Heterocyclic Compounds

اعداد

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Heterocyclic Compounds

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Those cyclic compounds in which **one or more** of the **ring carbons are replaced by another atoms** (referred as heteroatoms).

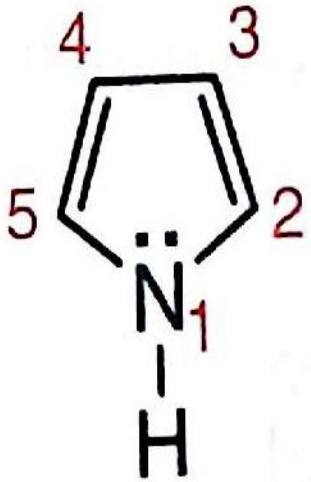
The most common heteroatoms are **Nitrogen, Oxygen and Sulphur.**

But,

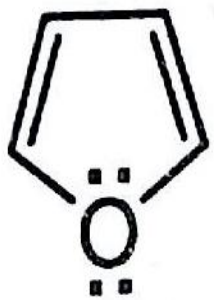
Other atoms such as **Boron, Phosphorous, or Silicon** can also be members of heterocyclic rings.

A variety of heterocyclic compounds of different ring sizes are known, the most important ones are made of **five and six-membered rings**.

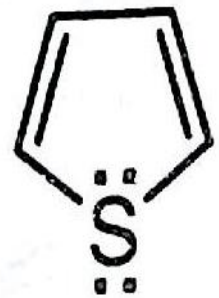
Five-membered Rings



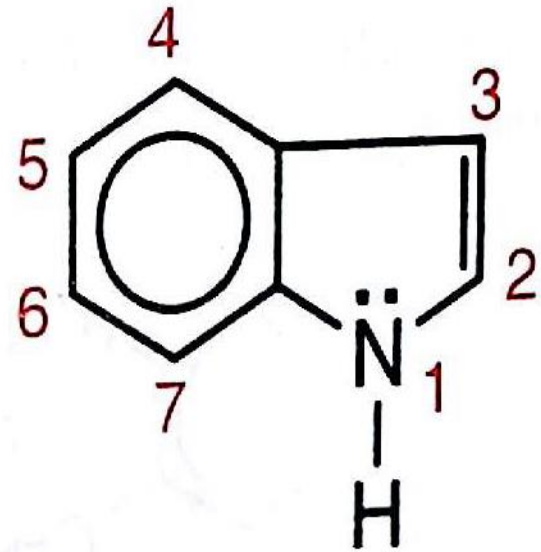
Pyrrole



Furan

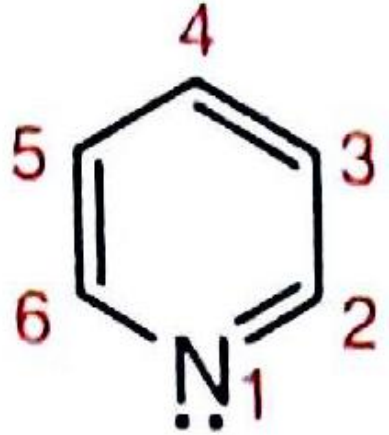


Thiophene

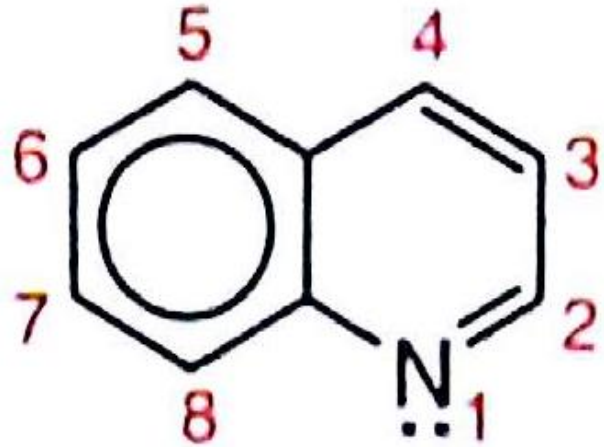


Indole

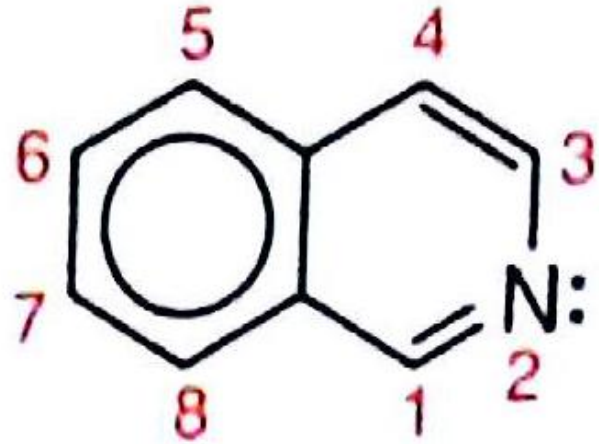
Six-membered Rings



Pyridine

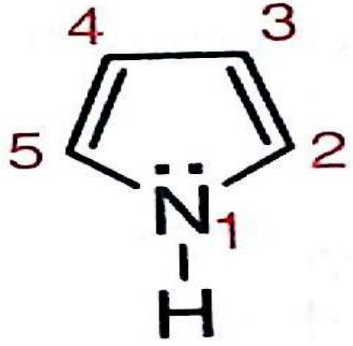


Quinoline

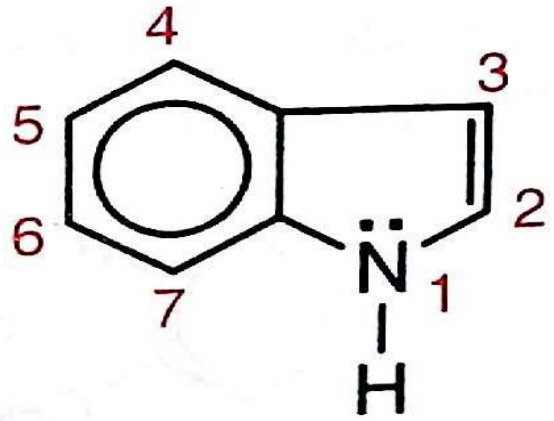


Isoquinoline

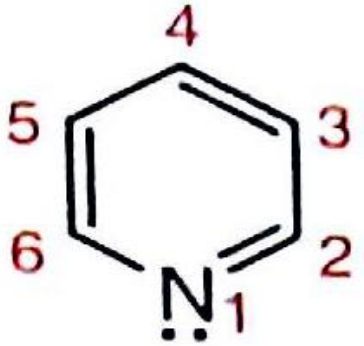
Notice that the rings containing nitrogen usually end with ***-ole*** **if five-membered** and with ***-ine if*** **six-membered**. The hetero atom is always numbered as 1 (**isoquinoline is an exception**



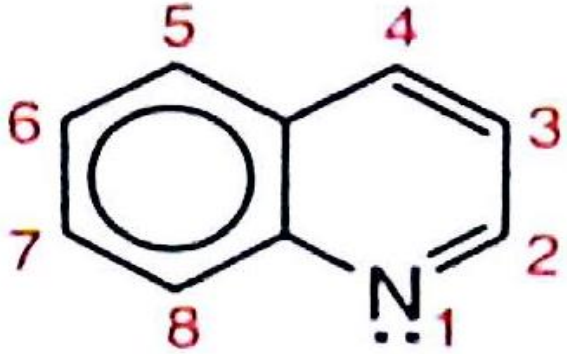
Pyrrole



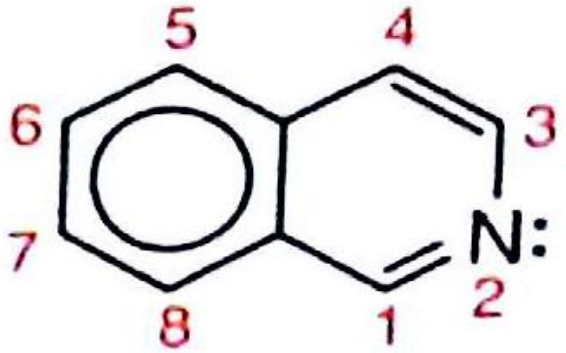
Indole



Pyridine

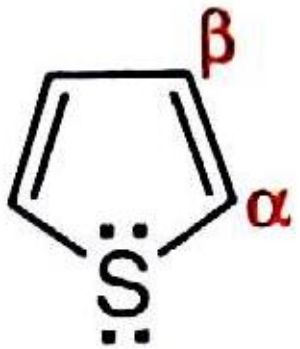


Quinoline

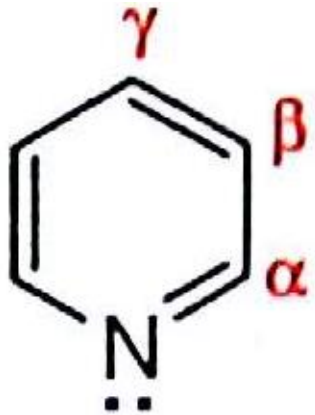


Isoquinoline

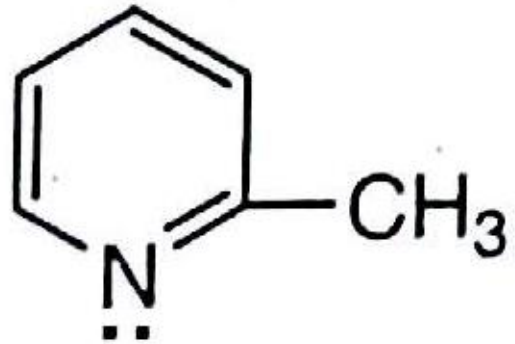
The carbon atoms next to the hetero atom are sometimes referred to as the **α-carbon** atoms and those further away as **β- and ϒ-carbon** atoms



Thiophene



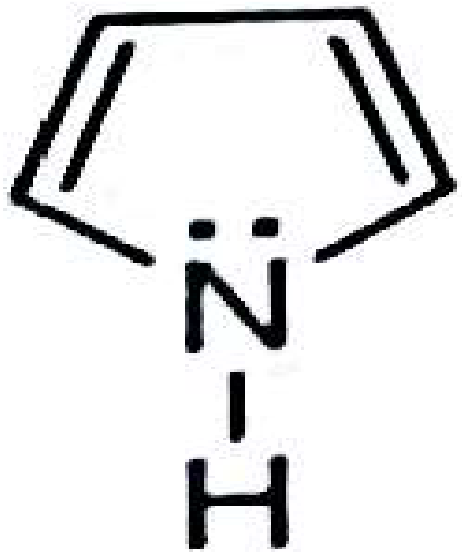
Pyridine



α-Methylpyridine
(2-Methylpyridine)

Pyrrole

It is an important five-membered heterocyclic compound because many naturally occurring substances contain the pyrrole ring e.g., **chlorophyll, hemoglobin and some of the alkaloids**.



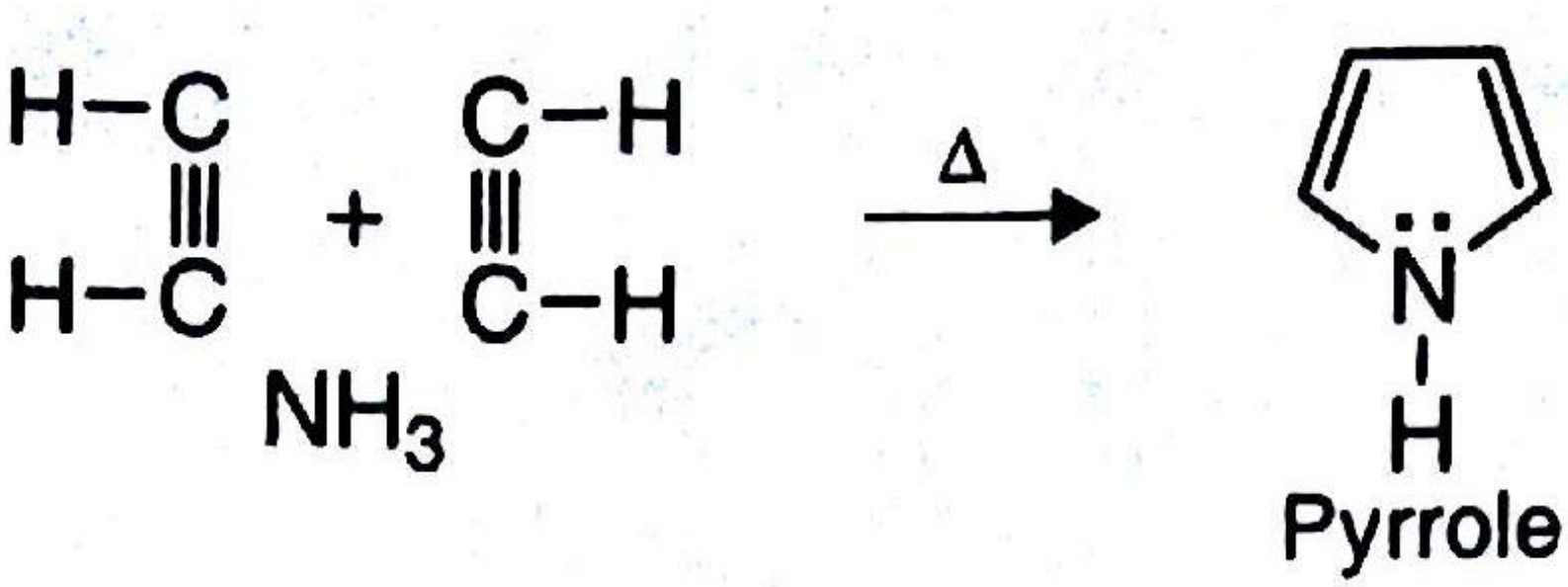
Occurrence

Pyrrole occurs in **coal-tar and in bone oil** (Dippel's oil). The latter is obtained by the dry distillation, or pyrolysis, of animal by-products such as horns, hooves, and bones.

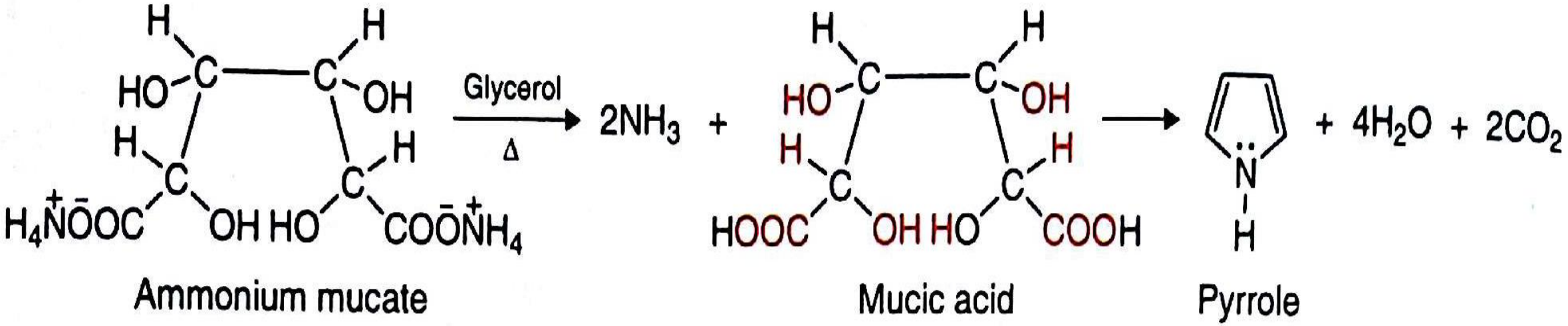
It may be isolated from bone oil by first washing it with **dilute sulphuric acid to remove the basic substances, and then with dilute alkali to remove the acidic substances.** It is next subjected to **fractional distillation**. The fraction passing over between **100°C to 150°C** contains pyrrole, which may be removed by **boiling with potassium hydroxide**. The potassium salt is formed which on steam distillation gives pyrrole. This is finally purified by **distillation**.

Preparation Methods

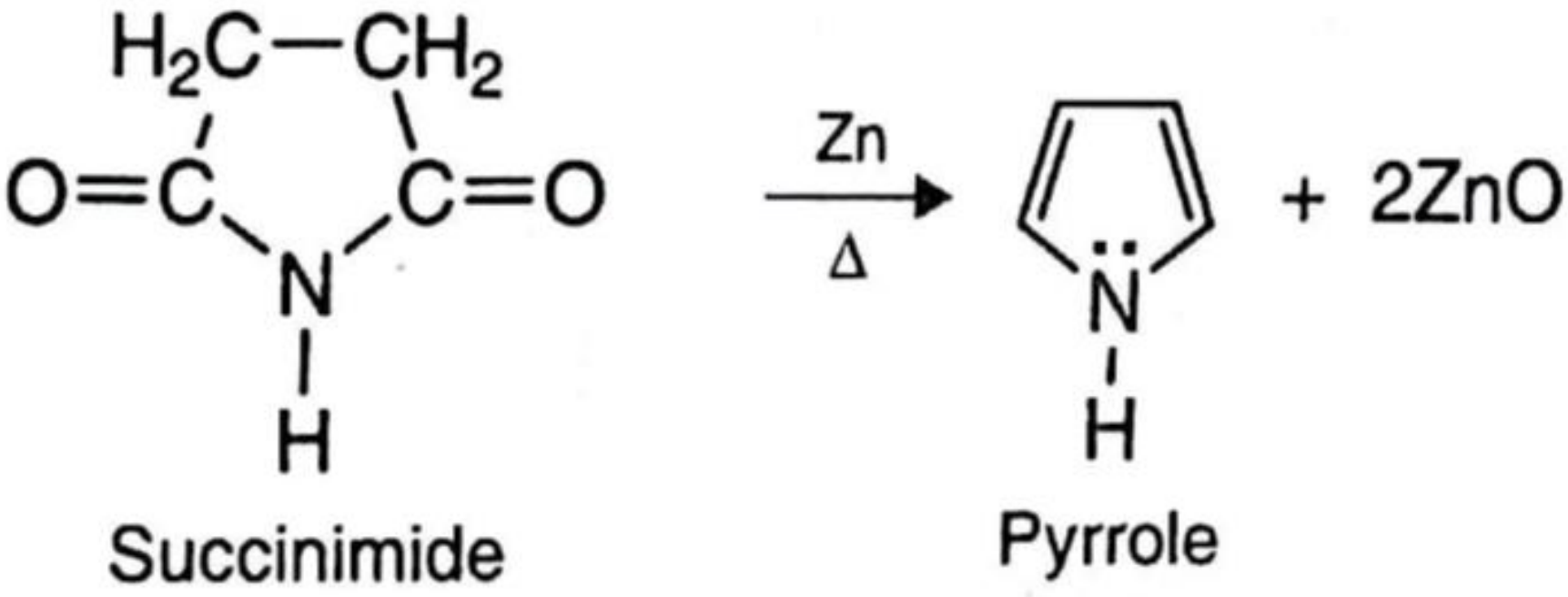
1. By passing a mixture of **acetylene and ammonia** through a red-hot tube



2. By heating **ammonium mucate** with glycerol at 200 degrees. At this temperature, ammonium mucate is dissociated into mucic acid and ammonia. The acid then undergoes dehydration, decarboxylation and ring-closure by reaction with ammonia.



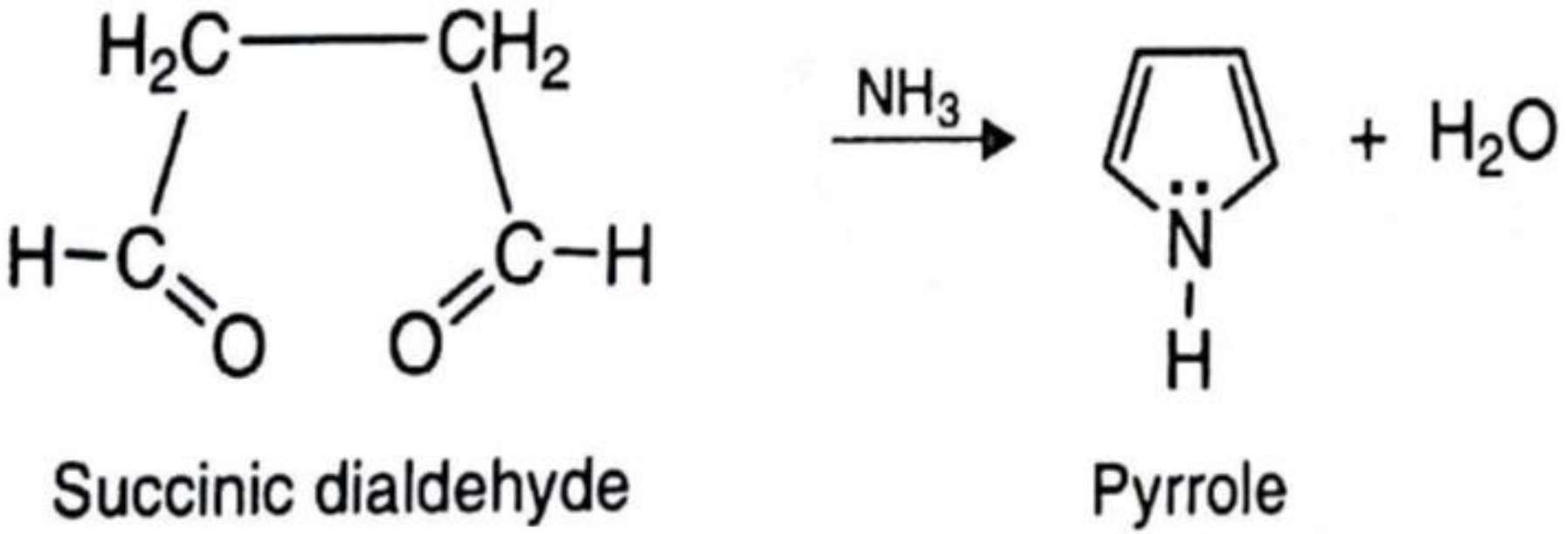
3. By heating **Succinimide** with zinc dust.



Succinimide

Pyrrole

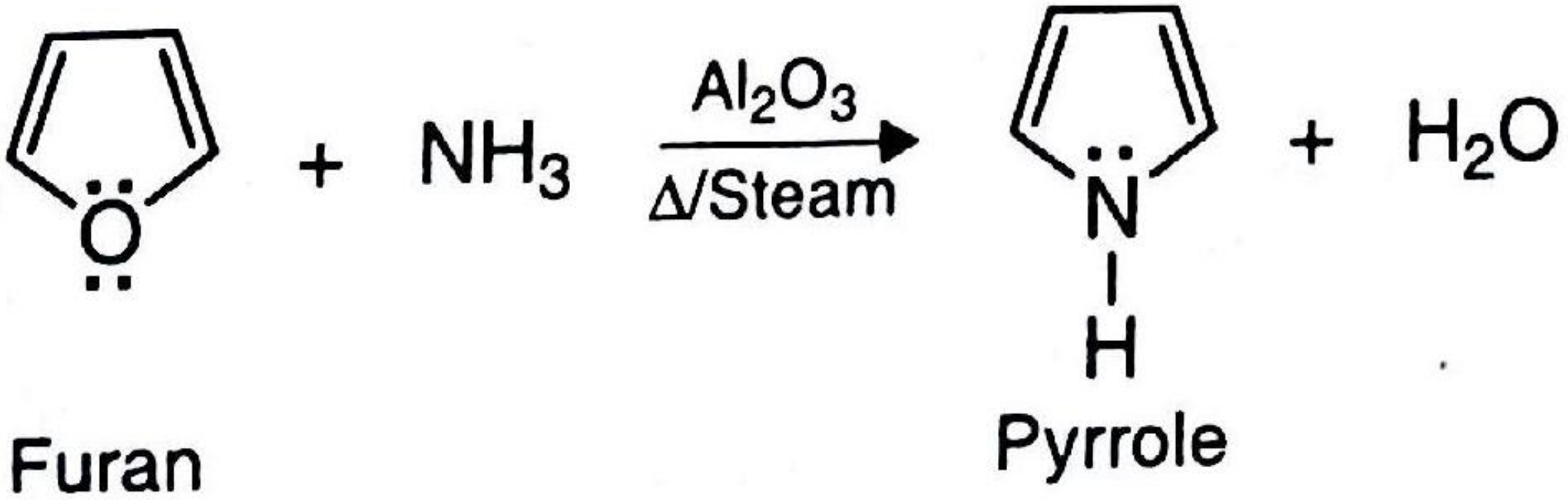
4. By warming succinic dialdehyde with ammonia



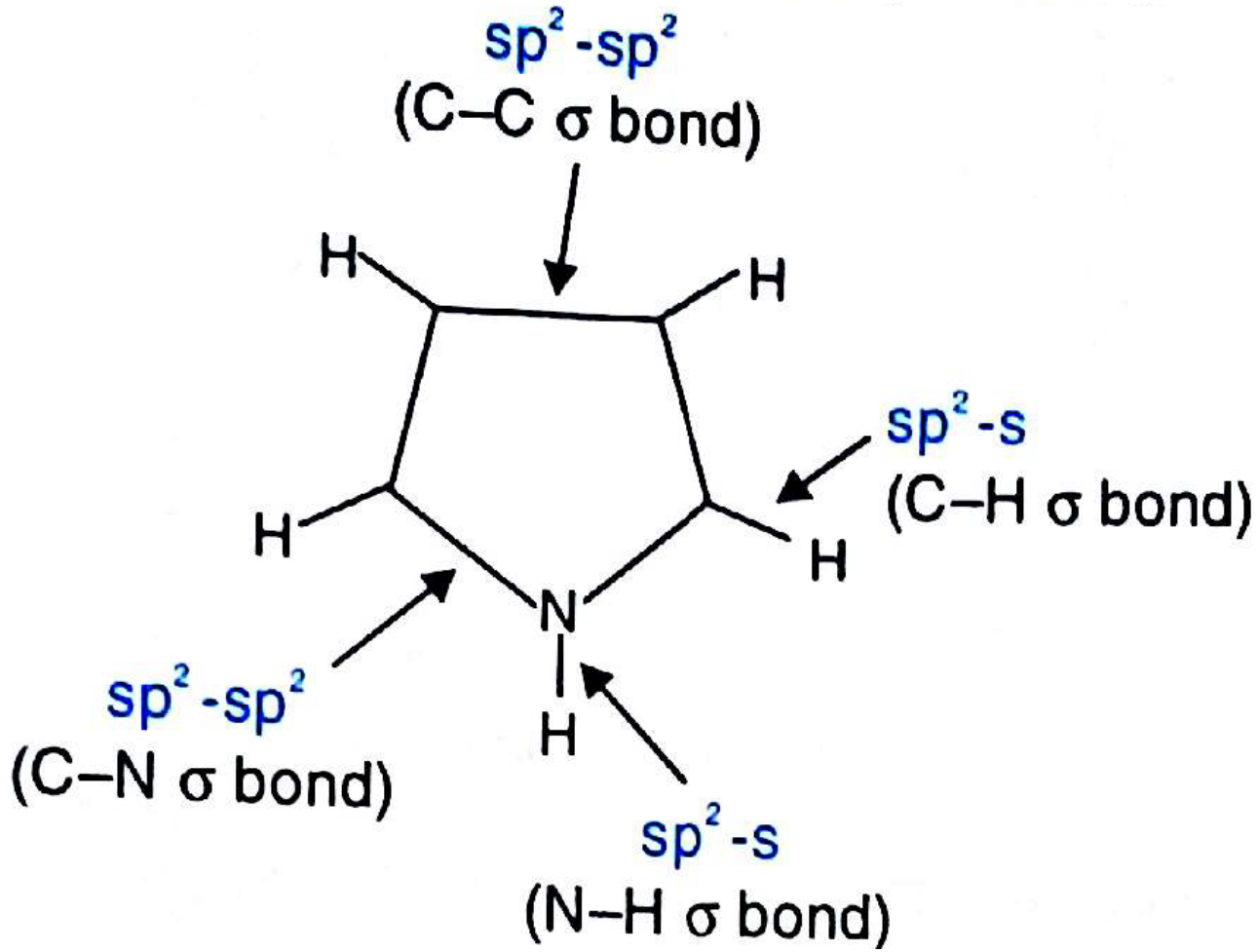
Succinic dialdehyde

Pyrrole

5. **Commercial Method:** By passing a mixture of furan, ammonia, and steam over aluminium oxide catalyst at 480-490°C.



Structure of Pyrrole



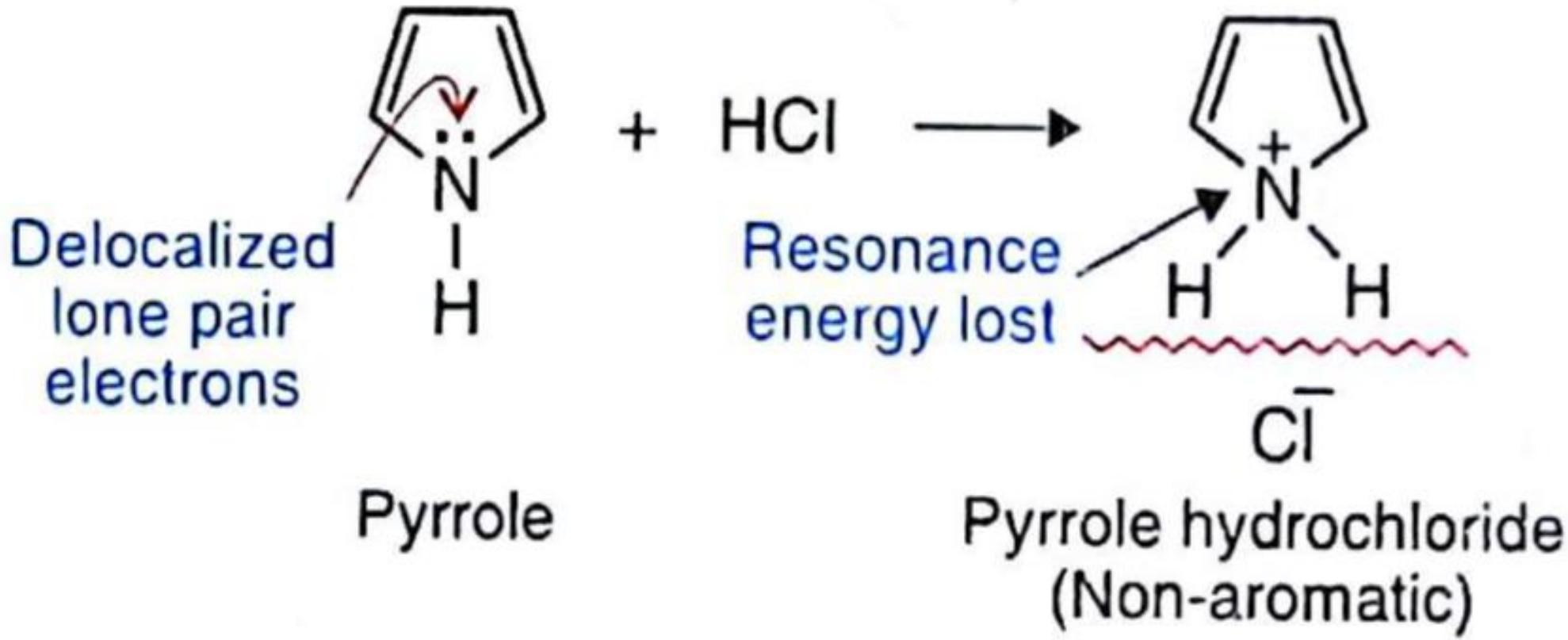
Physical Properties of Pyrrole

- Pyrrole is colorless liquid,
- Boiling point 131°C, which rapidly turns brown on exposure to air.
- Its odour is like that of chloroform.
- Pyrrole is sparingly soluble in water but dissolves in ethanol and ether.

Chemical Properties of Pyrrole

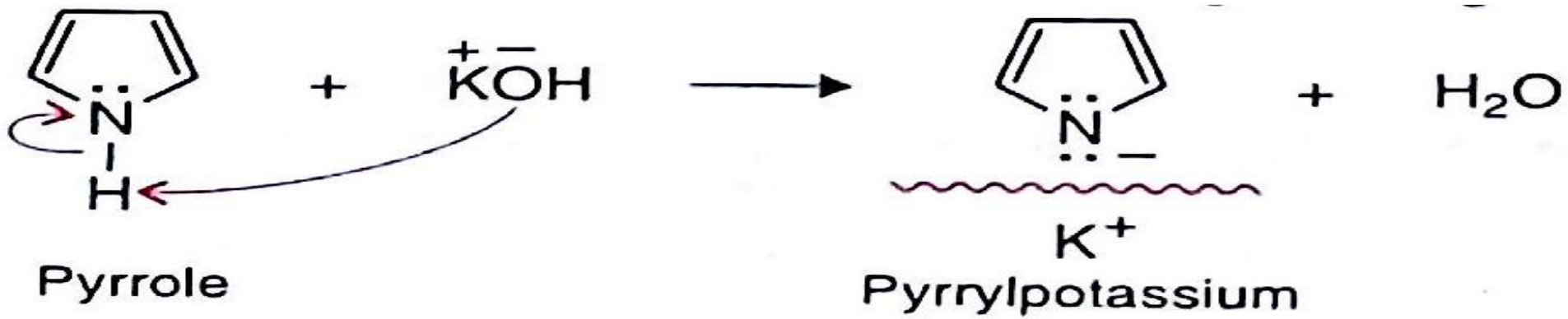
1. Basic Character:

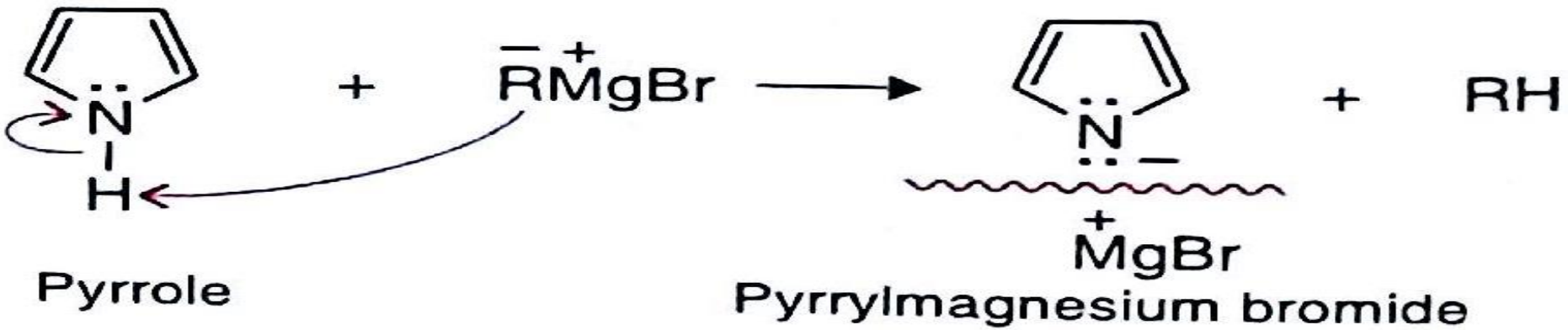
Pyrrole reacts with dilute hydrochloric acid to give a crystalline hydrochloride.



2. Acidic Character

Pyrrole is not only a weak base but also a very weak acid. This is shown by its reactions with potassium hydroxide and Grignard reagents.



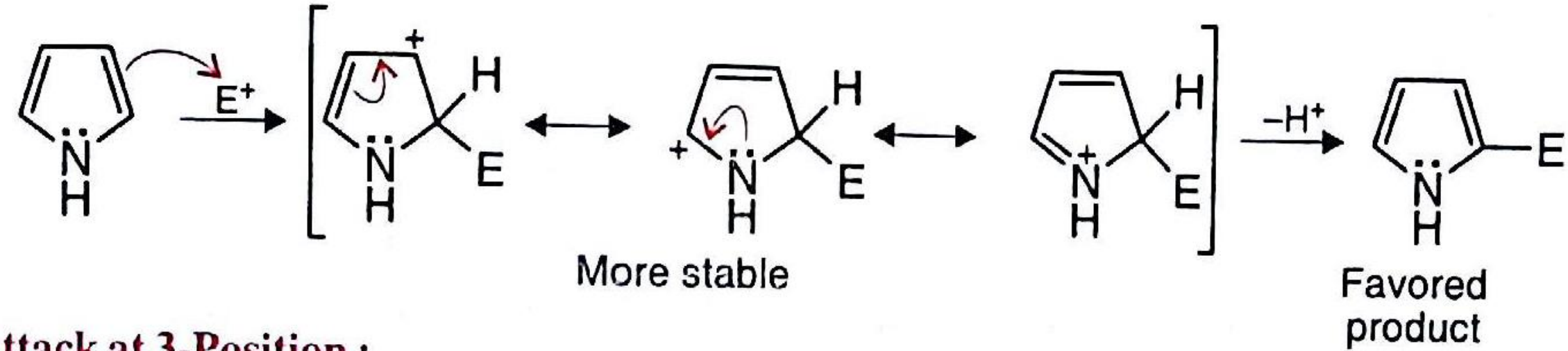


3. Electrophilic Substitution Reactions

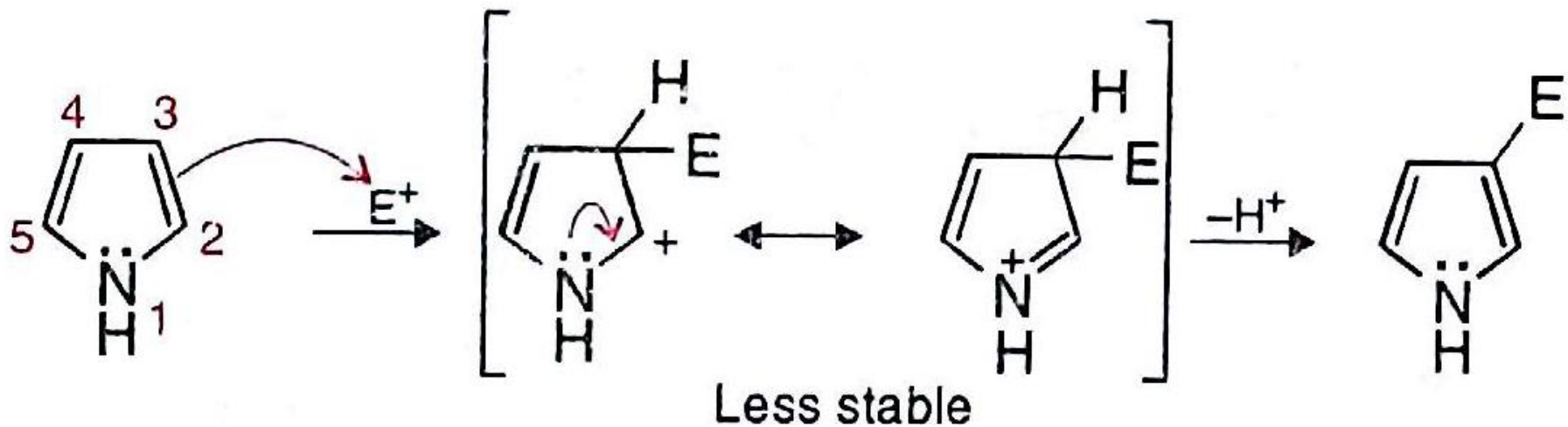
Pyrrole undergoes electrophilic substitution reactions at C-2 because three resonance forms can be written for the intermediate obtained from attack at C-2, whereas **only two** such forms are possible for substitution at C-3.

Consequently the C-2 intermediate is more stable and the product with a substituent at C-2 predominates. **Substitution at C-3 occurs only when both the 2-positions (that is, α and α') are blocked**.

Attack at 2-Position :

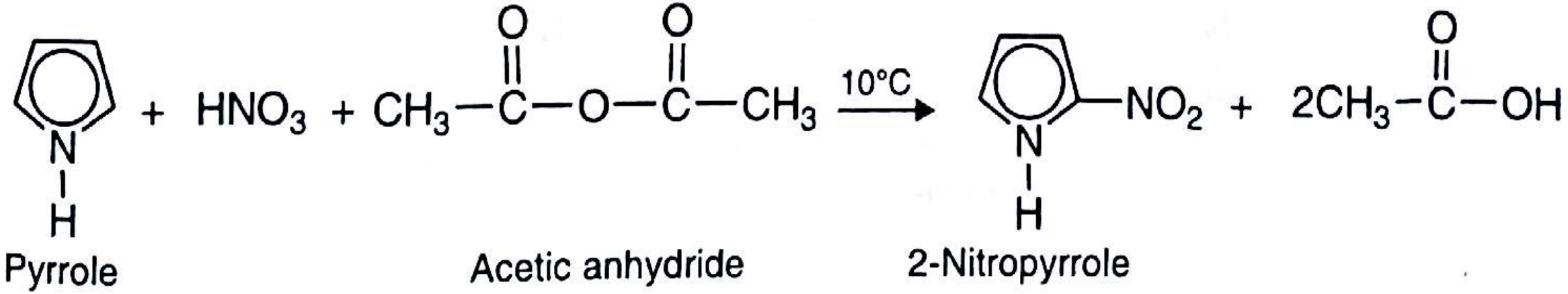


Attack at 3-Position :

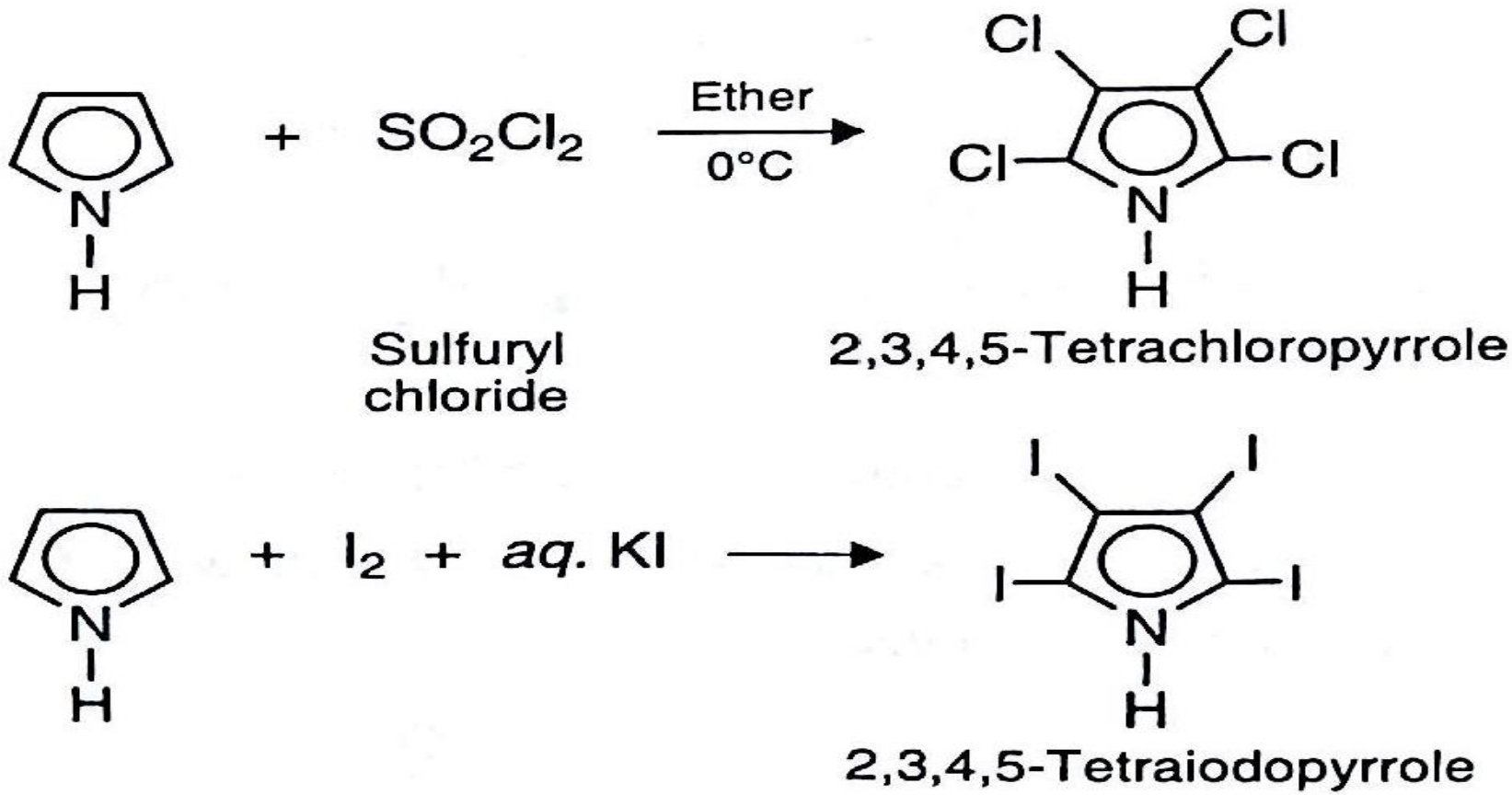


a. Nitration

Pyrrole can be nitrated by a *cold* solution of nitric acid in acetic anhydride to give 2-nitropyrrole.

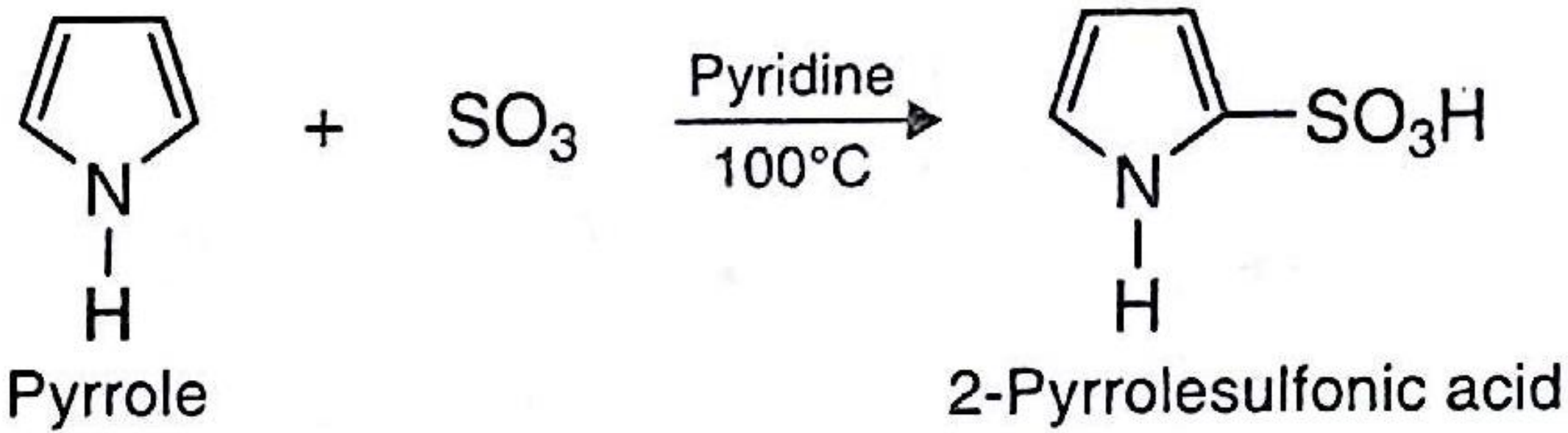


b. Halogenation



c. Sulphonation

Pyrrole may be sulphonated with sulphur trioxide in pyridine at about 100°C to yield 2-pyrrolesulfonic acid.

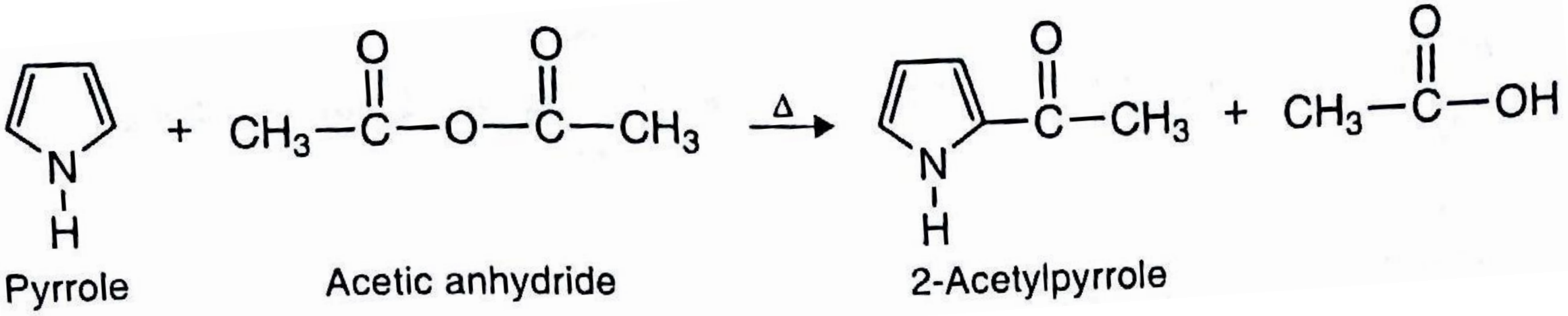


Pyrrole

2-Pyrrolesulfonic acid

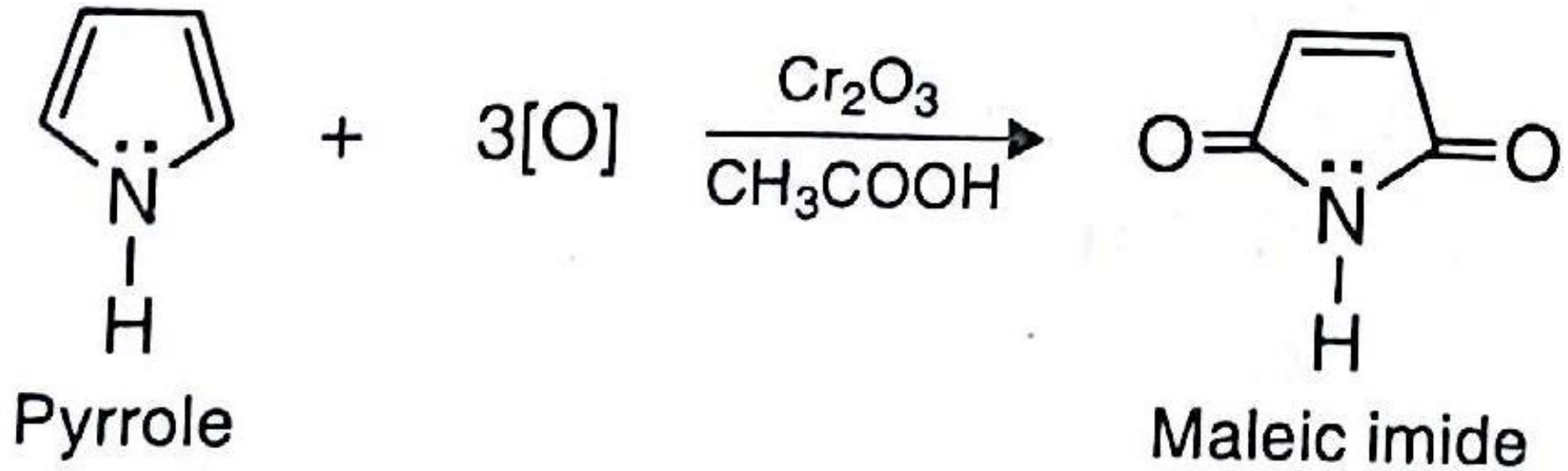
d. Friedel-Craft Acylation

Pyrrole may be acetylated with acetic anhydride at 250°C to give 2-acetylpyrrole. Notice that no catalyst is required in this reaction.



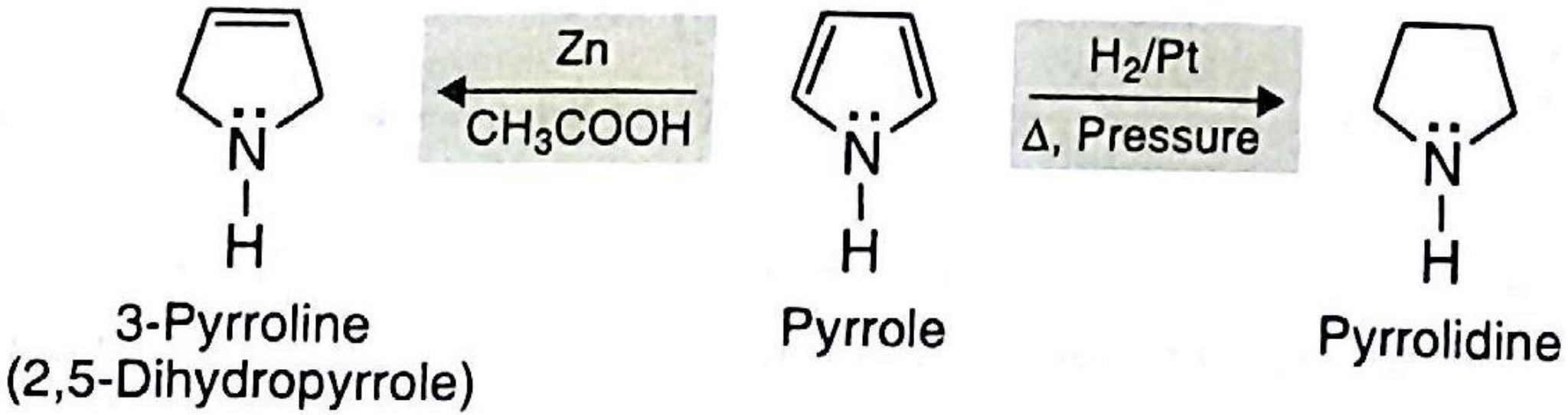
4. Oxidation

Pyrrole is oxidized by chromium trioxide in acetic acid to give the imide of maleic acid.



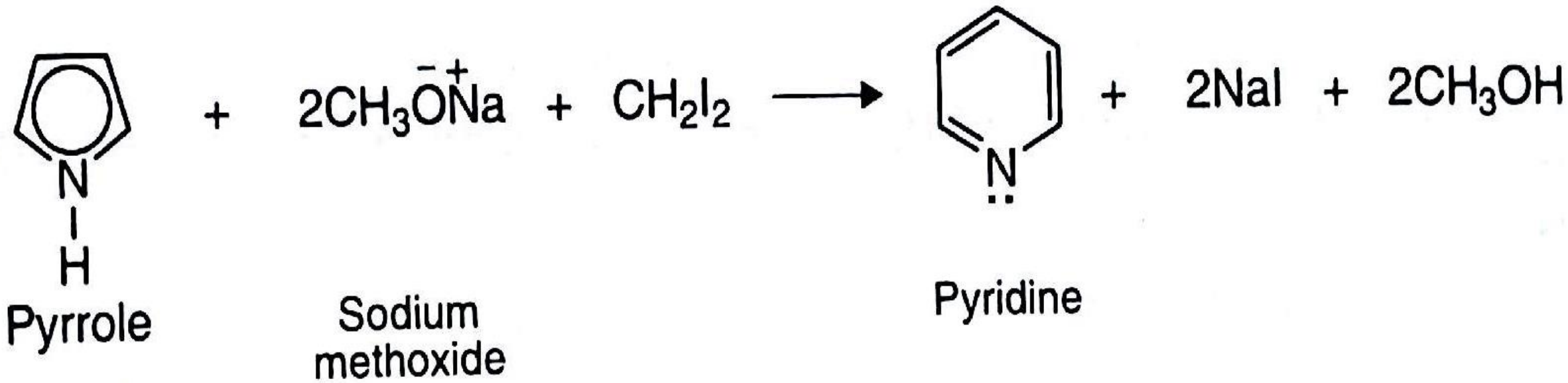
5. Reduction

Mild reduction of pyrrole with zinc and acetic acid yields 3-pyrroline (2,5-dihydropyrrole). Catalytic reduction completely hydrogenates the ring system and produces pyrrolidine.



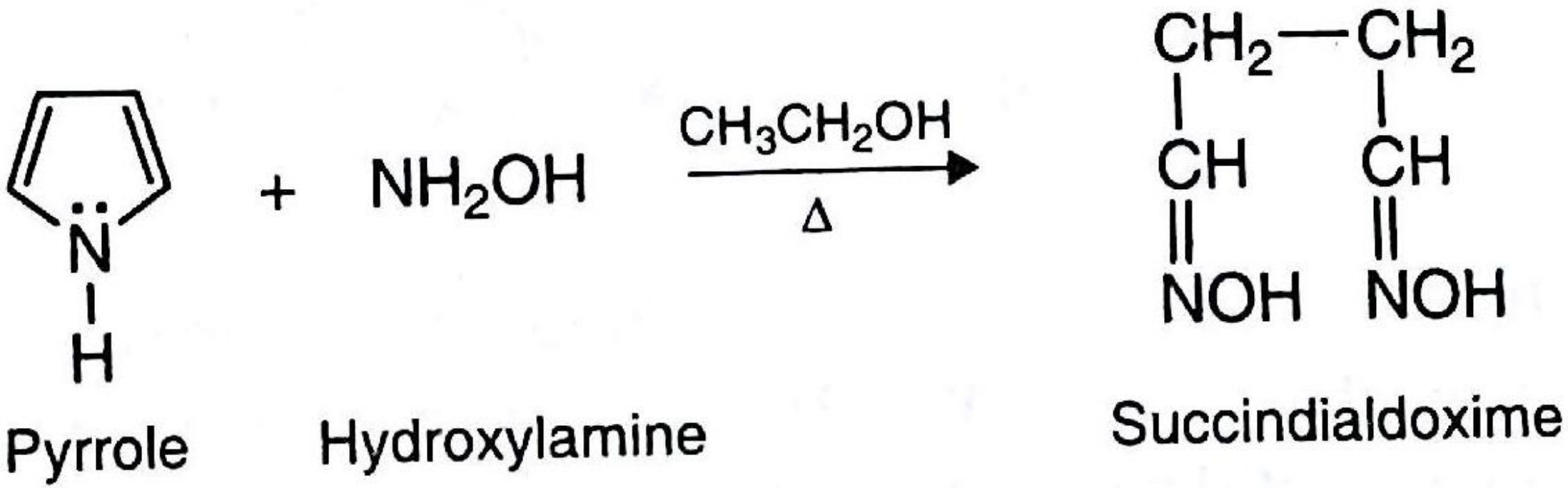
6. Ring Expansion Reaction

When treated with sodium methoxide and Methylene iodide, pyrrole undergoes ring expansion forming pyridine.



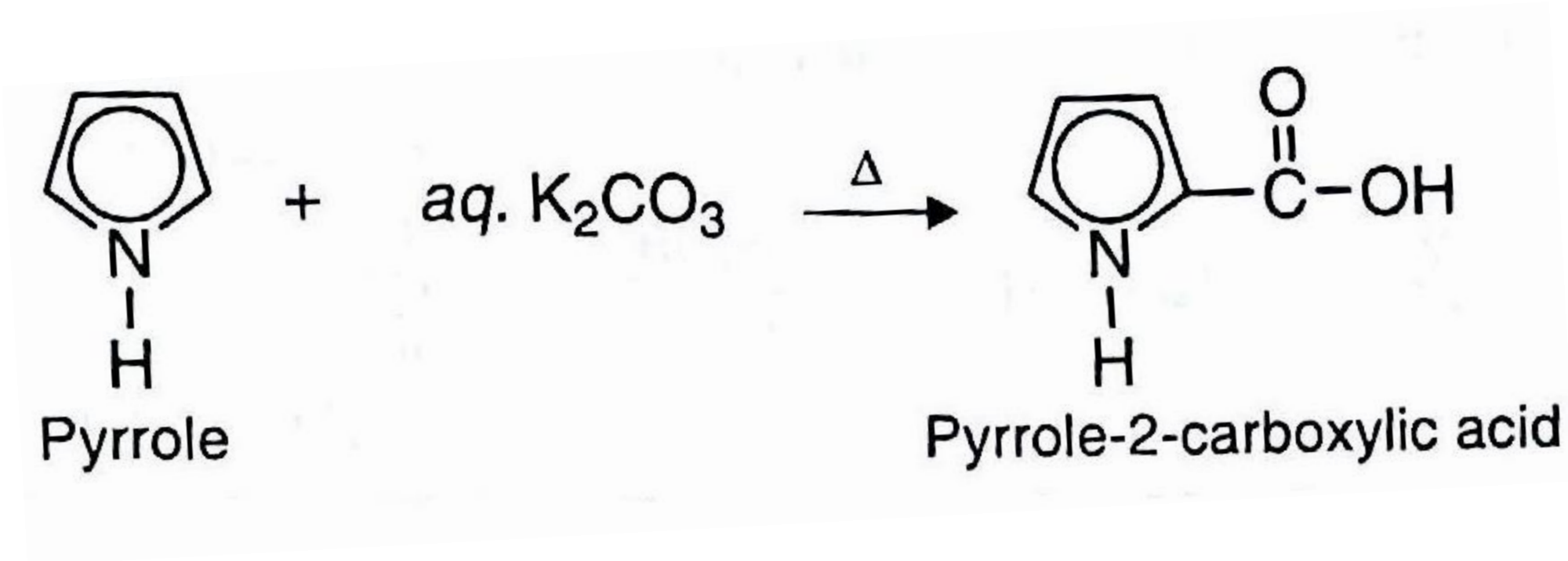
7. Ring Opening Reaction

When treated with hot ethanolic hydroxylamine, pyrrole undergoes ring opening forming the dioxime of succindialdehyde



7. Kolbe-Schmitt Carboxylation

Pyrrole reacts with aqueous potassium carbonate at 100°C to give pyrrole-2-carboxylic acid.

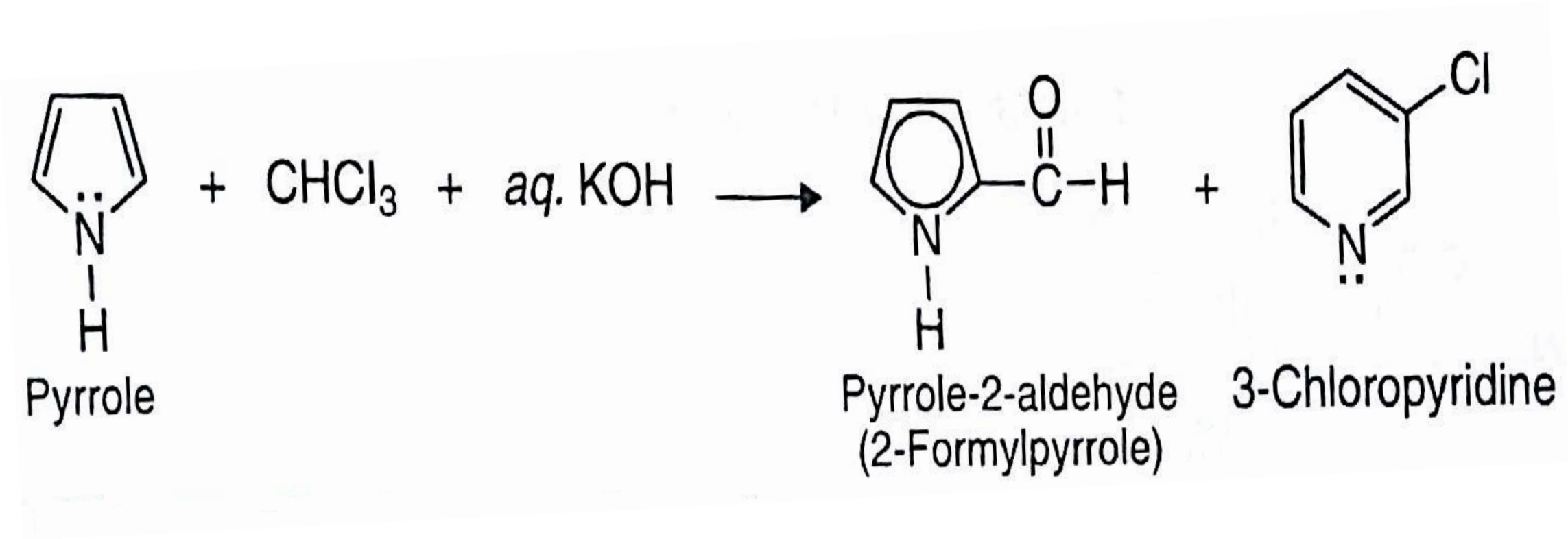


Pyrrole

Pyrrole-2-carboxylic acid

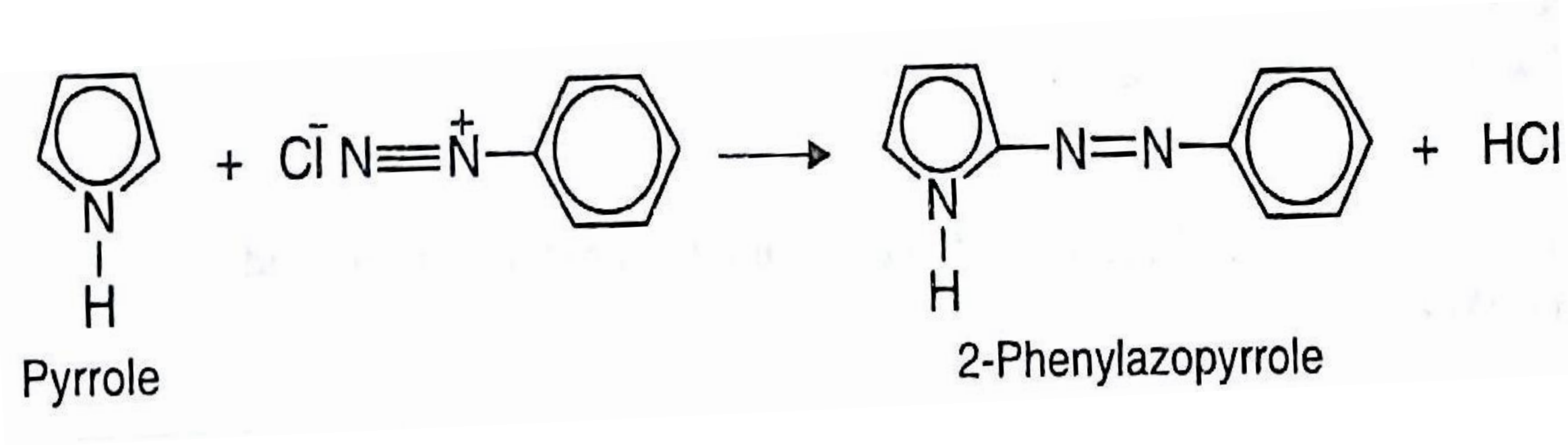
8. Reimer-Tiemann Formylation

Pyrrole reacts with chloroform in the presence of alkali to yield pyrrole-2-aldehyde (2-formylpyrrole) and 3-chloropyridine.

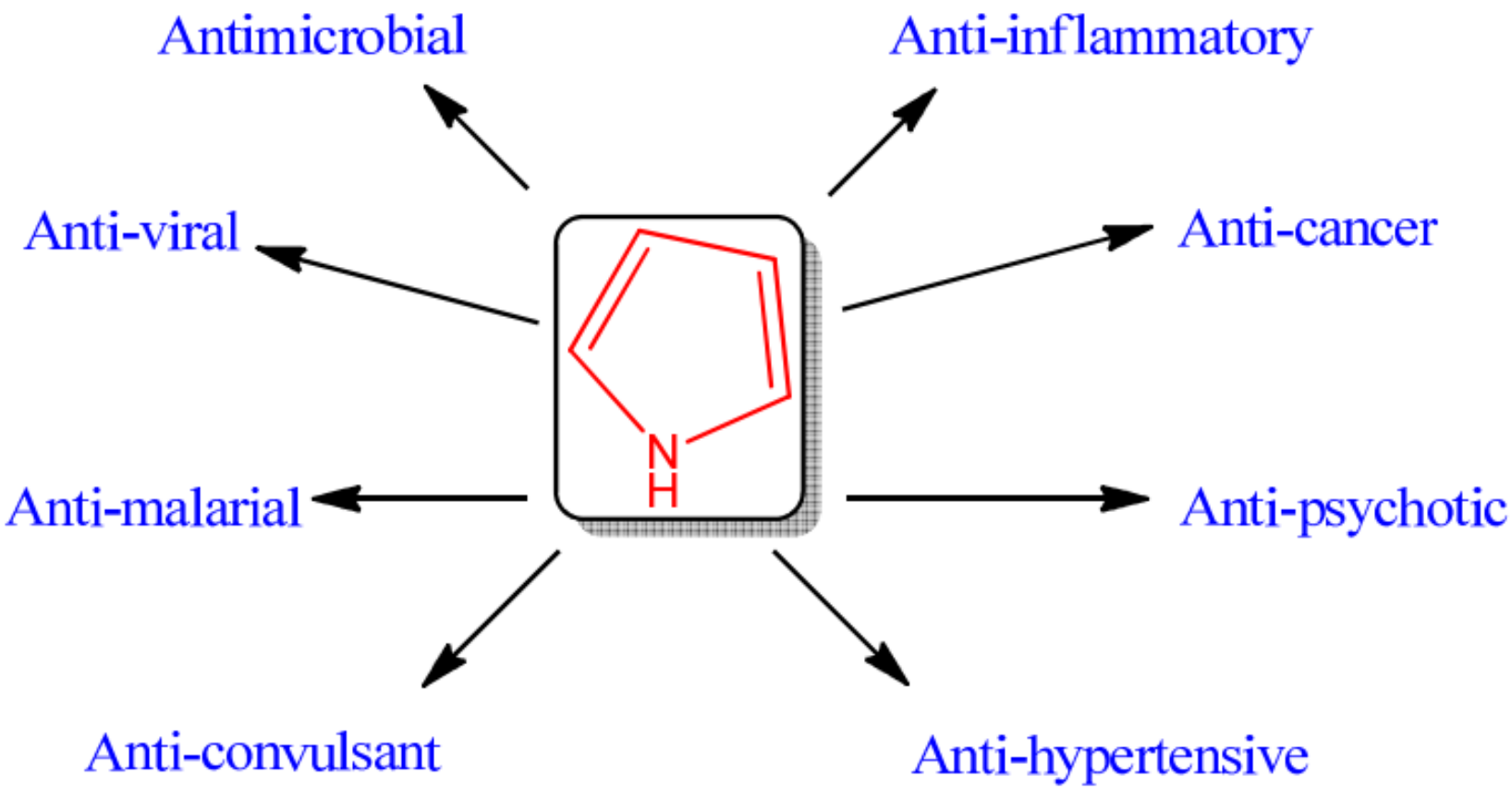


9. Diazo Coupling

Pyrrole couples with benzenediazonium chloride in a weakly acidic solution to give 2-phenylazopyrrole.



Medicinal Importance

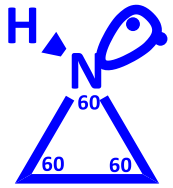


SYNTHESIS OF THREE MEMBERED HETEROCYCLES

Three-Membered Heterocycles

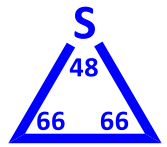
Structure

- The bond angles in all these systems fall far below the ideal 109.5° tetrahedral bond angle and therefore highly strained.



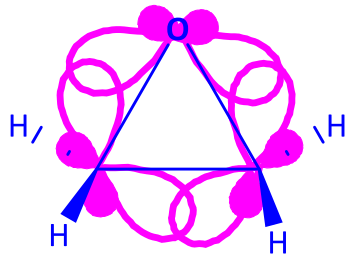
Aziridine

Oxirane



Thiirane

- Due to the strained bond angle, these three-membered heterocycles have bent bonds (banana bonds).

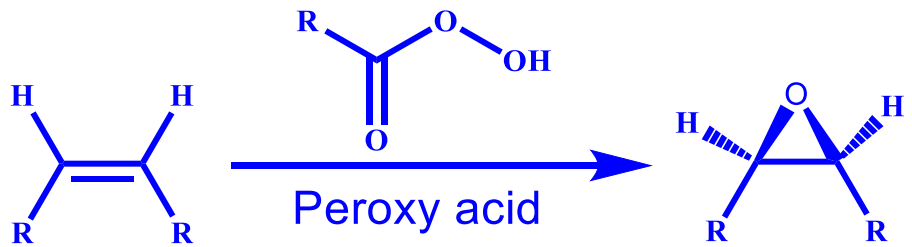


- Among these three-membered heterocycles, the oxiranes are the most common and easier to synthesize.

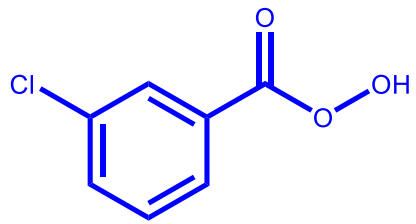
Synthesis of Oxiranes

Epoxidation of Alkenes to Oxiranes

- Oxiranes (epoxides), three-membered ring cyclic ethers, are commonly formed by epoxidation of alkenes.
- The most common epoxidation involves the reaction of alkenes with peroxy acids.



- The most commonly used peroxy acid is *m*-chloroperoxybenzoic acid (MCPBA).

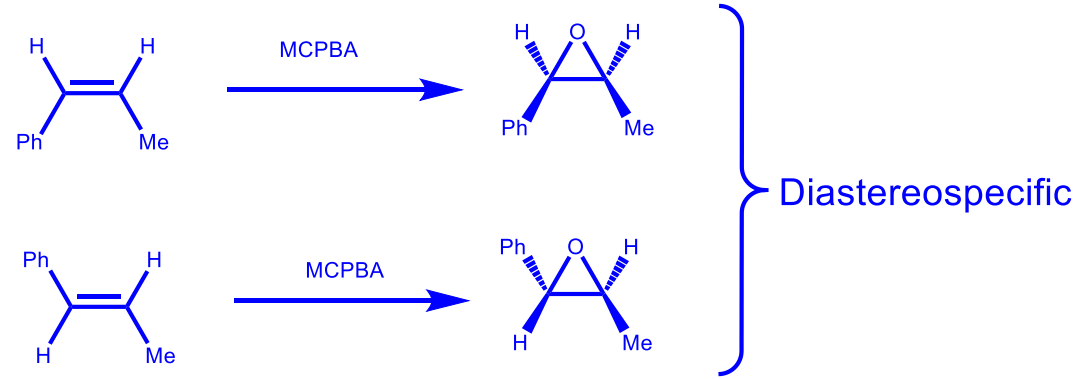


m-Chloroperoxybenzoic acid (MCPBA)

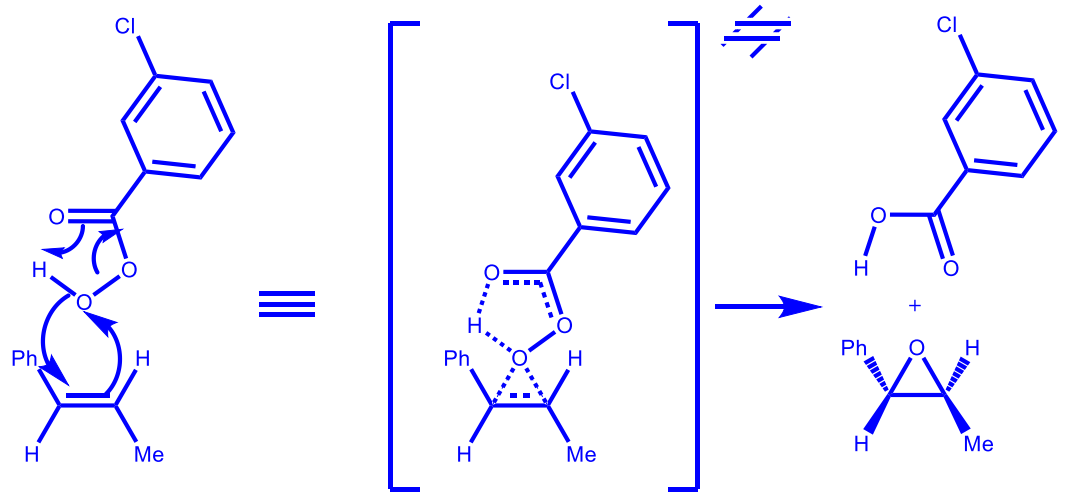
Synthesis of Oxiranes

Reaction of Alkenes with MCPBA to Oxiranes

- The epoxidation with MCPBA involves a concerted reaction that is stereospecific.



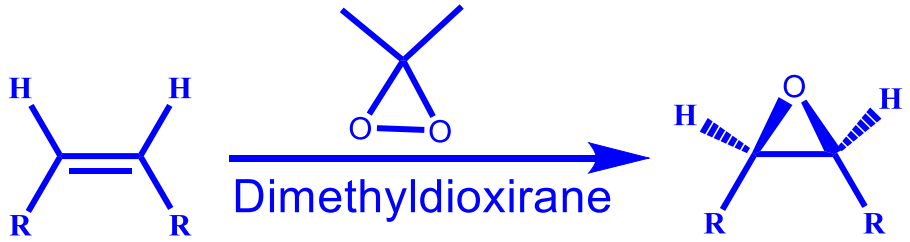
Mechanism



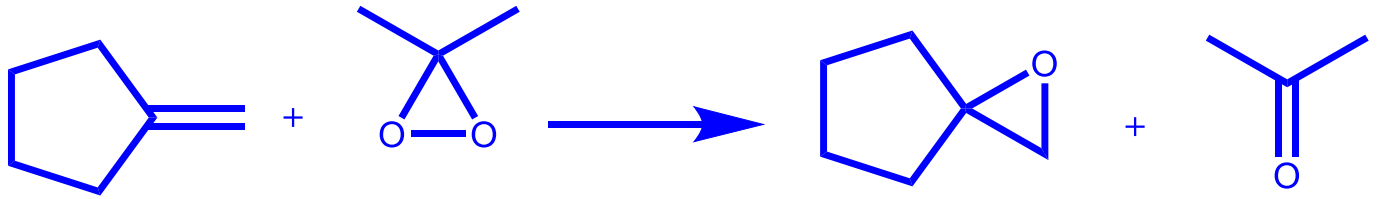
Synthesis of Oxiranes

Epoxidation of Alkenes to Oxiranes

- One of the mildest epoxidizing agent in current use is dimethyldioxirane (DMDO).



- The epoxidation with DMDO is a concerted reaction and DMDO behaves like an electrophilic reagent.
- The epoxidations with dimethyldioxirane can lend access to strained spiroheterocycles as illustrated below:

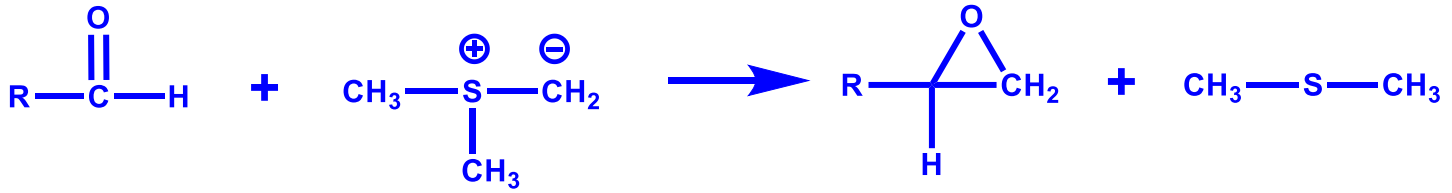


1-Oxaspiro[2.4]heptane

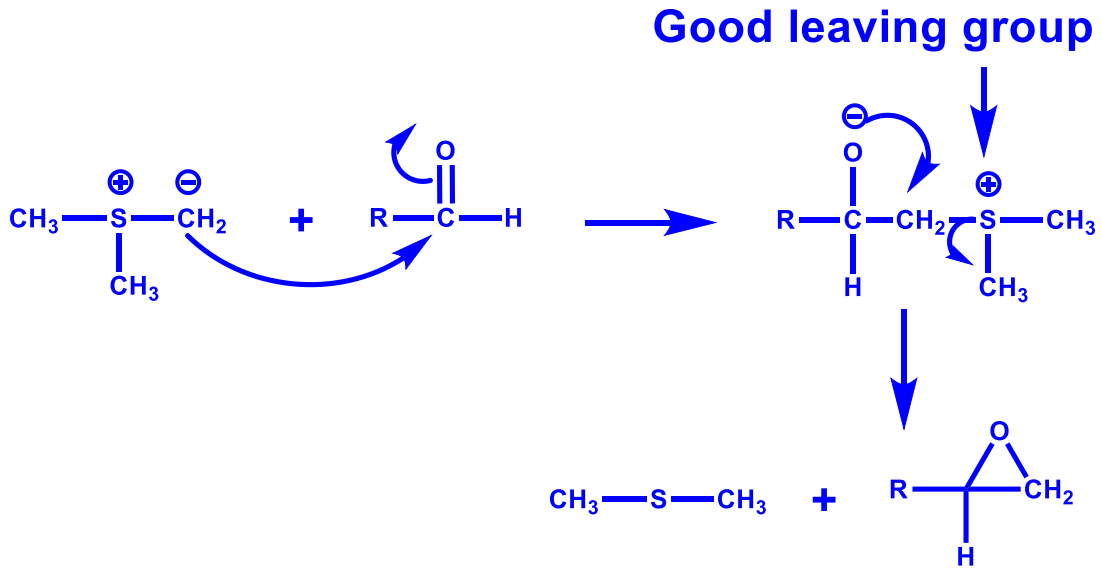
Synthesis of Oxiranes

Reaction of Sulphur Ylides with Aldehydes and Ketones to Oxiranes

- Sulphur ylides (e.g. dimethylsulfonium methylide) react with aldehydes and ketones to provide oxiranes.



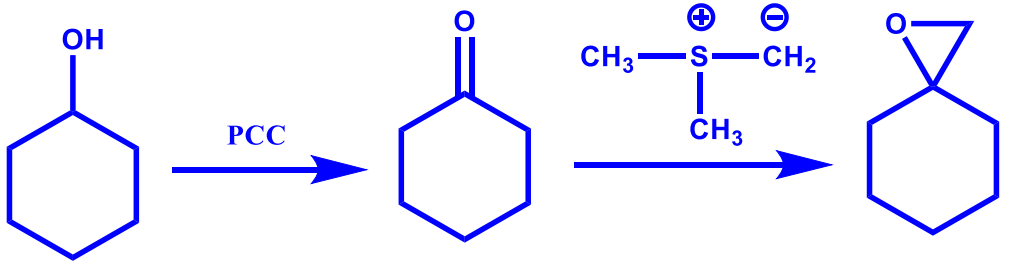
- The reaction is presumed to occur as illustrated below:



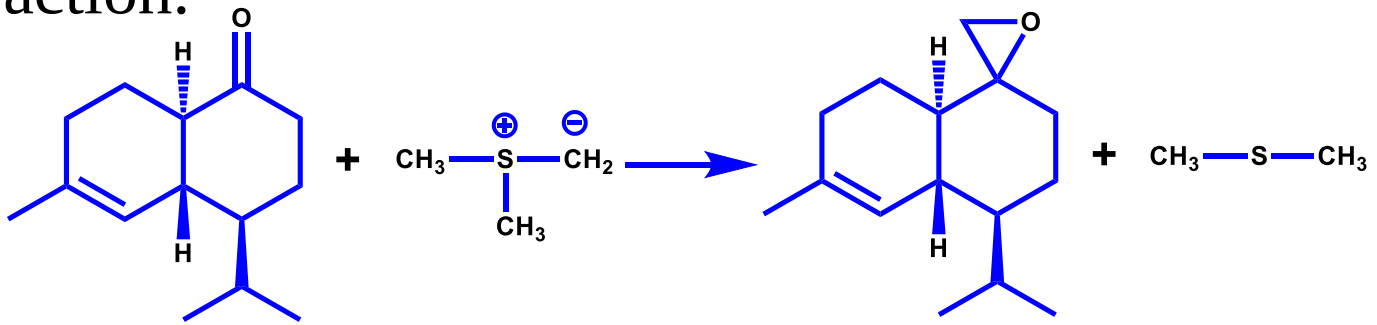
Synthesis of Oxiranes

Reaction of Sulphur Ylides with Ketones to Oxiranes

- The use of sulphur ylides is convenient since aldehydes and ketones can be readily obtained by oxidation of alcohols.



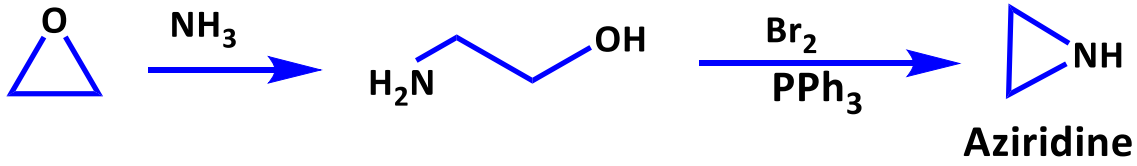
- The advantage of this strategy is that other functional groups (e.g. alkenes) can be readily tolerated during the reaction.



Synthesis of Aziridines

β-Aminoalcohols to Aziridines

- β-Amino alcohols, conveniently made from the reaction of oxiranes with ammonia or amines, react with bromine in the presence of triphenylphosphine to provide aziridines.

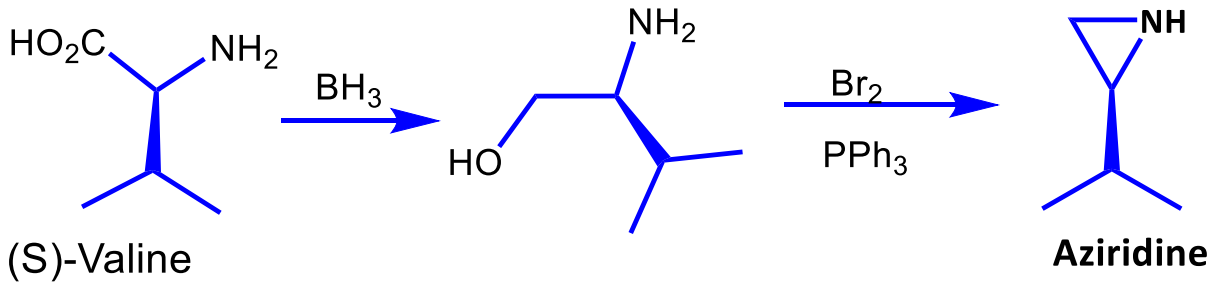


- To aid the formation of a strong P-O bond, the triphenylphosphine serves to convert the OH group into a good leaving group that is displaced intramolecularly by the amino group.
- Reduction of α-amino acids also provides β-amino alcohols and therefore could lends access to aziridines.

Synthesis of Aziridines

β-Aminoalcohols to Aziridines

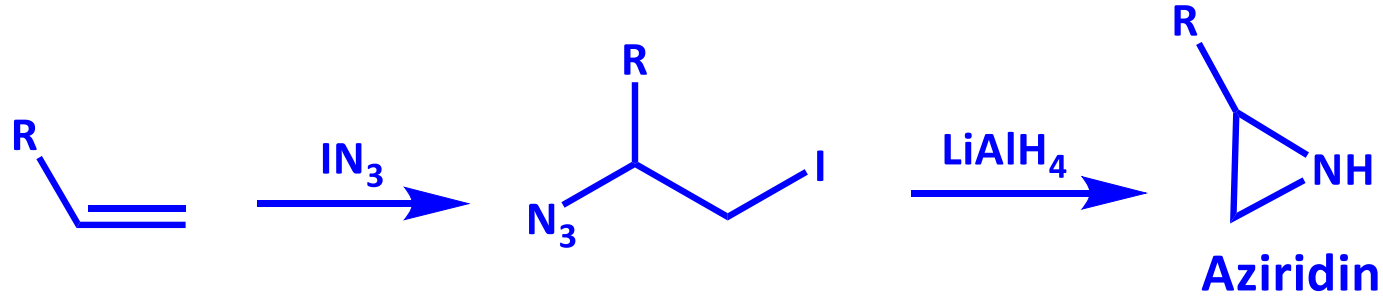
- α-Amino acids are prevalent in natural proteins. Hydrolysis of the peptide bonds of these natural proteins followed by separation using electrophoresis provides amino acids.



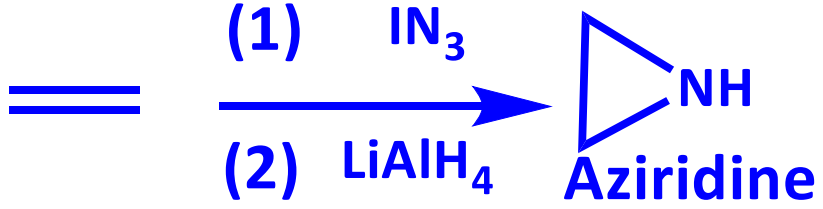
- With the diversity of α-amino acids available in nature, diverse aziridines can be accessed.

Synthesis of Aziridines

Alkenes to Aziridines



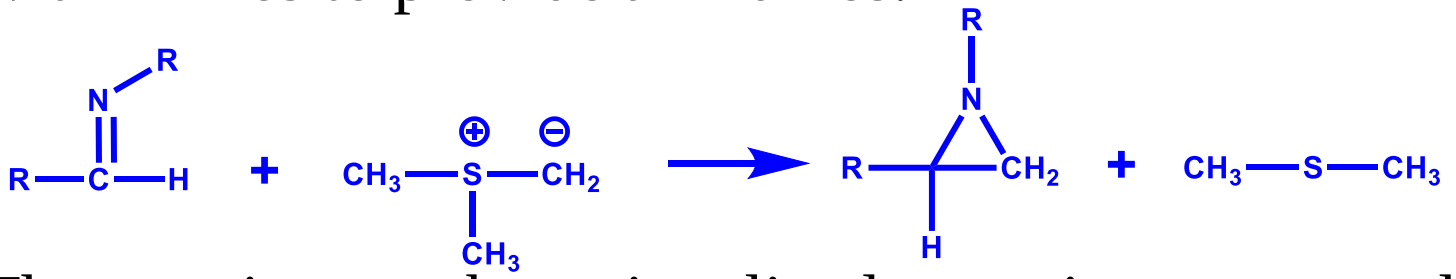
- Alkenes react with iodonium azide with the addition of IN_3 proceeding via a three-membered ring iodonium species, resulting from attack of I^+ on the double bond.
- The amino group resulting from reduction of the azide is sufficiently nucleophilic to displace the halide.
- Thus, airidine can be prepared as illustrated below:



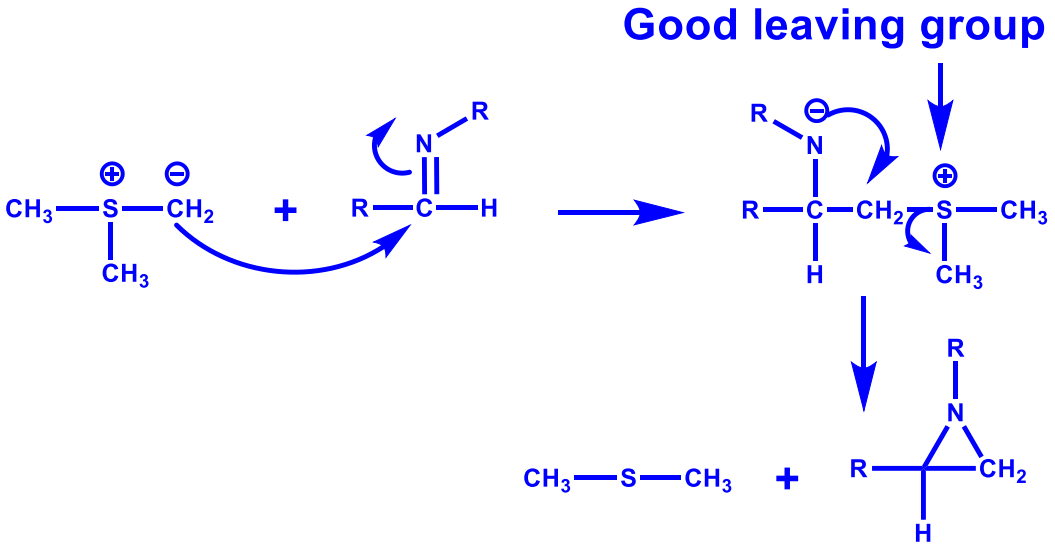
Synthesis of Aziridines

Reaction of Sulphur Ylides with Imines to Aziridines

- Sulphur ylides (e.g. dimethylsulfonium methylide) react with imines to provide aziridines.



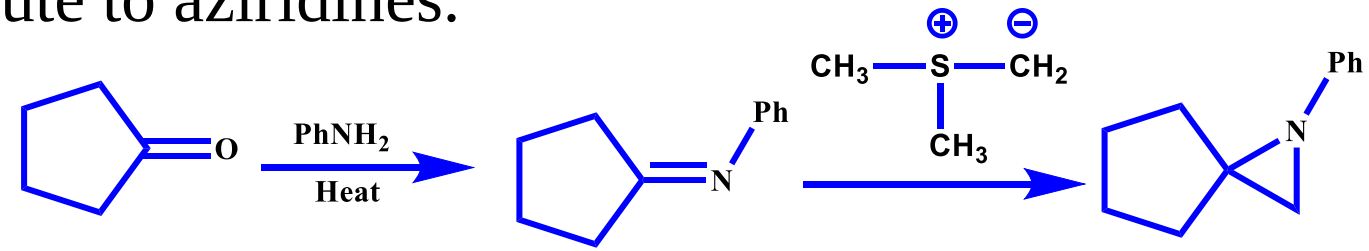
- The reaction can be rationalized stepwise as proceeding as illustrated below:



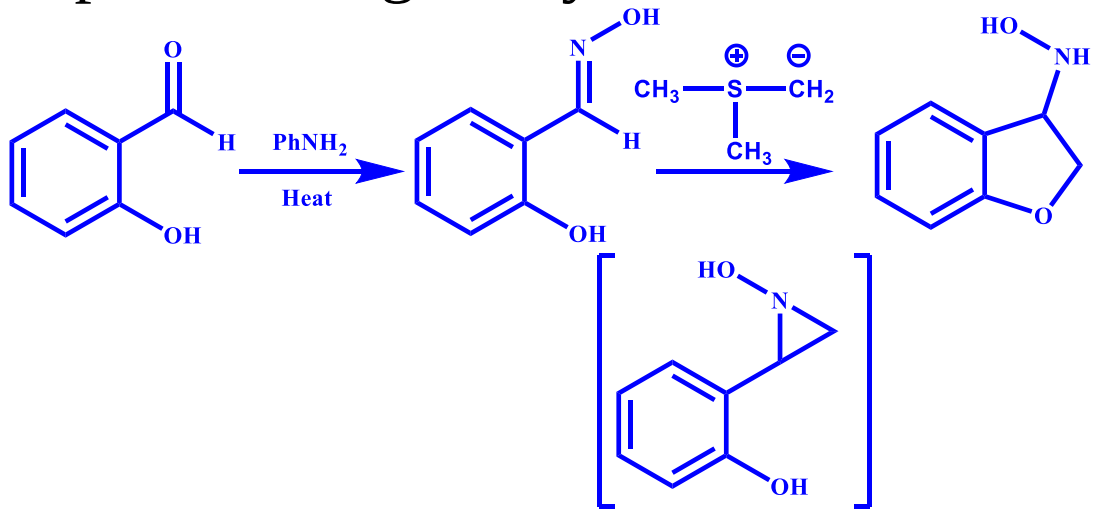
Synthesis of Aziridines

Reaction of Sulphur Ylides with Imines

- The use of sulphur ylides with imines is convenient route to aziridines.



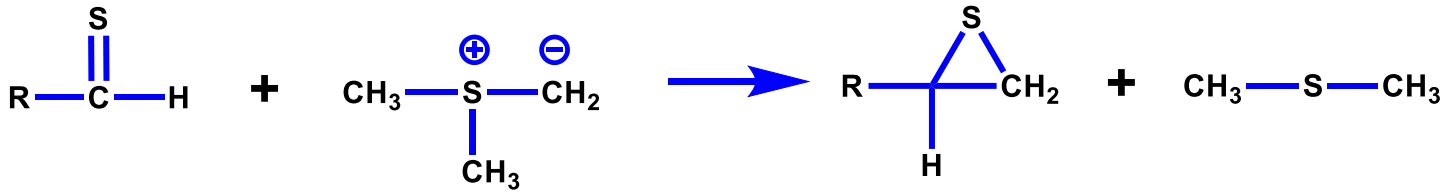
- Due to the strain and reactivity associated with these aziridines intramolecular ring opening reactions of these systems provide rings of synthetic interest.



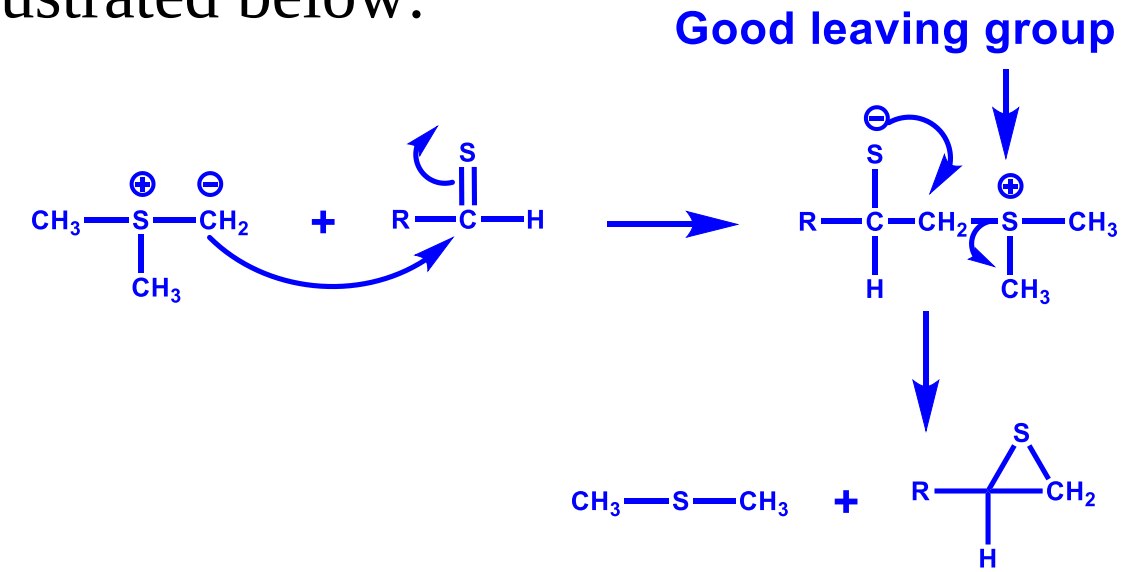
Synthesis of Thiiranes

Reaction of Sulphur Ylides with Thiocarbonyls to Thiiranes

- Sulphur ylides (e.g. dimethylsulfonium methylide) react with thiocarbonyl compounds to provide thiiranes.



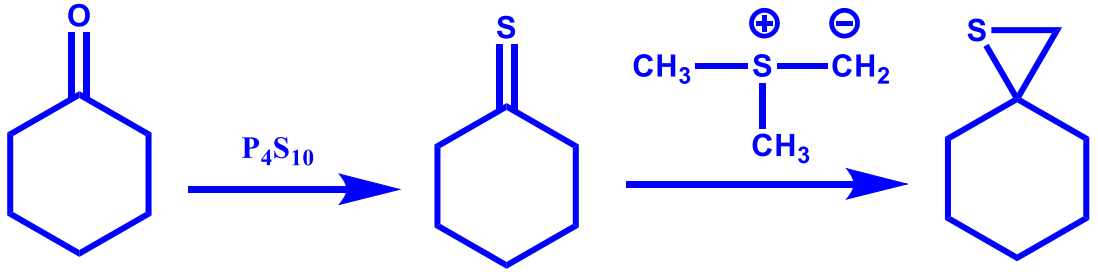
- The reaction can be rationalized stepwise as proceeding as illustrated below:



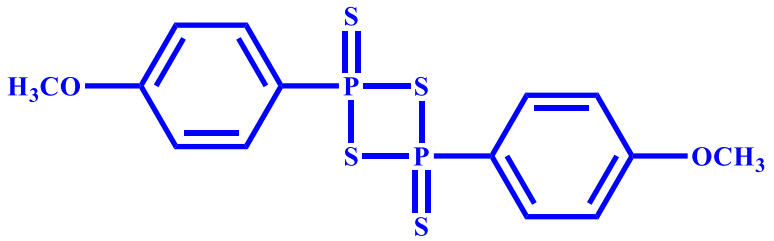
Synthesis of Thiiranes

Reaction of Sulphur Ylides Providing Thiiranes

- The use of sulphur ylides is convenient in converting thiocarbonyl compounds, prepared by thionation of ketones and aldehydes with phosphorus pentasulphide, to thiiranes.



- The Lawessons reagent is also commonly used in the thionation of carbonyl compounds.

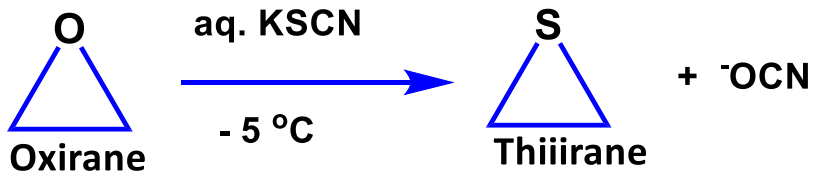


Lawessons Reagent

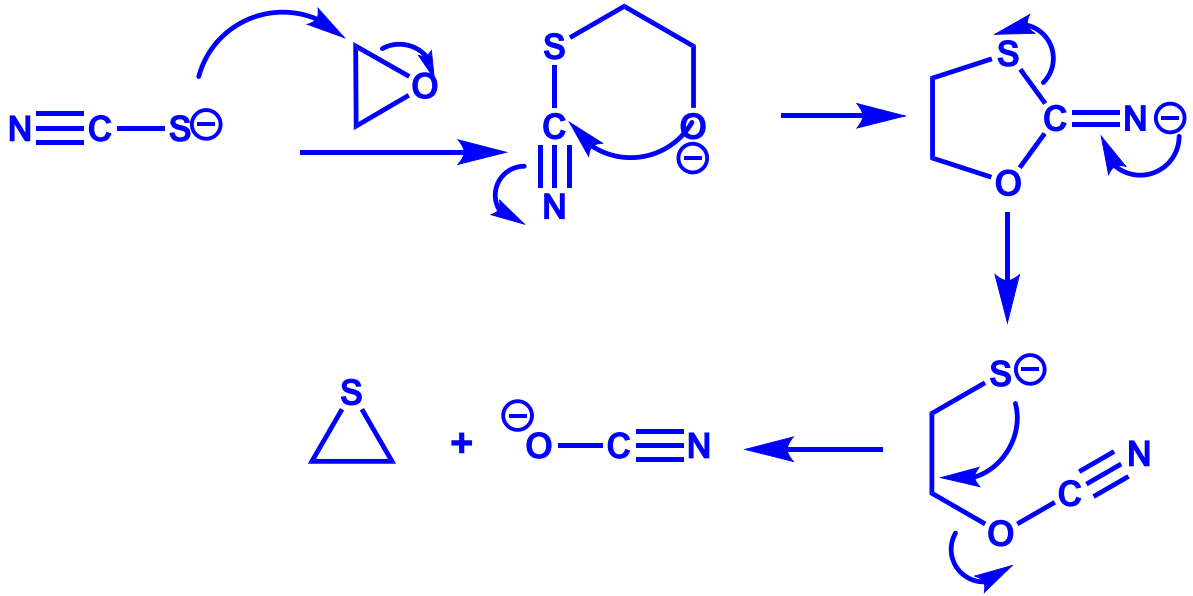
Synthesis of Thiiranes

Oxiranes to Thiiranes

- Oxiranes can be converted directly to thiiranes using aqueous potassium thiocyanate.



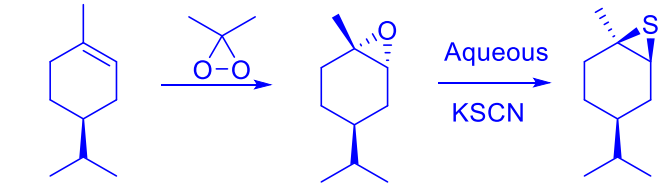
- This transformation occurs as rationalized below:



Synthesis of Thiiranes

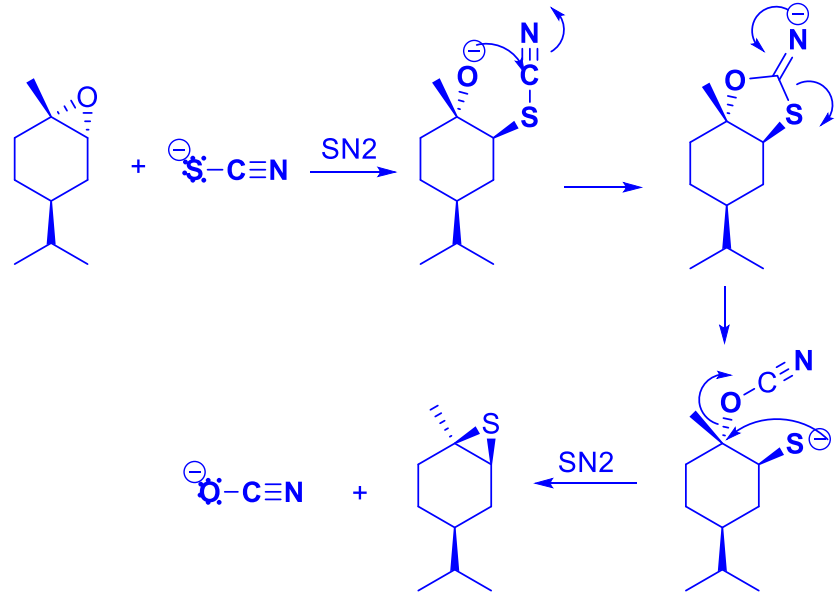
Oxiranes to Thiiranes

- The conversion of oxiranes to thiiranes is stereospecific.



(R)-Dihyrolimonene

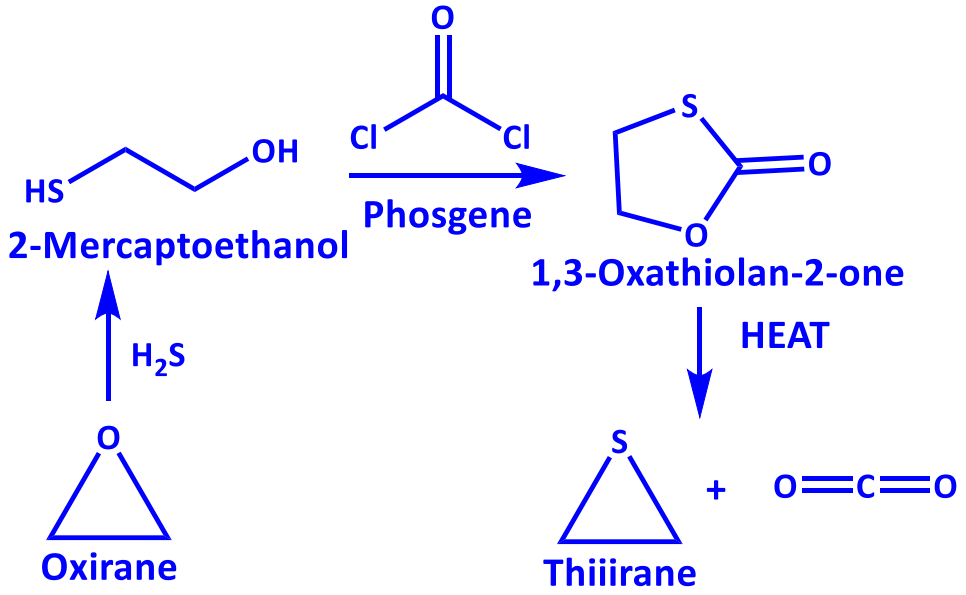
- The stereospecificity of the transformation is rationalized based on S_N2 steps below:



Synthesis of Thiiranes

β-Mercaptoalcohols to Thiiranes

- Reacting β-thioalcohols, obtained from ring opening of oxiranes, with phosgene and subsequent heating also generates thiiranes.

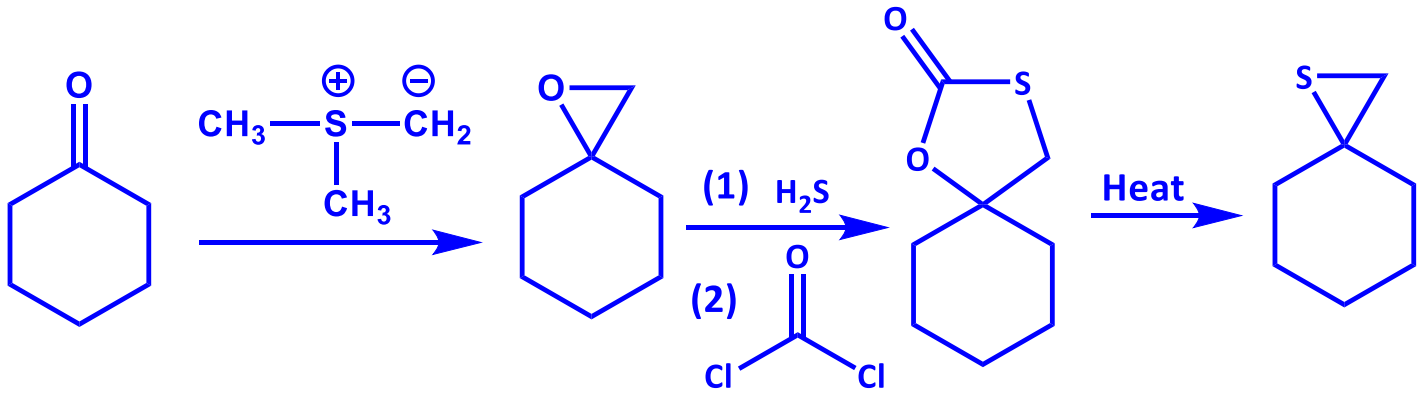


- Different oxiranes can therefore provide access to diverse thiiranes.

Synthesis of Thiiranes

β-Mercaptoalcohols to Thiiranes

- For instance, cyclohexanone can be converted to 1-thiaspiro[2,5]octane based on the sequence below.

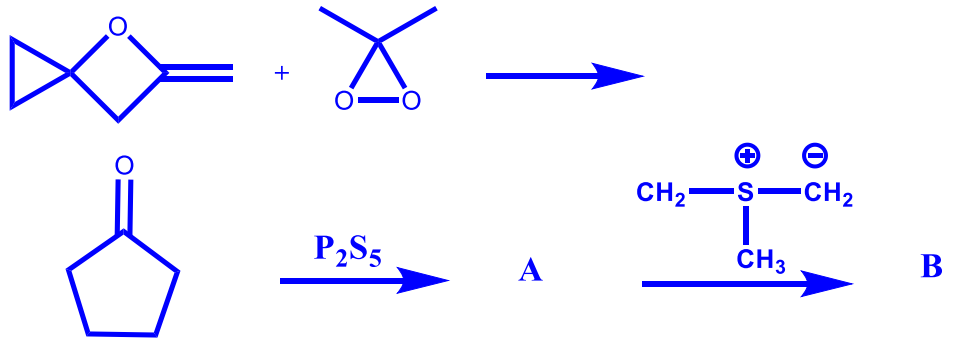


- The reactions of these strained three-membered heterocycles have a potential of lending access to diverse structures.

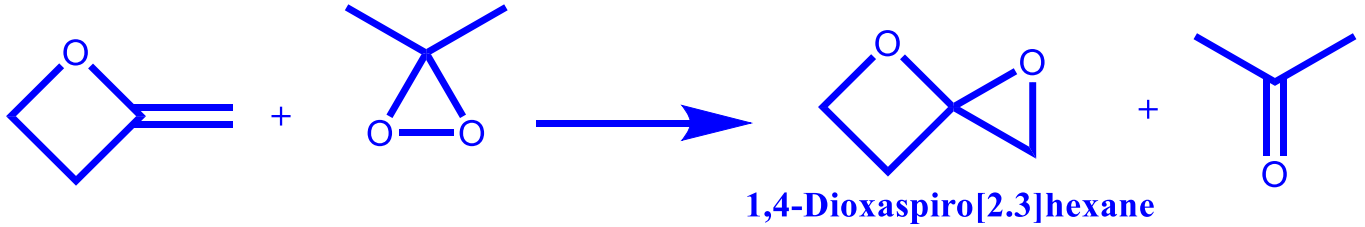
Practice Questions

Synthesis of Three Membered Heterocycles

Complete the following reactions by giving the principal organic product.



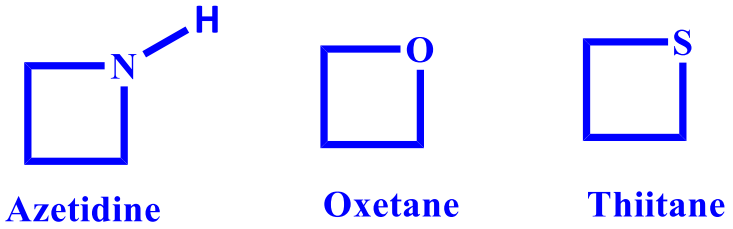
Propose a reasonable and stepwise reaction mechanism for the transformation below:



SYNTHESIS OF FOUR MEMBERED HETEROCYCLES

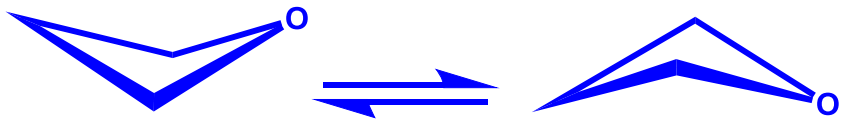
Four-Membered Heterocycles

Structure



Azetidine Oxetane Thiitane

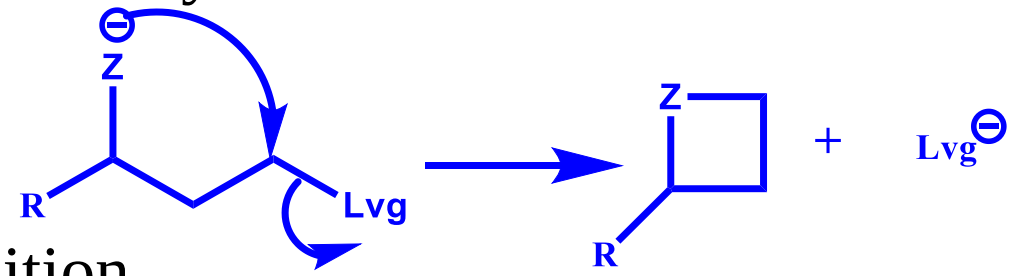
- In four-membered heterocycles, the ring strain is less than in the corresponding three-membered compounds.
- For example, the oxetane ring represents a slightly distorted square approximately equal to that of cyclobutane with a bond angle at the O-atom of 92°.



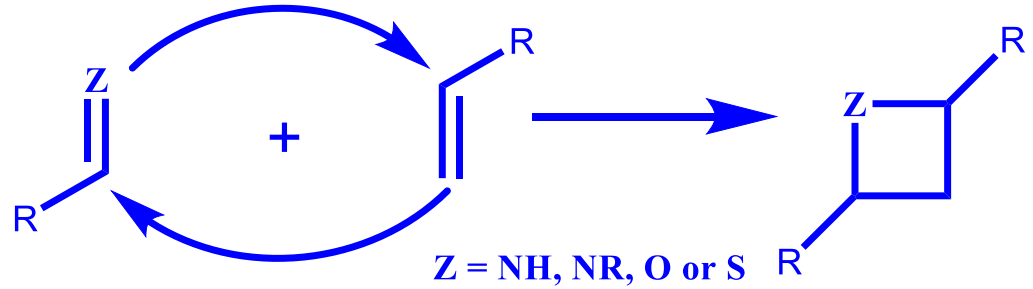
- The strain in oxetanes is reduced by ring-puckering between two nonplanar structures, which simultaneously leads to a reduction in the bond angles.

Strategies for Synthesis of Four-Membered Heterocycles

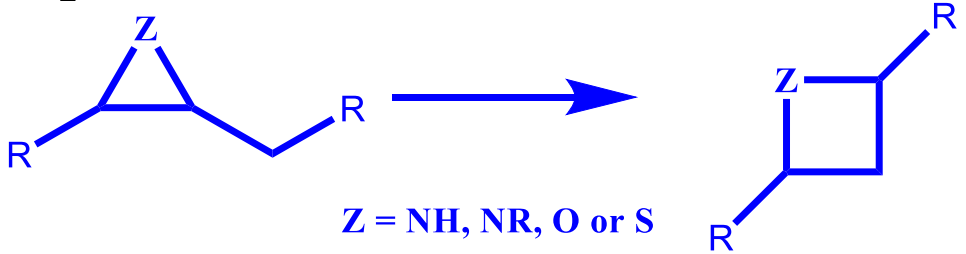
- The three common strategies for accessing four membered heterocycles are:
- Intramolecular cyclization



- Cycloaddition



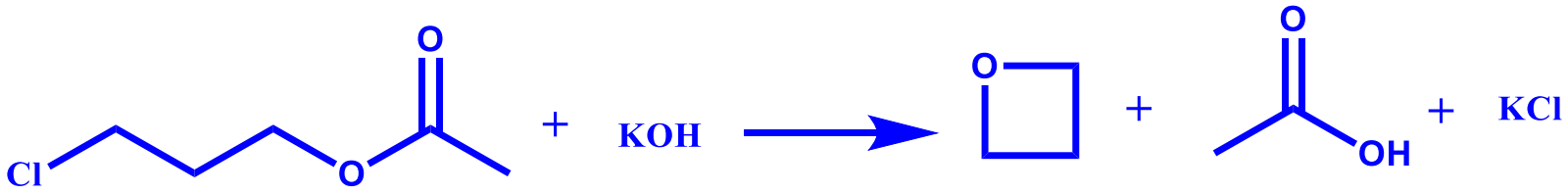
- Ring expansion



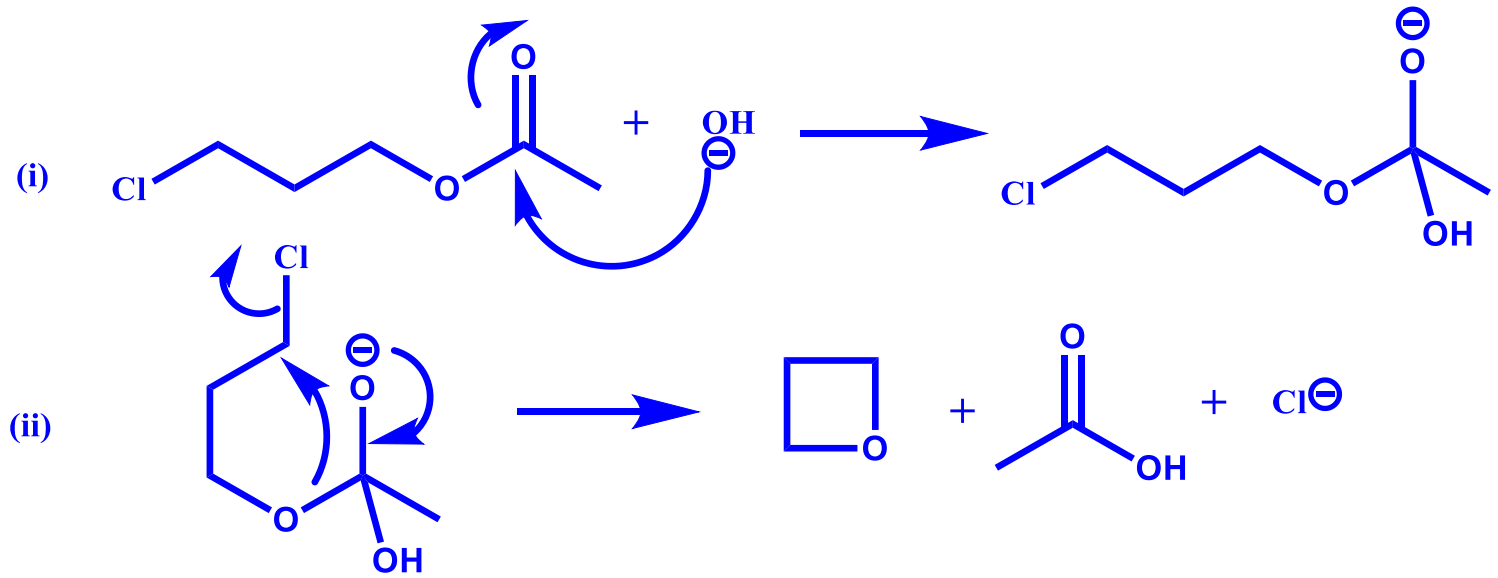
Synthesis of Oxetanes

Intramolecular SN_2 Cyclization

- Although the intramolecular Williamson ether synthesis is a common approach to oxetanes, the esterification of 1,3-halohydrins enhances the efficiency.



- The reaction mechanism is illustrated below:

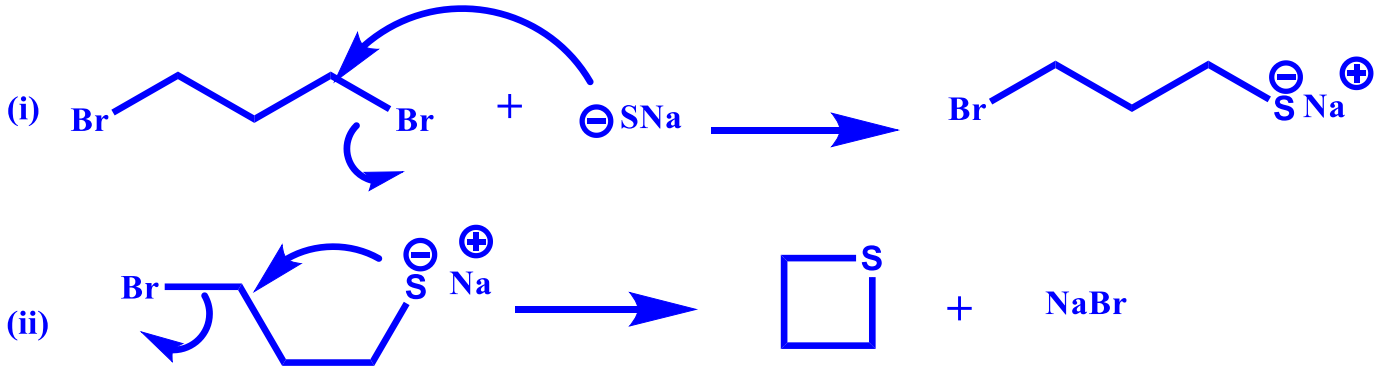


Synthesis of Thietanes

Intramolecular Cyclization with Sodium or Potassium sulflde

- Intramolecular cyclization of 1,3-dihaloalkanes using sodium or potassium sulphide provides thietanes.

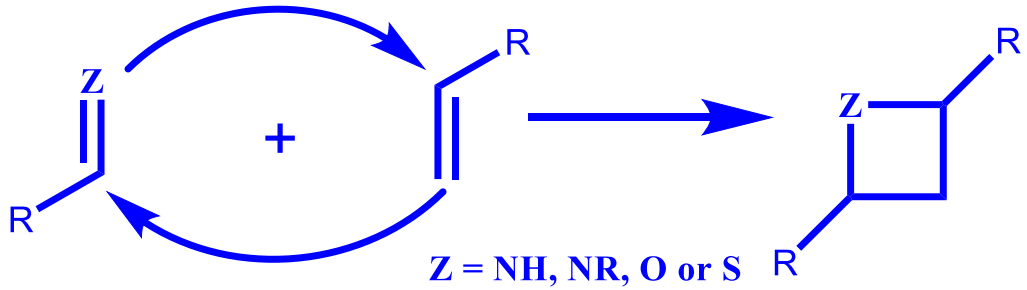
- The reaction mechanism is illustrated below:
- The reaction proceeds through two sequential nucleophilic substitutions.



Synthesis of Four-Membered Heterocycles

Cycloaddition

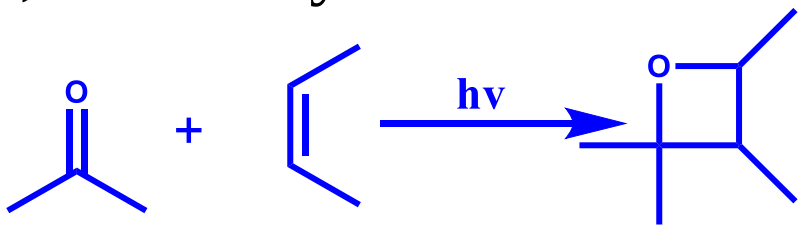
- Cycloaddition is the union of two π-systems to form a ring through a cyclic movement of electrons.
- A cycloaddition reaction is categorized as a [m + n]-cycloaddition when a system of m conjugated atoms combines with another system of n conjugated atoms.
- Photochemical [2+2] cycloaddition of carbonyls, imines and thiocarbonyls with alkenes lends access to four-membered heterocycles.



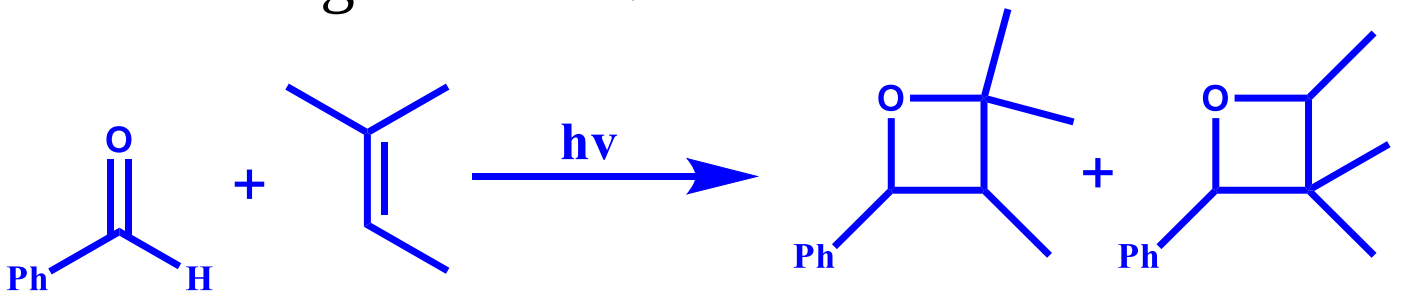
Synthesis of Oxetanes

Photochemical [2+2] Cycloaddition

- Photochemical [2+2] cycloaddition of aldehydes or ketones with alkenes provides oxetanes. Through this approach, a diversity of oxetanes can be accessed.



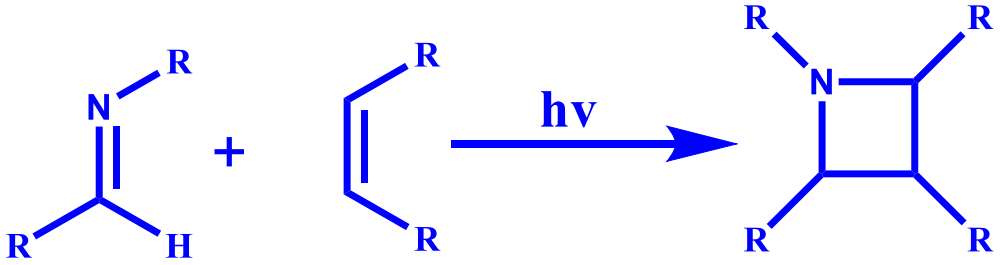
- The carbonyl is usually the light absorbing species.
- One of the challenges of this approach for unsymmetrical alkenes is the potential to produce a mixture of regioisomers.



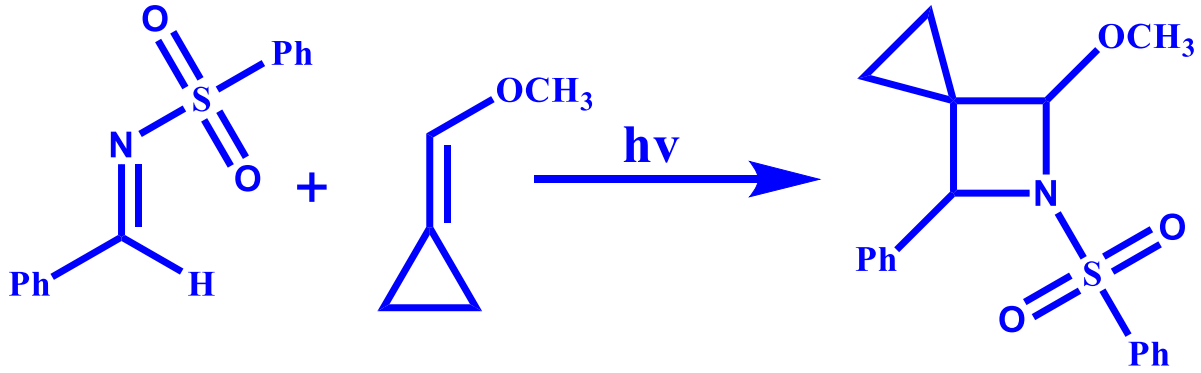
Synthesis of Azetidines

Photochemical [2+2] Cycloaddition

- Photochemical [2+2] cycloaddition of imines with alkenes lends access to azetidines.



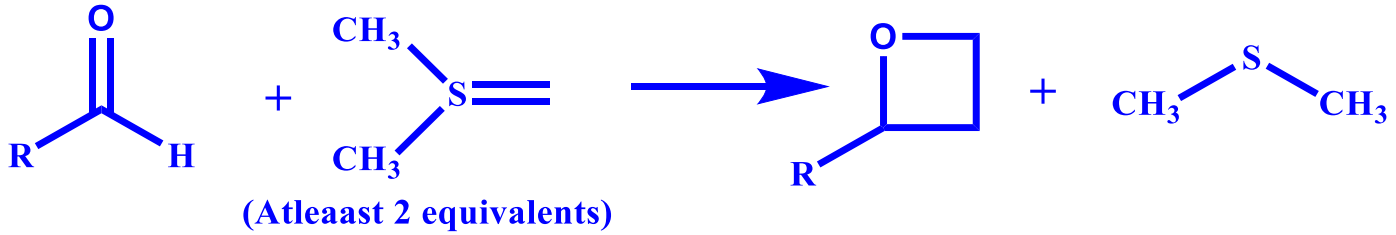
- Through this approach, a diversity of azetidines can be accessed.



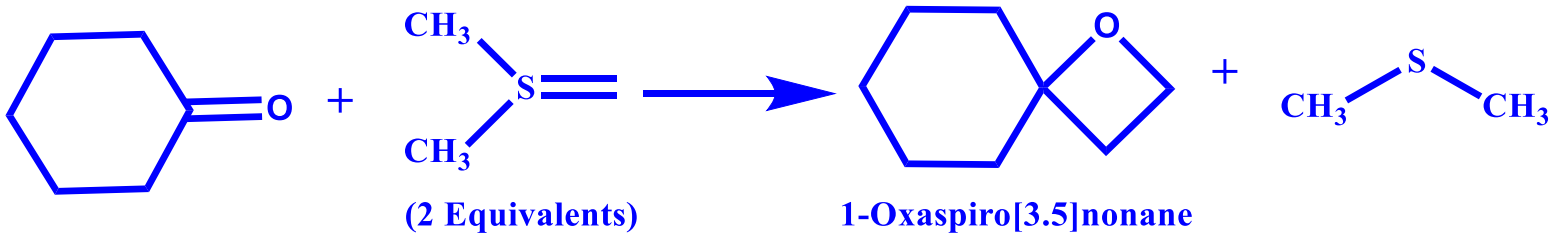
Synthesis of Oxetanes

Reaction of Ketones with Sulphur Ylides

- Although the more common reaction of sulfonium ylides with aldehydes and ketones provides oxiranes, the use of excess sulfonium ylide leads to the ring expansion of epoxides to oxetanes.
- This allows for a one-pot conversion of aldehydes/ketones to 2-substituted oxetanes.



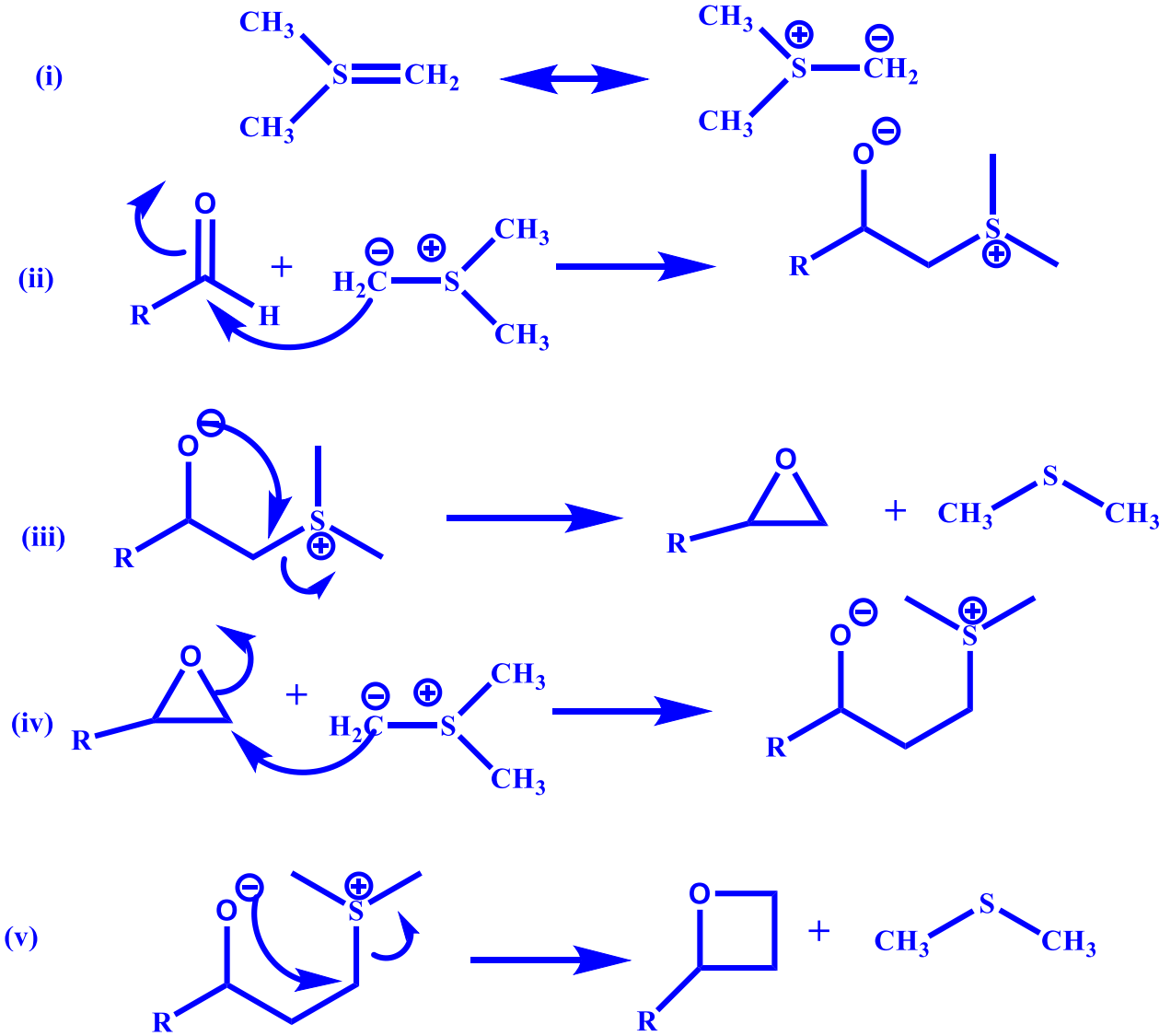
- 1-Oxaspiro[3.5]nonane can be obtained based on the reaction shown below:



Synthesis of Oxetanes

Reaction of Ketones with Sulphur Ylides

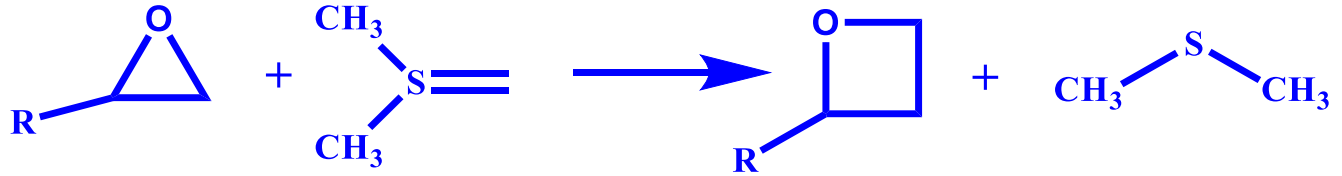
- The mechanism of the reaction is illustrated below:



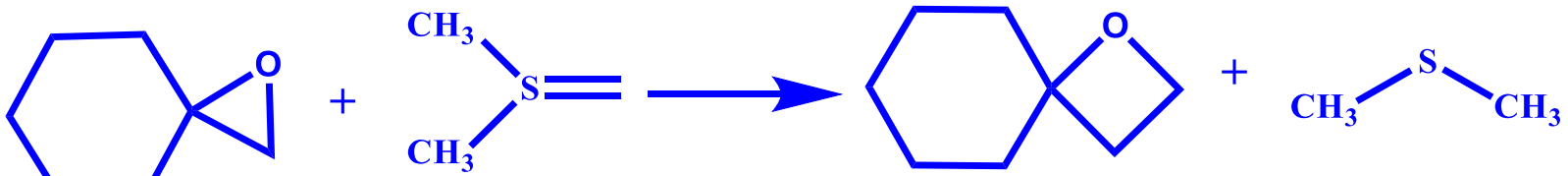
Synthesis of Oxetanes

Ring Expansion of Oxiranes

- A more efficient approach to oxetanes based on sulfonium ylides is through the ring opening of oxiranes with dimethylsulfonium methylide.
- Subsequent cyclization in the same step with release of dimethyl sulfide affords 2-substituted oxetanes.



- 1-Oxaspiro[3.5]nonane can be obtained based on the reaction shown below:

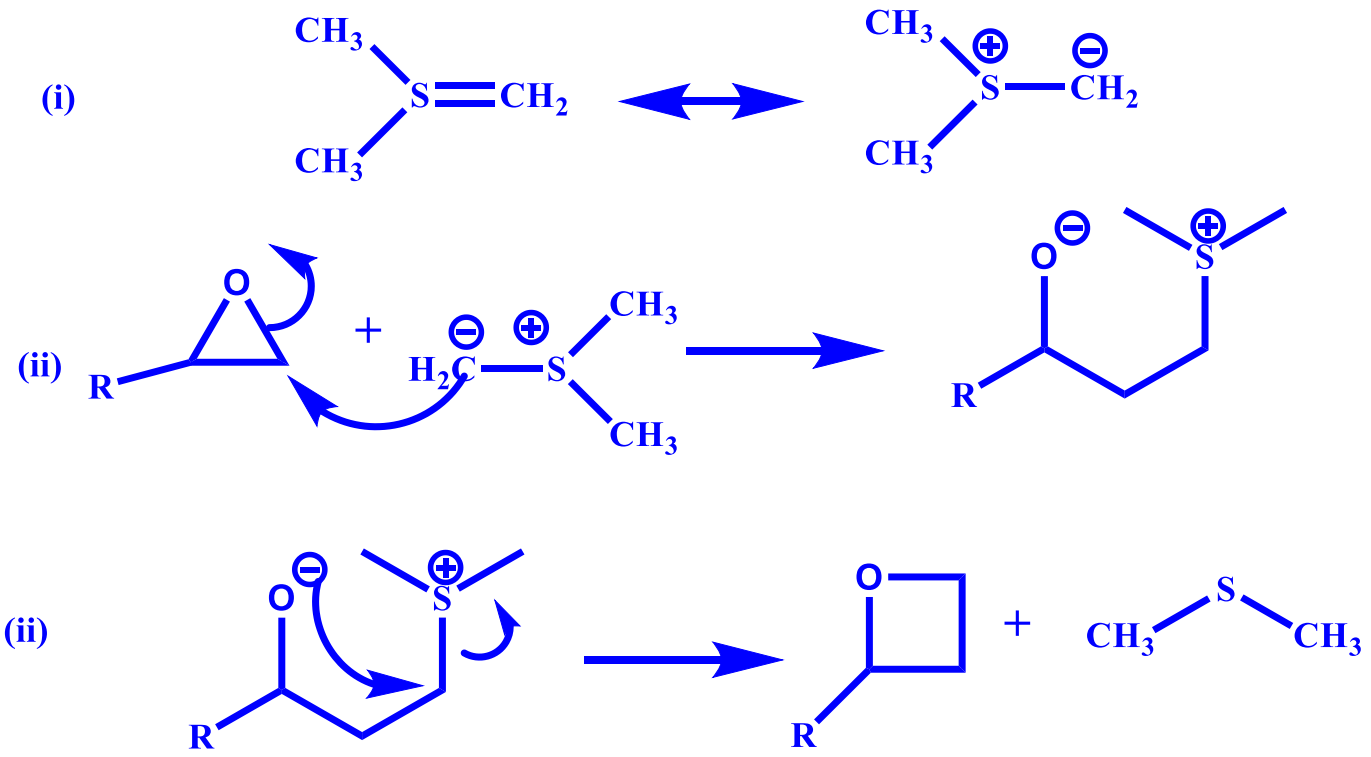


1-Oxaspiro[3.5]nonane

Synthesis of Oxetanes

Ring Expansion of Oxiranes

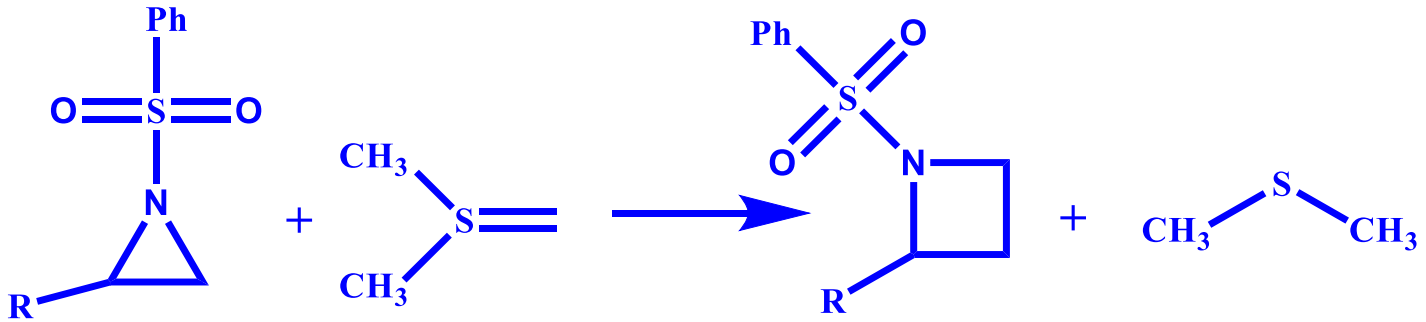
- The mechanism of the reaction is illustrated below:



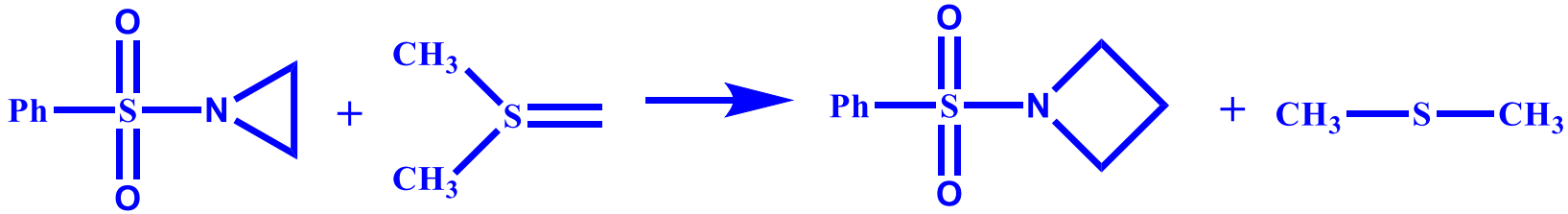
Synthesis of Azetidines

Ring Expansion of Aziridines

- Azetidines can be accessed through ring expansion of aziridines with dimethylsulfonium methylide.
- The reaction starts with ring opening of the aziridine. Subsequent cyclization affords 2-substituted azetidines.



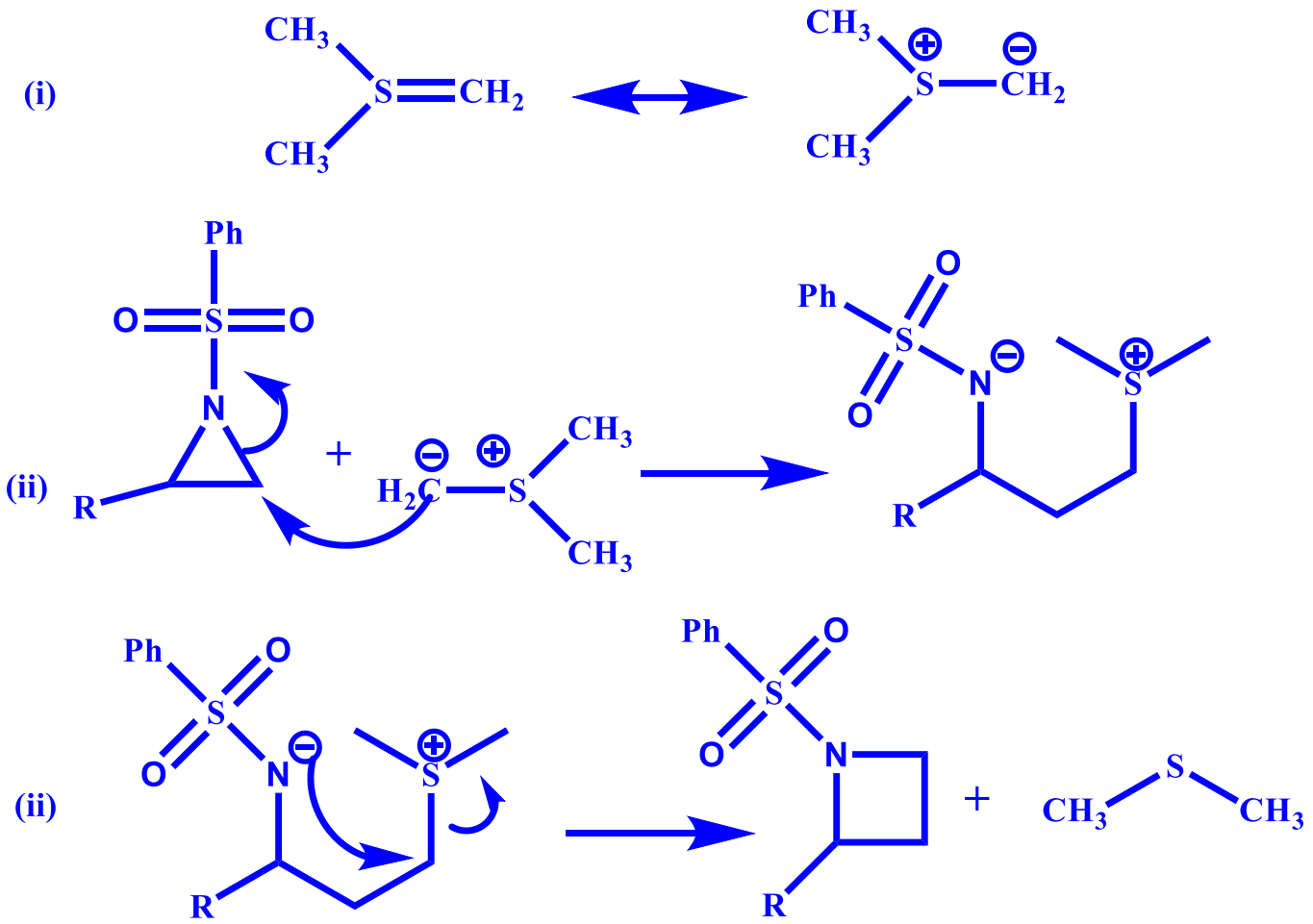
- 1-Benzenesulphonyl-azetidine can be obtained based on the reaction shown below:



Synthesis of Azetidines

Ring Expansion of Aziridines

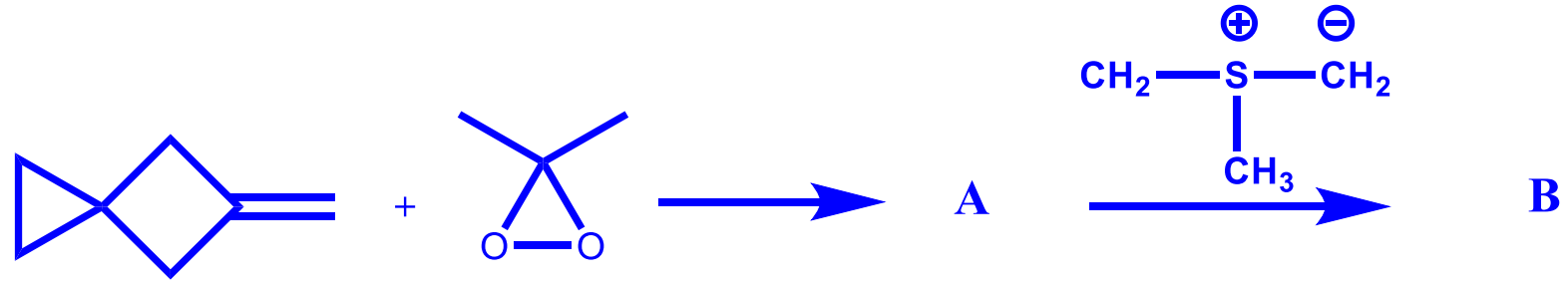
- The mechanism of the ring expansion is illustrated below:



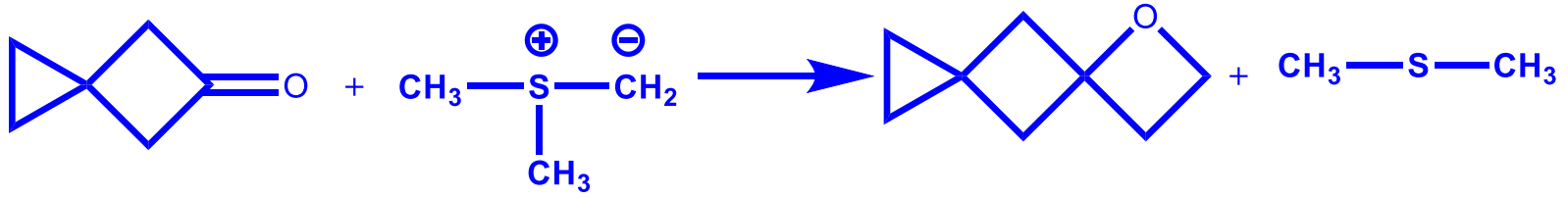
Practice Questions

Synthesis of Four Membered Heterocycles

Complete the following reactions by giving the principal organic product.



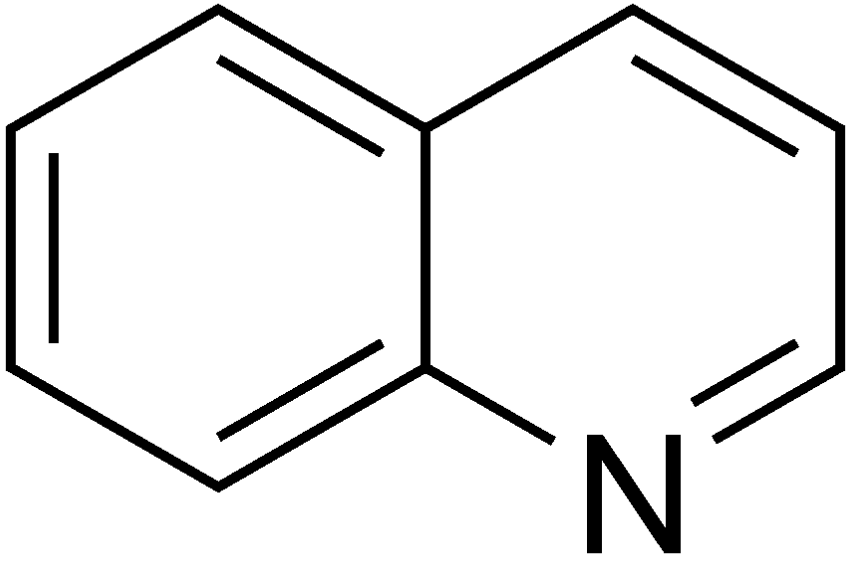
Propose a reasonable and stepwise reaction mechanism for the transformation below:



(Excess)

Preparation and Properties of Quinoline

Quinoline



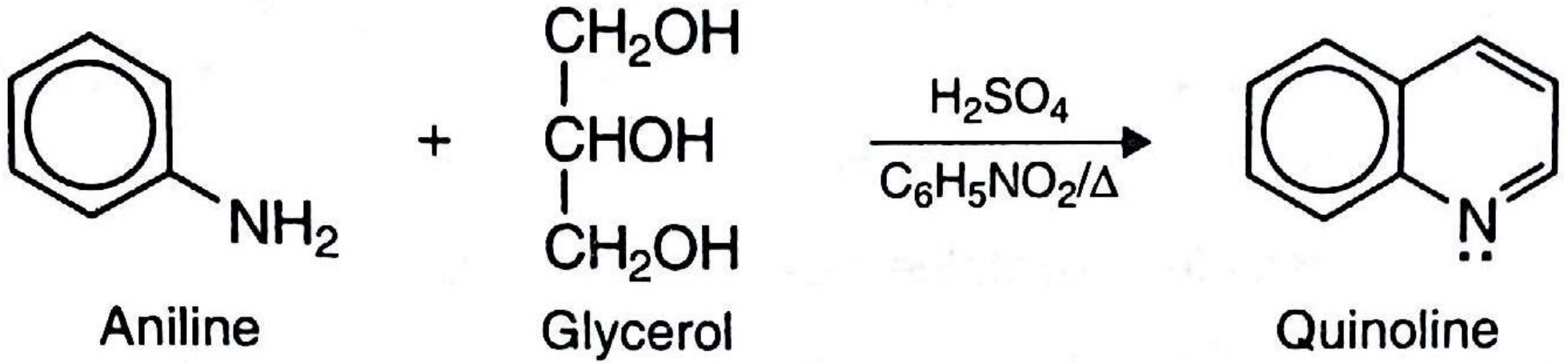
Quinoline consists of a benzene ring fused to the **Alpha and Beta** positions of a pyridine ring. It derives its name from the fact that it was first obtained by heating the famous **antimalarial alkaloid "*quinine*"**, with alkali.

Quinoline occurs in coal-tar, bone oil, and in *angostura* bark.

Preparation Methods

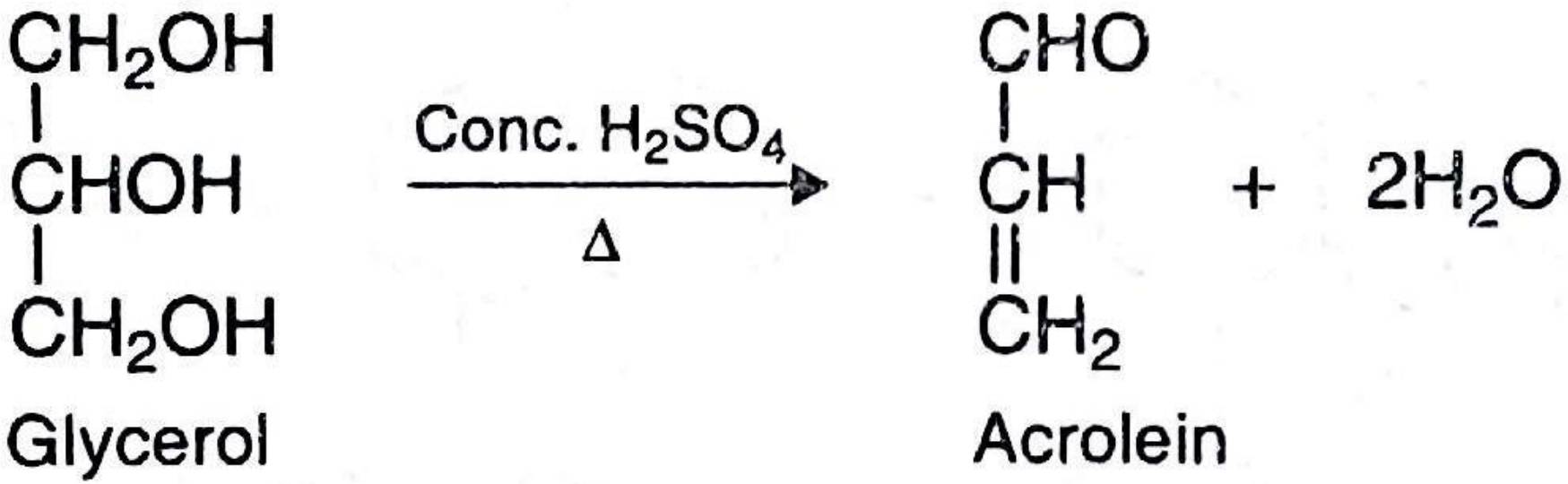
(1) By Skraup Synthesis: (Commercial method)

In this reaction, a mixture of aniline and glycerol is heated in the presence of sulphuric acid and a mild oxidizing agent, usually nitrobenzene or arsenic pentoxide. The reaction is exothermic and tends to become very violent. Ferrous sulphate or boric acid is generally added to make the reaction less violent.

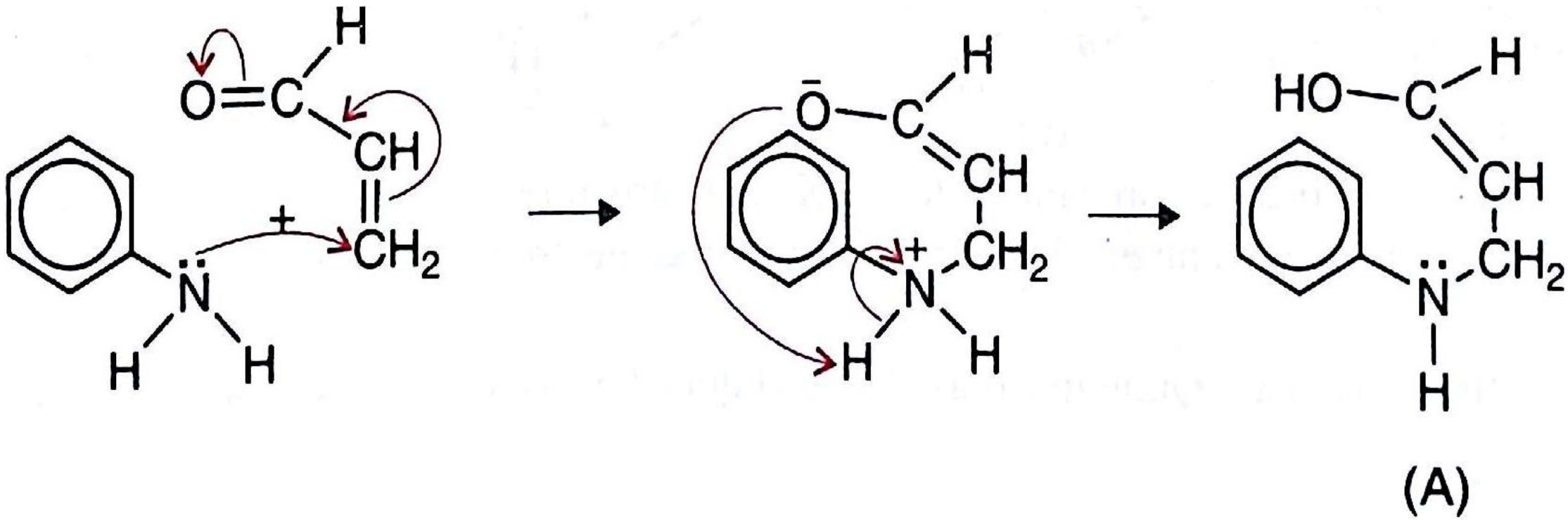


Mechanism

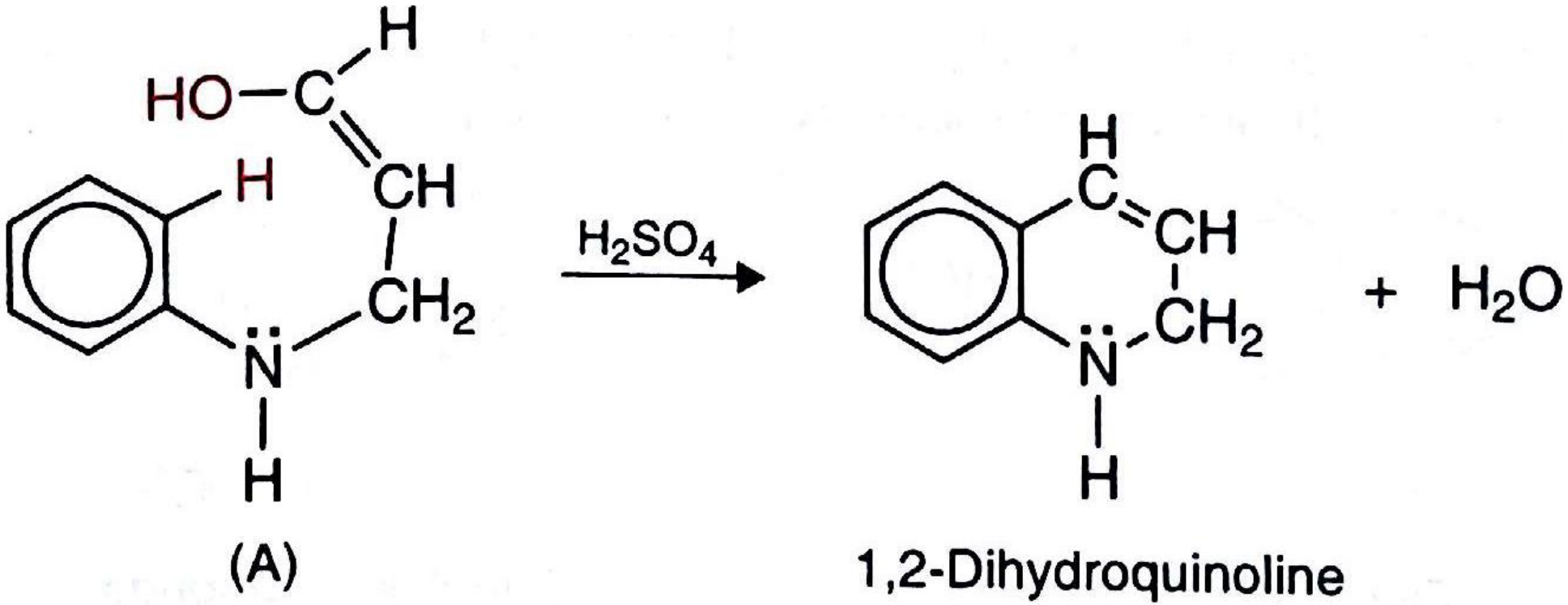
Step 1: Glycerol undergoes dehydration with sulphuric acid to give acrolein.



Step 2: Aniline adds to acrolein (1,4-addition) to give (A).



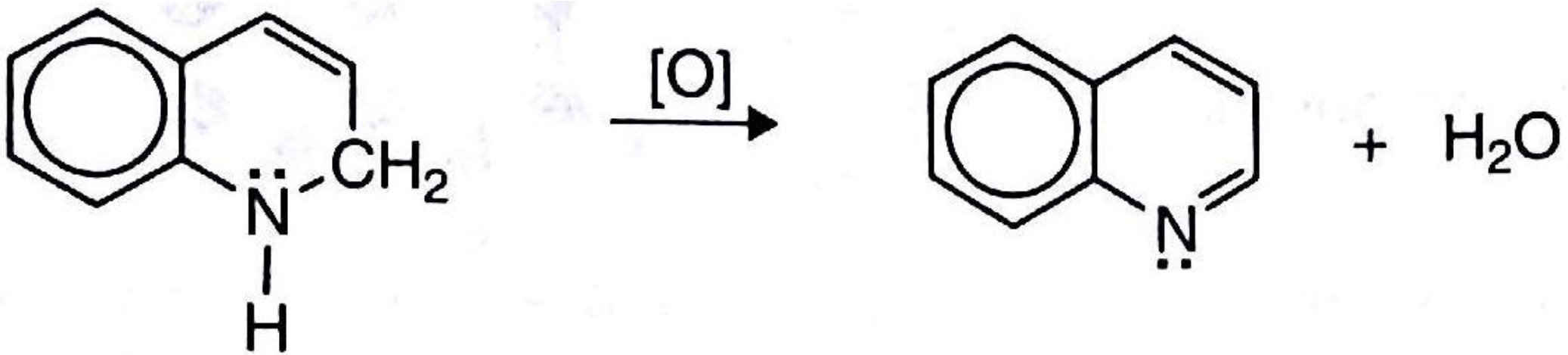
Step 3: Compound (A) Undergoes ring closure in the presence of sulphuric acid to form 1,2- dihydroquinoline.



(A)

1,2-Dihydroquinoline

Step 4: 1,2-Dihydroquinoline undergoes oxidation with nitrobenzene to finally yield quinoline. Nitrobenzene itself is reduced to aniline which is reused in step (2).

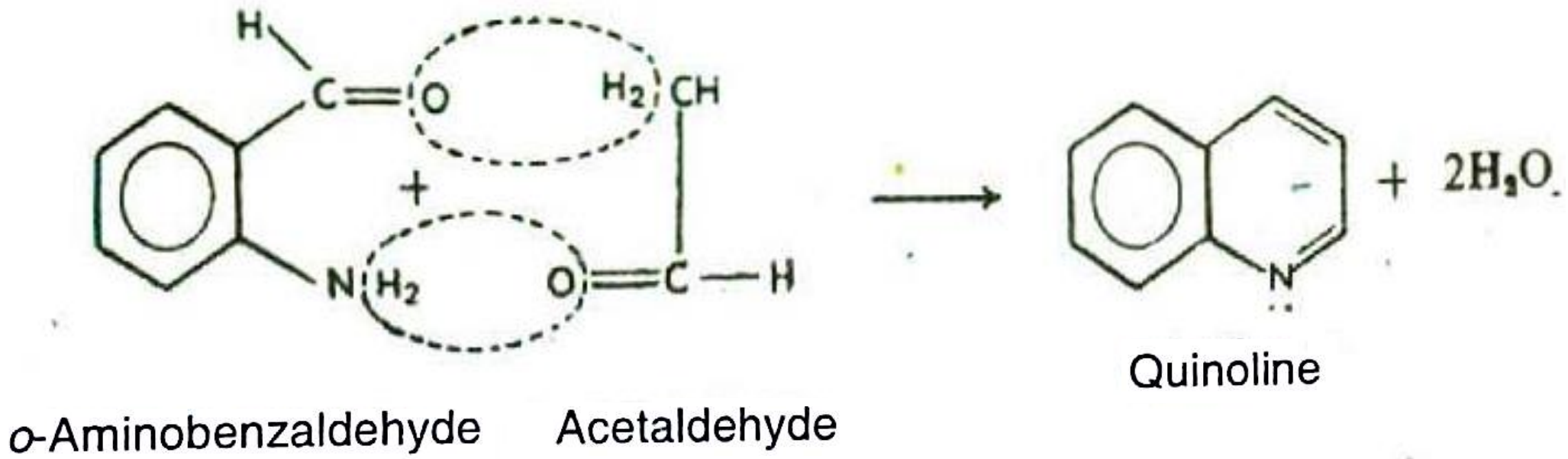


1,2-Dihydroquinoline

Quinoline

(2) By the Friedlander Synthesis:

This involves the condensation of o-aminobenzaldehyde with acetaldehyde in the presence of an alkali.



Physical properties of Quinoline

Quinoline is a colorless liquid,

Boiling Point is **237°C**

It turns yellow on standing, and has pyridine-like smell

Quinoline is miscible with most organic solvents, and dissolves in water to about **0-7 %** at room temperature

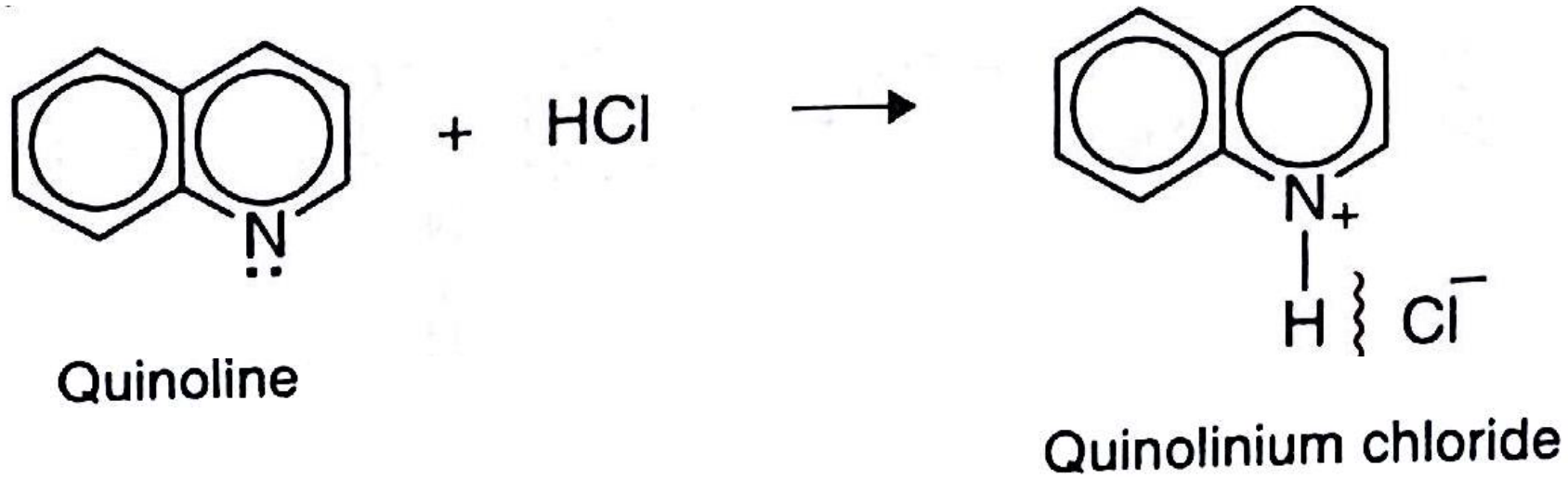
Chemical Properties

1. Basic character
2. Electrophilic Substitution Reaction (at C-5, and C-8)
3. Nucleophilic Substitutions Reaction (C-2 or at C-4 if C-2 is blocked)
4. Oxidation
5. Reduction
6. Reaction with alkyl halides

Chemical properties of Quinoline

Basic Character:

Quinoline is a slightly weaker base. It reacts with acids to yield salts which are sparingly soluble in water.



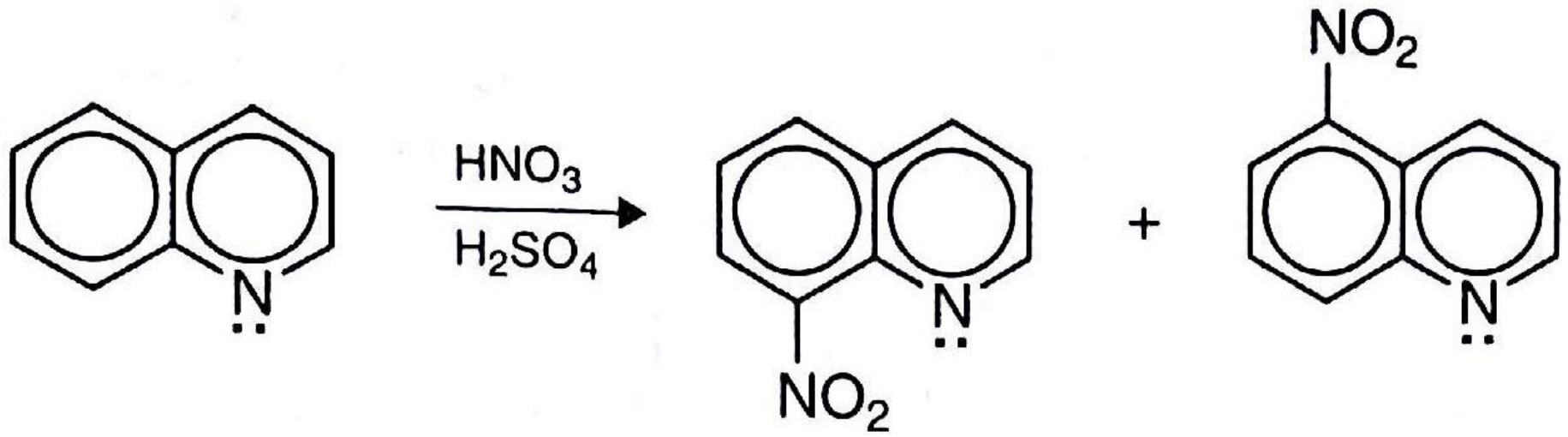
Quinoline

Quinolinium chloride

Electrophilic Substitutions

Quinoline undergoes electrophilic substitution reactions only under vigorous conditions. Substitution occurs at C-8 and C-5.

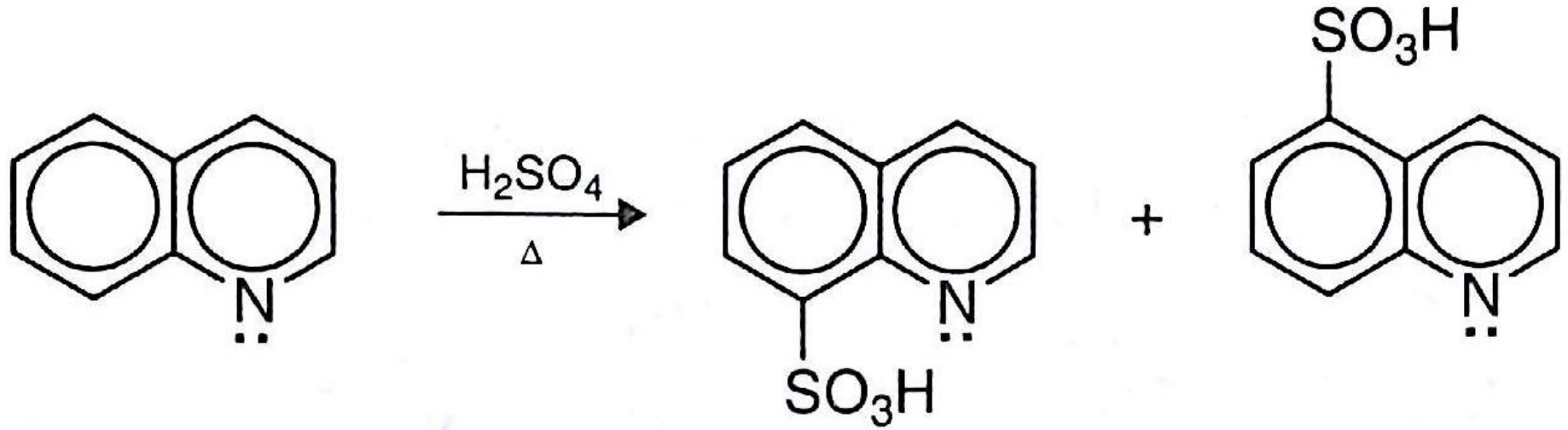
a) Nitration: Quinoline undergoes nitration with fuming nitric acid in the presence of fuming sulphuric acid to give a mixture of 8-nitroquinoline and 5-nitroquinoline.



Quinoline

8- and 5-Nitroquinoline

(b) Sulphonation: Quinoline may be sulphonated with fuming sulphuric acid at 220°C to yield a mixture of quinoline-8-sulphonic acid and quinoline-5-sulphonic acid.



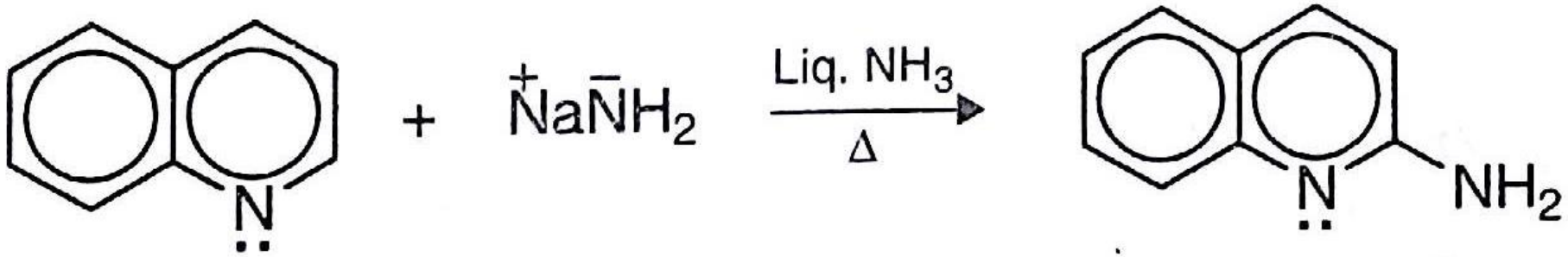
Quinoline

8- and 5-Quinolinesulfonic acid

(3) Nucleophilic Substitutions

Quinoline also undergoes nucleophilic substitution reactions. Substitution occurs at C-2 (or at C-4 if C-2 is blocked).

(a) **Reaction with Sodamide:** Quinoline reacts with sodamide in liquid ammonia at about 100°C to form 2-aminoquinoline.

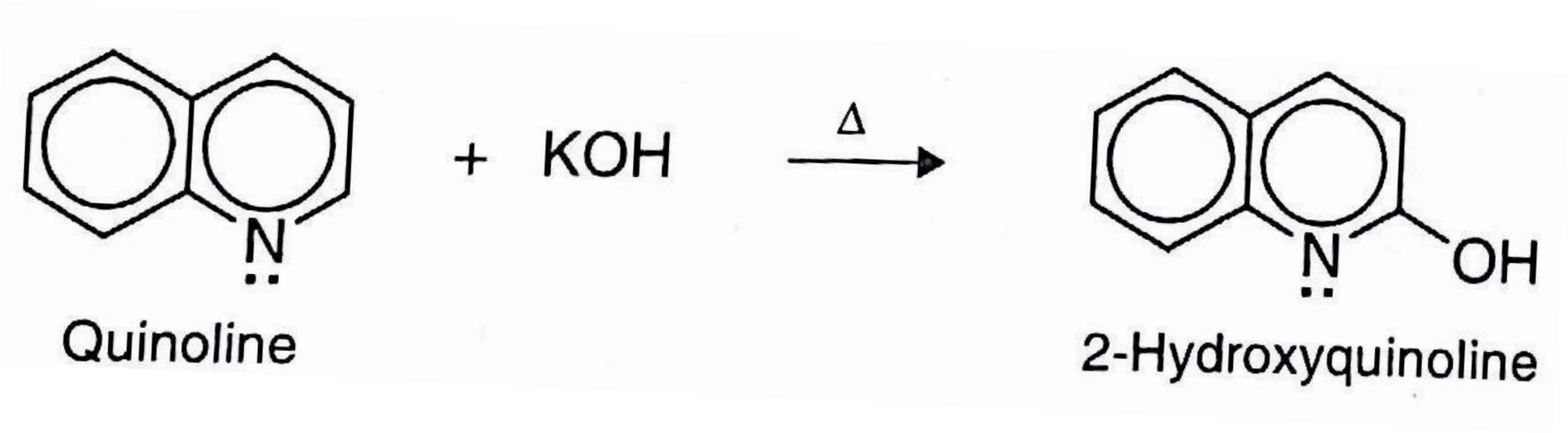


Quinoline

2-Aminoquinoline

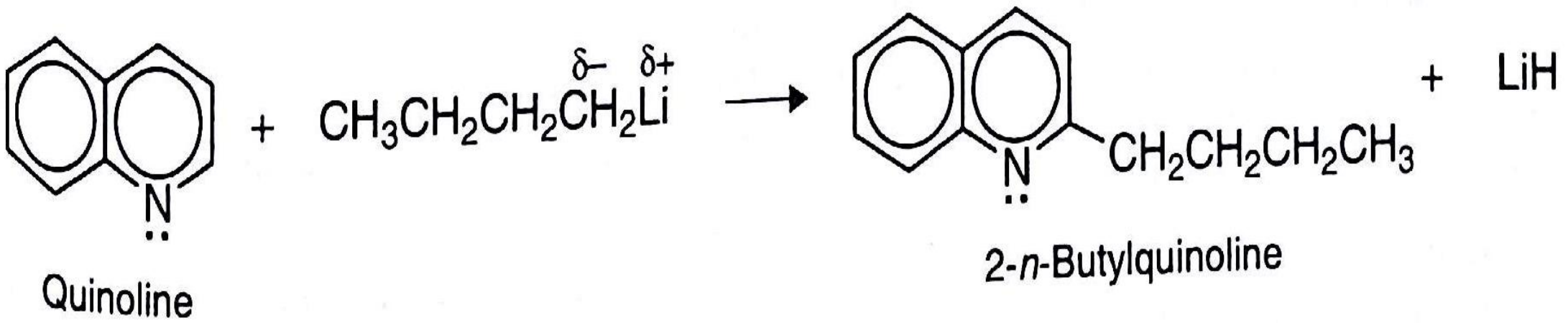
(b) Reaction with Potassium Hydroxide.

Quinoline reacts with potassium hydroxide at 220°C to give 2-hydroxyquinoline.



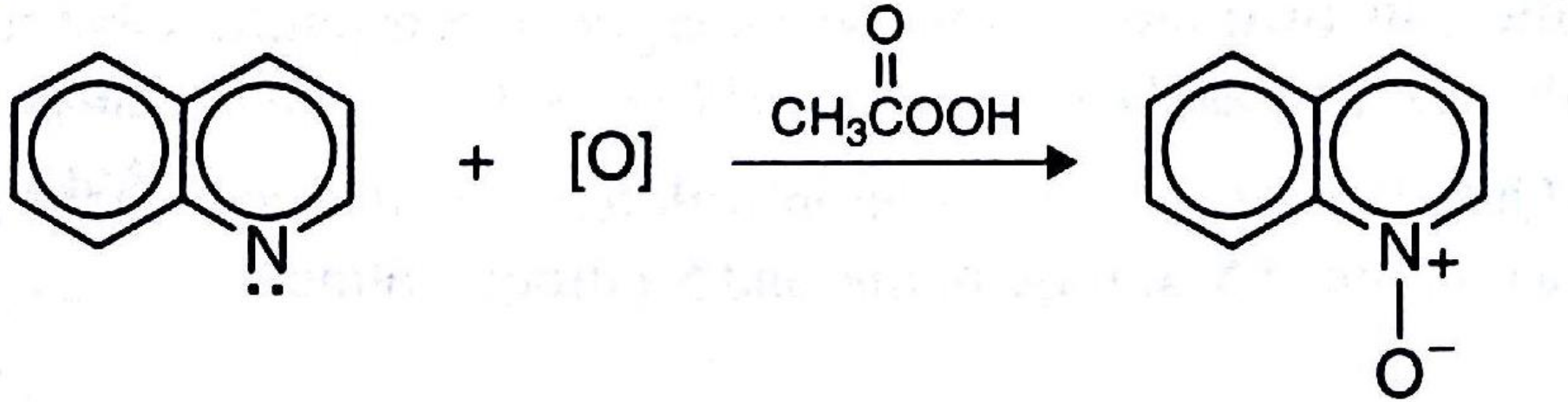
(c) Reaction with n-Butyl-lithium

Quinoline reacts with n-butyl-lithium to yield 2-n-butylquinoline.



(4) Oxidation.

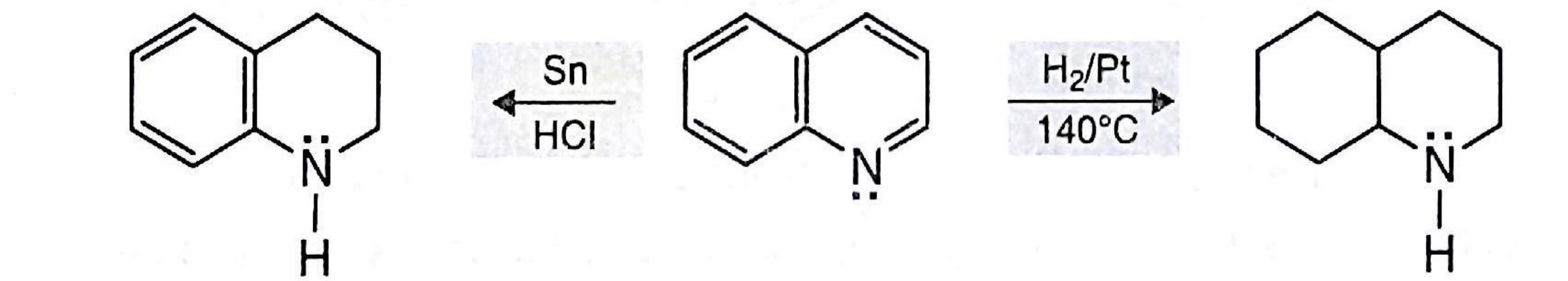
Quinoline is oxidized by peracetic acid to give quinoline-N-oxide



Quinoline

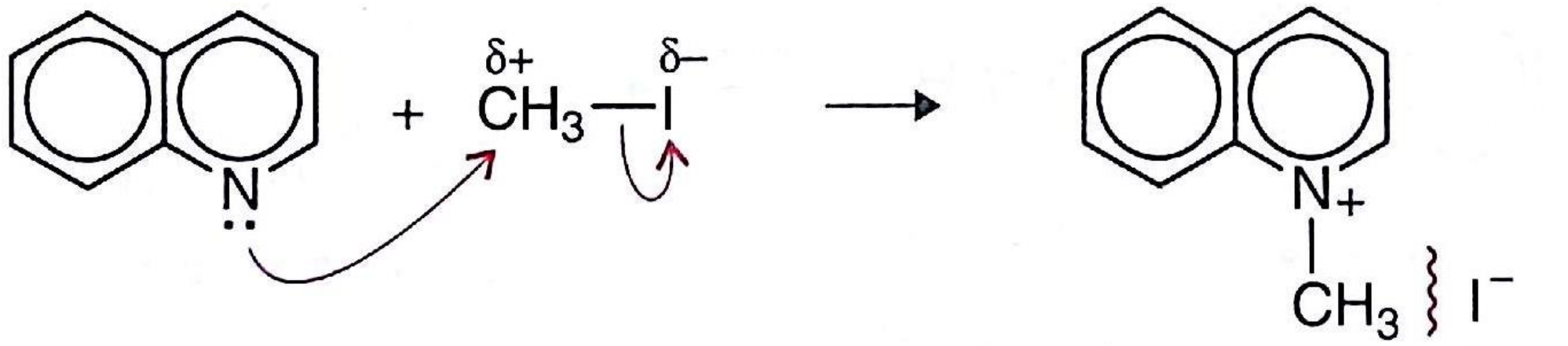
Quinoline-*N*-oxide

(5) Reduction: Mild reduction of quinoline with tin and hydrochloric acid gives 1,2,3,4-tetrahydroquinoline. Whereas, reduction with hydrogen and platinum catalyst produces decahydroquinoline.



(6) Reaction with alkyl halides:

Quinoline give *N*-alkylquinolinium halides by reacting with alkyl halides. For example, with methyl iodide it give *N*-methylquinolinium halide



Quinoline

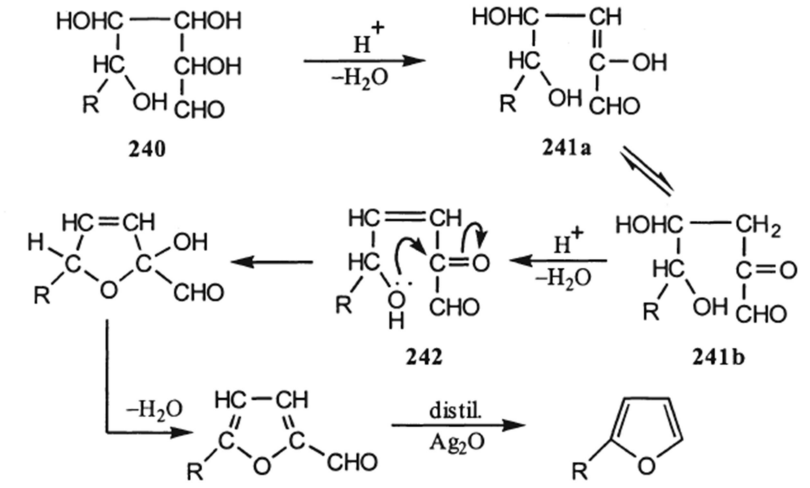
N-Methylquinolium iodide
(1-Methylquinolium iodide)

Furan:

Synthesis

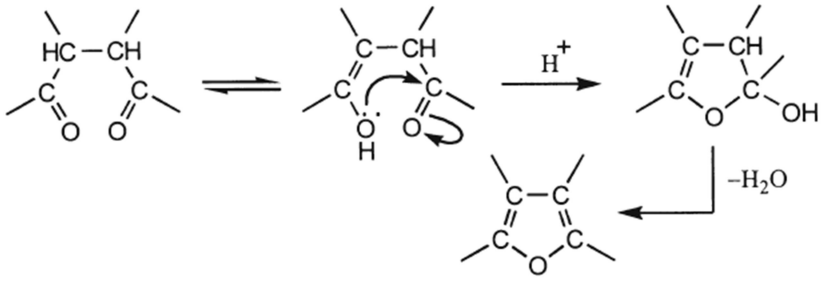
1. **Commercial Method (From Aldopentoses or Ketopentoses)**

Acid catalyzed consecutive dehydrations of aldoses or ketoses 240 result in the formation of a-ketoaldehydes 242 via 1,2-enediol 241. The resulting a-ketoaldehyde 242 undergoes acid catalyzed cyclization involving carbonoxygen bond formation to provide furfural which on steam distillation at 400°C in the presence of oxide catalyst gives the corresponding furan.



2. **From 1,4-Diketones**

Acid catalyzed intramoleculardehydrative cyclization of 1,4-diketones provides furans. The reaction is known as Paal-Knorr synthesis and proceeds with the intramolecular addition of enolic -OH of one carbonyl group to the other carbonyl group (scheme-116). Although sulfuric acid is normally used, the other reagents such as zinc chloride, acetic anhydride, phosphorus pentaoxide and phosphoric acid are also used to cause cyclization and dehydration of 1 ,4-diketones. This reaction is limited only to the easily available 1 ,4-diketones which are not sterically hindered. However, numerous alternative methods involving 1,4-diketones directly or indirectly have also been used to synthesize furans in excellent yields 60-63 .



3. **Ring Expansion of Small Ring Heterocycles**

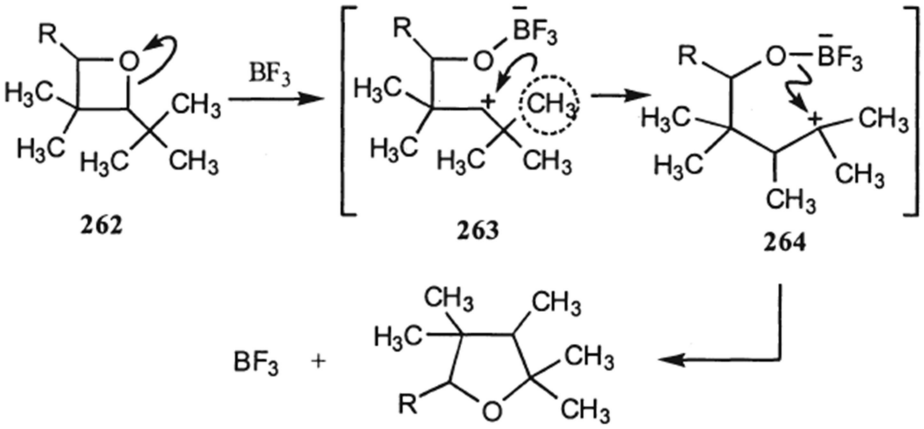
3.1.Three-Membered Heterocycles

Alkynicoxiranes 260 undergo ring-expansion reaction under the influence of sulfuric acid and mercury (II) sulfate and produce furans via alkynicdiols 261 . But

in the presence of sulfuric acid alone, alkynicdiols 261 are obtained as the major products (scheme-124)

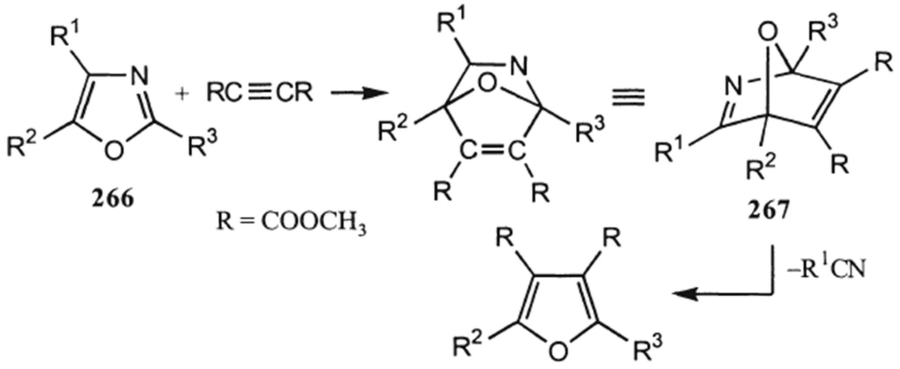
3.2. Four-Membered Heterocycles

The reaction of oxetanes 262 with boron trifluoride in diethyl ether results in the formation of the ring expanded products, tetrahydrofurans 265, via a carbocation intermediate 263 (scheme-125f



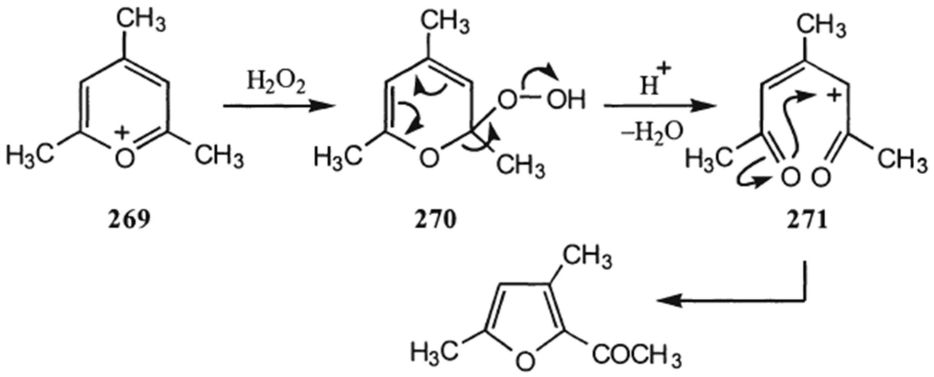
4. Transformation of Five-Membered Heterocycles

Oxazoles 266 undergo (4 + 2) Diels-Alder cycloaddition reaction with alkynic dienophiles (DMAD) with the formation of cycloaddition products 267 which subsequently provide the corresponding furans 268 via retro-Diels-Alder reaction with the loss of nitrile. In this transformation C-3 and C-4 of the resulting furan are provided by the alkynic moiety



5. Ring Contraction

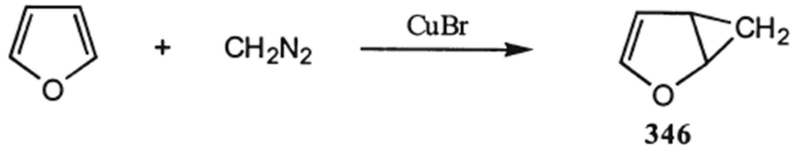
Oxidative ring contraction of pyrylium salts **269** with aqueous hydrogen peroxide andperchloric acid provides 2-acylfurans **272** (scheme-127)74. The reaction proceeds with the formation of hydroperoxide intermediate **270** which undergoes an acid catalyzed degradation through an open-chain oxocation**271 .**



Reactions

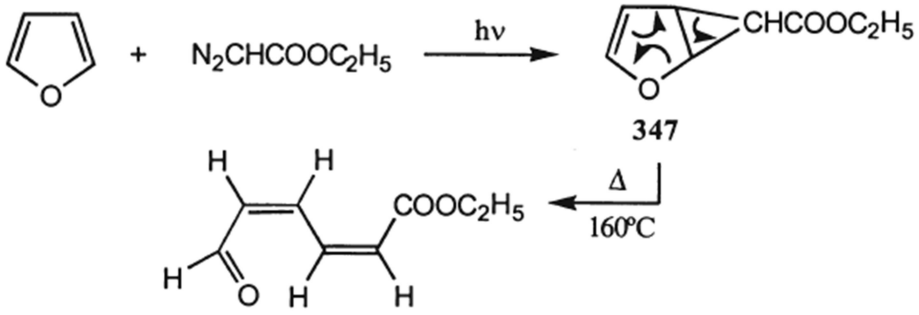
1. Reactions with Electron-Deficient Species

Furan undergoes addition reaction with carbene, generated from diazomethane in the presence of copper bromide, and leads to cyclopropanation with the insertion ofcarbene into the C2-C3 bond (scheme-170)97 .



Scheme-170

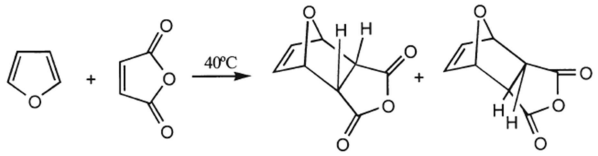
The reaction of furan with carbene, generated by ultraviolet radiation of a solution of ethyl diazoacetate, also produces cyclopropane derivative **347** which, however, on brief heating at 160°C is rearranged to the ring-opened aldehyde **348** (scheme-171)[98].



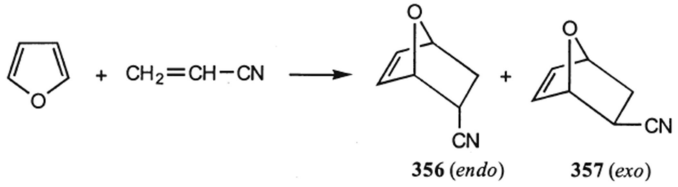
"Endo" and "exo" describes the orientation of the substituents on the dienophile (in this case, the carboxylic acids) with the diene. In the endo orientation, the substituents point "down" towards the diene and the bridge is sticking "up." In the exo orientation, the substituents point "up," away from the diene.

2. Cycloaddition Reactions

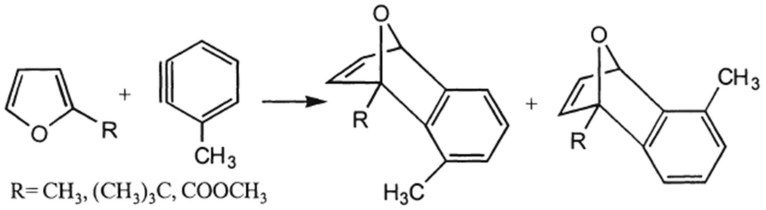
Furan, inspite of being n-excessive heterocycle, behaves as a diene and undergoes (4 + 2) cycloaddition reactions with dienophiles with the formation of thermodynamically more stable exo-products than the kinetically favoured*endo*products. The reaction of furan with maleic anhydride in acetonitrile at 40°C provides initially *endo-adduct* 352 , which is coverted to exo-adduct 353 by retroaddition followed by readdition in an alternativ e orientation. The exo-adduct is 8.0 kJ/ mol more stable than the *endo-adduct* (scheme-173)



The ethylenicdienophiles substituted with only one electron-withdrawing substituent (acrylonitrile and methylacrylate) react very slowly with furan at room temperature providing moderate yields of both *endo*- 356 and *exo*- 357 adducts (scheme-175). The reaction is greatly accelerated either by the addition of Lewis acid (zinc iodide) which increases the electrophilicity of the dienophile or by using high pressure and the adducts are obtained in improved yields

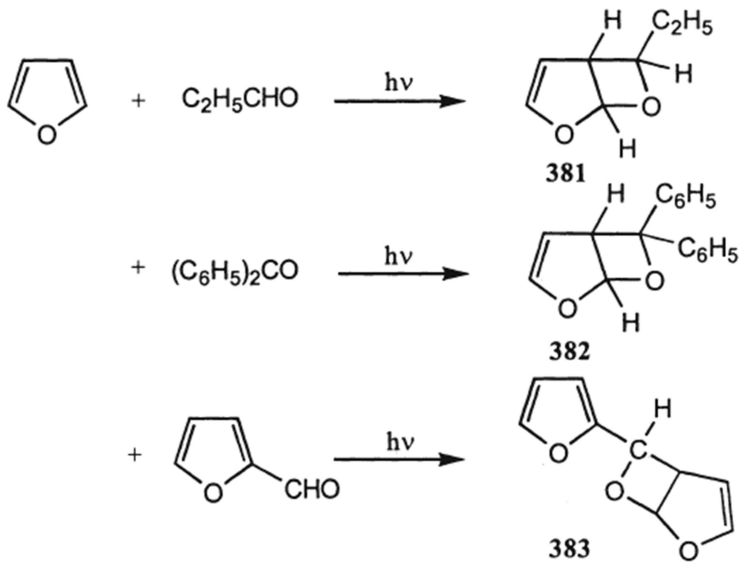


Furans substituted with varying substituents undergo cycloaddition reactions readily with benzynes.Thecycloaddition of an unsymmetrical benzyne with furan is however, not considerably effected and the ratio of the products remains almost the same (scheme-184

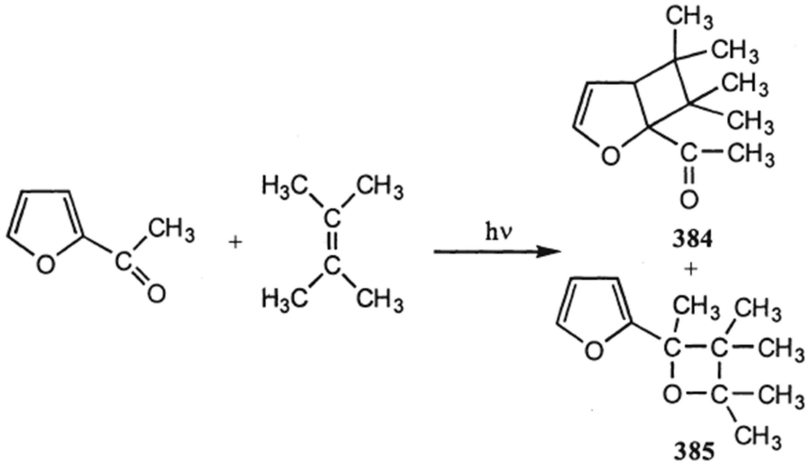


3. Photochemical Reactions

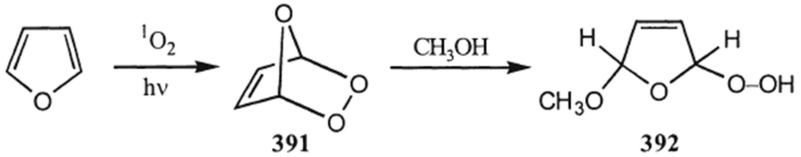
Furans undergo photochemical (2 + 2) cycloaddition reactions when irradiated with carbonyl compounds (such as aliphatic aldehydes and ketones, a,[3-unsaturated aldehydes, diketones and aromatic and heteroaromatic aldehydes and ketones) to provide oxetanes.



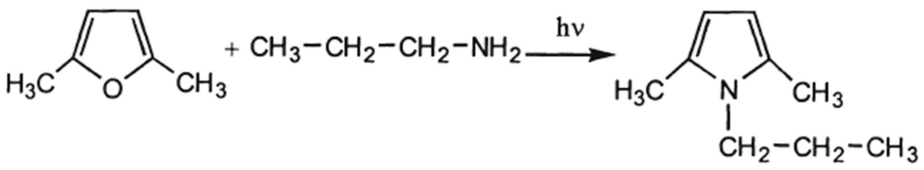
The photochemically sensitized (2 + 2) cycloaddition of 2-acylfuran with 2,3-dimethyl-2-butene produces two products 384 and 385 in which product 384 is obtained by the addition of 2,3-dimethyl-2-butene to the furan ring, while 385 is produced by (2 + 2) addition of an alkene to the carbonyl group



The photo-oxygenation of furan with singlet oxygen at low temperature gives a bicyclic peroxide 391 which with methanol forms hydroperoxide 392 involving nucleophilic attack at an a-position



The irradiation of alkylfurans with an excess of propylamine results in photochemical transformation with the formation of N-propylpyrroles.

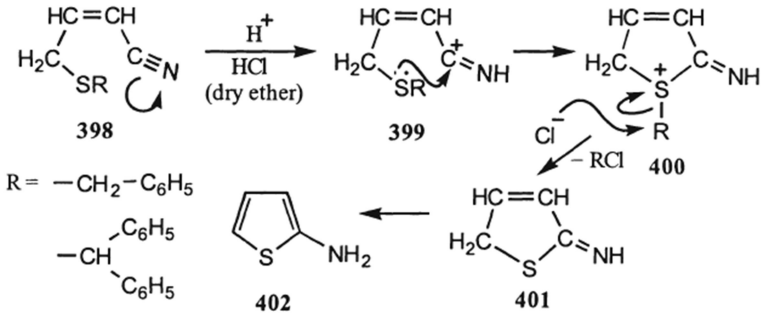


THIOPHENES

Synthesis

1. **From 4-Aralkylthiocrotononitriles**

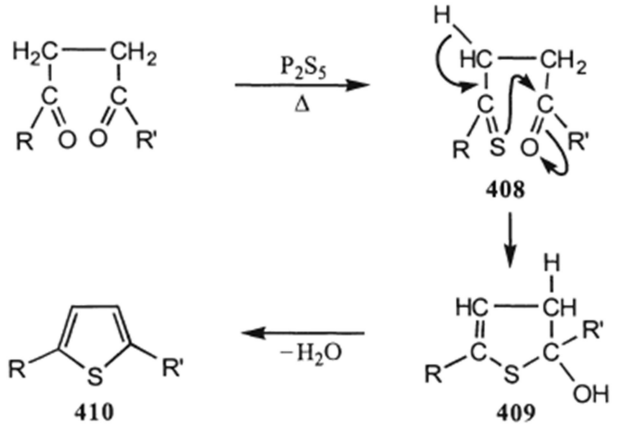
Intramolecular cyclization of cis-4-aralkylthiocrotononitriles 398 in the presence of hydrochloric acid in dry ether provides 2-aminothiophene 402 with the formation of C-S bond.



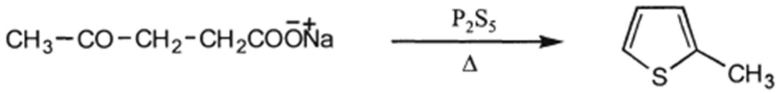
The mechanism is supported by the fact that trans-aralkylcrotononitriles fail to undergointramolecular cyclization to provide 2-aminothiophene.

2. **From 1,4-Diketones (Paal Synthesis)**

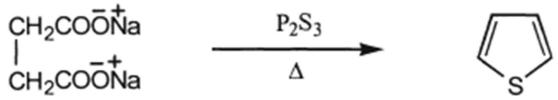
This is the most widely used method and involves the reaction of 1,4-diketones with phosphours pentasulfide (P_2S_5). The reaction is considered to involve the steps as in (scheme-197). The reaction of keto acids or diacids (salts) with phosphorus pentasulfide results in the formation of thiophenes in poor yield, but with phosphorus trisulfide thiophenes are obtained in much improved yields (scheme-198). Thiophenes are prepared in excellent yields on laboratory scale from appropriately substituted succinic acid salts by heating with phosphorus trisulfide (scheme-199).



Scheme-197

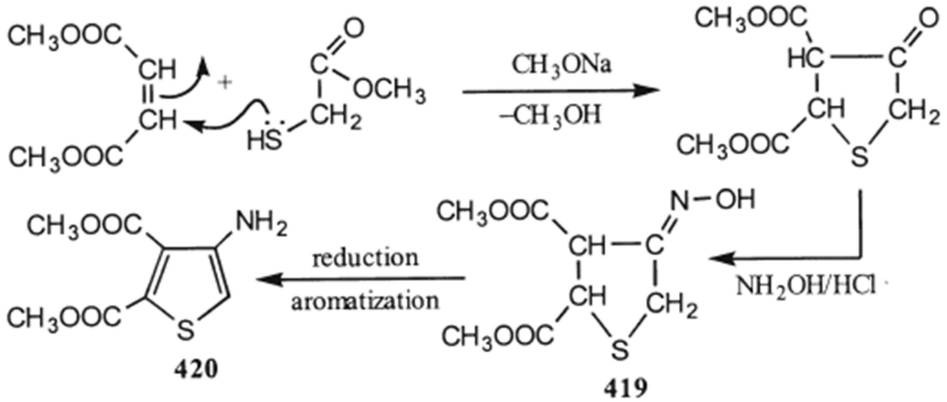


Scheme-198



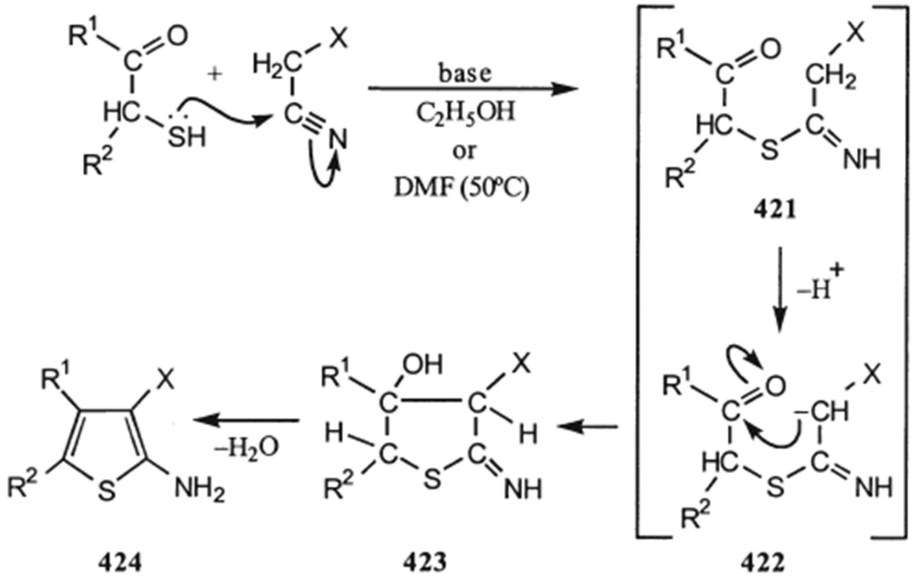
3. Reaction of Dimethyl Fumarate with Mercapto Esters

The reaction of dimethyl fumarate, constructing a two-atoms unit, with mercapto ester as a three-atoms unit in the presence of a base involves (3 + 2) cyclization providing tetrahydrothiophene **418** which on treatment with hydroxylamine followed by the reduction and aromatization affords the corresponding thiophene **420**



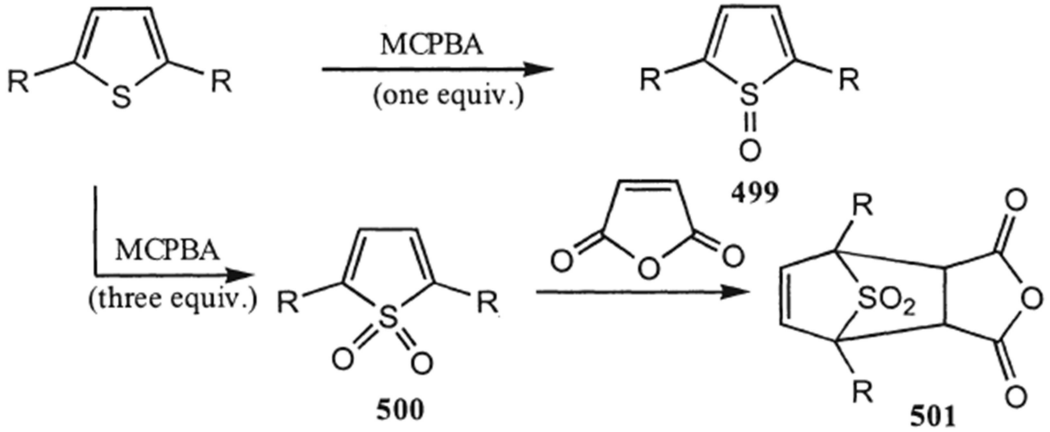
4. Reaction of a.-Mercapto Ketones with Activated Methylene Nitrites (Gewald Synthesis)

The condensation of a-mercapto Ketones (three-atoms unit) with activated methylene nitriles (two carbon-atoms unit) in the presence of a base (pyridine or triethylamine) leads to the formation of 2-aminothiophenes **424** involving following steps

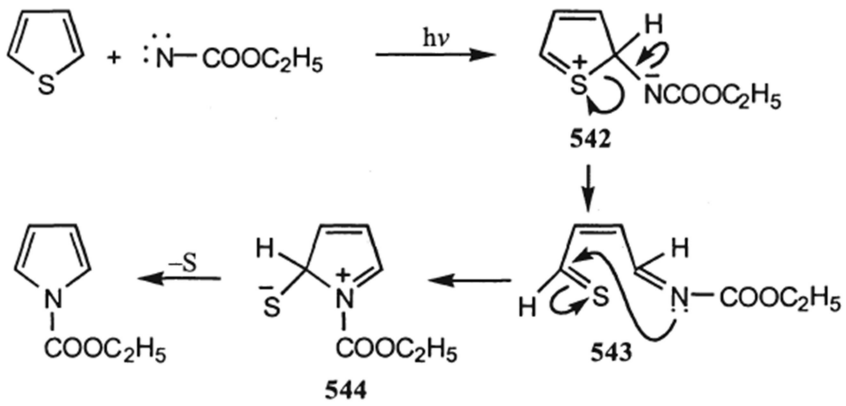


Chemical Reactions of thiophene

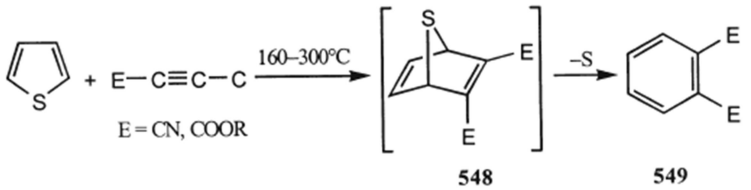
1. **Formation of Thiophene Sulfoxides and Sulfones:** oxidation of thiophenes, containing sterically hindered group, with one equivalent of m-chloroperbenzoic acid produces the corresponding sulfoxides 499, but with three equivalents of m-chloroperbenzoic acid the sufones 500 are obtained139 . Thiophene sulfones behave as dienes and undergo Diels-Alder reaction with dienophiles providing Diels-Alder adducts 501



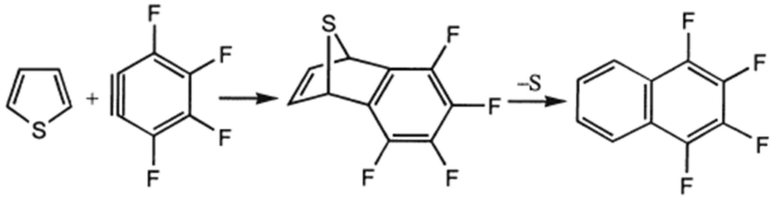
2. **Reactions with Nitrenes:** The reaction of thiophene with ethoxycarbonylnitrene results in the formation of N-ethoxycarbonylpyrrole. The reaction is considered to involve the attack of nitrene at C-2 and the ring opening to thiocarbonyl intermediate 543 followed by cyclization and extrusion of sulfur

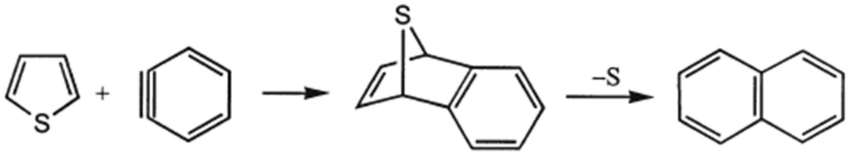


3. Thermal [4 + 2] Cycloaddition Reactions: Thiophene reacts with activated alkynes with the formation of benzene derivatives 549 involving (4 + 2) cycloaddition and the extrusion of sulfur from the resulting unstable cycloadduct 548

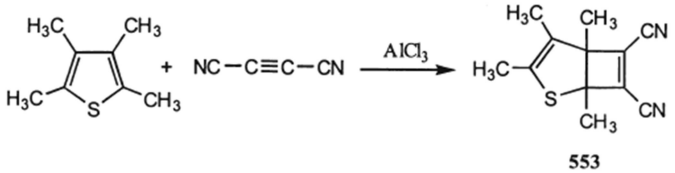


The reaction of thiophene with tetrafluorobenzyne gives cycloadduct 550 which loses sulfur to provide tetrafluoronaphthalene 551 (scheme-284) 160 . However, thereaction of thiophene with benzyne has been reported to yield naphthalene in low yield (33%).

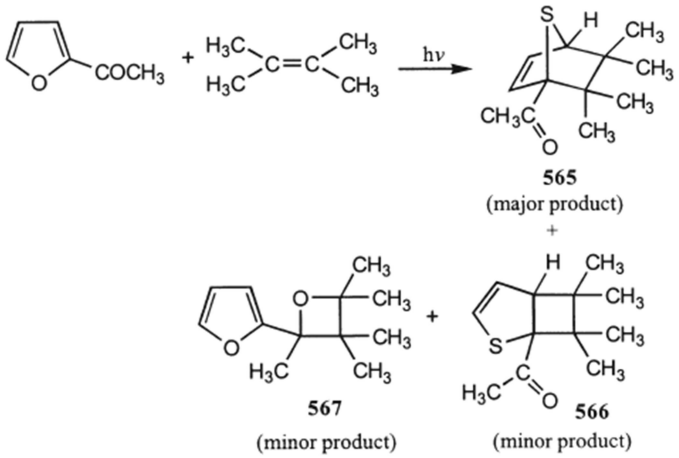




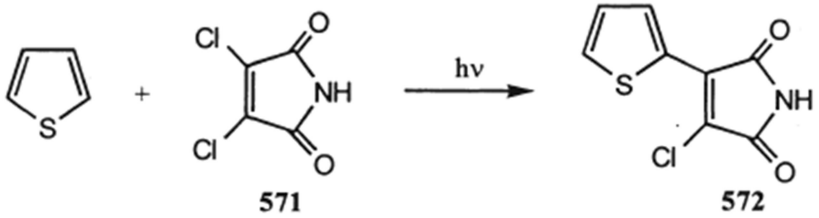
4. **Thermal [2 + 2] Cycloaddition Reactions:** Tetramethylthiophene undergoes (2 + 2) cycloaddition reaction with dicyanoacetylene in the presence of aluminium chloride providing cycloadduct 553(scheme-286)



5. **Photocycloaddition Reactions:** Photochemical reaction of 2-acetylthiophene with alkenes (2,3-dimethylbutene) leads to the formation of major product 565 involving (4 + 2) cycloaddition but the minor products 566 and 567 are obtained by (2 + 2) cycloadditioin(scheme-290

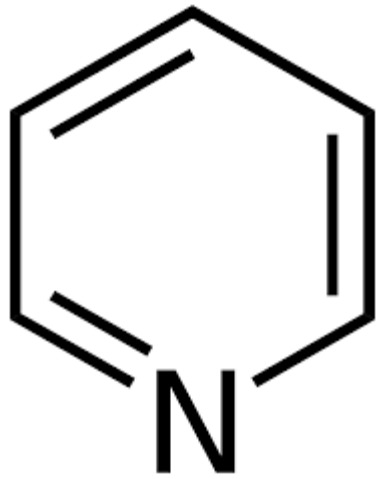


6. **Photosubstitution:** Thiohene undergoes photosubstitution at the position-2 rather than photocycloaddition when irradiated in the presence of 3,4-dichloromaleimide 571and leads to the formation of 2-substituted product 572 (scheme-292)



Preparation and Properties of Pyridine

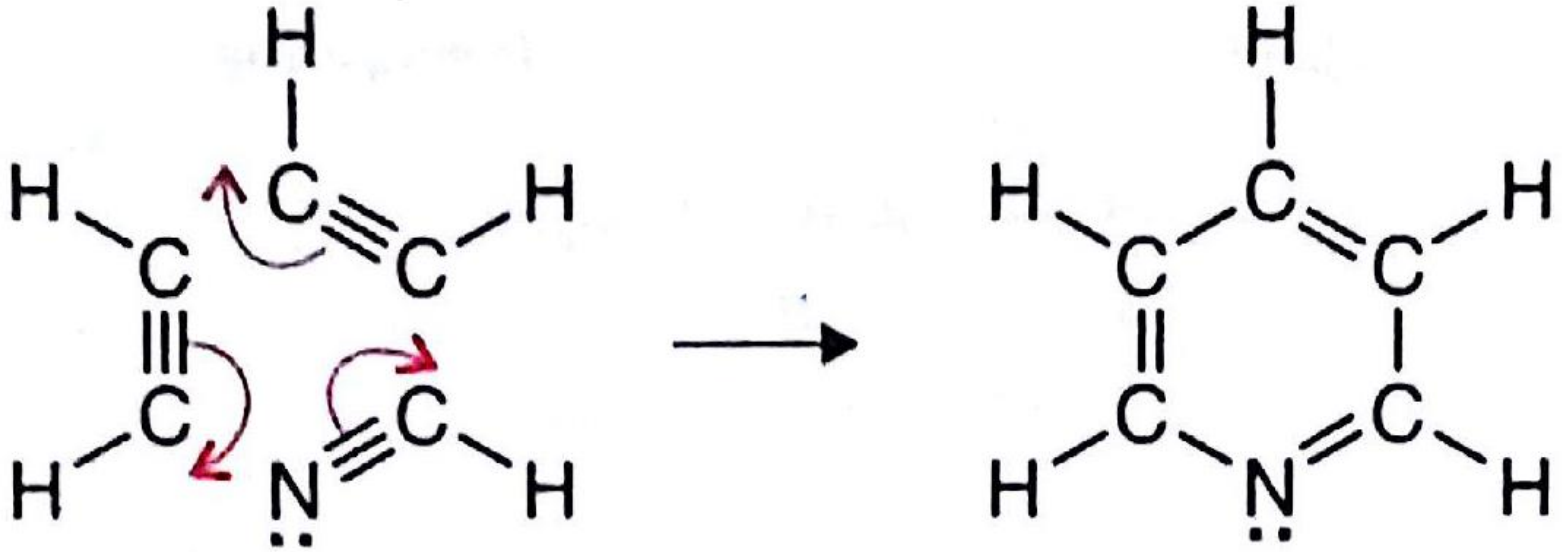
Pyridine



- Pyridine is the most important of the heterocyclic ring systems. It occurs along with pyrrole in bone oil and in the light oil fraction of coal tar (boiling point up to 170 C).
- It can be isolated from the latter by extracting it with dilute sulphuric acid. This removes pyridine and other bases in the acid layer as soluble sulphates.
- The acid layer is then treated with sodium hydroxide when a dark brown liquid separates. Pyridine is obtained from this oily liquid by fractional distillation.

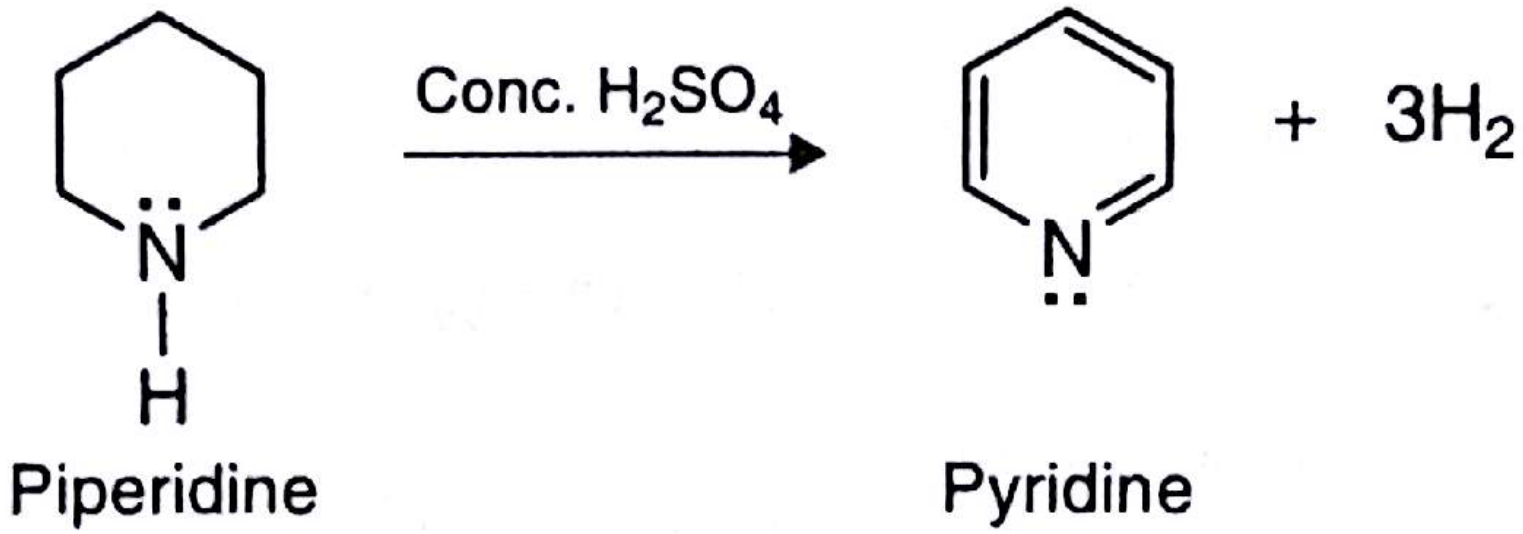
Preparation Methods

(1) By passing a mixture of acetylene and hydrogen cyanide through a red-hot tube.

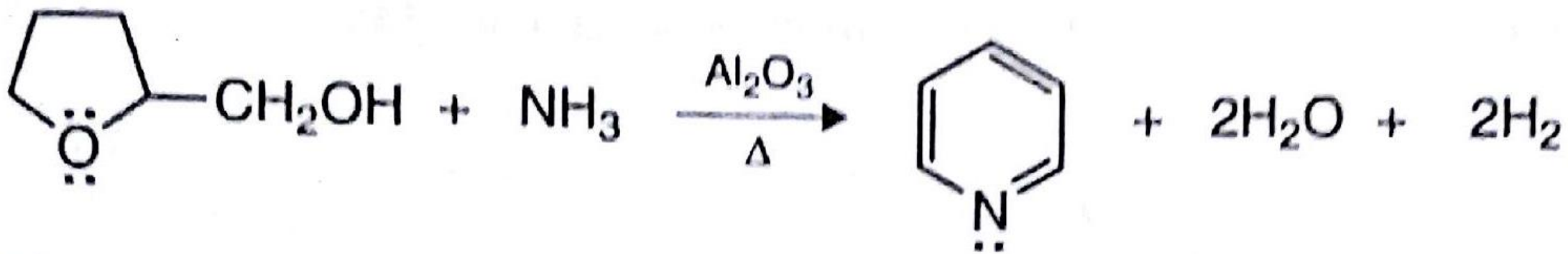


Pyridine

(2) By dehydrogenation of piperidine with concentrated sulphuric acid at 300°C or with nitrobenzene at 260°C.



(3) By heating tetrahydrofurfuryl alcohol with ammonia in the presence of aluminium oxide at 500°C. (Commercial Method of Preparation).



Tetrahydrofurfuryl alcohol

Pyridine

Physical properties of Pyridine

Pyridine is a colourless liquid, bp 115C°.

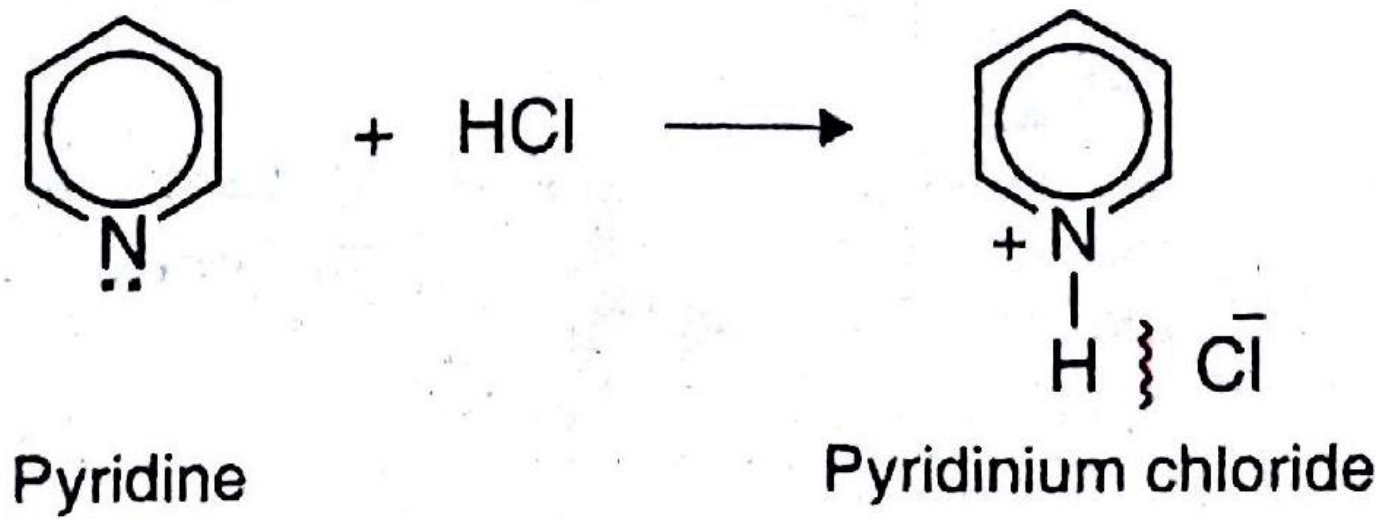
It has a very characteristic pungent and disgusting odour. Pyridine is miscible with water and most organic solvents.

Almost all classes of organic compounds are soluble in pyridine, even many of the high melting solids which scarcely dissolve in solvents such as ethanol and benzene. It is consequently used as a solvent.

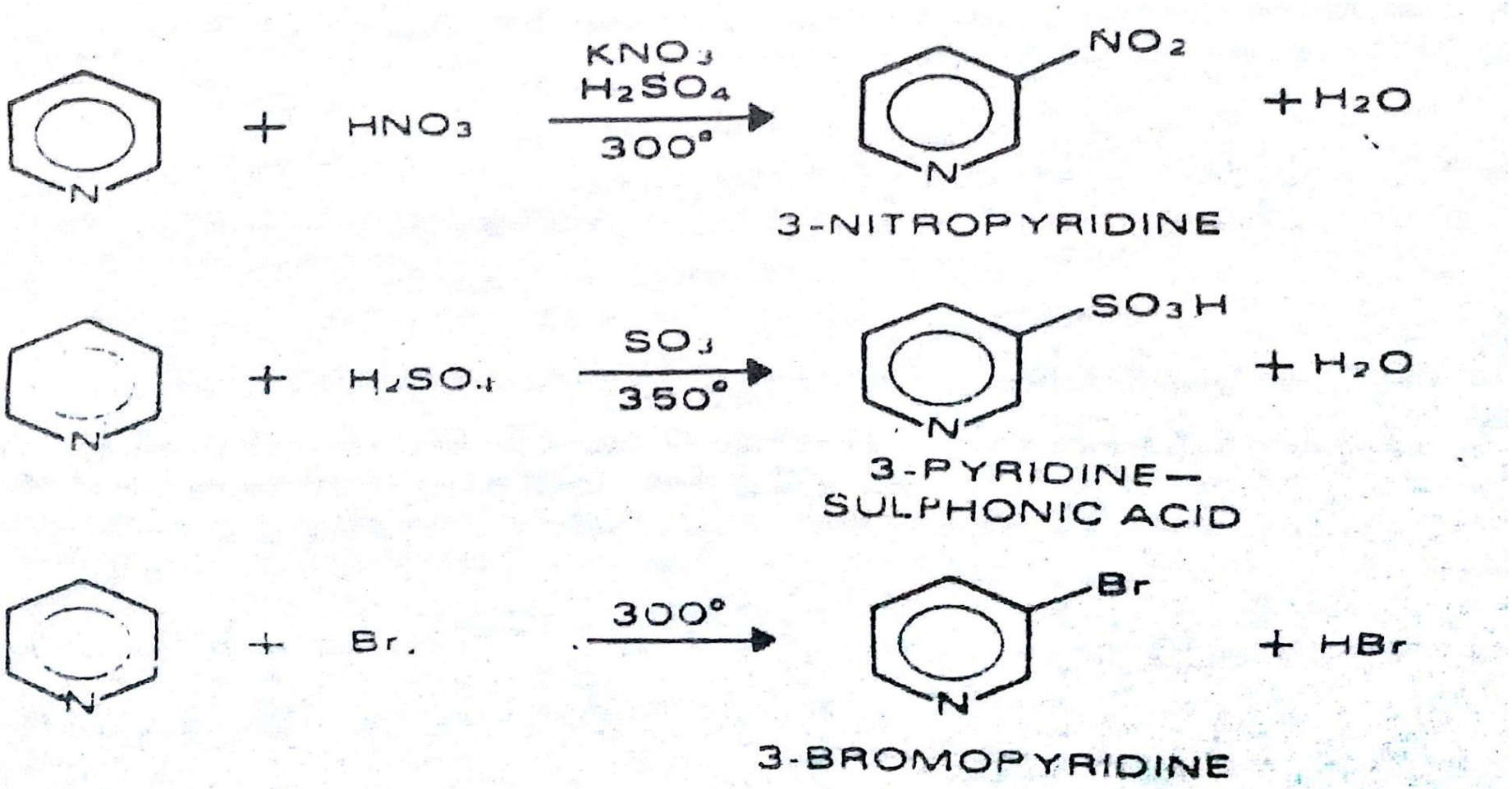
It is very hygroscopic.

Chemical properties of Pyridine

(1) Basic Character: Pyridine behaves as a base. It reacts with acids to form fairly stable salts..



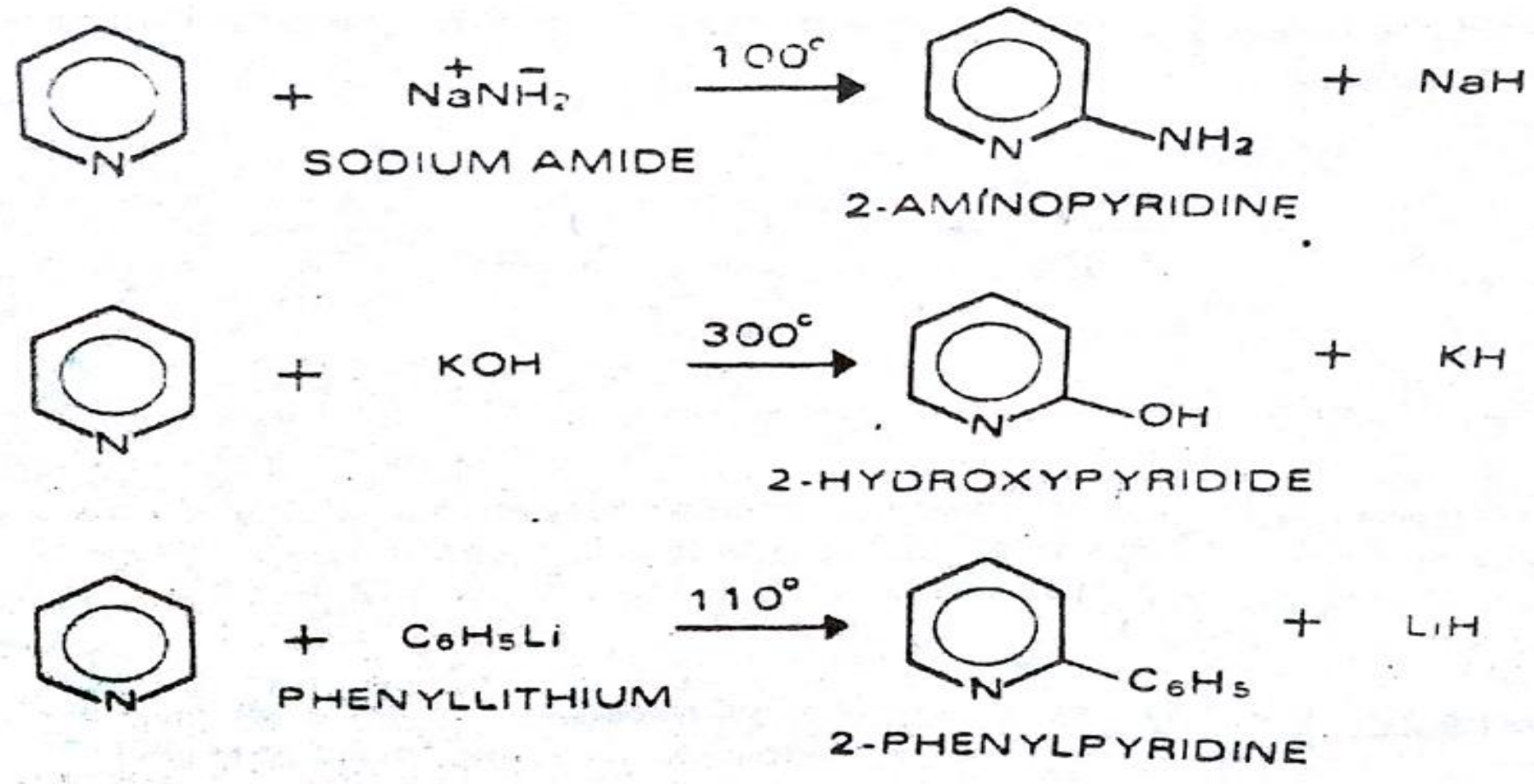
(2) Electrophilic Substitution: Pyridine, however, does undergo electrophilic substitution reactions when extremely vigorous reaction conditions are used. Substitution occurs almost exclusively at ***C-3*** (β-Position).



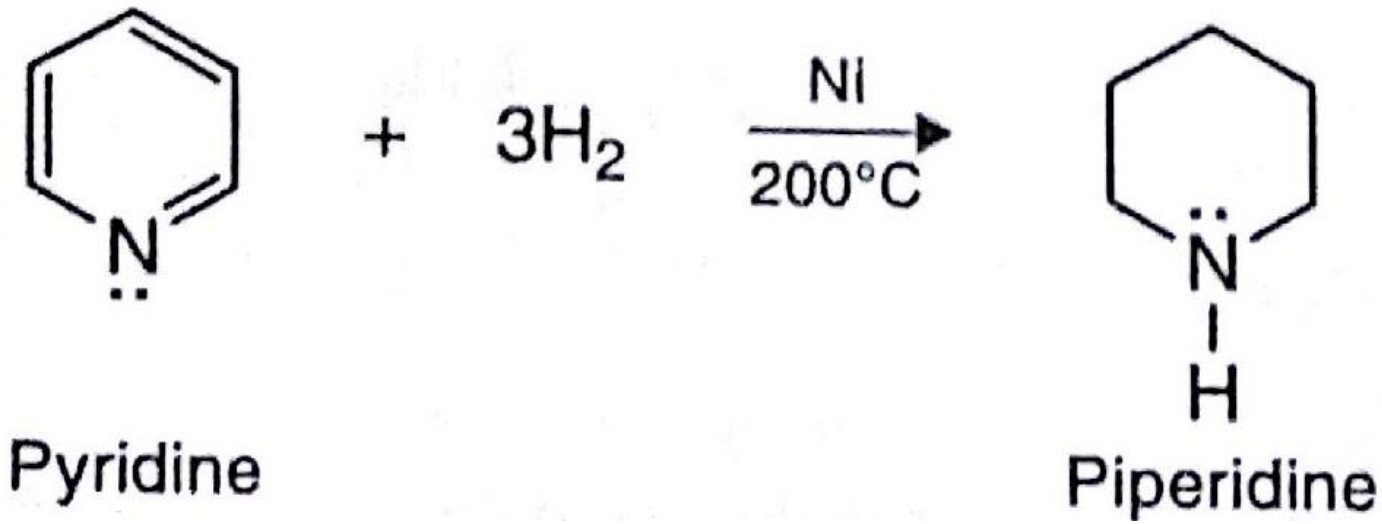
Pyridine does not undergo Friedel-Crafts acylation and alkylation. This is because the Lewis acids (e.g., $AlCl_3$) which are used as catalysts in these reactions coordinate with the lone pair of electrons on nitrogen.

(3) Nucleophilic Substitution:

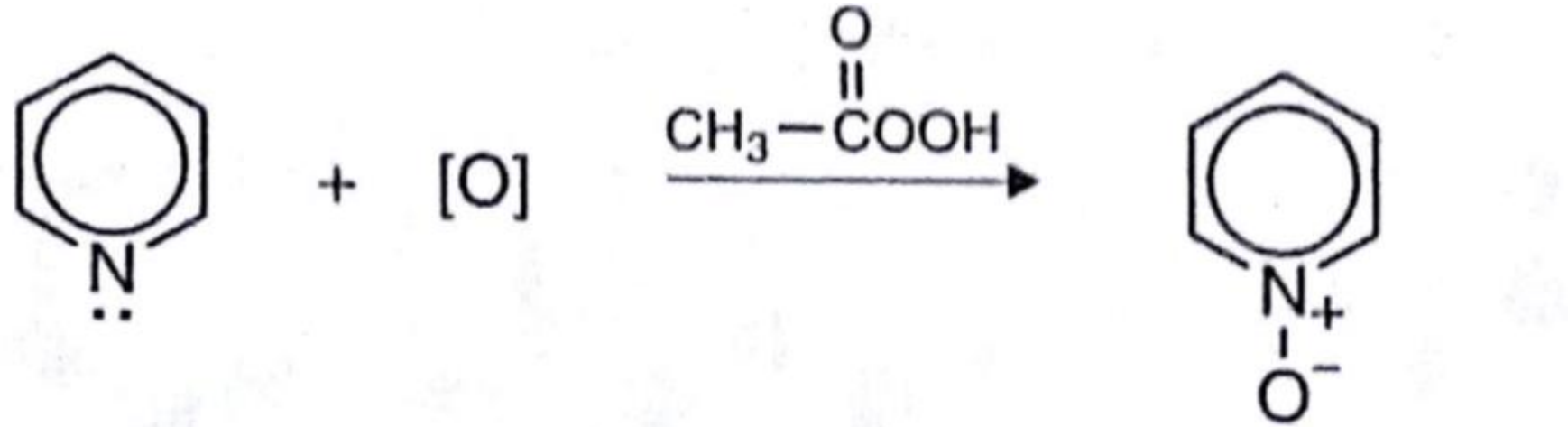
Pyridine undergoes nucleophilic substitution reactions mainly at C-2 (or at C-4 if C-2 is blocked)



(4) Reduction: Pyridine undergoes reduction with lithium aluminium hydride (LIAIH4), or hydrogen in the preSence of nickel catalyst to form piperidine.



(5) Oxidation: Like benzene, pyridine is quite stable towards mild oxidizing agents. It does not react with chromic acid or nitric acid. However, it may be oxidized by peracetic acid to give pyridine-*N*-oxide.



Pyridine

Pyridine-*N*-oxide
(Pyridine-1-oxide)

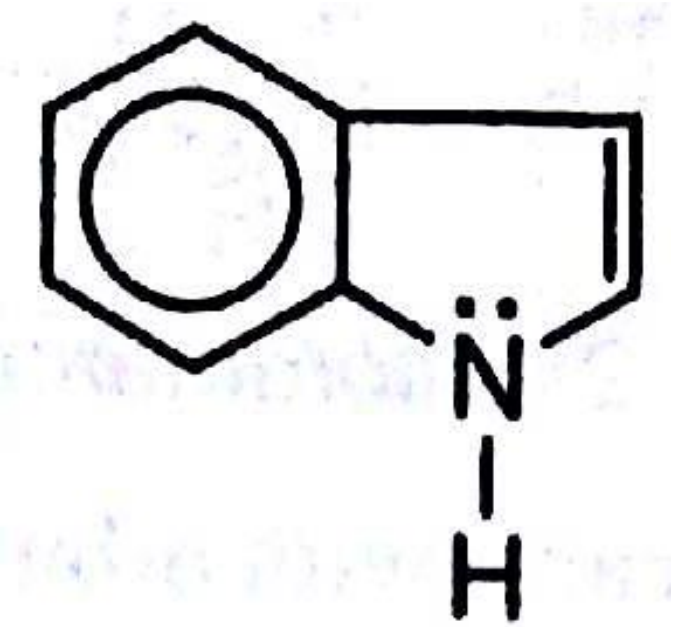
Preparation and Properties of INDOLE

Indole

Indole consists of a benzene ring fused to the **Alpha and Beta positions of a pyrrole ring.**

Indole occurs in coal-tar and in the oils of jasmine and orange blossoms.

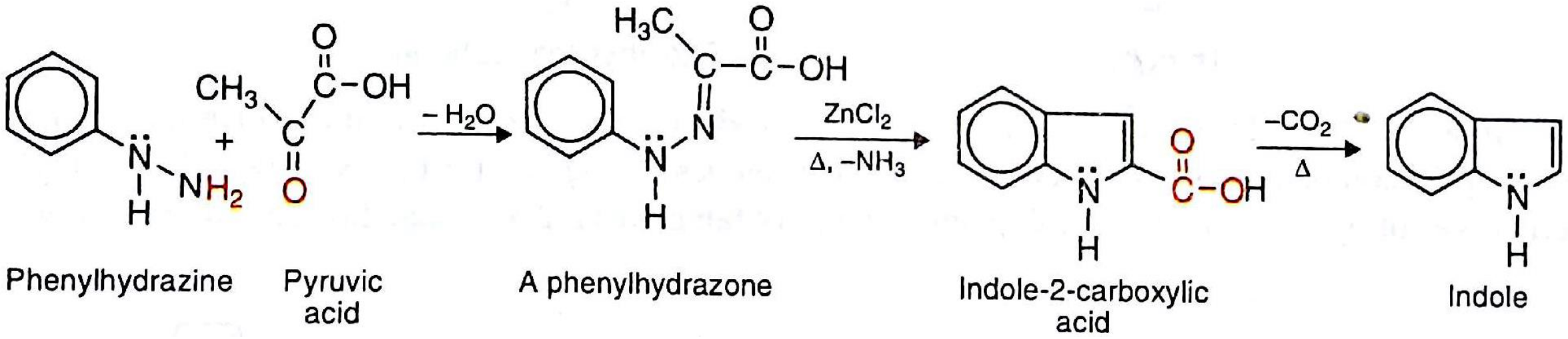
It is also found as a part of the total structure of a number of alkaloids and amino acids e.g., **serotonin, reserpine, and tryptophan**.



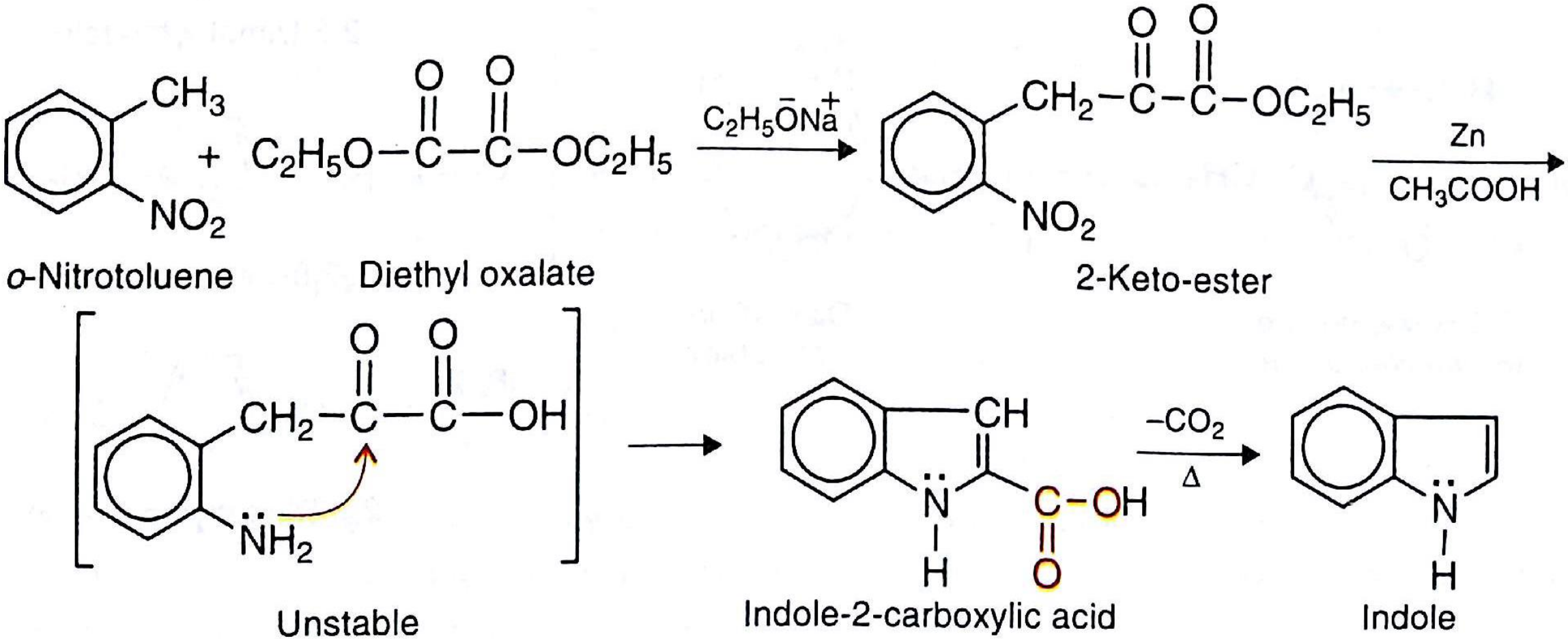
Preparation Methods

Indole may be obtained;

1. <u>By Fischer-indole synthesis:</u> In this method pyruvic acid is first treated with phenylhydrazine to form the corresponding phenylhydrazone. The hydrazone is heated with anhydrous zinc chloride to give indole-2-carboxylic acid which on decarboxylation yields indole.



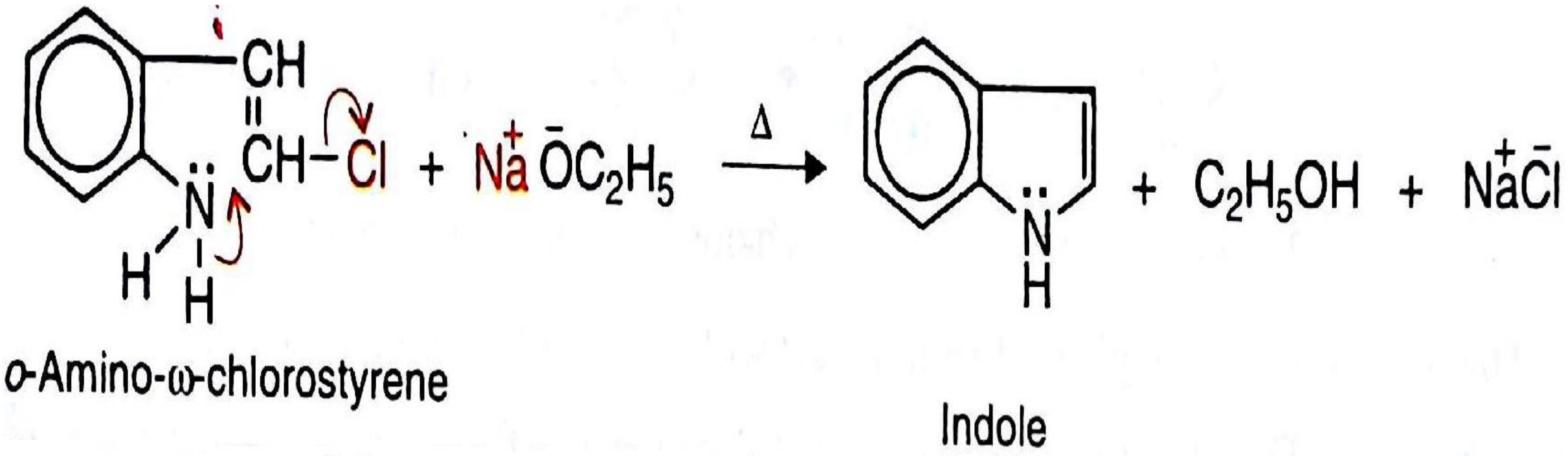
2. By the Reissert Synthesis. In this method o-nitrotoluene is condensed with diethyl oxalate in the presence of a base to form a 2-keto-ester. This is then reduced with zinc and glacial acetic acid to give indole-2-carboxylic acid which on decarboxylation gives indole.



3. From o-Toluidine: This involves treatment of o-toluidine with formic acid to form N-formyl-o-toluidine. This undergoes dehydration on heating with potassium t-butoxide to yield indole.

o-Toluidine Formic acid *N*-Formyl-*o*-toluidine Indole

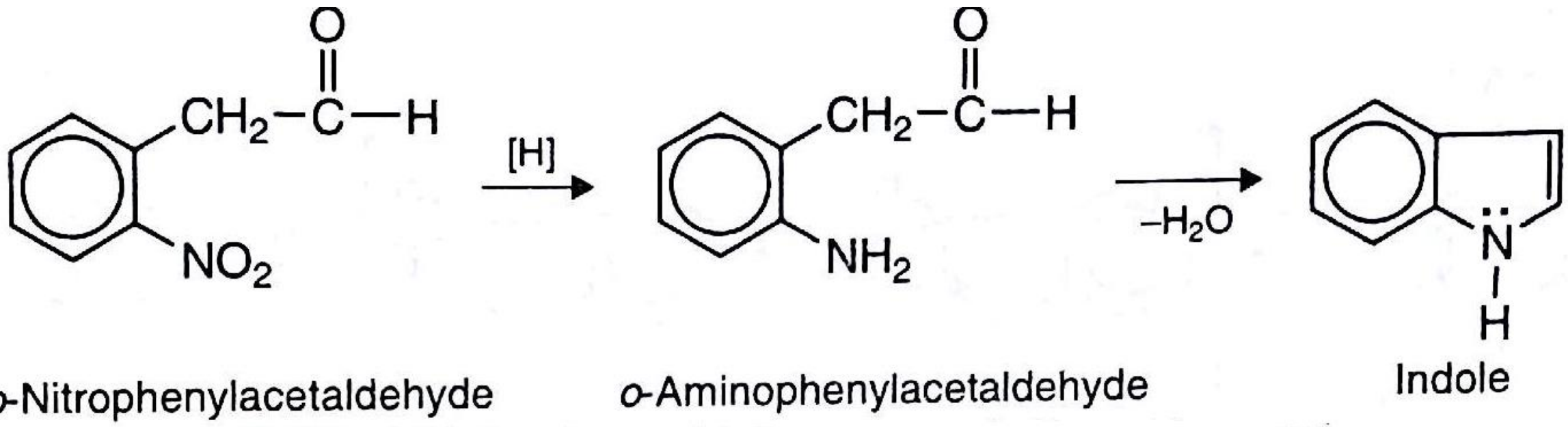
4. By the Lip Synthesis. In this method o-amino-w-chlorostyrene is heated with sodium ethoxide at l60-170°C,



o-Amino-ω-chlorostyrene

Indole

5. From o-Nitrophenylacetaldehyde: This involves reduction of o-nitrophenylacetaldehyde with iron powder and sodium bisulphite to give o-aminophenylacetaldehyde which cyclises spontaneously to yield indole.



o-Nitrophenylacetaldehyde *o*-Aminophenylacetaldehyde Indole

Physical Properties of Indole

- Indole is a colorless, volatile solid,
- Melting point **52C**
- It is sparingly soluble in cold water, but dissolves in hot water and most organic solvents.
- Indole has a powerful odour which is pleasant and flowery in low concentrations. It is, in fact, used commercially as a perfume base. In contrast, indole and its 3-methyl derivative (Skatole) are responsible for the strong offensive odour of faeces.

Chemical Properties of Indole

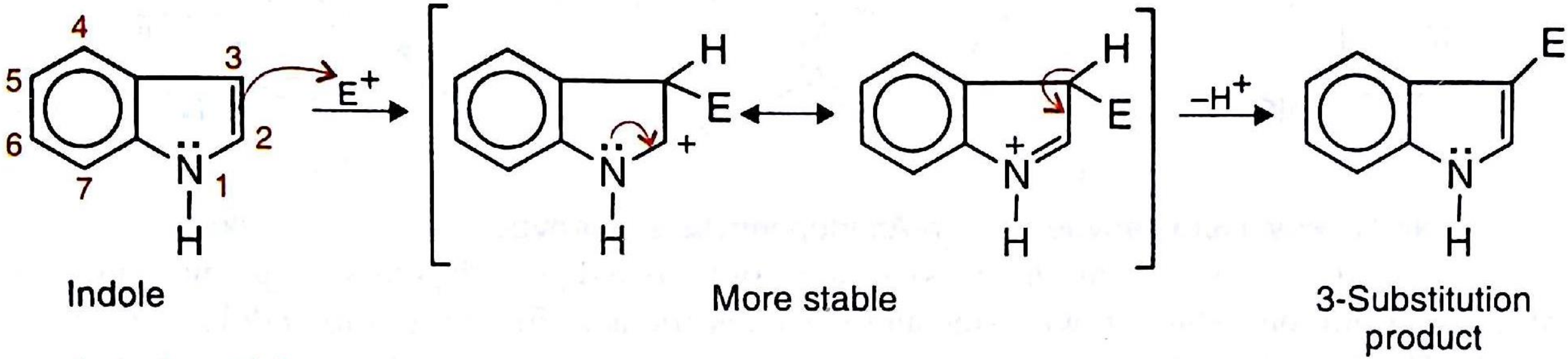
1. **Basic and Acidic Character:**

   Like pyrrole, indole is a weak base and also *a* weak acid. It is polymerized by strong acids and reacts with potassium hydroxide and Grignard reagents.

2. Electrophilic Substitutions:

Unlike pyrrole, indole undergoes electrophilic substitution at C-3. This is because two resonance forms can be written for intermediate cation obtained from attack at C-3 (without disturbing the benzene ring), whereas only one such form is possible for substitution at C-2.

Attack at C-3 :

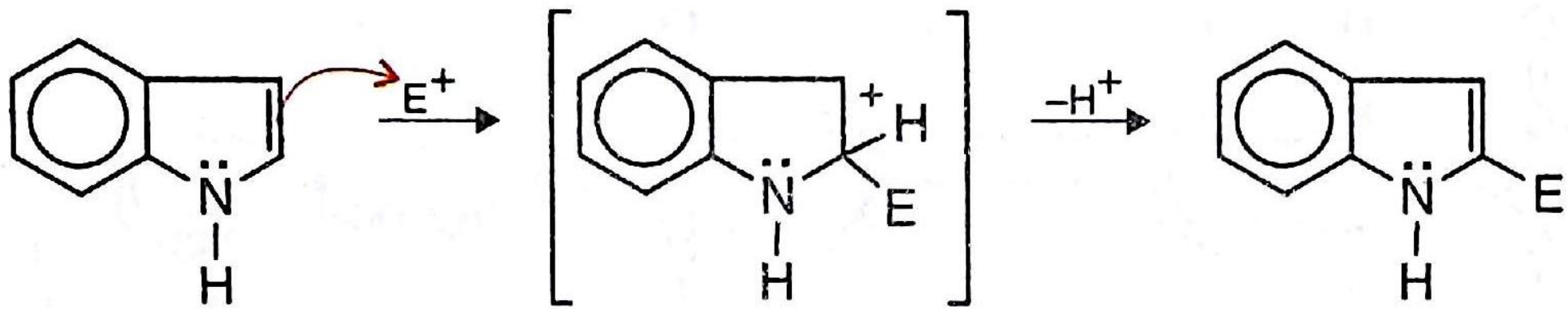


Indole

More stable

3-Substitution product

Attack at C-2 :



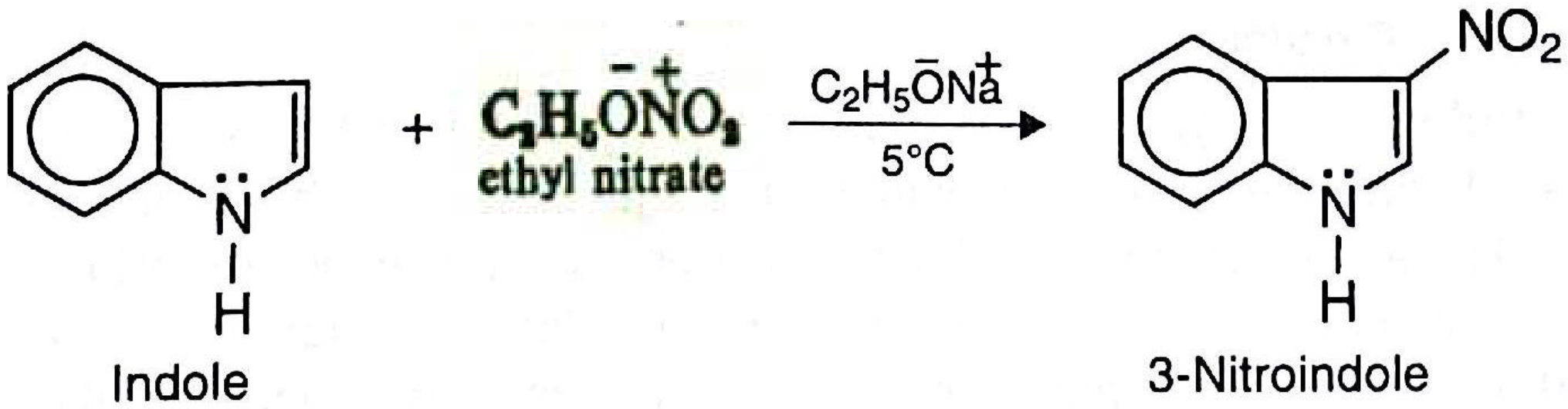
Indole

Less stable

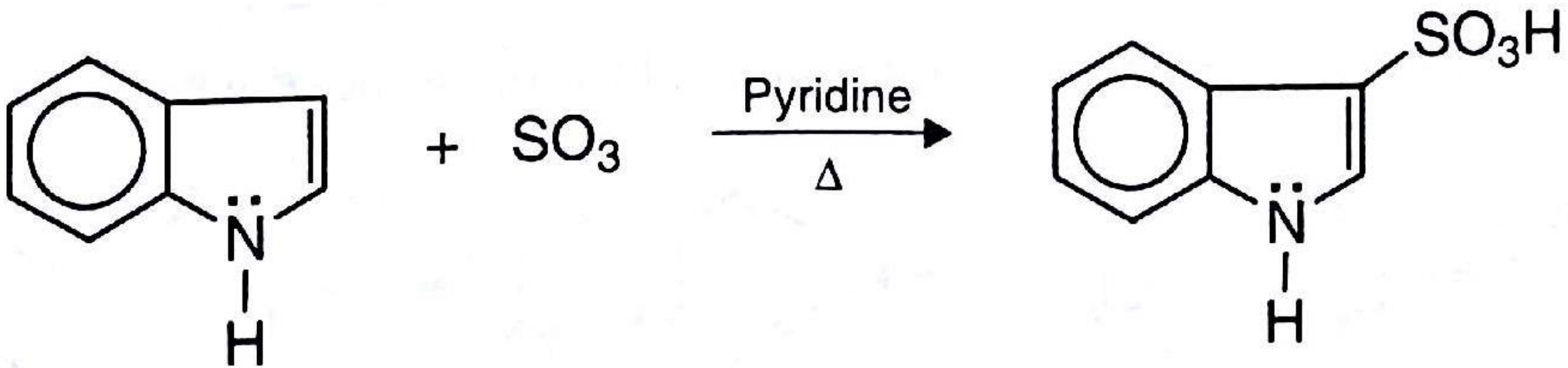
2-Substitution product

a. Nitration

Indole may be nitrated at low temperature with ethyl nitrate in the presence of sodium ethoxide to yield 3-nitroindole.



(b) Sulphonation: Indole undergoes sulphonation with sulphur trioxide in pyridine at 110°C to give indole-3-sulphonic acid.

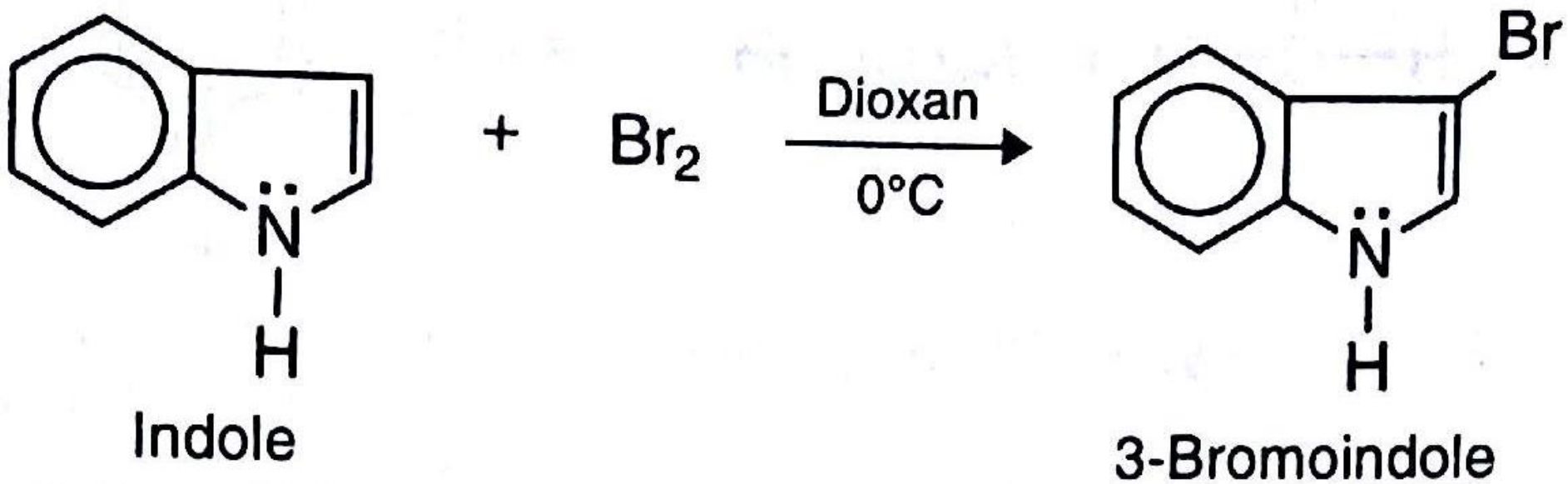


Indole

Indole-3-sulfonic acid

C. Bromination

When treated with sodium methoxide and Methylene iodide, pyrrole undergoes ring expansion forming pyridine.

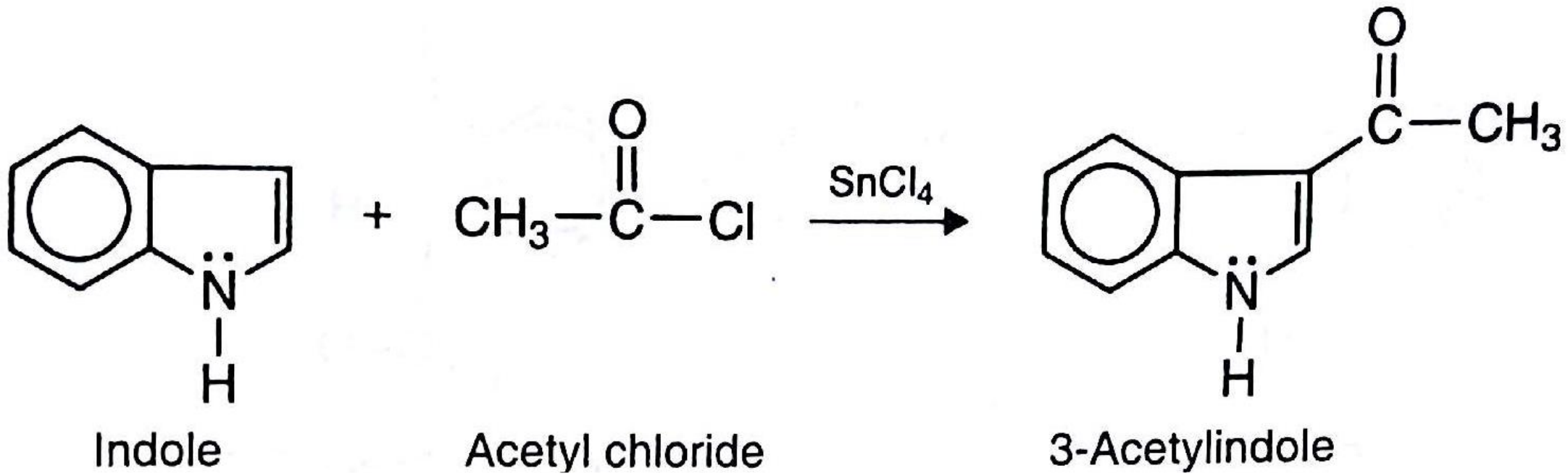


Indole

3-Bromoindole

d. Friedel-Craft Acylation

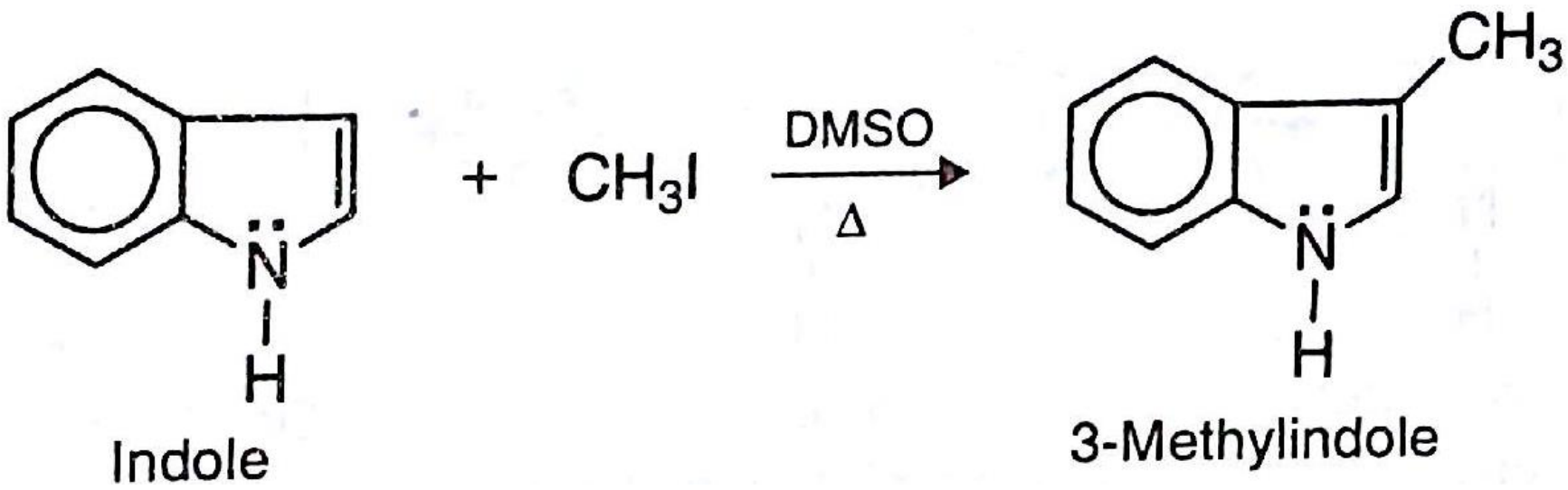
- Indole may be acetylated with acetyl chloride in the presence of $SnCl_4$ (Tin tetrachloride) to yield 3-acetylindole.



Indole + Acetyl chloride → 3-Acetylindole

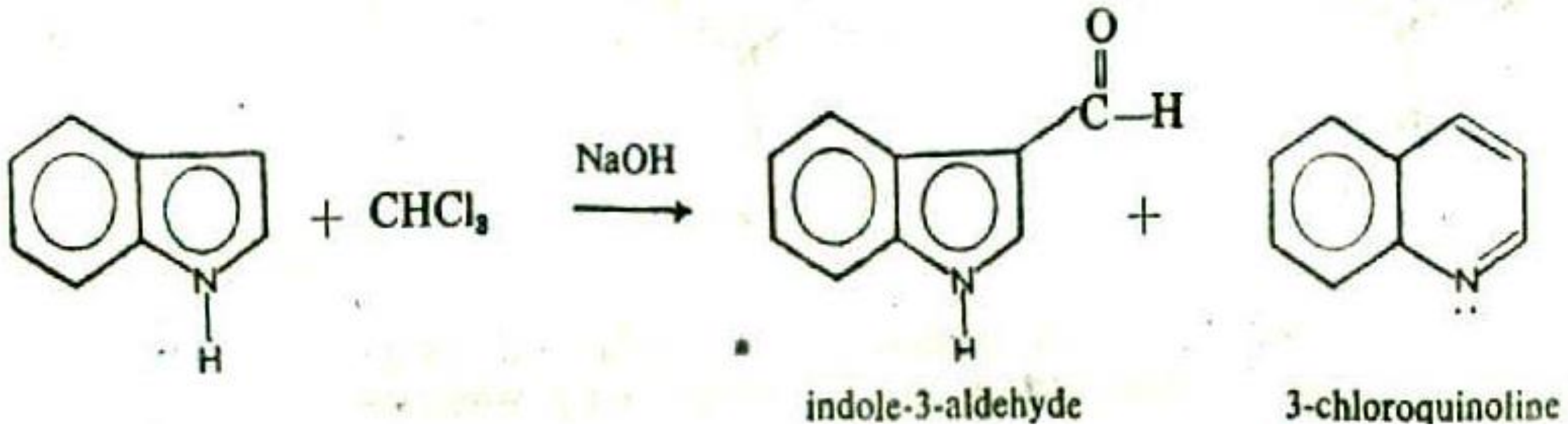
e. Alkylation

- Indole reacts with methyl iodide in dimethyl sulphoxide *(DMSO)* at about 80°C to give 3-methylindole *(skatole).*



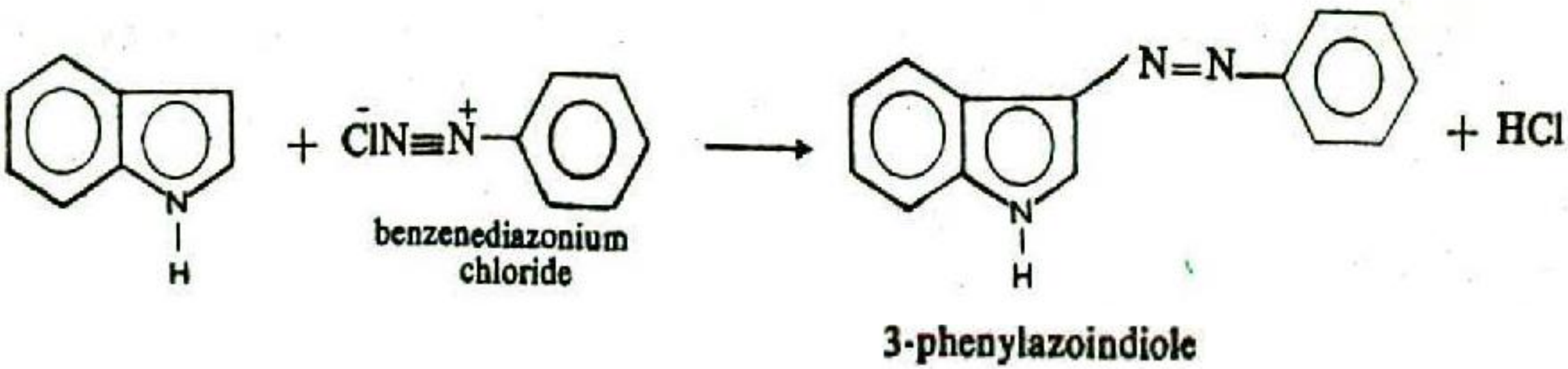
Reimer-Tiemann Formylation

- Indole reacts with chloroform in the presence of alkali to yield indole-3-aldehyde (3-formylindole) and 3-chloroquinoline.



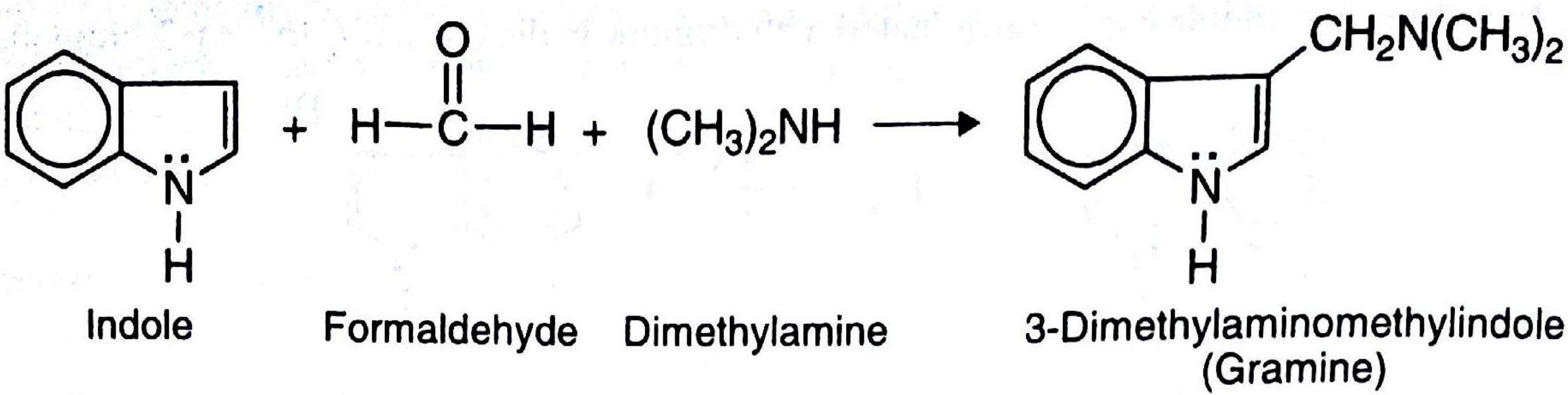
Diazo Coupling

Indole couples with benzenediazonium chloride in a weakly acidic solution to yield 3-phenylazoindole.



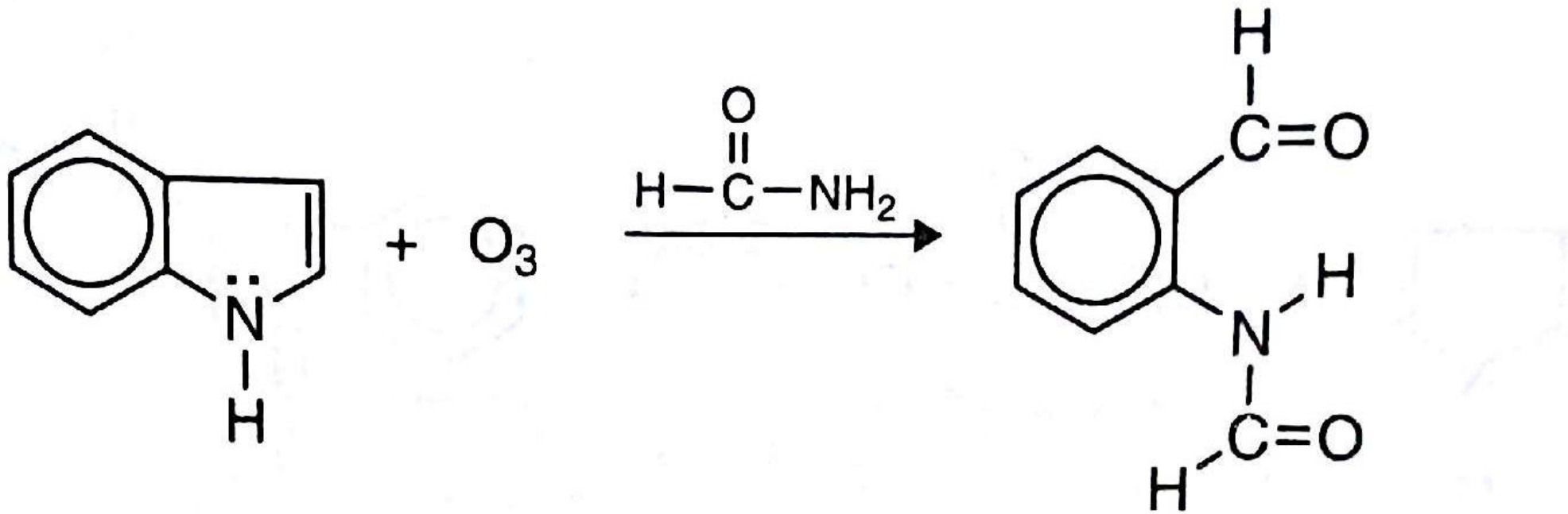
Mannich Reaction:

Indole undergoes Mannich reaction with formaldehyde and dimethylamine to give 3-dimethylaminomethylindole (**Gramine**).



(3) Oxidation

Indole may be oxidized by ozone in formamide to give 2-formamido-benzaldehyde.

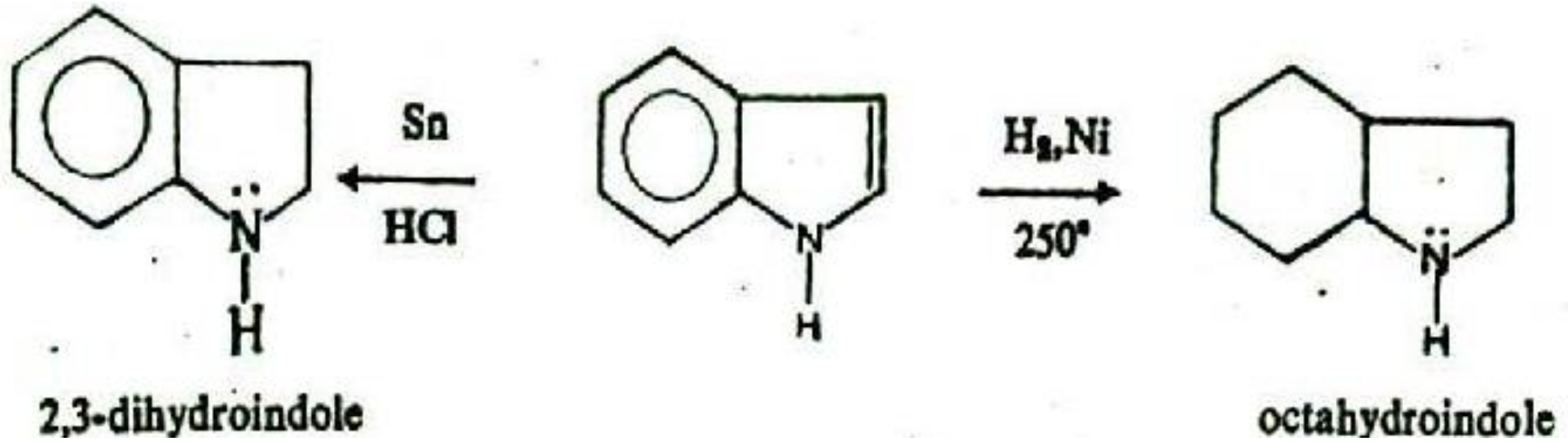


Indole

2-Formamidobenzaldehyde

(4) Reduction

Mild reduction of indole with zinc (or tin) and hydrochloric acid yields 2,3-dihydroindole *(Indoline).* Catalytic reduction hydrogenates both rings and produces ocatahydroindole.



Medicinal Importance of indole

List of drugs containing indole

Drug	*Application*	*Drug*	*Application*	*Drug*	*Application*
Vincristine	Anticancer	**Vincamine**	Vasodilator	**Roxindole**	Schizophrenia
Vinblastine	Anticancer	**Reserpine**	Antihypertensive	**Delavirdine**	Anti-HIV
Vinorelbine	Anticancer	**Peridopril**	Antihypertensive	**Atevirdine**	Anti-HIV
Vindesine	Anticancer	**Pindolol**	Antihypertensive	**Arbidol**	Antiviral
Mitraphylline	Anticancer	**Binedaline**	Antidepressant	**Zafirlukast**	Anti-Asthmatic
Cediranib	Anticancer	**Amedalin**	Antidepressant	**Bucindolol**	β-Blockers
Panobinostat	Anti-leukamic	**Oxypertine**	Antipsychotic	**Pericine**	Opioid agonist
Apaziquone	Anticancer	**Siramesine**	Antidepressant	**Mitragynine**	Opioid agonist
Tropisetron	Antiemetic	**Indalpine**	Antidepressant	**Pravadoline**	Analgesic
Doleasetron	Antiemetic	**Yohimbine**	Sexual Disorder	**Bufotenidine**	Toxin
Oglufanide	Immunomodulatory	**Indomethacin**	Anti-inflammatory	**Proamanullin**	Toxin