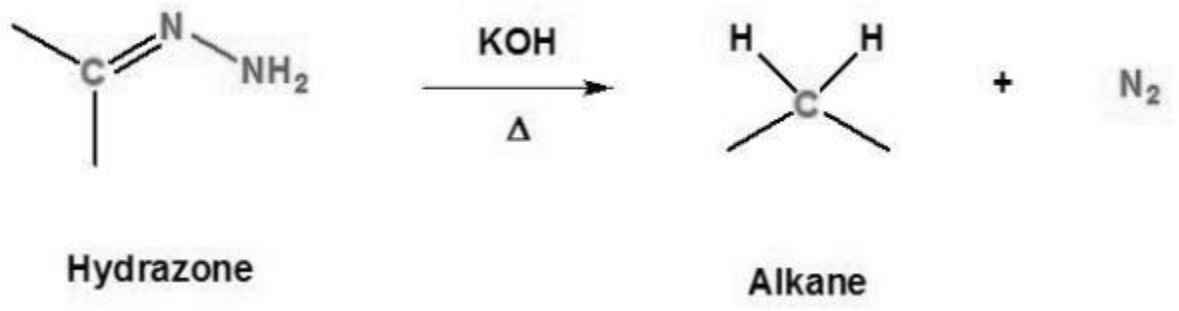




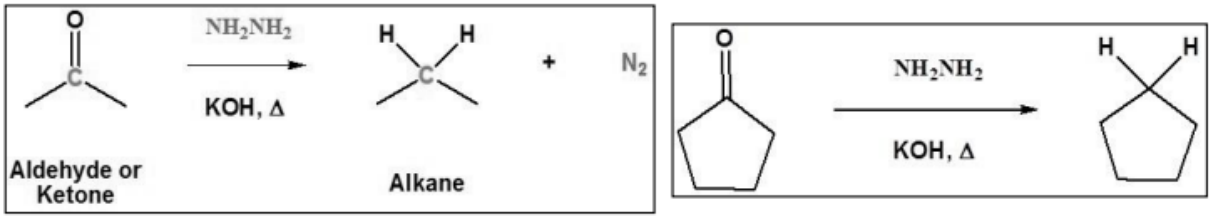
Wolff Kishner Reduction Reaction

- The reduction of aldehydes and ketones to alkanes. Condensation of the carbonyl compound with hydrazine forms the hydrazone, and treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane. - Reaction of Aldehydes or Ketones with Hydrazine Produces a Hydrazone.

Reaction with a Base and Heat Converts a Hydrazone to an Alkane



Both Reactions Together Produces the Wolff-Kishner Reduction



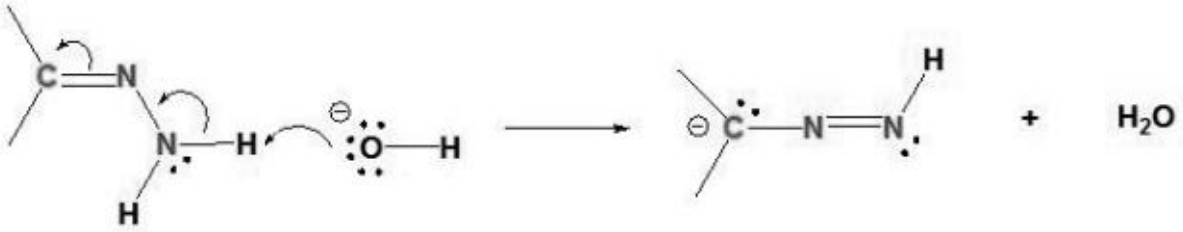
- The Wolff-Kisher reduction is used to convert ketones to methylene groups, and aldehydes to methyl groups. It cannot be used to reduce the carbonyl groups of amides and esters. - Wolff-Kishner vs. Clemmensen Reductions

Clemmensen reduction is done for aldehyde or ketones in presence of Zn-Hg (Zinc amalgam)/Conc. HCl to form alkane. This reaction occurs on the zinc metal surface. There are two types of mechanism for these reactions. A. Cabanionic mechanism, B. Cabenoid mechanism.

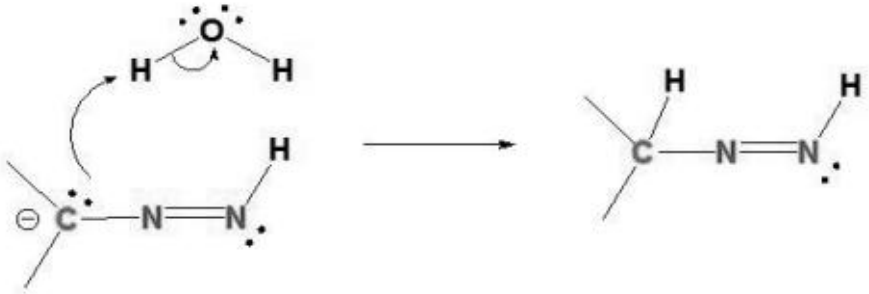
WOlff-Kishner reduction is also for aldehyde/ ketones in presence of hydrazine (N2H4), KOH, H2O and 180 °C temperature to form alkane.

- Mechanism of the Wolff-Kishner Reduction

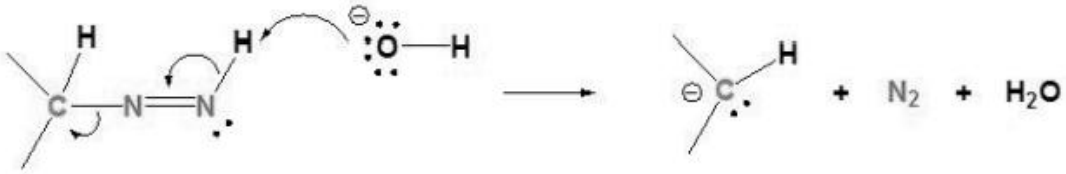
Step 1: *Deprotonation of Nitrogen*



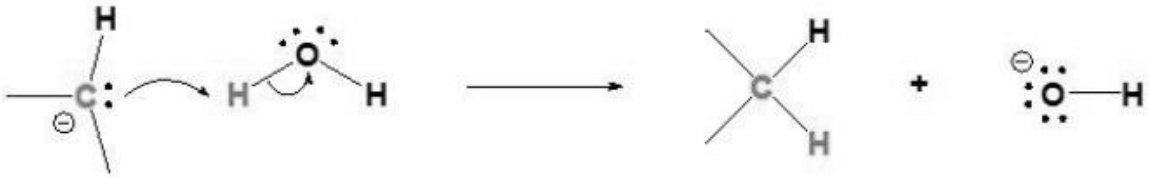
Step 2: *Protonation of the Carbon*



Step 3: *Deprotonation of Nitrogen*



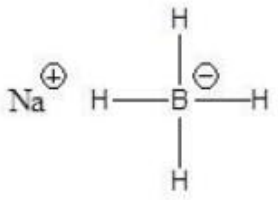
Step 4: *Protonation of Carbon*



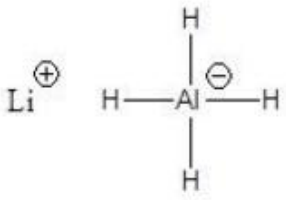
Metal Hydride Reduction Reaction (NaBH4 and LiAlH4)

- The most common sources of the hydride Nucleophile are lithium aluminum hydride (LiAlH4) and sodium borohydride (NaBH4).

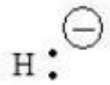
- The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond. Because aluminium is less electronegative than boron, the Al-H bond in LiAlH4 is more polar, thereby, making LiAlH4 a stronger reducing agent.



Sodium Borohydride

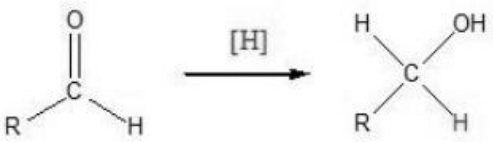


Lithium Aluminum Hydride

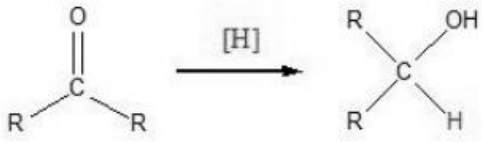


Hydride Nucleophile

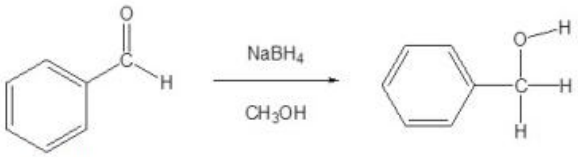
Addition of a hydride anion (H) to an aldehyde or ketone gives an alkoxide anion, which on protonation yields the corresponding alcohol. Aldehydes produce 10 -alcohols and ketones produce 20 -alcohols.



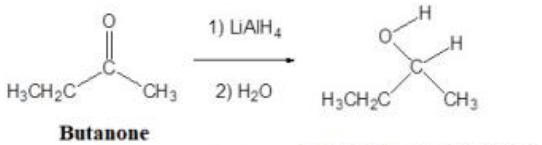
Aldehyde **1° Alcohol**



Ketone **2° Alcohol**



Benzaldehyde **Benzyl alcohol**



Butanone
(methyl ethyl ketone) or MEK **2-Butanol, or *sec*-butanol**

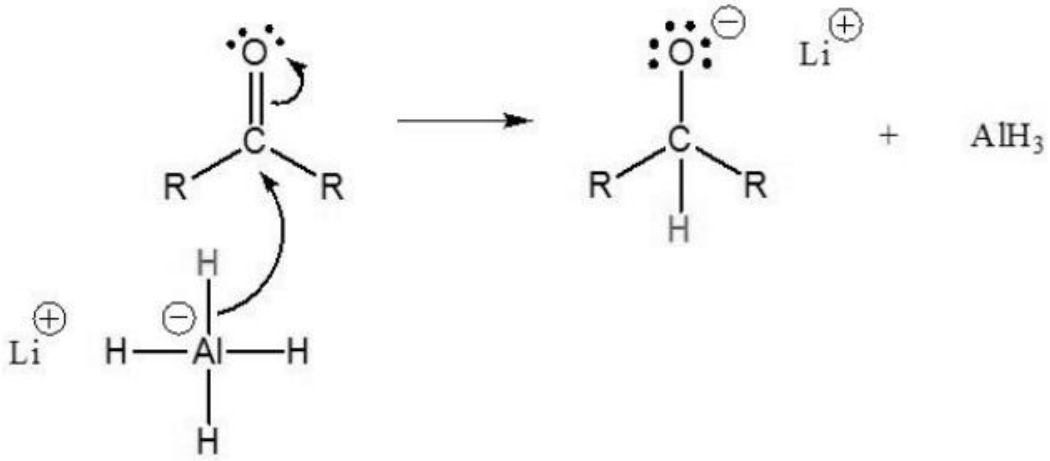
Note By: It reacts violently with water by producing hydrogen gas. Hence it should not be exposed to moisture and the reactions are performed in inert and dry atmosphere. The reaction must be carried out in anhydrous non protic solvents like diethyl ether, THF etc. It is highly soluble in diethyl ether.

$$LiAlH4 + 4H2O \rightarrow LiOH + Al(OH)3 + 4H2\ LiAlH4$$

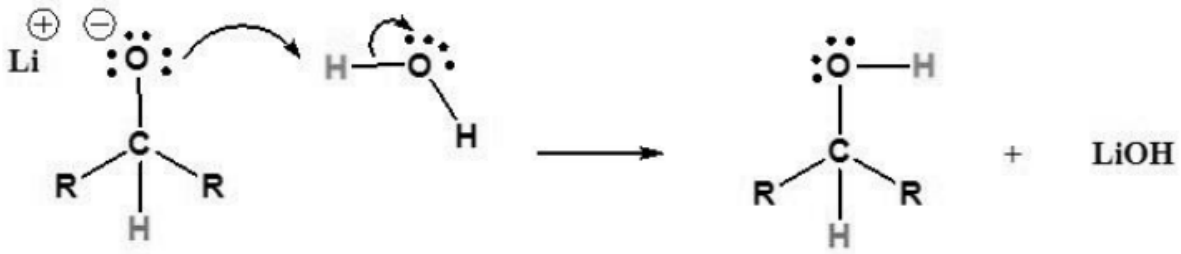
is prepared by the reaction of lithium hydride (LiH) with aluminium chloride (AlCl3). Sodiumborohydride is prepared by the reaction of sodium hydride (NaH) with trimethyl borate, B(OMe)3

- ***Reaction Mechanism for*** **$LiAlH_4$** ***Reduction:***

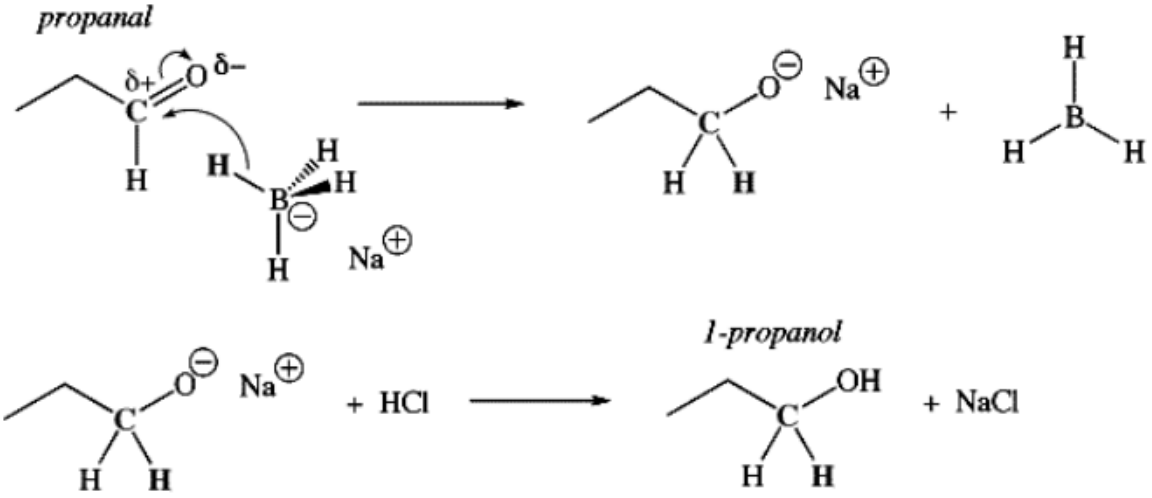
Step 1: *Nucleopilic attack by the hydride anion*



Step 2: *The alkoxide is protonated*



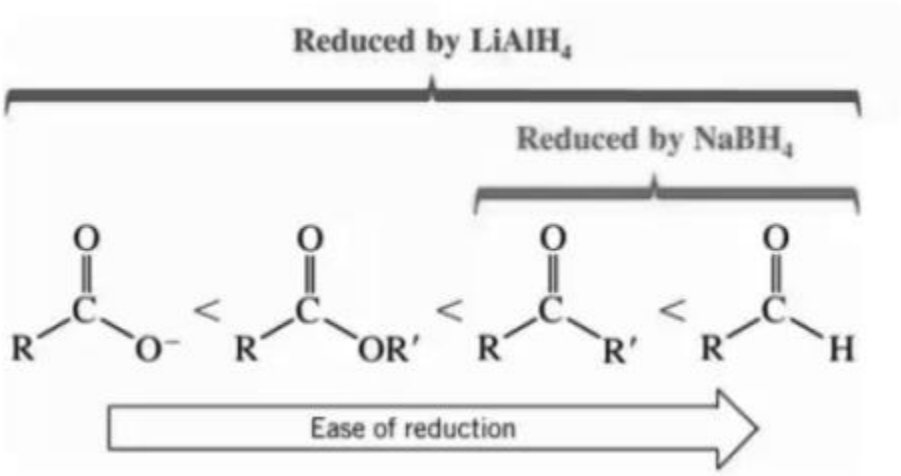
- ***Reaction Mechanism for*** **$NaBH_4$** ***Reduction:***



Why does LiAlH4 reduce esters, amides, or carboxylic acids, while NaBH4 cannot reduce them?

Carboxylic acids and esters are much less reactive to reduction than are ketones and aldehydes and sodiumborohydride, NaBH4 (aq) is too weak a reducing agent for them.

NaBH4 is preferred for aldehydes and ketones because it does not react violently with H2O, the way LiAlH4 does and can be used as an aqueous solution, whereas the LiAlH4 must be delivered in an anhydrous solution of diethyl-ether, Et2O, and then neutralized by water and acid to isolate the product/s. But, ultimately, LiAlH4 can be used for all of these reactions.



Sodium borohydride	***Lithium aluminium hydride***
Boron being part of second period makes shorter and stronger bond with hydrogen	Aluminium being part of third period makes longer and weaker bond with hydrogen.
The **B-H** bond of **$NaBH_4$** has more ***covalent character***	The **Al-H bond** has more ***ionic character*** in **$LiAlH_4$**
It is less reactive	It is more reactive
It is a weak base	It is a stronger base