A TEXT BOOK ON HETEROCYCLIC COMPOUND

[For U.G. and P.G. Students]

- By -
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DEDICATED TO MY BELOVED
LATE MOTHER AND FATHER

PREFACE

We happy to place in the hands of reads, A Text Book On

Hetercyclic Compound for U.G. and P.G. Students. This book is written according to the revised syllabus prepared by Swami Ramanand Teerth Marathwada University, Nanded.

The students of U.G and P.G were facing the problems to collect the study material in Hetercyclic Compounds which include in revised syllabus.

Keeping in the view the needs of the students of U.G. and P.G. The effort is made to present the topics in simple and lucid language and explained the same with suitable examples, structures and figures.

The newly introduced topics in revised syllabus. Hetercyclic Compound We hope that, simple and lucid explanation of the curriculum will help to understand and will make the students perfect in organic chemistry

I am tried our level best to present a complete text book. I welcome suggestions from teachers and students for further improvement of the book.

CONTENTS

1. Nomenclature of Heterocyclic Compounds

Introduction :

Cyclic compound that contains at least one atom other than carbon atom as heteroatom within the ring are called heterocyclic compounds. The most common hetero atoms are Nitrogen, Sulphur and oxygen .heterocyclic compound.

Heterocyclic compounds possess aromatic stability and they are called as heterocyclic aromatic compounds. These compounds are generally five or six member, stable, having alternate double bonds and exhibits aromatic character. They obey the Huckel rule i.e. [4n+2] π electrons.

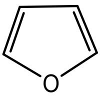
Ethlene oxide , succinic anhydride, γ-lactone etc. are also be considered as heterocyclic compounds but these compounds are easily converted into open chain derivative (acyclic compounds) and do not have any aromatic properties therefore above three compounds are not considered to be heterocyclic compound.

Heterocyclic compound having great importance to life, occur in nature. A wide variety of heterocyclic compounds are manufactured primarily by the drug industries, all the heterocyclic compounds having pharmacological activities.

Classification:

Heterocyclic compounds are classified as follows.

- Five member heterocyclic compounds containing one heteroatom.



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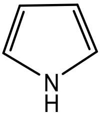

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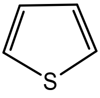
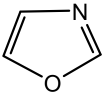


Thiophene

Five member heterocyclic compounds containing two heteroatom.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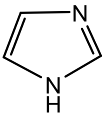
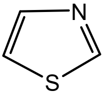
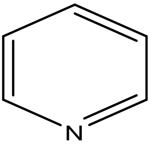

1,3-diazole


Thioazole

Six member heterocyclic compounds containing one heteroatom.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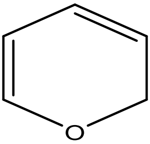
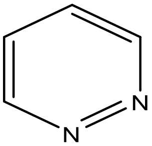

a-pyran

Six member heterocyclic compounds containing two heteroatoms.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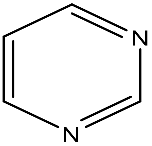
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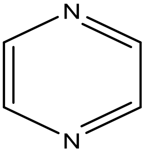
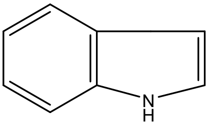

Pyrazine

Bicyclic compounds containing one hetero atom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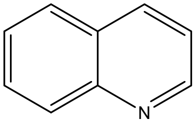
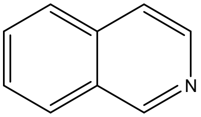
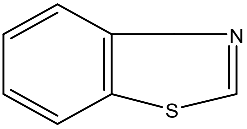
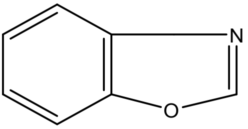

Quinoline

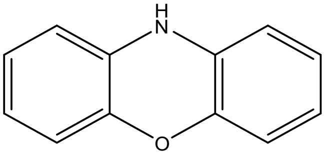

Isoquinoline

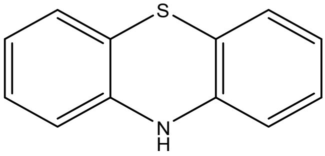
Bi-cyclic compounds containing two hetero atom.


Benzothiazole


Benzoxazole

- **Polycyclic compounds**





Importance of heterocyclic compounds:

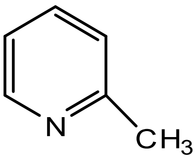
- Nitrogen containing heterocyclic compounds have pharmacological applications for ex. Triazole used as tranquilizers and sedatives.
- Some nitrogen containing heterocyclic compounds shows antipyretics, anti-inflammatory, and analgesics activities.
- Quinoline is used as an antiseptic.
- Fused trazolothiazoles are reported to be acts as insectcidaland fungicidal agents.
- Triazolobenzothiazole and Triazolobenzoxazole were found to be plant protective agents and used as agricultural fungicidal.

Nomenclature:

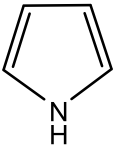
Trivial Name system

Nomenclature Based on Trivial Method Early organic chemists named heterocyclic organic compounds according to when they arose, how they were prepared, and a few other characteristics.

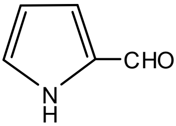
The sources of heterocyclic compounds are normally identified by their names. So, the name of the compound was determined by its source. Examples include picoline, a product derived from coaltar. The word pictus, translated as tarry in English, is derived from Latin.



As with heterocyclic compounds, heterocyclic compounds were also named based on the properties they possessed.

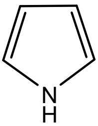


In the same way, Furfural's name is derived from its source. Furfural refers to barn oil. The compound is extracted from distilling barn oil.

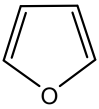


In the history of heterocyclic chemistry, trivial nomenclature is considered to be the first nomenclature method. Nevertheless, some disadvantages exist with the system. A trivial system will only reveal the formula and not the structure of a compound. There are approximately 60 trivial names recognized by the IUPAC system of nomenclature. This recognition is important because it can be used to create alternative compounds that have more systematic names or derivatives. The following examples illustrate how trivial names may be recognized for heterocyclic compounds.

Compounds



Pyrrole



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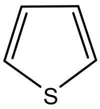
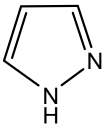
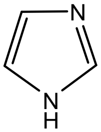


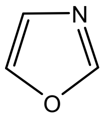
Thiophene



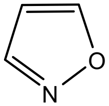
Pyrazole



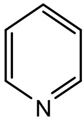
Imidazole



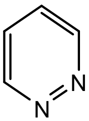
oxazole



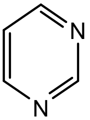
isoxazole



pyridine



pyridazine



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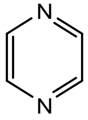

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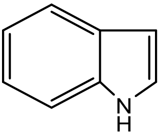
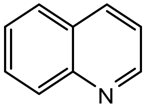
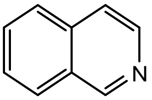


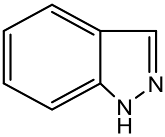
1*H*-indole



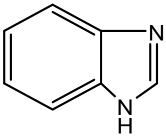
quinoline



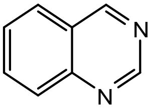
isoquinoline



1*H*-indazole



1*H*-benzo[*d*]imidazole



quinazoline

SYSTENATIC METHOD OF NOMENCLATUTRE: IUPAC Name System

This is most widely used nomenclature system for monocyclic heterocyclic compounds especially for three to ten membered ring systems. These members have various degree of unsaturation containing one or more heteroatoms. The systematic nomenclature gives important structural information. The most relevant system that is recommended by IUPAC for nomenclature of heterocyclic compounds is the Hantzch-Widmann system of nomenclature. This nomenclature system specifies the nature, position, ring size, number, and types of heteroatoms present in any heterocyclic compounds. This systematic method generally derived the nomenclature using the following syntax;

Name = prefix + stem + suffix

The stem: From 3 to 10 members, it determines the ring size.

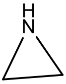
The suffix: Based on these factors, it determines whether a system is saturated or unsaturated

Whether N is present or absent It is the size of the ring.

Classification Heterocyclic compounds can be divided into two categories based on their structural and electronic arrangements

Aliphatic heterocyclic compounds
Aromatic heterocyclic compounds

Cycles amines, amides, ethers, and thio-ethers are examples of aliphatic heterocyclic compounds. A polycyclic heterocyclic containing only single bonds is called a saturated heterocyclic. Aliphatic heterocyclic are mainly affected by ring strain. In the figure above, you can see examples of such compounds.



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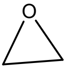

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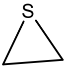

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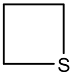

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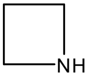

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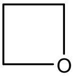

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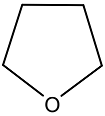
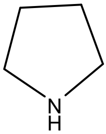


tetrahydrofuran



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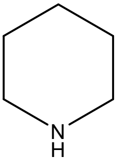

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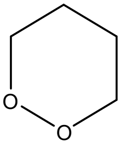
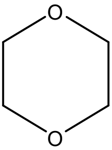


1,2-dioxane



1,4-dioxane

Following are the important points to be remembered during the systematic nomenclature of heterocyclic compounds.

In this nomenclature the nomenclature of heterocyclic compounds are assigned by combining 'prefix' (that indicate the heteroatom present) with 'stem' (that indicate the ring size as well as the saturation and unsaturation in the ring) and 'suffixes'. The common prefixes are shown in Table 1

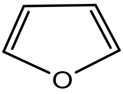
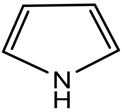
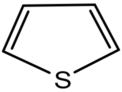
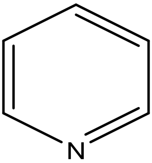
S. No.	**Heteroatom**	**Symbol**	**Prefix**
1	Oxygen	O	Oxa
2	Sulphur	S	Thia
3	Selenium	Se	Selena
4	Nitrogen	N	Aza
5	Phosphorous	P	Phospha
6	Arsenic	As	Arsa
7	Antimony	Sb	Stiba
8	Bismuth	Bi	Bisma
9	Silicon	Si	Silia
10	Boron	B	Bora

2. Common Prefix for Heteroatoms (arranged in the preferential order)

Last vowels of prefixes are replaced by the respective name ending words. Depending upon the size of ring.

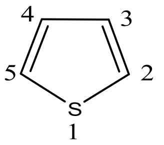
S.No	Ring Size	Unsaturated Ring	Saturated Ring
1	3	iren	Irane
2	**4**	ete	Etane
3	**5**	**ole**	Olane
4	**6**	**ine**	Inane
5	**7**	**epine**	Epane
6	**8**	**ocine**	Ocane
7	**9**	onine	Onane
8	**10**	ecine	Ecane

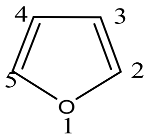
For ex:

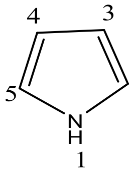
formula	trivalname	IUPAC name
 Furan	Furan	oxole
	Pyrrole	azole
	Thiophene	thiole
	Pyridine	azine

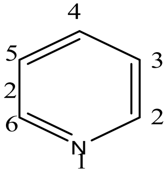
3. In a monocyclic compounds containing only one heteroatom, the numbering is started from hetroatom.

For ex.

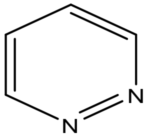
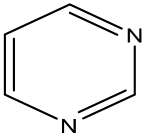
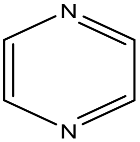






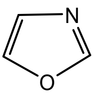


4. When two or more same type of heteroatom's are presents, the prefixes di, tri, etc. are used.

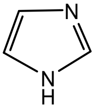
formula	trivalname	IUPAC name
	Pyridiazine	1,2-diazine
	Pyrimidine	1,3-diazine
	Pyrazine	1,4-diazine

5. When the ring contains more than one type of heteroatom's then the position 1(first preference) is given to the element from the highest group number of the periodic table, for ex. first preference is go to Oxygen(O) (gr. no. VI) before Nitrogen (N) (gr. no. V), and Sulphur (S) (gr. no. VI) Before Nitrogen (N) (gr. no. V).

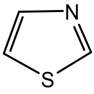
6. **Similarly, preference is given to Nitrogen (N) (gr. no. V) before Silicon (Si) (gr. no. IV) and Phosphorous (P) (gr. no. V) Before Silicon (Si) (gr. no. IV)**
7. **If two heteroatoms presents in the same group number then the preference is given to the element of lowest atomic number. For ex. first preference is go to Oxygen(O) (gr. no. VI, atomic no. 8) before Sulphur (S) (gr. no. VIatomic no. 16) The order of preference is used in the naming of heterocycles.**
8. **The direction of numbering round the ring is such thst the numbers are kept to a minimum. For ex.**



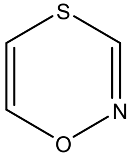
1,3-Oxazole



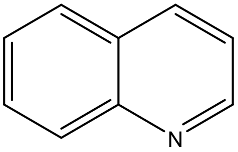
1,3-diazole



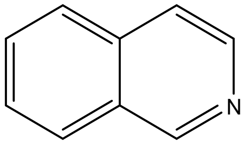
1,3-Thioazole



1,4,2-oxathiazine

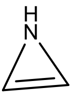


1-azanaphthalene

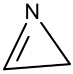


2-azanaphthalene

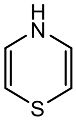
9. If the ring contains maximum number of non-cumulative double bonds and saturated atom, the position of this saturated atom is given the lowest possible locant and is numerically shown by an italic capital prefix-H



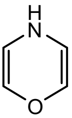
1*H*-azirine



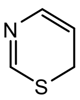
2*H*-azirine



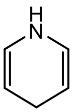
4*H*-1,4-thiazine



4*H*-1,4-oxazine



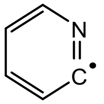
6*H*-1,3-thiazine



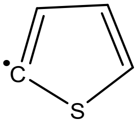
1,4-dihydropyridine

10. Naming of different anion radicals and cations of heterocyclic ring system:

i) Naming of radical: in the radical name, the parent name ends 'e' is deleted by '–yl' and radical name is used as suffix.

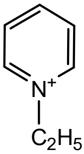


2-Pyridyl/
Pyridin-2-yl

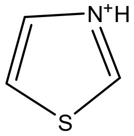


Thiophen-2-yl

ii) Naming of cations: the parent name ends in **–e** is deleted by **-ium**.

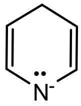


1-ethylpyridinium

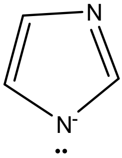


thiazol-3-ium

iii) Naming of anions: the parent name ends in **–e** is deleted by **-ide**.



4*H*-pyridin-1-ide

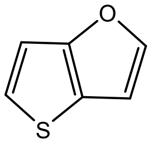


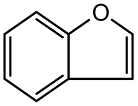
imidazol-1-ide

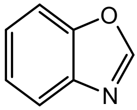
II] The naming of Fused Ring System:

The systematic name of this type of ring system is derived by regarding common atoms as belonging to both ring system.

In fused heterocyclic system, two components are present then one is chosen as the base component and the other is attached component.

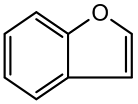

thieno[3,2-*b*]furan

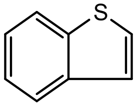

benzofuran


benzo[*d*]oxazole

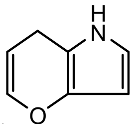
Rules for deriving the base component of a fused ring system;

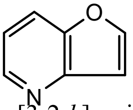
1. When one heterocyclic ring is present, this is considered as the parent or base component.


benzofuran


benzo[*b*]thiophene

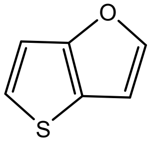
2. If more than one heterocyclic ring are present, the nitrogen containing ring is selected as the base component.

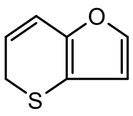

1,7-dihydropyrano[3,2-*b*]pyrrole


furo[3,2-*b*]pyridine

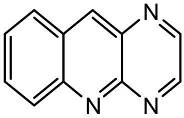
3. If nitrogen is absent and both the components contain hetero atoms other than nitrogen, the order of preference is
$O > S > Se > Te > P > As > Si > B$.

If two heteroatoms presents in the same group number then the preference is given to the element of lowest atomic number. For ex. first preference is go to Oxygen (O) (gr. no. VI, atomic no. 8) before Sulphur (S) (gr. no. VIatomic no. 16) the order of preference is used in the naming of heterocycles.

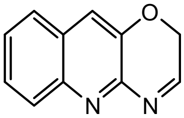

thieno[3,2-*b*]furan


5*H*-thiopyrano[3,2-*b*]furan

4. If the components have larger number of rings, select the component containing the largest number of ring as base.

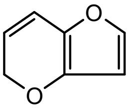


pyrazino[2,3-*b*]quinoline

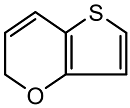


2*H*-[1,4]oxazino[3,2-*b*]quinoline

5. If the rings are different size, choose the larger one

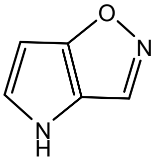


5*H*-furo[3,2-*b*]pyran

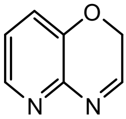


5*H*-thieno[3,2-*b*]pyran

6. If the rings contain different hetero atoms and if the hetero cyclic ring contains rings of same size with different number of hetero atoms, the ring with greater number of hetero atoms is selected as base component.

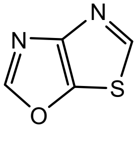


4*H*-pyrrolo[2,3-*d*]isoxazole

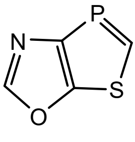


2*H*-pyrido[3,2-*b*][1,4]oxazine

7. If rings are equal size and contains equal number of different hetero atoms of same group, the ring is selected as per following preference.
O > S > N > P > As > Si >Ge> B

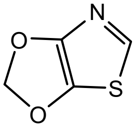


thiazolo[4,5-*d*]oxazole

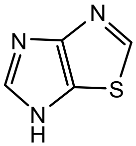


[1,3]thiaphospholo[4,5-*d*]oxazole

8. If rings are of equal size and contains equal number of hetero atoms, the ring is selected as base component which contain different hetero atoms.

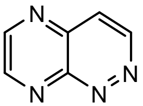


[1,3]dioxolo[4,5-*d*]thiazole

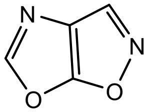


6*H*-imidazo[4,5-*d*]thiazole

9. If rings are of equal size and contains same kinds of hetero atoms, the ring is selected as base component which the lower number before fusion.



pyrazino[2,3-*c*]pyridazine



oxazolo[4,5-*d*]isoxazole

The naming of second component or attaché component is as follows

The second component is added as prefix to the name of the base component, the prefix is derived by replacing 'e' of the name of ring system by 'o'.

Prefixes for some heterocycles and second component:

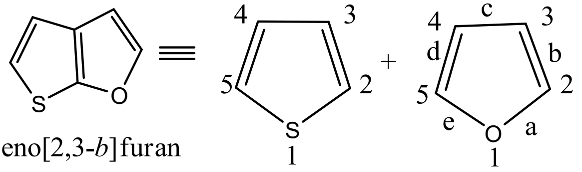
Pyrazine : pyrazino
Pyrazole : pyrazolo
Benzene : Benzo

Some non- standards prefixes in fusion names

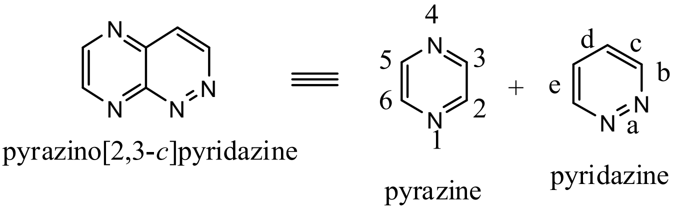
Thiophene : Thieno
Quinoline : quino
Puridinepyrido
Isoquinoline : Isoquino
Imidazole : Imidazo
Furan Furo

a, b, c identification:

Bonds present in the ring system of base component are identified by the letters **a, b, c, d** etc. to distinguish isomers, the peripheral sides of parent compound are given the letters **a, b, c, d** etc. begning with a for side-1,2. b for side-2,3. c for the side-3,4 etc. these numbers applied to the prefixed component (as separate unit) not to combined system.



thieno[2,3-*b*]furan

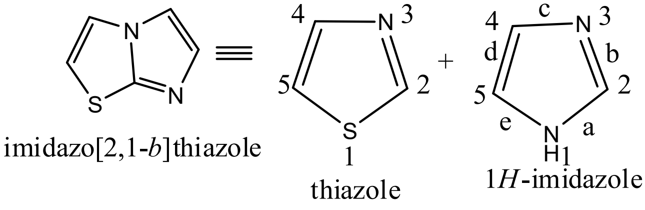


pyrazino[2,3-*c*]pyridazine

pyrazine

pyridazine

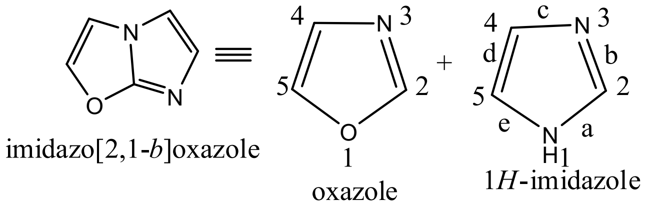
The common hetero atoms of both the ring are considered to posses that heteroatom.



imidazo[2,1-*b*]thiazole

thiazole

1*H*-imidazole



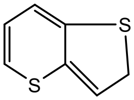
imidazo[2,1-*b*]oxazole

oxazole

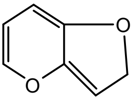
1*H*-imidazole

Numbering of Fused Heterocyclic compounds:

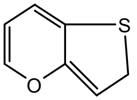
1. The position of hydrogen atom is denoted by italic H and attached before the second component and smallest possible number is given.



2*H*-thieno[3,2-*b*]thiopyran

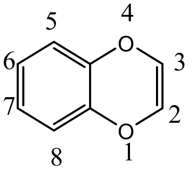


2*H*-furo[3,2-*b*]pyran

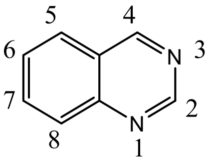


2*H*-thieno[3,2-*b*]pyran

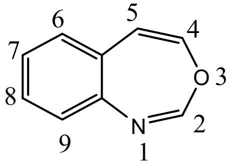
2. Fusedheterocyclic rings are numbered indendently as base component and attached component. The numbering is started from bridge head and having smallest possible number. If the more than one hetero atoms presents rule number 5 is to be used.



benzo[*b*][1,4]dioxine

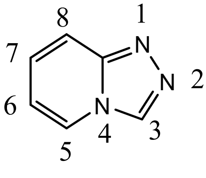


quinazoline



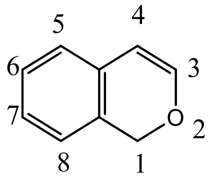
benzo[*d*][1,3]oxazepine

3. Common carbon atom OF TWO rings having smallest number and cannot be denoted.



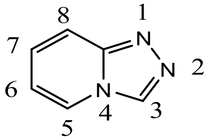
[1,2,4]triazolo[4,3-*a*]pyridine

4. The presence of additional His indicated by italic capital H having lowest possible number.

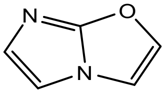


1*H*-isochromene

5. In systematic nomenclature system, the hetero atom at ring junction having individual number.



[1,2,4]triazolo[4,3-*a*]pyridine



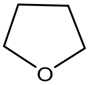
imidazo[2,1-*b*]oxazole

4. Replacement Nomenclature:

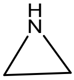
i) Replacement nomenclaturebased on replacement of carbon atom of carbocycle by hetero atom.

ii) The hetero atoms present are indicated by prefixing.

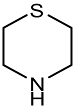
iii) carbocyclic ring is named by IUPAC name system.



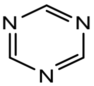
Oxacyclopentane



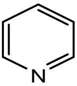
Azacyclopropane



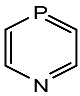
1-thia-4-azacyclohexane



1,3,5-triazabenzene



Azabenzene



1,4-azaphosphabenzene

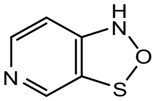
In the replacement nomenclature the sequence rules and numbering of heteroatoms are decided as follows.

1. Heteroatoms having higher priority are selected as first preference.

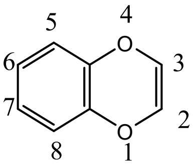
2. Multiple bonds are selected as second preference.

3. Substituents are selected as third preference.

The carbocyclic ring system with saturation is designated without using prefix for H.

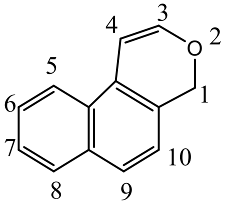


2-oxo-3-thia-1,5-diazindane



benzo[*b*][1,4]dioxine

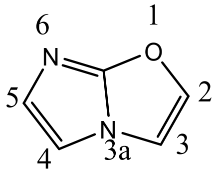
1,4-dioxanaphthalene



4*H*-benzo[*f*]isochromene

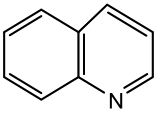
1-H-2-oxophenanthrene

Heteroatoms at the ring junction is designated the same position with suffix ‘a’ or ‘b’ as an adjacent nonjunction carbon atom.

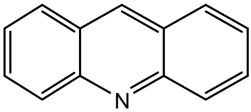


imidazo[2,1-*b*]oxazole

1-oxo-3a-diazapentalene



quinoline
Azanaphthalene



acridine
Azaanthracene

Nomenclature of Bridge heterocyclic compounds:

Bicycle bridged structure of heterocycles having following rules.

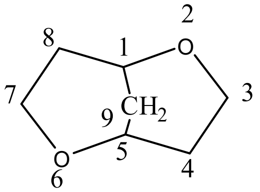
- In bicycle bridged structures, numbering is started in such a way that lowest possible number is given to bridged atom.

- If bicycle bridged structures contain hetero atom and multiple bond , then preference is given to hetero atom.
- In the nomenclature of such structure prefix bicycle.
- Number of carbon atoms separating the bridge heads is written in square bracket with descending order of numbers; the numbers are separated by full stop.
- The numbering starts from one of the bridged atoms and proceeds through the longest possible path to the second bridge head and then by the second longest path to the first bridge head carbon atom and at last by shortest path from one bridge head to second bridge head atom.
- If two hetero atoms present, then preference order is given as

O > S > N > P > As > Si >Ge> B

Example:

1.



2,6-dioxabicyclo[3.3.1]nonane

Hetero atom = O

No. of hetero atom = 2 - di

total no. of atoms = 09

Acyclic hydrocarbon = Nonane

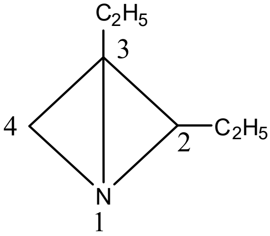
no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [3.3.1]

therefore = 2,6-dioxabicyclo[3.3.1]nonane

2.



2,3-diethyl-1-azabicyclo[1.1.0]butane

Hetero atom = N

total no. of atoms = 04

Acyclic hydrocarbon = Butane

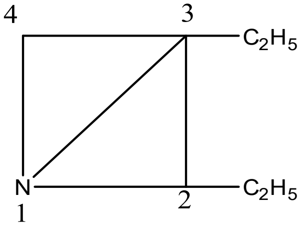
no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [1.1.0]

therefore = 2,3-diethyl-1-azabicyclo[1.1.0]butane

3.



2,3-diethyl-1-azabicyclo[1.1.0]butane

Hetero atom = N

total no. of atoms = 04

Acyclic hydrocarbon = Butane

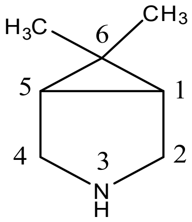
no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [1.1.0]

therefore = 2,3-diethyl-1-azabicyclo[1.1.0]butane

4.



6,6-dimethyl-3-azabicyclo[3.1.0]hexane

Hetero atom = N

total no. of atoms = 06

Acyclic hydrocarbon = Hexane

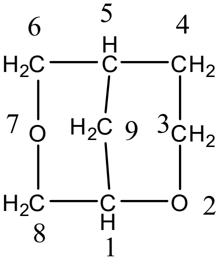
no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [3.1.0]

therefore = 6,6-dimethyl-3-azabicyclo[3.1.0]hexane

5.



2,7-dioxabicyclo[3.3.1]nonane

Hetero atom = O

no. of hetero atom = 02= di

total no. of atoms = 09

Acyclic hydrocarbon = Nonane

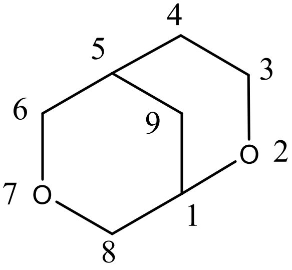
no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [3.3.1]

therefore = 2,7-dioxabicyclo[3.3.1]nonane

6.



2,7-dioxabicyclo[3.3.1]nonane

Hetero atom = O

Total no. of hetero atom = 02- di

total no. of atoms = 09

Acyclic hydrocarbon = nonane

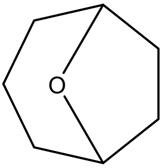
no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [3.3.1]

therefore = 2,7-dioxabicyclo[3.3.1]nonane

7.



8-oxabicyclo[3.2.1]octane

Hetero atom = O

Total no. of hetero atom = 01

total no. of atoms = 08

Acyclic hydrocarbon = octane

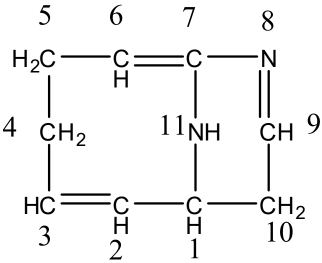
no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [3.2.1]

therefore = 8-oxabicyclo[3.2.1]octane

8.



8,11-diazabicyclo[5.3.1]undeca-2,6,8-triene

Hetero atom = N

Total no. of hetero atom = 02-di

total no. of atoms = 11

Acyclic hydrocarbon = undeane

no. of rings = 02

prefix= bicyclo

no. of atoms which seperate bridge head atom in three ways and arrangement is in descending order= [5.3.1]

therefore = 8,11-diazabicyclo[5.3.1]undeca-2,6,8-triene

•••

2. NONAROMATIC HETEROCYCLES

Synthesis, Reactivity and importance of following ring systems

1. Azirines
2. Oxaranes
3. Thiiranes
4. Diazirines
5. Diazridines
6. Azetidines

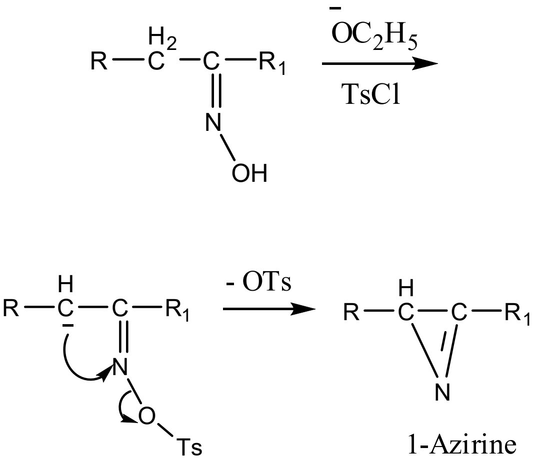
1] Azirines:

There are two possible isomers of aziridines only 2H-aziridine have been isolated.

Synthesis:

1) Neber rearrangement:

1-azirine is an intermediate in base catalyzed rearrangement of oxime P-toluene sulphonyl derivative to á-aminoketone. This reaction is known as Neber rearrangement.

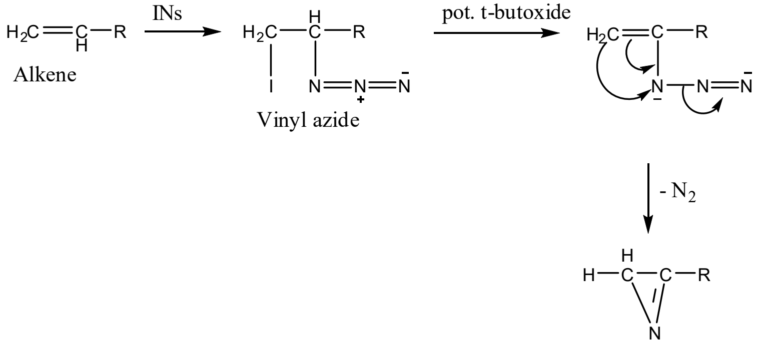


2) From vinyl azide:-

i) The first general synthesis of 1-azirine was developed by Smollinsky.

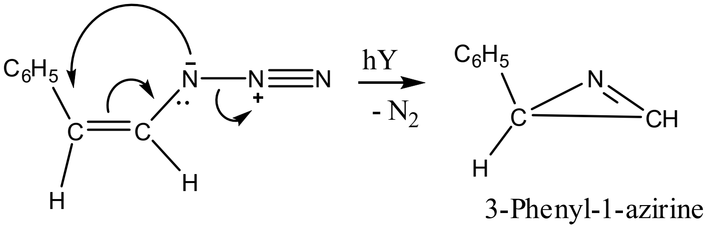
ii) Vinyl azide prepared by the addition of iodine azide to an alkene.

iii) Vinyl azide on hydrolysis/ thermolysis with pot. t-butoxide gives 1-azirine.



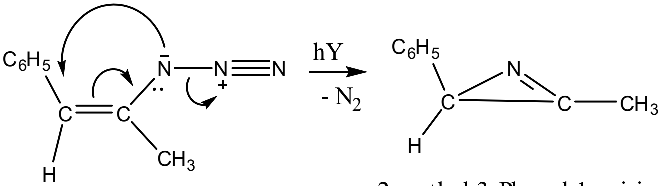
1-Azirine

iv) Photolysis of vinyl azide under nitrogen atomosphere at - 30^0C.



3-Phenyl-1-azirine

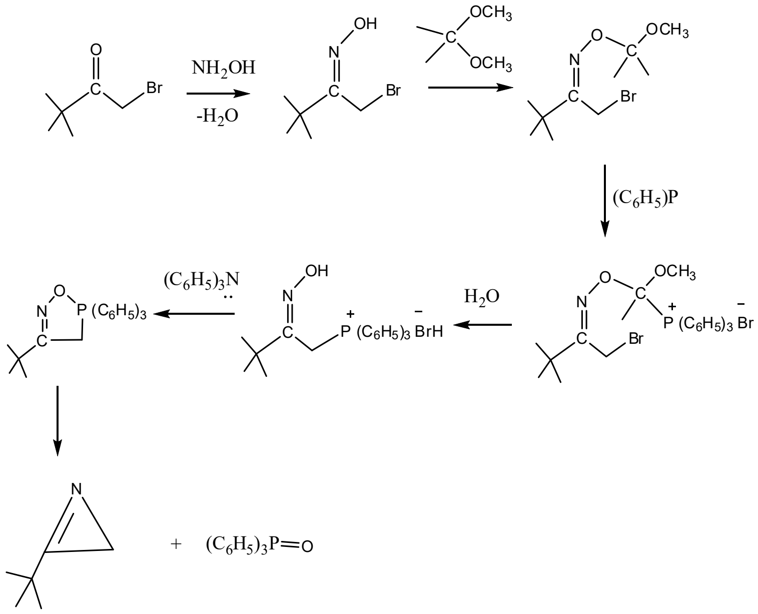
v)



2-methyl-3-Phenyl-1-azirine

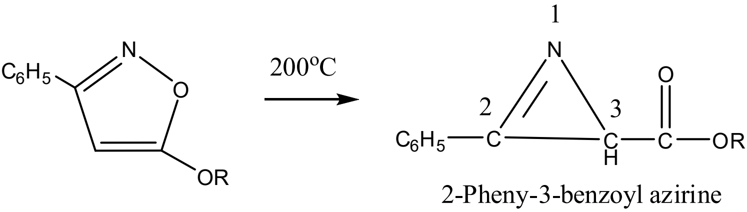
3) From á-bromoketoxime:

Preparation of 1-azirine using á-bromoketoxime.



4) From Pyrolysis or Photolysis of isoxazole:

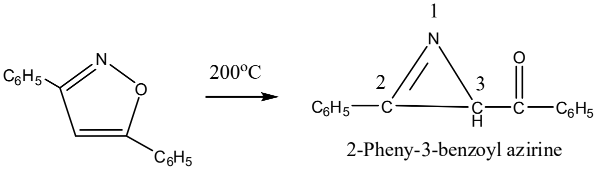
i) Pyrolysis of 5-alkoxy substituted isoxazole gives 1-azirine.



5-alkoxy-isoxazole

2-Pheny-3-benzoyl azirine

ii)



3,5-diphenylisoxazole

2-Pheny-3-benzoyl azirine

phenyl(3-phenyl-2*H*-azirin-2-yl)methanone

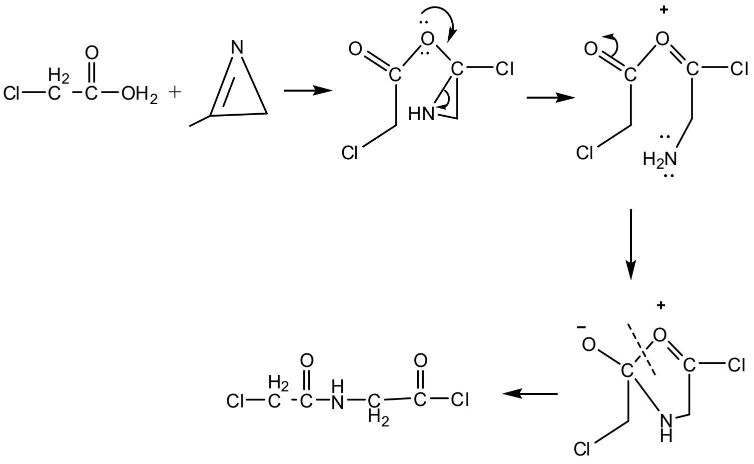
Chemical Properties:

1-azirines undergoes several types of reactions and is an extremely useful reagent for the preparation of different heterocycles.

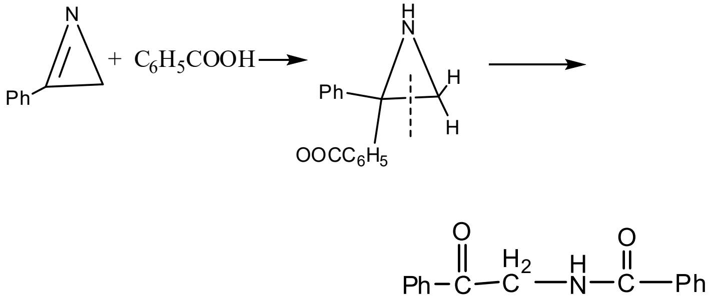
1] Reaction with acids:

Azirines are non-basic and thus insoluble in dilute acids. Azirines gives ring opening reactions with strong acids.

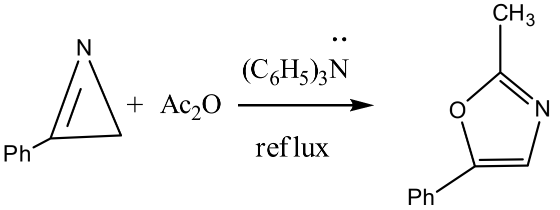
The reaction with chloroacetic acid or benzoic acid opens the ring which subsequently undergoes rearrangement to give product.



iii)

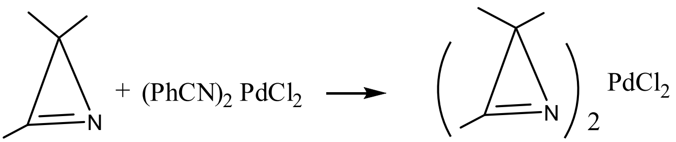


iii) 2- phenyl azirine with acid chloride or acid anhydride in the presence of triethylamine gives oxazole.



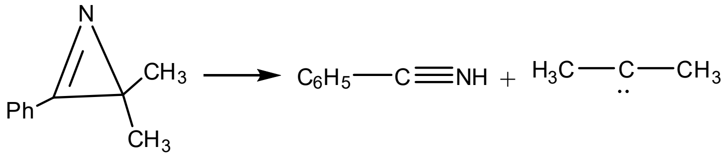
2] Formation of complex:

1-azirine form stable complexes with dichloro bis-(benzonitrile) palladium.

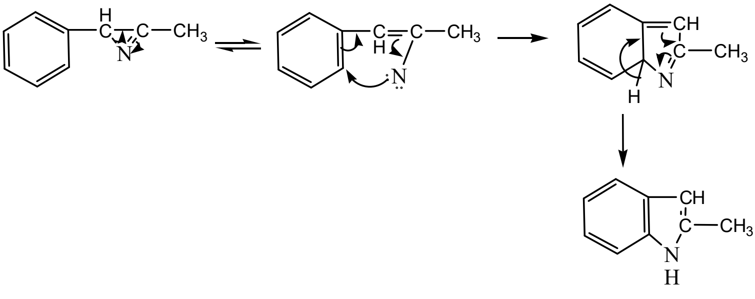


3] Ring opening reaction:

2-phenyl-3,3-dimethyl-2H- azirine thermally or photo chemically undergoes ring opening reactions to carbine and nitrile molecule.



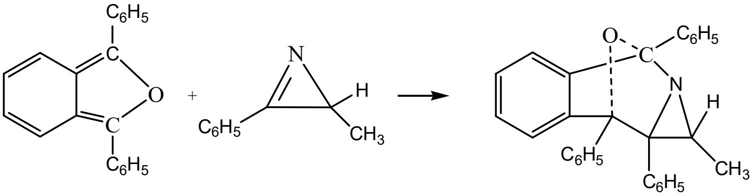
ii) –methyl-phenyl-2H azirine rearranges to 2-methylindole via C-N bond cieavage.



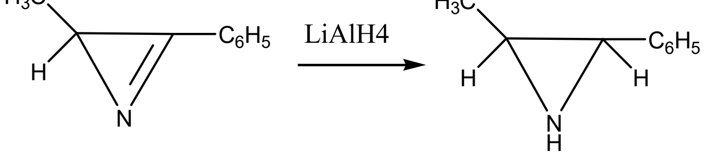
2-Methylindole

4] The Diel's Alder Reaction:

1,3-diphenylisobenzofurancycloadds to 3-methyl-2-phenylazirine to form adduct.



5] Reduction: A number azirine have been reduced by lithium aluminium hydride [$LiAlH_4$] to aziridine.



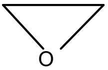
2-Methyl-3-phenylaziridine

II] Oxiranes :

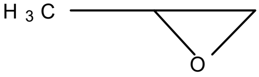
The saturated hetero-cyclic three member three member ring containing oxygen atom is known as oxirane.

Oxirane ring has also been designated as an ‘epoxide’ ‘ethylene oxide’ or some times as á,â-epoxyethane or 1,2-oxidoethane.

For ex:



oxirane



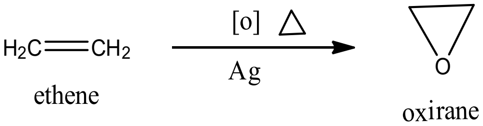
2-methyloxirane

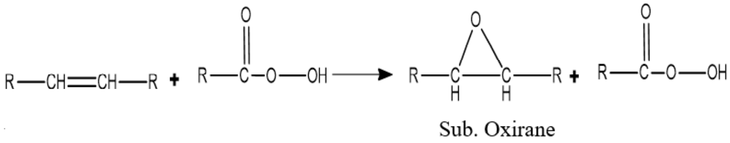
Oxirane used in the manufacture of 1,2-ethanediol, emulsifier, plastic and resins. Methyloxirane also used to make detergents and lubricants.

Synthetic Methods:-

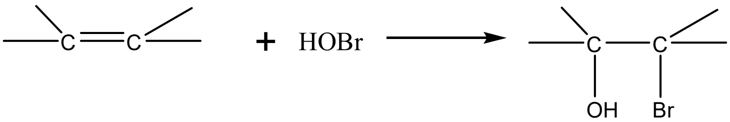
1) From oxidation of alkenes :-

(a) Oxirane can be prepared by the direct oxidation of ethylene by air over silver catalyst at elevated temperature.

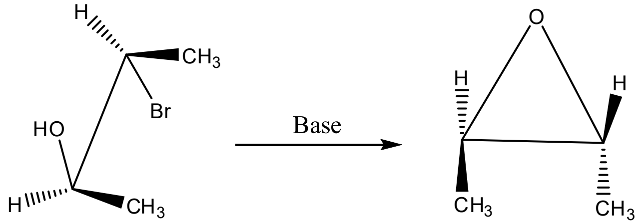




(b) Alkenes react with HOBr or HOCl to give halohydrin which is converted in to oxirane by alkali.

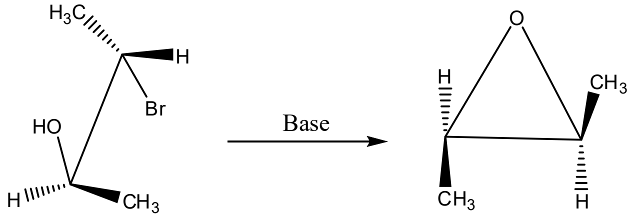


Threo-3-bromo-2-hydroxy butane gives cis epoxide & erythreo-3-bromo-2-hydroxy butane gives trans epoxide



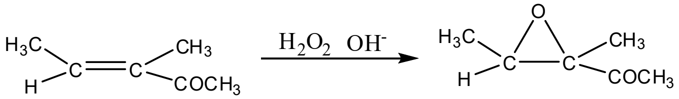
(2*R*,3*R*)-3-bromobutan-2-ol (2*R*,3*R*)-2,3-dimethyloxirane

Threo-3-bromo-2-hydroxy butane 2,3-dimethyl oxirane
cis-epoxidey butane



(2*R*,3*S*)-3-bromobutan-2-ol (2*R*,3*S*)-2,3-dimethyloxirane

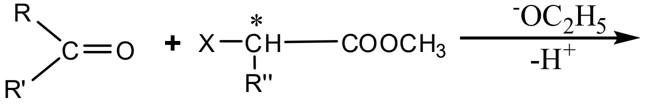
Erythreo-3-bromo-2-hydroxy butane 2,3-dimethyl oxirane
trans-epoxidey butane

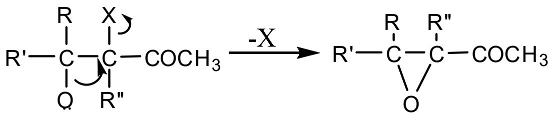


(*E*)-3-methylpent-3-en-2-one
3-methylpent-3-en-2-one

1-(2,3-dimethyloxiran-2-yl)ethanone
2-acetoxy-2,3-dimethyl oxirane

2] Nucleophilic Alkylation of carbonyl compounds:-

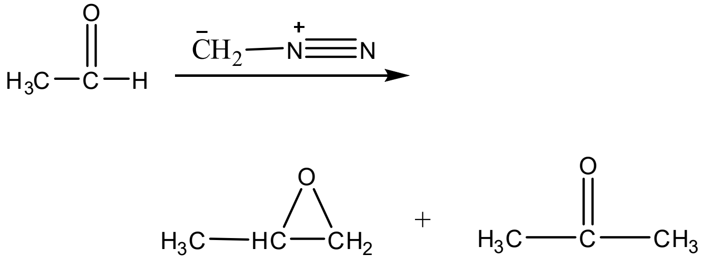




2-acetoxy oxirane

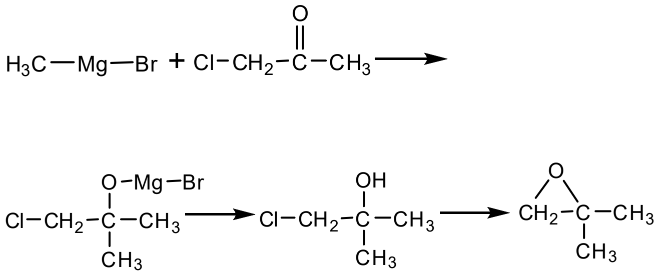
3] Methylene Insertion:-

This method is useful for epoxide formation in which addition of diazoalkane, particularly diazomethane.



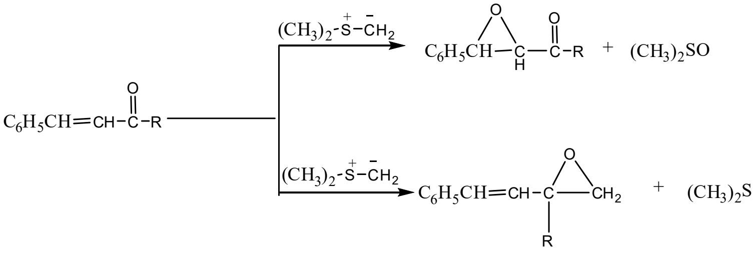
2-methyloxirane

4] α-haloketone on condensation with Grignard reagent gives halohydrin which on dehydrohalogenation from oxirane.



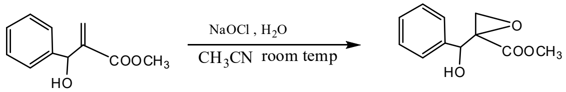
2,2-dimethyloxirane

5] Dimethylsulfonium methylide [(CH$_3$ S$^+$-CH$^-_2$] as methylene transfer agent to the carbonyl group for oxirane formation.



[R = H or C$_6$H$_5$]

Miscellaneous method: hydroxy alkenes under goes oxidation of ketone with the simultaneous epoxidation of the methylene group in the presence of sodium hypochlorite.



methyl 2-(hydroxy(phenyl)methyl)acrylate

methyl 2-(hydroxy(phenyl)methyl)oxirane-2-carboxylate

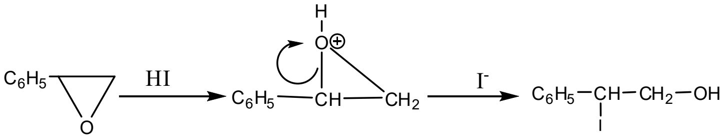
Chemical properties:-

Ring opening reactions:

The ring is readily cleaved by variety of reagent because of strain present in the oxirane ring . In the solution, the reaction of oxiranes involve both electrophile as well as nucleophilic attack.

1) Electrophilic ring opening reaction :-

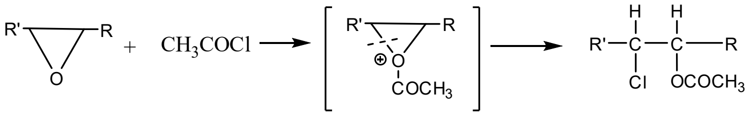
Electrophilic reagent attack on oxirane most readily with the opening of bond between oxygen and the least substituted carbon atom the direction of the ring opening is considerably affected by the nature of substituent's present on oxirane ring.



2-phenyloxirane
styrene oxide

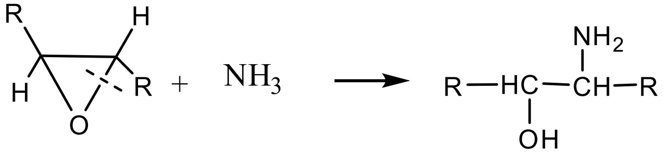
2-iodo-2-phenylethanol

Acid chloride react with oxiranes as follows, electrophillic attack on the hetero atom results in the formation of an intermediate oxonium ion ,which being most reactive is readily attacked by chloride ion at the carbon atom with opening the ring.



2) Nucleophilic ring opening reactions :-

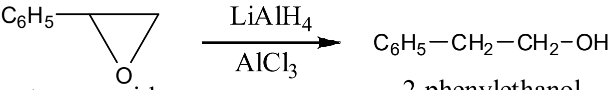
i) Nucleophilic reaction involves attack at the opposite to the oxygen atom with inversion of configuration. Reaction with aq. ammonia at room temperature produce amino alkanol.



amino alkanol

ii) Reduction:-

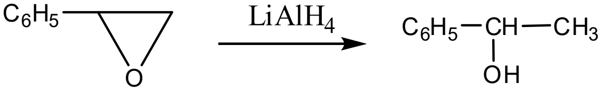
a) Reduction of asymmetrical oxirane with $LiAlH_4$ in presence of $AlCl_3$ produces 2-phenylethanol.



styrene oxide

2-phenylethanol

b) Reduction of asymmetrical oxirane with $LiAlH_4$ produce highly substituted alkanol,



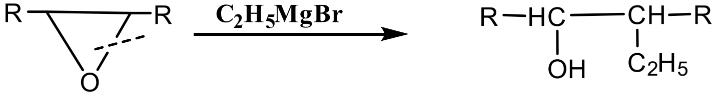
styrene oxide

1-phenylethanol

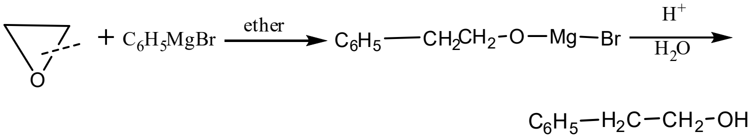
α-phenylethanol

iii) Reaction with Grignard Reagent:-

Oxirane react with Grignard reagent to produce long chain alkanol.



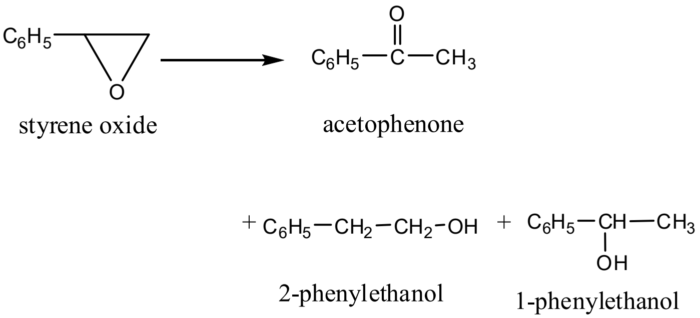
Reaction between oxirane and grignard reagent is extensively employed for the preparation of primary alcohol.



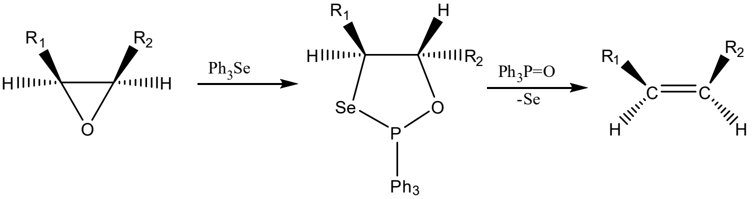
2-phenylethanol

3) Thermal or Photochemical Reaction :-

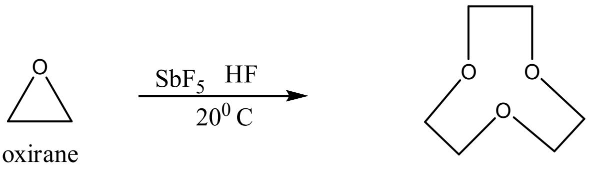
i) On thermal or photochemical reaction styrene oxide in solution yields a mixture of products.



ii) Triphenylphosphine selenide also deoxygenate oxirane in the presence of trifluoroacetic acid and produces olefins with retention of configuration.



iii) Oxirane react with antimony penta fluoride [SbF_5] it convert to its trimeric form 1,4,7-trioxonane

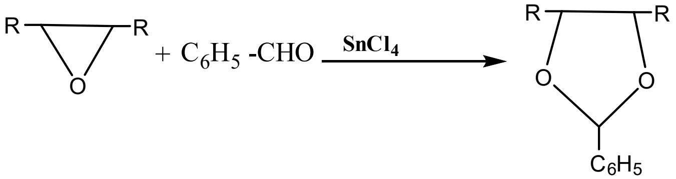


oxirane

1,4,7-trioxonane

iv) Reaction with carbonyl compounds

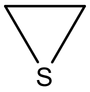
Carbonyl compounds reacts with oxiranes and provide dioxalanes with cleavage of C–O bond and undergo ring expansion.

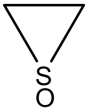


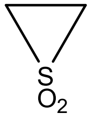
III] Thiiranes:-

Thiirane is three membered ring containing one sulfur atom. Thiirane has also be designated as ethylene sulfide, episulfide or thiacyclopropane.

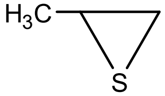
Thiiranes have much in common with the other three membered hyterocycles but some of their chemistry is associated specifically with the presence of sulfur atom. Thiirane because of ability of 'S' atom to expand its valence shell, exits in two oxidized forms (I) the monoxide and (II) the dioxide.

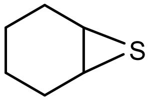






The higher homolog's of Thiirane have been called by the name alkene sulfides for ex. Propylene Sulfide, Cyclohexane Sulfides respectively.





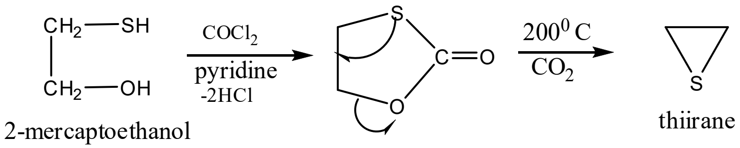
Synthetic compounds having considerable application in the textile industry. Ethylene sulfide has been used as an intermediate in polymeric composition. Fluorinated thiiranes may be used as refrigerants and as fire extinguishers. Dithioglycidyl thiophosphate have been used as strong insecticidal effect.

Synthetic Methods:-

Thiirane and its derivatives have been prepared by following methods:

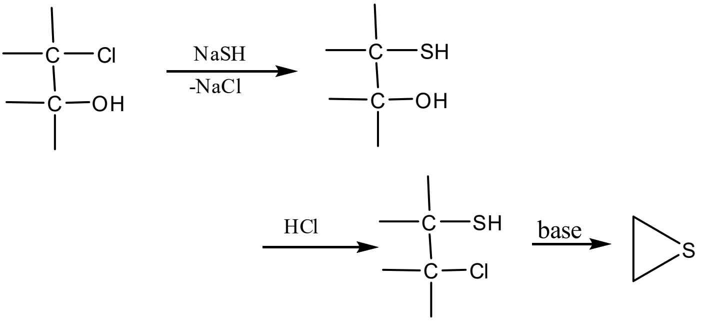
1) From Mercaptoethanol:-

Thiirane is prepared from 2-mercaptoethanol by treating it with phosgene [$COCl_2$] in ethyl acetate and pyridine to give monothioethylene carbonate which on decarboxylation gives thiirane.



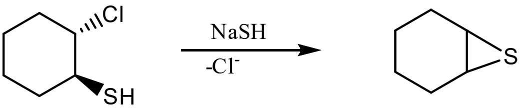
2) Ring Closure Reaction:-

i) Thiirane have also been prepared by treatment of 2-halosulfides (or 2-halomercaptons) with alkali.



2-halosulphides are prepared from 2-hydroxysulphides which in turn can be made from 1,2-halohydrin.

ii) Cyclohexane sulfide is obtained by the reaction of sodium bicarbonate on trans-2-chlorocyclohexane thiol.



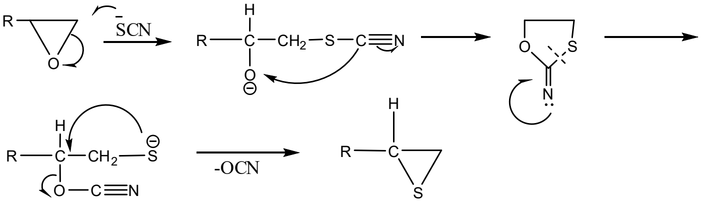
(1*S*,2*S*)-2-chlorocyclohexanethiol

7-thiabicyclo[4.1.0]heptane

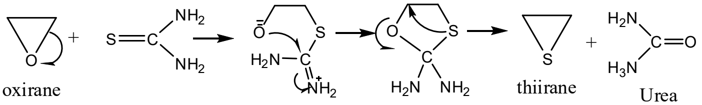
3) From Epoxide [oxirane]:-

Thiiranes are obtained from oxiranes by reaction with thiocyanate ions or with thiourea, cyclic intermediate is formed in this reaction.

i)



ii)



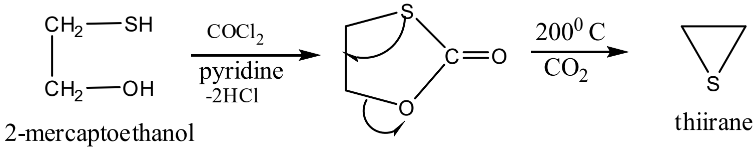
oxirane

thiirane

Urea

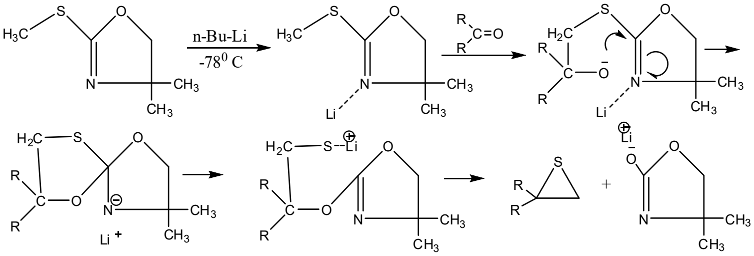
4) From Mercaptoethanol:-

2-mercaptoethanol react with phosgene in ethyl acetate and pyridine gives monoethylene carbonate which on decarboxylation gives Thiirane.



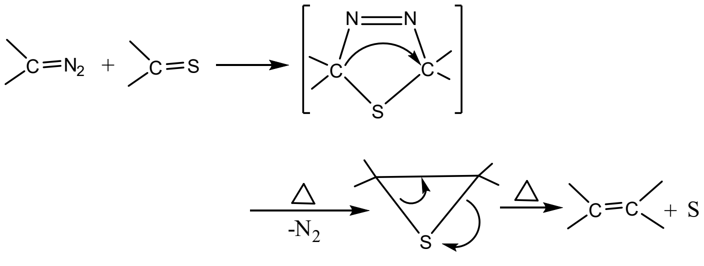
5) From Aldehyde and Ketone:-

Thiirane derivatives have been prepared from 2-(thiomethyl)-2-oxazoline and an aldehyde or ketone in the presence of n-butyl lithium in the following manner.



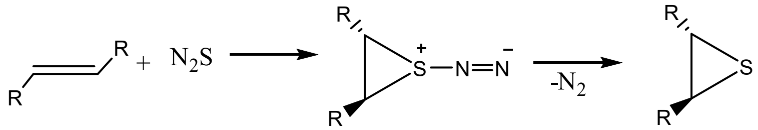
6) From Diazoalkane:-

The reaction between diazoalkane and thioketone has been extensively studied and useful for alkene synthesis.



7) From alkene Episulfidation:-

An alkene on Episulfidation by nitrogen sulphide (N_2S) generated in situ from 5-aryloxy-2,3,4-thiadiazole forms a three membered zwitter ionic species. This on denitrogenation gives thiiranes derivative.



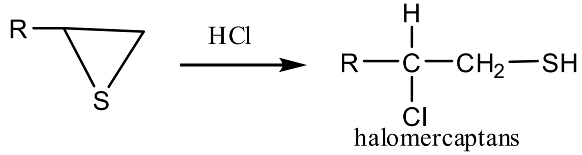
Chemical properties:-

I) Ring Opening Reaction :-

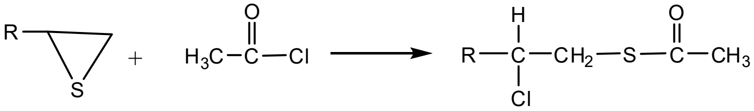
All reaction of thiiranes involve ring opening reactions electron density of sulfur atom is lower than that of oxygen atom in oxirane, thus thiiranes less reactive towards electrophillic reagent and reactivity toward nucleophilic substitution similar to or greater than oxirane.

a) Electrophilic Ring opening reactions:-

i) Reaction with HCl :- Thiiranes react with HCl to give halomercaptans



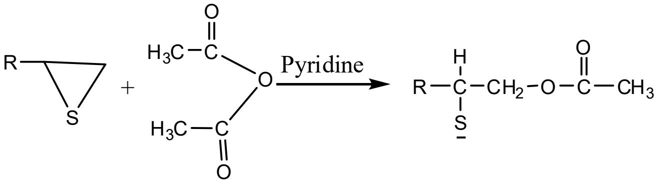
ii) Reaction with Acid Chloride:-

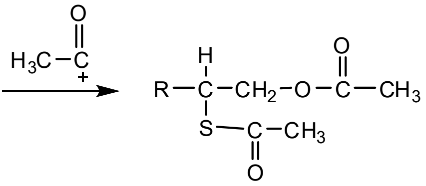


In this reaction electrophillic attack of the reagent on the 'S' atom.

iii) Reaction with Acetic anhydride :-

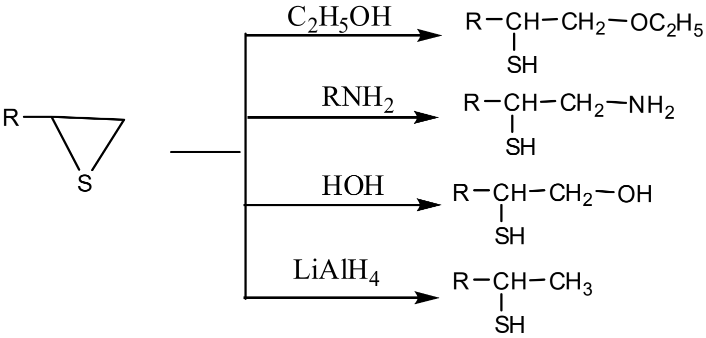
Thiirane react with acetic anhydride in pyridine the attack of acetate ion takes place at less substituted carbon atom.





b) Nucleophilic Ring opening reaction:-

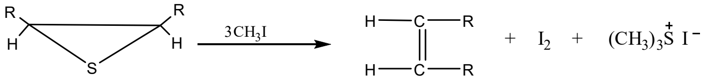
A nucleophile first attack at an unsubstituted carbon atom to open the ring in an unsymmetrical episulphide.



II) Desulfurization :- [Removal of sulfur atom]

Desulfurization take place more efficiently by the reaction of thiirane with trialkyl phosphate or triphenyl phosphite or triphenyl phosphine. The reaction of thiiranes with CH_3I involve the desulfurization of episulphonium salt as intermediate to produce stereo selective alkene.

i)



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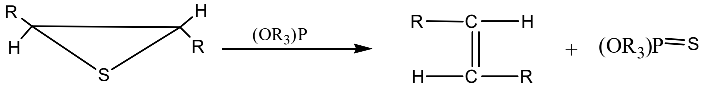

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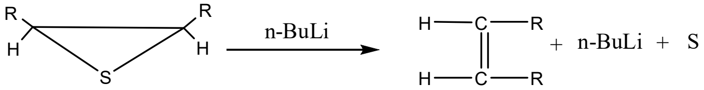

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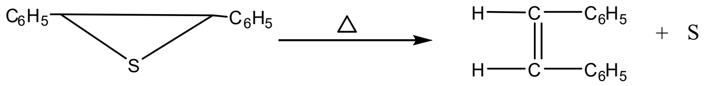
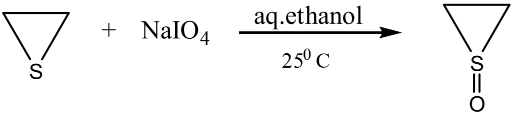


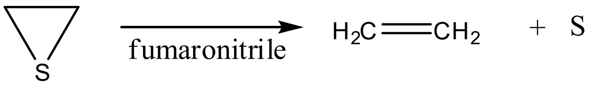
(*Z*)-1,2-diphenylethene

III) Oxidation :- When thiirane is oxidized with peroxy acid or sodium periodate ($NaIO_4$) in aq ethanol gives thiirane monoxide.

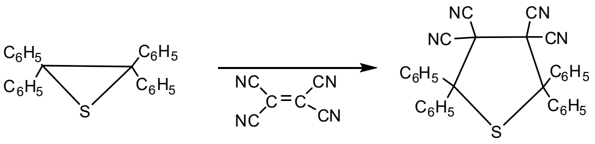


IV) Thermal or Photochemical Reactions :-

i) When a mixture of thiiranes and fumaronitrile exposed to ultraviolet radiation gives alkene by desulfurization.

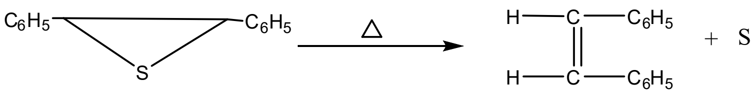


ii) The ultraviolet irradiation of thiirane in presence of tetracyanoethylene gives tetracyano thiophene



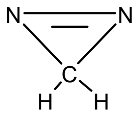
2,2,5,5-tetraphenylthiophene-3,3,4,4(2*H*,5*H*)-tetracarbonitrile

iii) The pyrolysis of thiirane gives alkene.

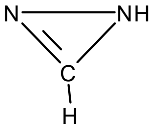


3] Diazirines :-

Diazirines is the compound containing two nitrogen atoms in an unsaturated three membered ring . Two isomeric diazirines (I) and (II) are possible but (II) has antiaromatic character.



(I)

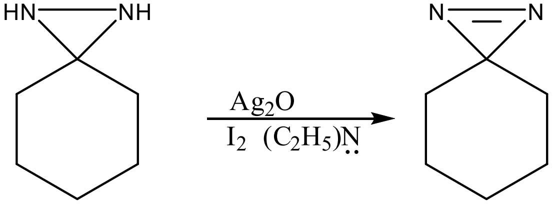


(II)

Synthetic Methods:-

I] By the oxidation of Diaziridines:-

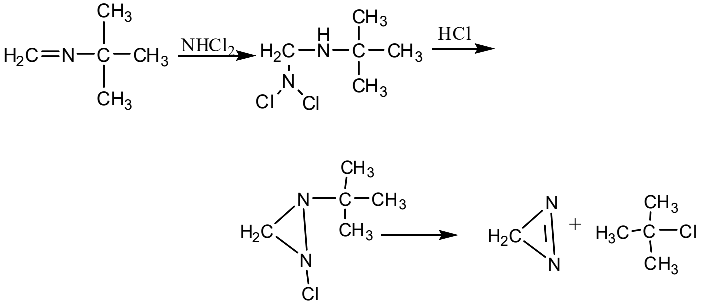
Diaziridines can be readily oxidized by a number of common oxidizing agent i.e Ag_2O,HgO and $KMnO_4$.



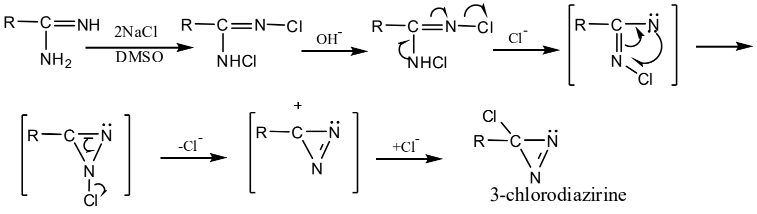
1,2-diazaspiro[2.5]oct-1-ene
3,3-pentamethylene diazirine

II) From t-alkylazomethane and Dihalomaine:-

i) A superior method for the synthesis of diazirines involve the addition of dichloro or difluoroamine to a formaldehyde imine (t-butylazomethine) in carbon tetrachloride.



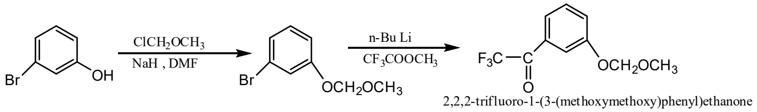
ii) 3-halogenodiazirines are easily obtained by halogenations of alkyl or aryl amidines in aqueoud dimethyl sulphoxide.



3-chlorodiazirine

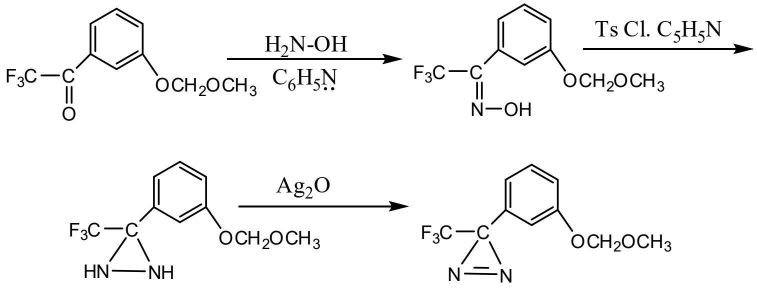
iii) From m-bromophenol:-

It was first converted in to acetal followed by its reaction with n-butyl Lithium and methyl trifluro acetate to give ketone.



2,2,2-trifluoro-1-(3-(methoxymethoxy)phenyl)ethanone

Its reaction with hydroxylamine, formation of aziridine and finally oxidation with silver oxide gives diazirines.



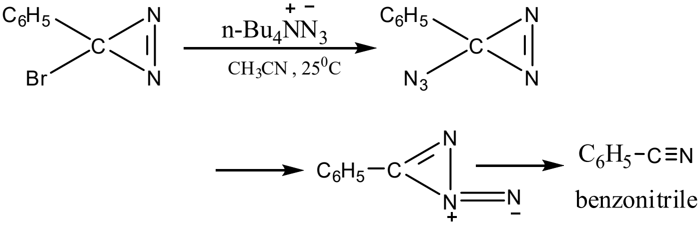
diazirines derivative

Chemical Reaction:-

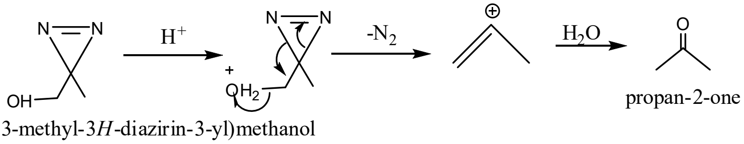
I] Reaction with Nucleophile and Electrophile

i) Diazirine shows sensitivity toward attack of nucleophile and electrophile.

Aryl bromodiazirine is attacked by an azide ion to give sub.product,which subsequently convert in to benzonitrile.

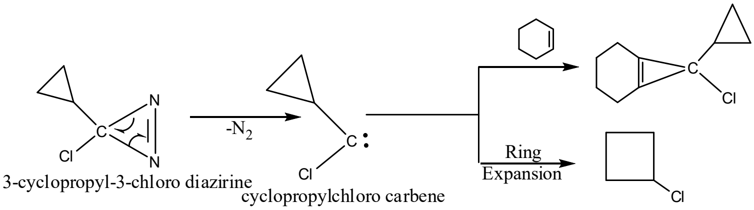


ii) When attack by acid on Diazirine ring opening proceeds by initial protonation of functional group in hydroxydiazirine and methylvinylazirine.

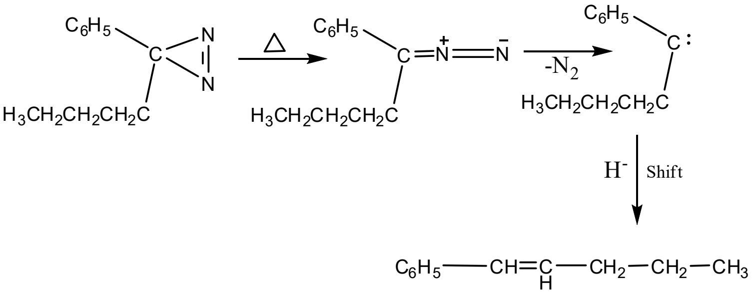


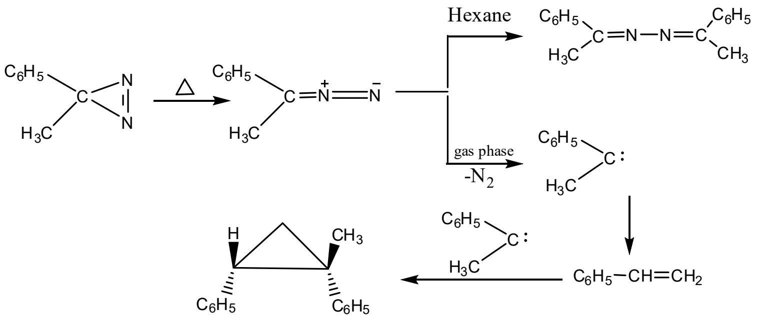
II] Photochemical and Thermal Decomposition:-

i) When 3-cyclopropyl-3-chlorodiazirine on photolysis yields, cyclopropyl chloro carbon ,which can be trapped by an alkene or can alternatively undergoes ring expansion to give 2-chlorocvclobutane.



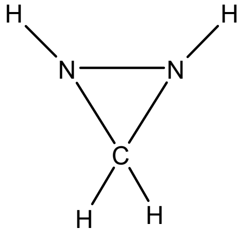
ii) 3-phenyl-3-n-butyldiazirine on thermolysis gives carbene which by a hydride shift gives a mixture at cis and trans 1-phenyl-1-pentene.





V] Diaziridines:-

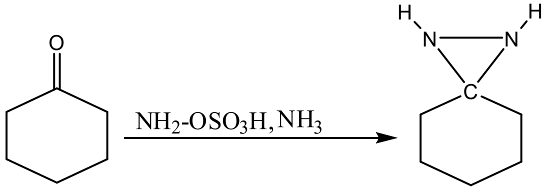
Diaziridines is a saturated compound containing two nitrogen atoms in a three membered ring.

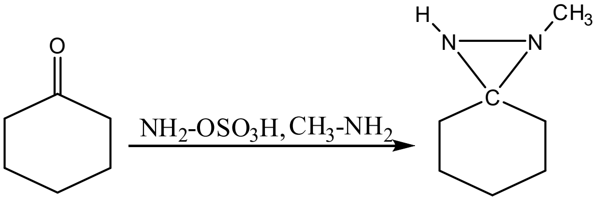


It was first synthesized by Schmitz in 1959.

Synthesis Methods:-

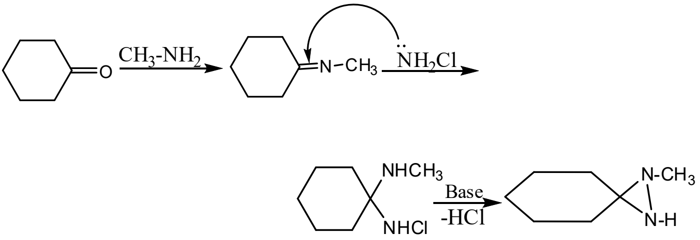
1) From Hydroxylamine-o-sulfonic acid and ketone. Cyclopentanone treated with hydroxylamine-o-sulfonic acid and ammonia gives rise to a diaziridines.





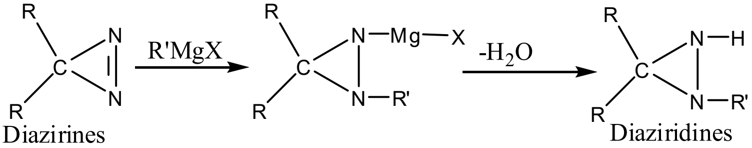
2) **From Schiff's Base :-**

Cyclopentanone on treatment with methyl amine to give Schiff base, A Schiff's adds on to a molecule of chloramines and then ring closer agent of terminal addition product in the presence of base gives diaziridines.



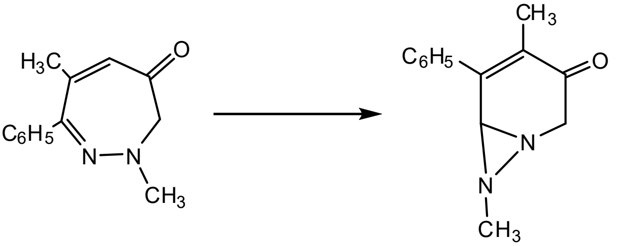
3) From Diazirines :-

Substituted diaziridines can also be prepared by the addition of grignard reagent to reactive double bond of Diazirine.



4) Photoisomerization:-

Diazepine converts rapidly in sunlight to its diaziridines isomers.



Diazepine

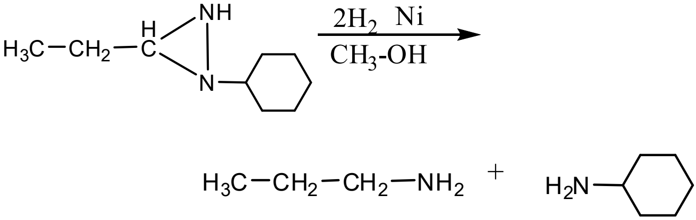
Diaziridines isomer

Chemical Properties:-

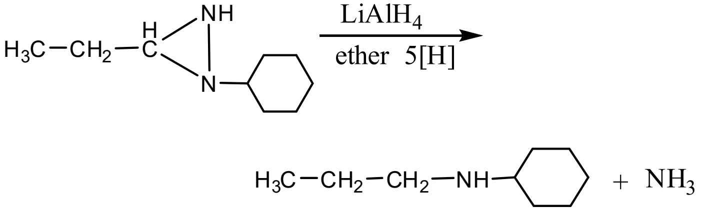
Diaziridine gives substitution reaction at nitrogen atom or fission of C-N bond takes place.

1) Reduction :-

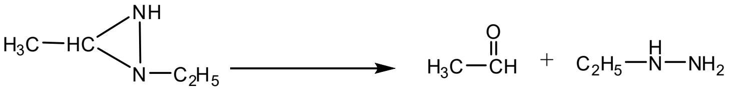
i) On catalytic reduction of substituted diaziridines gives two molecules of amines.



ii) Diaziridine on reduction with $LiAlH_4$ it gives ammonia and N-cyclohexylpropanamine.



2) Hydrolysis:-

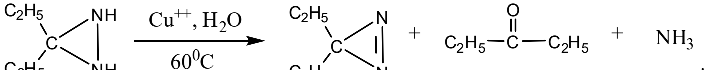


1-ethyl-3-methyldiaziridine acetaldehyde ethylhydrazine

1ethyl-3-methyldoaziridine on hydrolysis gives acetaldehyde and ethylhydrazine.

3) Oxidation:-

3,3-diethyl diaziridines under goes decomposition at 125^0 C by redox reaction, to give one mole of Diazirine, ketone & ammonia.

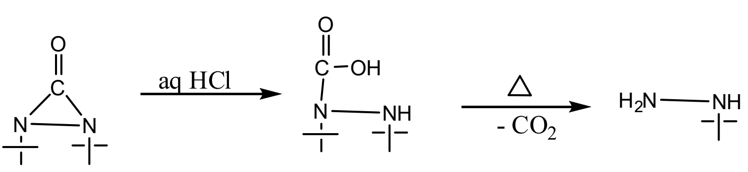


pentan-3-one ammonia

3,3-diethyldiaziridine 3,3-diethyl-3*H*-diazirine

4) Diaziridinone:-

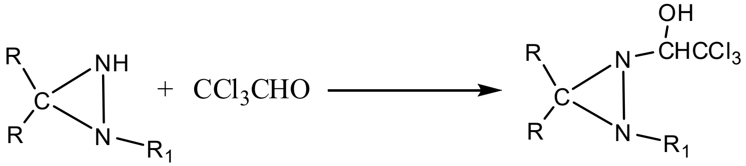
Diaziridinone undergo facile ring opening in eq. hydrochloric acid and subsequently decarboxylate to hydrazine derivative.



Sub-diaziridinone

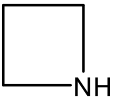
5) **Reaction with chloral:-**

Diaziridine contatining at N-H bond undergo certain reaction with chloral.



VI] **Azetidines:-**

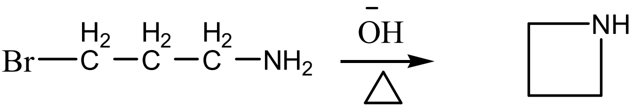
Azetidine is fully saturated four membered nitrogen containing compound, it is also called trimethylene imine.



azetidine

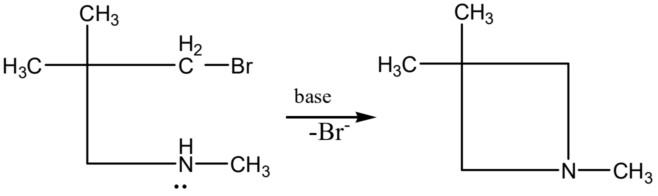
<u>Synthetic methods:</u>

1] Cyclization methods:- Azetidine and its derivatives can be prepared by intramolecular cyclization and cycloaddition. Azetidine is prepared from γ-bromopropylamine in the presence of base.



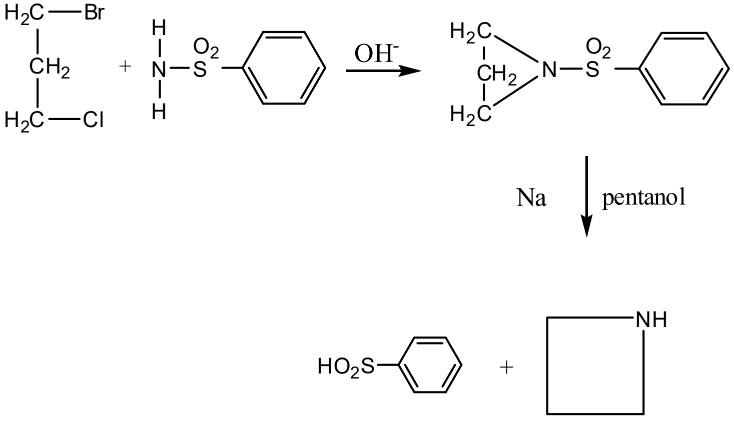
Azetidine

2] Cyclization takes place by nucleophilic displacement of halo group at one end of chain for ex. 1,3,3-dimethyl-N-methyl propane.



3] From trimethylene chlorobromide:

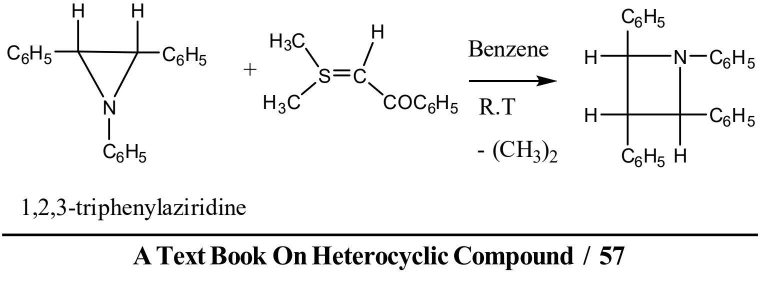
The cycloaddition of trimethylene chlorobromide with P-toluene sulphonamide, followed by reduction with sodium and pentanol.



azetidine

3] From Aziridines:-

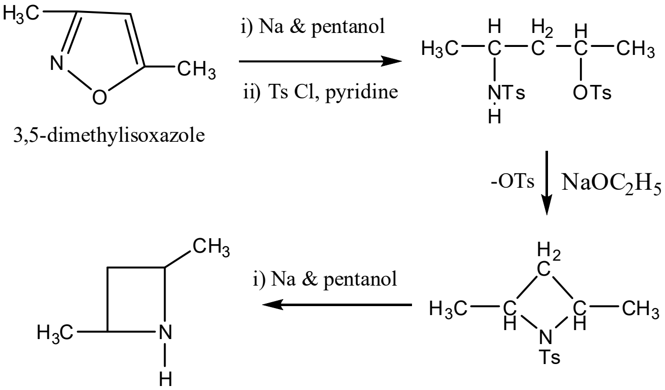
When substituted aziridine reacts with sulphur ylides (sulphurane) gives substituted azetidine in the presence of benzene at room temperature.



1,2,3-triphenylaziridine

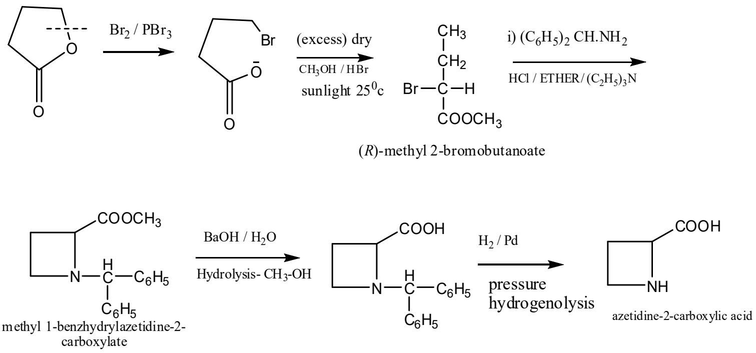
4] From Isoxazole Derivatives:-

3,5-dimethylisoxazole ring is first opened by treatment with sodium in n-pentanol and subsequently react with tosyl chloride and pyridine. Cyclisation then takes place in the presence of strong base to give 2,4-dimethyl(Ts) substituted azetidine. Which on reduction with Na & pentanol gives 2,4-dimethylazetidine.



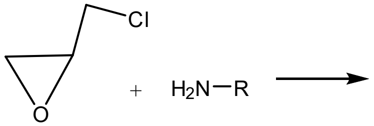
5] From Ò-lactone:- [Crom well and Rodebaugh]

Following sequence of the reactions involving ring opening and cyclization is Ò-lactone provides yield of azetidine-2-carboxylic acid.

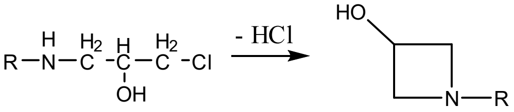


6] Reaction of Amines with Halogenoalkyl oxirane:-

Amines reacts with epichlorohydrin to give 1-alkyl-amino-3-chloro-2-alkanols. Which on heating at 50^{0}C cyclizes to give 3-hydroxyazetidine.



2-(chloromethyl)oxirane



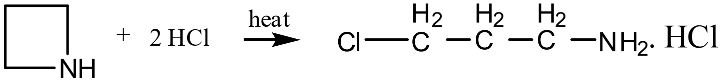
Chemical Properties:-

1] Ring opening reactions:-

Azetidine are more stable than aziridines because of less strained ring. These compounds shows less degree of reactivity and the opening of ring is more sluggish.

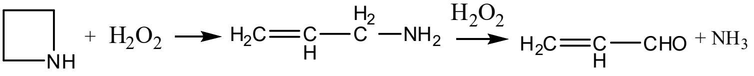
a) With HCl:-

Azetidine on heating with HCl gives 3-chloropropylamine hydrochloride.



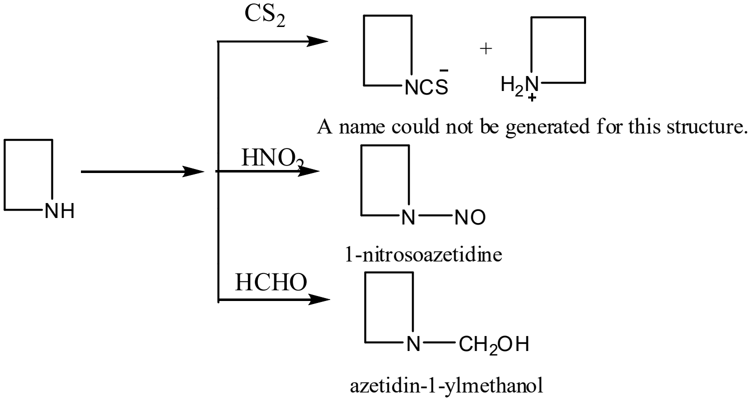
b) With H_2O_2:-

Opening of azetidine ring with H2O2 gives acrolein and ammonia.



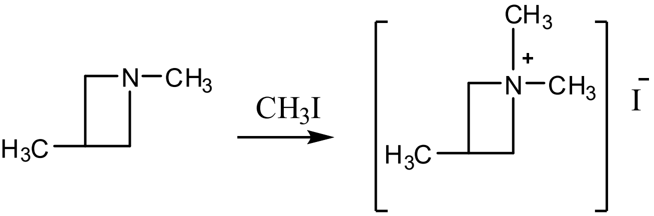
2] Formation of Azetidine derivative:-

Azetidine behaves like secondary aliphatic amines and shows similar reactions, such as carbon disulphide, form a salt, with nitrous acid form N-nitrosoazetidine and with formaldehyde to form N-hydroxymethyl azetidine.



4] Reaction with alkyl halide:-

N-methyl-3-methylazetidine react with CH_3I to give quaternization.



•••

3. FIVE AND SIX MEMBERED HETEROCYCLES WITH TWO HETERO ATOMS

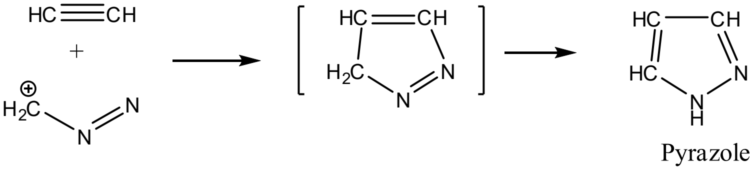
Synthesis, reactivity, aromatic character, and importance of following heterocycles:

1] PYRAZOLE:

The physical properties and the presence of pyrrazole nucleus in several important compounds led a special interest in the study of these compounds in a number of directions.

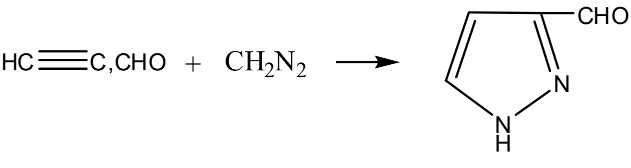
Synthesis of Pyrazoles;

i) By passing acetylene into a cold etheral solution of diazomethane

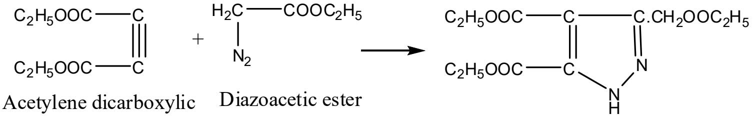


Pyrazole

ii) Proparglyceraldehyde and diazomethane



iii) Pyrazole derivative can be obtained from acetylene dicarboxylic ester and diazoacetic acid.

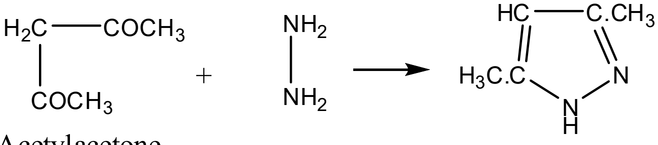


Acetylene dicarboxylic ester

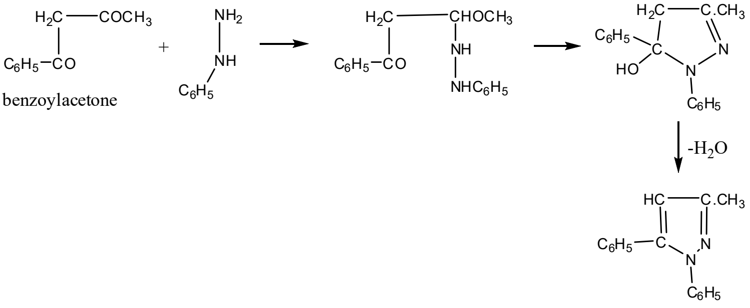
Diazoacetic ester

Pyrazoletricarboxylic ester

iv) Preparation of pyrazole involve the condensation of hydrazine with â-dicarbonyl compounds, (â-diketones and â-ketoaldehyde), â-ketoester , malondialdehydediethylacetal.

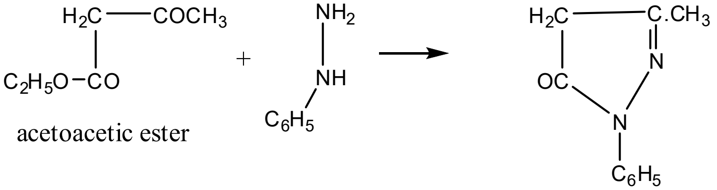

Acetylacetone

3,5-DimethylPyrazole


benzoylacetone

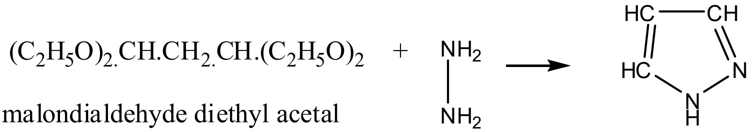
3-methyl-1,5-diphenyl Pyrazole

v) β-dicarbonyl compoundsmay be replaced by esters of β-ketoacids or malondialdehyde diethyl acetal (1,1,3,3-tetraethoxypropane) for ex.


acetoacetic ester

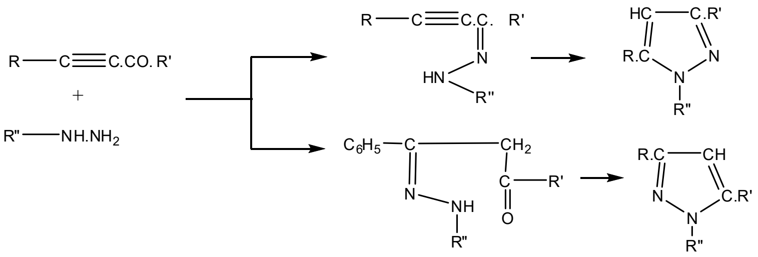
1- Phenyl-3-methyl-5-pyrazolone

vi)



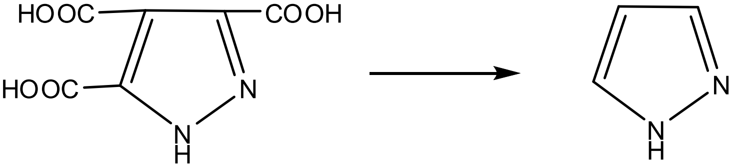
Pyrazole

vii) Pyrazoles may also be prepared by the reaction between acetylenic carbonyl compounds and hydrazine.



viii) The simpler pyrazole are obtained from their derivatives. For example.

Decarboxylation of various pyrazolecarboxylic acid, on heating gives pyrazole.

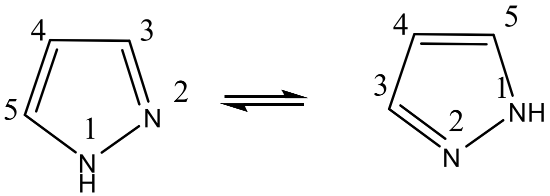


Pyrazole-3,4,5-tricarboxylic acid pyrazole

Properties:

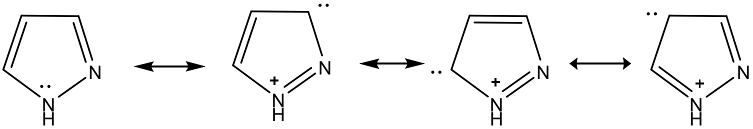
Pyrazole, a colourless solid with melting point 70^0c. and boiling point 185^0c, the most important property of pyrazole is the existence of tautomerism; which can only demonstrated in pyrazole derivative and not in the pyrazole itself.

Thus the two tautomeric form of pyrazole are I and II which clearly indicate that position 3 and 5 are equivalent and thus pyrazole forms only two C-alkyl derivatives, namely 3-(or5) and 4. It is interesting to note that although pyrazole it self form two C-alkyl derivatives and the N-alkyl or N-aryl pyrazole forms three C-alkyl derivative viz. 3,4 and 5.since in N-alkyl or N-aryl pyrazole derivatives tautomerism is not possible. And hence position 3 and 5 not longer equivalent.



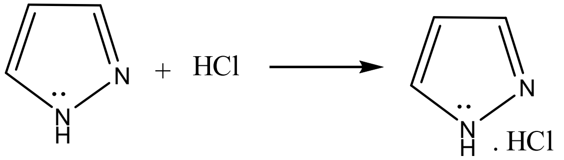
Tautomerism inpyrazole

Although pyrazole resembles with pyrrole in formula I, it differ strongly from pyrrole in it remarkable stability and more definitely basic character. In chemical property pyrazole is more nearer to pyridine and benzene than to pyrrole. It exhibits the aromatic properties even more than thiophene. In aromatic properties.viz. halogenations, nitration, and sulphonation, the group enters at position 4 due to a longer pi-electron density on C_4 than any other nuclear carbonatoms. The resonating structures of pyrazole are as shown.



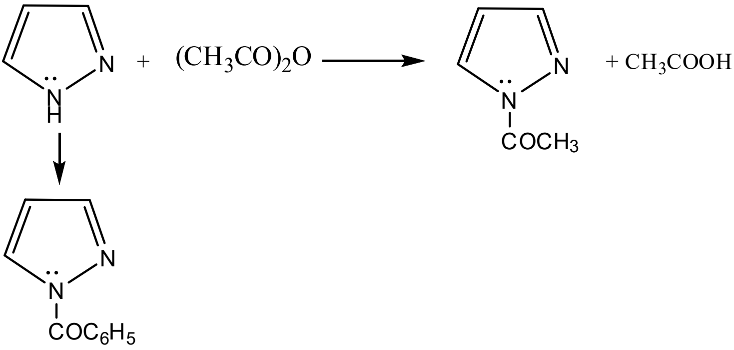
Chemical properties of pyrazole:

1] pyrazole is a feebly basic compound and forms salt with inorganic acids.



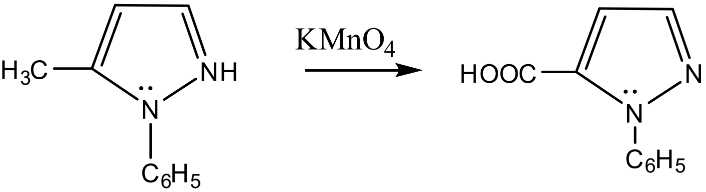
pyrazole hydrochloride

2] Acetylation and Benzoylation: the imino hydrogen of the pyrazole nucleus may be replaced by an acyl or benzoyl group.



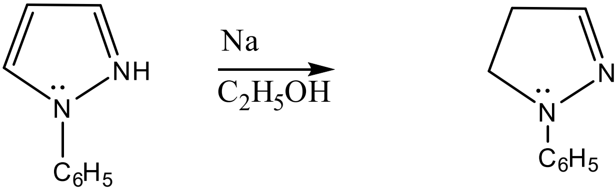
3] OXIDATION :

Like benzene pyrazole is very resistant to oxidation. But again like alkylated benzene, C-alkylated pyrazole may be readily oxidized to the corresponding carboxylic acid.

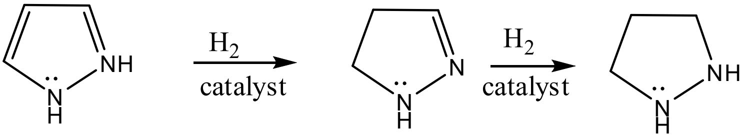


4] REDUCTION:

Although pyrazole it self is resistant to reduction by sodium-ethanol, its N-phenyl derivative may be reduced by sodium-ethanol to the corresponding pyrazoline.



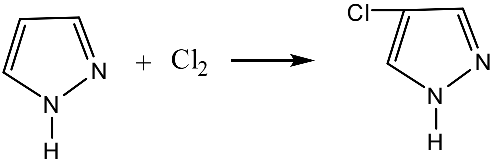
However, pyrazole it self may catalytically reduced to pyrazoline and pyrazolidine.



pyrazoline
pyrazolidine

5] HALOGENATION:

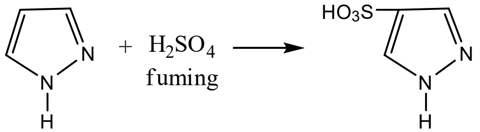
Halogenation takes place at position 4 to form 4-halopyrazole.



Pyrazole
4-chloropyrazole

6] SULPHONATION:

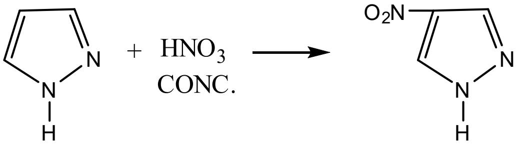
Fuming sulphuric acid leads to sulphonation at 4-position



Pyrazole
pyrazole-4-sulphonic acid

7] NITRATION:

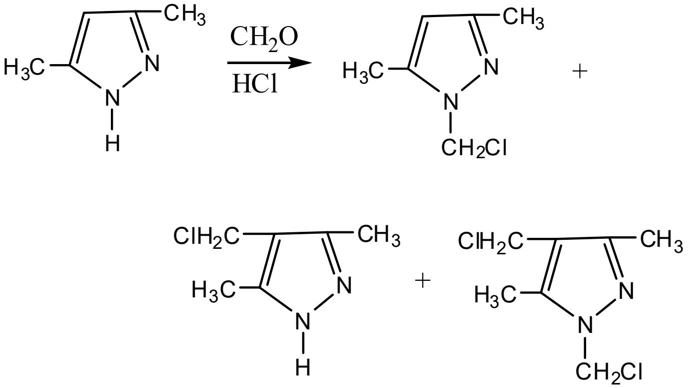
Pyrazole may readily nitrated by concentrated nitric acid.



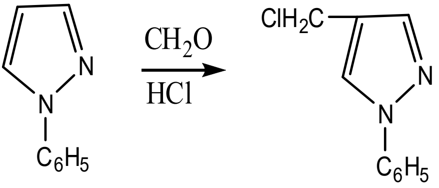
Pyrazole 4-Nitropyrazole

8] CHLOROMETHYLATION:

Pyrazole having free imino group cannot be chloromethylated; and in such cases carbinols are obtained.



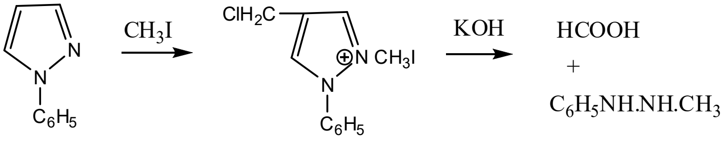
N-phenylpyrazole can readily be chloromethylated.



N-phenylpyrazole 4-chloromethyl-N-phenylpyrazole

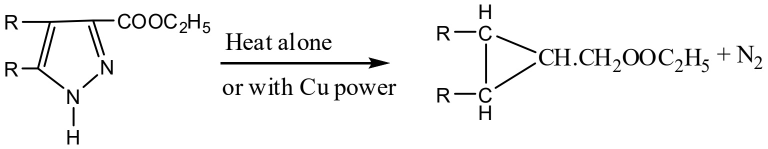
9] REACTION WITH ALKYL HALIDE:

N-phenylpyrazole when treated with methyl iodide forms quaternary pyrazole which on boiling with conc. Aq. KOH decompose to substituted hydrazine.



N-phenylpyrazole

10] EFFECT OF HEATING:

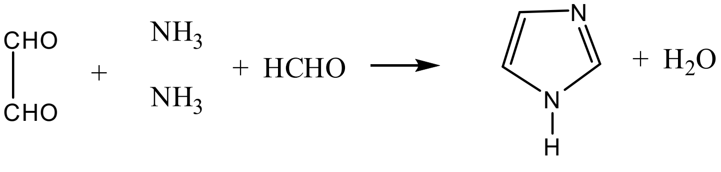


2] <u>IMIDAZOLE:</u>

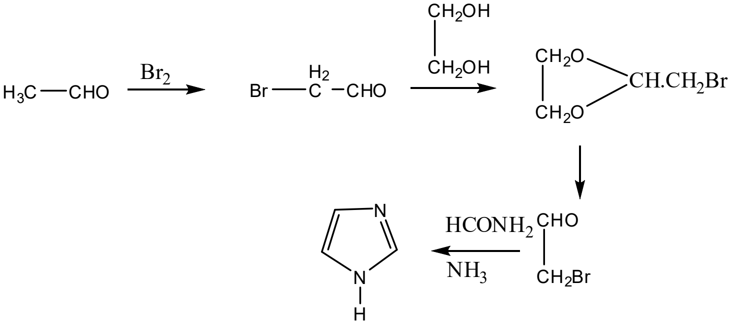
Imidazole is isomeric of pyrazole. The imidazole nucleus is found in certain natural products, viz. histidine, purines and also as riboside.

The parent compound imidazole can be prepared by the following methods.

i) By the action of ammonia on glyxol.

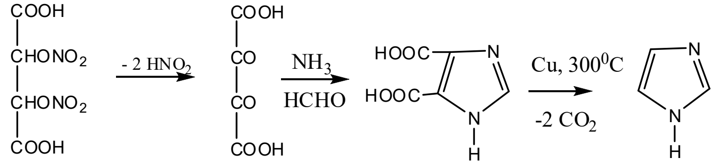


ii) By treating acetaldehyde with bromine in ethylene glycol and heating the resulting product, 2-bromomethyl-1,3-dioxolan with formamide and ammonia.



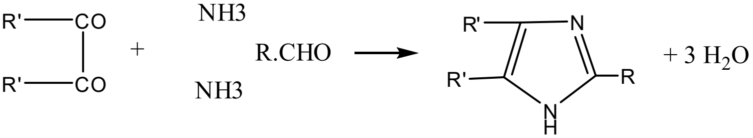
Imidazole

iii) Imidazole is prepared by action of ammonia on a mixture of formaldehyde and tartaric acid dinitrate and decarboxylating the product.

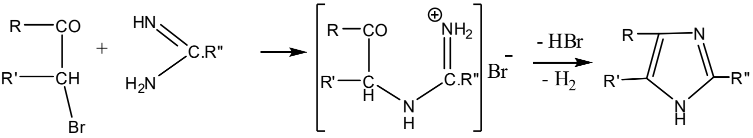


dinitrotartaric acid

iv) By the action of ammonia and aldehyde on glyoxal of other 1,2-diketocompounds.



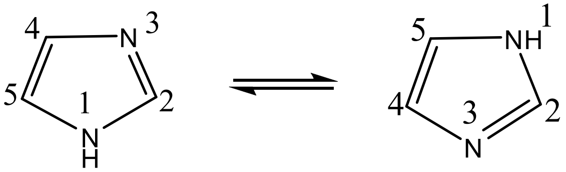
v) Imidazole can be prepared from á-bromoketone and an amidine.



Properties :

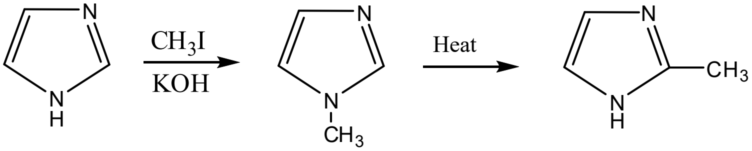
Imidazoles are although weak bases, they are stronger bases than the isomeric pyrazoles.

Like pyrazole, imidazole exhibits tautomerism as a result of which position 4 and 5 are equivalent and thus only one C-alkyl derivative corresponding to 4 or 5- alkyl imidazole is obtained.

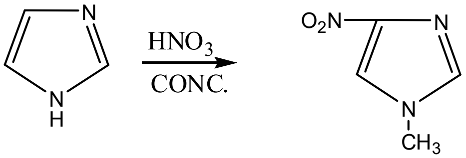


Chemical properties:

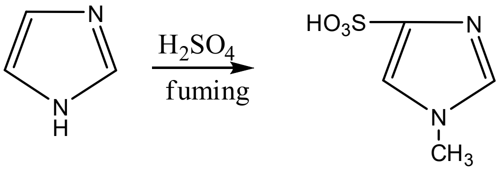
i) The iminohydrogen atom of imidazole can be replaced by metals and alkyl groups. N-alkylimidazole isomerises on passing through red hot tube to 2-alkylimidazole.



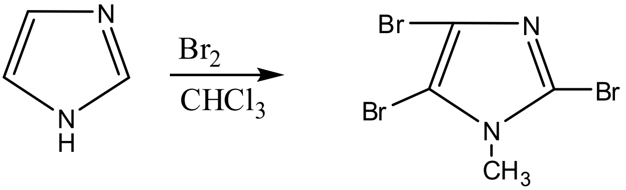
ii) Nitration, Sulphonation, and bromination of imidazole produce 4(5)-derivative. In case, position 4 and 5 are blocked substitution takes place at 2 position.



4-nitroimidazole

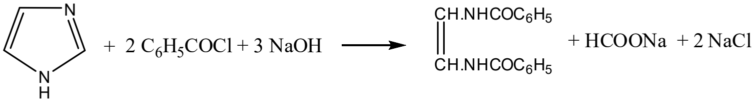


imidazole-4-sulphonic acid

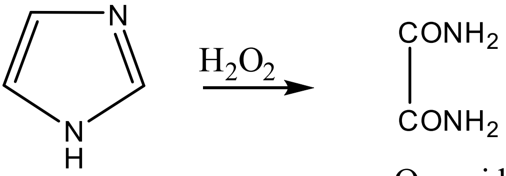


2,4,6-tribromoimidazole

iii) When benzoyl chloride react with imidazole in the presence of NaOH to form di-(benzoylamino)ethylene.



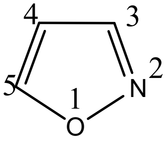
iv) Although imidazole is extremally stable to oxidising and reducing agents, hydrogen peroxide opens the nucleus to form oxamide.



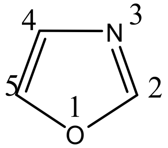
Oxamide

3] OXAZOLE :

This group of heterocyclic compounds posseses five membered ring; the ring is compose of three carbon atom. One nitrogen atom and one oxygen atom. They may again be of two types on the basis of the relative position of the two hetero atom, viz. oxazoles when two hetero atoms are seperated by one carbon atom. Oxazole do not occur in nature.



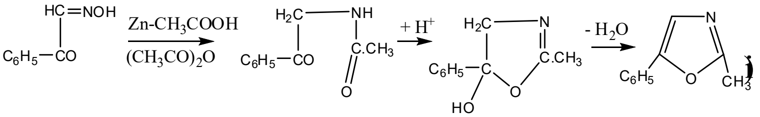
Isoxazole



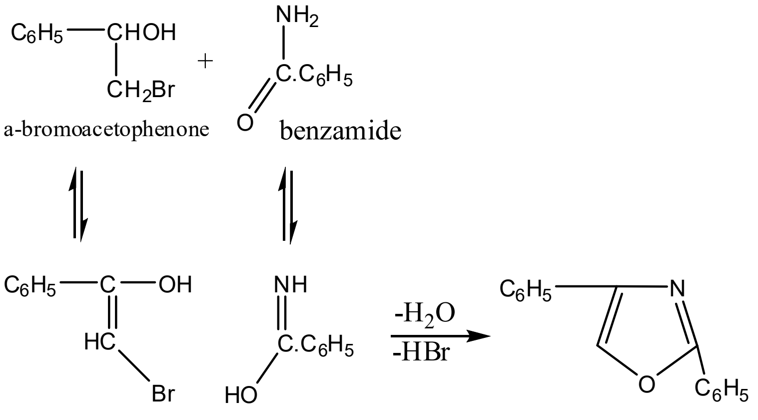
Oxazole

Oxazoles may be prepared by the following methods.

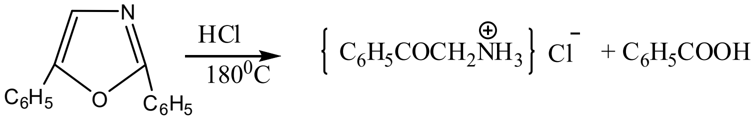
i) By the reductive acetylation of the á-oximino derivative of a ketone followed by dehydrative cyclisation.



By the interaction of acid imides and á-halogenoketone.

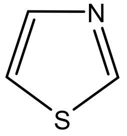


Oxazoles are basic compounds. Unlike isoxazoles they are stable towards alkali, however, they can be decomposed by means of conc. Acids.

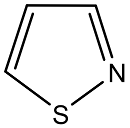


4] THIAZOLE:

Thiazoles are the five membered heterocyclic compounds in which ring is composed of three carbon, one nitrogen and one sulphur atom. like oxazoles, there are two isomeric thiazoles, viz. thiazole it self and isothiazole.



Thiazole

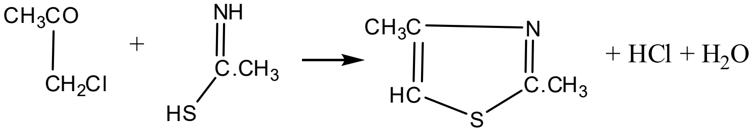


Isothiazole

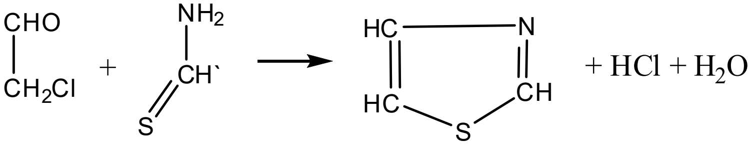
Thiazole and their derivatives are found in certain natural product, viz. vitamin B1(THIAMINE) and Penicellins.

The following general methods have been devised to synthesise thiazoles.

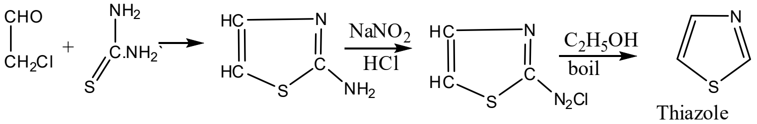
i) By the interaction of thioamides and á-halocarbonyl compounds (Hantzach)



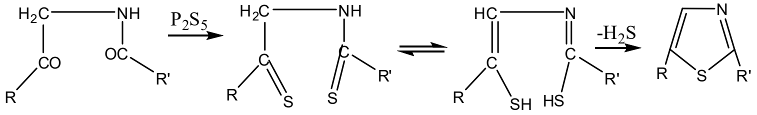
ii) Thiazole may be prepared from chloroacetaldehyde and thioformamide.



iii) By the interaction of thiourea and á-halocarbonyl compounds



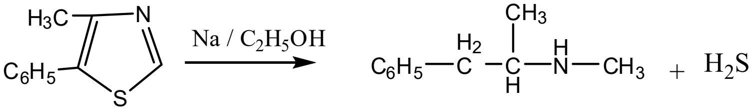
iv) By the action of phosphorous pentasulphide on an á-acylamino carbonyl compounds.



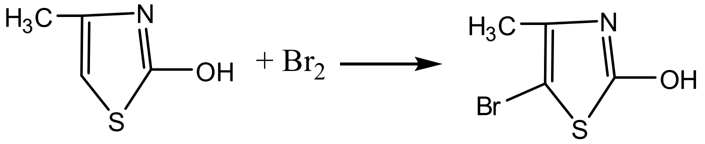
PROPERTIES;

Thiazole is weakely basic liquid b.p. at 117^{0}c, with pyridine like smell. It resembles like with pyridine in physical and chemical properties.

i) Thiazole is resistant to hydrogenation, but some substituted thiazole undergo ring cleavage by means of sodium and ethanol.

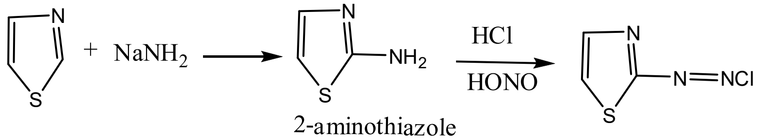


ii) Thiazole is very resistant to substitutions but if a hydroxyl or an amino group is present in position 2, electrophilic substitution occurs readily at position5.

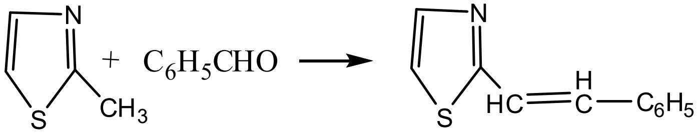


2-hydroxy-4methyl-
5-bromothiazole

iii) Thiazole reacts with sodamide to form 2-aminopyridine, which undergoes diazotization to form thiazolediazonium chloride.

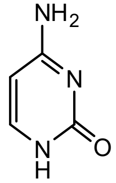


iv) 2-methylthiazole readily condense with benzaldehyde in the presence of alkali.

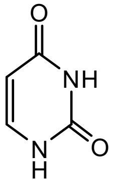


5] PYRIMIDINES:

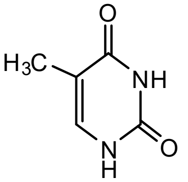
Pyrimidine are the most important among the three isomeric diazines. Several (mainly uracil, thymine, and cytosine) pyrimidines have been isolated from the nucleic acid hydrolysate. The nucleic acid are the essential constituent of all cells. And thus of all living matter. Cytosine is present in both type of nucleic acids, i.e. ribonucleic acid (RNA) and deoxyribonucleic acid (DNA); Uracil is present in only RNA and thymine only present in DNA.



Cytosine



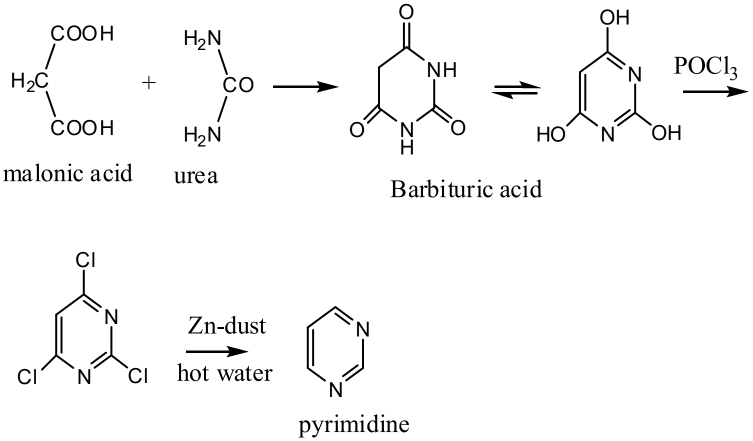
Uracil



Thymine

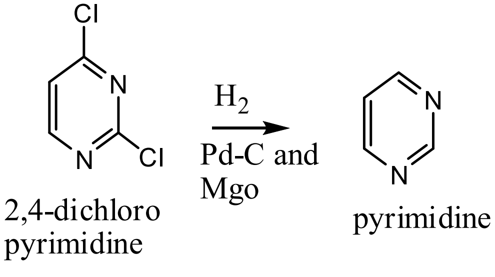
Preparation of Pyrimidine:

i) Gabriel in 1900 prepared polyamide from barbituric acid which in turn can be obtained from urea and malonic acid.



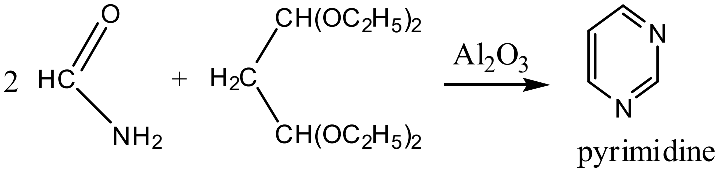
malonic acid urea Barbituric acid pyrimidine

ii) Whittaker (1955) prepared pyrimidine by the catalytic reductive dechlorination of 2,4-dichloropyrimidine.



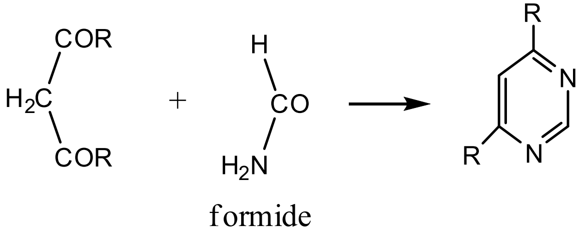
2,4-dichloro pyrimidine pyrimidine

iii) Pyrimidine may be conveniently prepared by the interaction of 1,1,3,3-tetraethoxypropane and formide.

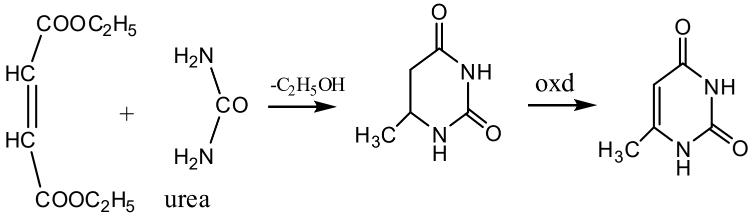


pyrimidine

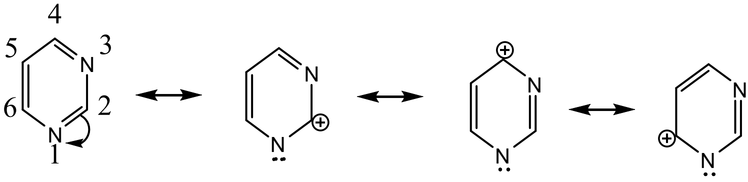
iv) Condensation ofâ- diketones with formamide at $180-200^0$c. also provides a general method for the synthesis of pyrimidines.



v) Pyrimidine are also obtained by the Michael-type addition to an á,â-unsaturated ester, e.g.

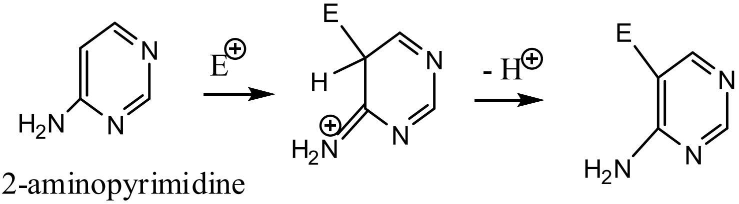


Pyrimidine (m.p.22.5^0c, b.p. 124^0c) in neutral solution, but forms salts with acids. It is resonance hybrid of the following resonating structures.



The resonance of pyrimidine molecule indicate that in pyrimidine position 5 has the greatest electron density, but attack by electrophile reagent is difficult as expected since the pyrimidine ring on the whole is deactivated

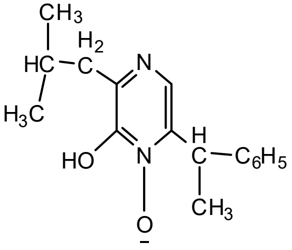
Pyrimidine undergoes electrophilic substitution reaction if electro releasing group (-OH, or –NH_2)is present in the 2,4,-or 6-position.



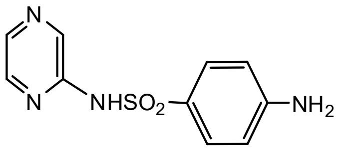
2-aminopyrimidine

6] PYRAZINES:

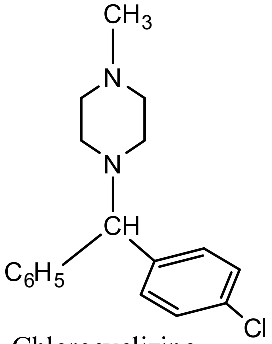
A few pyrazines are natural products (e.g. aspergillic acid, an antibiotic); and other are important synthetic drugs, e.g. sulphapyrazine (a sulpha drug) and chlorocyclizine (antihistidine).



Aspergillic acid



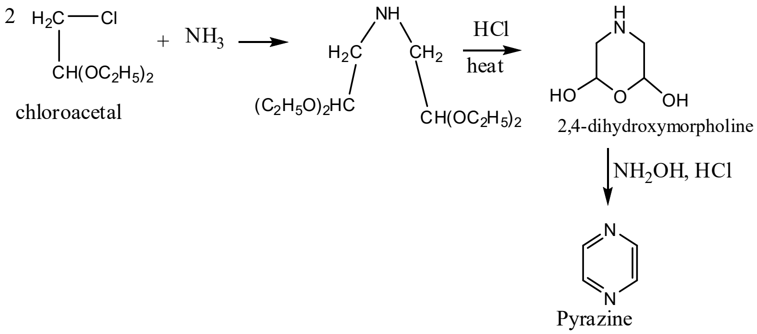
Sulphapyrazine



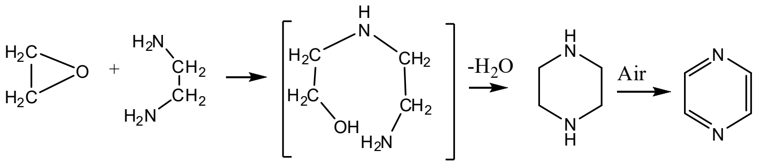
Chlorocyclizine

Pyrazine itself may be prepared from the following two methods.

i) Wolf et.al. 1908.

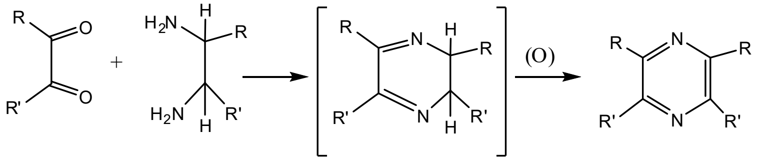


ii) A convenient method of synthesizing pyrazine ring from ethylene oxide and ethylenediamine.

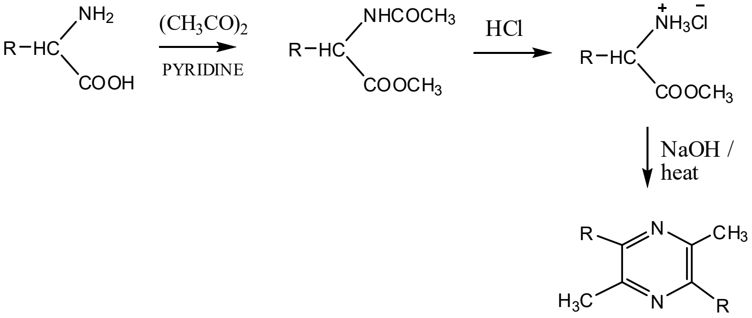


Pyrazine derivative may be prepared by following methods.

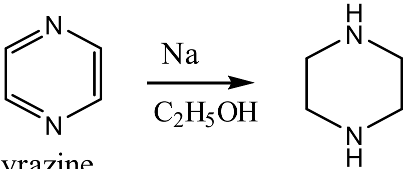
i) From 1,2-diketones and á,â-diamines.



ii) By heating an á-amino acid with acetic anhydride in presence of pyridine followed by hydrolysis with acid and then warming with sodium hydroxide in the presence of mercuric chloride (Dakin et. al. 1928).



Pyrazine is a solid (m.p. 55^0c) Pyrazine and its derivatives are readily reduced by sodium and alcohol to the corresponding hexahydro product (piperazine)



pyrazine

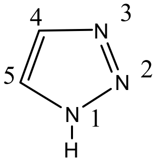
Piperazine

•••

4. HETERROCYCLES WITH MORE THAN TWO HETERO ATOMS

Synthesis, reactivity, aromatic character, and importance of following heterocycles:

1] TRIAZOLE:

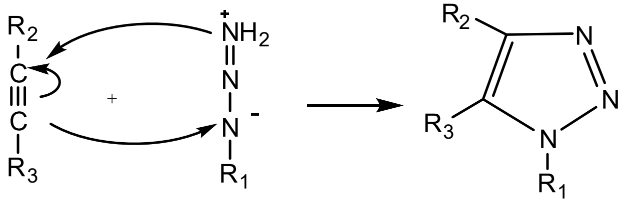


M.P = 24^{0}C
B.P = 209^{0}C

- Triazole forms colourless, sweetin taste, hydroscopic crystal which are soluble in water.
- 1,2,3-Triazole is the five membered heterocyclic compound containing one pyrrole like and two pyridine nitrogen atom in the position 1,2,3.
- It was known as v-triazole (v-meaning Nicinal)
- In triazole all ring atoms are SP^{2}hybridized hence 6ð-electrons gives delocalisation of ð-electrons thus 1,2,3-triazole is an aromatic compound.

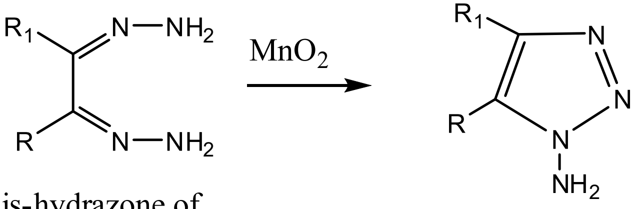
Synthesis of triazole:

1] From Hydrzoic acid or azide with alkyne in 1,3-dipolar cycloaddition.



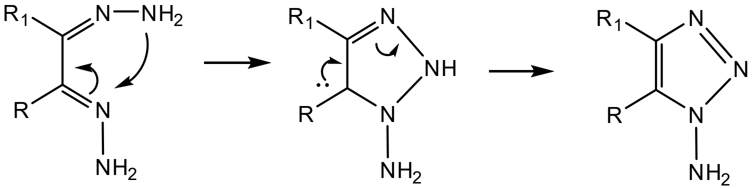
Alkyne Azide Sub. 1,2,3-triazole

2] the oxidation of the bishydrazone of 1;2-dicarbonyl compounds yields 1-amino1,2,3-triazole.

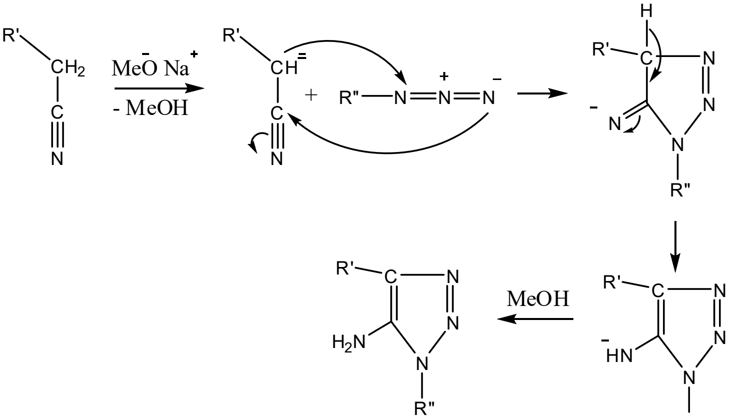


Bis-hydrazone of dicarbonyl

Mechanism:

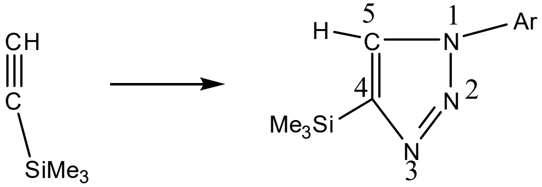


3] The cyclo addition of azide to –ch acidic compounds in presence of sodium methhoxide leads to 5- amino1,2,3-triazole.



5-amino-1,4-diphenyl 1,2,3-triazole

4] Trimethylsilyl acetylene reacts quantitatively with aryl azide to give 1-aryl-4-trimethylsilyl-1,2,3-triazole.



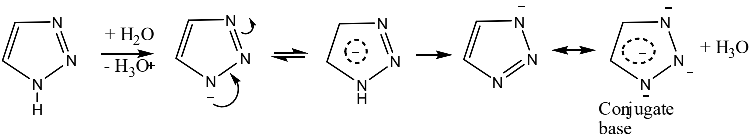
Trimethylsilyl acetylene   1-aryl-4-trimethylsilyl-1,2,3-triazole.

Chemical reactions:

1] Acid-Base Reaction:

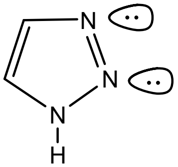
i) The 1,2,3-triazole are weak base with Pka = 1.17, less basic than pyrrole.

ii) N-atom unsubstituted triazole are N-H acidic. Acidity of triazole with Pka = 9.3 is greater than that of pyrazole and this is due to contnous delocalisation of ð-electron (-ve) charge in the conjugate base.

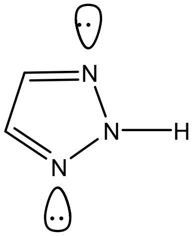


ii) Annular tautomerism:

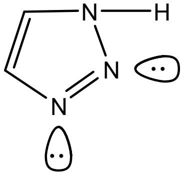
Unsubstituted 1,2,3-triazole has three tautomeric form, only two of which are identical. This is an contrast to imidazole and pyrazole.



1-H Form



2-H Form



3-H Form

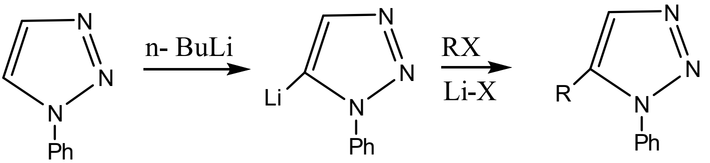
2H form is predominant in most of solvents, the equilibrium constant in wqter is

K_T = [2H- form] / [1H- form]

A destabilisation of the 1H form, owing to repulsive forces between the nonbonding electron pairs in the 2 and 3 positions, is considered to be responsible, therefore, for a C-monosubstituted 1,2,3-triazole, therefore three structural isomers are considerable i.e. 4-methyl-1,2,3-triazole, 4-methyl-2H-1,2,3-triazole and 5-methyl-1,2,3-triazole.

iii) Metalation:

N-substituted 1,2,3-triazole are metalated by n-butyllithium at low temperature.



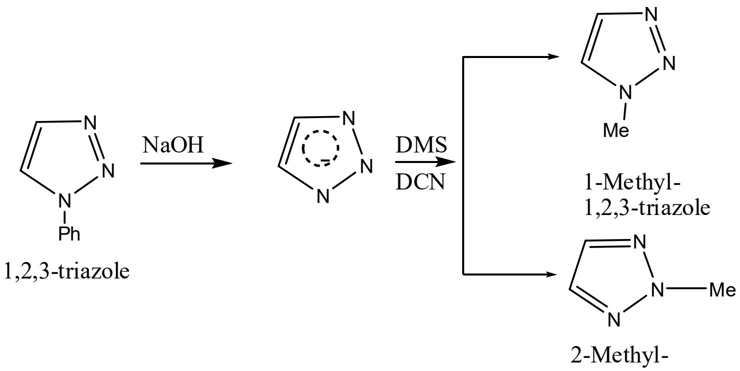
1-phenyl-
1,2,3-triazole

5-lithio-1-phenyl-
1,2,3-triazole

5-Alkyl-1-phenyl-
1,2,3-triazole

iv) Reaction with electrophilic reagent:

Sodium 1,2,3-triazoleon reaction with dimethyl sulphate will form 1-methyl and 2-methyl-1,2,3-triazole.

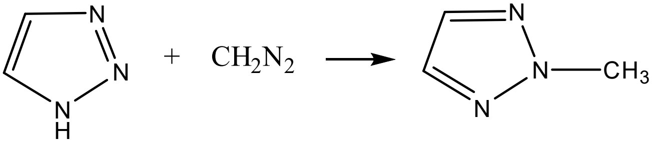


1,2,3-triazole

1-Methyl-
1,2,3-triazole

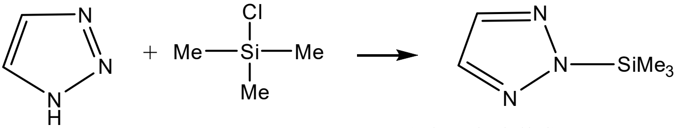
2-Methyl-
1,2,3-triazole

v) Diazomethane reacts with 1,2,3-triazole giving 2-methyl-1,2,3-triazole.



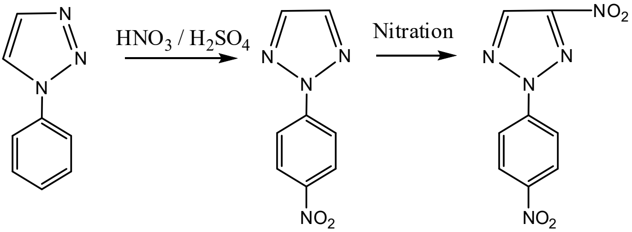
2-methyl-2*H*-1,2,3-triazole

vi) Chlorotrimethylsilane reacts to give 2-trimethylsilyl-1,2,3-triazole.



2-(trimethylsilyl)-2*H*-1,2,3-triazole

vii) Nitration of 2-phenyl-1, 2, 3-triazole

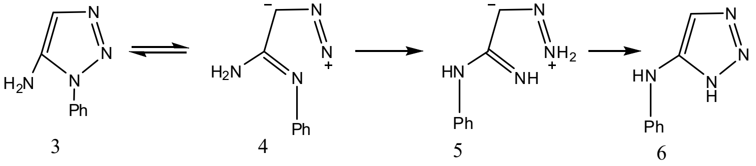


4-nitro-2-(4-nitrophenyl)-2*H*-1,2,3-triazole

viii) Dimroth Rearrangement:

With nucleophile 1,2,3-triazole, like pyrazole, donot react at all or react only slowly with ring opening. when1,2,3-triazole are heated in suitable solvent, ring fission often occurs to give intermediates which recyclize material, such isomerisations, which have also been obtained with other heterocycles sevaral N-atoms, are known as DIMROTH rearrangement. The rearrangement of 5-amino-1-phenyl-

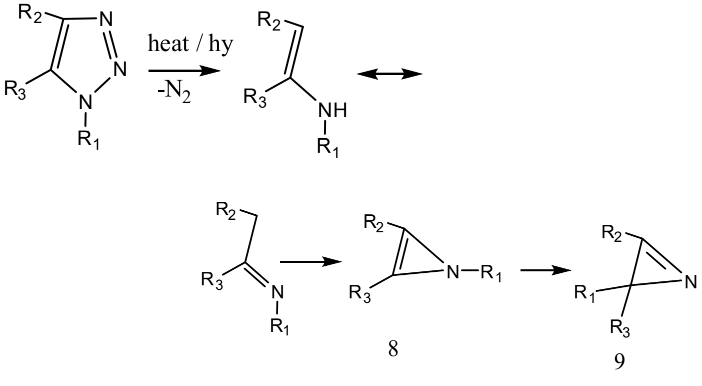
1,2,3-triazole (3) to give in boiling pyridine 5-phenylamino-1,2,3-triazole (3) is an example.



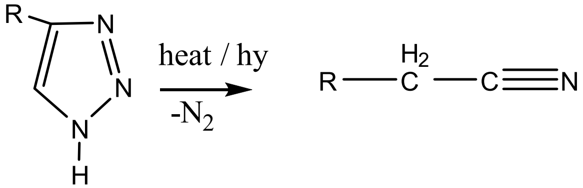
Ring opening occurs by cleavage of the N-Hbond in (3) to the diazoimine (4) this rearranged to another diazoimine (5) which cyclizes to the product (6).

ix) Dediazoniation:

1,2,3-triazoles are subject to ring cleavage by pyrolysis or photolysis with loss of nitrogen, the fragments arising from 1-substituted 1,2,3-triazoles have a diradical or an iminocarbene structure (7) they cyclize to give 1-H azirines (8)which isomerises in gas phase or in inert solvent to give mainly 2H-azirines (9)



X) Pyrolysis or Photolysis of 1-/ unsubstituted 1,2,3-triazoleyields nitriles.



2] OXDIAZOLE

1] The trival name is Furazan

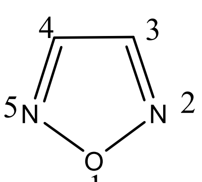
2] The 1,2,5-oxdiazole molecule is planner and exists as a regular pentgon.

3] Oxdiazole is an aromatic heterocycle the ð-electron density is so greater on heteroatoms hence carbons in the ring becomes electro deficient

4] The ionisation energy is 11.70 ev. And the the dipolemoment is 3.38 D both values are greater than those isooxazole . the chemical shift (ä) in the ^{1}H –NMR spectrum is 8.19 and in the ^{13}C- NMR spectru 139.4.

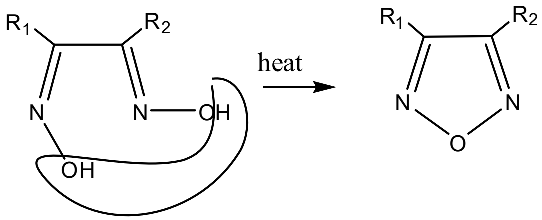
5] It is colourless water soluble liquid. M.P= 28^{0}C and B. P = 98^{0}C.

6] 1,2,5-oxdiazole is five membered ring containing two pyridine like nitrogen separated by one oxygen atom.

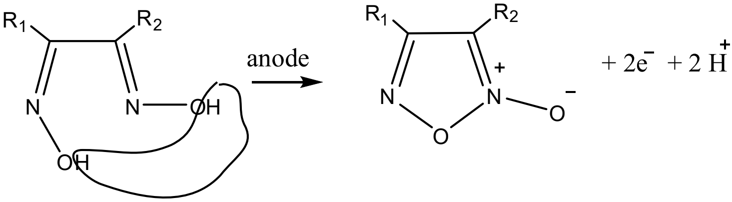


Synthesis:

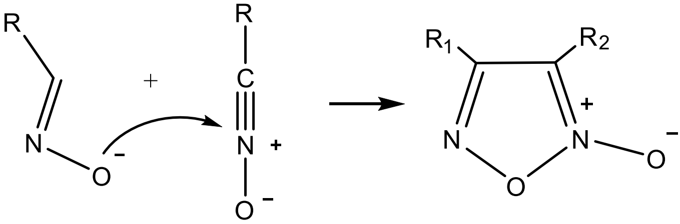
1] Cyclodehydration of dioximer of 1,2-dicarbonylcompounds has gives 1,2,3-oxdiazole.



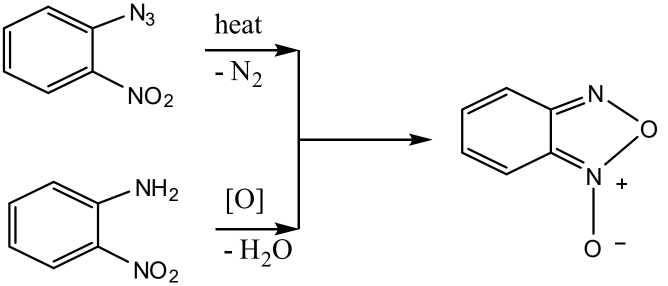
2] By electrochemical oxidation of 1,2-dicarbonyl oximes.



3] Dimerisation of nitrile oxides.



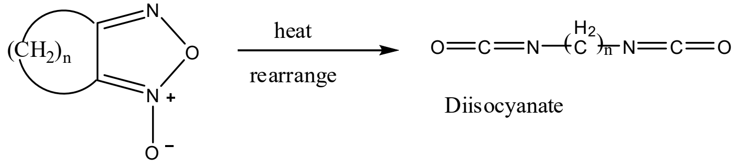
4] 1,2,3-oxdiazole- 1-oxide is obtained by heating O-nitrophenylazide in acetic acid or by oxidation of 0-nitroaniline with sodium hypochloride.



Chemical Reaction:

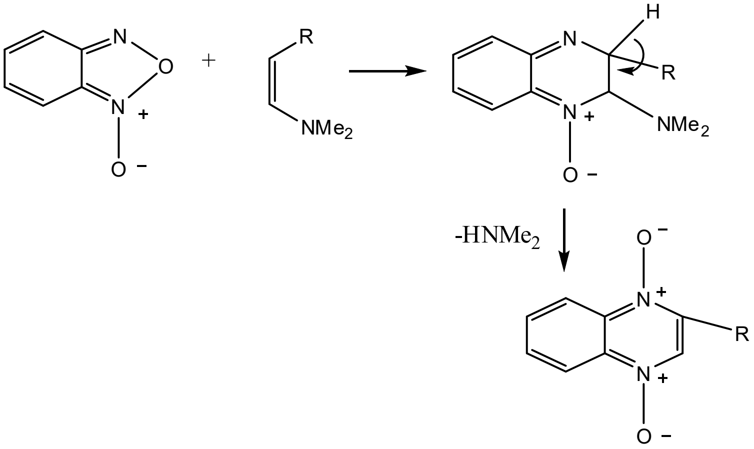
1] Synthesis of diisocyanate:

On thermolysis yield a bis-nitrile oxide which in the absence of dipolarophiles, isomerises to a diisocyanate.

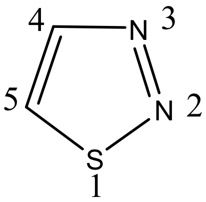


1,2,3-Oxdiazole-2-N-oxide

3] Synthesis of Quinoxdine-1,4-dioxide:

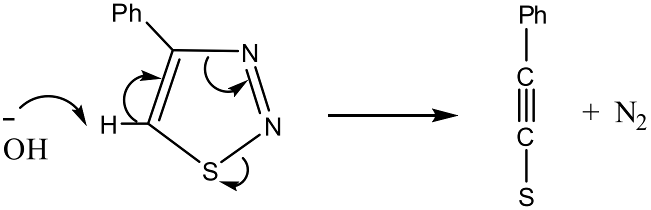


3] 1,2,3-THIADIAZOLE:

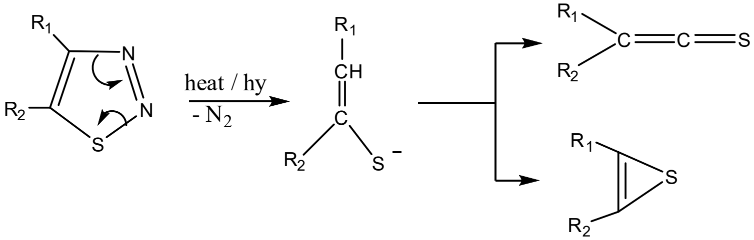


1,2,3-Thiadiazole in contrast 1,2,3-Oxdiazole, can be isolated and are thermally relatively stable.

- NMR spectra indicate that the molecues are diatropic.
- 1,2,3-Thiadiazole is aromatic.
- 1,2,3-Thiadiazole are weak bases on quaterrnization, e.g. with dimethyl sulphatemixture and 2- and 3-methyl 1,2,3-benzothiazole are formed, electrophilic substitution of the C-atoms could not be achived with 1,2,3-benzothiazole. Substitution occurs on the benzene ring.
- Nitric acid the 4 and 7 nitro 1,2,3-benzothiazole are obtained.
- 1,2,3-thiadiazole is yellow liquid, b.p. 157^{0}C, soluble in water.
- Nucleophile bring ring opening for e.g.

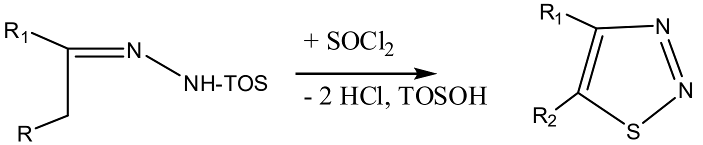


- Thermolysis and photolysis of 1,2,3-Thiadiazole and 1,2,3-benzothiadiazole lead to elimination of nitrogen.
- Depending on the substituents in the 4 and 5 position, the fragments attain stability to different degree, forming mainly thioketones and thiirines.

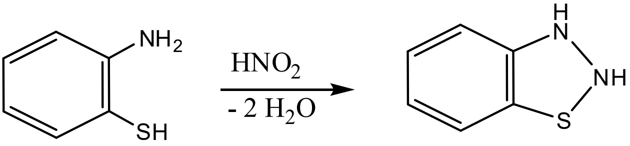


Synthesis of 1,2,3-Thiadiazole:

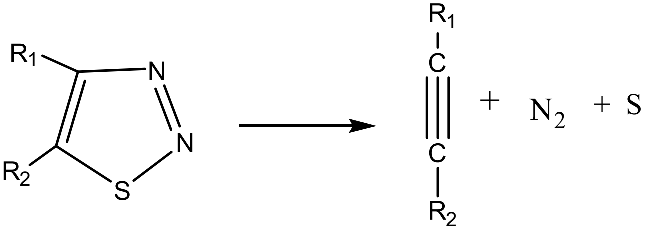
1] 1,2,3-Thiadiazole are prepared by cyclocondensation and tosylhydrazones derived from á-methylene ketone with thionyl chloride or sulphur dichloride [HURD MORI Synthesis}



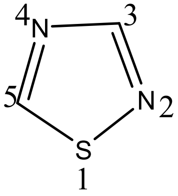
2] 1,2,3-benzothiadiazole are obtained by the reaction of 2-aminobenzenethiol with sodium nitrile in acetic acid.



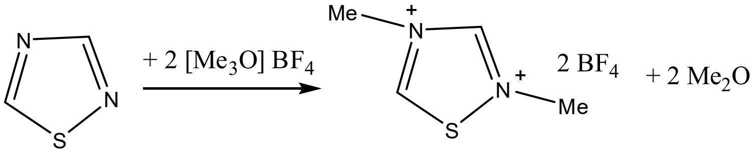
1,2,3-thiadiazole have found little application in organic synthesis, flash pyrolysis to give thioketenes and ring opening to produce acetylenes.



4] 1,2,4-THIADIAZOLE.

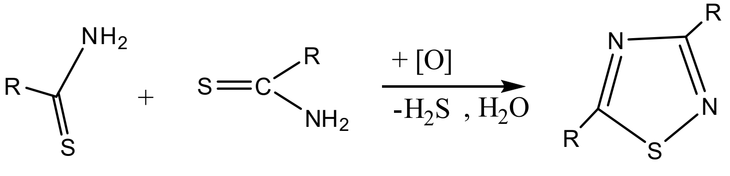


- * 1,2,4-Thiadiazole like its structural isomer of 1,2,3-Thiadiazole, is aromatic and is to be regarded as a ð-excessive heterocycles with relatively deficient C-atom.
- * 1,2,4-Thiadiazole are weak bases, methylation with iodomethane occurs at N-4, with trimethyl isooxonium tetrafluoroborate onto both N-atom.

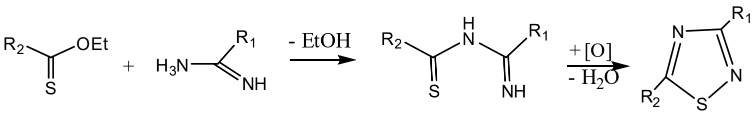


SYNTHESIS:

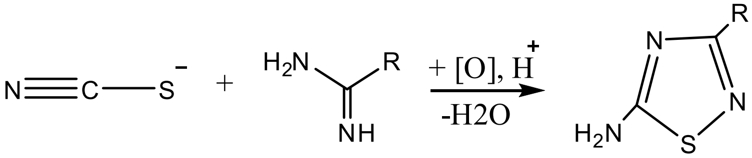
1] 1,2,4-Thiadiazole are obtained from thioamides by oxidation with hydrogen peroxide or by the action of $SOCl_2$, SO_2Cl_2 or PCl_5 .



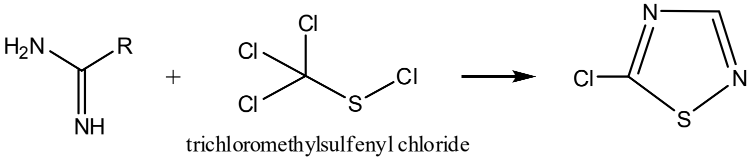
2] In the second synthesis, amidines are the starting material, they are for instance, thioacetyl by means of thiocarboxylic and subsequently oxidatively cyclized to give thiadiazole.



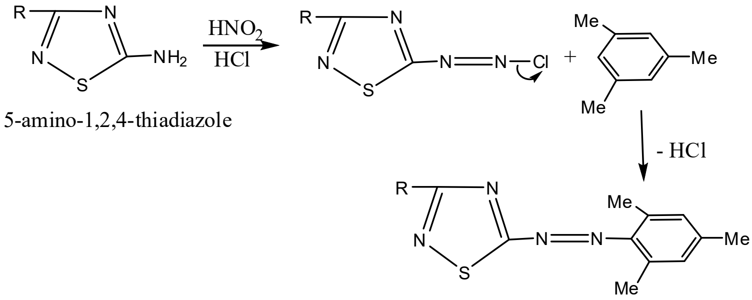
3] 5-Amino-1,2,4-thiadiazole are accessible from amidine and potassium thiocyanate by oxidation with sodium hypochlorite.



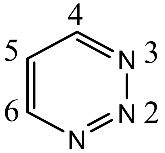
4] The cyclocondensation of amidines with trichloromethyl sulfenyl chloride furnishes 5-chloro-1,2,4-thiadiazole.



REACTIONS:



5] 1,2,3-TRIAZINE:



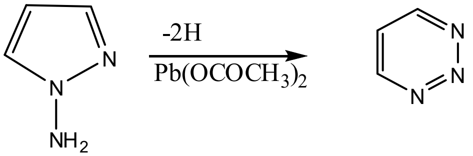
- 1,2,3-Triazine are six membered heterrocyclic ring containing three pyridine type nitrogen atoms at 1,2,and 3 position.

- It is aromatic but its resonance energy is low than benzene, hence ESR are difficult. Nucleophilic substitution reactions are possible.

Synthesis:

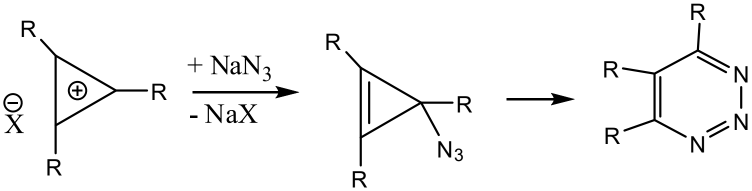
1] Oxidation of 1-aminopyrazole:

This oxidation carriedout in the presence of lead acetate or nickel peroxide.

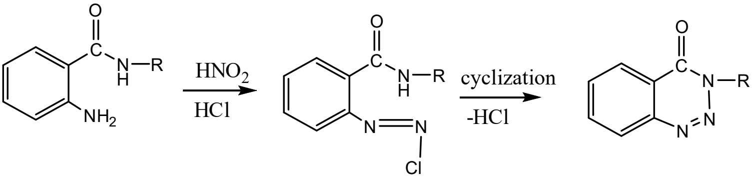


2] Tthermal rearrange ment of cyclopropyl azide:

This rearrangement takesplace even under mild conditions. The cyclopropynyl azide(2) are accesible from cyclopropenylium ions and NaN_3.



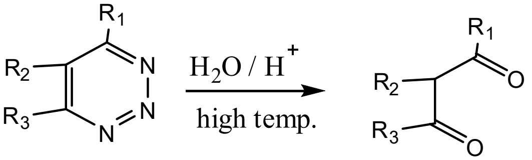
3] 3-Substituted 1,2,3-benzotriazine-4-(3H)-one e.g. in a reversal of the hydrolysis process are obtained by cyclization, the diazonium salt derived from the N-substituted anthranilic acid amides.



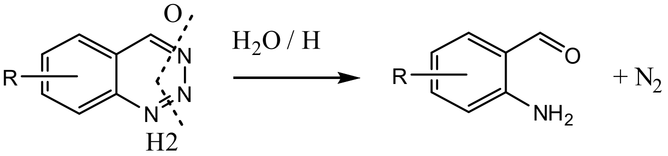
Chemical properties of triazine:

1] Hydrolysis:

1,2,3-Triazine undergo hydrolysis and oxidation at room temperature, monocyclic 1,2,3- triazine are stable towords aq. Acid , at higher temperature ring expansion occurs to form 1,3-dicarboxylic compound.



2] 1,2,3-benzotriazine react with aquous acid ring poens and O-aminobenzaldehyde is formed.

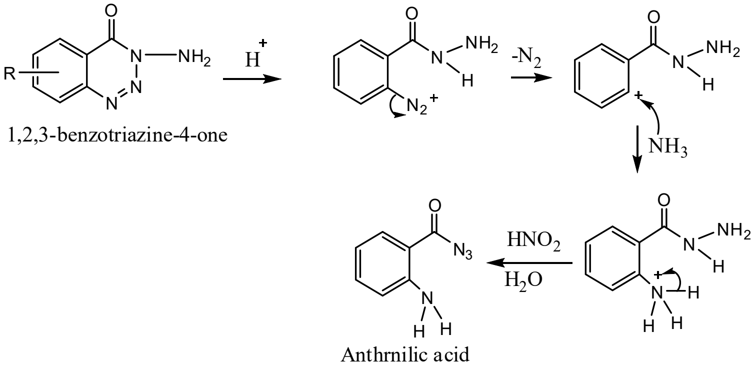


Benzotriazine

3] Ring opening reaction:

1,2,3-benzotriazine-4-one are opened by aq. Acid leads to the formation of anthranilic acid. Azide by internal redox disproportion reaction.

[oxidation and reduction are taking place in same reaction]



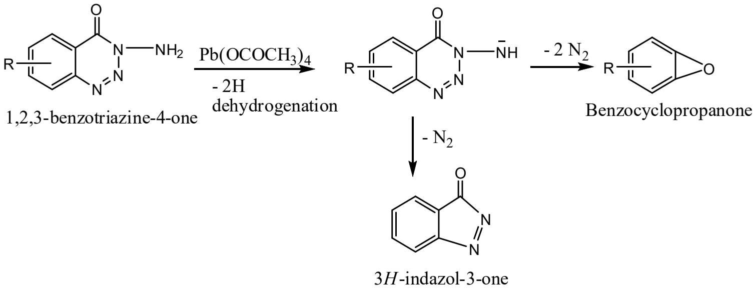
1,2,3-benzotriazine-4-one

Anthrnilic acid
reduced azide

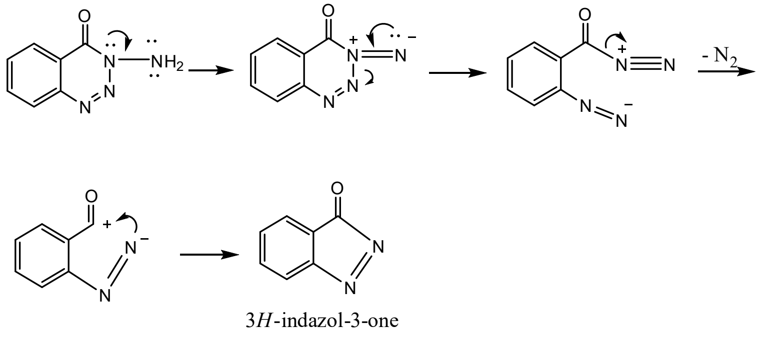
4] Oxidation:

3-amino-1,2,3-benzotriazine-4-one are oxidised by lead tetra acetate, dehydrogenation occurs.

Intermediate nitrene are stabilised by eliminating a molecule of N_2 yielding 3H-imidazolone, then ther is loss of two molecule of N_2 to form benzocyclo propenone.

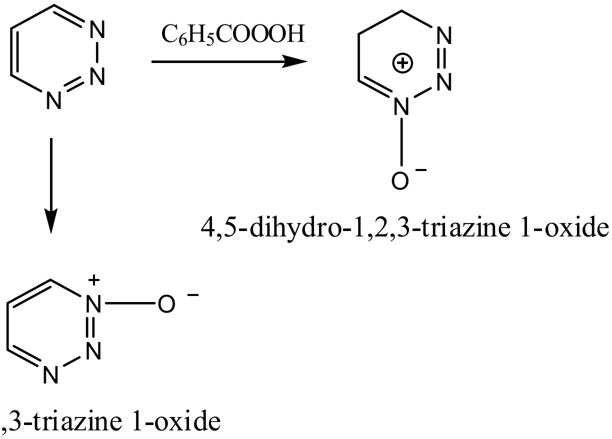


Mechanism:



5] Oxidation:

Oxidation of 1,2,3-triazine by peroxyacid yield



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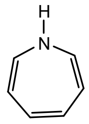
5. LARGER RING AND OTHER HETEROCYCLES

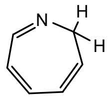
I] SYNTHESIS AND REACTIVITY OF AZEPINES:

These are sevan membered heterocyclic compounds containing one heterroatom (N). these are heterocyclic analogues of 1,3,2-cycloheptatriene. Xray crystallography has shown that these ring systems are not planner and hence behaves as polyenes.

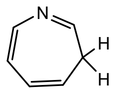
- Four isomeric form designed as 1H, 2H , 3H and 4H-Azepines, only the 3Hisomer is stable.
- 1H-Azepine unsubstituted at nitrogen readily rearrange to tautomeric 3H form.
- Stability of azepines tautomers recreases in the following order
  3H > 4H > 1H
- NH tautomer 2,3-benzazepine is stable.



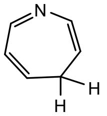
1H-Azzepine



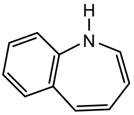
2H-Azzepine



3H-Azzepine



4H-Azzepine

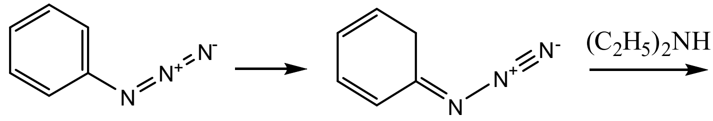


NH-2-Benzazzepine

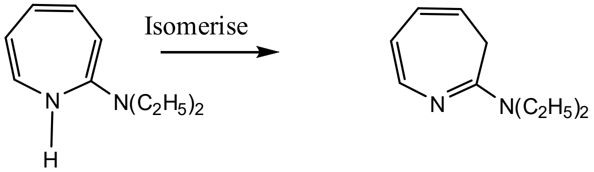
SYNTHESIS:

1] From phenyl Azide:

Phenylazide on decomposition in presence of primary or secondary amine yields 3H-azepine derivative.



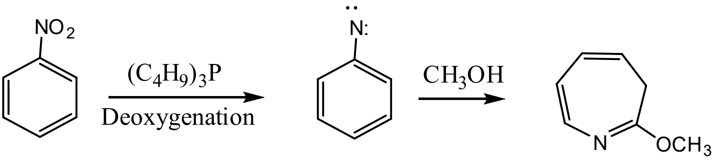
phenylazide



N,N-diethyl-1*H*-azepin-2-amine *N,N*-diethyl-3*H*-azepin-2-amine

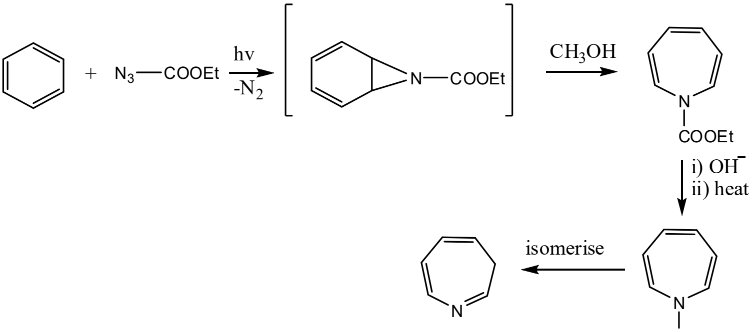
2] From nitrobenzene:

Nitrobenzene on treatment with tributylphosphine gives arylnitrene, which on reaction with an alcohol gives 2-alkoxy-3H-azepine.



2-methoxy-3*H*-azepine

3] From benzene and ethoxycarbonyl nitrile (valence bond isomerisation):

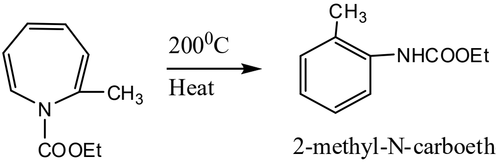


3*H*-azepine

CHEMICAL PROPERTIES:

1] Aromatization or thermal reaction:

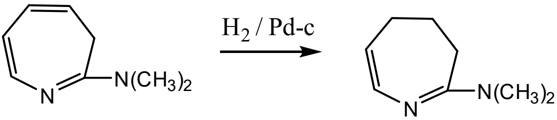
2-methyl-N-carboethoxy-3-H-aazepine on heating at 200^{0}c yields 2-methyl-N-carboethoxyaniline.



2-methyl-N-carboethoxyaniline.

2] Reduction:

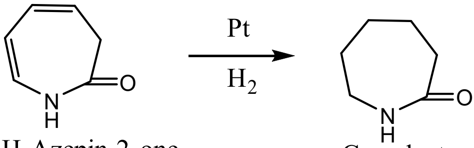
2-dimethylamino-3H-azepine may be reduced partially with molecular hydrogen in presence of 5% palladium and carbon to give 4,5-dihydro-2-dimethylamino-3H-azepine.



2-dimethylamino-
3H-azepine

4,5-dihydro-2-dimethylamino-
3H-azepine

3H-Azepin-2-one reduce to capralactum in presence of Pt catalyst with I_2

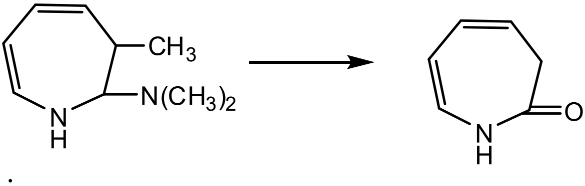


3H-Azepin-2-one

Capralactum

3] Oxidation:

3-alkyl-2-dialkylamino-1H azepine undergo aerial oxidation to 1H- azepine-2-one
(2-azatropones)



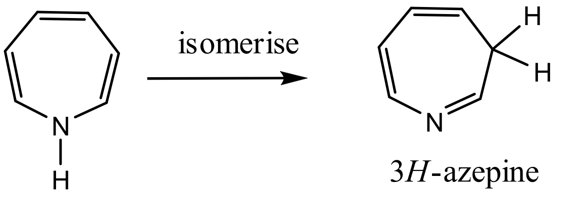
:

3-Methyl-2-dimethylamino-
1H azepine

1H- azepine-2-one

4] Isomerisation:

In presence of base the 1H-azepine isomerise into 3H-azepine.

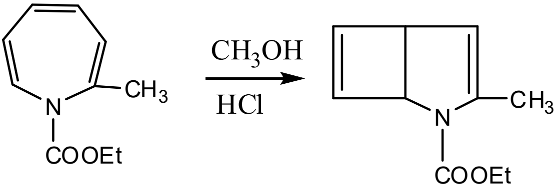


3*H*-azepine

1H- azepine

5] Ring contraction:

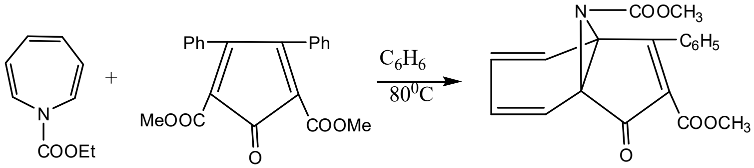
On photolysis in methanol 2-methyl-N-carboethoxyazepine yields 2-carbomethoxy-3-methyl-2-azabicyclo[3,2,0]hepta-3,6*diene.



ethyl 3-methyl-2-azabicyclo[3.2.0]
hepta-3,6-diene-2-carboxylate

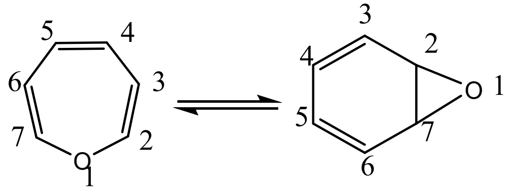
6] Cycloaddition reaction:

N-Carboethoxy azepine reacts with 1,5-dicarbomethoxy 3,4-diphenyl cyclopentadiene gives (6+4) pi-cycloadduct.



II] SYNTHESIS AND REACTIVITY OF OXEPINES:

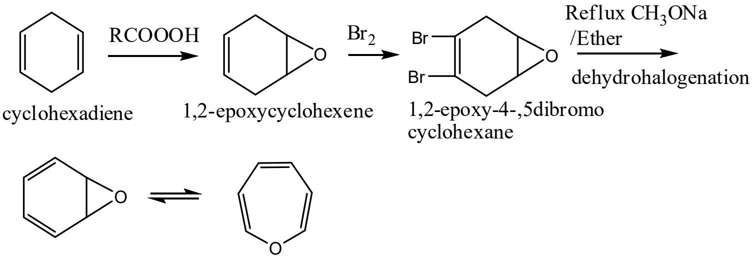
- Heterocyclic compound contain seven member ring
- Oxygen is one hetero atom
- Unsaturated
- It exist in equilibrium with its bicyclic tautomer benzene oxide.
- Both tautomers present at room temperature.



Synthesis:

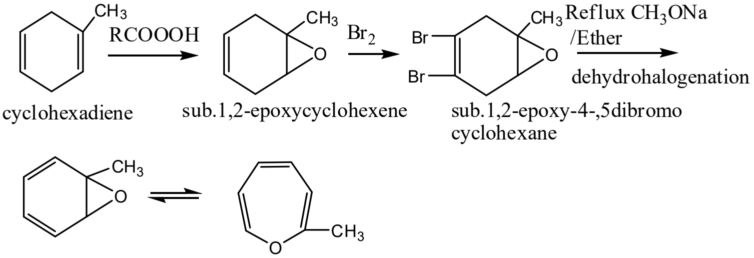
1. **From cyclohexadiene:**

   Oxepine is synthesized from 1,5-cyclohexadiene by epoxidation, addition of bromine and dehydrobromination, gives 80% yields.



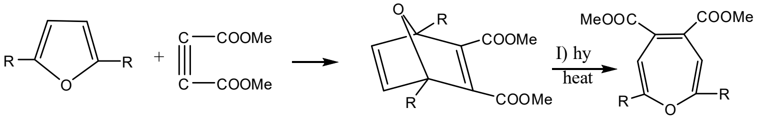
2. **From substituted cyclohexadiene:**

   Substituted oxepine is synthesized from 1,4-cyclohexadiene by epoxidation, addition of bromine and dehydrobromination,



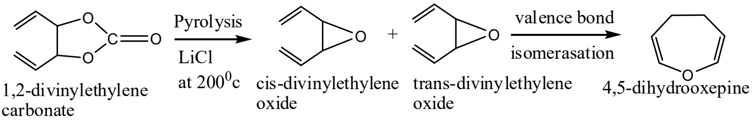
3. **From substituted furan:**

   2,5-disubstituted furan reacts with dicarboxy-methoxy acetylene in presence of light and I2 (Diels Alder Reaction) produces 7-oxaquadricyclane. Which on rearrangement by heat and gives oxepine.



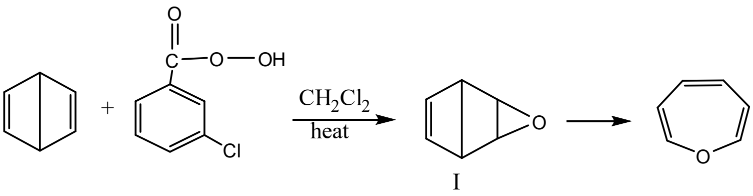
4. **Valence bond isomerization:**

   0n the pyrolysis of 1,2-divinylethylene carbonate in the presence of lithium chloride at 200^0C is transformed into a mixture of trans-divinyl ethylene oxide and cis-divinylethylene oxide. Both cis and trans form of divinyl ethylene oxide rearrange to the valence bond tautomer that is 4,5dihydroxyoxepine.



5. **From Dewarbenzene:**

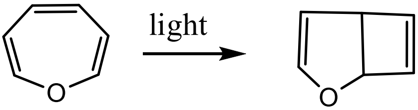
   By the epoxidation of Dewarbenzene with m-chloroperbenzoic acid in the presence of dichloromethane yields structure (I) Dewarbenzene oxide which on photolysis or pyrolysis, gives oxepine.



Chemical reactions:

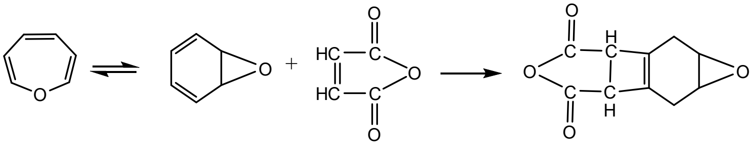
1. **Photochemical reaction:**

   Oxepine in the presence of light is converted into 2-oxobicyclo [3,2,0]hepta-3,6-diene.



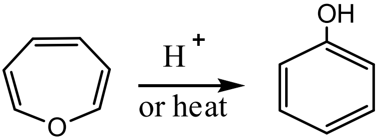
2. Diels-Alder reaction:

Oxepine react with maleic anhydride to give adduct.



3. Reaction with acid:

In the presence of acid or heat oxepine convert into phenol.



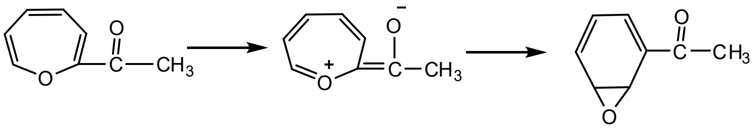
Both isomers of oxepine that is benzene oxide and oxepine exist in equilibrium. The equilibrium shift towards the benzene oxide at low temperature and in polar solvent.

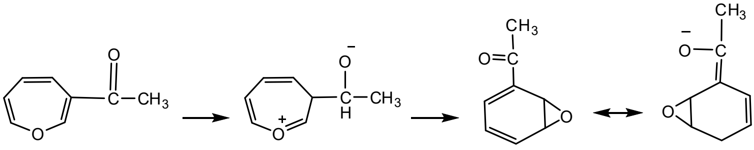
The position of substituent and nature of substituents effect the equilibrium.

2-substituents especially by conjugative electron withdrawing groups favours the oxepine form.

In 2-acetyloxepine, oxepine form is stabilised by resonance because of conjugative interactions.

In 3-acetyloxepine, benzene oxide form is resonance stabilised.





3] THIEPINES:

Thiepimes, the unsaturated even membered heterocycles, contains sulphur.

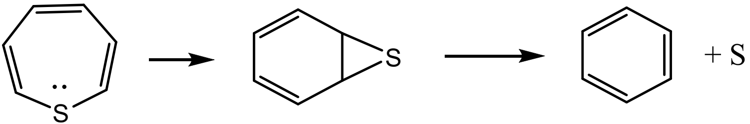
Analogues of 1,2,3-cycloheptatriene.

It contains 8 pi electrons.

Antiaromatic.

Non-polar.

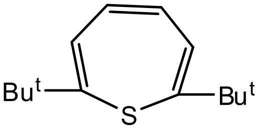
Thiepine and most substituted thiepine are thermally unstable because they readily remove sulphur atom from valence tautomer..



Benzene episulphide

Thiepine has been isolated only in the form of its iron tricarbonyl complex.

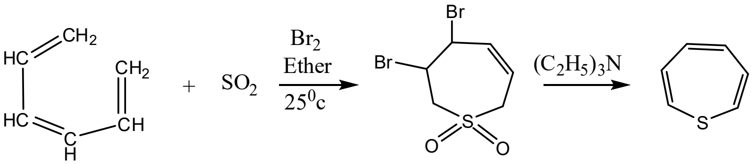
If the tautomerism is sterically inhibited, then the thiepine can be isolated.if bulky substituents are present in thiepine, they inhibits its isomerisation so 2,7-di-t-butylthiepine can be easily isolated in nalence tautomer.



Synthesis:

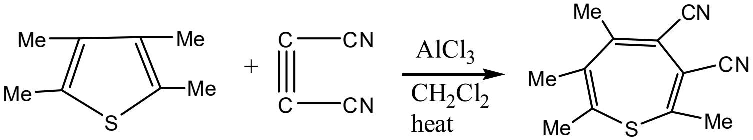
1. From 1,3,5-hexatriene:

Thiepine can be prepared from 1,3,5-hexatriene by addition of sulphur dioxide, bromination and dehydrobromination.



2. From 2,3,4,5-tetra-methylthiophene:

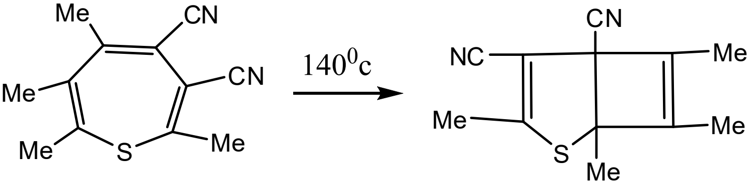
2,3,4,5-tetra-methylthiophene reacts with dicyanoacetylene in presence of $AlCl_3$ gives thiepine derivative.



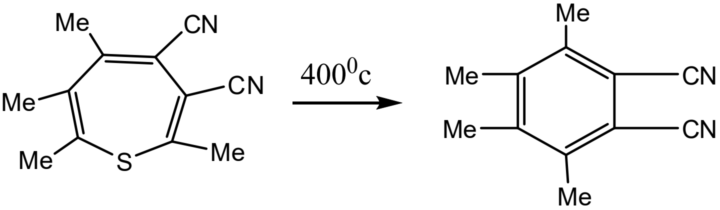
Chemical Reactions:

1. Heat action:

When heated at 140^{0}c it yields adduct.



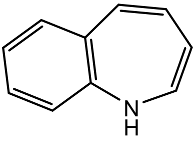
2. When heated at 400^{0}c it yields tetramethylphthalonitrile.



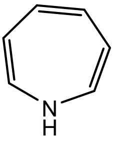
4] BENZOAZEPINE:

* benzoazepine is the derivative of azepine.

* the srtucture of benzoazepine is



1*H*-benzo[*b*]azepine



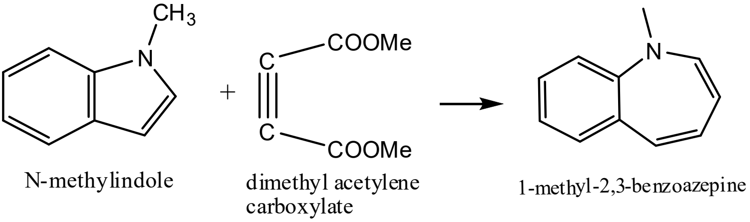
1*H*-azepine

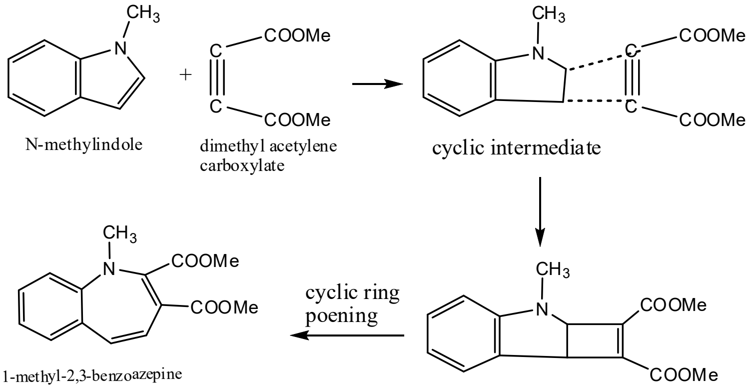
Synthesis of Benzoazepine:

1] Benzoazepine is synthesized from N-methyl indole and dimethyl acetylene carboxylate.

It is simple 2+2 cycloaddition reaction.

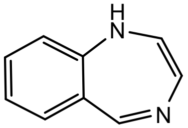
In this reaction methyl group of N-methyl indole is ð-electron donor, so it acts as diene and dimethyl acetylene carboxylate acts as dianophiles.



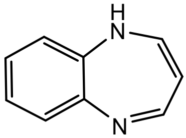


5] BENZODIAZEPINE:

- benzodiazepine is the derivative of diazepine.
- specially 1,4- benzodiazepine and 1,5-benzodiazepine have great importance in heterocyclic synthesis.
- following are the structure of the 1,4- benzodiazepine and 1,5-benzodiazepine.



1*H*-benzo[*e*][1,4]diazepine



1*H*-benzo[*b*][1,5]diazepine

The first benzodiazepine drug was discovered by Leo Sternbach in 1955.

Benzodiazepine are recommonded for treatment of anxiety.

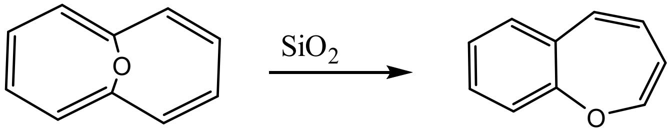
Benzodiazepine posses sedatives, hypnotic, anticonvulsant muscle reaxant action.

Benzodiazepine are well tolerated and their use for initial treatment for panic disorder.

6] BENZOOXEPINE:

Synthesis:

1] 1,6-oxido[10] Annulene in a non-polar solvent on silica gel rearranges to 1-benzoepine.



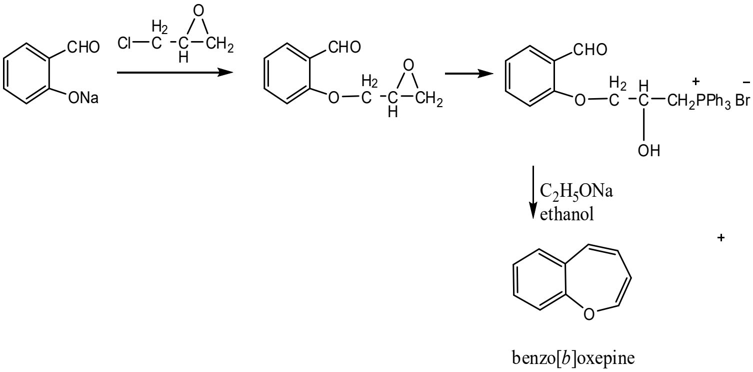
1,6-oxido[10]annulene

11-oxabicyclo[4.4.1]undeca-1,3,5,7,9-pentaene

benzo[*b*]oxepine

2] Schweizer and Coworker have reported the preparation of 1-benzooxepine from the sodium salt of salicylaldehyde and epichlorohydrin in the following steps.

Base treatment of the phosphonium salt induced an intramolecular Wittig reaction together with dehydration to give 1-benzooxepine though in poor yield.

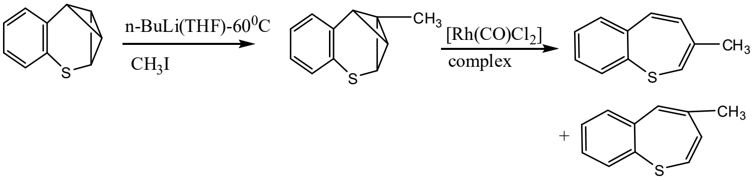


benzo[*b*]oxepine

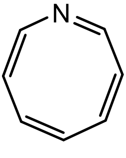
7] BENZOTHIEPINE:

Synthesis:

Murata and Co-workers developed a novel approch in the isomerization of 4,5-benzo-3-thiotricyclo-[4-1-0-0] heptene to 1-benzothiepine in the following steps.



8] AZOCINES:



Azacyclooctatetraene

IUPAC name is Azocine

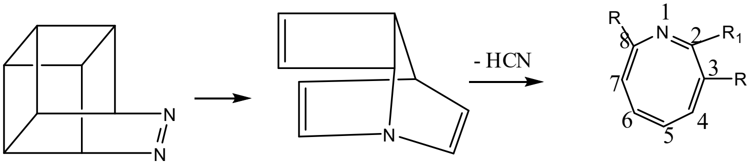
Molecular formula C_7H_7N

Azocine is an 8 membered heterocyclic unsaturated compound, containing seven carbon atom and one nitrogen atom. And four double bonds.

Azocine ring are found in many natural products including manzamine family of marine alkaloids. One such compound is Nakadomarin A.

Synthesis:

1. Azocine has been synthesized by the pyrolysis diazobasketone which loses hydrogen cyanide.



If R= R1 = H = Azocine

If R = H, R1 = Ome, = 2-methoxyazocine.

If R = Me, R1= OMe = 2-methoxy, 3,8-dimethylazocine which is more stable.

2. Synthesis of substituted azocine using Diels Alder reaction and RetroDiels-Alder reaction.

•••

6. Benzanelated Azole and Heterocycles With Ring Junction Nitrogen:

Benzanelated Azole:-

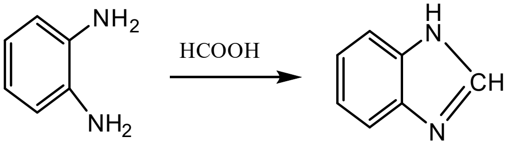
Synthesis and chemical properties.

BENZIMIDAZOLE

Benzo derivative of imidazole is reffered to as benzimidazolethese ring systems are numbered as shown below. The imino nitrogen is assigned position-1. While tertiary nitrogen atom position-3. Benzimidazole nucleus appears in vitamin B-12.

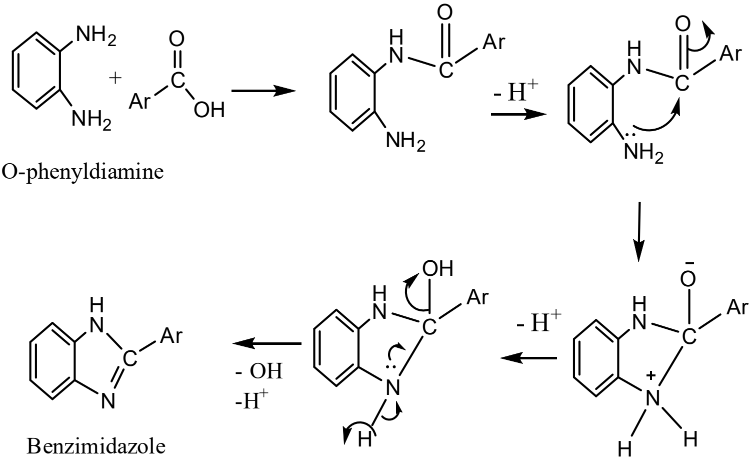
Synthetic methods:

1. From O-phenylene diamine:-

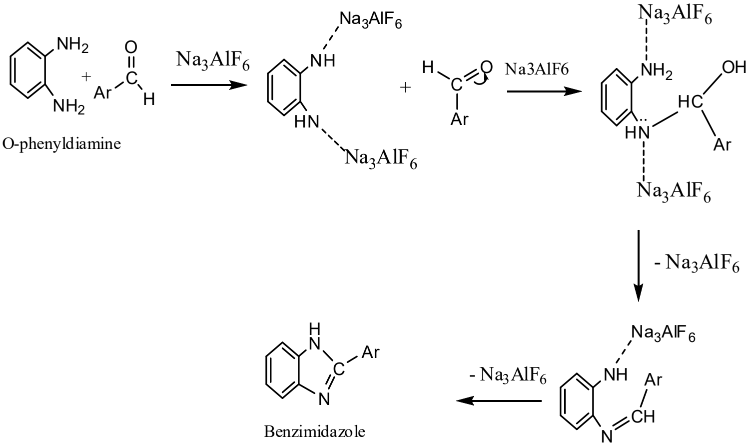


O-phenyldiamine Benzimidazole

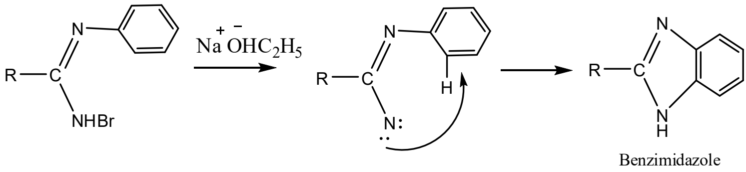
2. From O-phenylene diamine:-



3. From phenylene amine and aromatic aldehyde:



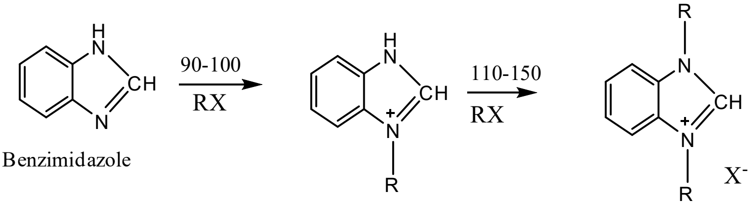
4. From N-haloamides:-



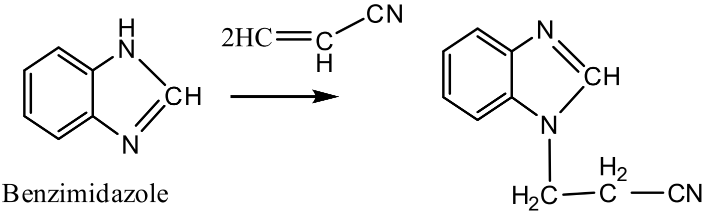
Chemical properties:

1. Alkylation:-

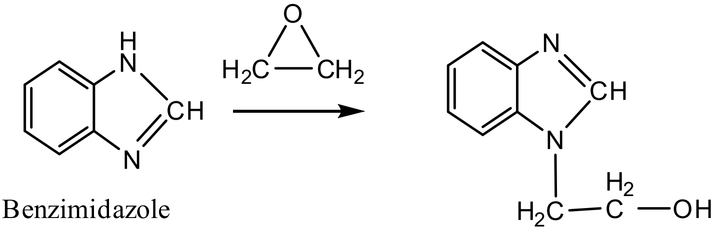
Benzimidazole is efficiently alkylated with alkyl halide to form 1-alkylbenzimidazole, while under vigorous conditions it formed 1,3-dialkylbenzimidazolium halide.



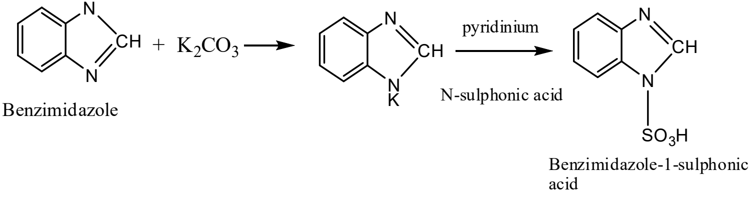
2. **Reaction with Acrylonitrile:**
Benzimidazole on reaction with acrylonitrile gives N-cyanoethyl-1-H-benzimidazole.



3. **Reaction with Oxime:**
Benzimidazole react with oxirane gives N-(2-hydroxyethyl)-1-H-benzimidazole.

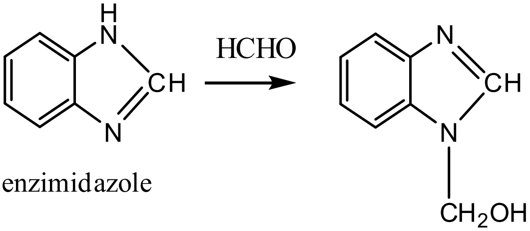


4. **Reaction with potassium carbonate:-**
Benzimidazole react with potassium carbonate gives alkali metal salt of benzimidazole. Followed by pyridinium sulphonic acid to give benzimidazole-1-sulphonic acid.



5. **Reaction with Formaldehyde;-**

Benzimidazole react with formaldehyde to give hydroxymethyl benzimidazole.

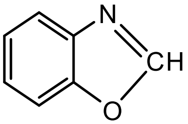


Benzimidazole

Hydroxymethyl
benzimidazole

II] BENZOXAZOLE:-

Benzoderivative of oxazole is known as benzoxazole.

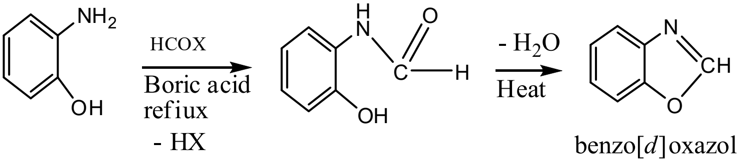


benzo[*d*]oxazole

Synthetic Methods:-

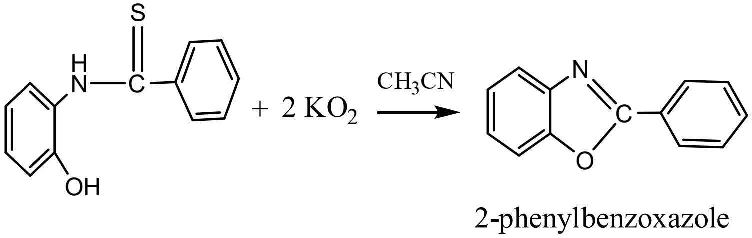
1. **From 2-aminophenol:-**

By heating 2-aminophenol derivatives of carboxylic acid with various leaving group present on the acid itself.

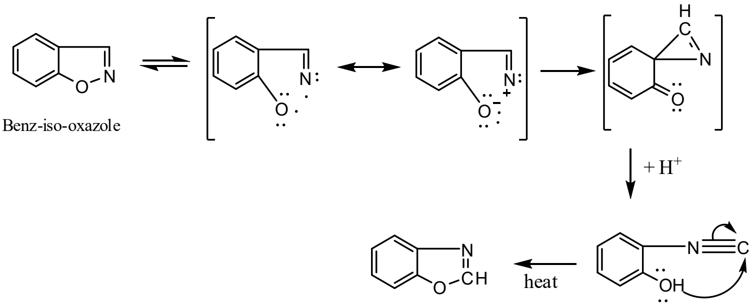


benzo[*d*]oxazole

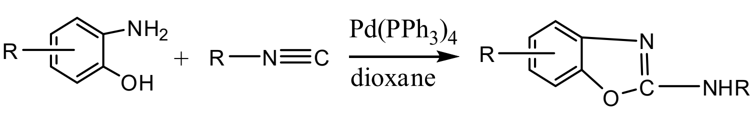
2. **From N(2-hydroxyphenyl)thioamide:**
On the treatment of N(2-hydroxyphenyl)thioamide with super oxide (O2) at room temperature in dry acetonitrile gives 2-phenylbenzoxazole.



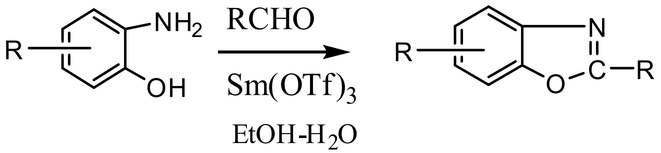
3. **From benziso-oxazole:-**
On photochemical irradiation of benziso-oxazole gives benzoxazole.



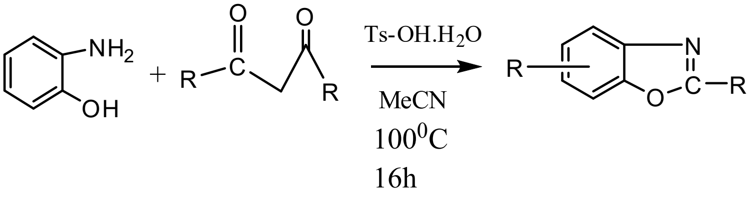
4. **From 2-aminophenol:**
2-aminophenol on heating with alkyl isonitrile in the presence of Pd(PPh3)4 and dioxane to give substituted benzoxazole.



5. From 2-aminophenol:



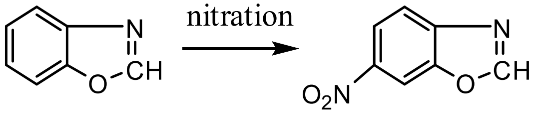
6. From 2-aminophenol;



Chemical properties:-

Benzoxazole having [M.P= 27-30⁰C & B. P= 182⁰C] it is planner molecule with aromatic chemical properties. Benzoxazole tend to react mainly at C-6 in electrophilic substitution and lesser extent at C-5.

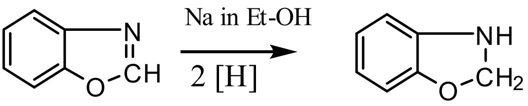
1. **Nitration:** Nitration of Benzoxazole give 6-nitrobenzoxazole.



6-nitrobenzoxazole

2. **Reduction:**

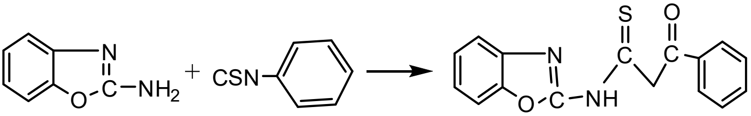
Benzoxazole are stable towords a range of reductive conditions, but the reductionof the ring to oxzolidines can be effect3ed with sodium in ethanol.



Benzoxazolidine

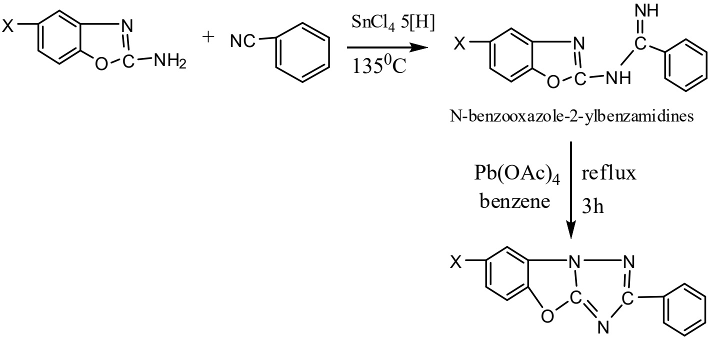
3. 2-aminobenzoxazole with aroyl isothiocyanate:

2-aminobenzoxazole react with aroyl isothiocyanate gives N-aroyl-N-(benzoxazolo-2-yl)thiourea



4. 2-aminobenzoxazole and benzonitrile:

2-aminobenzoxazole react with benzonitrile gives N-(benzoxazol-2-yl)benzamidines, which on oxidation with $Pb(CH_3COO)_4$ / benzene gives 2-aryl[1,2,4]triazolo[5,15]benzoxazole.

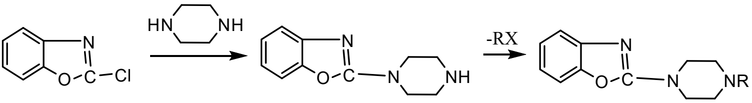


N-benzooxazole-2-ylbenzamidines

2-aryl[1,2,4]triazolo[5,1b]benzimidines

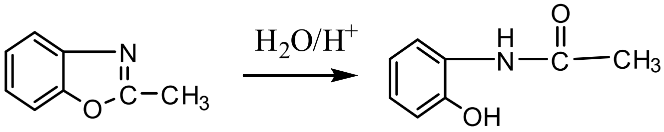
5. 2-chlorobenzoxazole:

Piperazine react with 2-chlorobenzoxazole gives

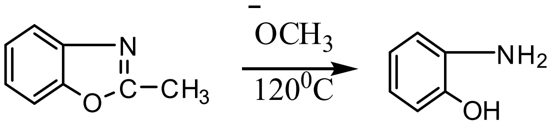


R= CH_3/Ph

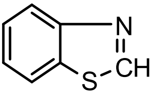
6. **Hydrolysis:**
   2-methylbenzoxazole on hydrolysis gives O-acetamido phenol in hot water and reaction is more rapid.



7. **Reaction with alkoxide:-**

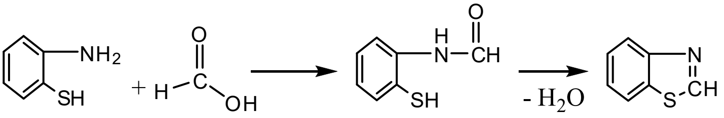


III] BENZOTHIAZOLE:-



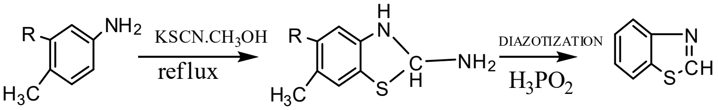
Synthetic methods:

1. Benzothiazole may be obtained from 2-aminothiophenol and a carboxylic acid or anhydride.



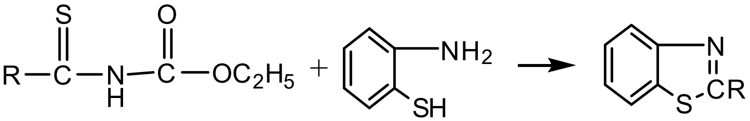
Benzothiazole

2. From thiaocyanation of substituted aniline:



Benzothiazole

3. Condensation Of N-carboxythiacetamine with O-aminothiophenol gives 2-substituted benzothiazole.

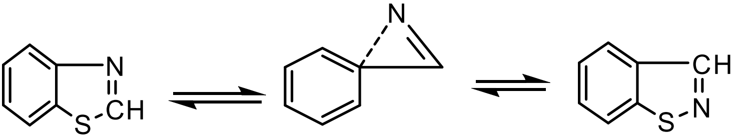


4. 2-arylbenzothiazole can be obtained directly from copper thiobenzoate and 2-iodoaniline on heating in hexamethyl phosphoric triamide.

Chemical Properties;

1. **Photochemical reaction:**

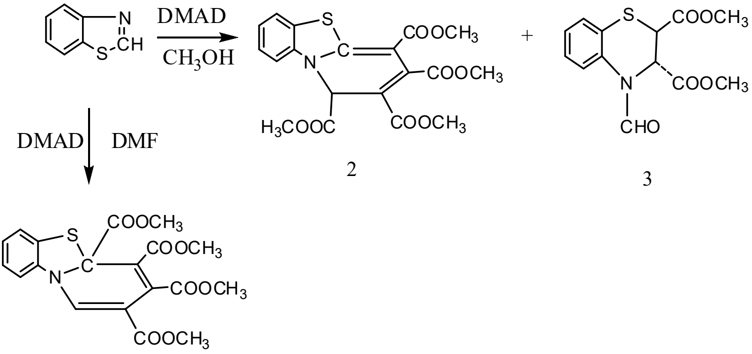
   Benzothiazole undergoes isomerisation to the corresponding benzothiazole photochemically or thermally.



Benzoisoxazole

2. **Reaction of benzothiazole with DMAD:**

   Benzothiazole react with dimethyl acetylene dicarboxylate (DMAD) to give (2), (3) & (4)

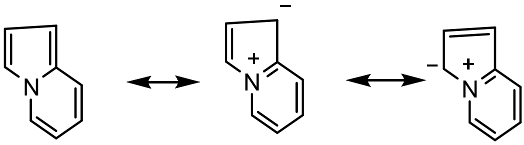


4

Heterocycles with Ring Junction nitrogen:

1. Indolizines:

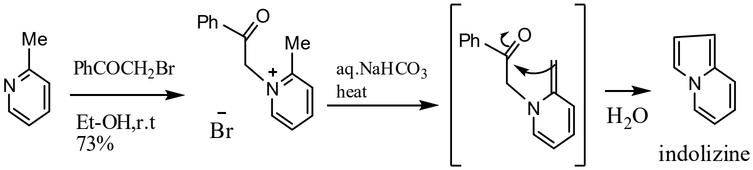
The aromatic indolizine is expressed by three main mesomeric contributors, two of which incorporate a pyridium moiety; other structures incarporatine neither a complete pyrrole nor pyridinium are less important.



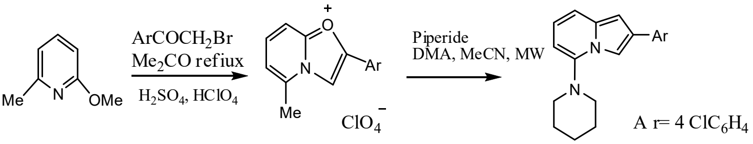
indolizine

Synthetic Methods:

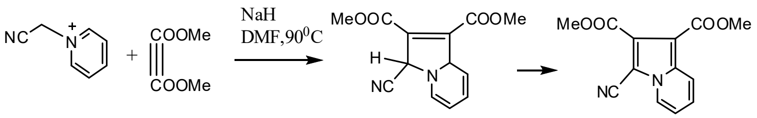
1. 2-alkylpyridine with an á-haloketone, followed by base catalysed cyclisation via deprotonation of the pyridium á-methyl.



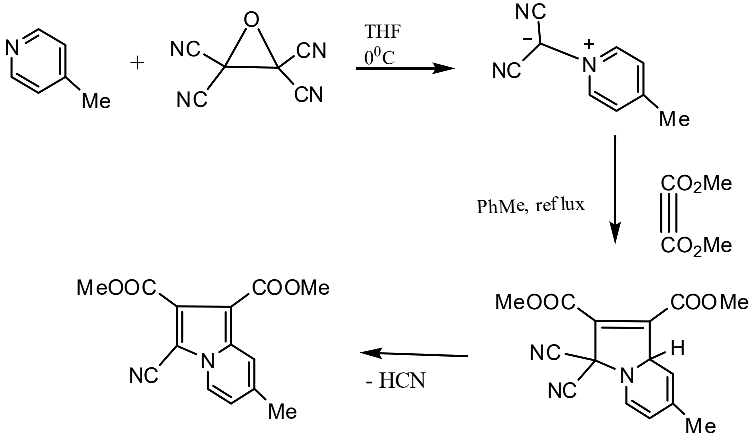
2. 2-methoxy-6-methylpyridine as a starting material and leads eventually to 5-aminoindolizine, the intermediate oxazolo[3,2á]pyridinium saltisolated as perchlorate salt.



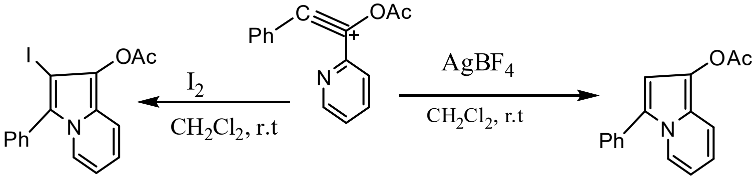
3. 1,3-dipole cycloaddition:



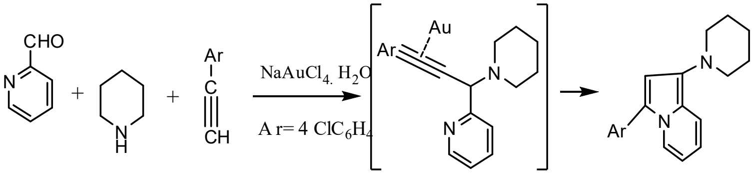
4. Aromatization can alternatively occur by loss of HX (HCN) when leaving group present in one of the reactants.



5. From 2-alkylmethyl pyridine or 2-alkylphenylpyridine: Substituent can be ring closed to indolizines. Iodine and tetrafluoroborate have been used To close precursors available conviently using 2-lithiated pyridine.



6. In a one pot three component sequence, 2-alkynylpyridine intermediate is generated. Pyridine-2-carbaldehyde being the starting material and 1-aminoindolizine is the product.



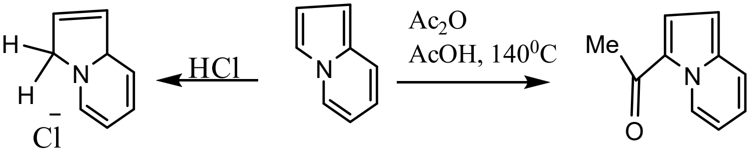
CHEMICAL PROPERTIES:

Indolizine is much more basic than indole and the implied relative stability the cation make less reactive.

Indolizine protonate at C-3 but 3-methylindolizine protonate mainly atC-1

1. **Electrophilic substitution:**

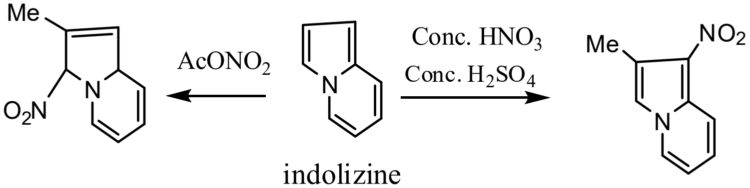
Electrophilic substitution such as acylation, Vilsmeier formylation and diazocoupling takes place at C-3.



indolizine

2. **Nitration:**

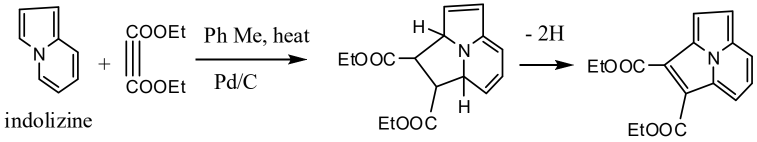
Nitration of 2-methylindolizine under mild condition gives substitution at C-3, but under strong acidic condition it takes place at C-1.



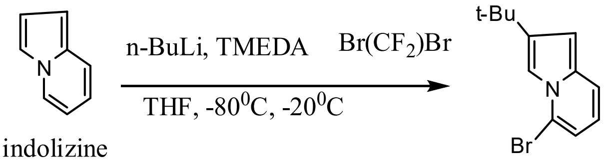
indolizine

3. Aromatic cyclisation:

Indolizine react with diethylacetylene dicarbolate, through the process may be stepwise, reaction carrying out the reaction in the presence of noble metal catalyst. Initial adduct converted into an aromatic cyclization.

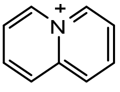


4. Reaction with n-butyllithium:



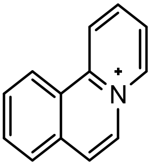
II] QUINOLIZINIUM SALT:

Quinolizinium salt and its derivative are stable, water soluble, crystalline solids , quinolizinium salt is parent compound of quinolizines.

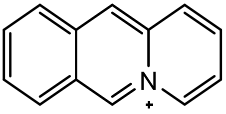


quinolizinium

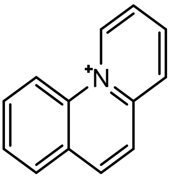
Quinolizinium salts are three types.



pyrido[2,1-*a*]
isoquinolinium



pyrido[1,2-*b*]
isoquinolinium

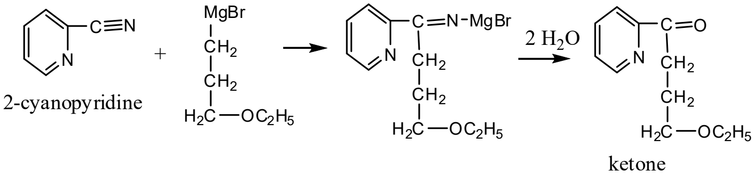


pyrido[1,2-*a*]
quinolinium

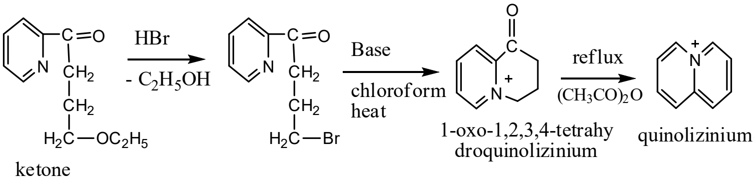
Synthetic methods: -

1) From 2-substituted pyridine:-

i) 2-cyanopyridine react with 3-ethoxypropyl magnesium bromide to form imine which is hydrolysed to ketone.

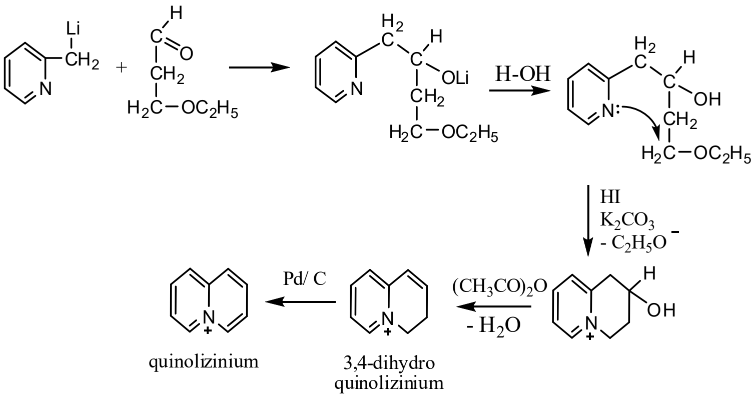


ii) Ketone treated with HBr and gives bromide derivative which can be converted into 1,2,3,4-tetrahydroquinolizinium salt, which is refluxed with acetic anhydride to form quinolizinium salt.



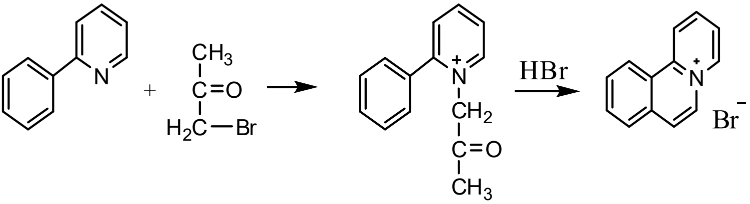
2) From 2-picolythium:-

By the condensation of 2-picolithium with â-ethoxypropionaldehyde, quinolizinium ion is synthesized in the following steps.



3) Synthesis of benzo(a)quinolizinium salt:

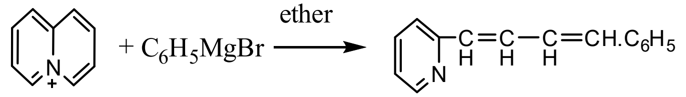
benzo(a)quinolizinium salt is synthesized from 1-phenylpyridine and á-haloketone or á-haloaldehyde in the following steps.



Chemical properties:-

1. Nucleophilic substitution reaction:-

a) Quinolizinium ion react with nucleophilic at C-4position. The ring system is easily cleared by nucleophile to form derivative of 2-butadiphenylpyridine.

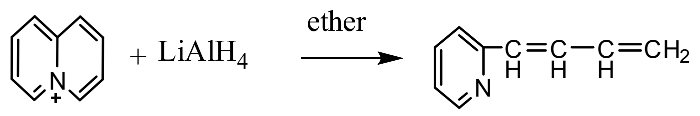


quinolizinium

2-(4-phenylbuta-1,3-dienyl)pyridine

b) Reaction with Lithium Aluminium hydride:

Quinolizinium ion react with lithium aluminum hydride in the presence of tetrahydrofuran gives 2-butadienylpyridine.

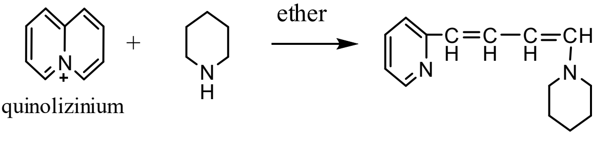


quinolizinium

2-(buta-1,3-dienyl)pyridine

c) Reaction With Piperidine:

Quinolizinium ion on heating with piperidine gives piperidyl-2-butadienylpyridine.

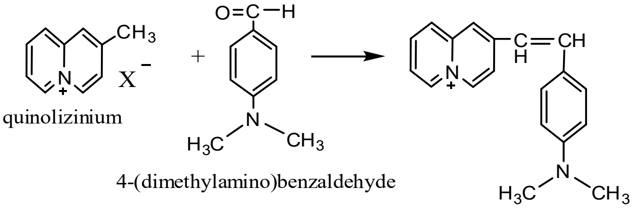


2-(4-(piperidin-1-yl)buta-1,3-dienyl)pyridine

2] Condensation Reaction and coupling reaction:

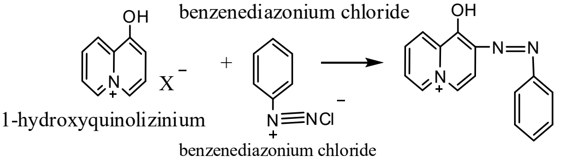
Hydroxy, amino and alkyl substituent at C-2 and C-4 positions are activated these salts are condensed with P-N, N-dimethylaminobenzaldehyde to give the corresponding styryl derivatives of Schiff's bases.

i)



2-(4-(dimethylamino)styryl)quinolizinium

ii)

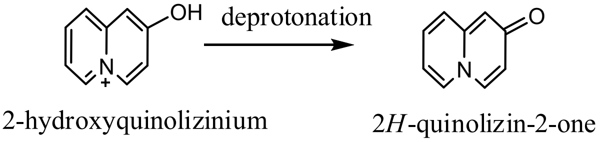


1-hydroxy-2-(phenyldiazenyl)quinolizinium

1-hydroxyquinolizinium bromide on coupling with benzene diazonium chloride form azo derivative.

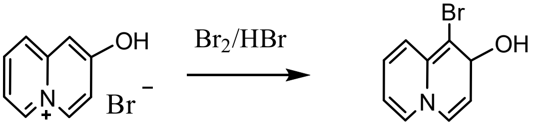
3] Deprotonation:-

2-hydroxyquinolizinium salt are easily deprotonated to quinolizones.

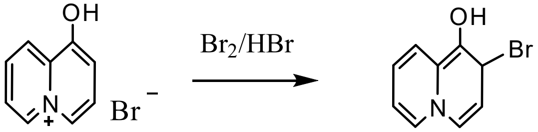


4] Bromination:

When 1 and 2-hydroxyquinolizinium salts on rapid bromination form corresponding bromoderivative, bromination takes place at 2 and 1-position.



2-hydroxyquinolizinium bromide 1-bromo-2*H*-quinolizin-2-ol



1-hydroxyquinolizinium bromide 2-bromo-2*H*-quinolizin-1-ol

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