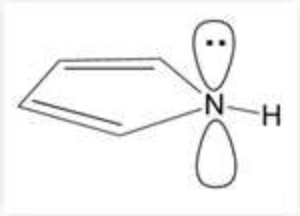
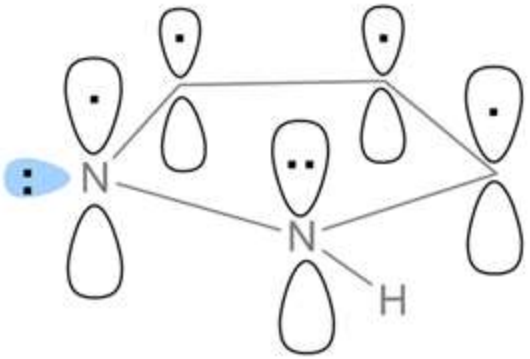
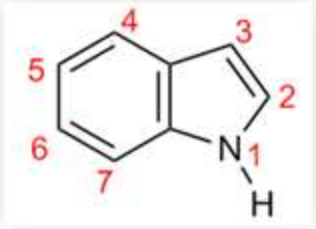
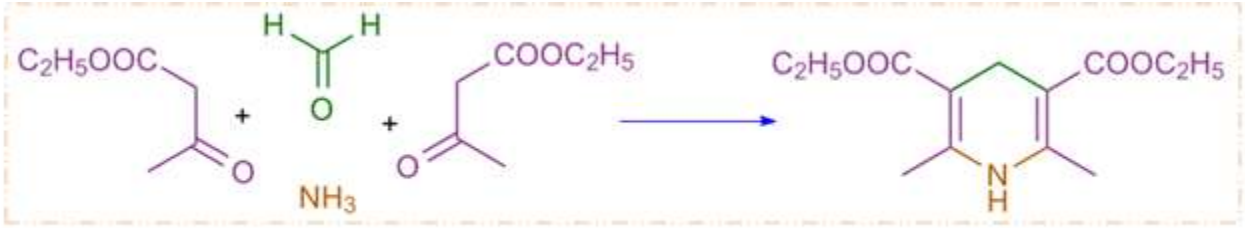


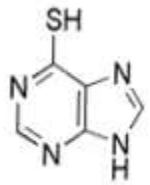




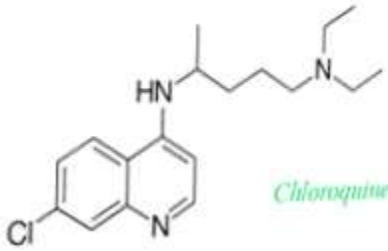
HETEROCYCLIC

C O M P O U N D S

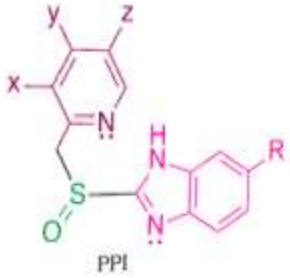




6-Mercaptopurine



Chloroquine

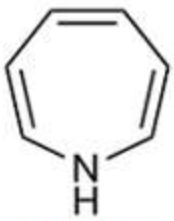


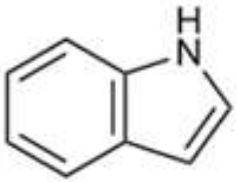
PPI

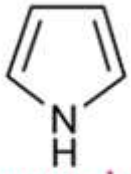
Amit Z Chaudhari

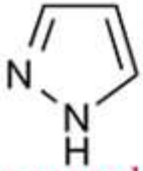
CONTENT

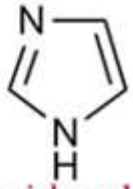
Properties, synthesis, reactions & medicinal uses of…


azepine

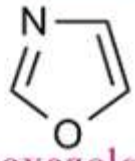

indole

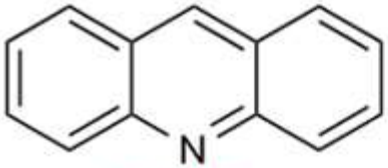

pyrrole


pyrazole


imidazole

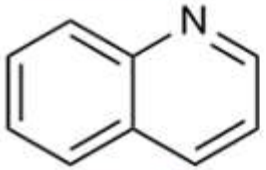

furan

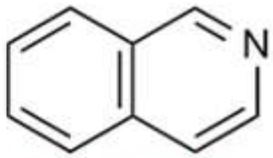

oxazole

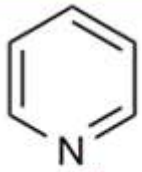

acridine

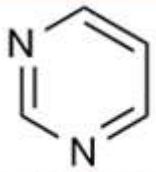

thiophene

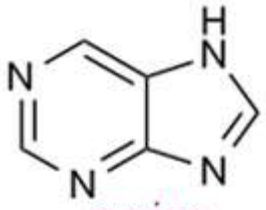

thiazole


quinoline


isoquinoline


pyridine

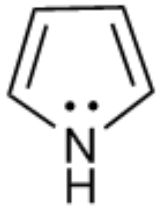

pyrimidine

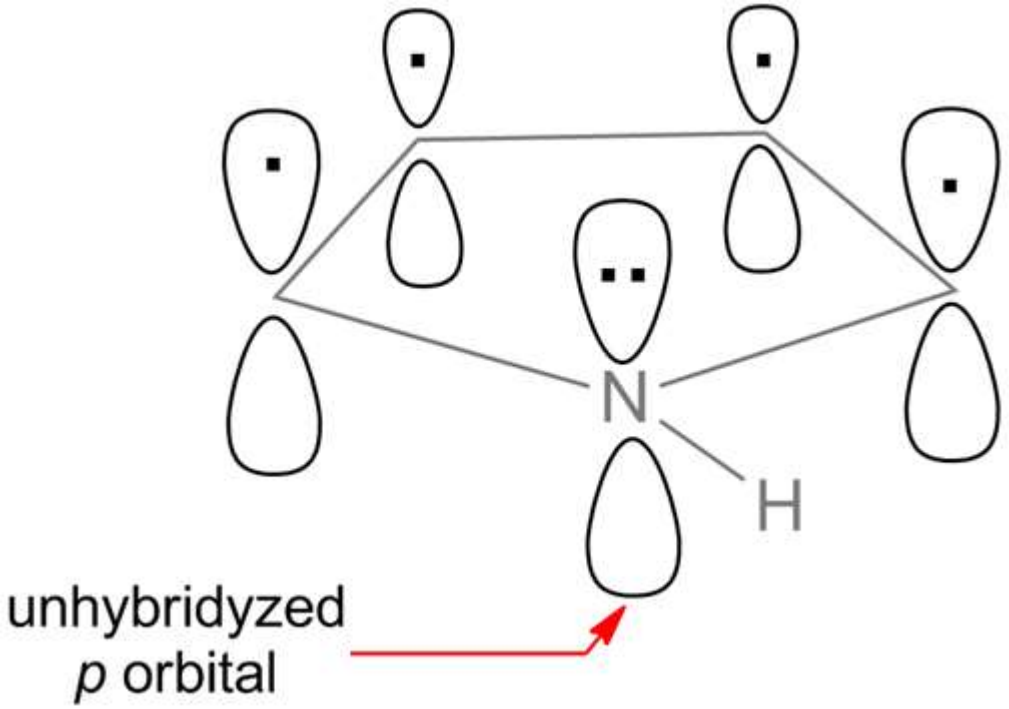

purine

PYRROLE

Properties

1. Aromaticity





PYRROLE

Properties

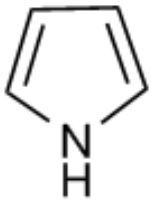
1. Aromaticity

- Pyrrole have 4 C and 1 N , all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar pyrrole ring structure.
- Each ring atom also contains unhybridized *p* orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here *p* orbitals are parallel to each other, so overlapping btwn *p* orbitals is possible.
- the total nu of non bonding e- are 6 (4 of four C, 2 from one N)
- The resonance of 6 e- follows the Hückel's rule
- So the pyrrole is aromatic .

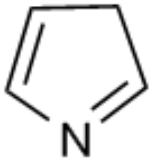
Properties

2. Tautomerism

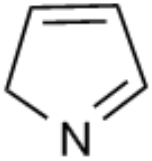
- Rapid migration of hydrogen from N to the C.



1*H*-pyrrole

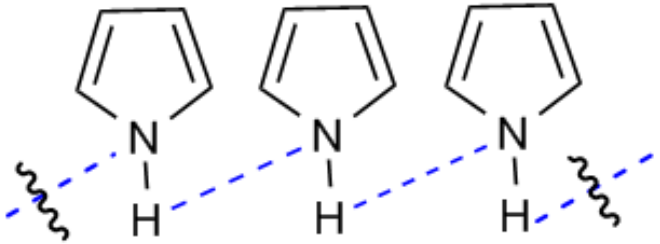


3*H*-pyrrole

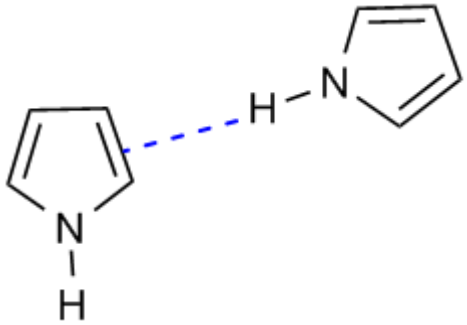


2*H*-pyrrole

3. Hydrogen bonding



Intramolecular H-bonding
(rise b.p.)

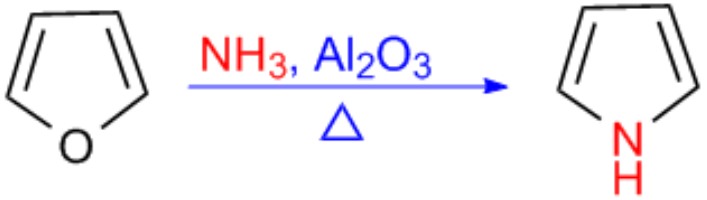


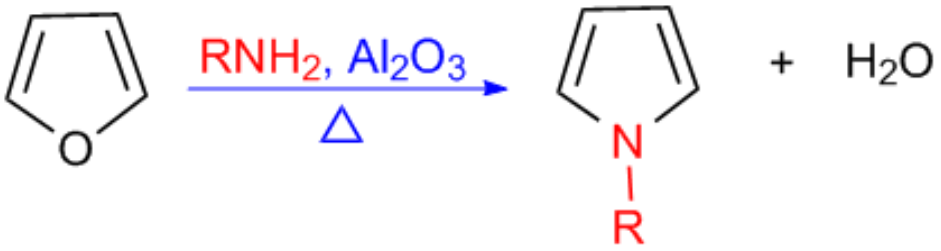
Intramolecular H-bonding
btwn N-H & π- e- system

Synthesis

1. From Furans

- Industrial process
- Passing furan over ammonia in presence of alumina as catalyst at high temp.





Synthesis

2. Paal-Knorr synthesis

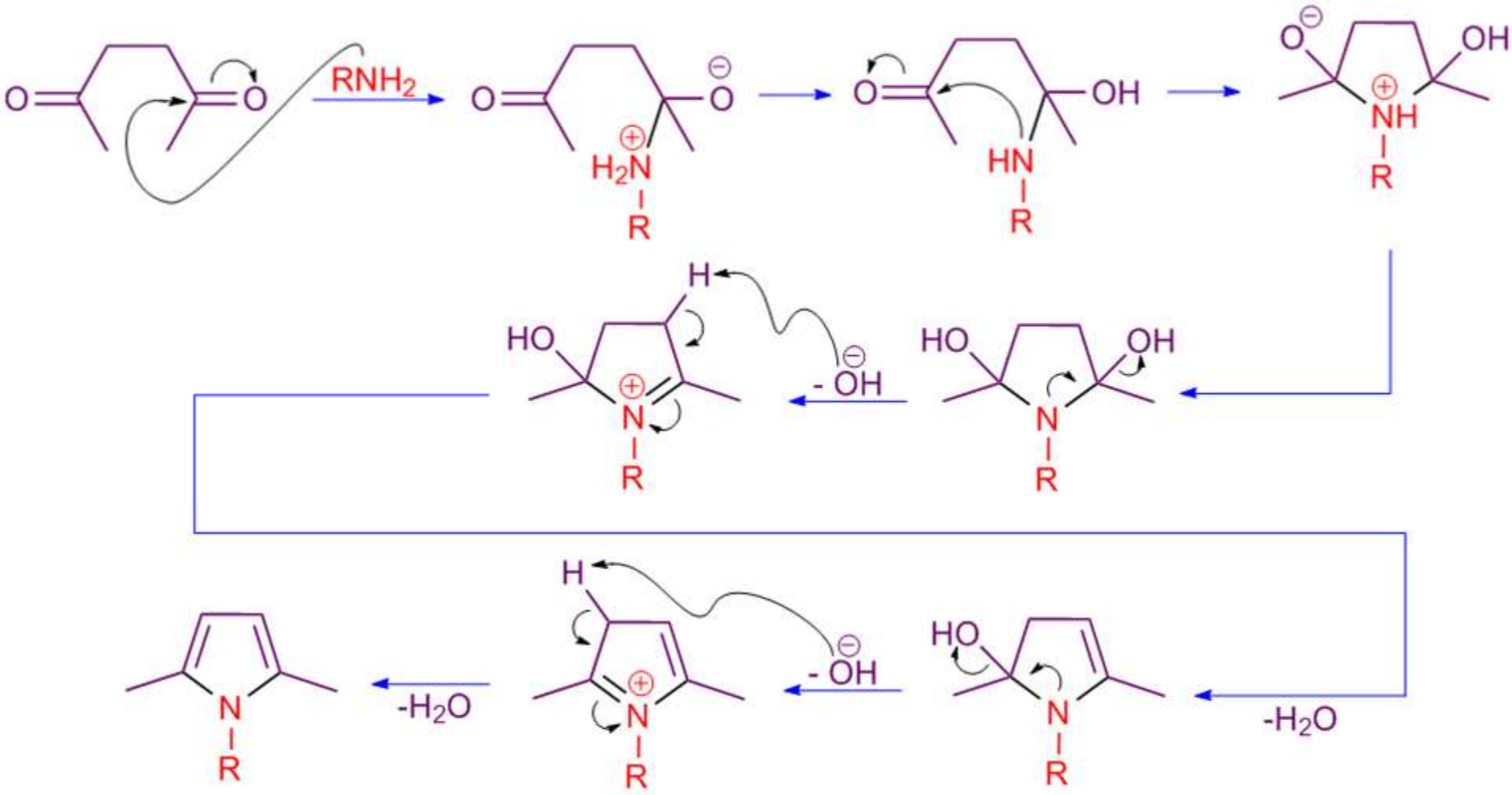
- 1,4 - Dicarbonyl compounds react with ammonia *or* primary amines to give pyrroles.

Mechanism

- Successive nucleophilic additions of the amine nitrogen to each of the two carbonyl carbon atoms, imine formation and the dehydration represent the net course of the synthesis.

Synthesis

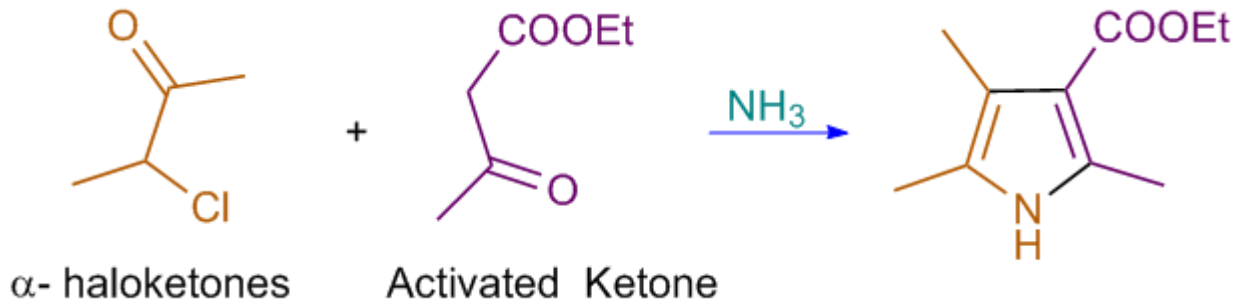
2. Paal-Knorr synthesis



Synthesis

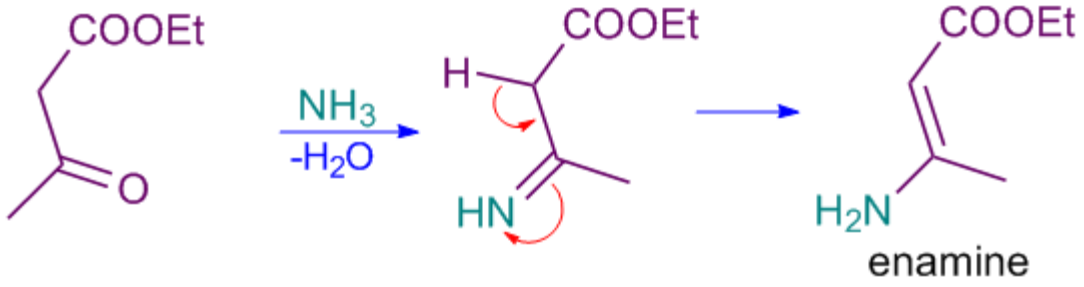
3. Hantzsch Pyrrole synthesis

- Reaction of α-haloketones with β-ketoesters and ammonia results in pyrrole



α- haloketones Activated Ketone

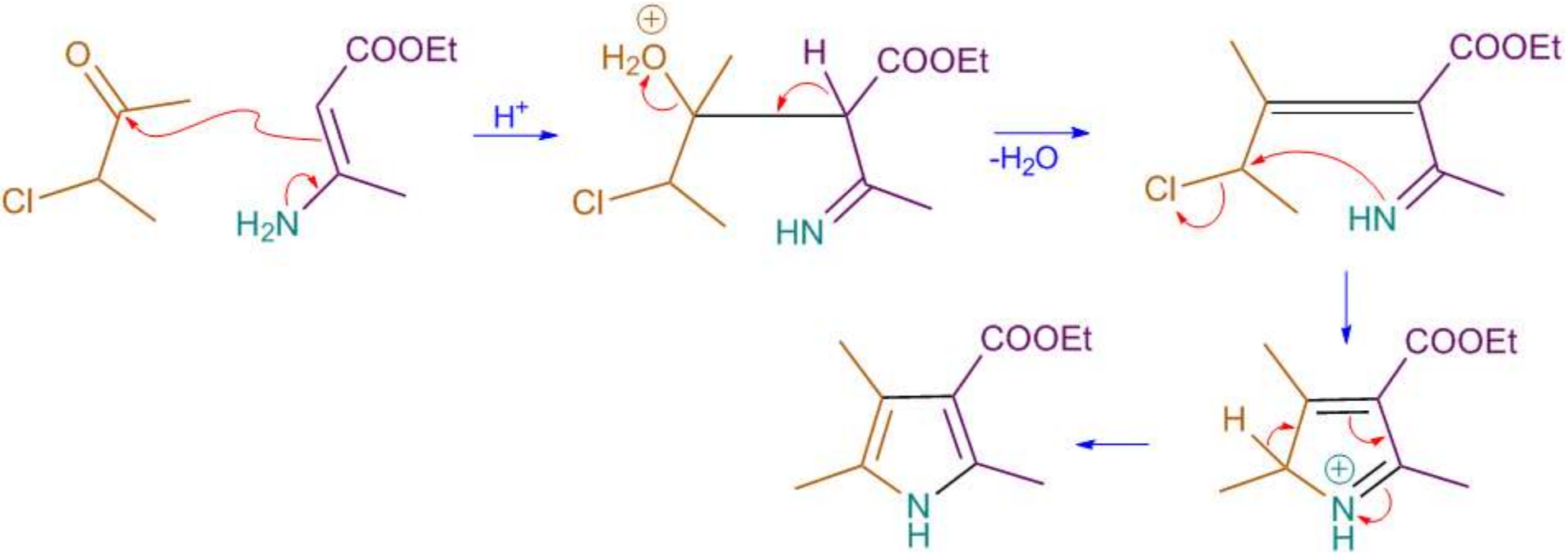
Mechanism



enamine

Synthesis

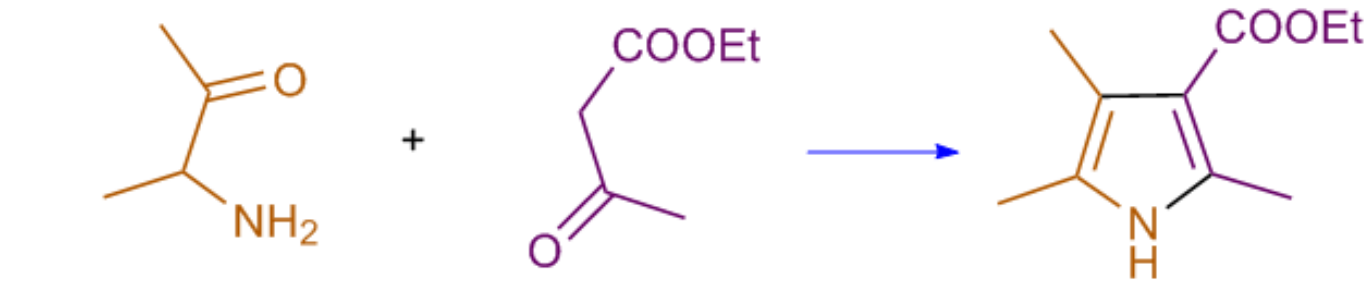
3. Hantzsch Pyrrole synthesis



Synthesis

4. Knorr synthesis

- Condensation of α- aminocarbonyl component with 2nd component containing an electron-withdrawing group (e.g. an ester) α to a carbonyl group

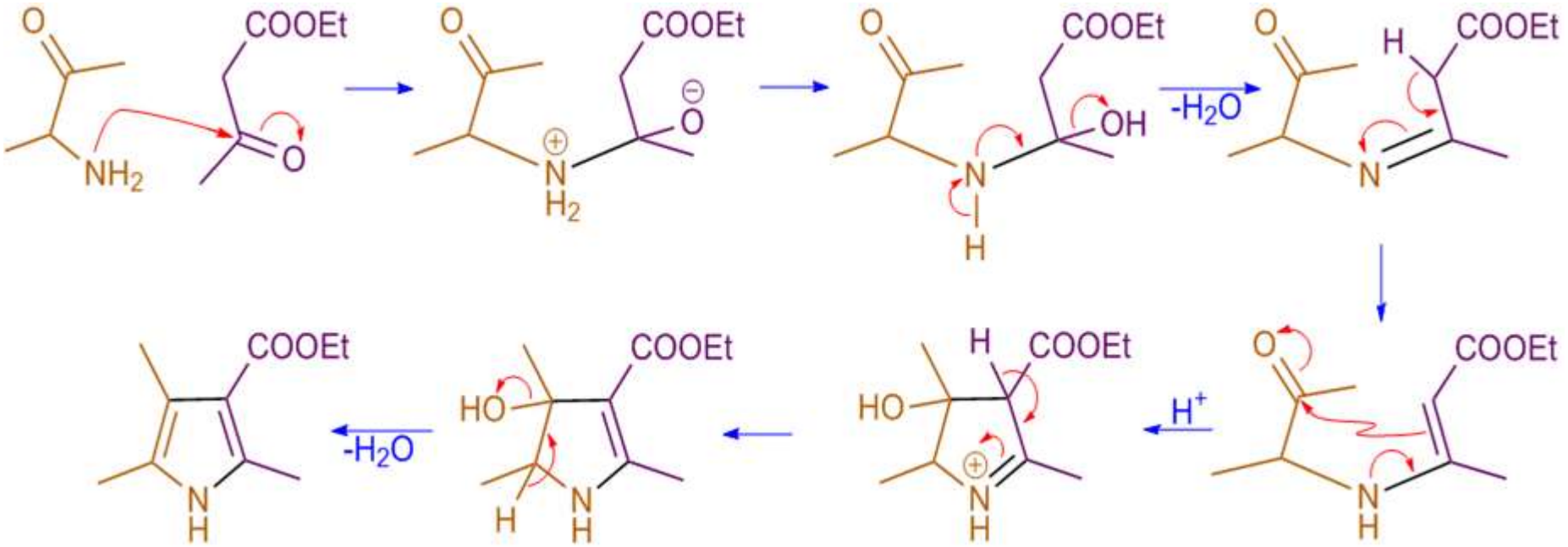


α- Aminocarbonyl compounds Activated Ketone

Synthesis

4. Knorr synthesis

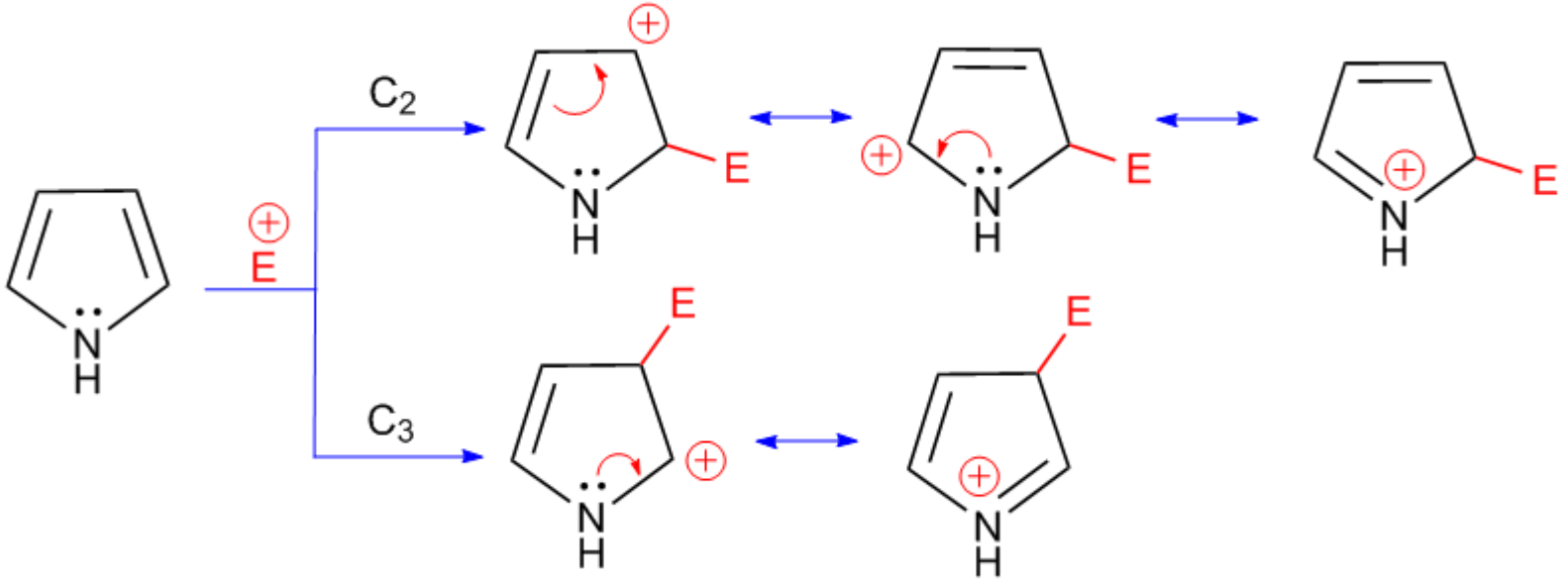
Mechanism



Reactions

1. Electrophilic substitution

Pyrrole undergoes electrophilic substitution reaction at 2nd position



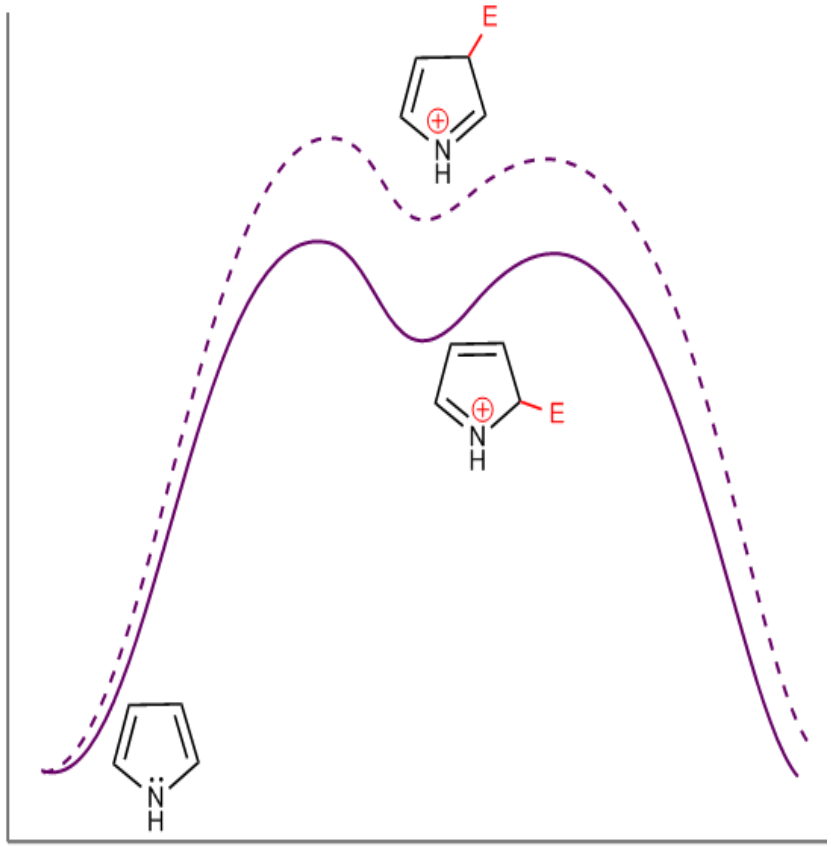
2 reasons…

- C2 attack gives more resonance contributing structures than C3.
- Extra stable contributing structure generates upon C2 attack

Reactions

1. Electrophilic substitution

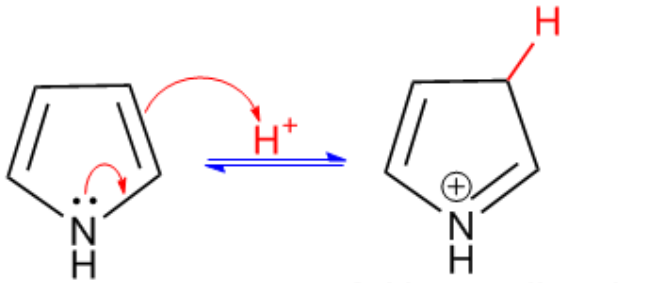
Pyrrole undergoes electrophilic substitution reaction at 2nd position

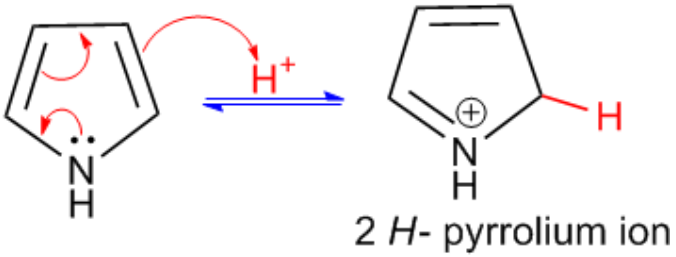


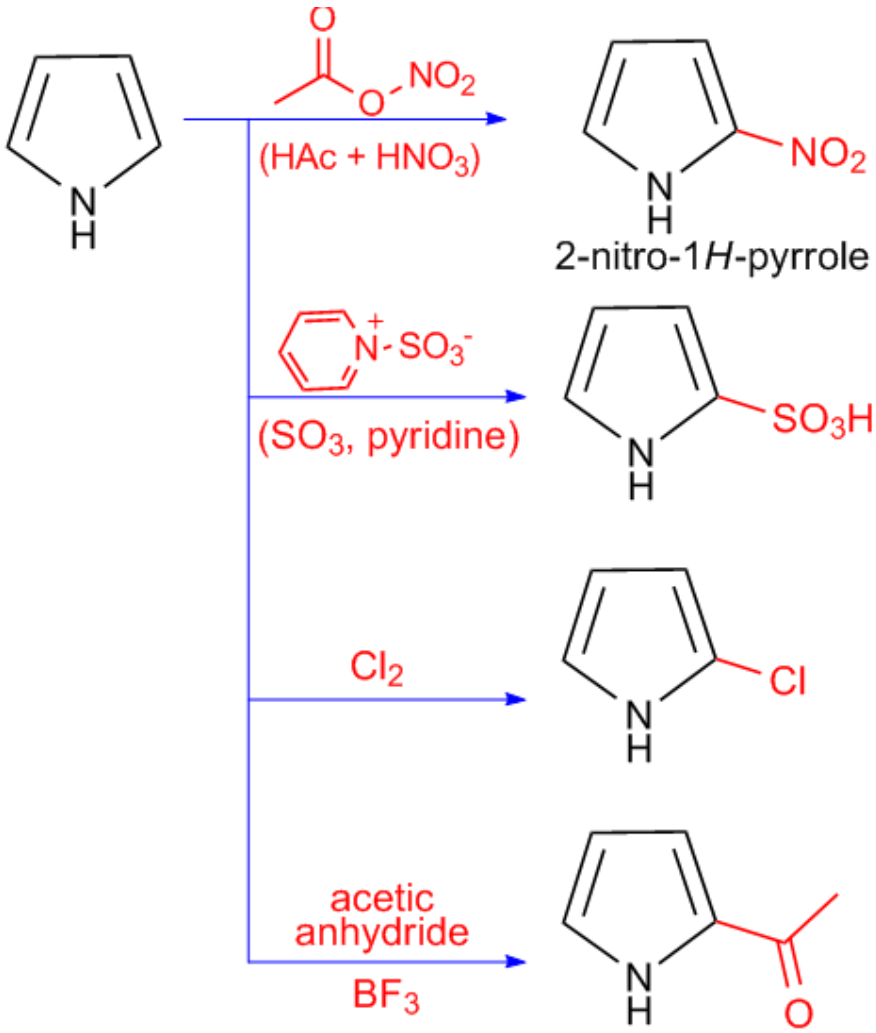
- Energy diagram shows C2 attack forms more stable intermediate than C3
- Hence C2 preferred over C3

Reactions

1. Electrophilic substitution

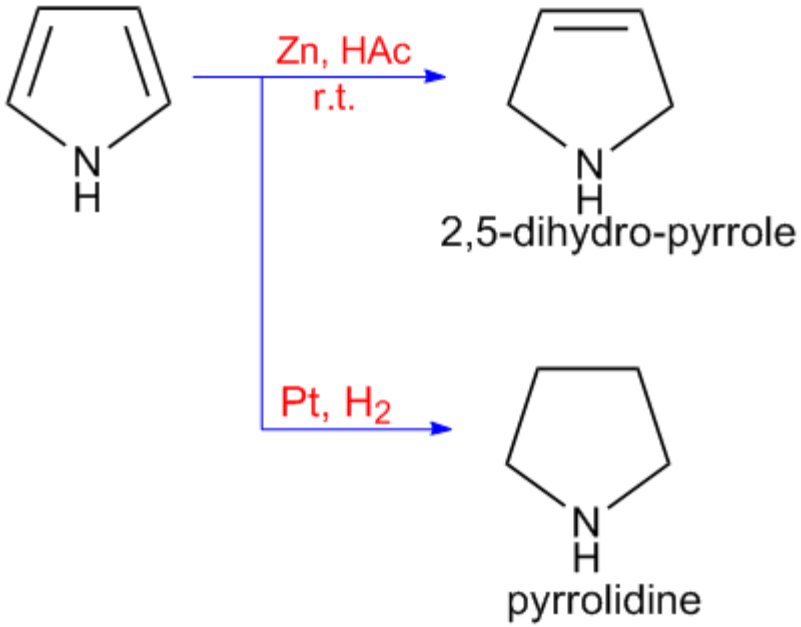






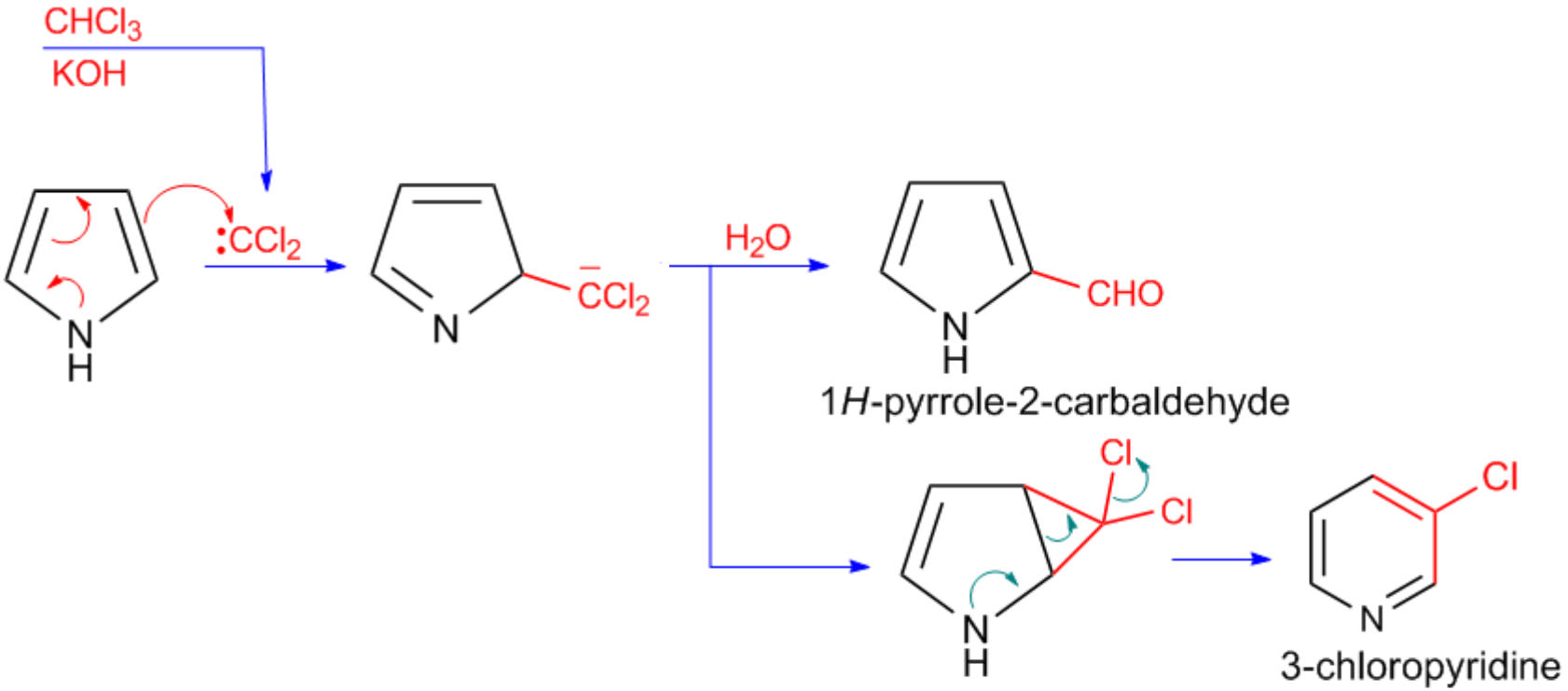
Reactions

2. Reduction

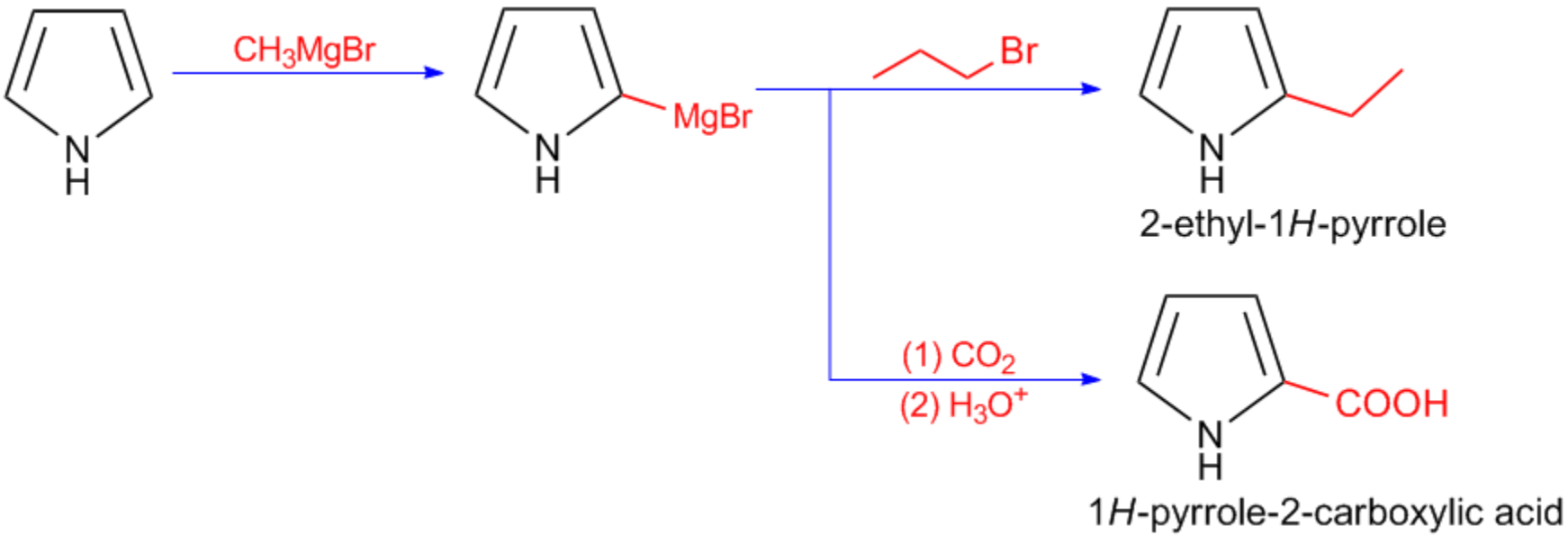


Reactions

3. Reimer Tiemann reaction

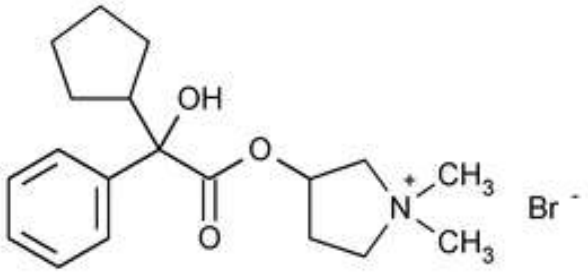


Reactions

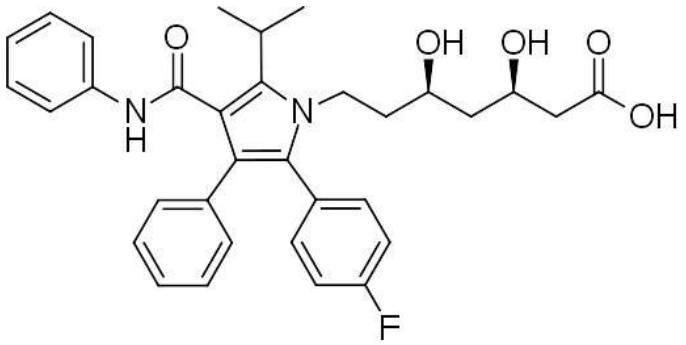

CH3MgBr
MgBr
Br
2-ethyl-1H-pyrrole
(1) CO2
(2) H3O+
COOH
1H-pyrrole-2-carboxylic acid

Medicinal uses

(1) *Glycopyrrolate* , anticholinergic drug: used in Peptic ulcer

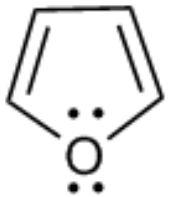


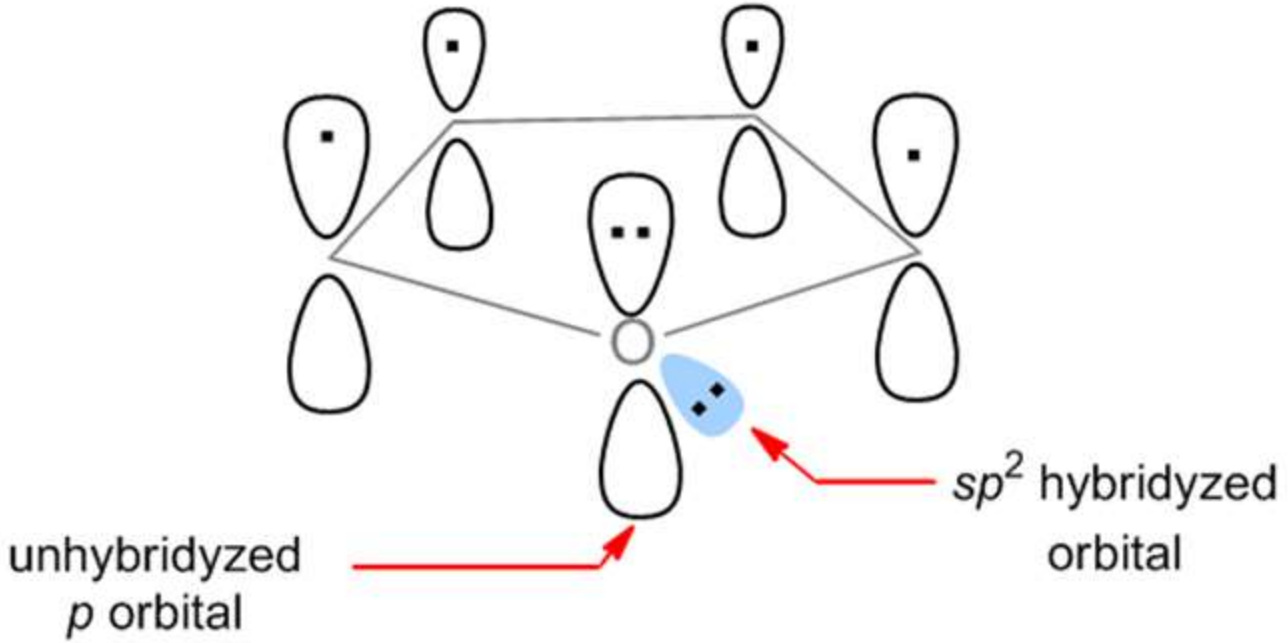
(2) *Atorvastatin* used in management of high cholesterol and high blood pressure.



Properties

1. Aromaticity





Properties

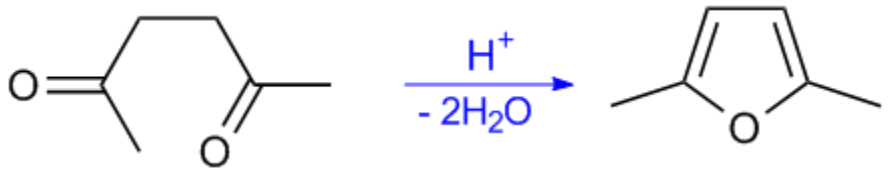
1. Aromaticity

- Furan have 4 C and 1 O , all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar furan ring structure.
- Each ring atom also contains unhybridized *p* orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here *p* orbitals are parallel to each other, so overlapping btwn *p* orbitals is possible.
- the total nu of non bonding e- are 6 (4 of four C, 2 from one O)
- The resonance of 6 e- follows the Hückel's rule
- So the furan is aromatic .

Synthesis

1. Paal-Knorr synthesis of furan

- Acid catalysed ,cyclising dehydration of 1,4 - dicarbonyl compounds.

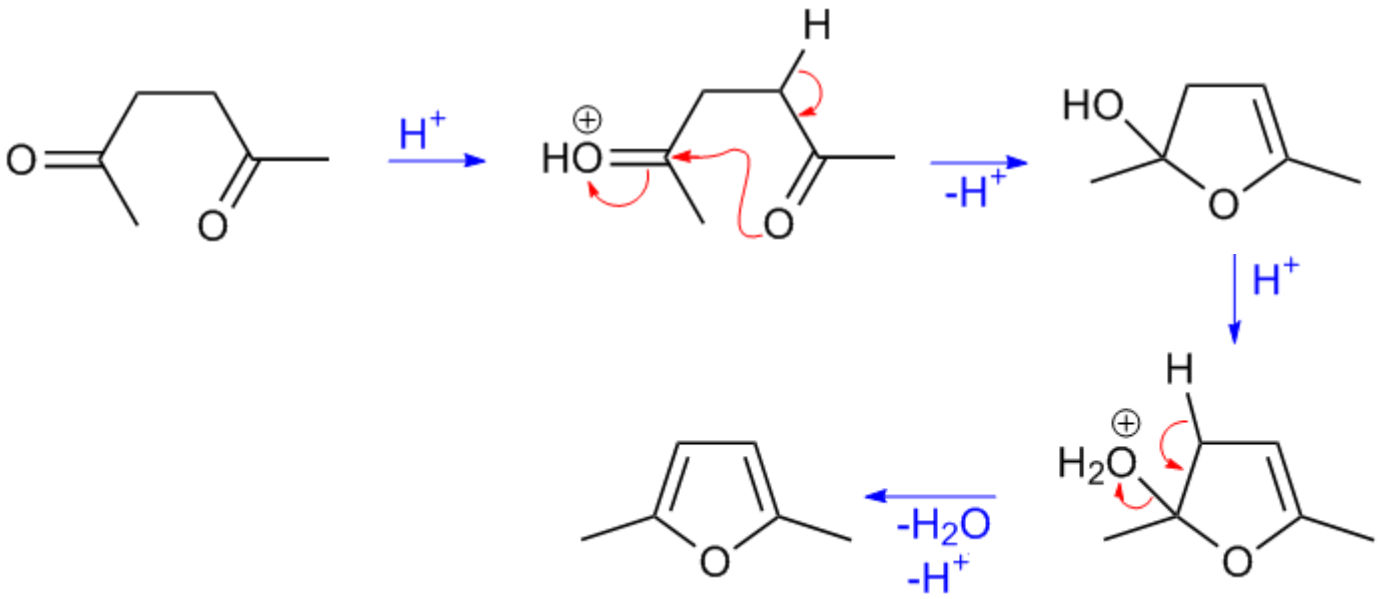


1,4 - Dicarbonyl compounds

Synthesis

1. Paal-Knorr synthesis of furan

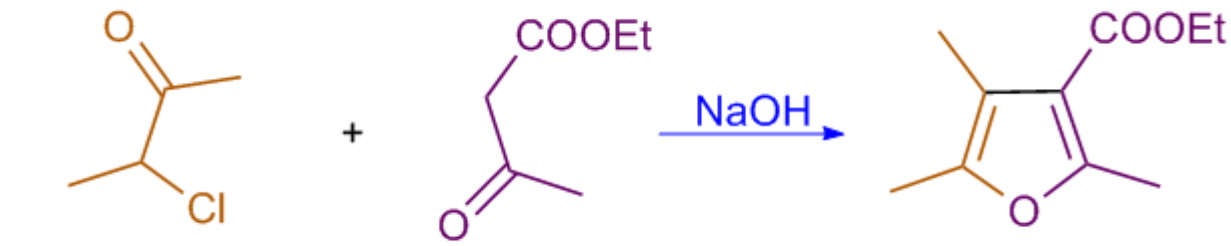
Mechanism



Synthesis

2. Feist – Benary Synthesis

- Reaction of α- haloketones with β-ketoesters in the presence of a base (not ammonia) to give furans.

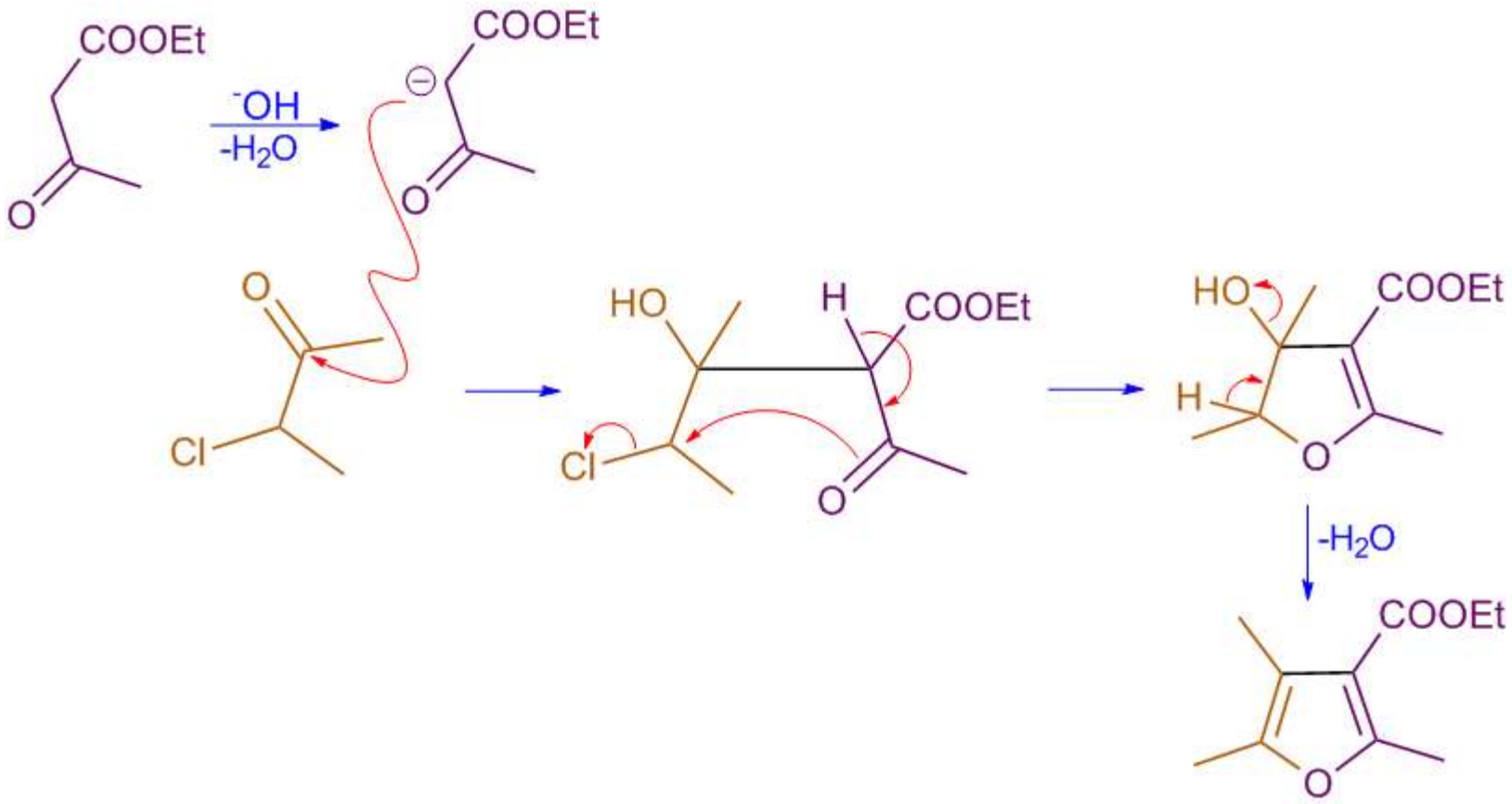


α- haloketones Activated Ketone

Synthesis

2. Feist – Benary Synthesis

Mechanism

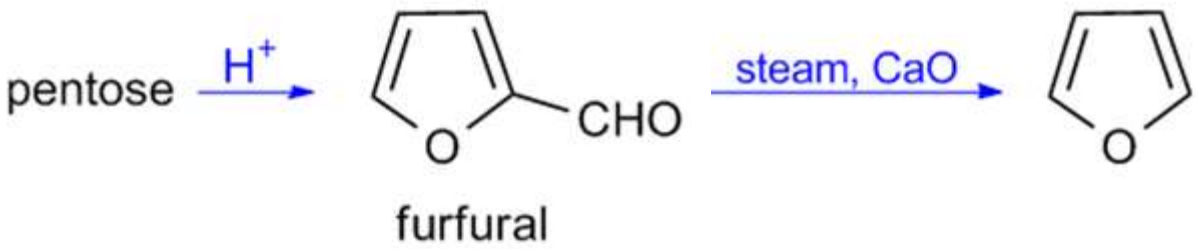


Synthesis

3. From carbohydrate

Step_1: distillation of CH with sulfuric acid

Step_2: catalytic decomposition of furfural in steam

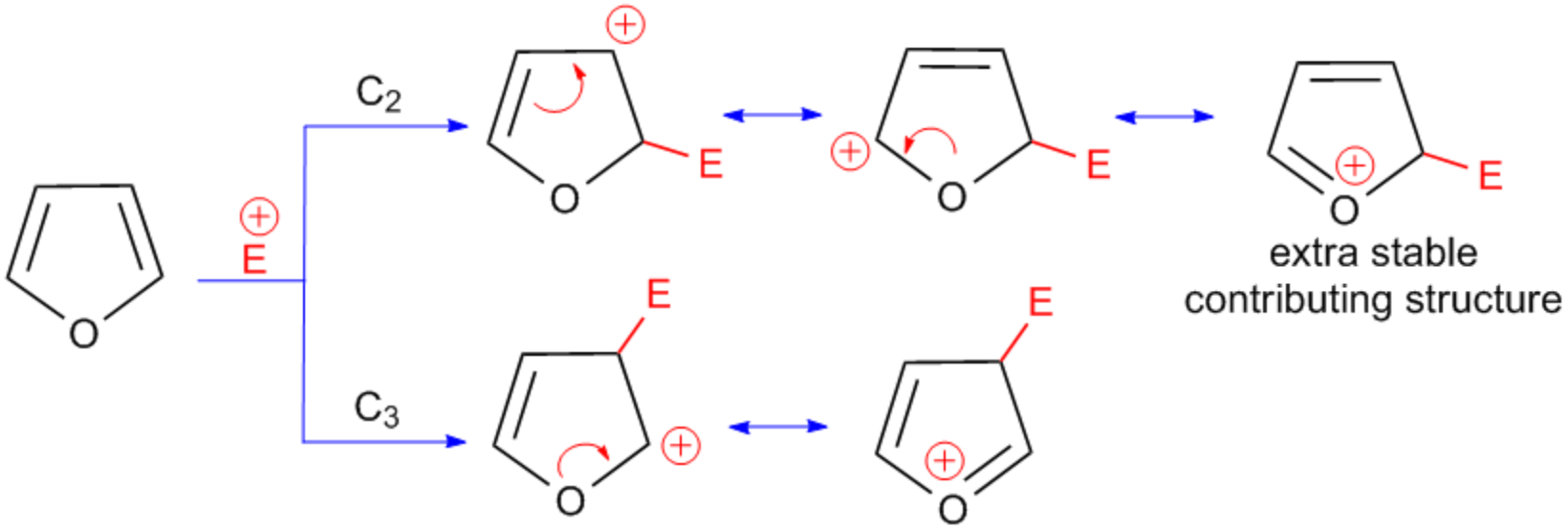


furfural

Reactions

1. Electrophilic substitution

furan undergoes electrophilic substitution reaction at 2nd position

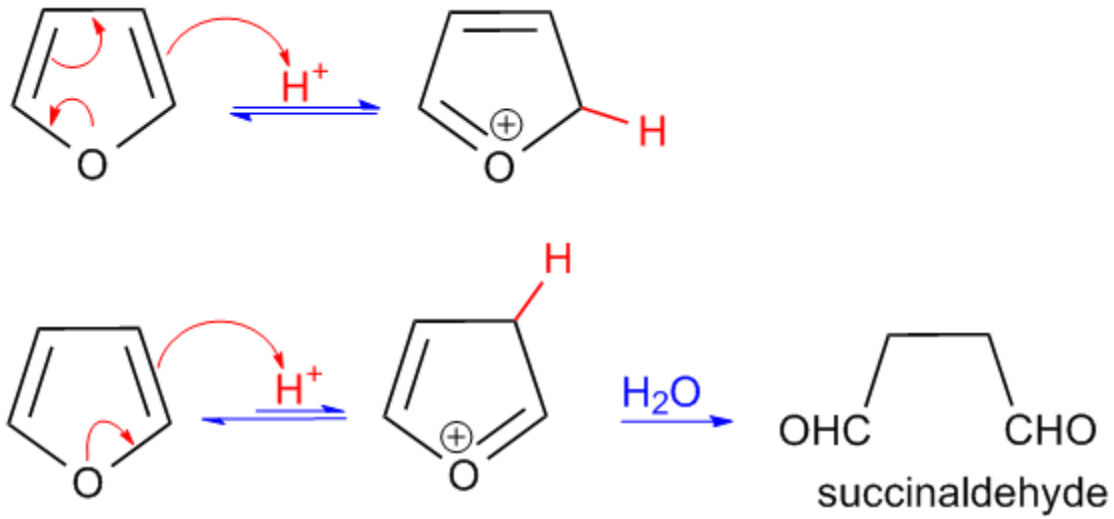


2 reasons…

- C2 attack gives more resonance contributing structures than C3.
- Extra stable contributing structure generates upon C2 attack

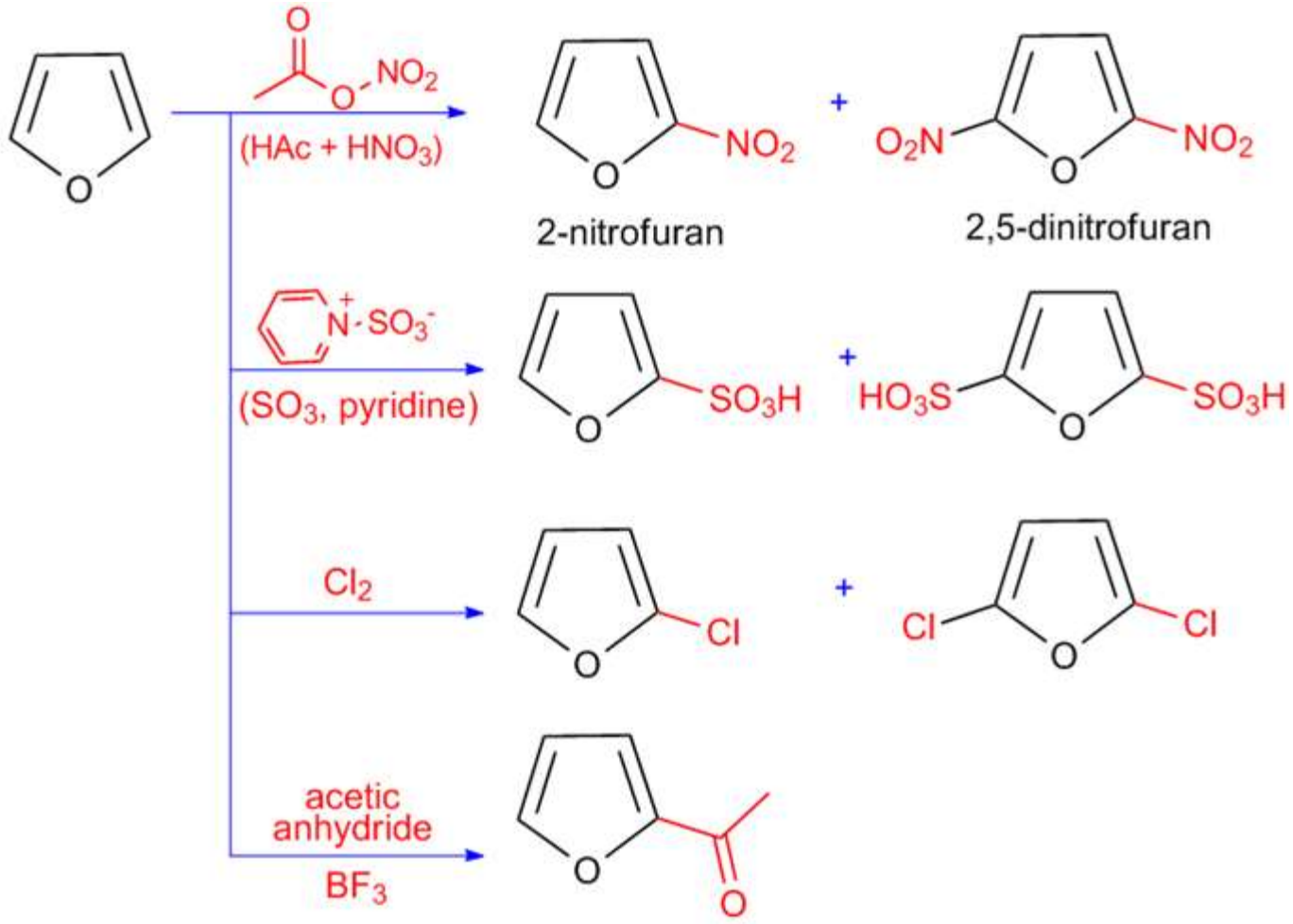
Reactions

1. Electrophilic substitution



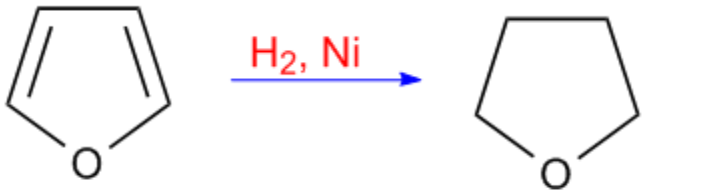
Reactions

1. Electrophilic substitution



Reactions

2. Reduction

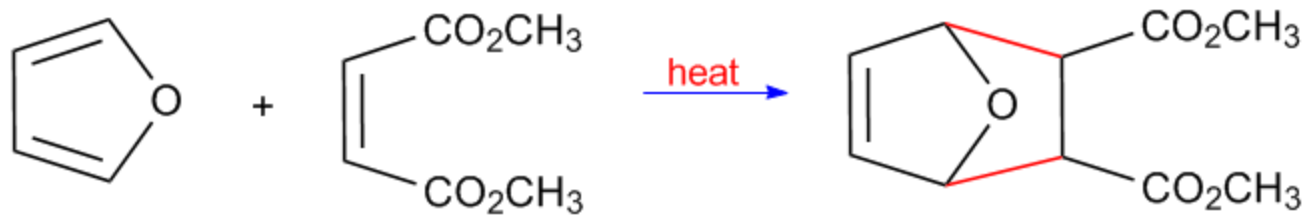


tetrahydrofuran

Reactions

3. Diels-Alder reaction

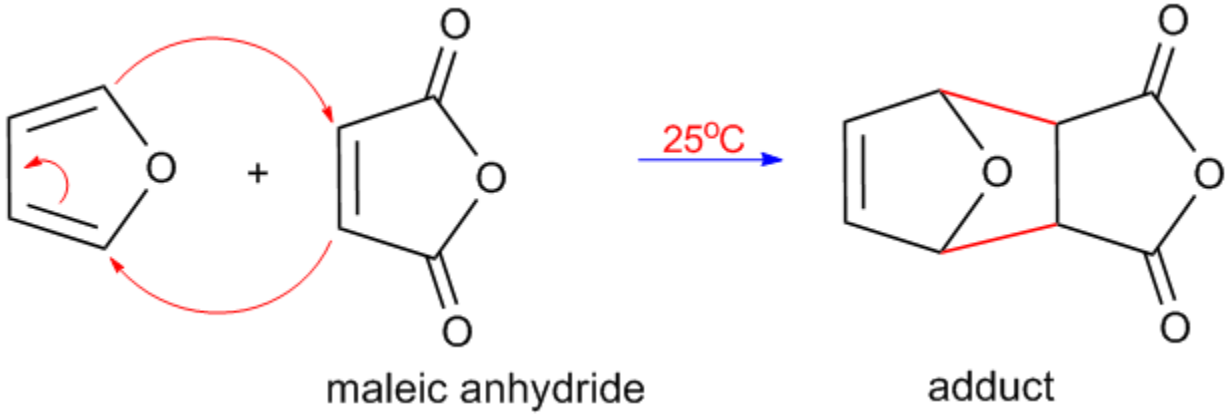
- O atom is highly electronegative, so the delocalization of lone pair e- (in aromatic system of furan) is not overly effective.
- Thus…Furan can behave as a dienophile and gives 4 + 2 cycloaddition.



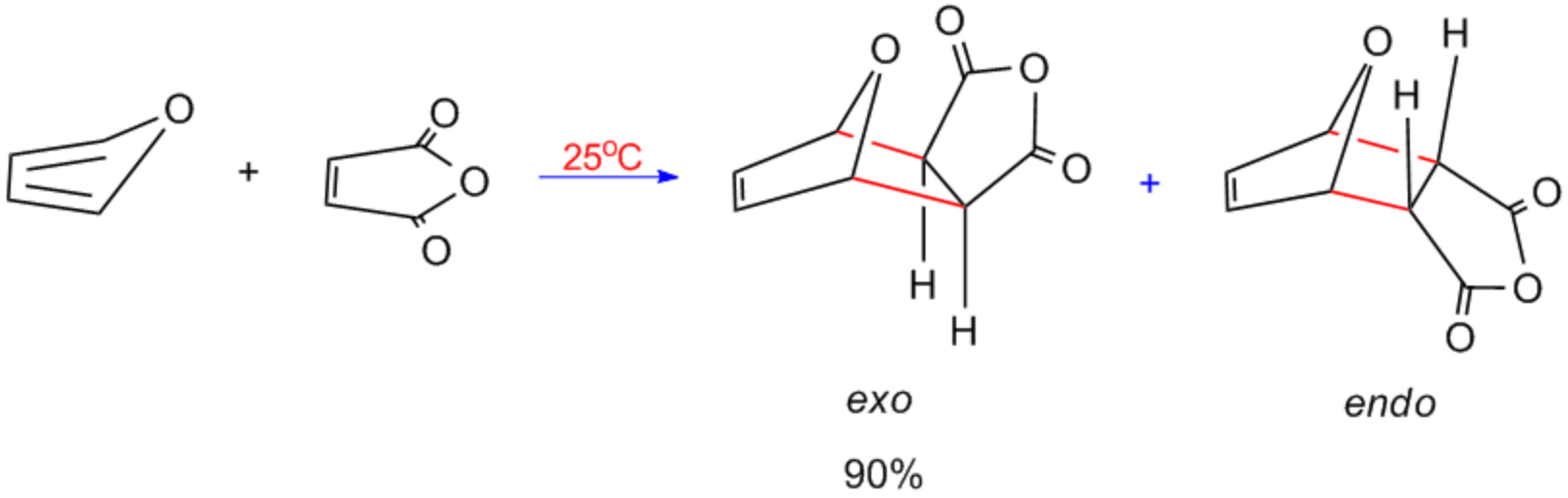
dimethyl maleate adduct

Reactions

3. Diels-Alder reaction



maleic anhydride adduct



exo *endo*

90%

Reactions

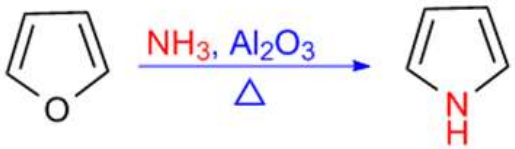
4. Pyrrole synthesis

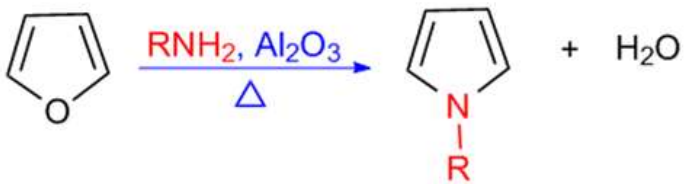
PYRROLE

Synthesis

1. From Furans

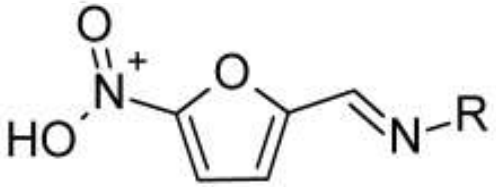
- Industrial process
- Passing furan over ammonia in presence of alumina as catalyst at high temp.



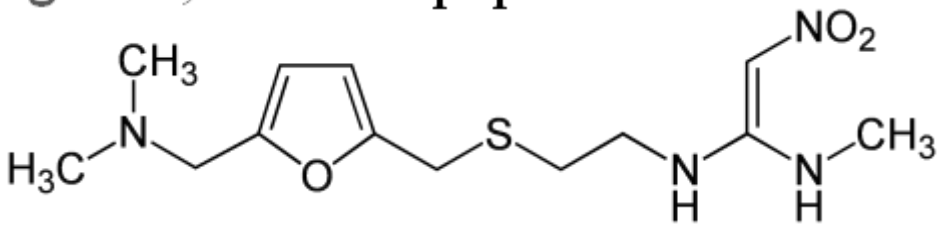


Medicinal uses

(1) Nitrofurans: *Nitrofurazone, Furazolidone, Nitrofurantoin* , Anti-infective Agents: used as an antiprotozoal agent to treat trypanosomiasis and leishmaniasis



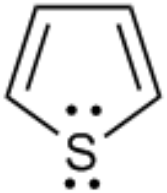
(2) *Ranitidine:* Antihistaminic Agents, used in peptic ulcer

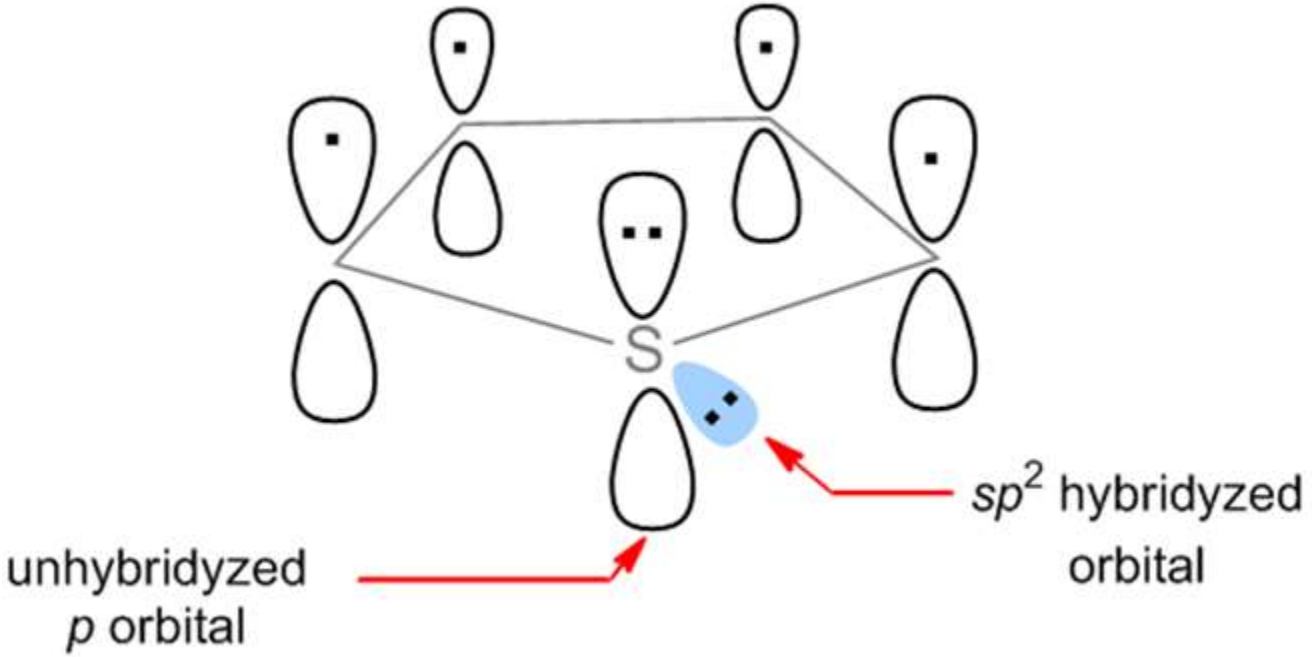


THIOPHENE

Properties

1. Aromaticity





THIOPHENE

Properties

1. Aromaticity

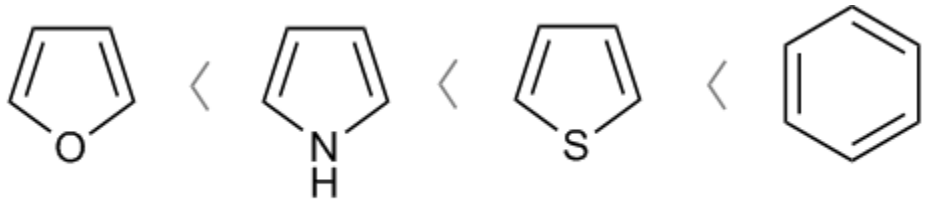
- Thiophene have 4 C and 1 S , all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar thiophene ring structure.
- Each ring atom also contains unhybridized p orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here p orbitals are parallel to each other, so overlapping btwn p orbitals is possible.
- the total nu of non bonding e- are 6 (4 of four C, 2 from one S)
- The resonance of 6 e- follows the Hückel's rule
- So the thiophene is aromatic .

Properties

1. Aromaticity

Furan is less aromatic / thiophene is more aromatic

Order of aromaticity



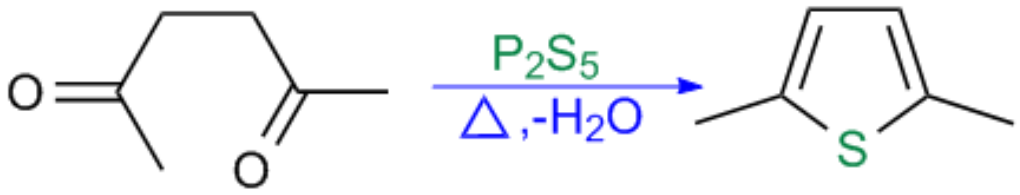
	furan	pyrrole	thiophene	benzene
Resonance energy	16	22	29	36

- This order depends on order of electronegativity of heteroatoms
- The more e-ve is the atom → the more tightly holds its lone pair of e- → more reduce the *ease of delocalization (aromaticity)*.
- So most e-ve O in furan most decrease aromaticity.
  & Least e-ve S in thiophene least decrease aromaticity.
- Thus ….

Synthesis

1. Paal-Knorr synthesis of thiophene

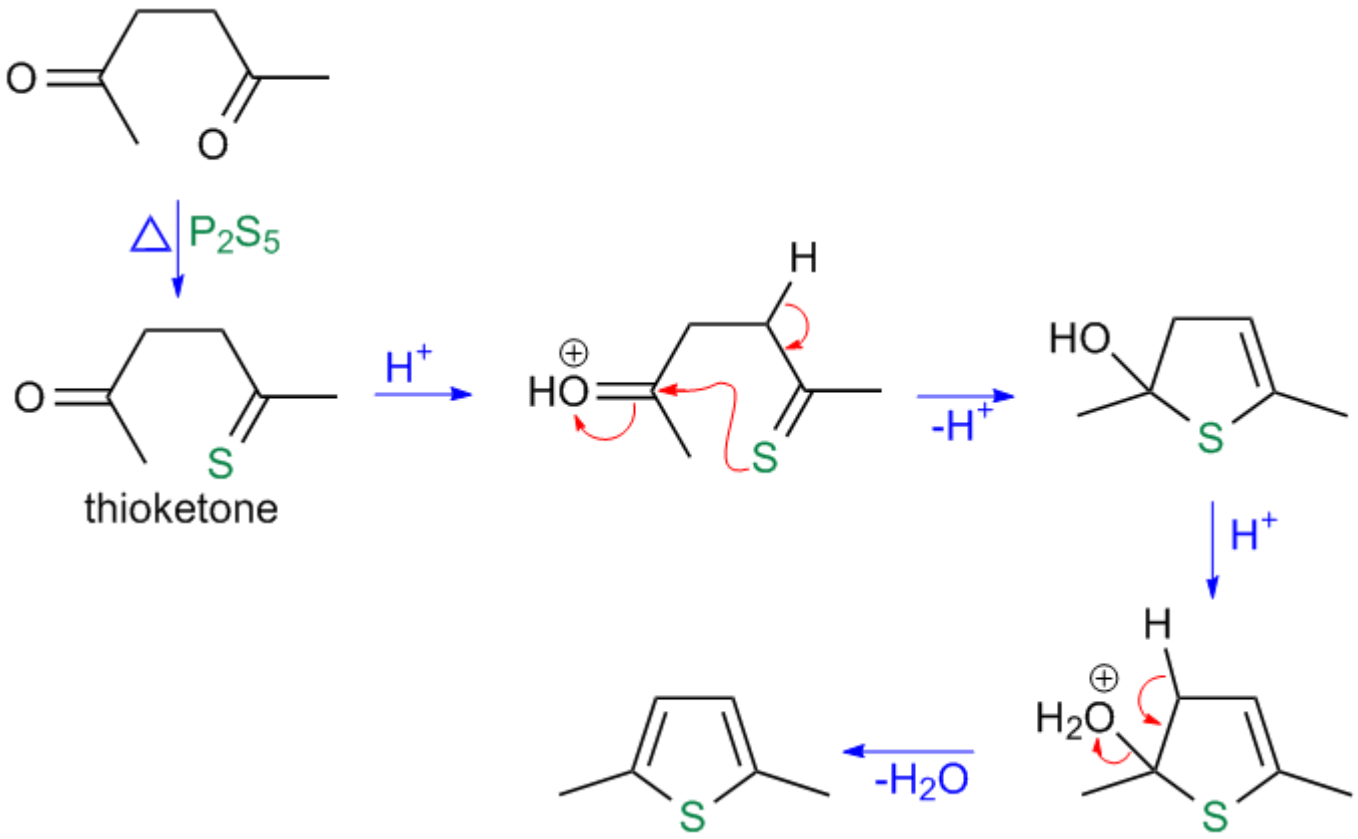
- The condensation of 1,4-dicarbonyl compounds with sulfur sources gives thiophene.



Synthesis

1. Paal-Knorr synthesis of furan

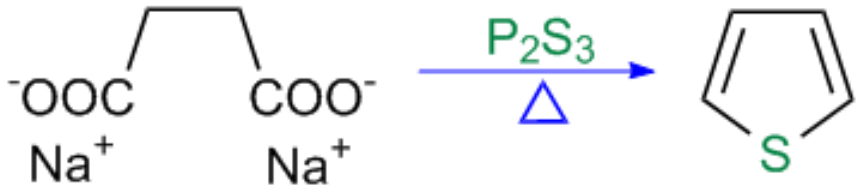
Mechanism



Synthesis

2. From sod. succinate

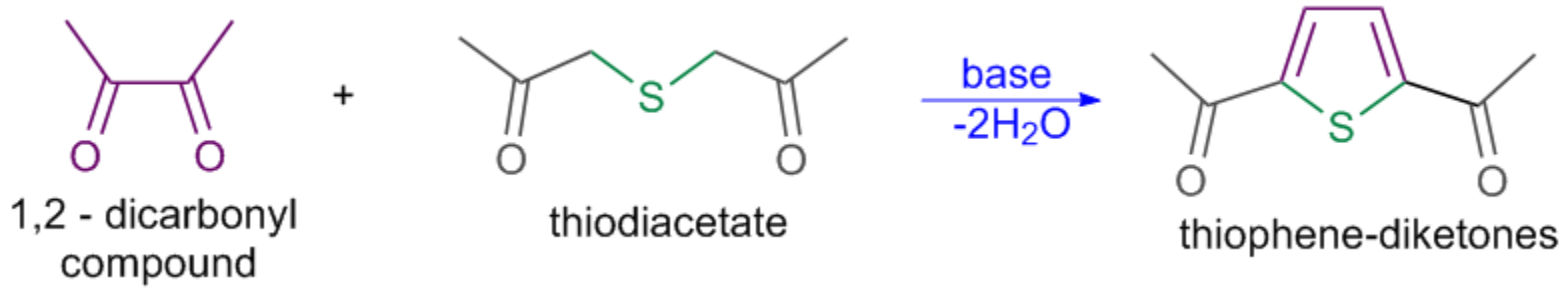
- Laboratory synthesis
- Heating a mix. of sod. succinate and phosphorus trisulfide.

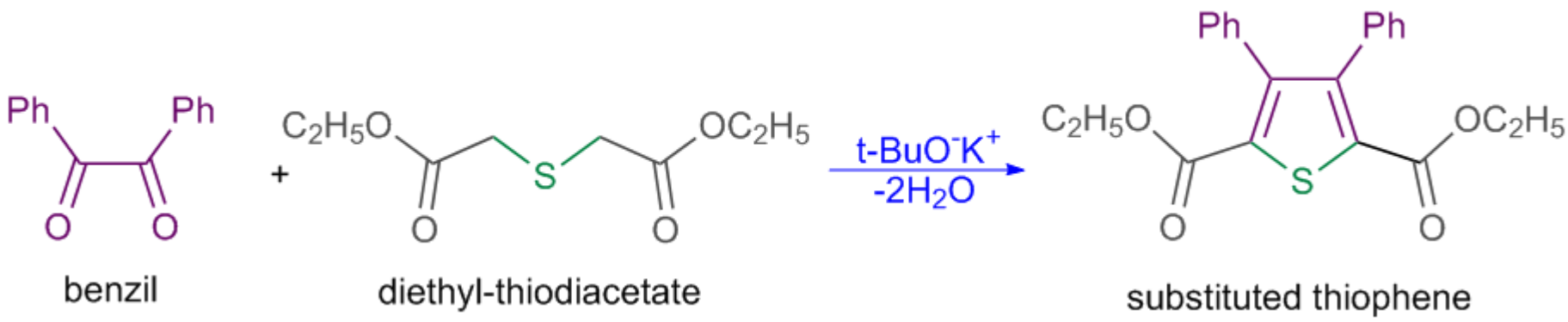


Synthesis

3. Hinsberg Synthesis

- Condensation between a 1,2 - dicarbonyl compound and diethyl thiodiacetate in presence of strong base give thiophene 2,5 - diacids (- diketone)

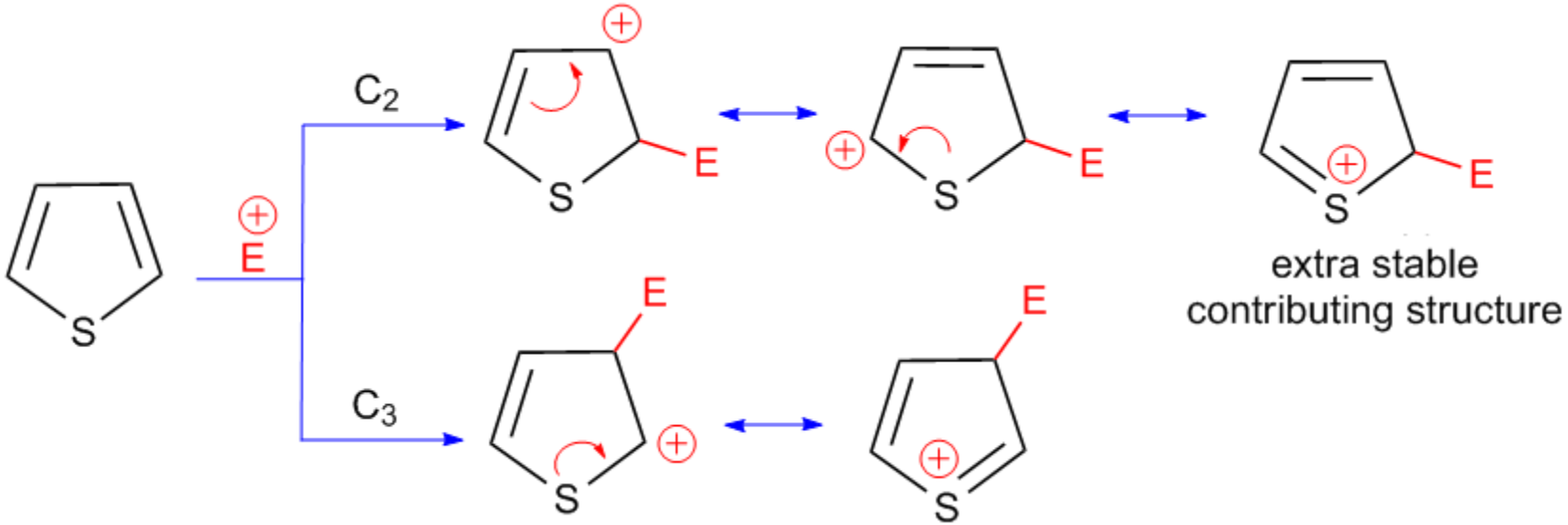




Reactions

1. Electrophilic substitution

thiophene undergoes electrophilic substitution reaction at 2nd position



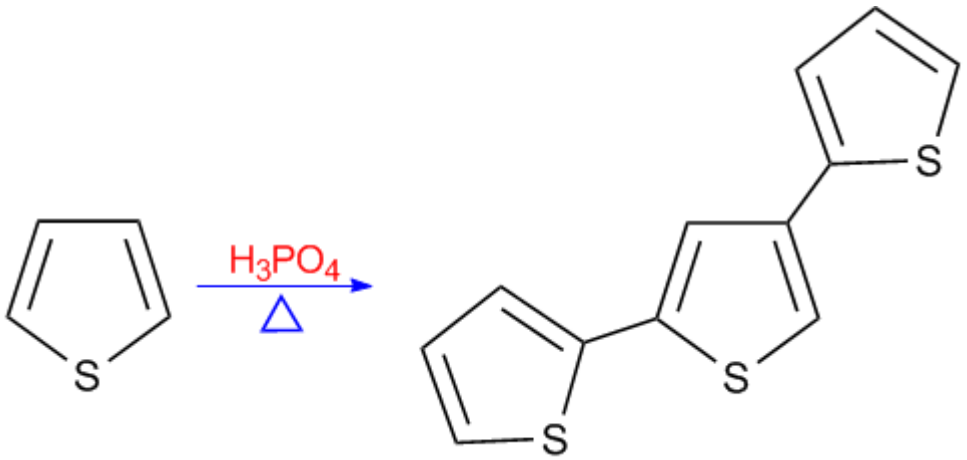
2 reasons…

- C2 attack gives more resonance contributing structures than C3.
- Extra stable contributing structure generates upon C2 attack

Reactions

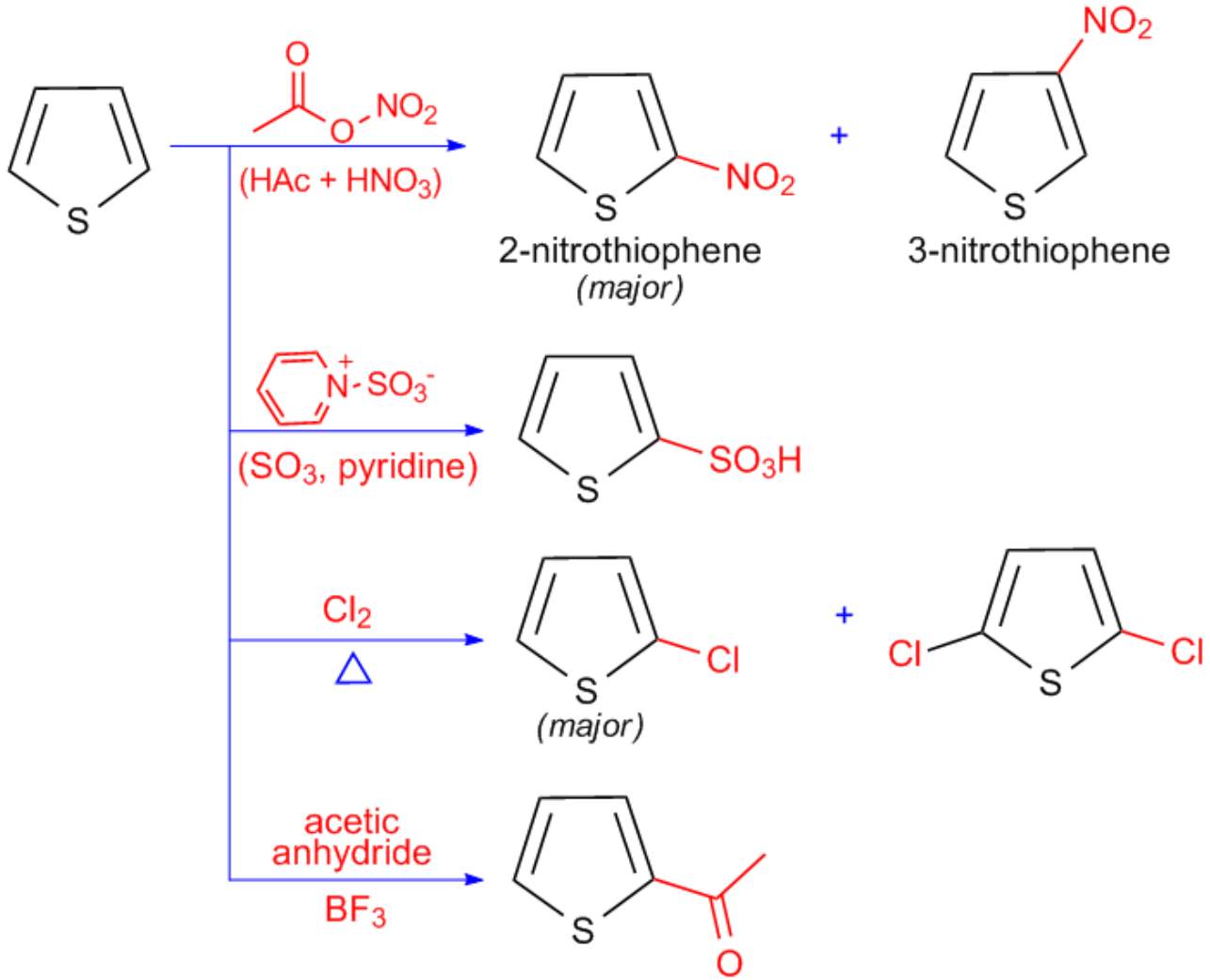
1. Electrophilic substitution

- Very strongly acidic conditions lead to acid – catalysed polymerization.
- The action of hot phosphoric acid on thiophene leads to a trimer.



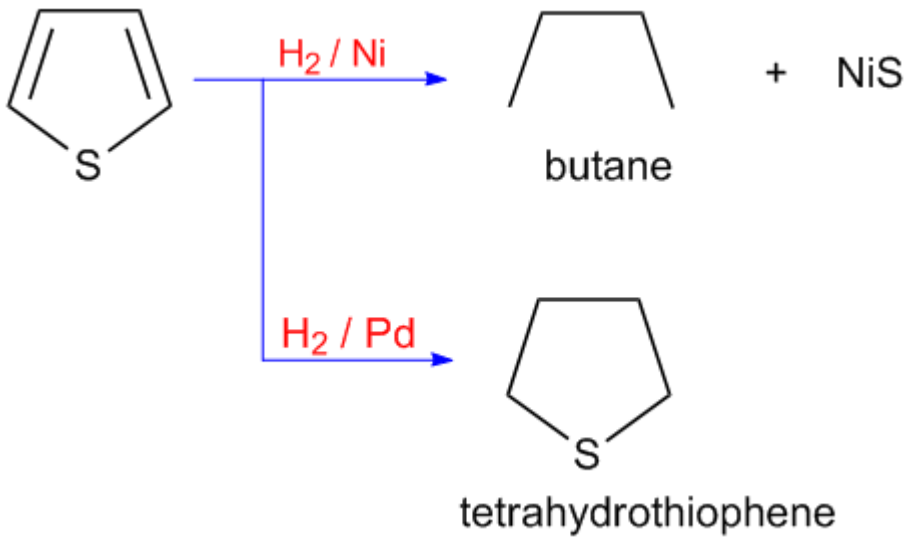
Reactions

1. Electrophilic substitution



Reactions

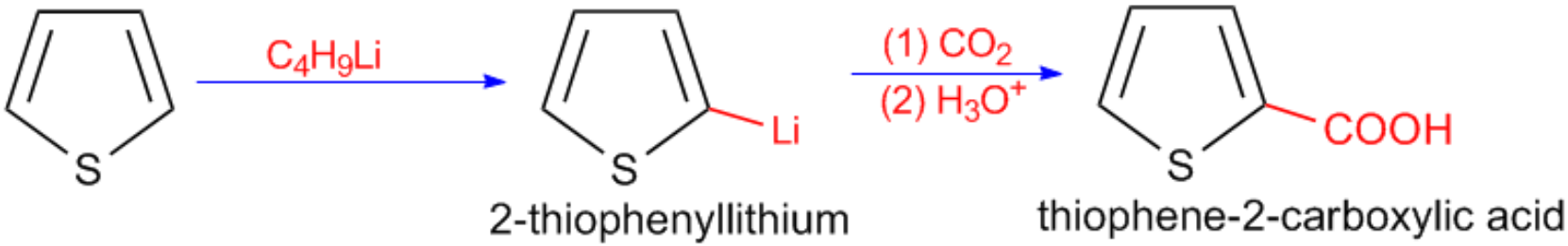
2. Reduction



Reactions

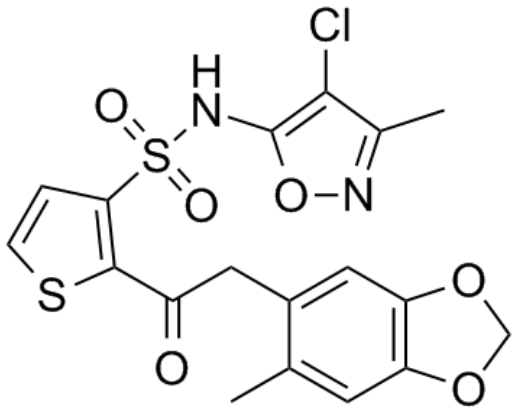
3. reaction

reaction with organolithium

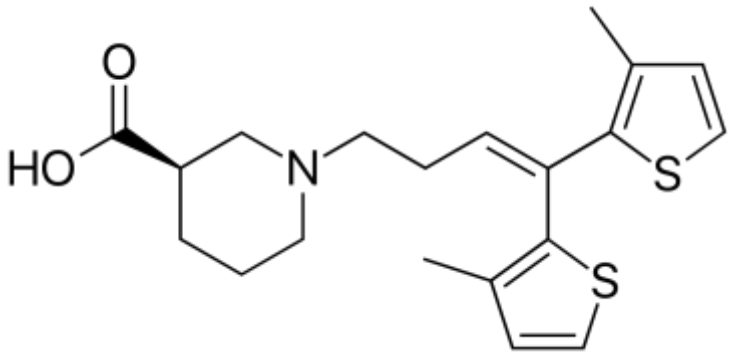


Medicinal uses

(1) *Sitaxsentan:* Cardiovascular Agent , used in pulmonary artery hypertension

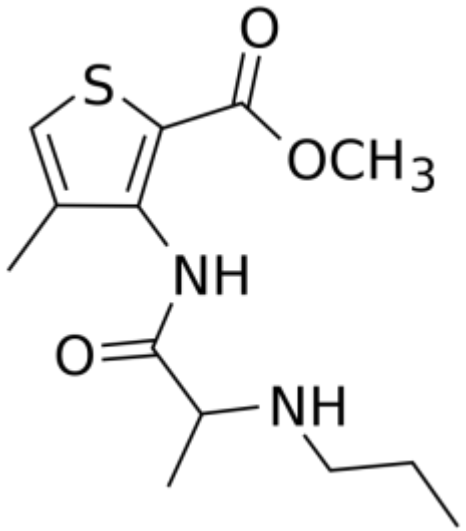


(2) *Tiagabine:* Anticonvulsant Agent, used in the treatment of epilepsy



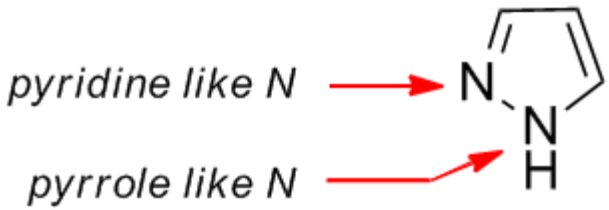
Medicinal uses

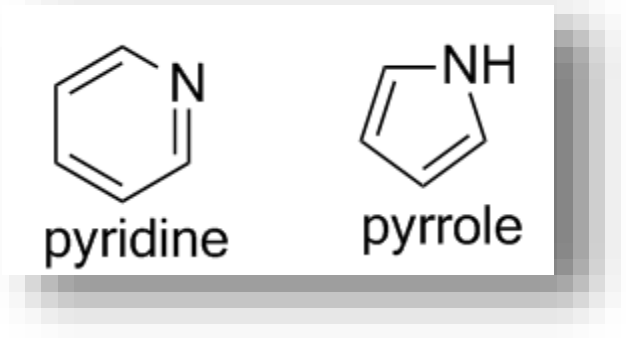
(3) *Articaine:* Anesthetic Agent

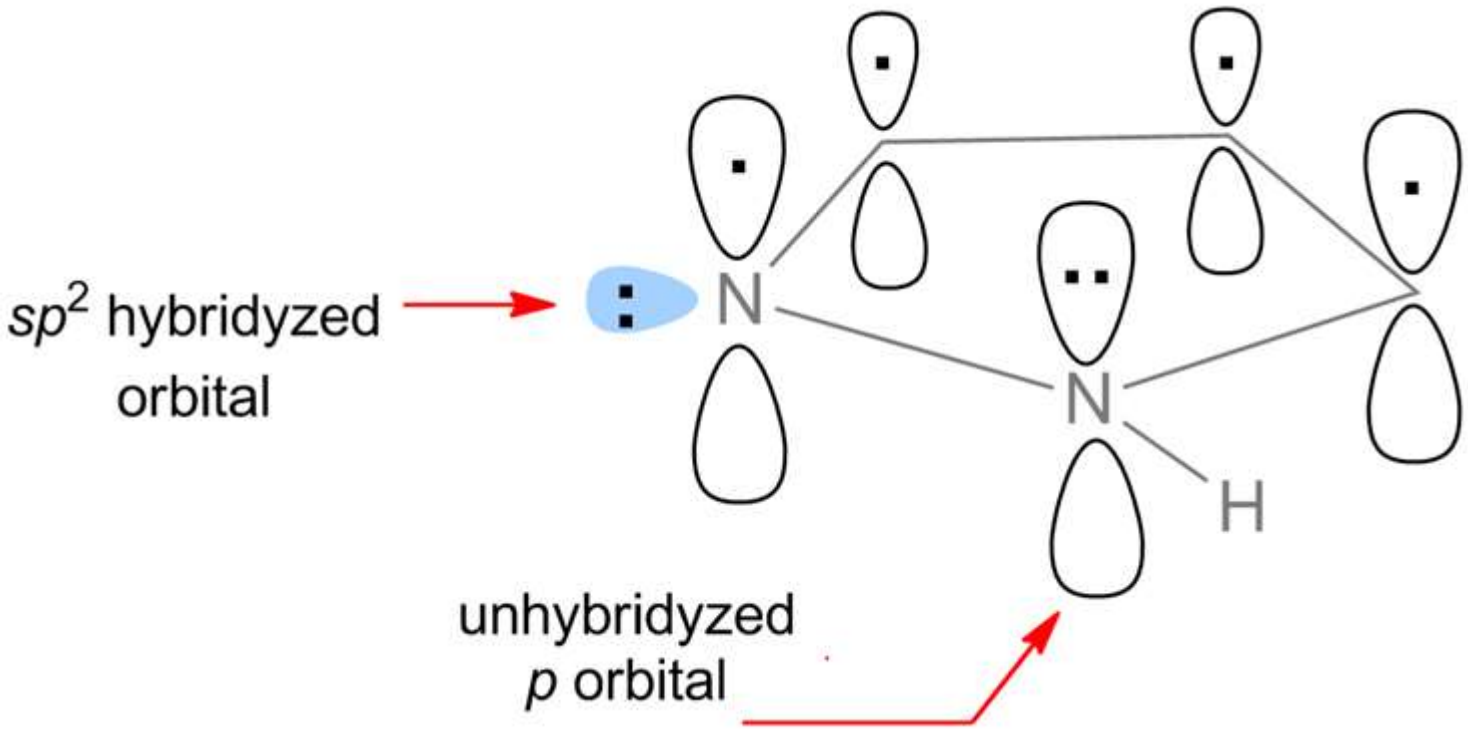


Properties

1. Aromaticity







PYRAZOLE

Properties

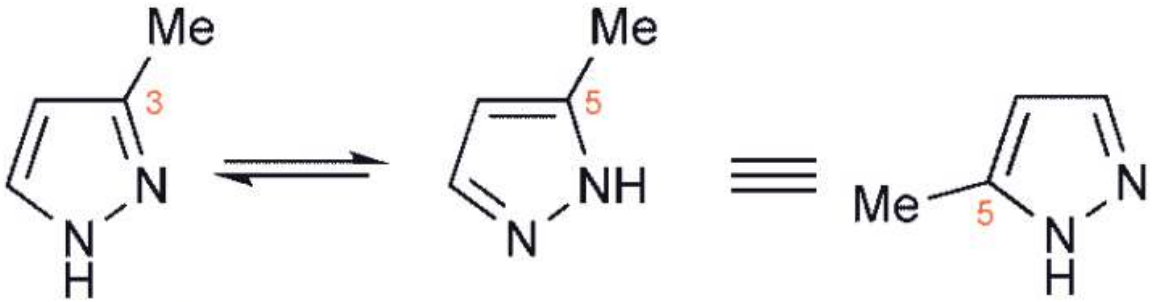
1. Aromaticity

- Pyrazole have 3 C and 2 N , all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar pyrazole ring structure.
- Each ring atoms also contains unhybridized *p* orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here *p* orbitals are parallel to each other, so overlapping btwn *p* orbitals is possible.
- the total nu of non bonding e- are 6 (3 of three C, 1 from one N and 2 of other N)
- The resonance of 6 e- follows the Hückel's rule
- So the pyrazole is aromatic .

Properties

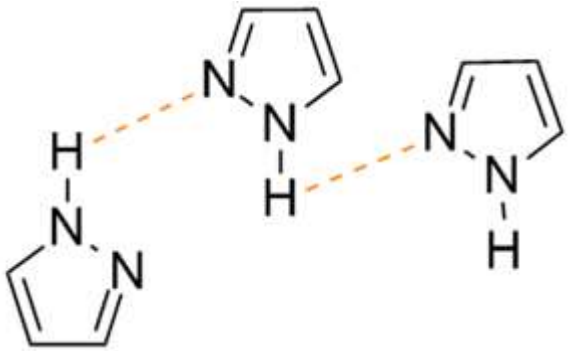
2. Tautomerism

- Rapid migration of hydrogen from one nitrogen to the other.



3(5)-methylpyrazole

3. Hydrogen bonding

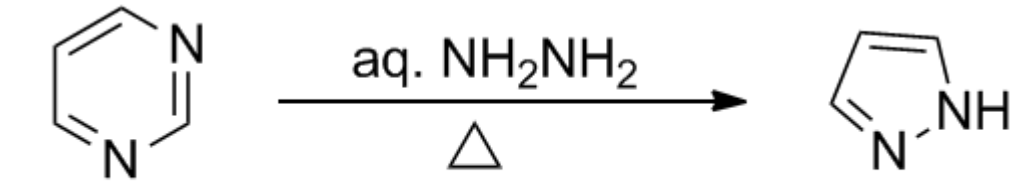


2 Hydrogen bonding within 2 molecules (cyclic dimer)

Synthesis

1. From pyrimidine

- Pyrimidine is very susceptible to nucleophilic addition.
- it reacts with hot hydrazine solution to give pyrazole.



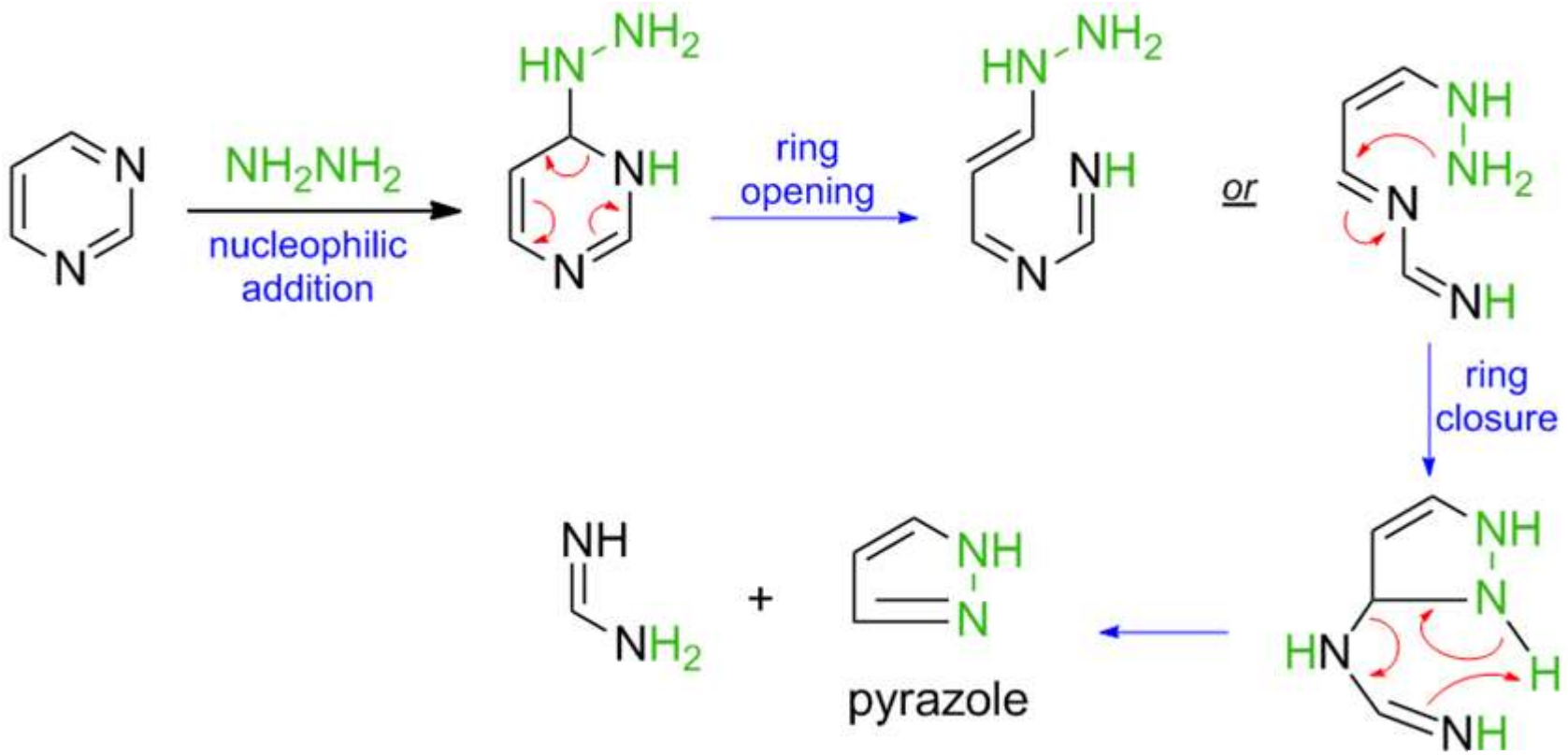
Pyrimidine pyrazole

Synthesis

1. From pyrimidine

mechanism

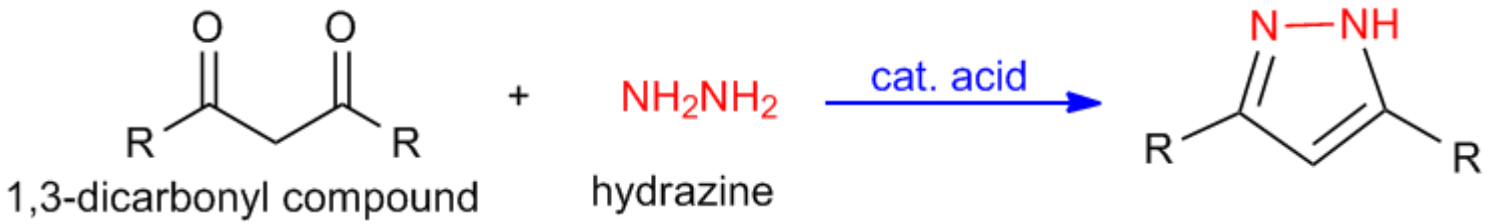
- Mechanism follows Addition of Nucleophile Ring Opening Ring Closure (ANRORC) sequence.



Synthesis

2. Knorr pyrazole synthesis

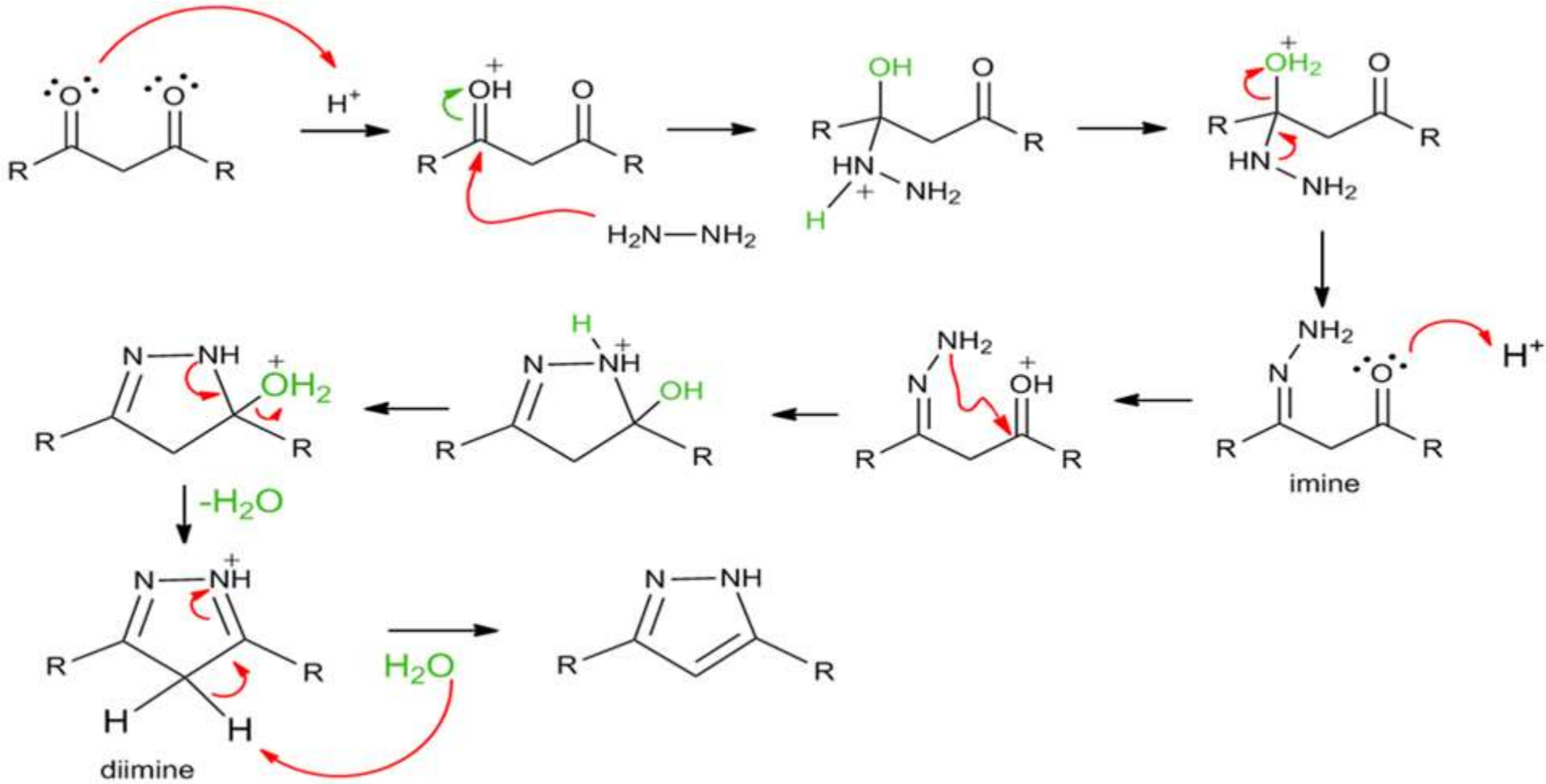
- Rxn convert a hydrazine or its derivatives and a 1,3-dicarbonyl compound to a pyrazole using an acid catalyst.



Synthesis

2. Knorr pyrazole synthesis

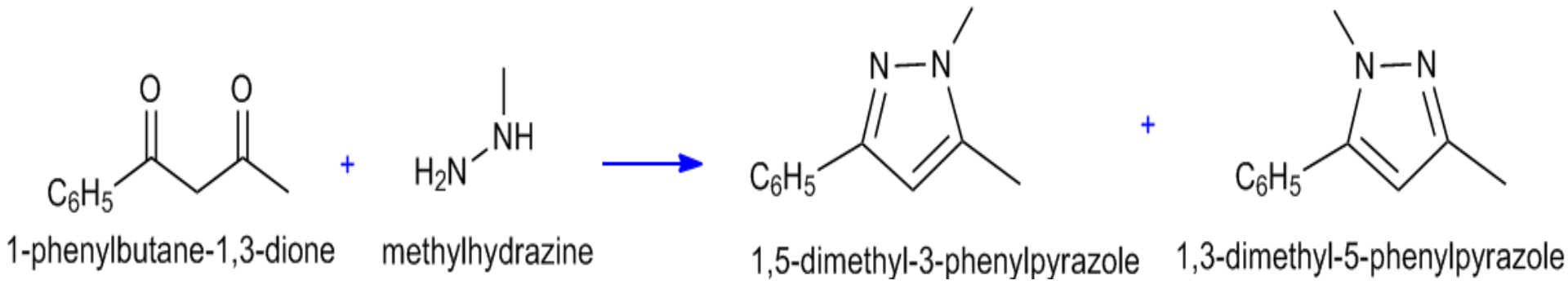
mechanism



Synthesis

2. Knorr pyrazole synthesis

Examples



1-phenylbutane-1,3-dione + methylhydrazine → 1,5-dimethyl-3-phenylpyrazole + 1,3-dimethyl-5-phenylpyrazole

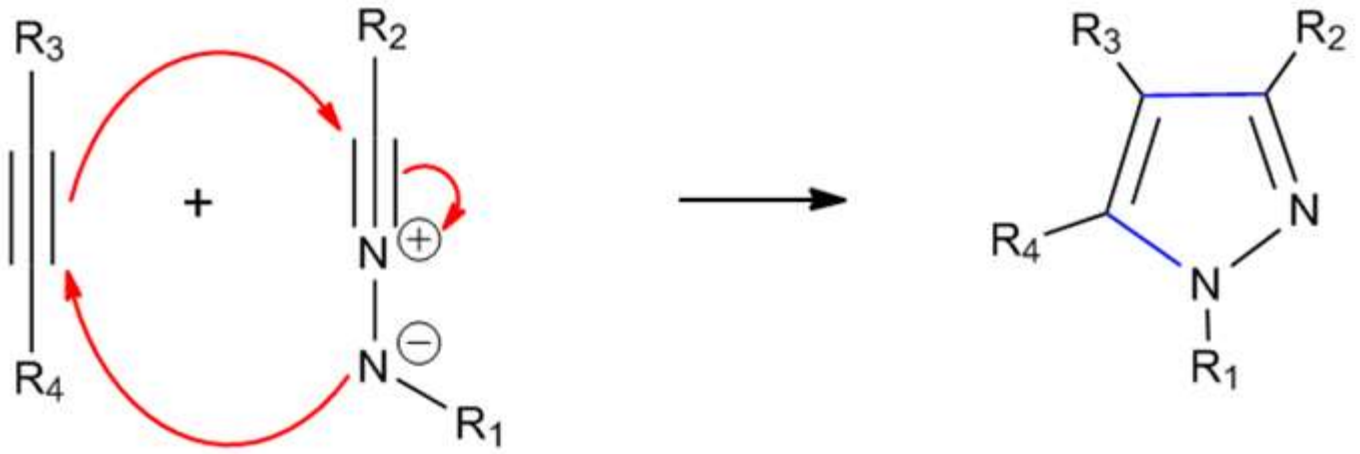
unsymmetrical dicarbonyl compound

isomeric mixture

Synthesis

3. From Nitrile Imines

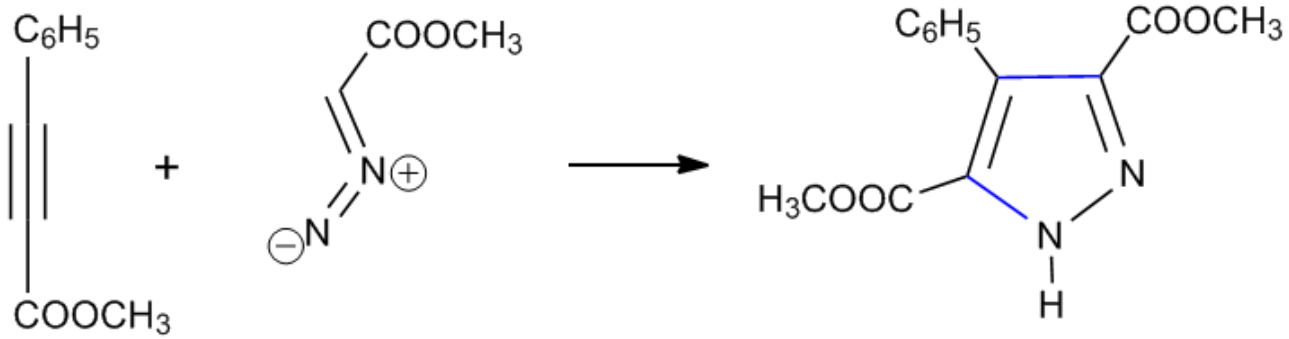
- Pyrazoles are produced by the dipolar cycloaddition btwn alkynes with nitrile imines.



Synthesis

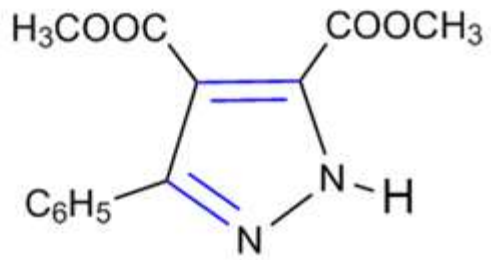
4. From diazo compound

- Diazo compound adds to an acetylenic derivative gives pyrazole



3,5-Dicarbomethoxy
-4-phenylpyrazole

+



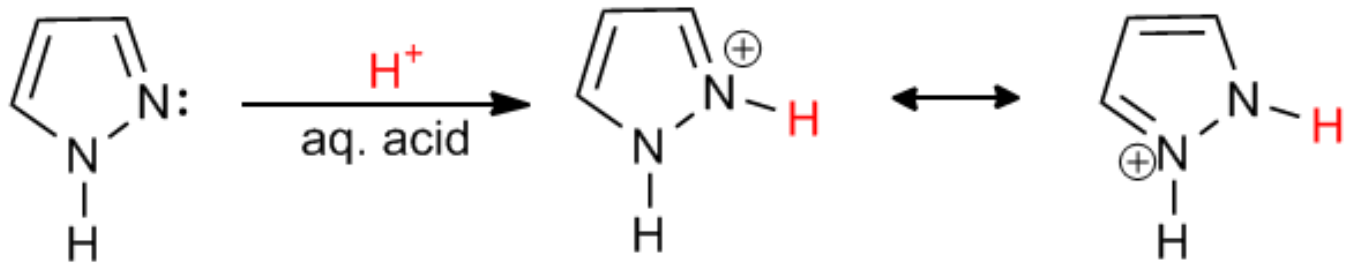
4,5-Dicarbomethoxy
-3-phenylpyrazole

Reactions

1. Electrophilic addition to N

a. Protonation (basic property)

- Pyrazole accept proton, act as base.

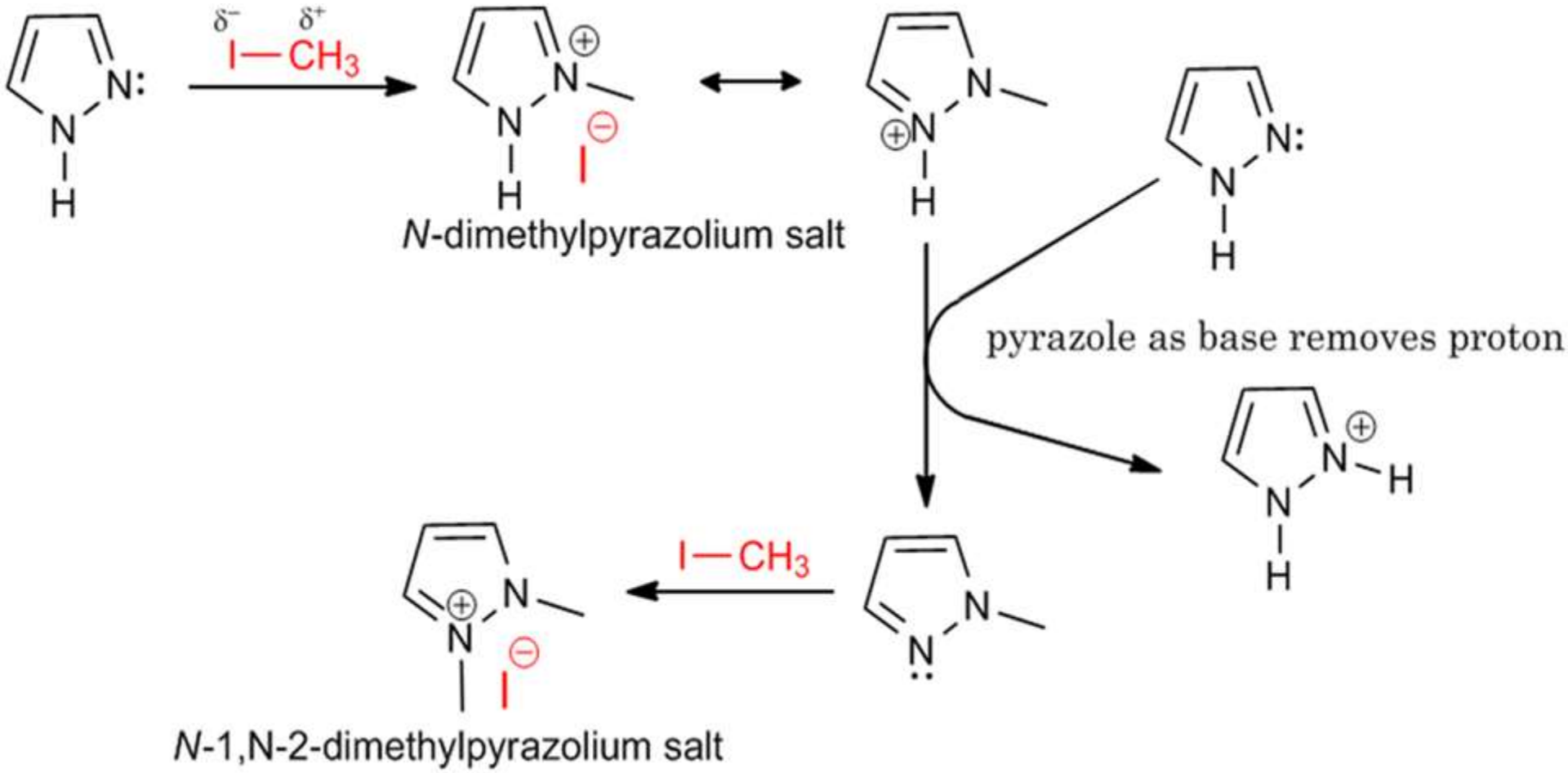


pyrazolium cation

Reactions

1. Electrophilic addition to N

b. *N*-alkylation



Reactions

1. Electrophilic addition to N

b. *N*-alkylation

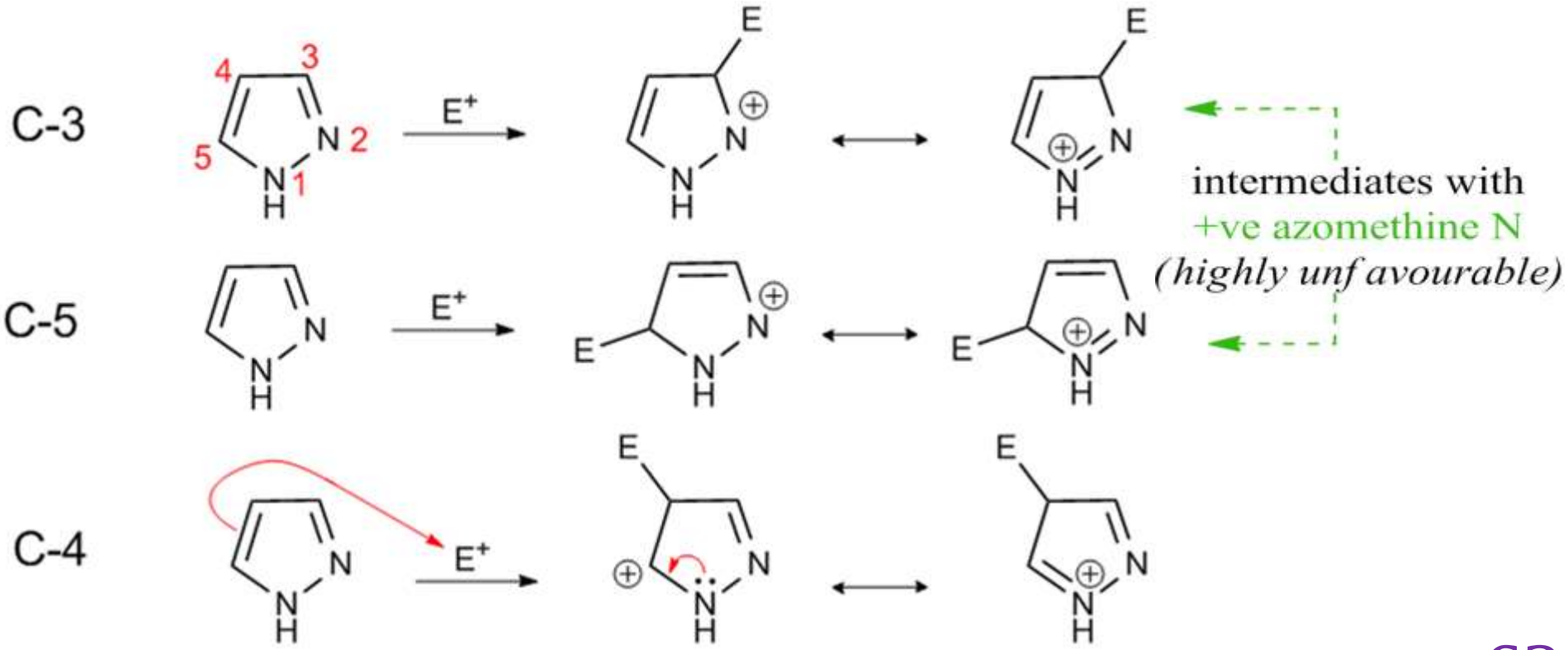
- Pyrazole reacts with alkyl halide and first gives *N*-alkyl pyrazolium salt.
- This salt can lose an *N*-proton in an equilibrium with unreacted pyrazole, generating *N*-alkyl pyrazole.
- *N*-alkyl pyrazole reacts with alkyl halide and gives *N*-1,*N*-2-dialkylpyrazolium salt.

Reactions

2. Electrophilic substitution to C

Pyrazole undergoes electrophilic substitution reaction at 4th position.

- Electrophilic attack at possible positions with intermediates,



Reactions

2. Electrophilic substitution to C

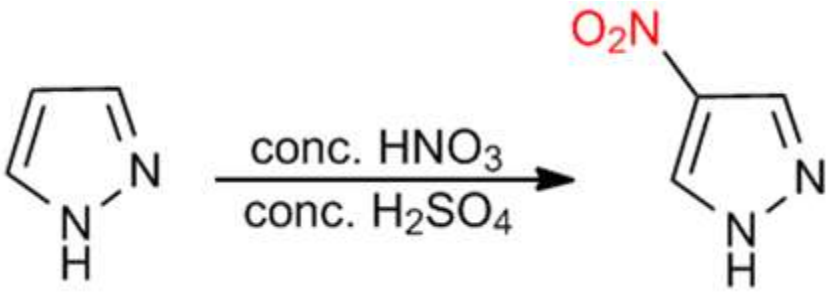
- Electrophilic attack at C-3 & C-5 generates highly unstable +vely charged azomethine intermediate.
- Electrophilic attack at C-4 completes without any such highly unstable intermediate.
- Thus Ts is much higher for C-3 & C-5 attack than C-4.
- So…

- Electrophilic attack takes place readily at neutral *or* alkaline media as pyrazole protonated pyrazole is more resistant to electrophilic attack than pyrazole.

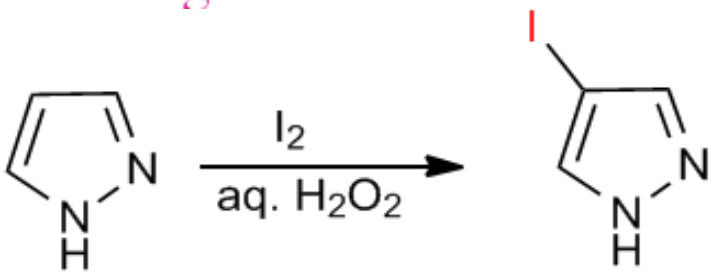
Reactions

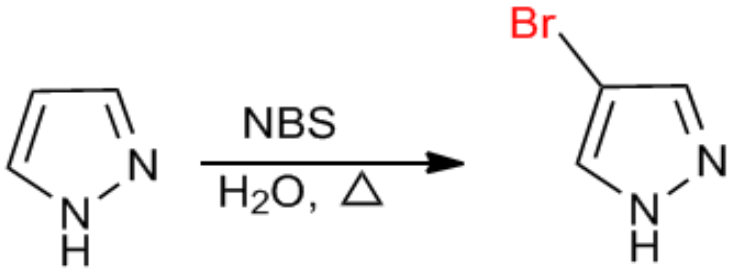
2. Electrophilic substitution to C

a. Nitration



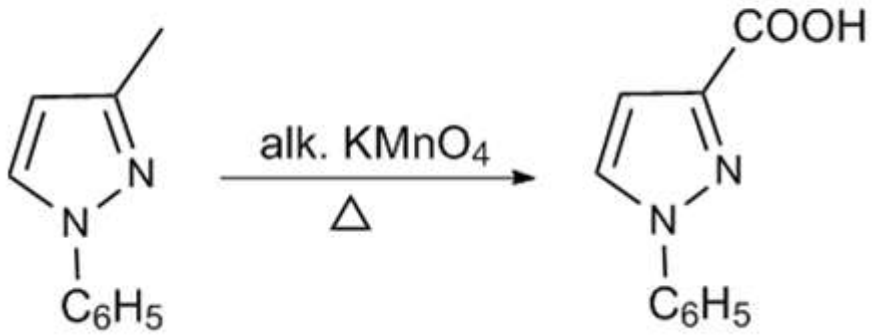
b. Halogenation



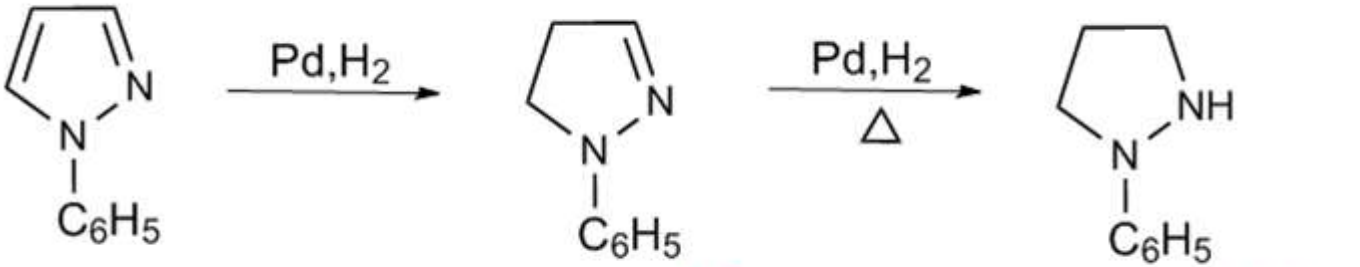


Reactions

3. Oxidation



4. Reduction



1-phenylpyrazole

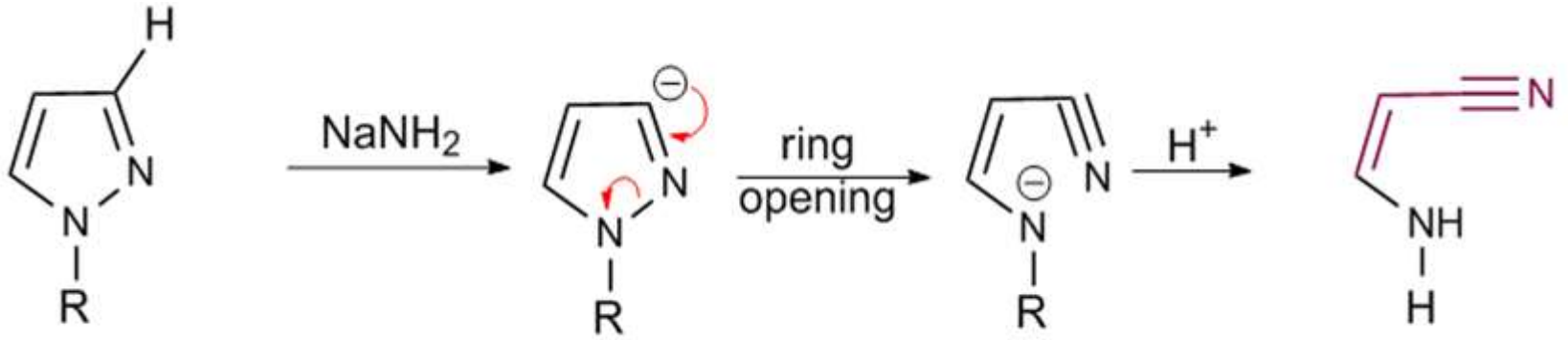
1-phenyl-4,5-dihydropyrazole

1-phenylpyrazolidine

Reactions

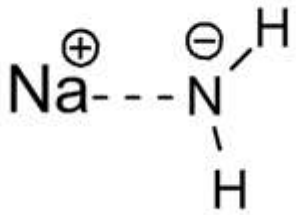
5. Ring opening

- *N*-substituted pyrazole reacted with strong base (sodamide) cause ring opening



N-substitutedpyrazole

acrylonitrile derivative

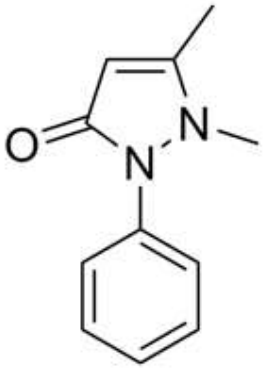


Medicinal Use

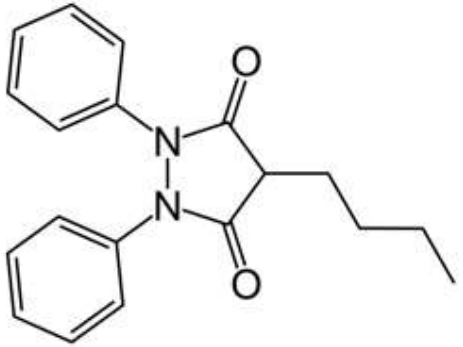
- Many synthetic pyrazole compounds are of importance as dyes and medicines.

E.g.

Antipyrine - used as an antipyretic ,analgesic
Tartrazine - as a yellow dye for food
Phenylbutazone - an anti-inflammatory drug



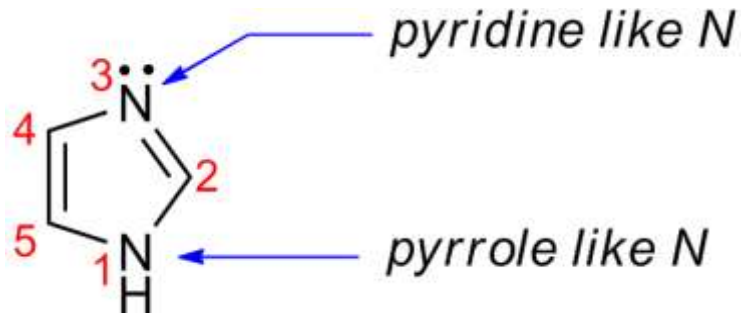
antipyrine

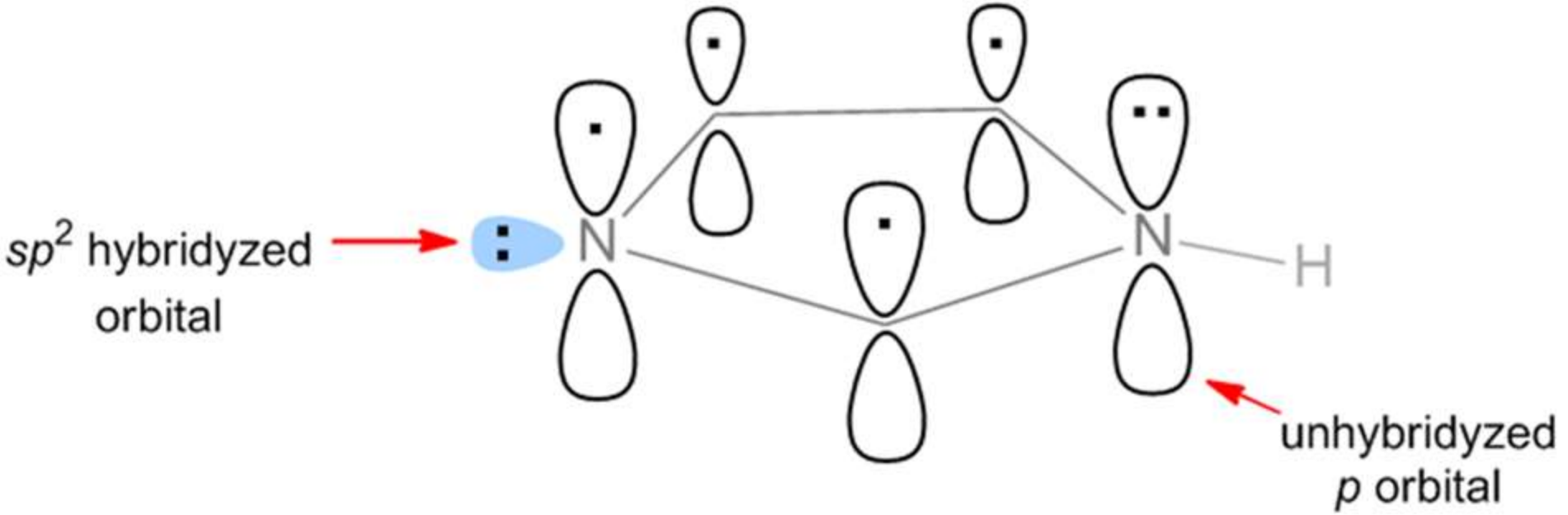


phenylbutazone

Properties

1. Aromaticity





IMIDAZOLE

Properties

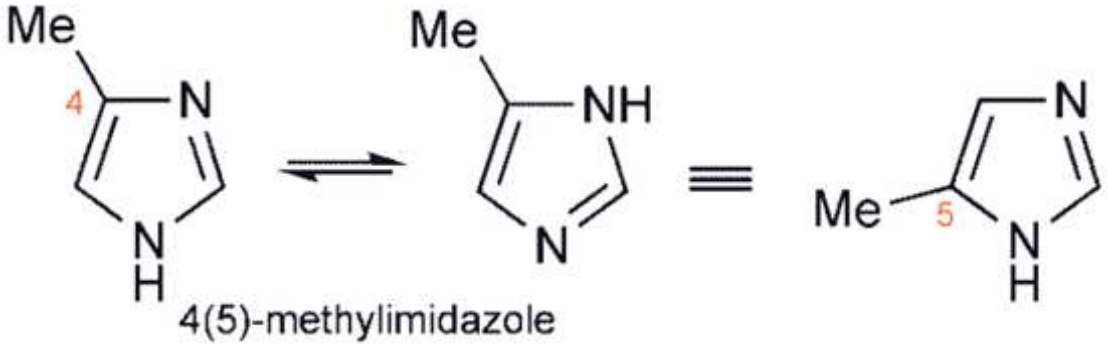
1. Aromaticity

- **Imidazole** have 3 C and 2 N , all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar imidazole ring structure.
- Each ring atoms also contains unhybridized *p* orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here *p* orbitals are parallel to each other, so overlapping btwn *p* orbitals is possible.
- the total nu of non bonding e- are 6 (3 of three C, 1 from one N and 2 of other N)
- The resonance of 6 e- follows the Hückel's rule
- So ….

Properties

2. Tautomerism

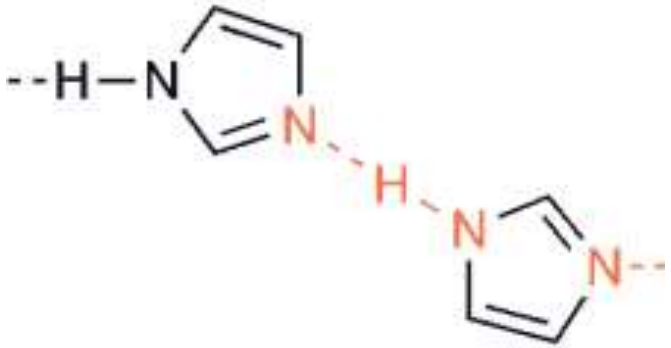
- Imidazole with a ring N- hydrogen are subject to tautomerism.



4(5)-methylimidazole

- 4 –methylimidazole equilibrium with 5 – methylimidazole

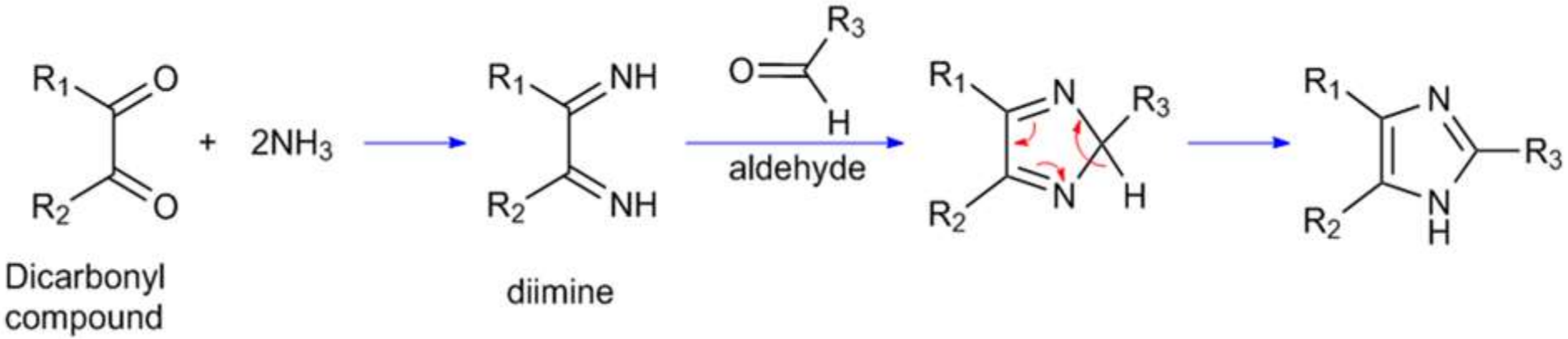
3. Hydrogen bonding



Synthesis

1. Radziszewski Imidazole synthesis

- Synthesis of imidazole from a dicarbonyl, an aldehyde & ammonia.
- The reaction completes in two stages.

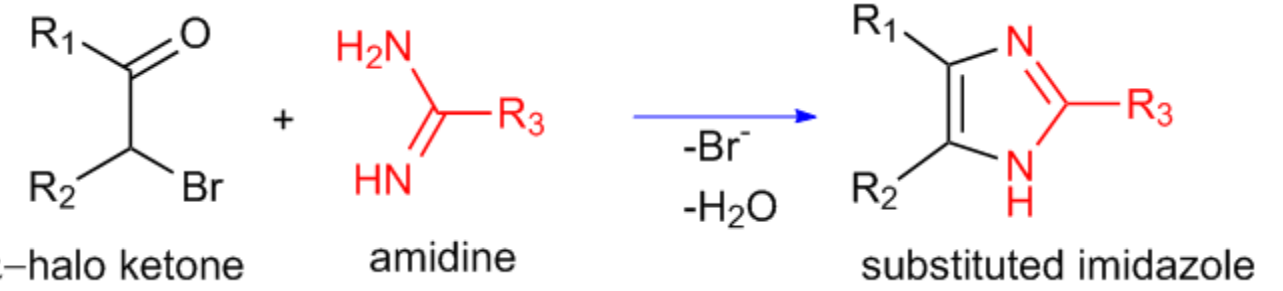


stage_1
the dicarbonyl and ammonia *condense* to give an diimine

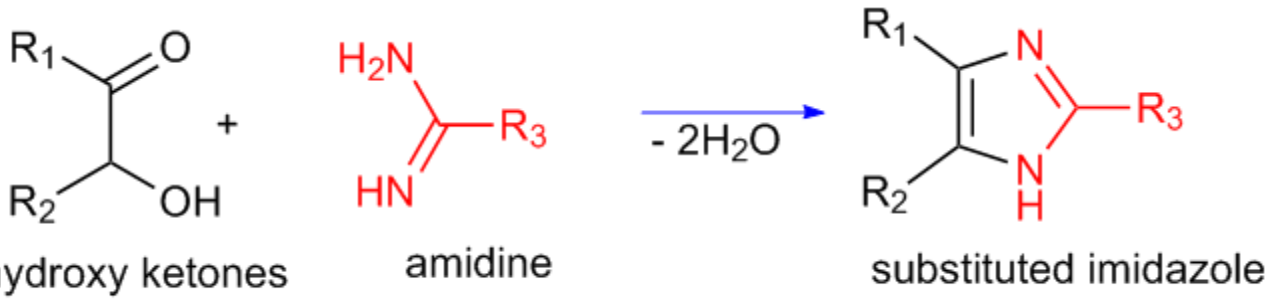
stage_2
diimine condenses with the aldehyde

Synthesis

2. From an α- Halo - Carbonyl Component



α–halo ketone amidine substituted imidazole

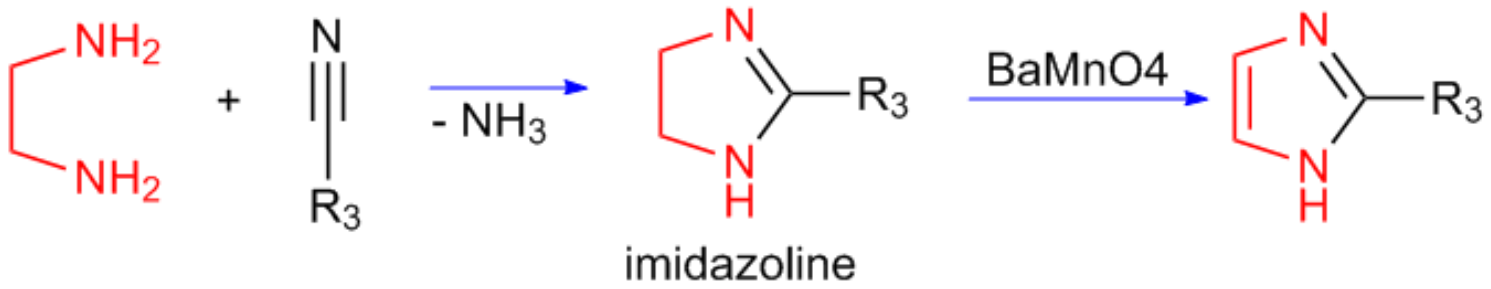


α-hydroxy ketones (acyloin) amidine substituted imidazole

Synthesis

3. From Dehydrogenation of Imidazoline

- Condensation of 1,2-diamines with nitriles gives imidazoline.
- Imidazoline reaction with barium manganate yiels 2-substituted imidazole.

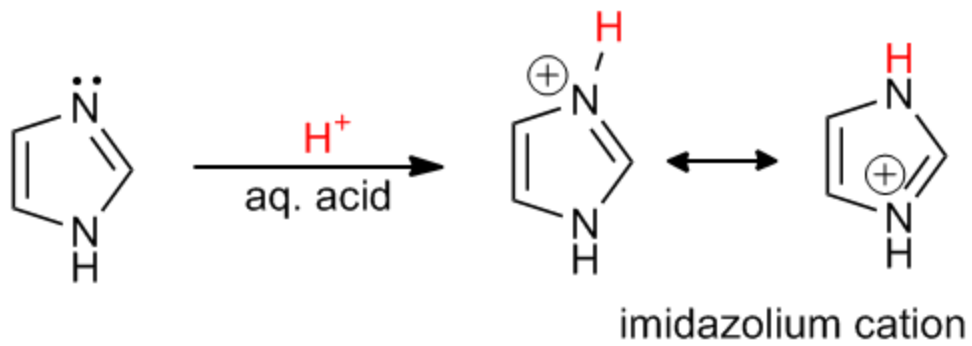


Reactions

1. Electrophilic addition to N

a. Protonation (basic property)

- imidazole accept proton, act as base.

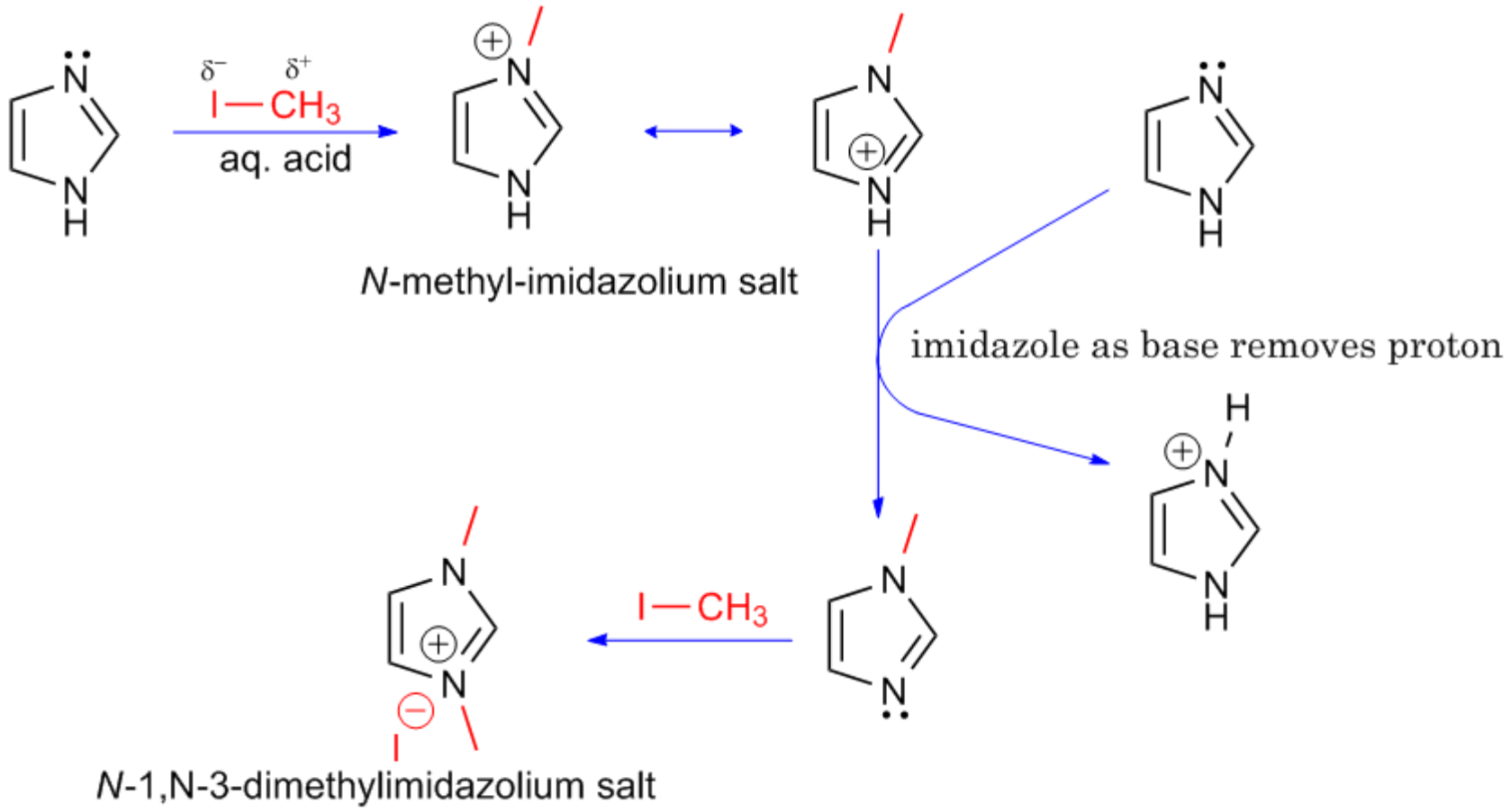


imidazolium cation

Reactions

1. Electrophilic addition to N

b. *N*-alkylation



Reactions

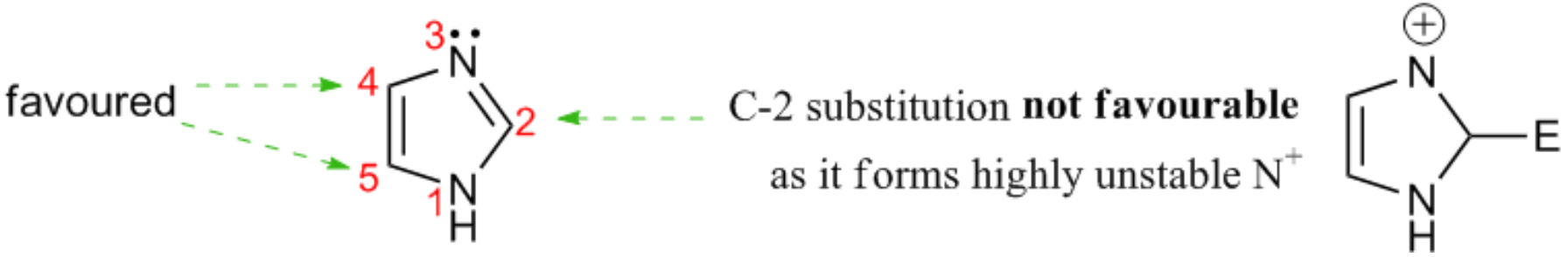
1. Electrophilic addition to N

b. *N*-alkylation

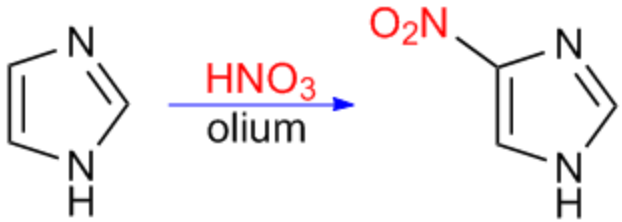
- imidazole reacts with alkyl halide and first gives *N*-alkyl imidazolium salt.
- This salt can lose an *N*-proton in an equilibrium with unreacted imidazole, generating *N*-alkyl imidazole.
- *N*-alkyl imidazole reacts with alkyl halide and gives *N*-1,*N*-3-dialkylimidazolium salt.

Reactions

2. Electrophilic substitution to C



a. Nitration



4(5)-nitroimidazole

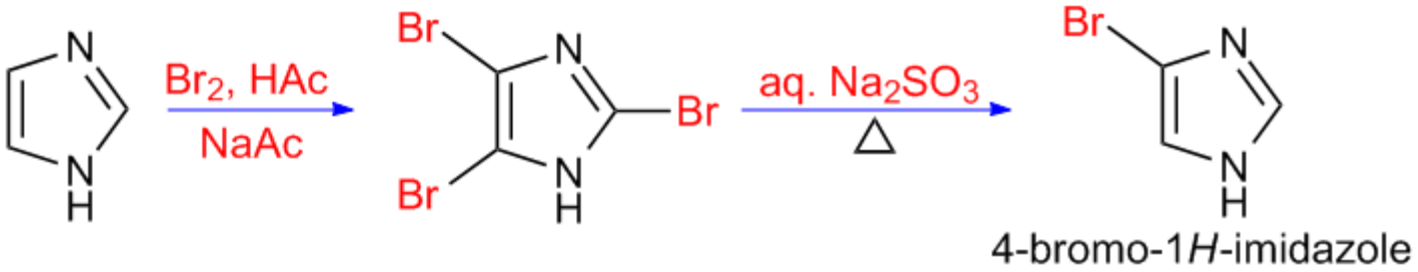
b. sulphonation

imidazole-4(5)-sulfonic acid

Reactions

2. Electrophilic substitution to C

c. Halogenation



4-bromo-1*H*-imidazole

- Bromination gives 2,4,5-tribromomidazole
- 4(5)-Bromoimidazole can be obtained by reduction of tribromoimidazole with sodium sulfite.

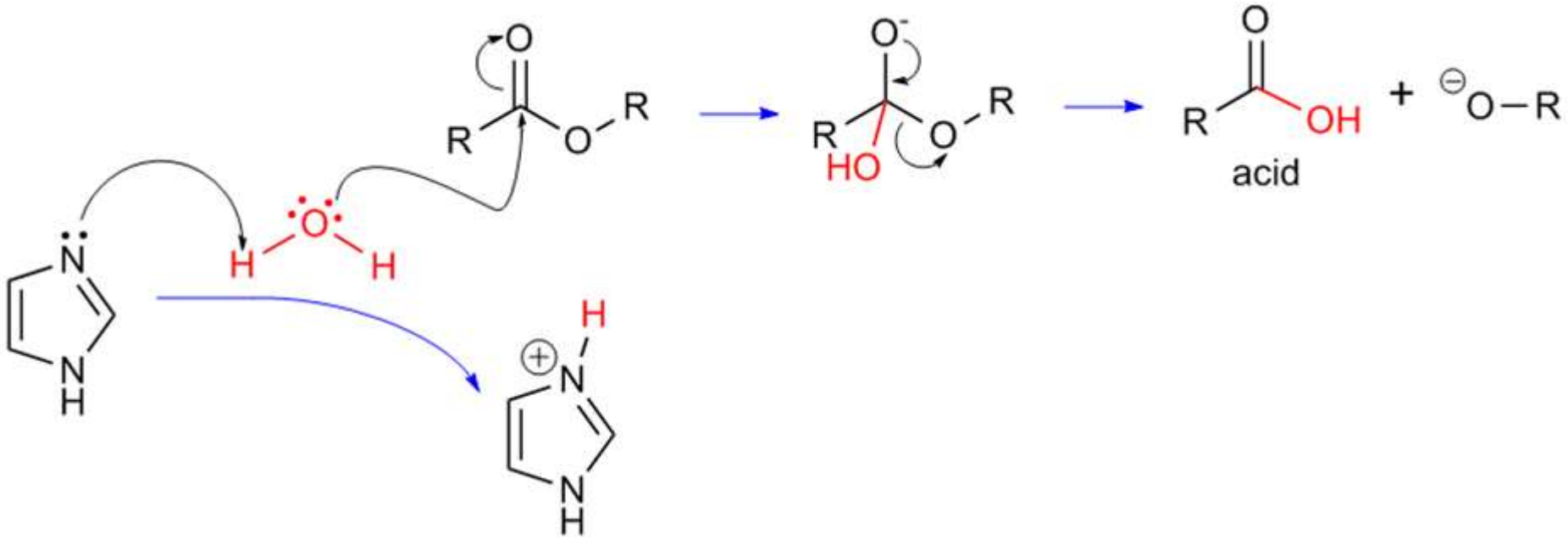
Reactions

3. Imidazole catalyzed ester HL

- Imidazolyl group of histidine residue present in hydrolytic enzymes.
- Functions as ester HL

(1) Imidazole as Base catalysis

- Activates water for attack at carbonyl C

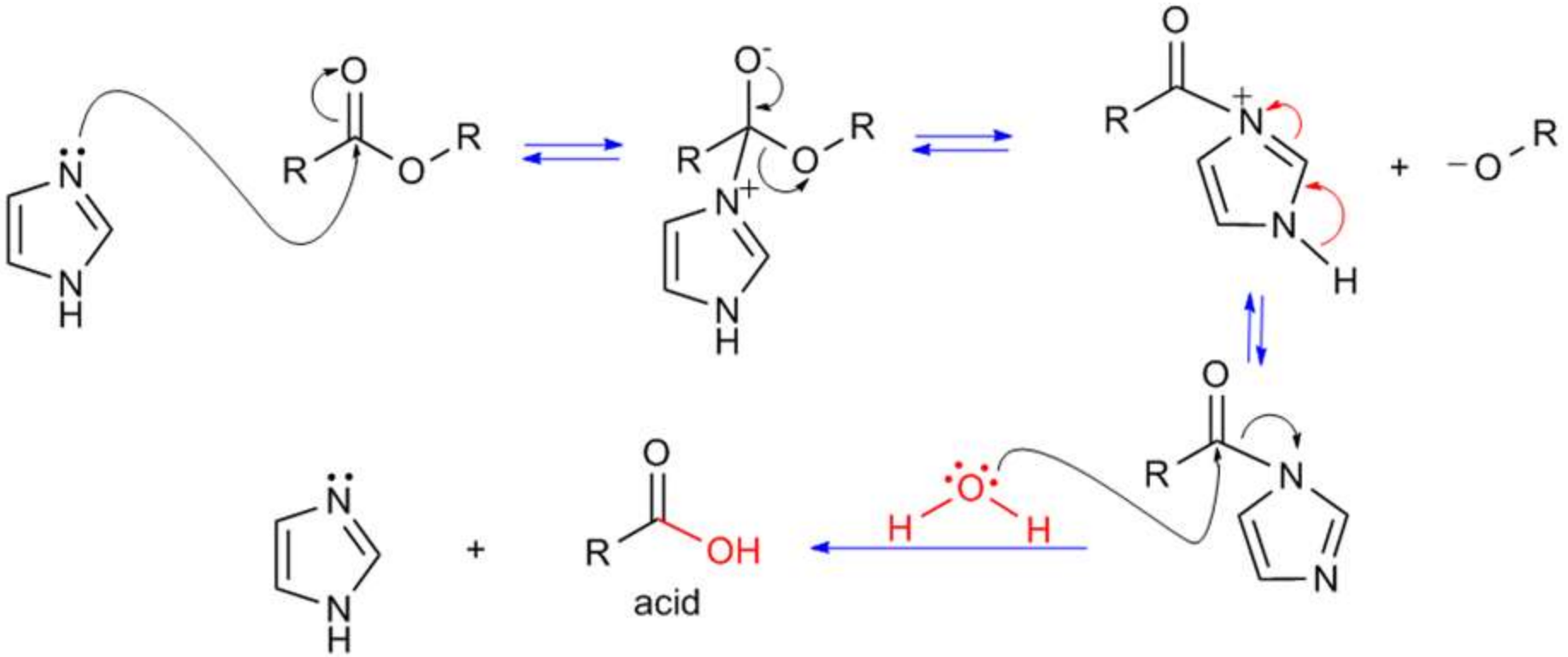


Reactions

3. Imidazole catalyzed ester HL

(2) Imidazole as nucleophilic catalysis

- Imidazole directly attack at carbonyl C



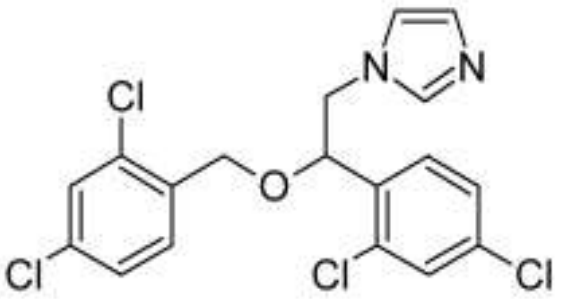
Medicinal uses

(1) Azole Antifungal Agents:

Ketoconazole

Miconazole

Clotrimazole



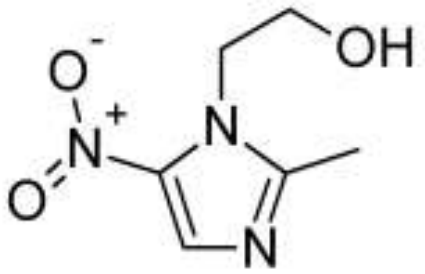
Miconazole

(2) Antihistaminic drug: *Cimetidine*

- used to treat and prevent peptic ulcer, gastro esophageal reflux disease (GERD) and heartburn.

(3) Antiprotozoal agents: *Metronidazole*

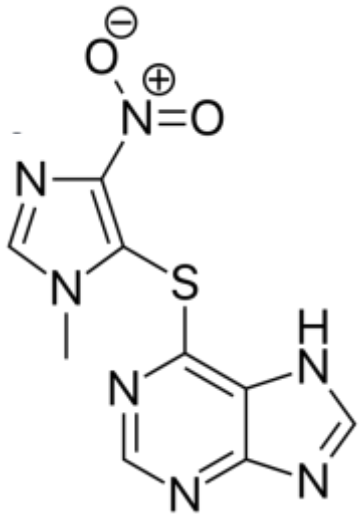
- used in amoebic dysentery



Medicinal uses

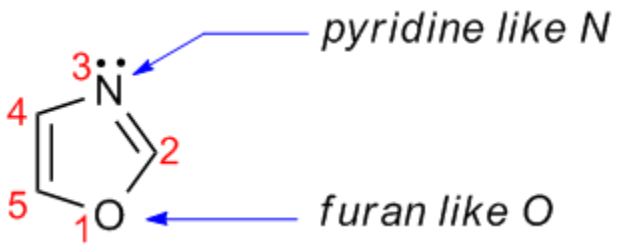
(4) *Azathioprine:* An immunosuppressive antimetabolite *pro-drug.*

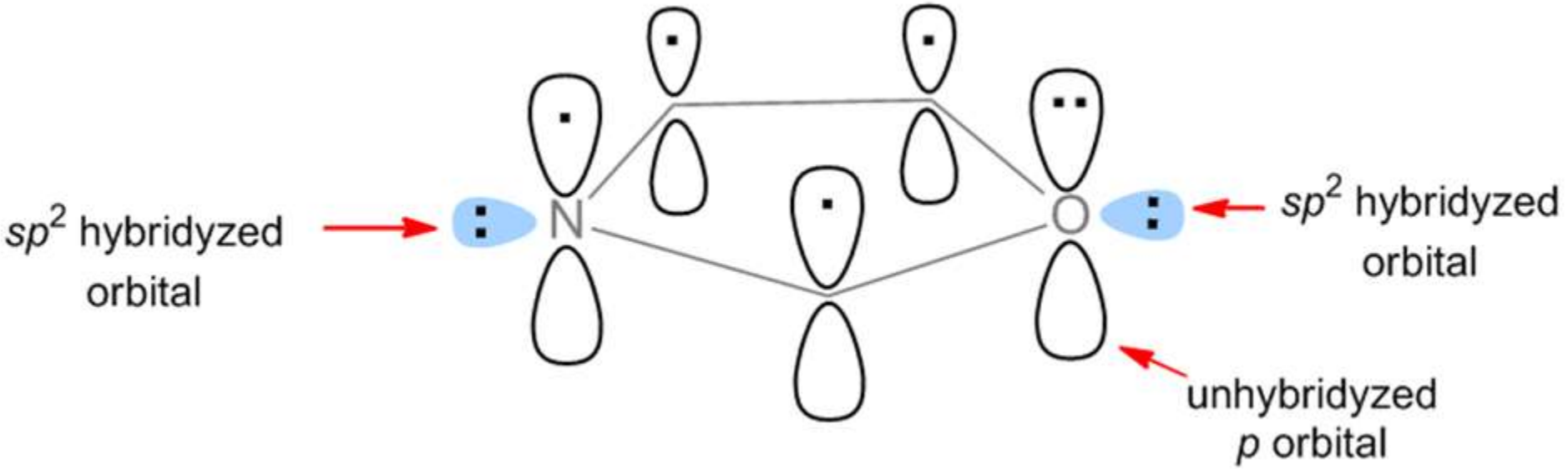
- Anticancer agent
- Immunosuppressive Agents



Properties

1. Aromaticity





OXAZOLE

Properties

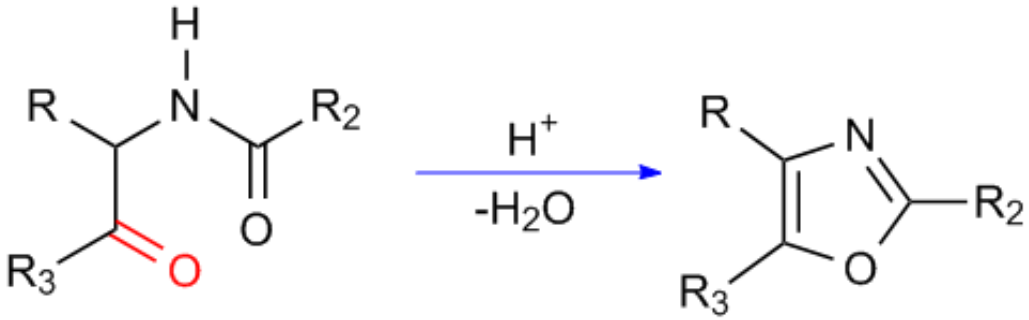
1. Aromaticity

- Oxazole have 3 C , 1 N and 1 O, all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar oxazole ring structure.
- Each ring atoms also contains unhybridized p orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here p orbitals are parallel to each other, so overlapping btwn p orbitals is possible.
- the total nu of non bonding e- are 6 (3 of three C, 1 from N and 2 of O)
- So ….
- However, an O atom is highly electronegative, so the delocalization is not overly effective.

Synthesis

1. Robinson-Gabriel synthesis

- Cyclising dehydration (acid - catalyzed closure) of an α- acylamino - carbonyl – compound.

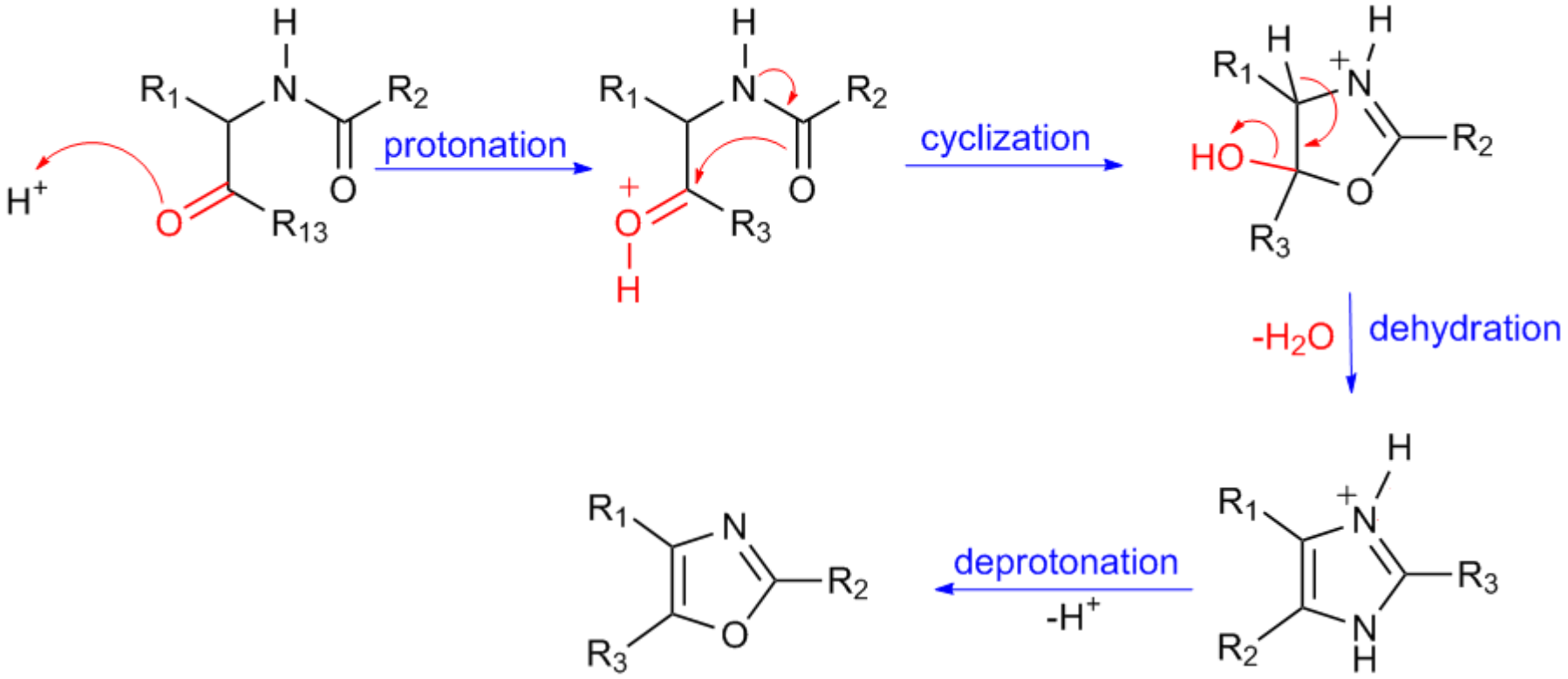


α- acylamino -carbonyl- compound

Synthesis

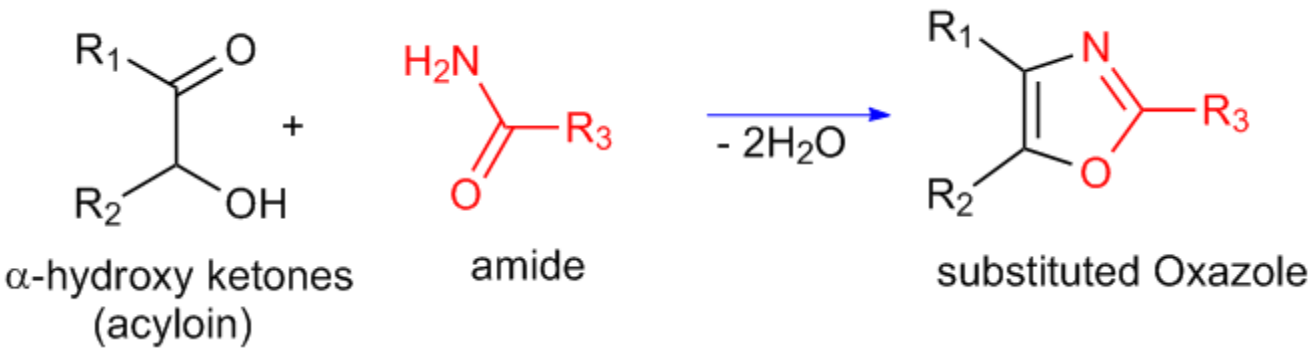
1. Robinson-Gabriel synthesis

Mechanism



Synthesis

2. From an α- Hydroxy - Carbonyl Component

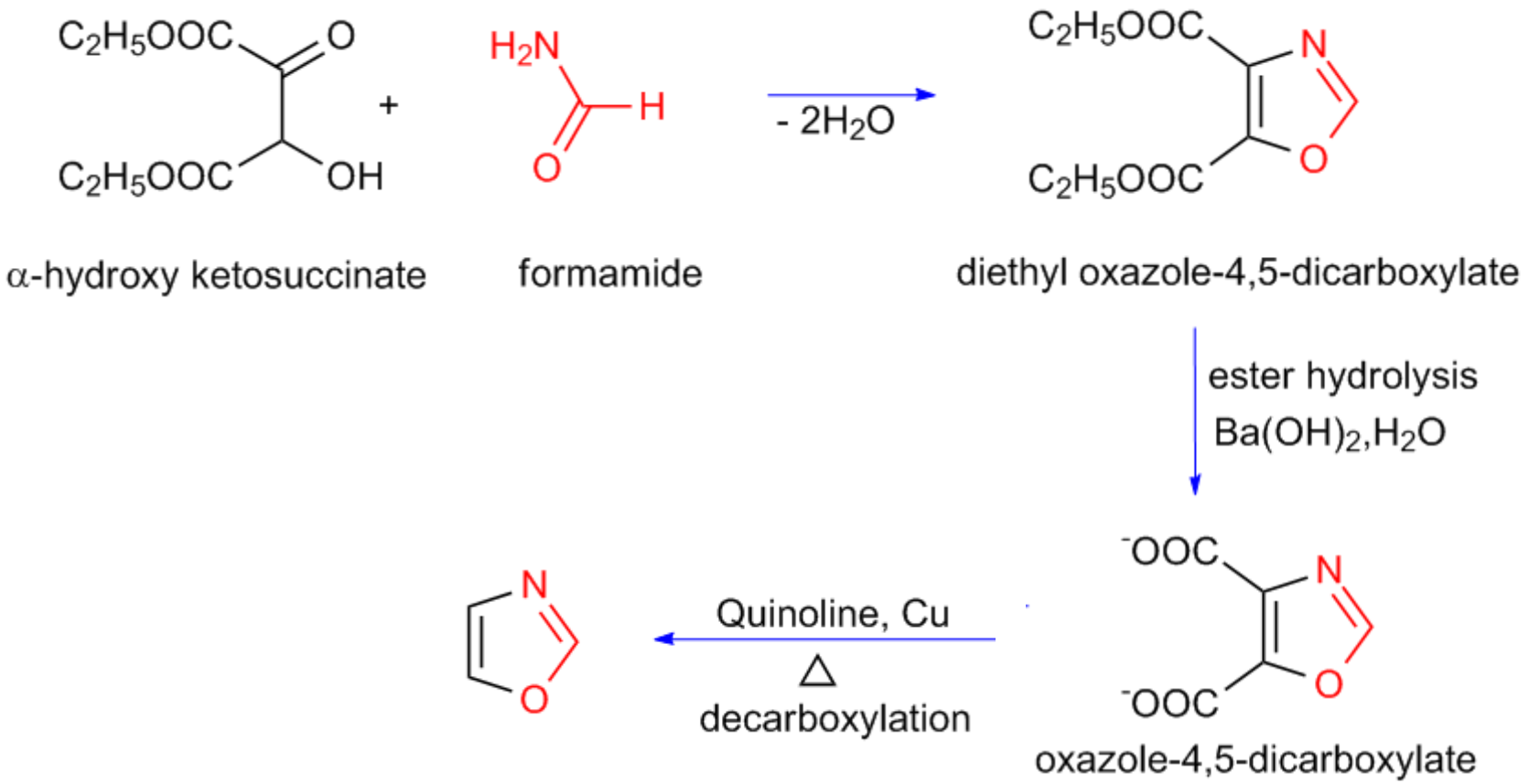


α-hydroxy ketones (acyloin) | amide | substituted Oxazole

Synthesis

2. From an α- Hydroxy - Carbonyl Component

E.g.

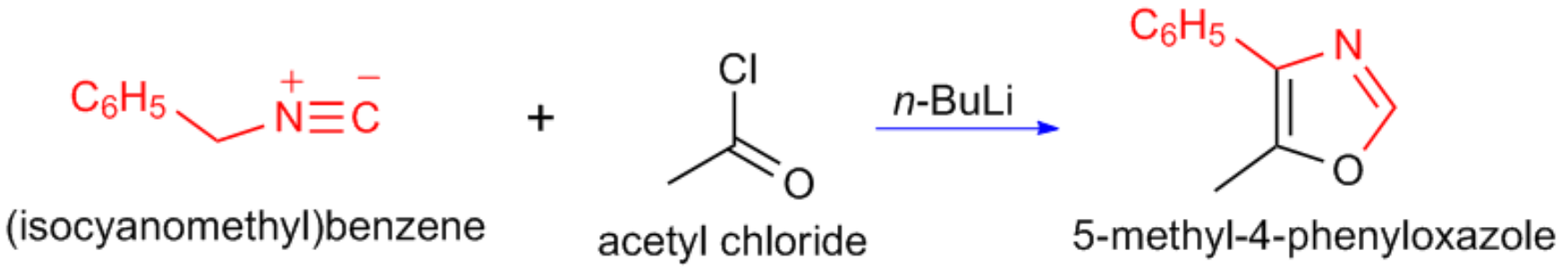


Synthesis

3. From Isocyanides

- Reaction of isocyanides with acid chlorides or anhydrides yields substituted oxazoles.

E.g.



(isocyanomethyl)benzene + acetyl chloride → 5-methyl-4-phenyloxazole

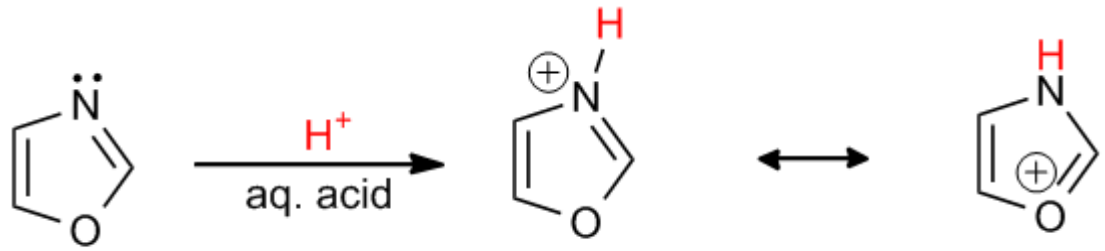
Reactions

1. Electrophilic addition to N

- Oxazole is less reactive compare to imidazole, because presence of more electronegative O

a. Protonation (basic property)

- Oxazole accept proton, act as base form oxazolium salts.



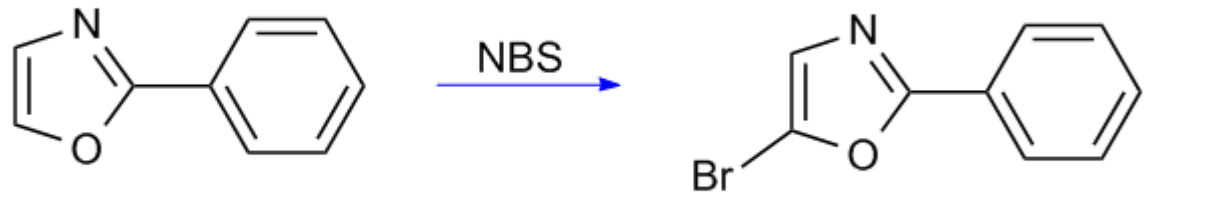
oxazolium cation

Reactions

2. Electrophilic substitution to C

- Less reactive due to O present in hetero skeletal
- Reaction is possible at 5th position, if ring is *activated by EDG.*
- Nitration and sulphonation are more difficult

E.g.



2-phenyloxazole

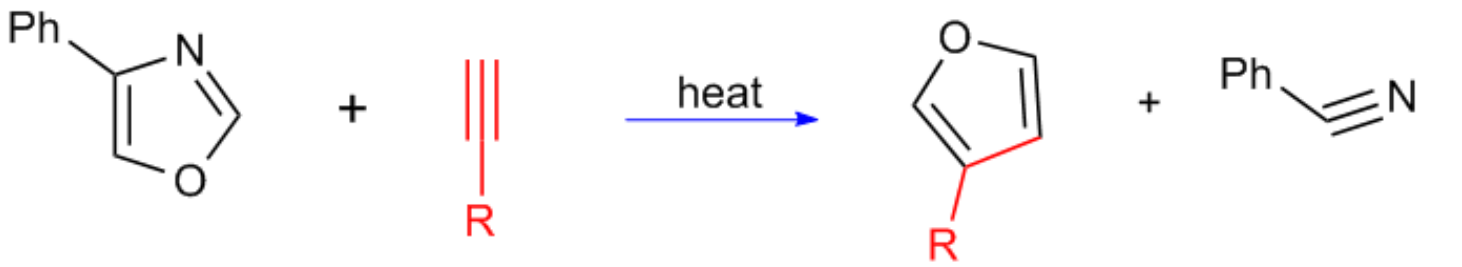
5-bromo-2-phenyloxazole

Reactions

3. Diels-Alder Reaction

- Act as Diene (4πcomponent)
- O atom is highly electronegative → so conjugated double bonds are readily available as diene in Diels-alder reaction.
- Oxazoles readily undergo Diels – Alder type cycloaddition across the 2,5 – positions
- E.g.

(1) Synthesis of furan

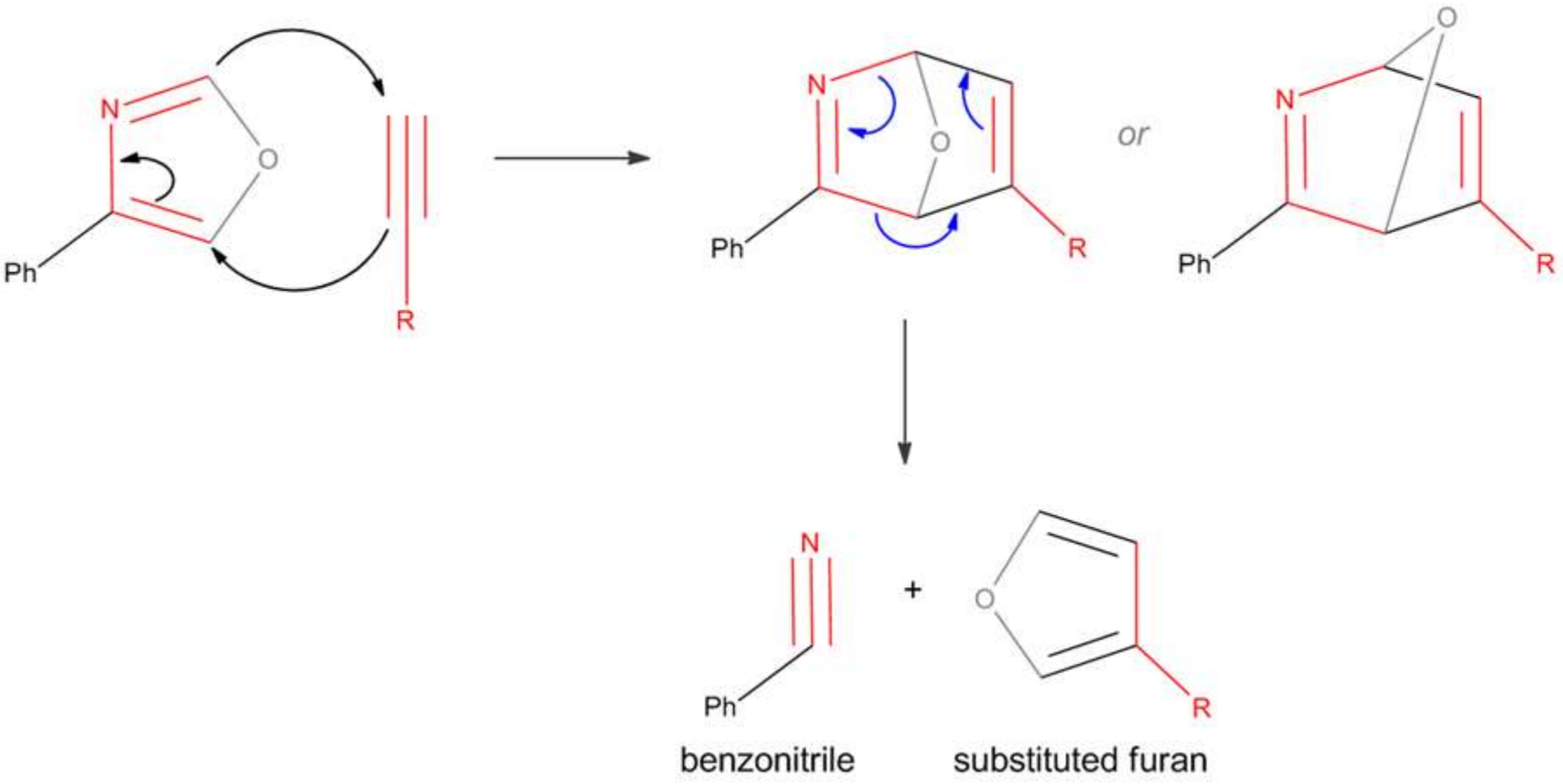


oxazole alkyne furan benzonitrile

Reactions

3. Diels-Alder Reaction

Mechanism

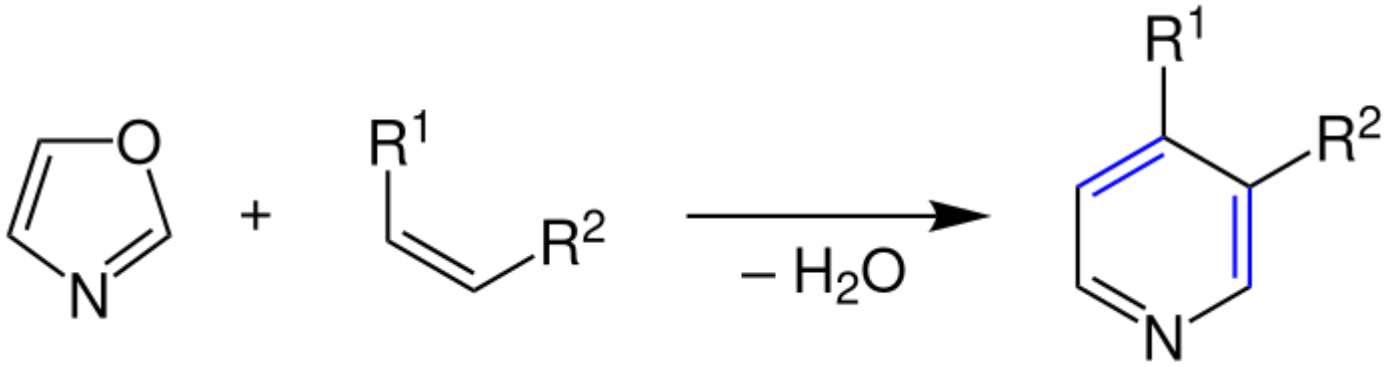


Reactions

3. Diels-Alder Reaction

(2) Kondrat'eva pyridine synthesis

- synthesizing pyridine derivatives by Diels–Alder cycloaddition between an azadiene and a dienophile followed by an extrusion of the resulting bridge of the bicyclic intermediate.

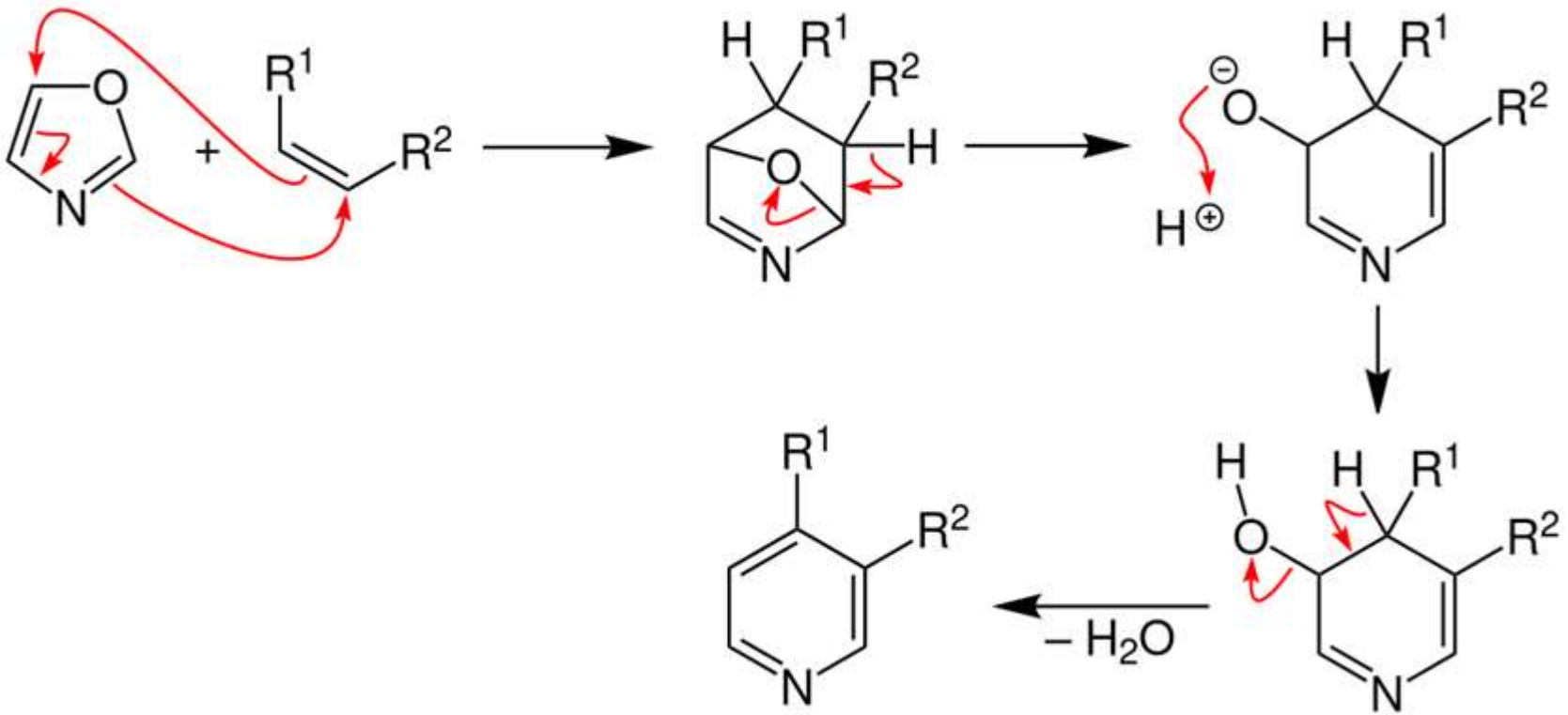


Reactions

3. Diels-Alder Reaction

(2) Kondrat'eva pyridine synthesis

Mechanism



Medicinal uses

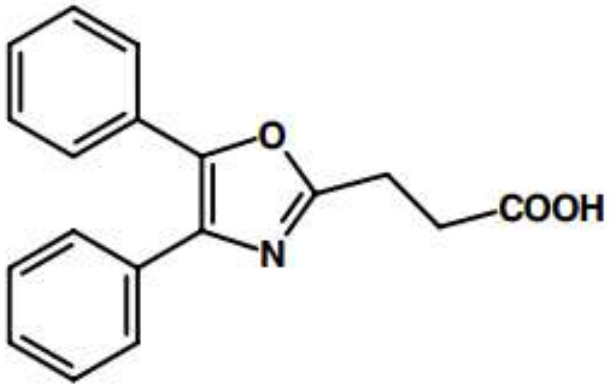
(1) Antifungal agent

- *Bengazoles* are natural products with two oxazole groups

Bengazole A

(2) *Oxaprozin*

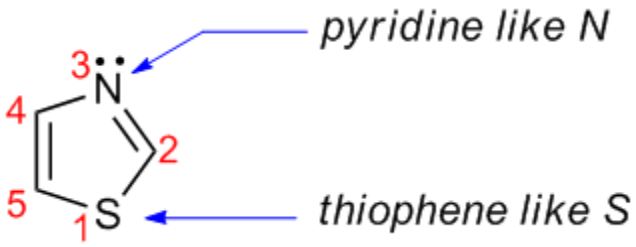
- is a non- steroidal anti-inflammatory agent (NSAID)
- Used to symptomatically treat inflammation, pain, and rheumatoid diseases.

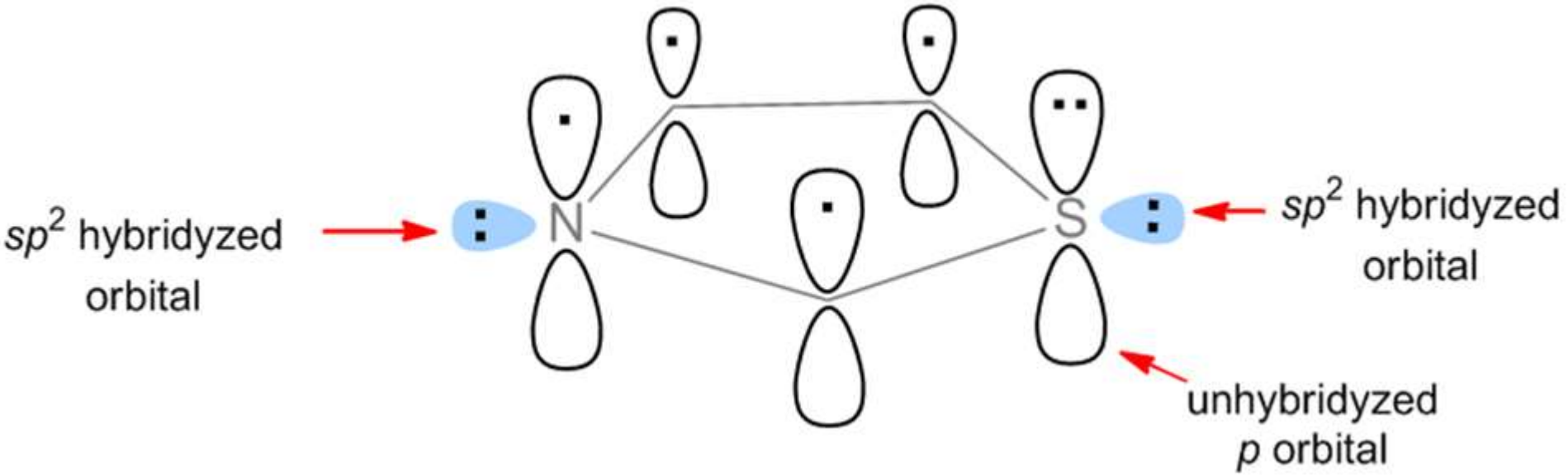


Oxaprozin

Properties

1. Aromaticity





Properties

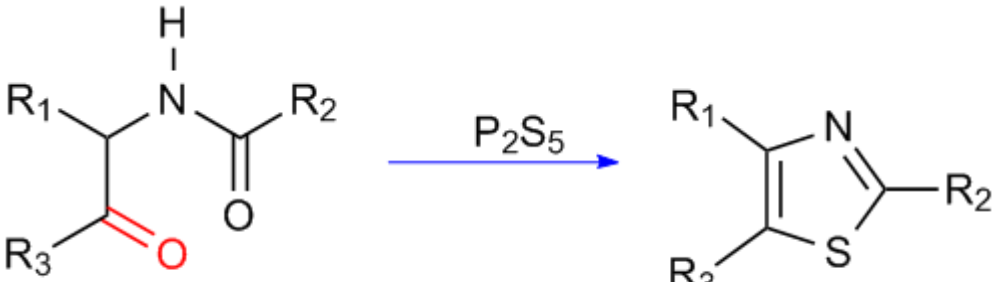
1. Aromaticity

- Thiazole have 3 C , 1 N and 1 S, all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar thiazole ring structure.
- Each ring atoms also contains unhybridized *p* orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here *p* orbitals are parallel to each other, so overlapping btwn *p* orbitals is possible.
- the total nu of non bonding e- are 6 (3 of three C, 1 from N and 2 of S)
- The resonance of 6 e- follows the Hückel's rule
- So ….

Synthesis

1. Gabriel synthesis

- Condensation of acylaminocarbonyl compound in presence of Phosphorus pentasulfide.

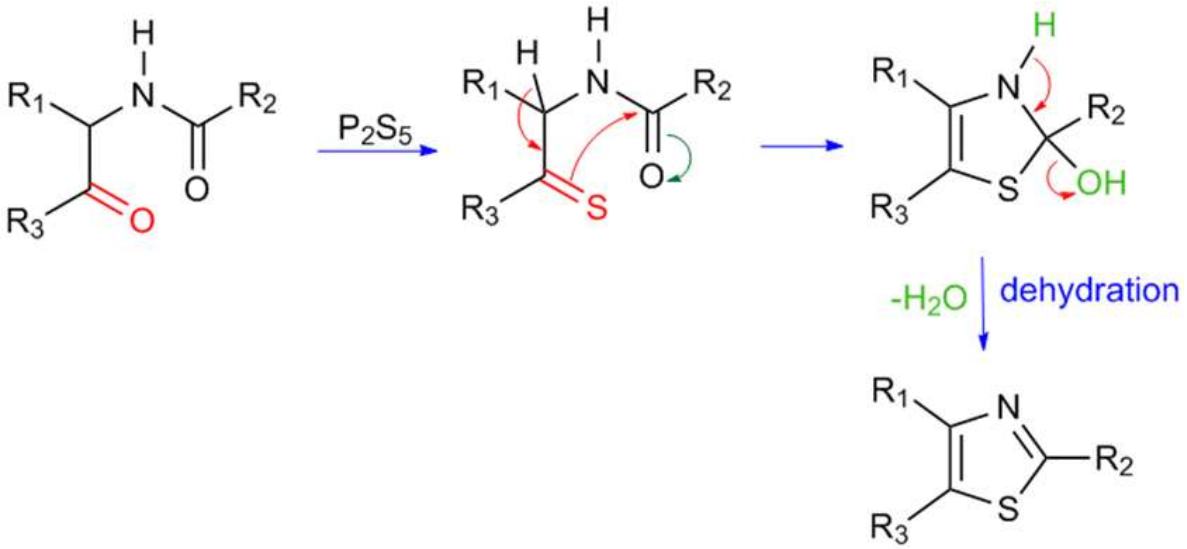


α- acylamino -carbonyl-compound

Synthesis

1. Gabriel synthesis

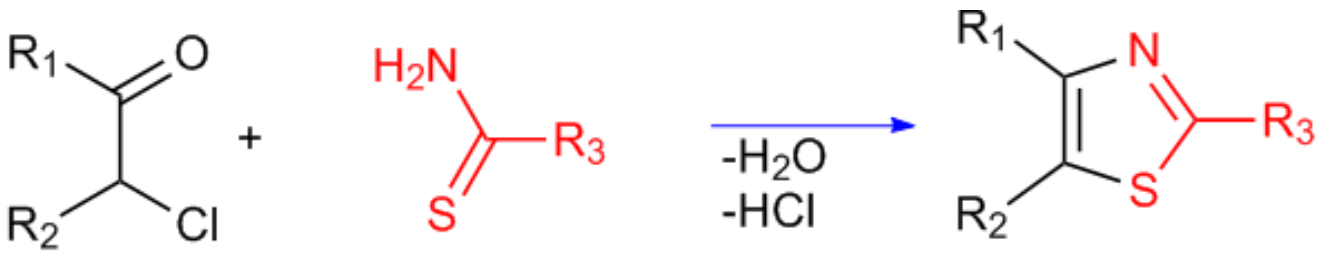
Mechanism



Synthesis

2. From an α- Hydroxy - Carbonyl Component (Hantzsch Thiazole Synthesis)

- condensation of α-haloketones and thioamides referred to as the Hantzsch thiazole synthesis.

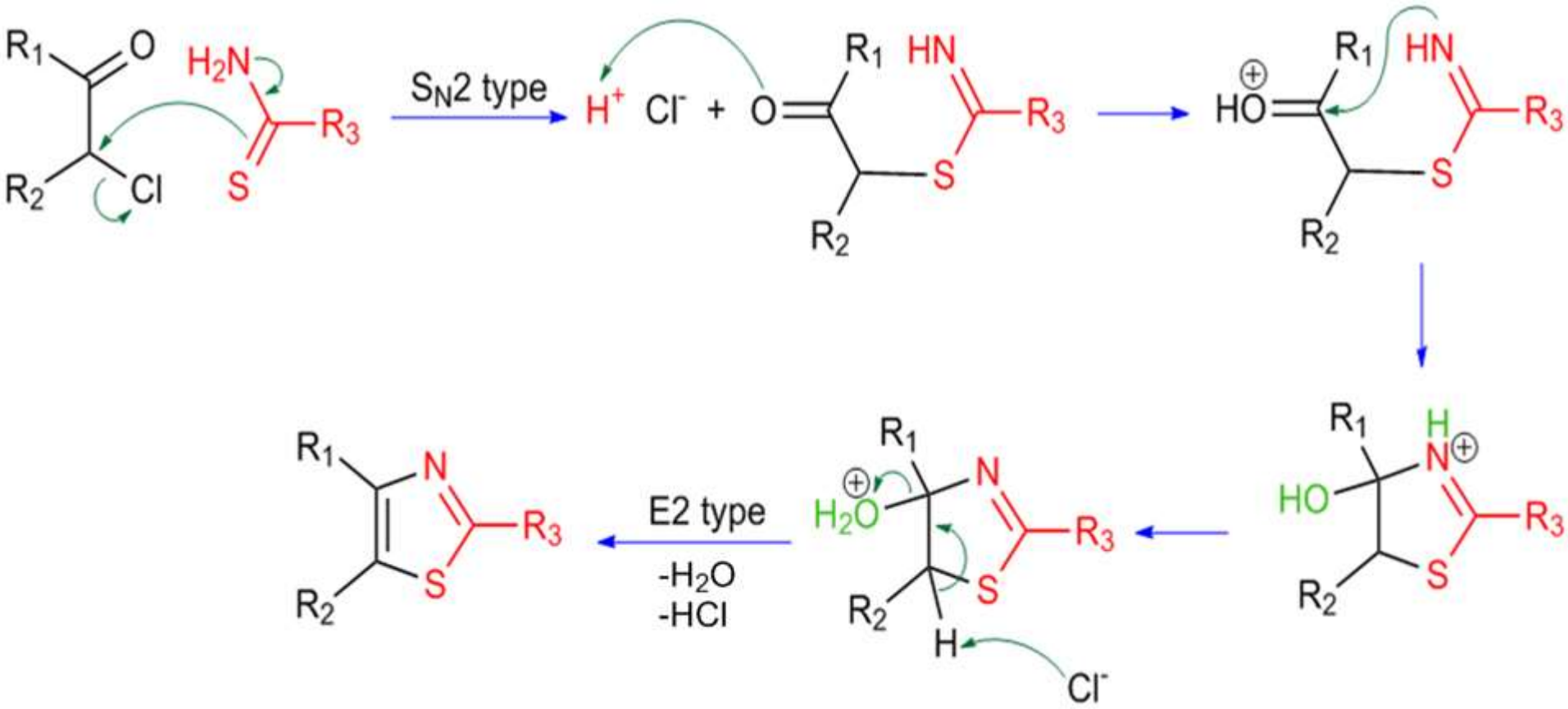


α-halo ketones thiamide substituted thiazole

Synthesis

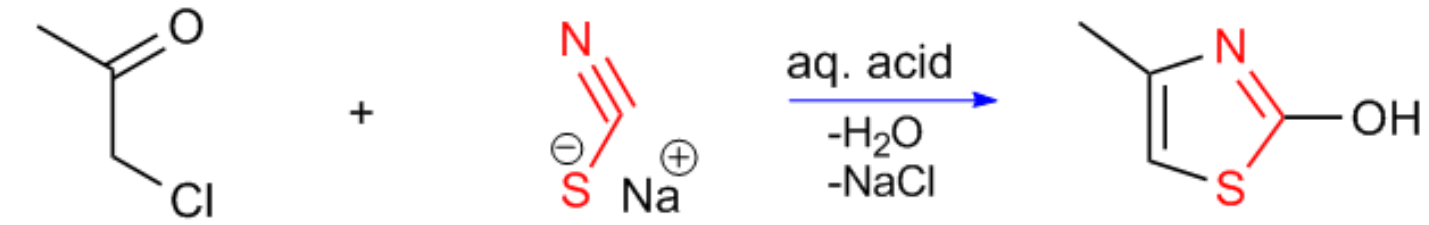
2. From an α- Hydroxy - Carbonyl Component (Hantzsch Thiazole Synthesis)

Mechanism



Synthesis

3. From an thiocyanate salts

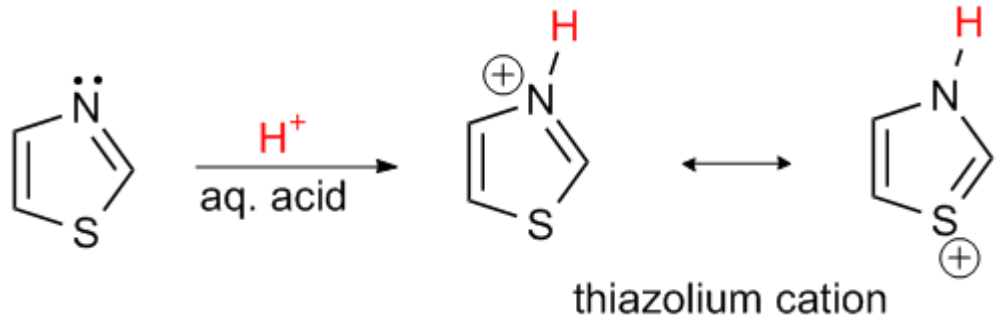


chloroacetone thiocyanate salt 2-hydroxy-4-methylthiazole

Reactions

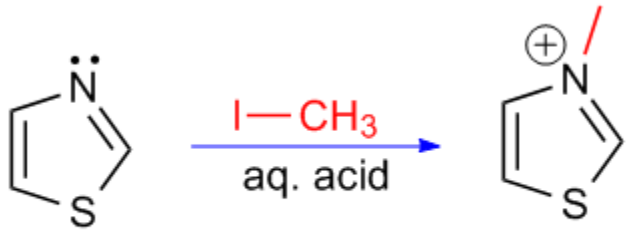
1. Electrophilic addition to N

a. Protonation (basic property)



thiazolium cation

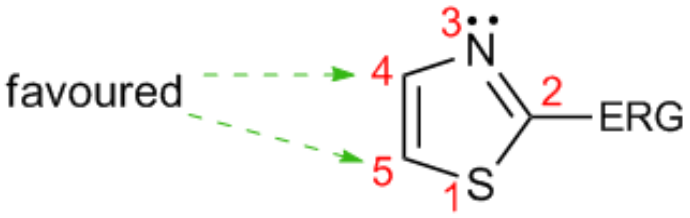
b. *N*-alkylation



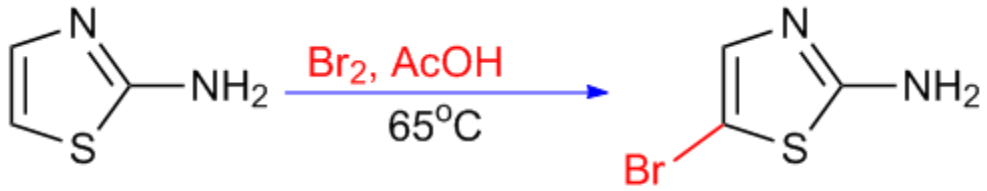
N-methyl-thiazolium salt

Reactions

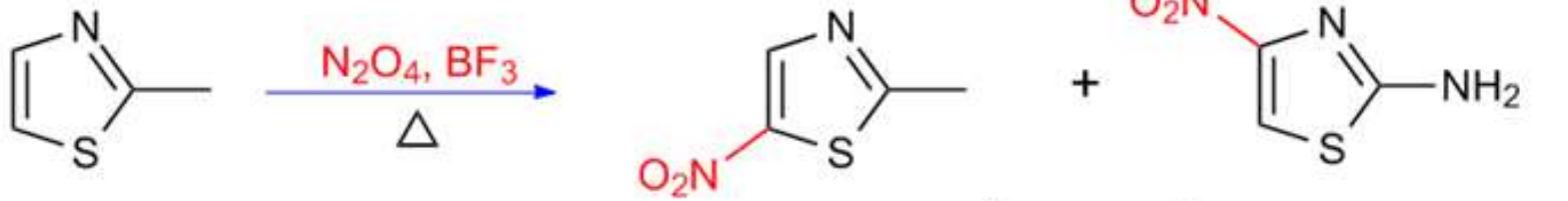
2. Electrophilic substitution to C



a. Nitration



2-aminothiazole — 2-amino-5-bromothiazole



2-Methylthiazole

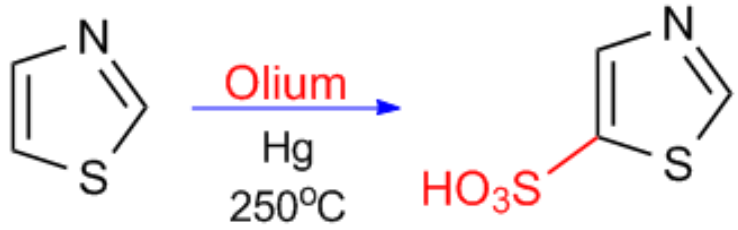
2 : 1

2-methyl-5-nitrothiazole — 2-methyl-4-nitrothiazole

Reactions

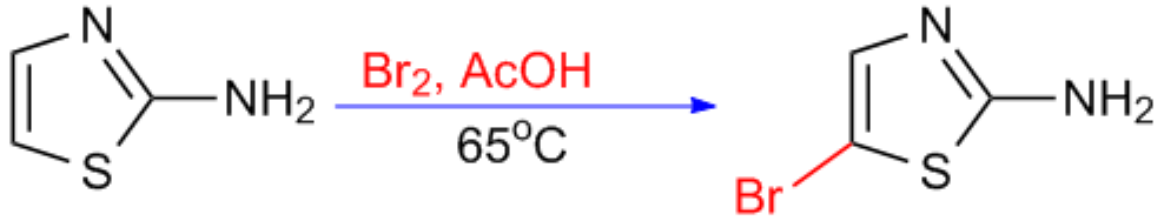
2. Electrophilic substitution to C

b. Sulphonation



thiazole-5-sulfonic acid

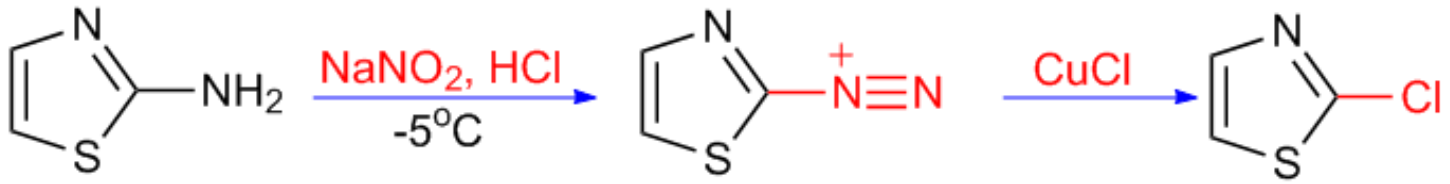
c. Halogenation



2-Methylthiazole

2-amino-5-bromothiazole

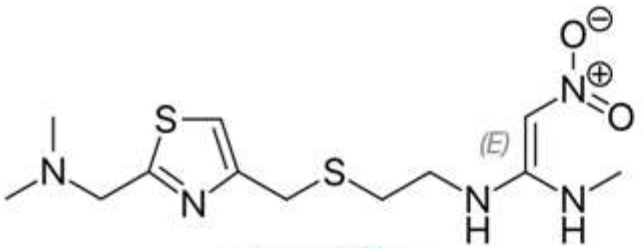
Reactions



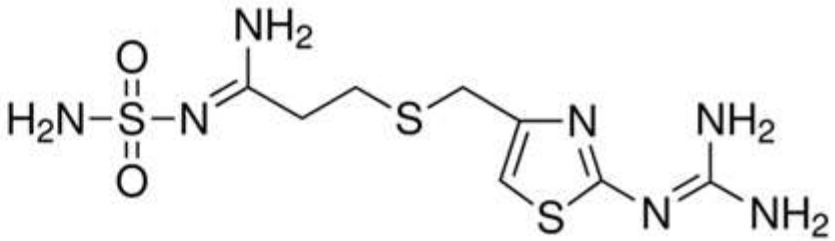
2-aminothiazole thiazole-2-diazonium 2-chlorothiazole

Medicinal uses

(1) H_2-receptors blockers: *famotidine, nizatidine* used in Peptic ulcer

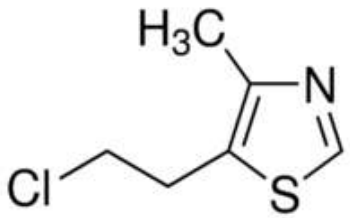


nizatidine



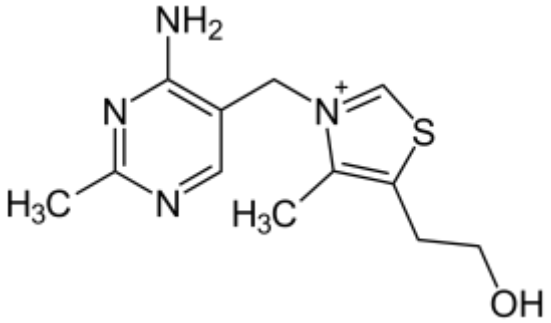
famotidine

(2) *Chlormethiazole* used as sedative hypnotic

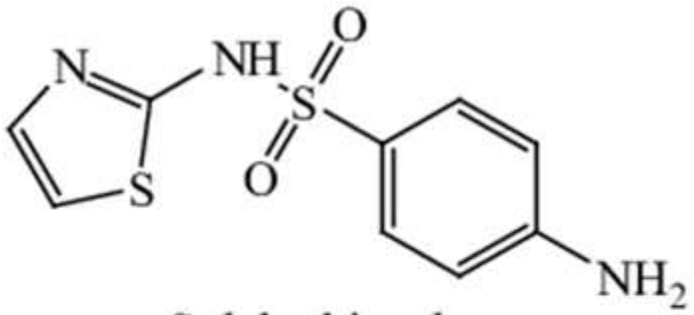


(3) *Vitamin B1 (Thiamine):*

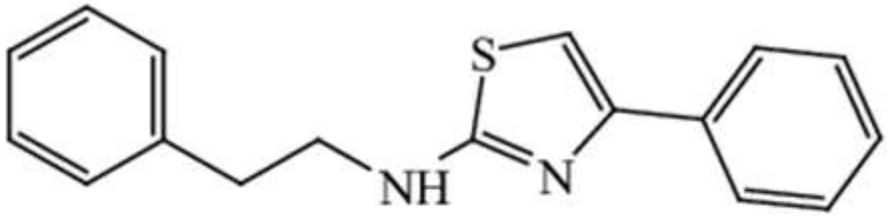
- Used in thiamine deficiency



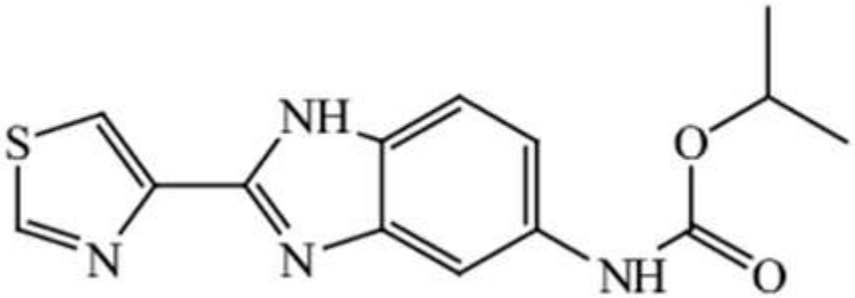
Medicinal uses



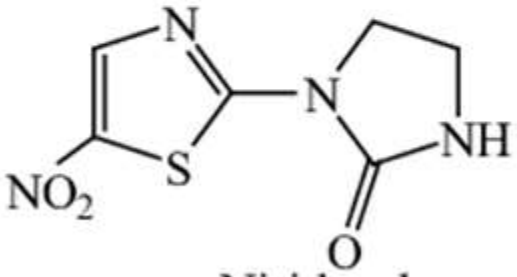
Sulphathiazole
(Antibiotic)



Fanetinole
(Anti-Inflammatory)



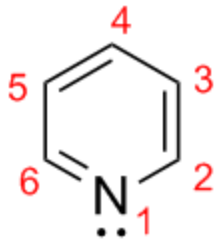
Combendazole
(Fungicidal)

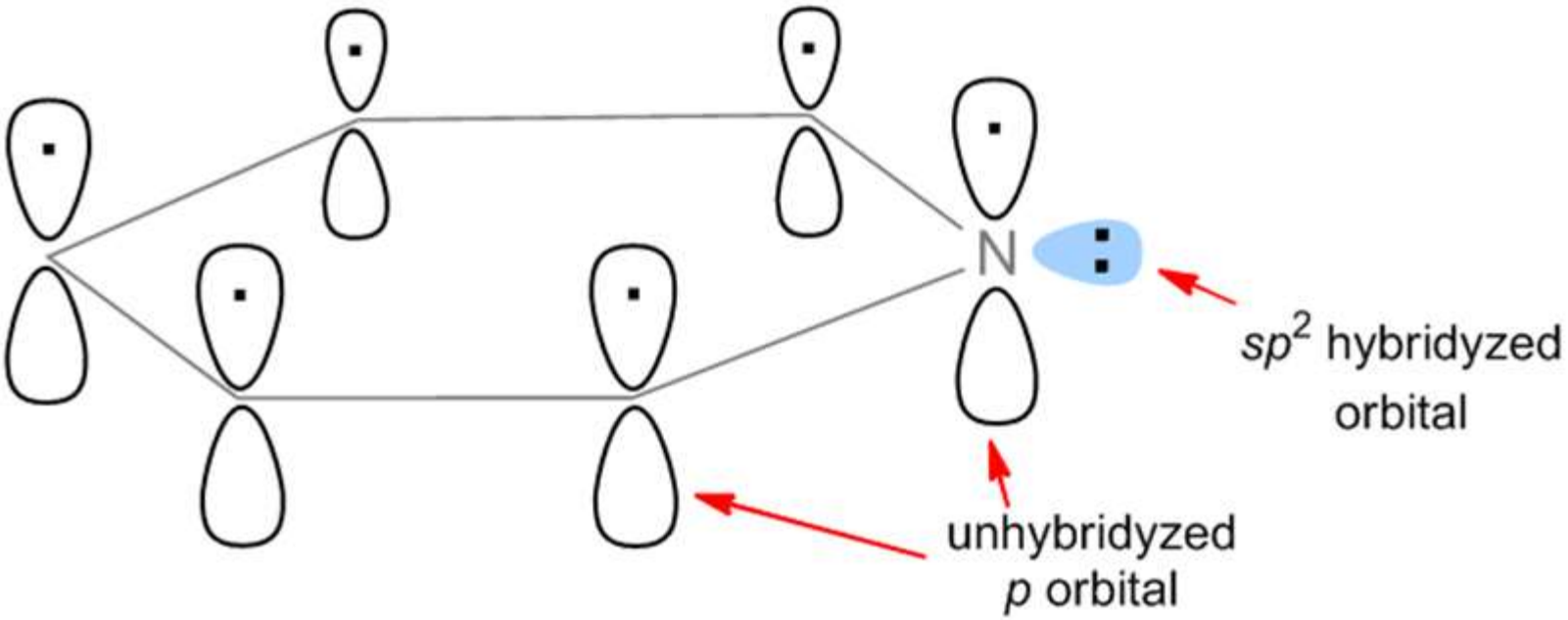


Niridazole
(Schistozomicidal)

Properties

1. Aromaticity





PYRIDINE

Properties

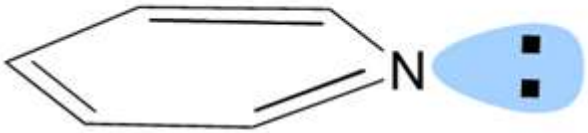
1. Aromaticity

- **Pyridine** have 5 C and 1 N , all are sp^2 hybridized
- sp^2 hybridization is planar, it makes a planar pyridine ring structure.
- Each ring atoms also contains unhybridized p orbital that is perpendicular to the plane of σ bonds (plane of ring).
- Here p orbitals are parallel to each other, so overlapping btwn p orbitals is possible.
- the total nu of non bonding e- are 6 (5 of five C, 1 from N)
- The resonance of 6 e- follows the Hückel's rule
- So ….

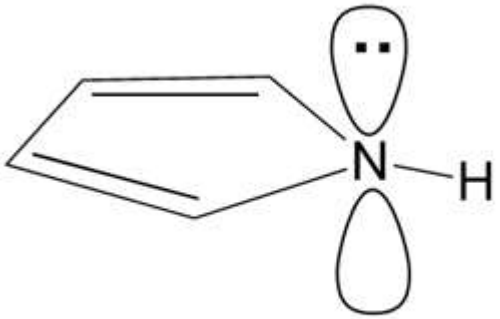
Properties

2. Basicity

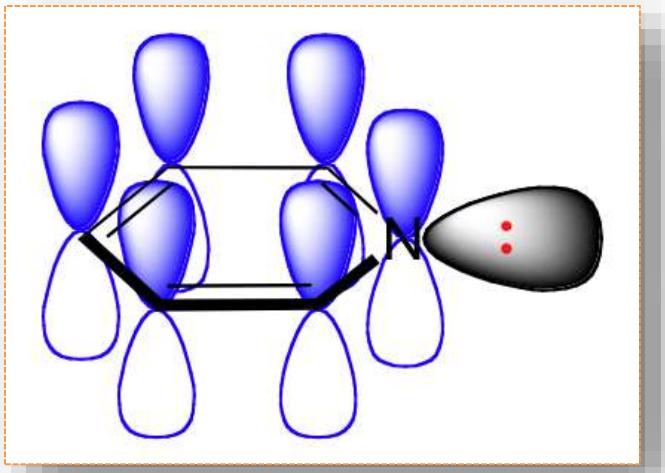
Pyridine is more basic than pyrrole

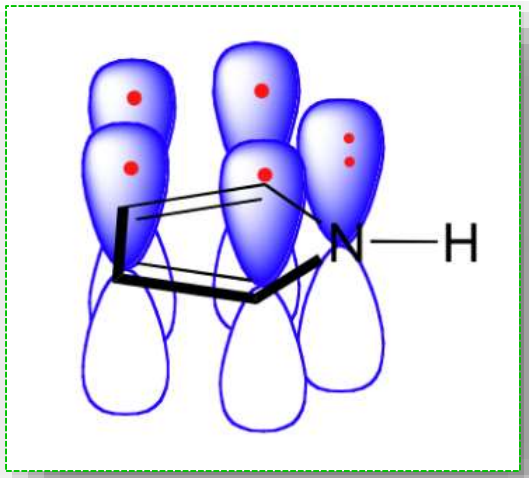


pyridine



pyrrole

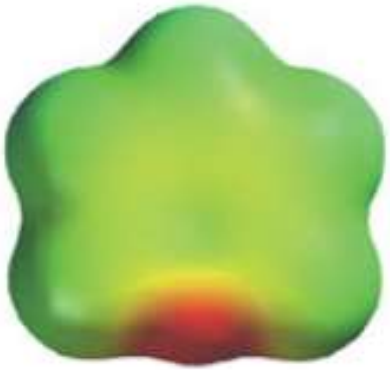




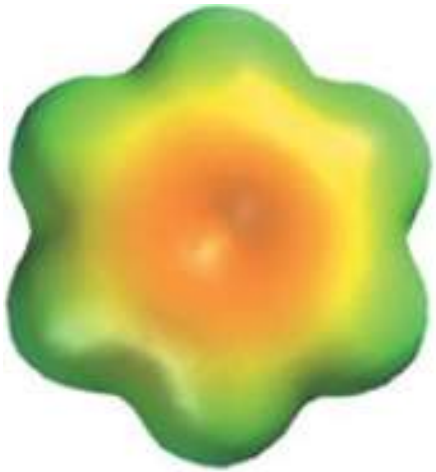
Properties

2. Basicity

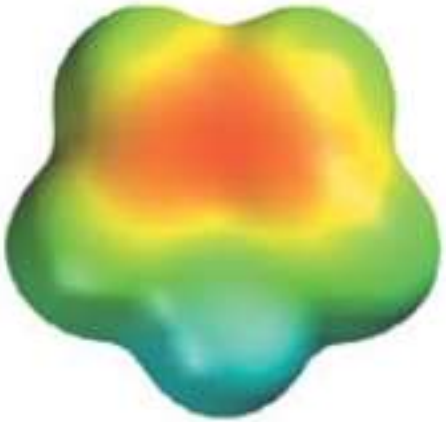
Pyridine is more basic than pyrrole



pyridine



benzene



pyrrole

Properties

2. Basicity

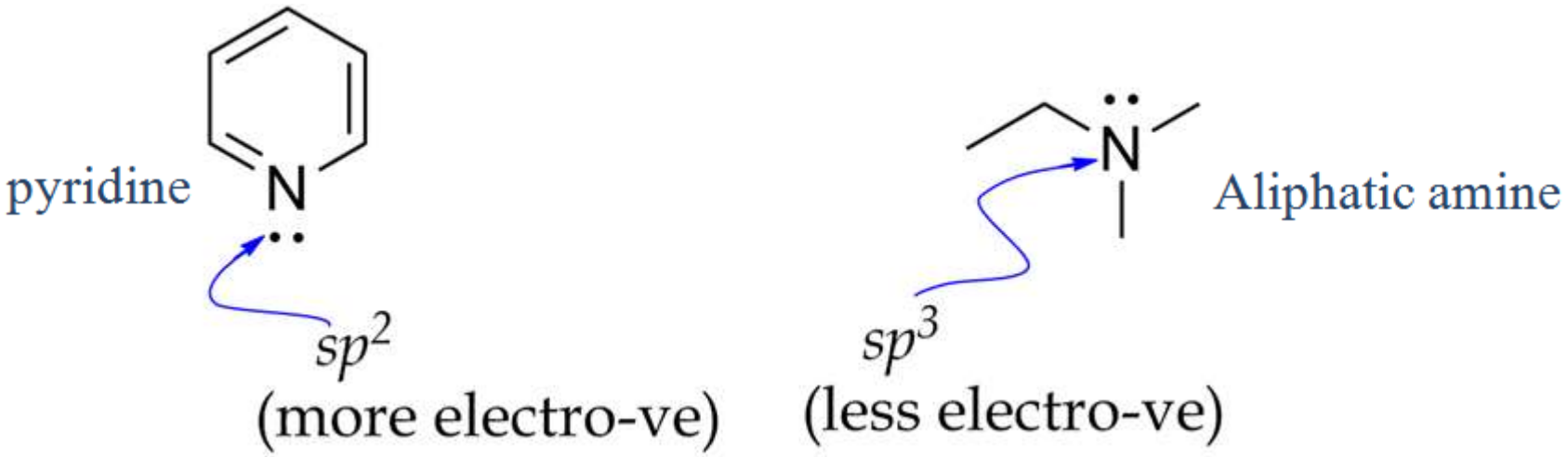
Pyridine is more basic than pyrrole

- Basicity depends on availability of lone pair.
- Pyridine N have lone pair of $\bar{e}$ in same plane of pyridine hybridized orbitals plane → So it is not participating to resonance phenomena → lone pair is readily available for acid-base reaction.
- Pyrrole N have lone pair of $\bar{e}$ perpendicular to plane of pyridine hybridized orbitals plane. → it participates in resonance (delocalization of lone pair) → not readily available for acid-base reaction.
- As lone pair of $\bar{e}$ of pyridine are readily available than pyrrole…
  … Pyridine is more basic than pyrrole

Properties

2. Basicity

Pyridine is less basic than aliphatic amines

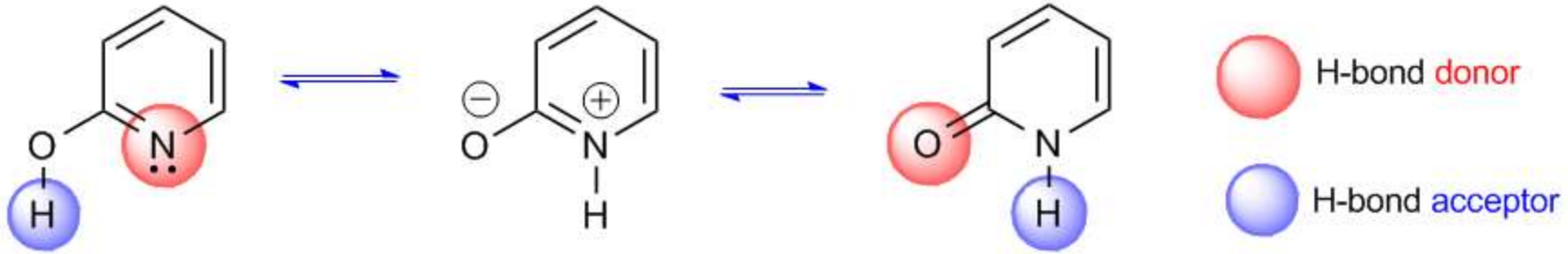


- Sp^2 hybridized N is more electro-ve (more *s* character) than Sp^3 → lone pair of $\bar{e}$ more closely held toward more electro-ve N → less available for acid-base reaction.
- As lone pair of $\bar{e}$ is not readily available in pyridine , it is less basic than aliphatic amines.

Properties

3. Tautomerism

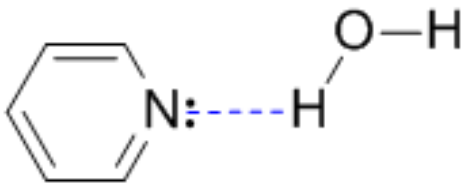
- Tautomeric structures involve when pyridine substituted at 2nd - / 4th - position with groups such as –XH (X = O,N or S)



2-hydroxypyridine 2-pyridone

4. Hydrogen bonding

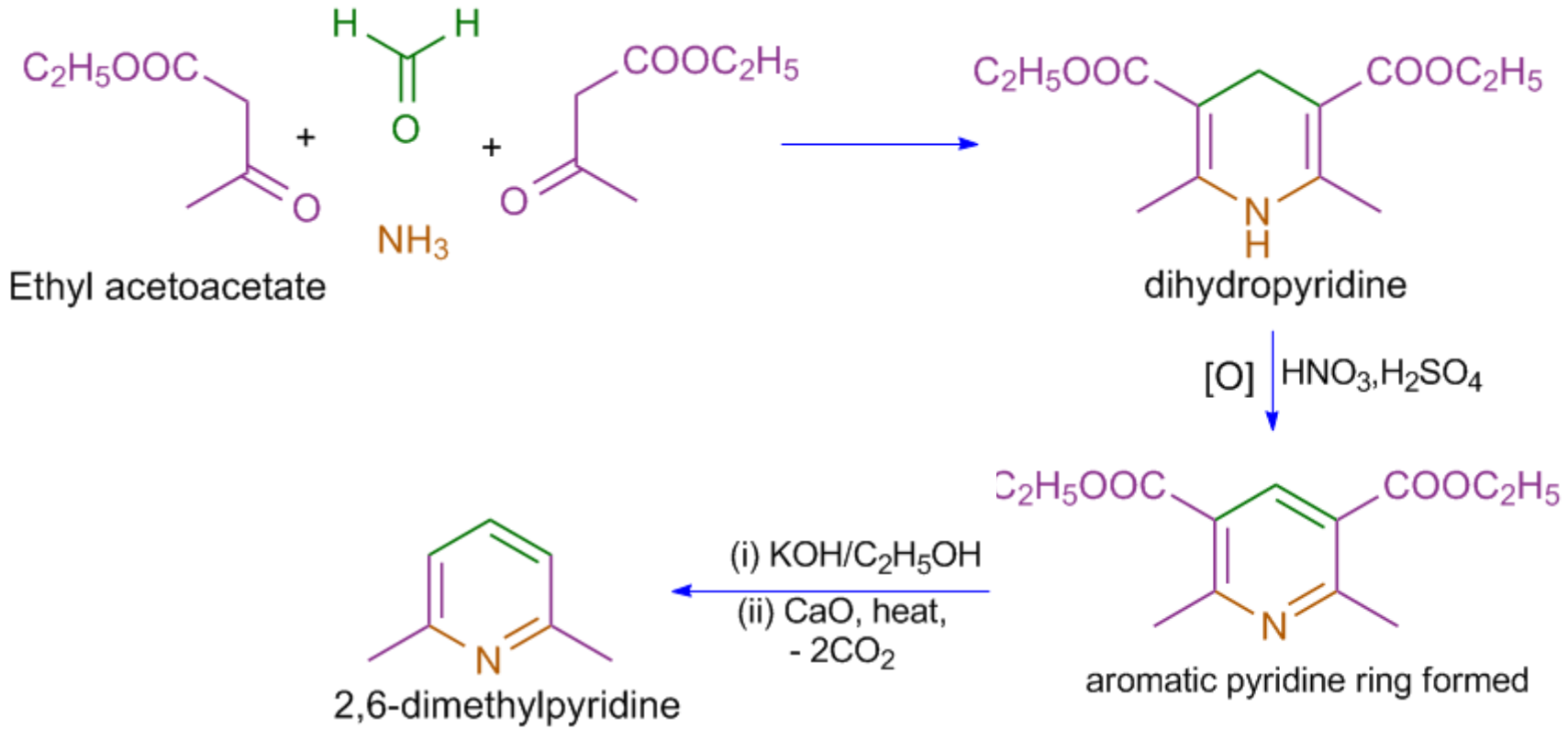
- Pyridine is water soluble



Synthesis

1. Hantzsch pyridine synthesis

- Condensation of an aldehyde with two moles of a β-dicarbonyl compound and ammonia.

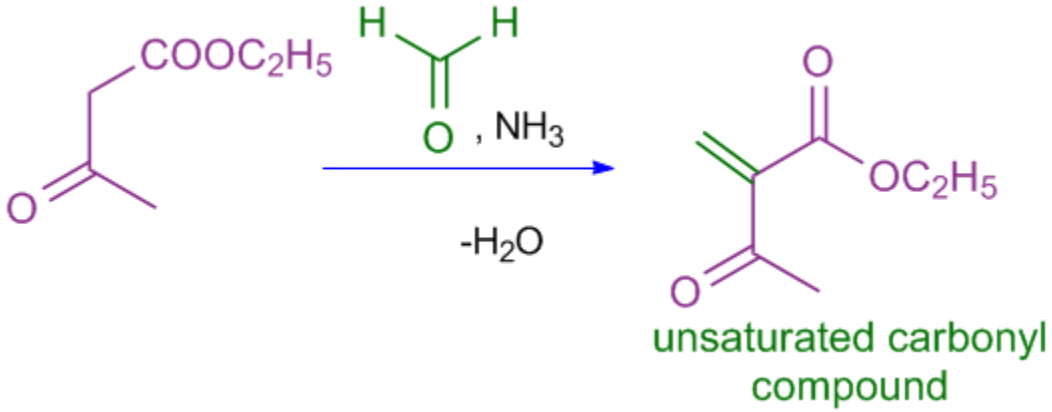


Synthesis

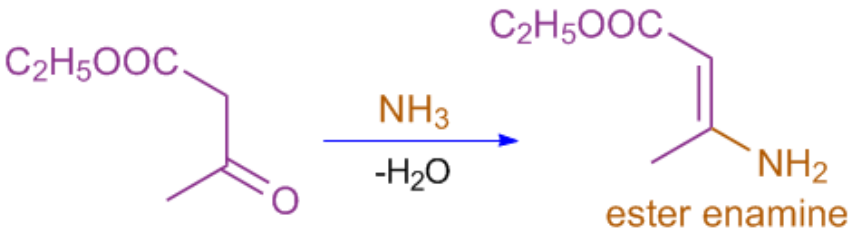
1. Hantzsch pyridine synthesis

Mechanism

Step 1: Knoevenagel Condensation between the β-ketoester and aldehyde



Step 2: Formation of the ester enamine

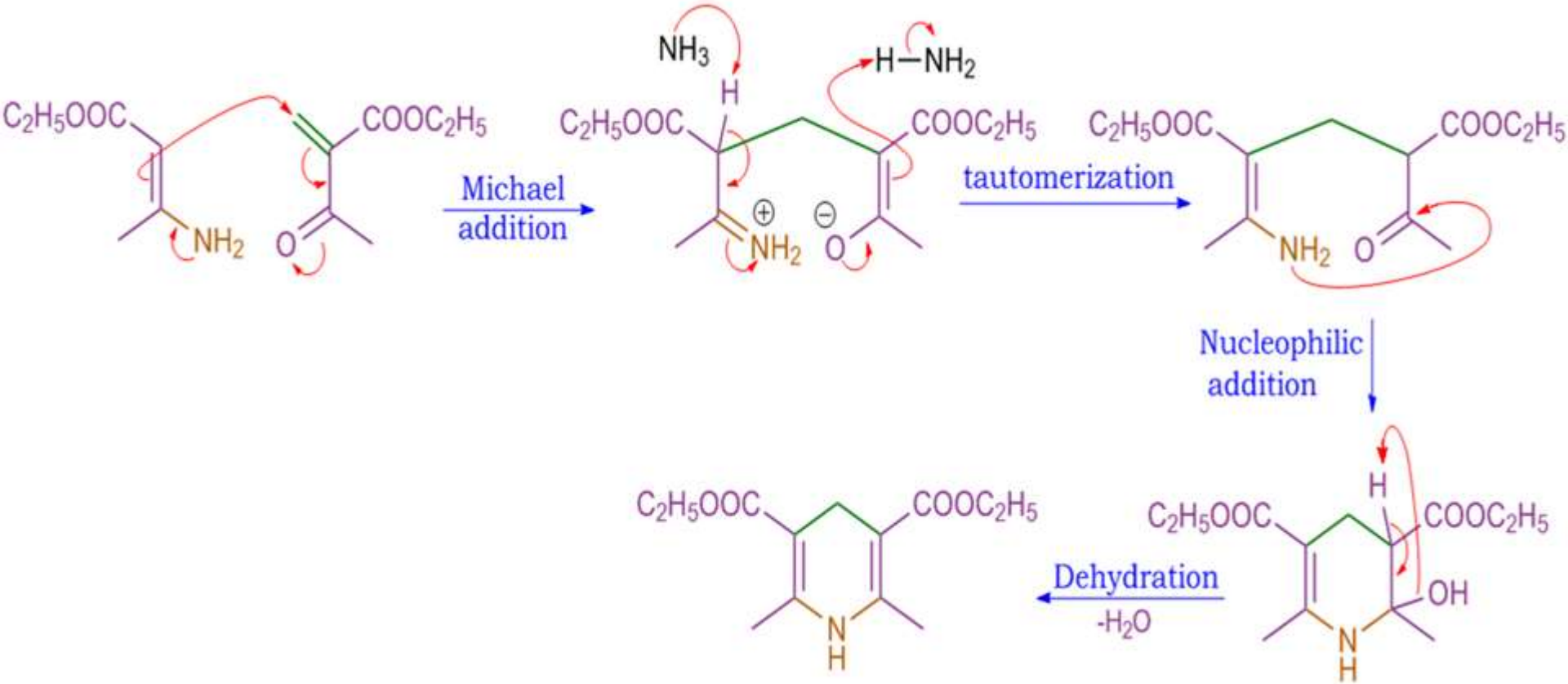


Synthesis

1. Hantzsch pyridine synthesis

Mechanism

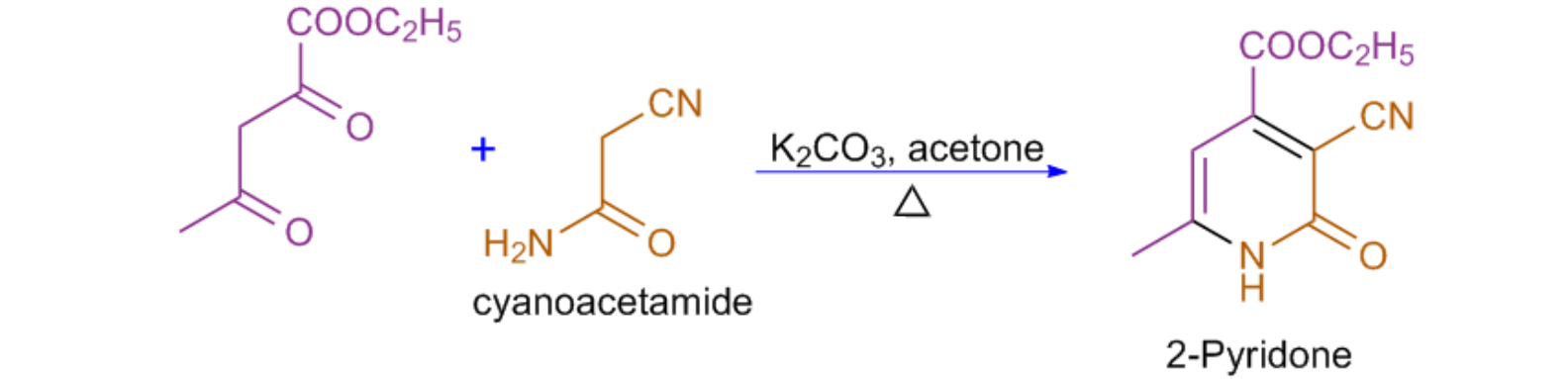
Step 3: Formation of the dihydropyridine



Synthesis

2. The Guareschi Synthesis

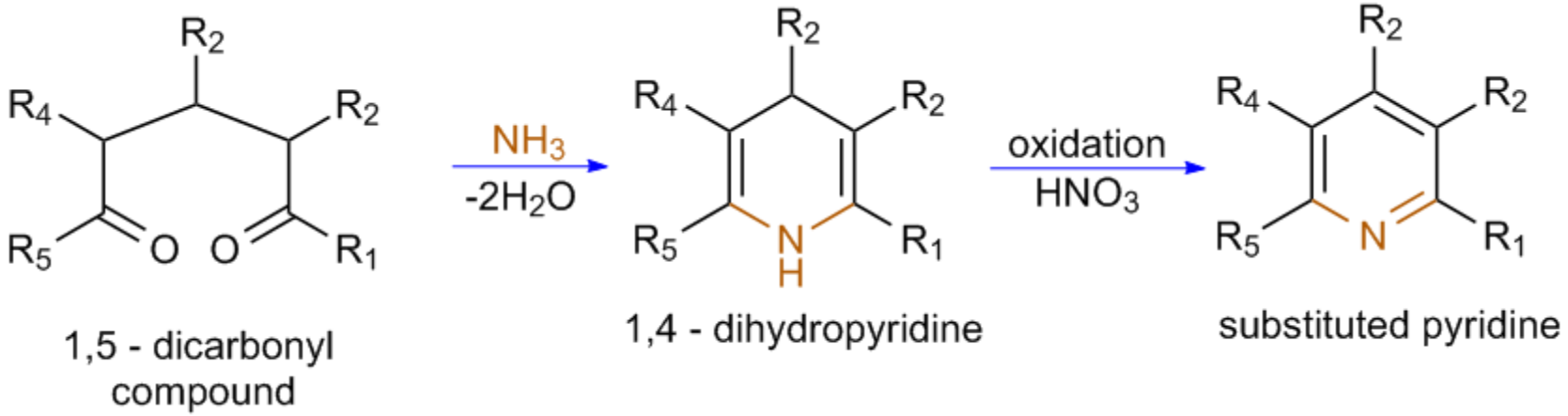
- Modification of Hantzsch synthesis, use of cyanoacetamide as the nitrogen - containing component.



Synthesis

3. From 1,5 - Dicarbonyl Compounds

- Ammonia reacts with 1,5 - dicarbonyl compounds to give 1,4 - dihydropyridines, which are easily dehydrogenated to pyridines.



1,5 - dicarbonyl compound

1,4 - dihydropyridine

substituted pyridine

Synthesis

4. From Oxazoles Kondrat'eva pyridine synthesis

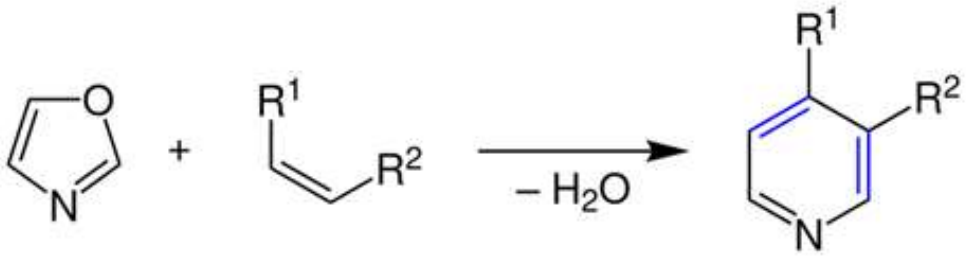
OXAZOLE

Reactions

3. Diels-Alder Reaction

(2) Kondrat'eva pyridine synthesis

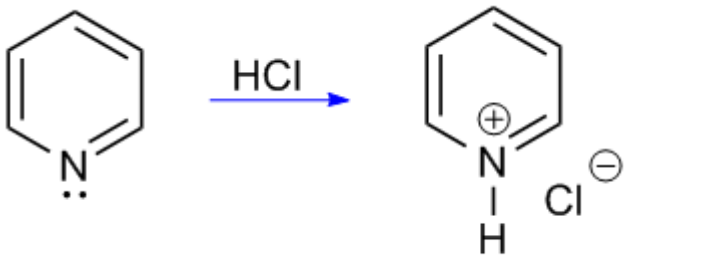
- synthesizing pyridine derivatives by Diels–Alder cycloaddition between an azadiene and a dienophile followed by an extrusion of the resulting bridge of the bicyclic intermediate.



Reactions

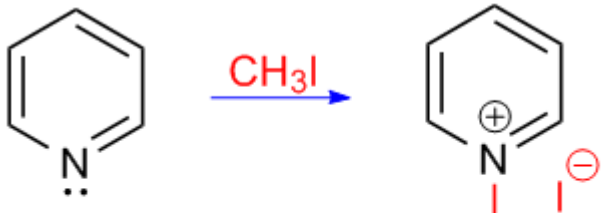
1. Electrophilic addition to N

a. Protonation (basic property)



pyridinium chloride

b. *N*-alkylation

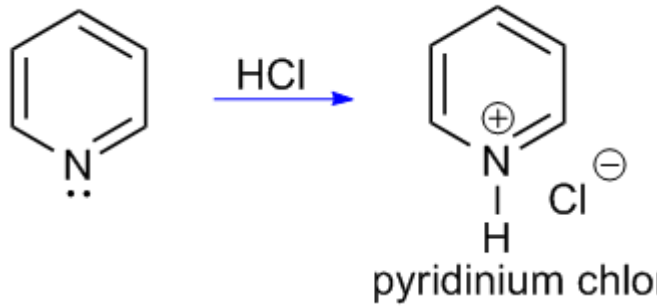


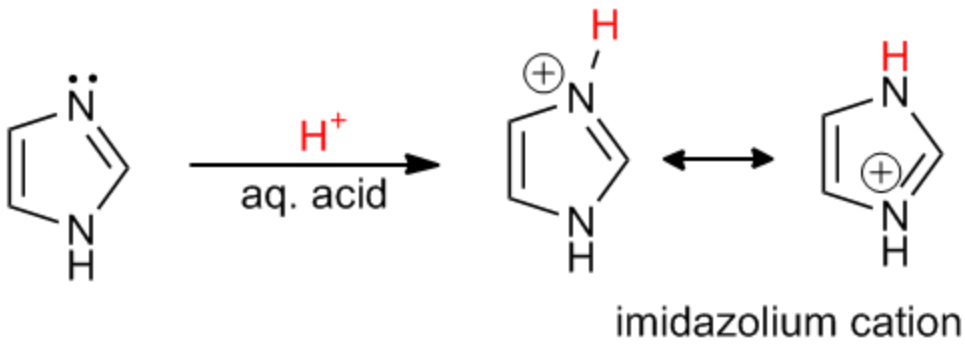
1-methylpyridinium iodide

Reactions

Imidazole is approximately 100 times more basic than pyridine.

- Protonation of imidazole yields an ion that is stabilized by the electron delocalization



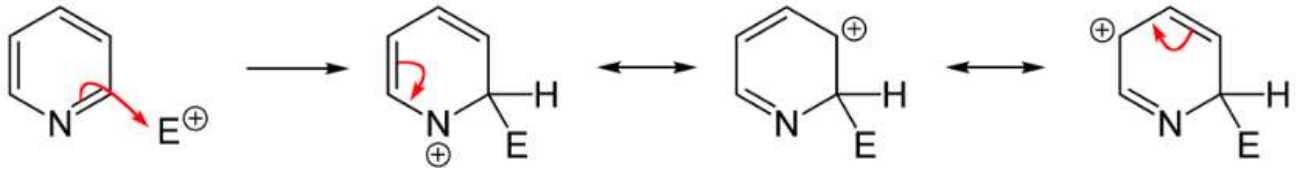


Reactions

2. Electrophilic substitution to C

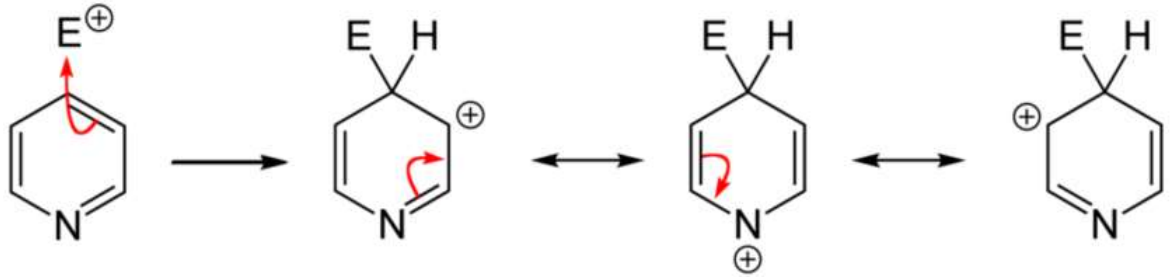
Pyridine gives electrophilic substitution reaction at 3rd position.

C2



C3

C4

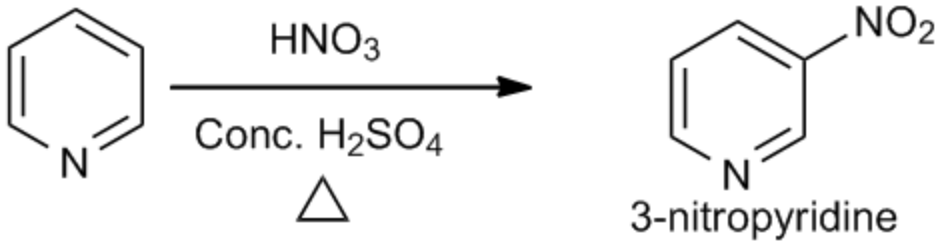


- N is electro-ve , so *+ve charge on N destabilize structure* → here attack at C2 , C4 generates N+ intermediates → less favourable → only C3 is favourable as it can not generate N+ intermediate.

Reactions

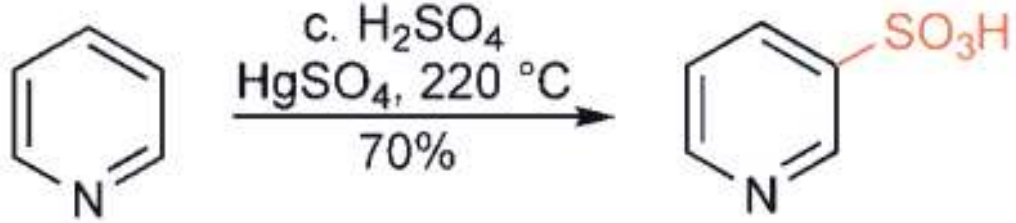
2. Electrophilic substitution to C

a. Nitration



b. sulphonation

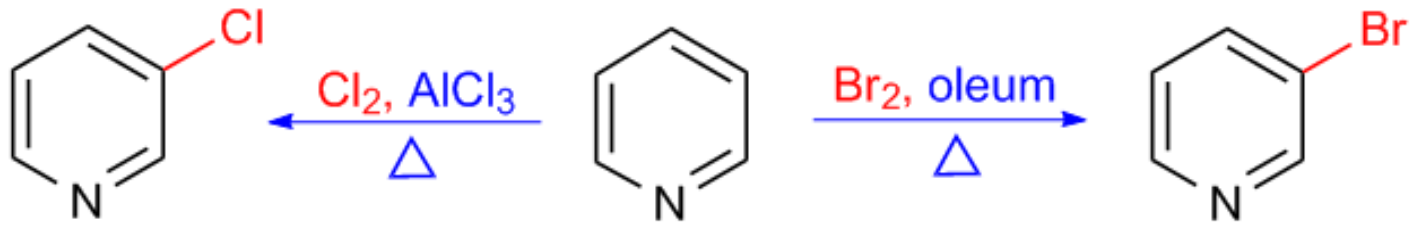
- Pyridine is very resistant to sulfonation using concentrated sulfuric acid *or* oleum, addition of mercuric sulfate in catalytic quantities allows smooth sulfonation.



Reactions

2. Electrophilic substitution to C

c. Halogenation



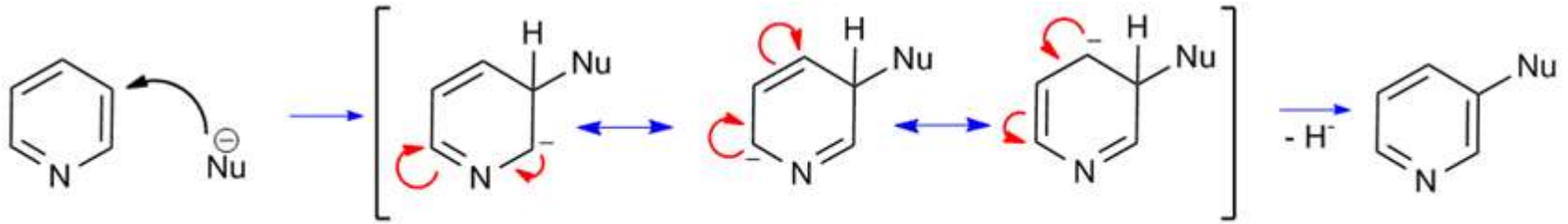
- 3-Bromopyridine is produced in good yield by the action of bromine in oleum.
- 3-Chloropyridine can be produced by chlorination in the presence of aluminium chloride.

Reactions

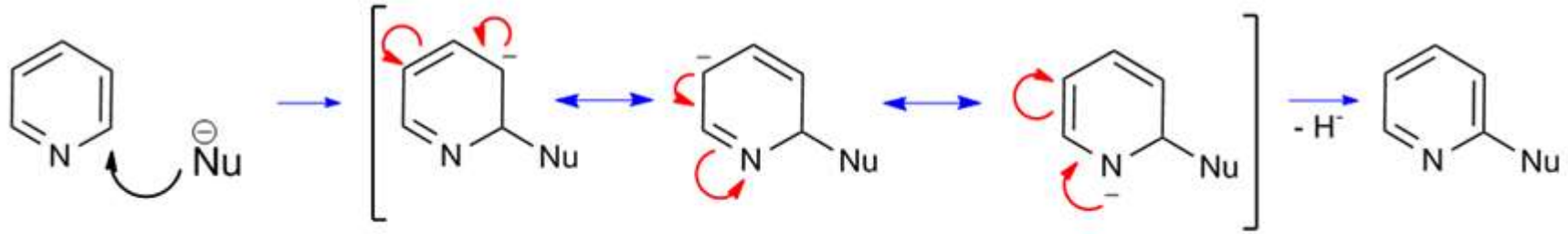
3. Nucleophilic substitution

Why pyridine undergoes nucleophilic substitution reaction at 2-position.

C3



C2



[Especially stable]
-ve Charge on N

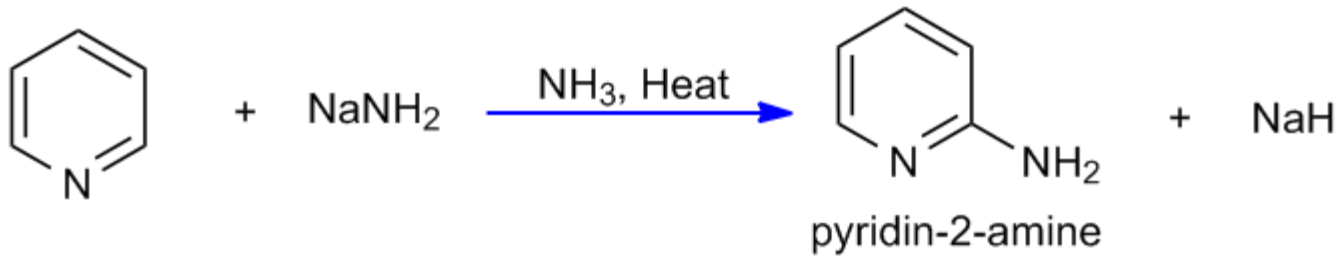
- Attack on 2nd position gives more stable intermediate containing –ve charge on N. thus…

Reactions

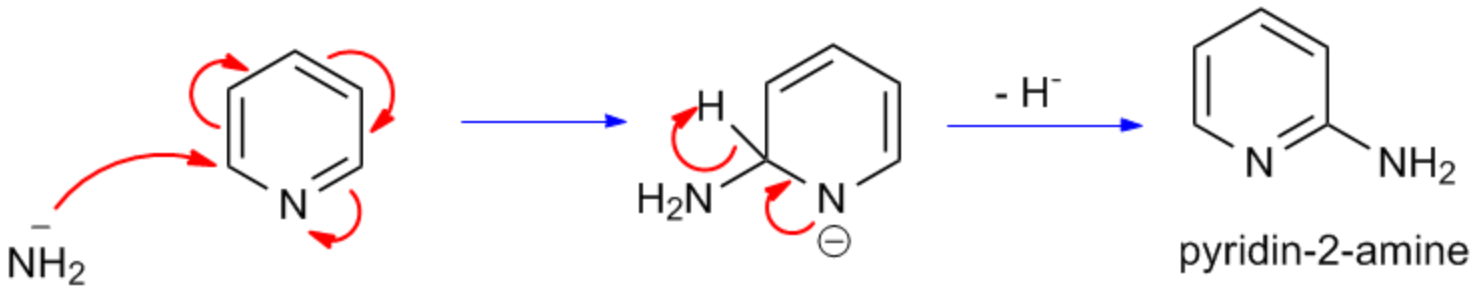
3. Nucleophilic substitution

Chichibabin rxn

- Rxn of pyridine with sodamide at high temp.



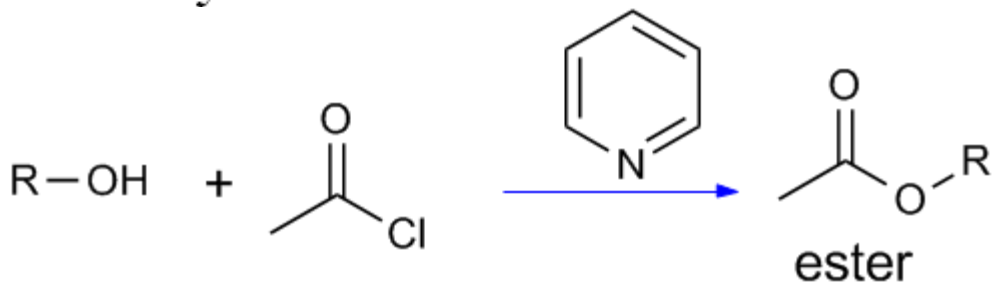
Mechanism



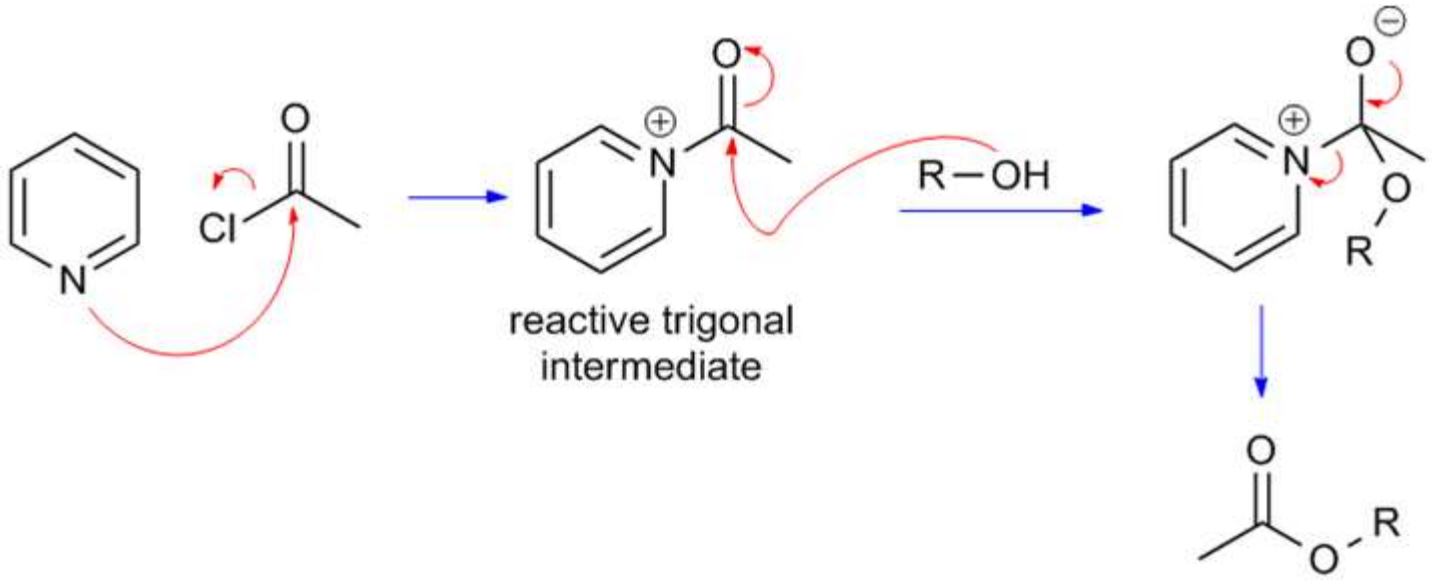
Reactions

4. Pyridine as Nucleophilic catalyst

- Used as catalyst for *acylating* phenols, alcohols and amines using acyl chlorides / anhydrides.

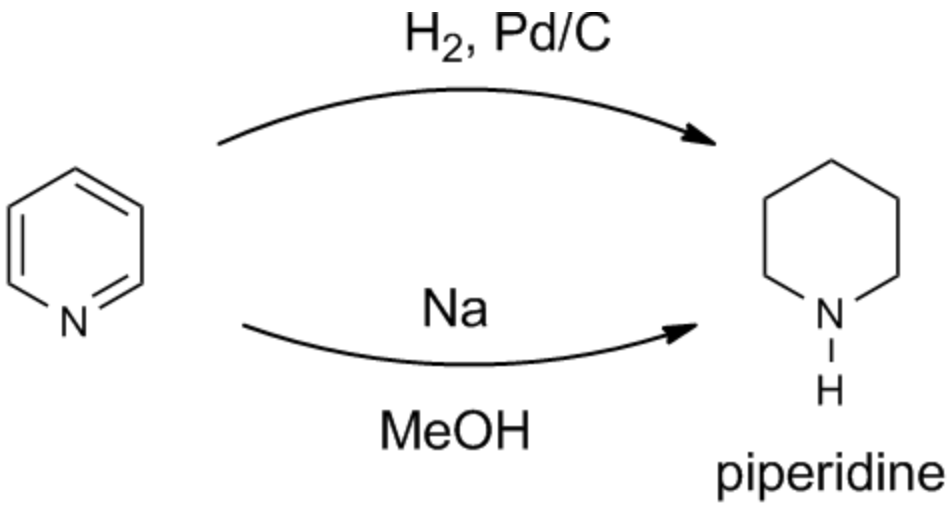


Mechanism



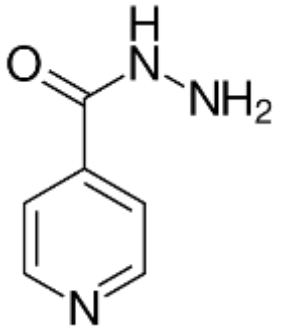
Reactions

5. Reduction

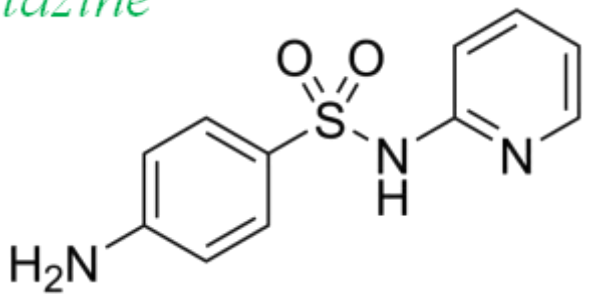


Medicinal uses

(1) Antitubercular Agent : *Isoniazid*

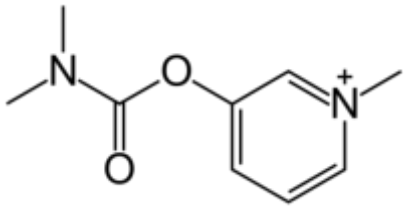


(2) Antibacterial agent: *Sulfapyridine, Sulfasalazine*



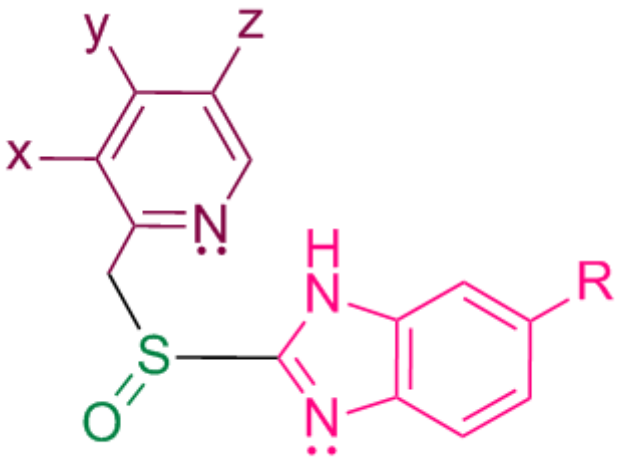
(3) Anticholinesterase agent : *pyridostigmine*

- used in myasthenia gravis



Medicinal uses

(4) Proton Pump Inhibitors : *Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole* - used in peptic ulcer

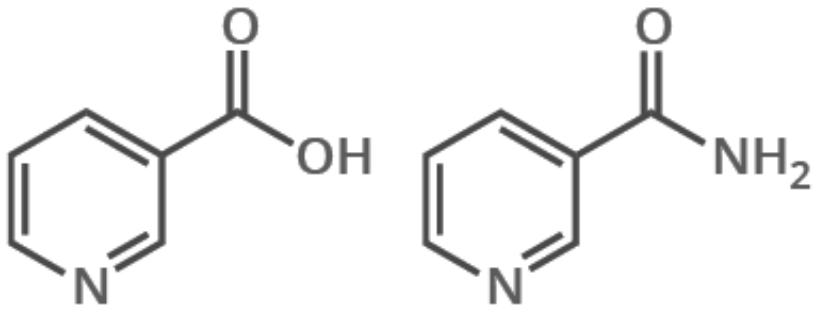


PPI

PPI	X	Y	Z	R
Omeprazole	CH_3	CH_3O	CH_3	CH_3O
Lansoprazole	CH_3	CF_3CH_2O	H	H
Pantoprazole	CH_3O	CH_3O	H	CHF_2O
Rabeprazole	CH_3	$CH_3OCH_2CH_2CH_2O$	H	H

Medicinal uses

VITAMIN B3

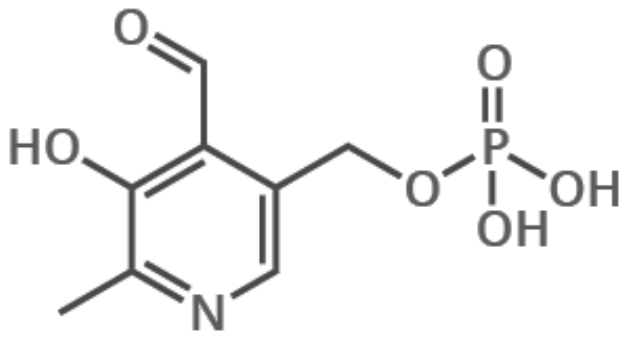


NICOTINIC ACID **NICOTINEAMIDE**

niacin is collective name for these compounds

Helps with digestion and digestive system health. Also helps with the processing of carbohydrates.

VITAMIN B6



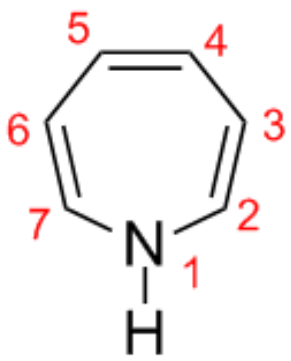
PYRIDOXAL PHOSPHATE

active form in mammalian tissues

Helps make some brain chemicals; needed for normal brain function. Also helps make red blood cells and immune system cells.

Properties

1. Aromaticity



boat conformation
(with 22% chair conformation)

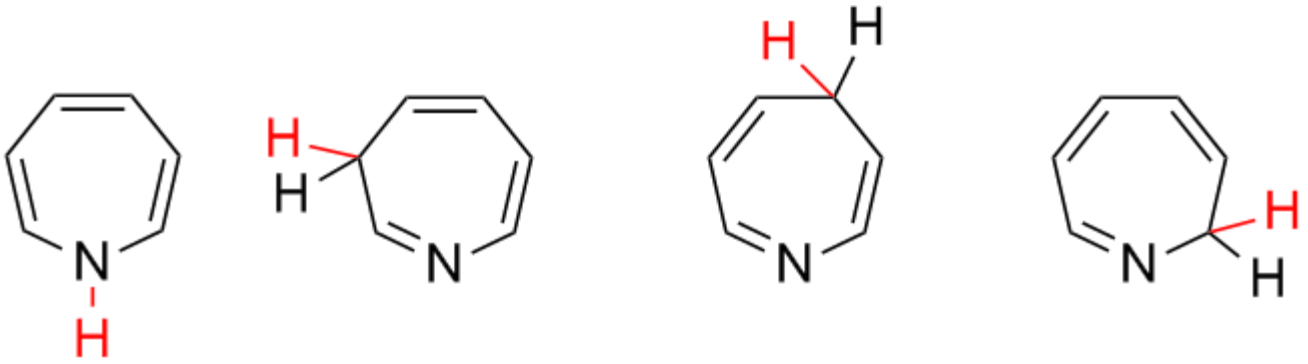
- Planar Azepines (N is Sp^2) have potential 8 e- systems → cyclic & planar with 4n π e- is antiaromatic character → least stable.

  thus ..azepines and its tautomers exist in non-planar conformation (boat conformation , one atom with Sp^3).

- Compound do not comply with Hückel's rule of (4n + 2) π e-
- So… azepine is non- aromatic compound

Properties

2. Tautomerism



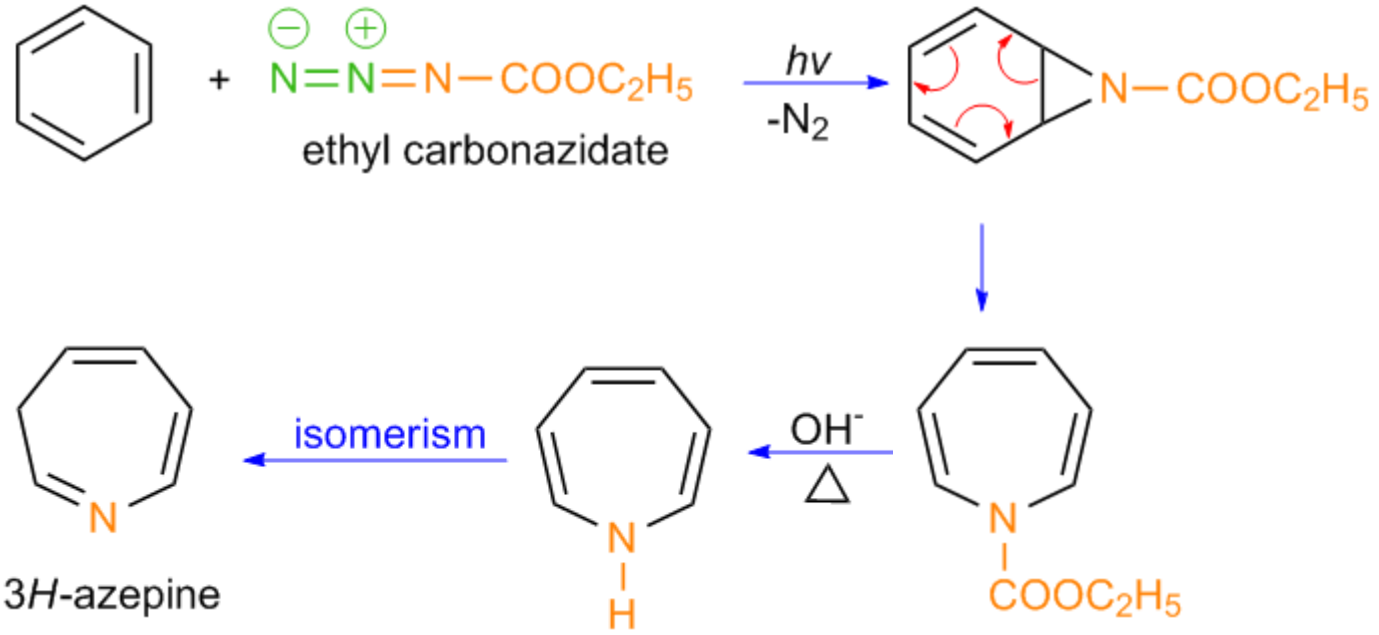
1*H*-azepine 3*H*-azepine 4*H*-azepine 2*H*-azepine

- Stability order : $3H > 4H > 1H$

Synthesis

1. Valence-bond Isomerization

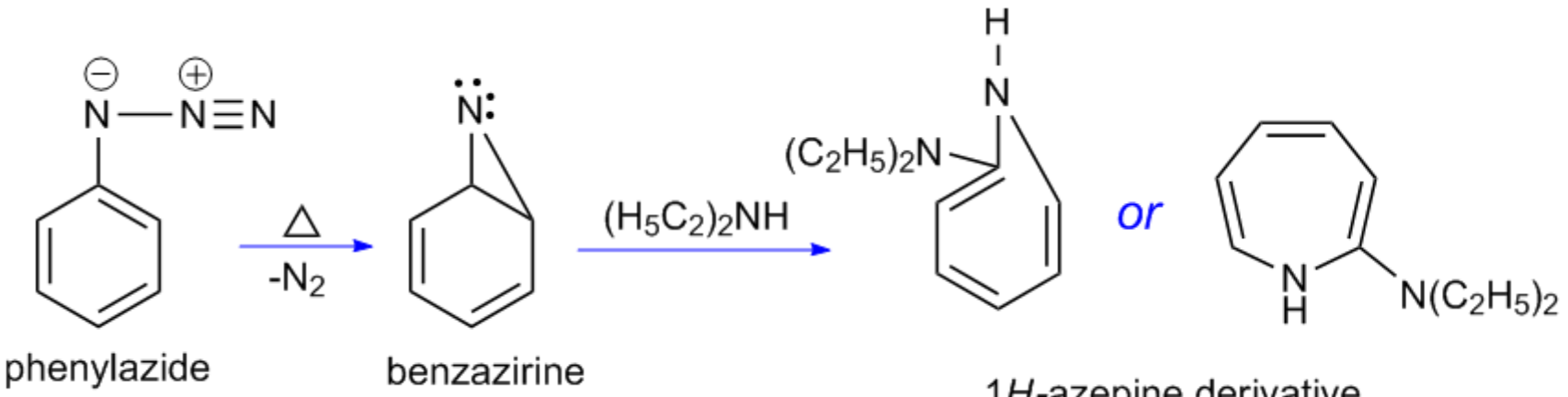
↳ Organization accompanied by change in atomic distance and bond angles.



- Bond reorganization, reorganization of σ- & π- electrons without rearrangement of atoms.

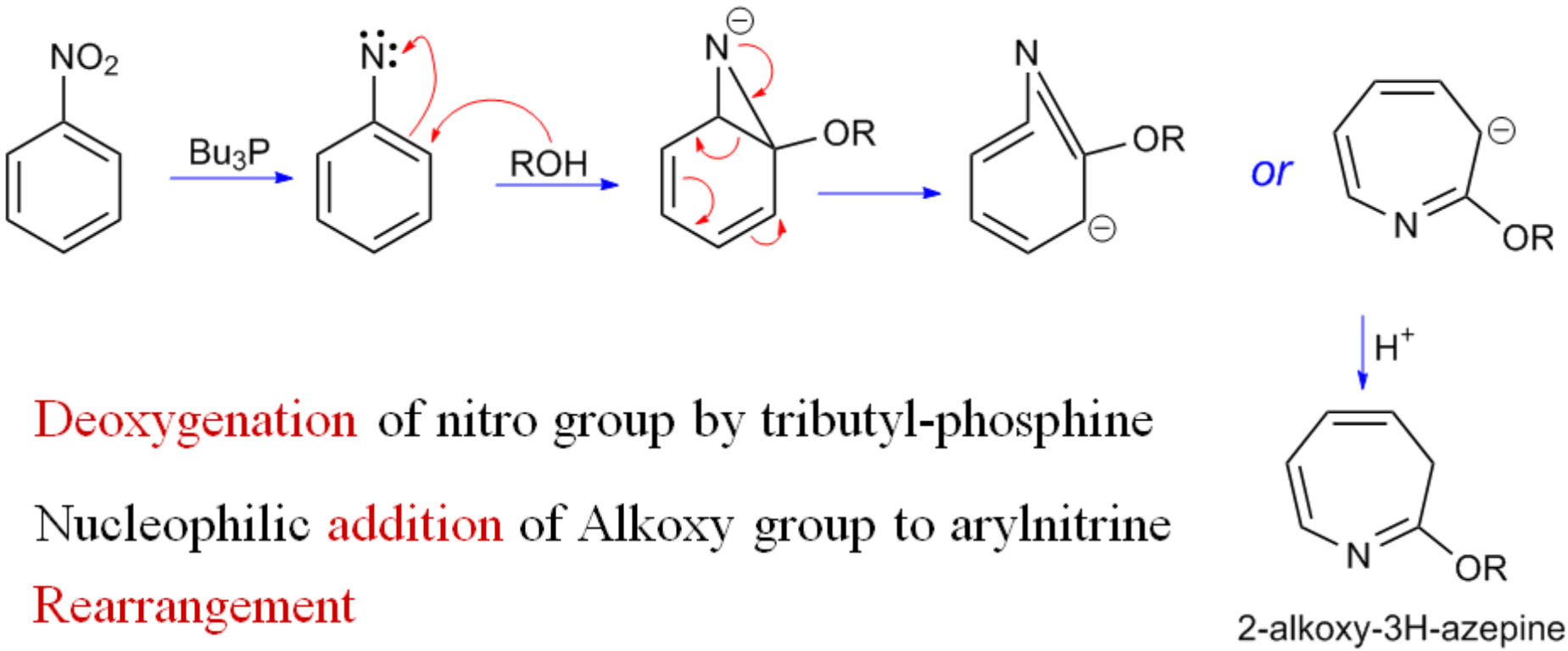
Synthesis

2. From Phenylazide



Synthesis

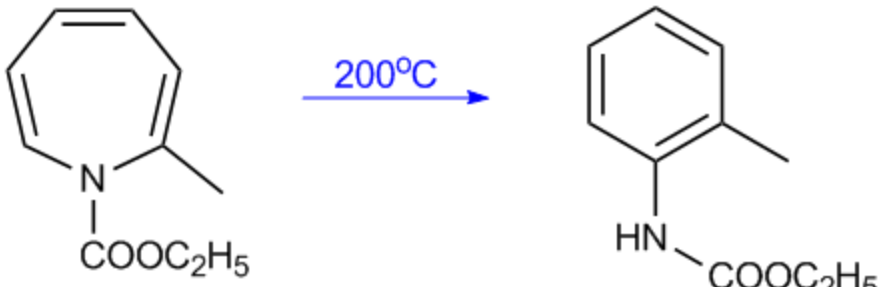
3. From Nitrobenzene



- Deoxygenation of nitro group by tributyl-phosphine
- Nucleophilic addition of Alkoxy group to arylnitrine
- Rearrangement

Reactions

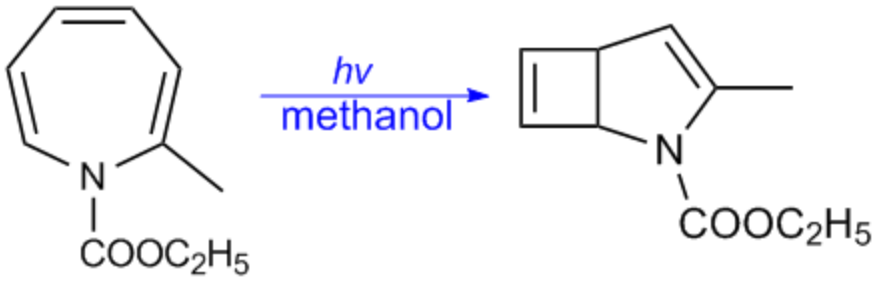
1. Thermal reaction



N-carboethoxy-1-Hazepine *N*-phenylcarbamate

2. Ring contraction

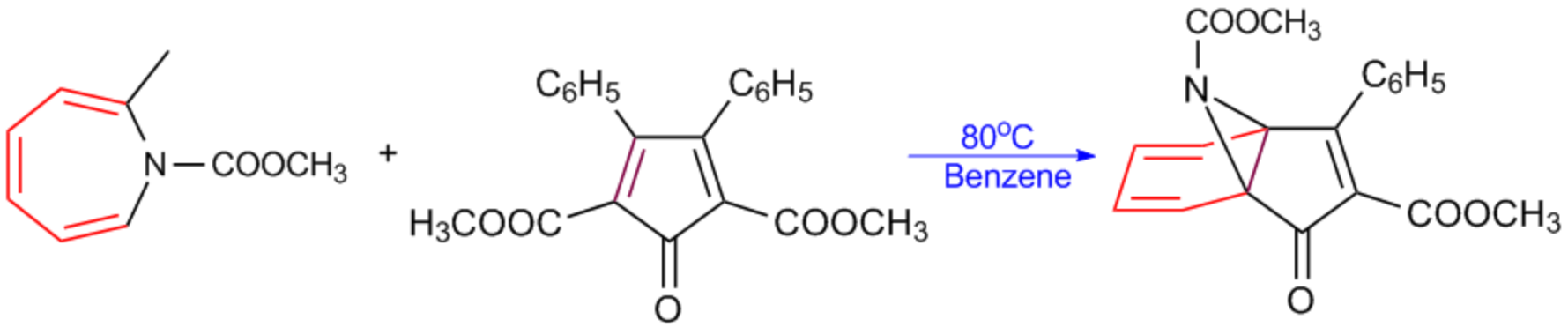
- Orbital symmetry controlled disrotatory electrocyclic process.



Reactions

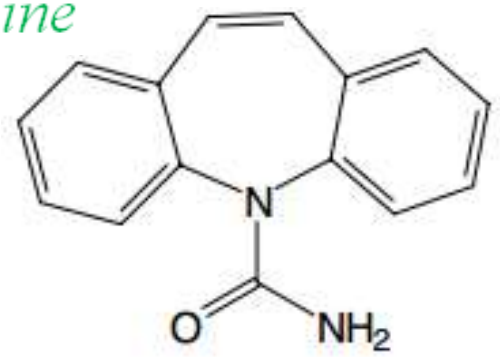
3. Diels-Alder reaction

- 6+2 π electron reaction



Medicinal Uses

(1) Anticonvulsants: *Carbamazepine , Oxcarbazepine*



Carbamazepine (CBZ)

(2) Tricyclic Antidepressants:

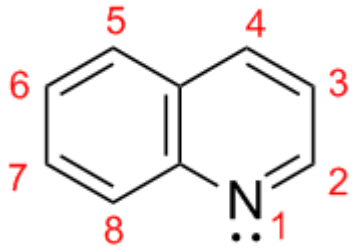
Imipramine, Desipramine,
Clomipramine, Trimipramine

Imipramine

QUINOLINE

Properties

1. Aromatic



1-azanaphthalene
benzo[b] pyridine

- Each atom is sp^2 hybridized , planar
- the total nu of delocalized e- are 10 (9 from nine C, 1 from N) follows the Hückel's rule

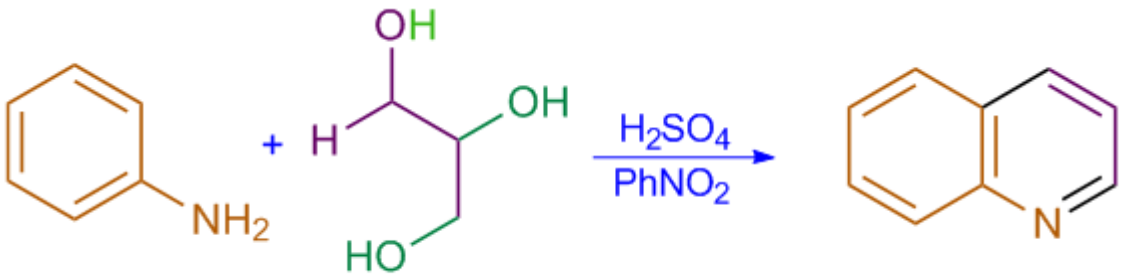
2. Weak base

3. H bonding

Synthesis

1. Skraup Quinoline synthesis

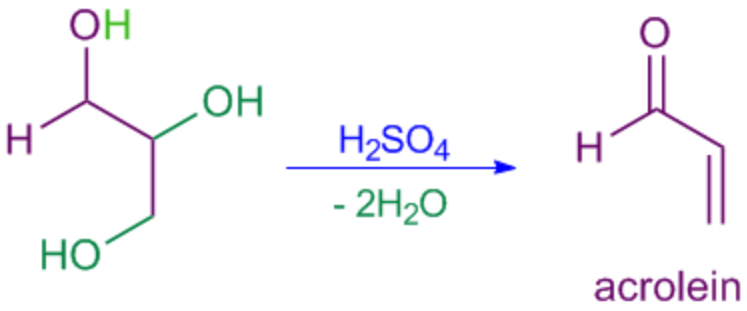
- Quinoline from aniline, glycerol, sulfuric acid and mild oxidizing agent (e.g. nitrobenzene)
- Rxn is exothermic and tends to be violent, thus $FeSO_4$ is added to make it less violent



Synthesis

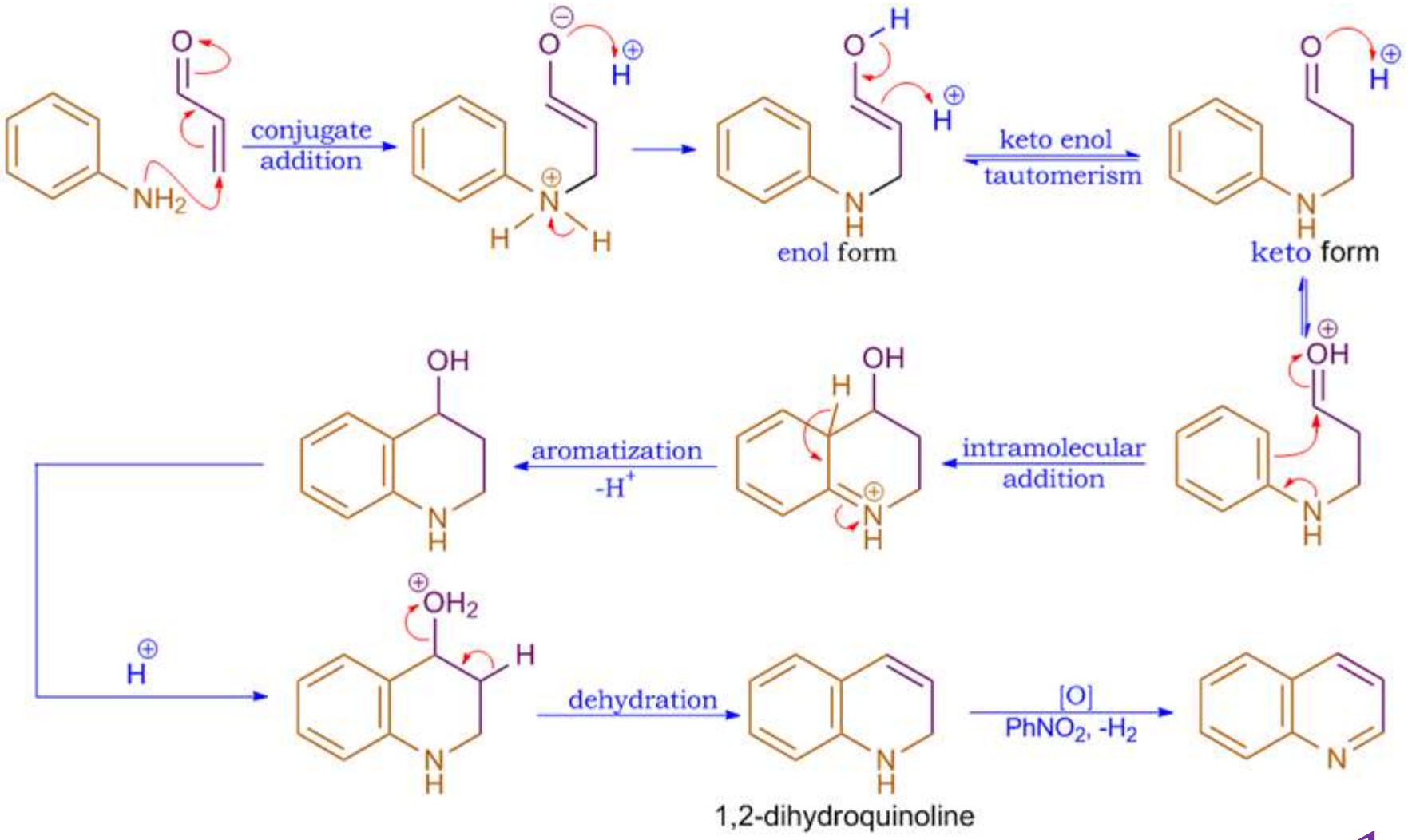
1. Skraup Quinoline synthesis

Mechanism



Synthesis

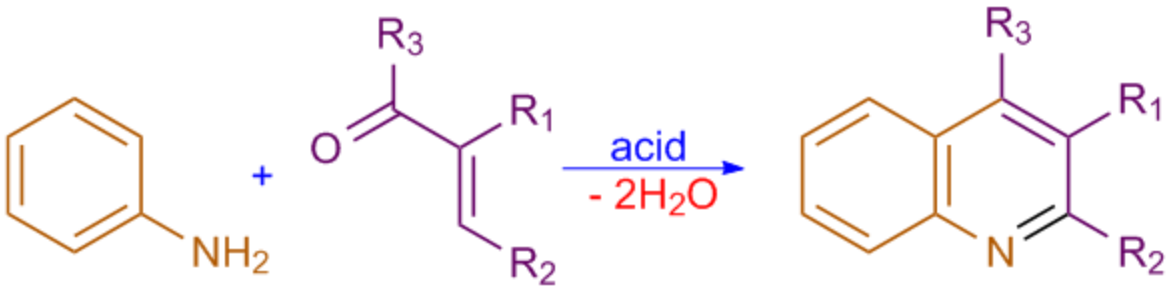
1. Skraup Quinoline synthesis



Synthesis

2. Doebner-Miller Synthesis

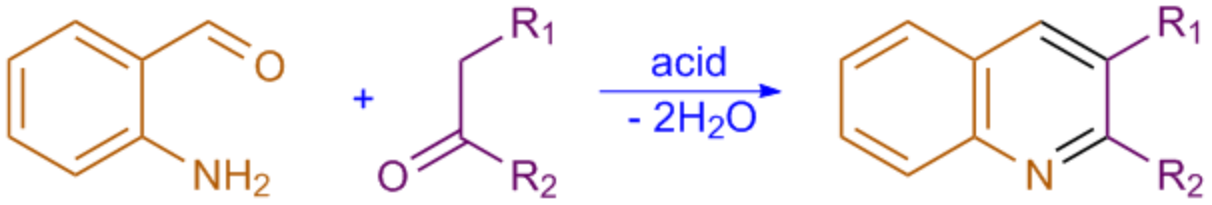
- The organic reaction of an aniline with α,β-unsaturated carbonyl compounds to form quinolines



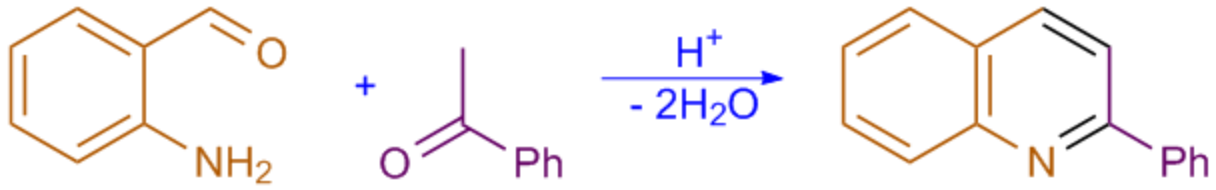
Synthesis

3. Friedlander Synthesis

- Chemical reaction of 2-aminobenzaldehydes with ketones to form quinoline derivatives.



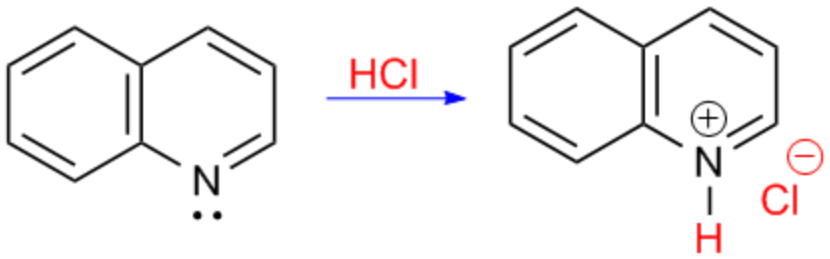
E.g.



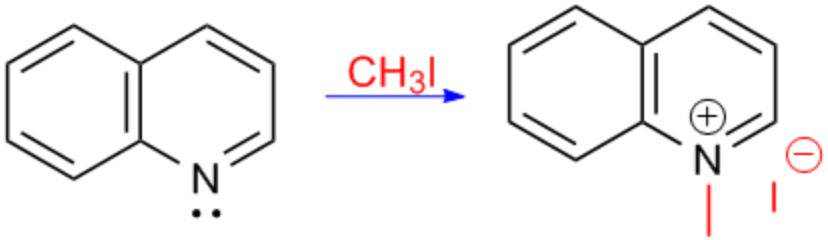
2-aminobenzaldehyde acetophenone 2-phenylquinoline

Reactions

1. Electrophilic addition to N



quinazolium salt chloride

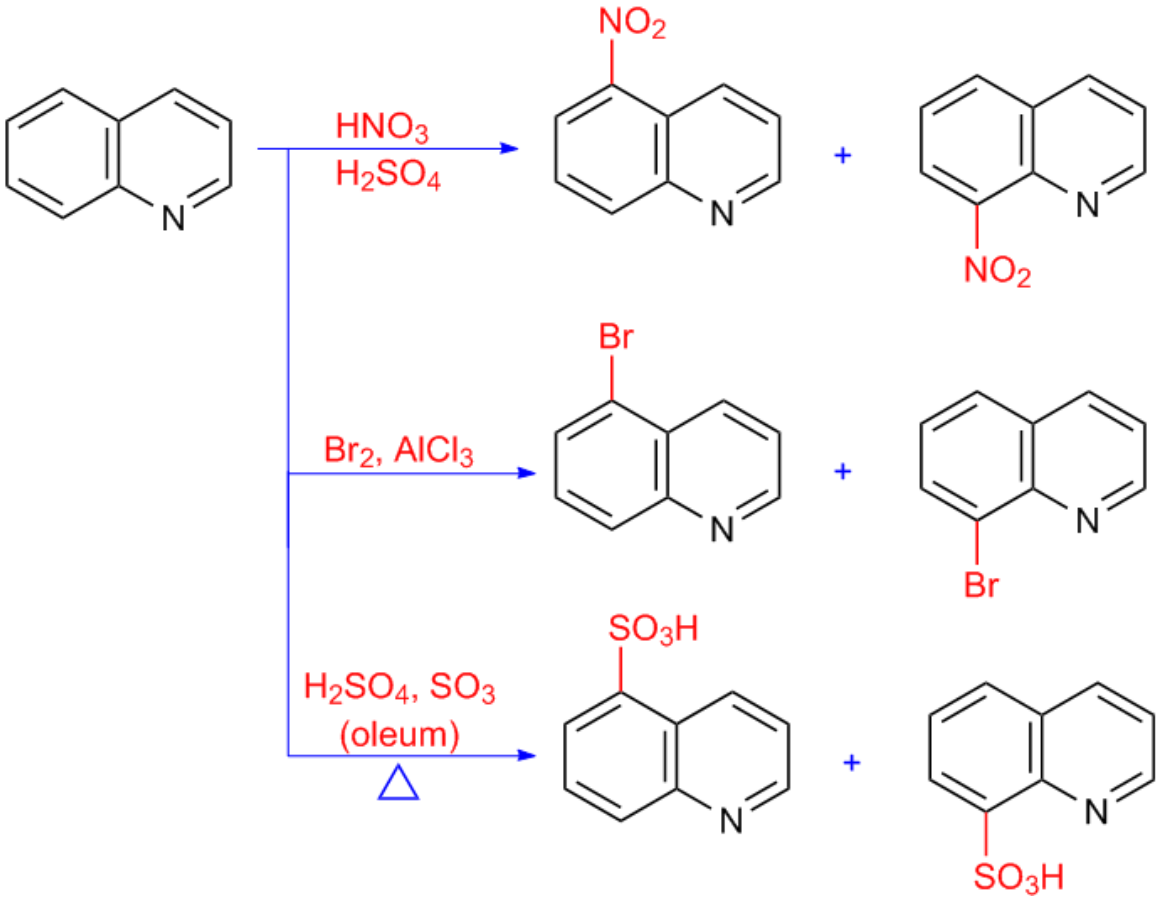


1-methylquinolinium iodide

Reactions

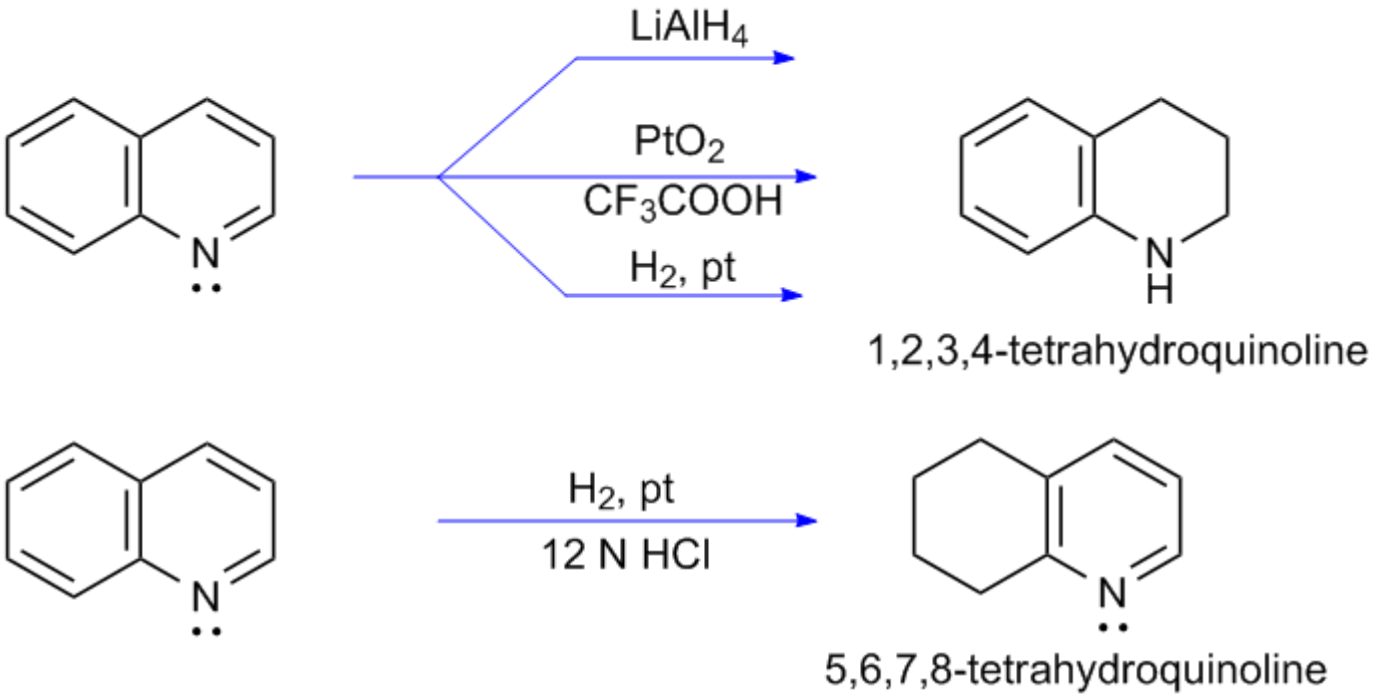
2. Electrophilic aromatic substitution

- Electrophilic aromatic substitution occurs at the benzene ring at positions 5 & 8.



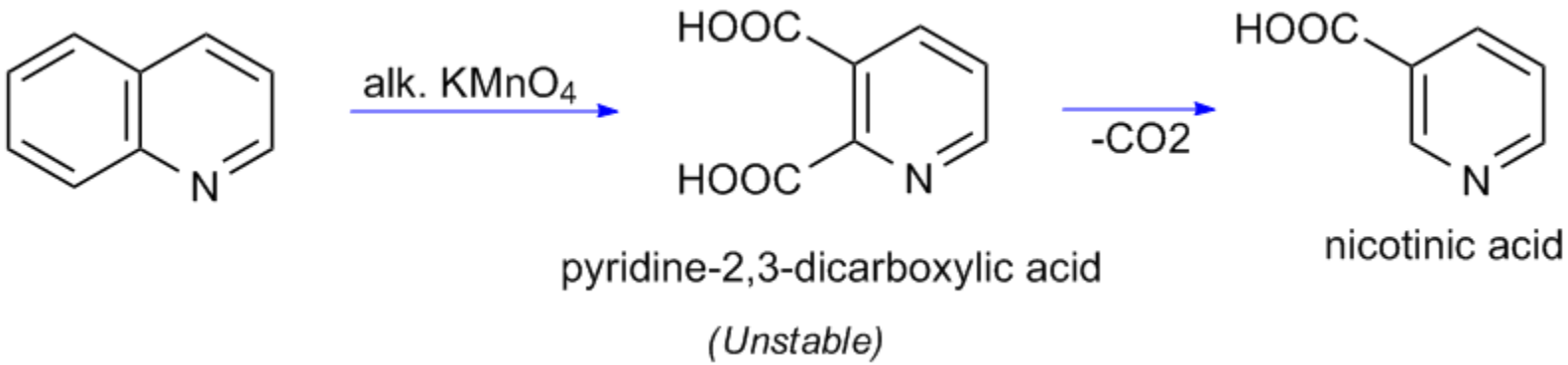
Reactions

3. Reduction reactions



Reactions

4. Oxidation



pyridine-2,3-dicarboxylic acid

(Unstable)

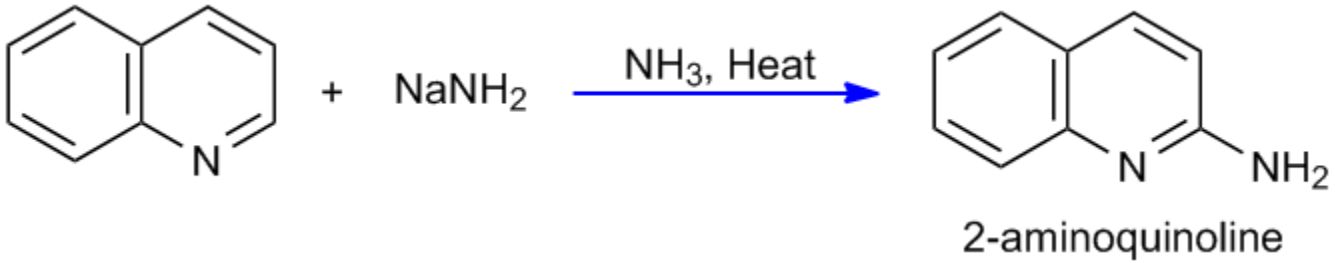
nicotinic acid

Reactions

5. Nucleophilic substitution

Chichibabin rxn

- Rxn with sodamide at high temp.



2-aminoquinoline

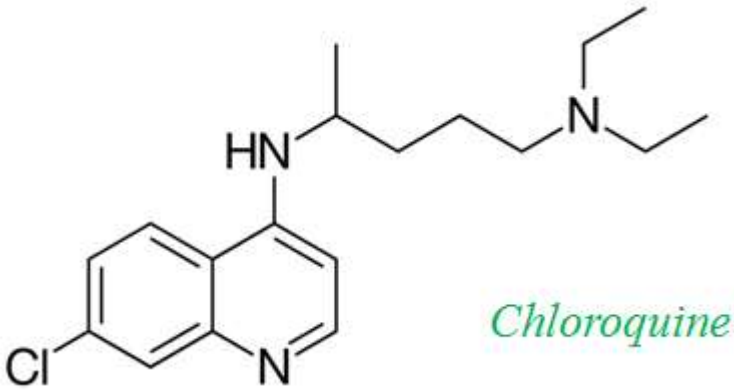
Medicinal uses

(1) Drugs Used to Prevent and Treat Malaria:

Cinchona alkaloid : *Quinine, Quinidine*

4-Aminoquinolines: *Chloroquine, Amodiaquine*

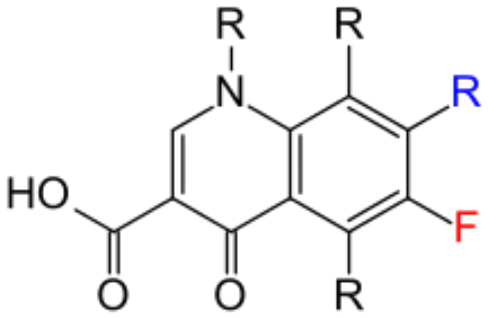
8-Aminoquinolines: *Primaquine, Bulaquine*



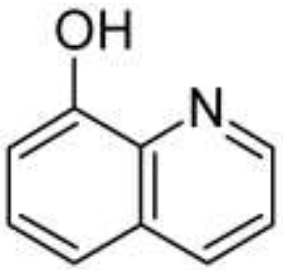
Chloroquine

Medicinal uses

(2) Quinolone antibiotic: *Ciprofloxacin, ofloxacin, norfloxacin, lomefloxacin, and sparfloxacin*



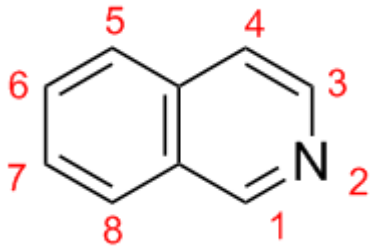
(3) *8-Hydroxyquinoline*: used as topical antiseptics



ISOQUINOLINE

Properties

1. Aromatic



2-azanaphthalene
benzo[c] pyridine

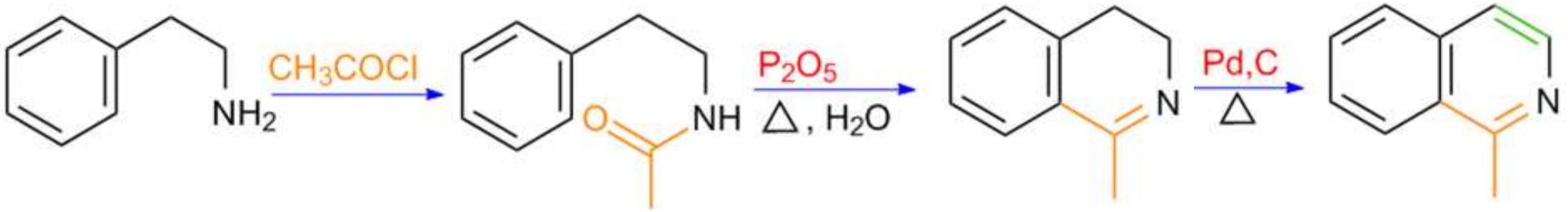
- Each atom is sp^2 hybridized , planar
- the total nu of delocalized e- are 10 (9 from nine C, 1 from N) follows the Hückel's rule

2. Weak base

3. H bonding

Synthesis

1. Bischler-Napieralski Isoquinoline synthesis

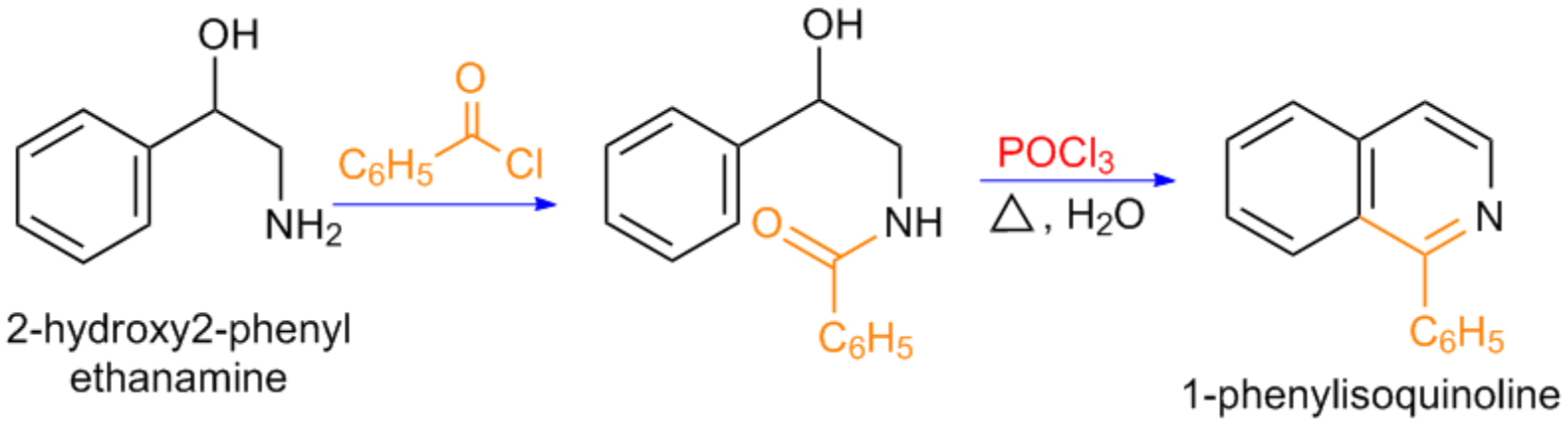


- 2 - aryl - ethanamine reacts with a acyl chloride *or* anhydride to form an amide
- Amide can be cyclised, with loss of water, to a 3,4 – dihydro isoquinoline by treatment with either phosphorus pentoxide *or* phosphorus oxychloride.
- Reduction of dihydro compound to isoquinoline

Synthesis

2. The Pictet – Gams synthesis

- Modification of Bischler-Napieralski method → direct fully aromatic isoquinoline synthesis from 2-hydroxy-substituted reagent



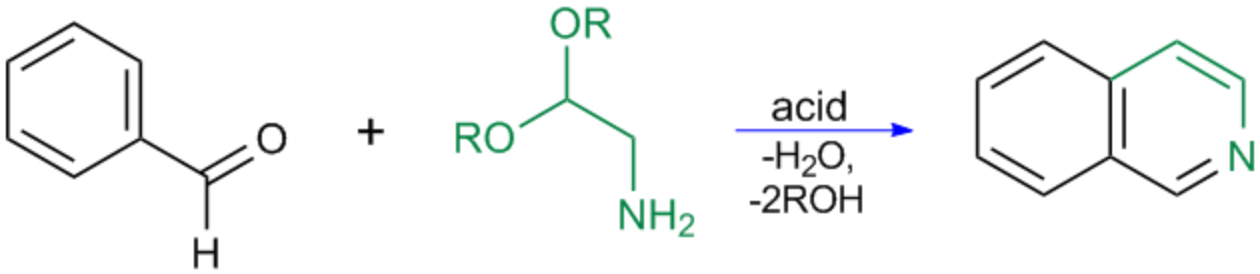
2-hydroxy2-phenyl ethanamine

1-phenylisoquinoline

Synthesis

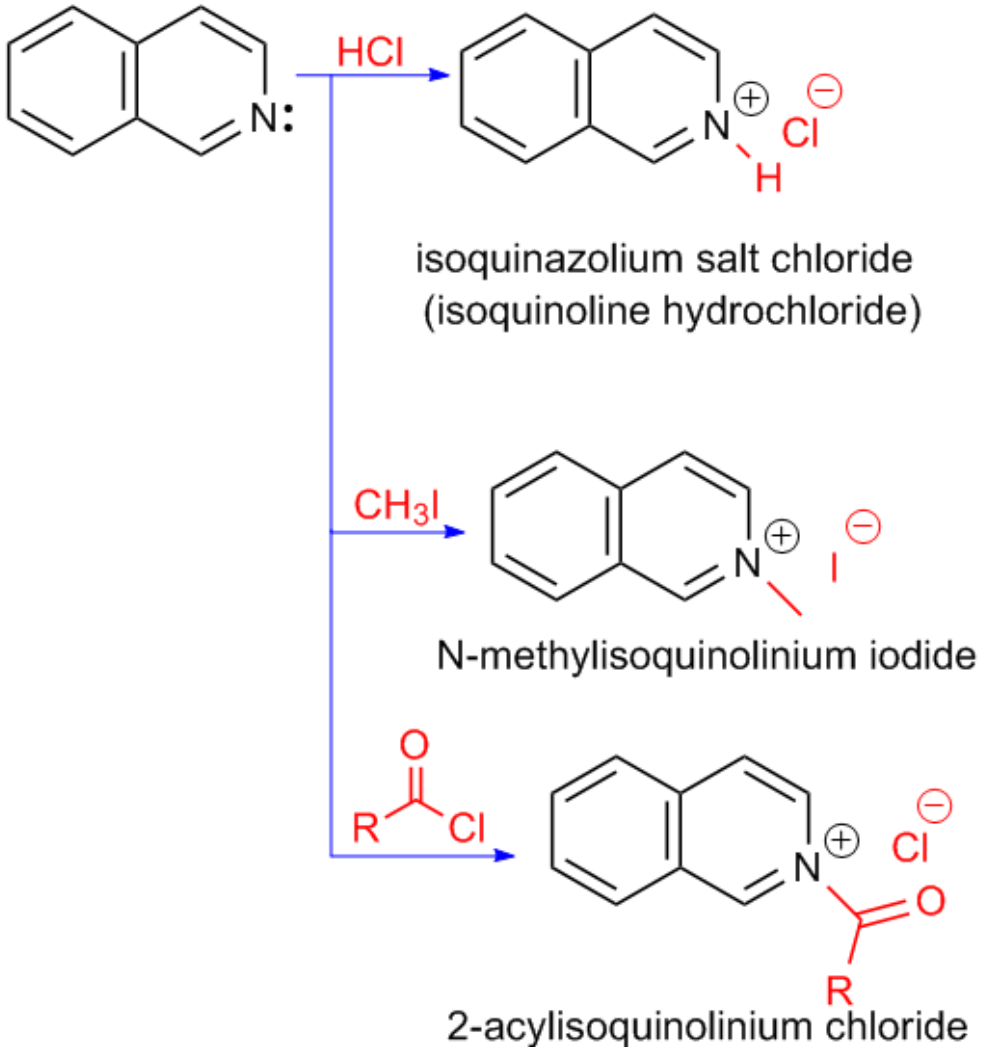
3. Pomeranz–Fritsch synthesis

- Acid-promoted synthesis of isoquinoline from benzaldehyde & 2,2-dialkoxyethylamine.



Reactions

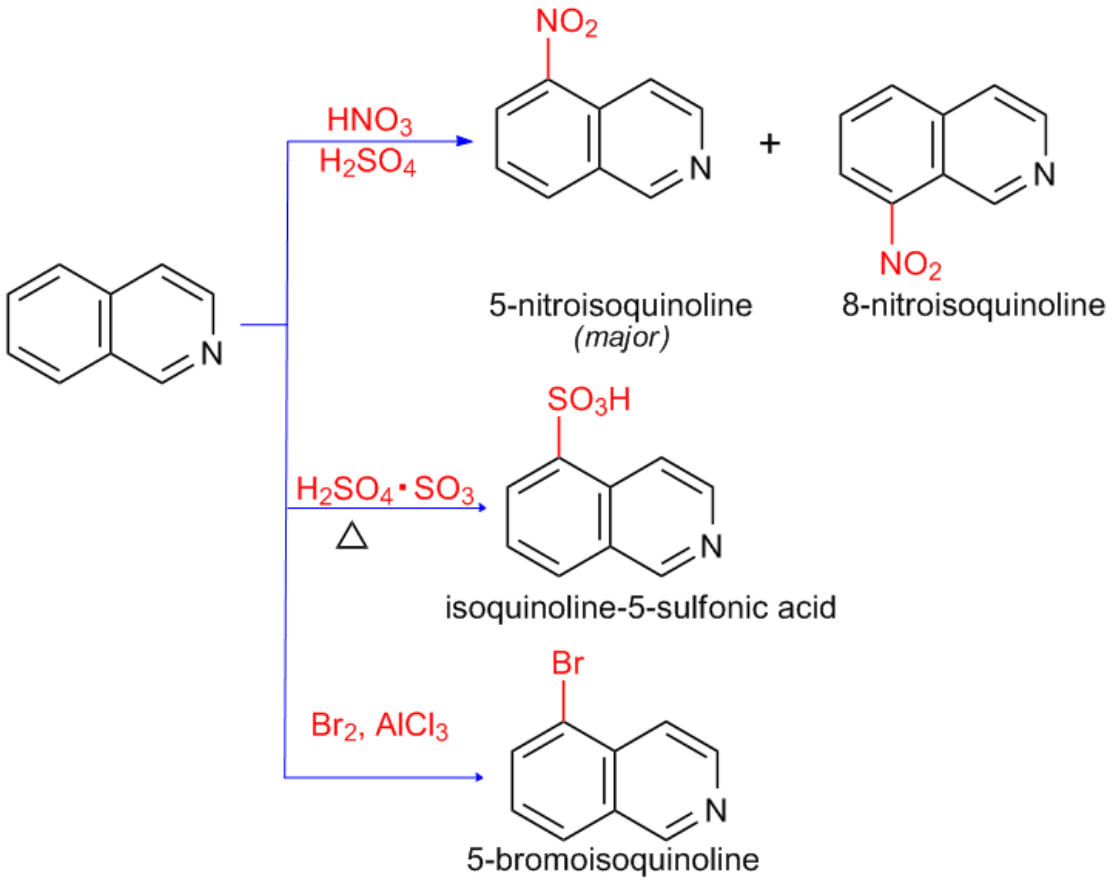
1. Electrophilic addition to N



Reactions

2. Electrophilic aromatic substitution

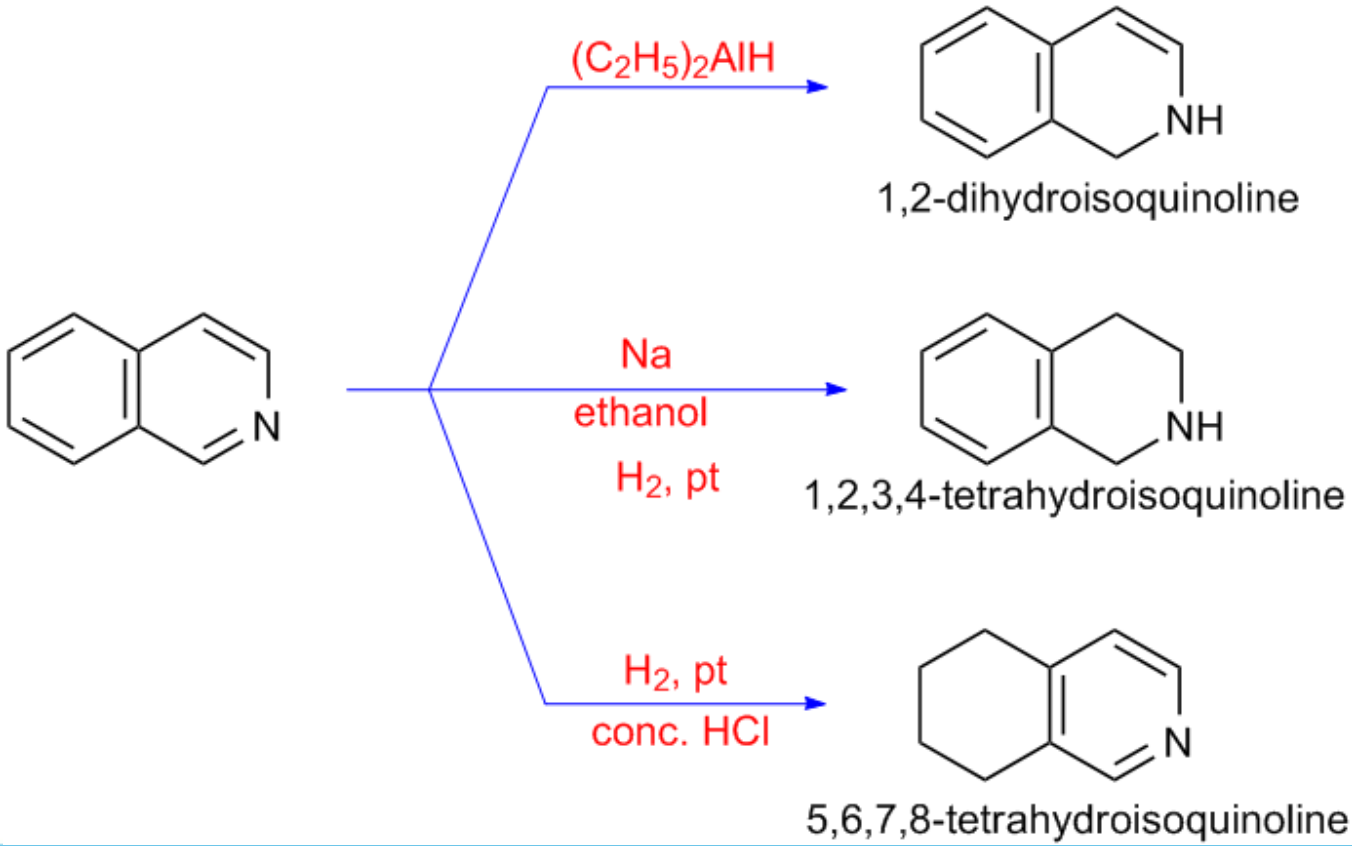
- Electrophilic aromatic substitution occurs at the benzene ring at positions 5 and 8.



Reactions

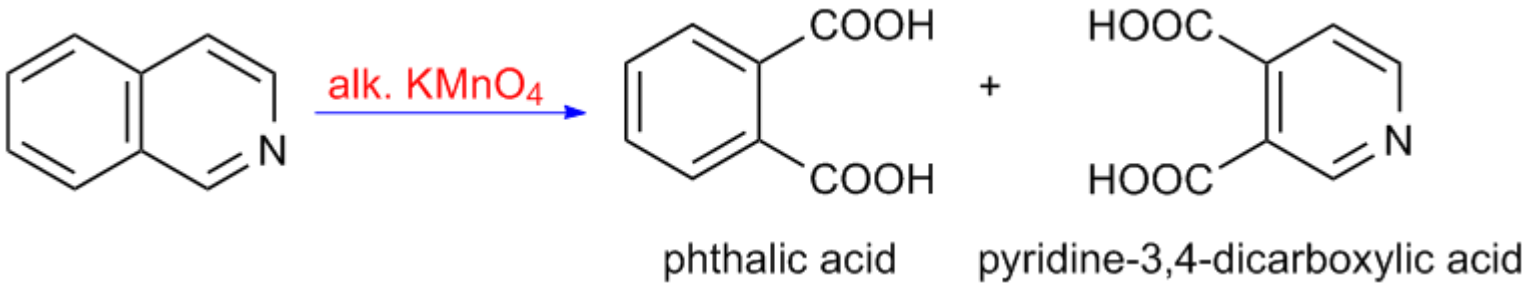
3. Reduction reactions

- Isoquinoline can also be converted to 1,2-dihydro *or* 1,2,3,4-tetrahydroisoquinoline with diethyl aluminium hydride and sodium-ethanol, respectively

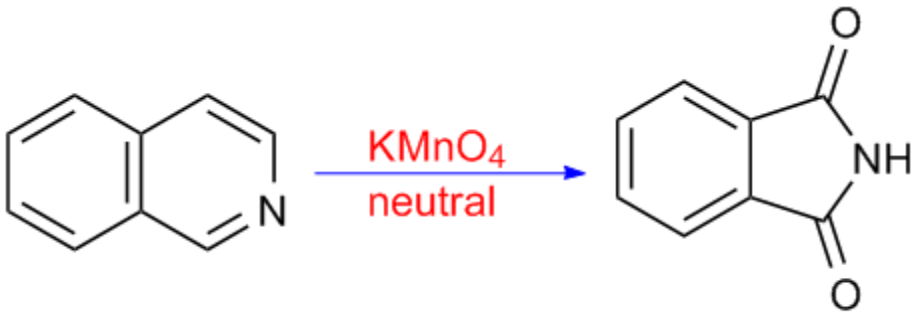


Reactions

4. Oxidation



phthalic acid pyridine-3,4-dicarboxylic acid



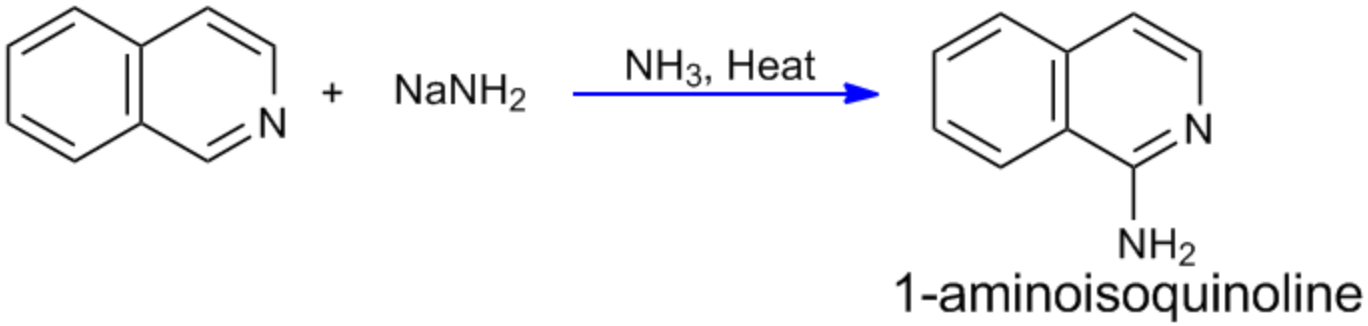
phthalimide

Reactions

5. Nucleophilic substitution

Chichibabin rxn

- Rxn with sodamide at high temp.

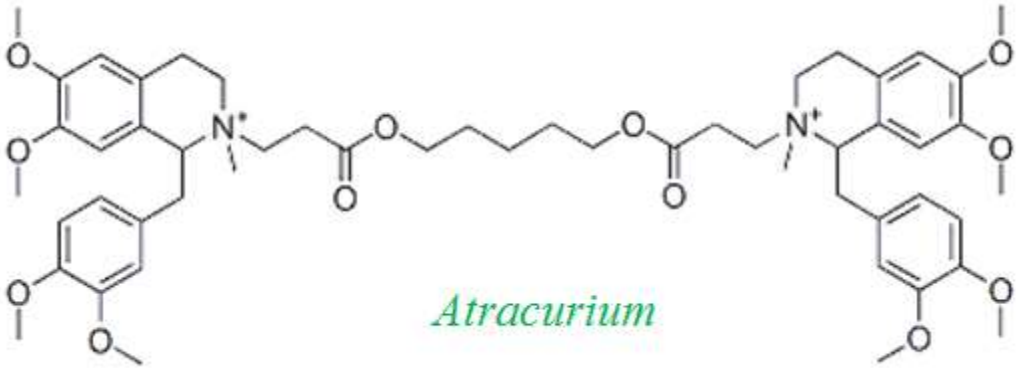


1-aminoisoquinoline

Medicinal uses

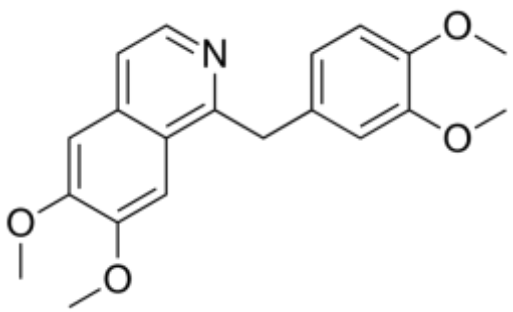
(1) Neuromuscular blocking agents:

Curare Alkaloids, Atracurium, Doxacurium, Mivacurium



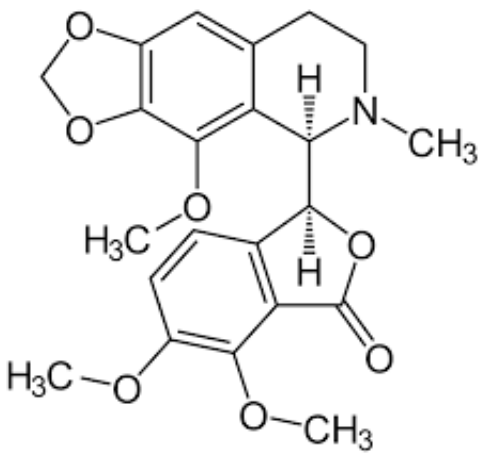
Atracurium

(2) *Papaverine* , used as antispasmodic agent on smooth muscles



Medicinal uses

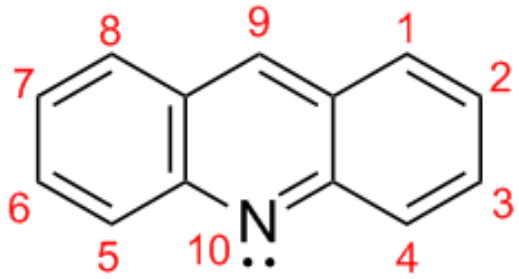
(3) *Noscapine*: used as antitussive (cough-suppressing agents)



ACRIDINE

Properties

1. Aromatic



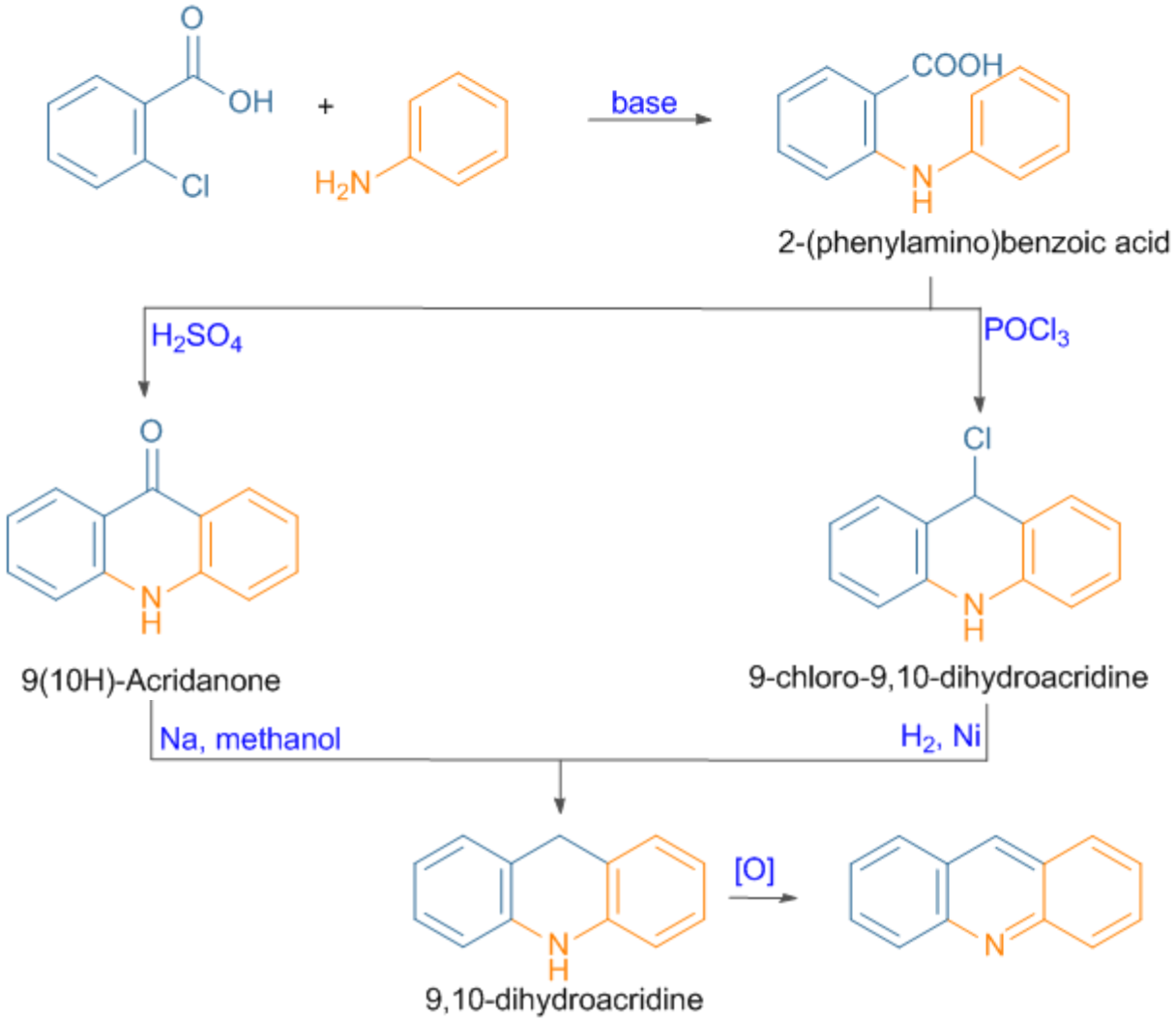
2,3-Benzoquinoline
Dibenzo[b,e]pyridine

- Each atom is sp^2 hybridized , planar
- the total nu of delocalized e- are 14 (13 of Cs, 1 from N) follows the Hückel's rule

2. Weak base

Synthesis

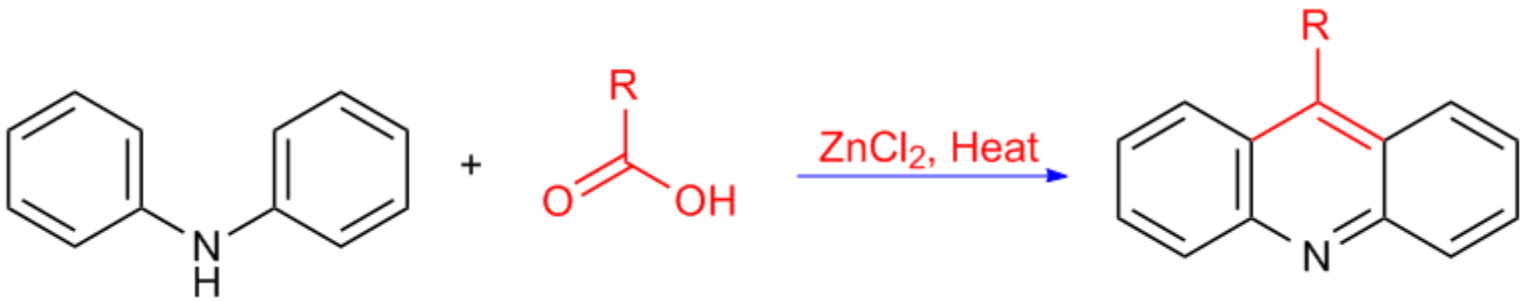
1. From diphenyl amine-2-carboxylic acid



Synthesis

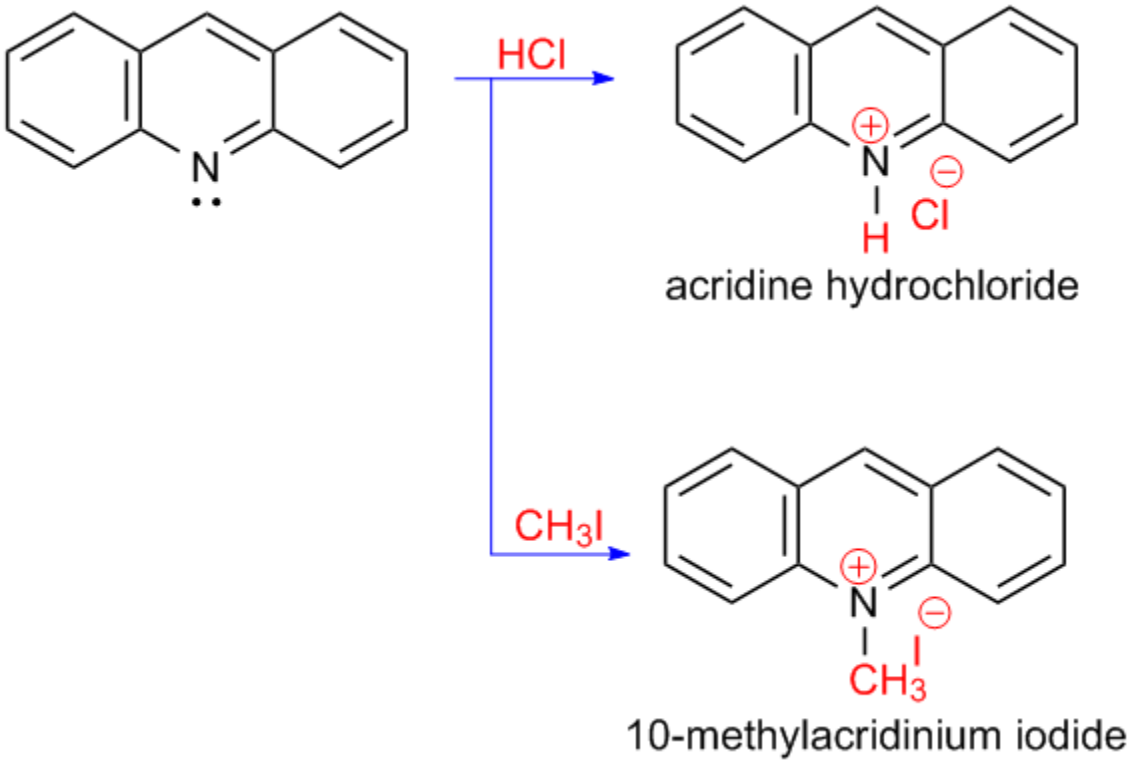
2. Bernthsen acridine synthesis

- diarylamine heated with a carboxylic acid (*or* acid anhydride) and zinc chloride to form a 9-substituted acridine



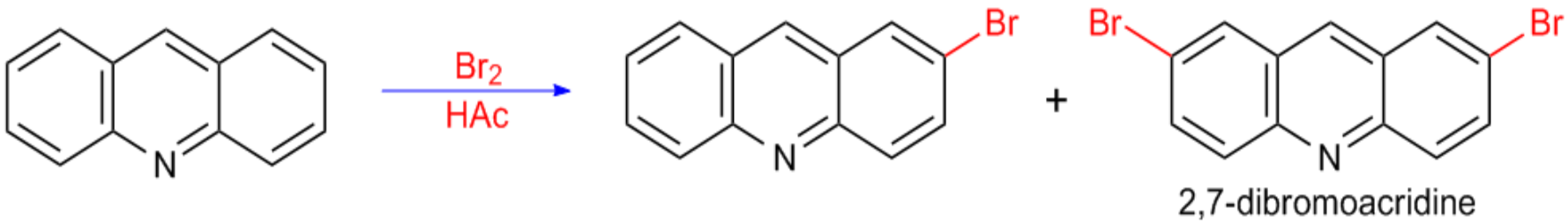
Reactions

1. Electrophilic addition to N



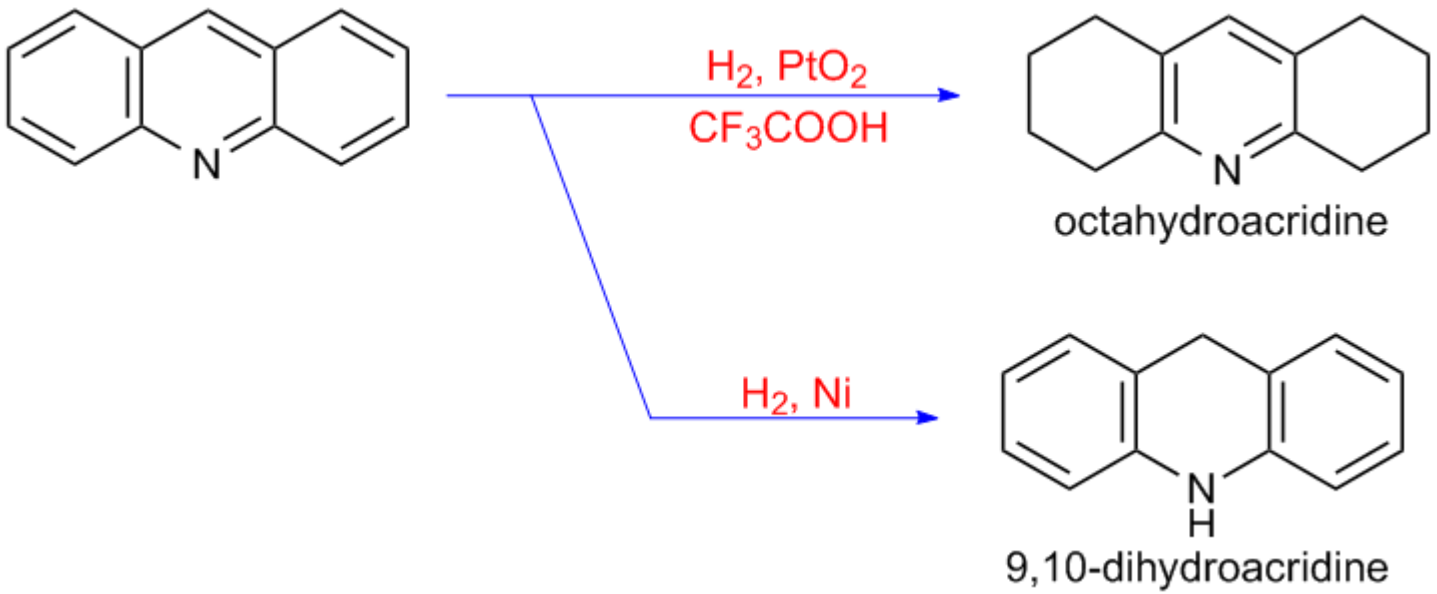
Reactions

2. Electrophilic aromatic substitution



Reactions

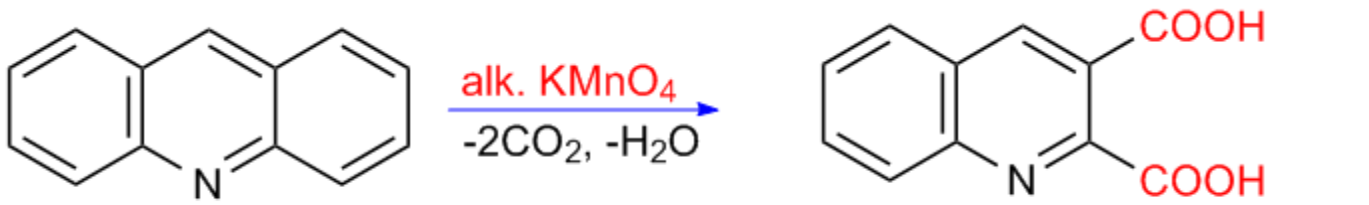
3. Reduction reactions



Reactions

4. Oxidation

- Acridine is degraded by permanganate in an alkaline medium forming quinoline-2,3-dicarboxylic acid.



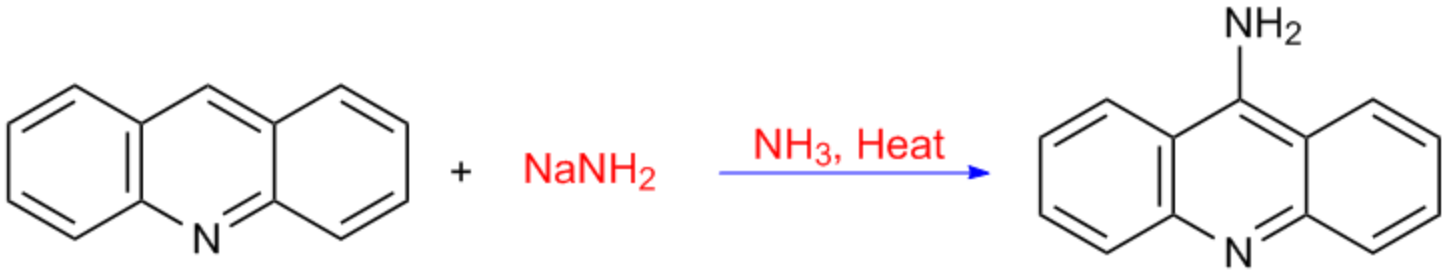
quinoline-2,3-dicarboxylic acid

Reactions

5. Nucleophilic substitution

Chichibabin rxn

- Acridine readily reacts with nucleophiles.
- The chichibabin amination with sodamide in liquid ammonia leads to 9-aminoacridine.

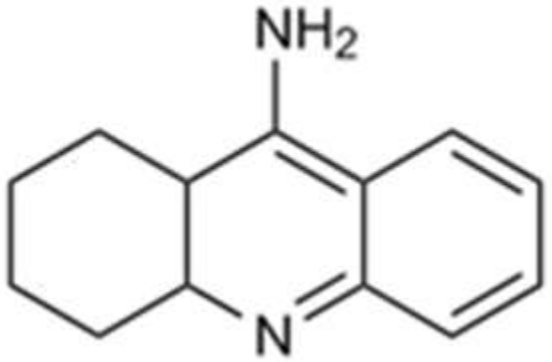


acridin-9-amine

Medicinal uses

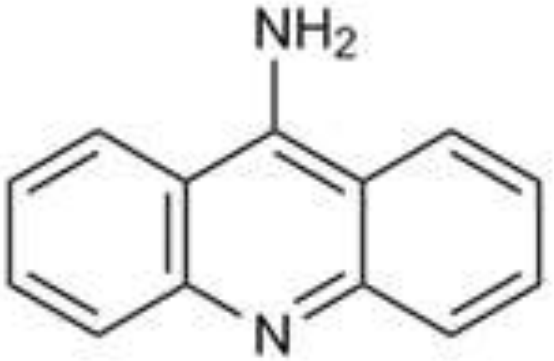
(1) *Tacrine :*

- Is a reversible cholinesterase inhibitor that has been used in the treatment of *Alzheimer disease*



(2) *9- Aminoacridine*

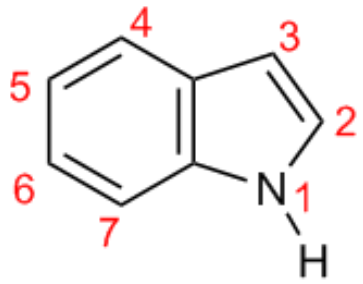
- Is highly fluorescent dye
- Used as antiseptic and disinfectant.



INDOLE

Properties

1. Aromatic



2,3-Benzopyrrole
1*H*-benzo[b] pyrrole

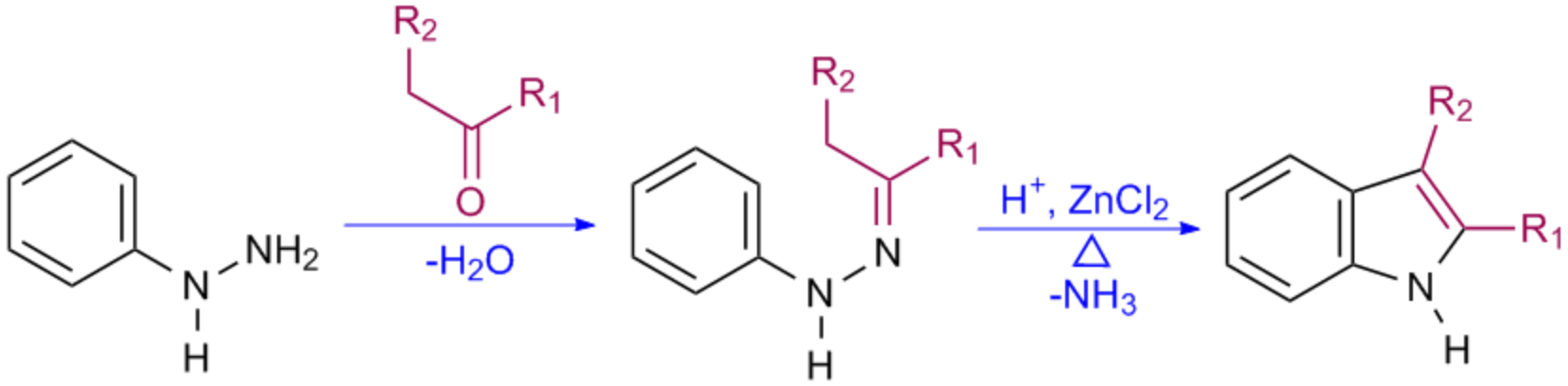
- Each atom is sp^2 hybridized , planar
- the total nu of delocalized e- are 10 (8 of eight C, 2 from N) follows the Hückel's rule

2. Very weak base

Synthesis

1. Fischer indole synthesis

- Acid - catalysed rearrangement of an arylhydrazone to indole with the elimination of ammonia.
- Reaction can be carried out simply by heating together the aldehyde *or* ketone and arylhydrazine
- Formation of the arylhydrazone and its subsequent rearrangement take place to give indole, $ZnCl_2$ is used as catalyst.

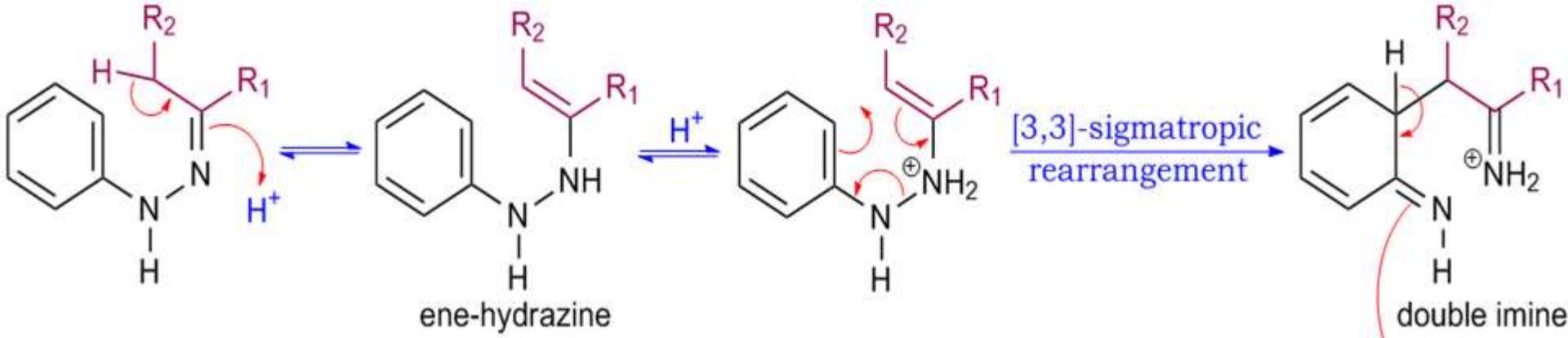


phenylhydrazine phenylhydrazone

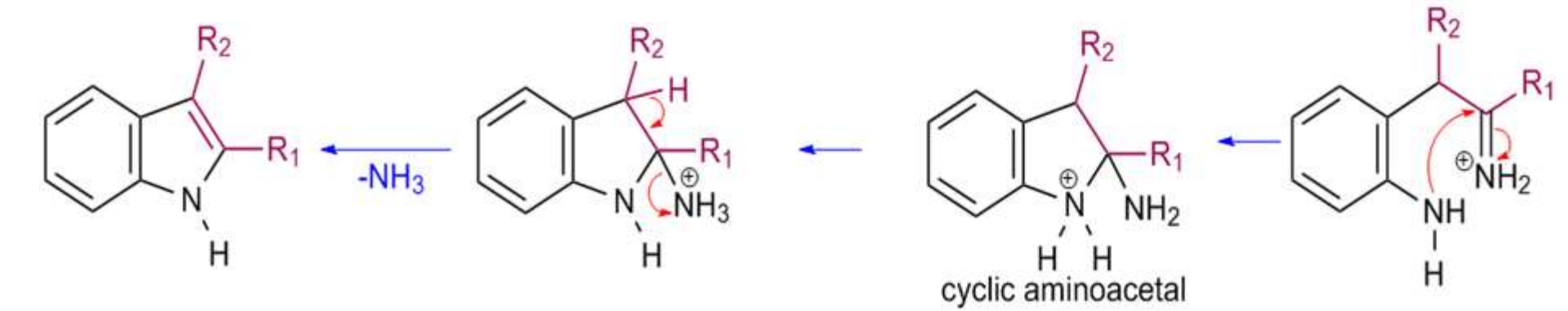
Synthesis

1. Fischer indole synthesis

Mechanism



Deamination, resulting in the *aromatic* indole.



Synthesis

1. Fischer indole synthesis

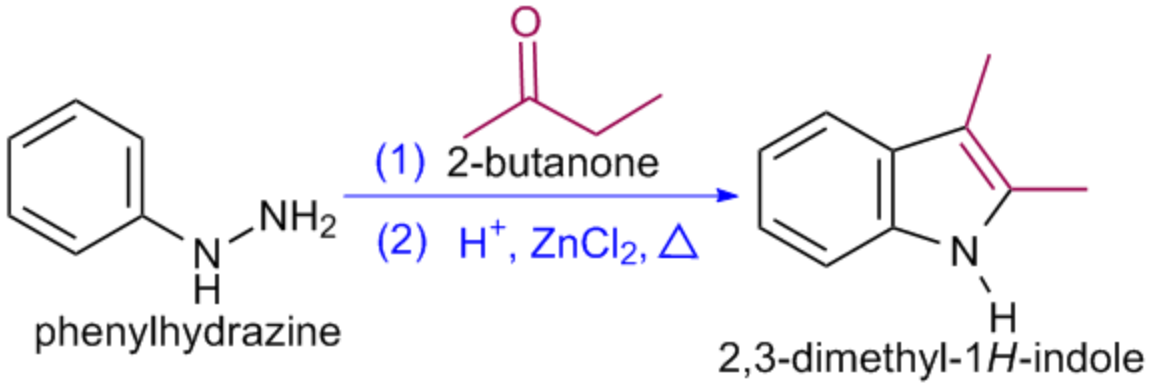
Mechanism

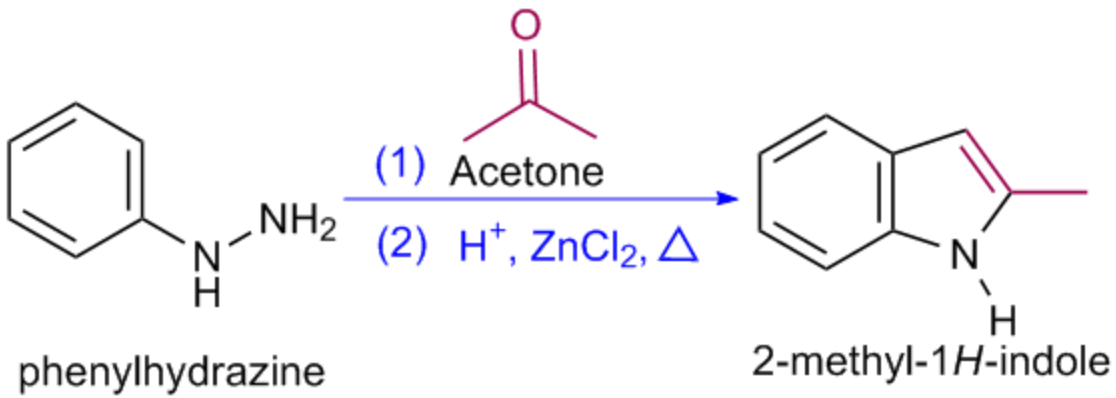
- a reversible rearrangement of hydrazone to give the reactive ene-hydrazine
- protonation produced protonated ene-hydrazine
- [3.3]-sigmatropic rearrangement ("ene reaction"), formation of a *new C-C bond*, *diimine* and *loss of aromaticity*.
- Rearomatization of aryl ring
- Nucleophilic addition, formation of a *cyclic aminoacetal (aminal)*
- Deamination , resulting in the *aromatic* indole.

Synthesis

1. Fischer indole synthesis

E.g.

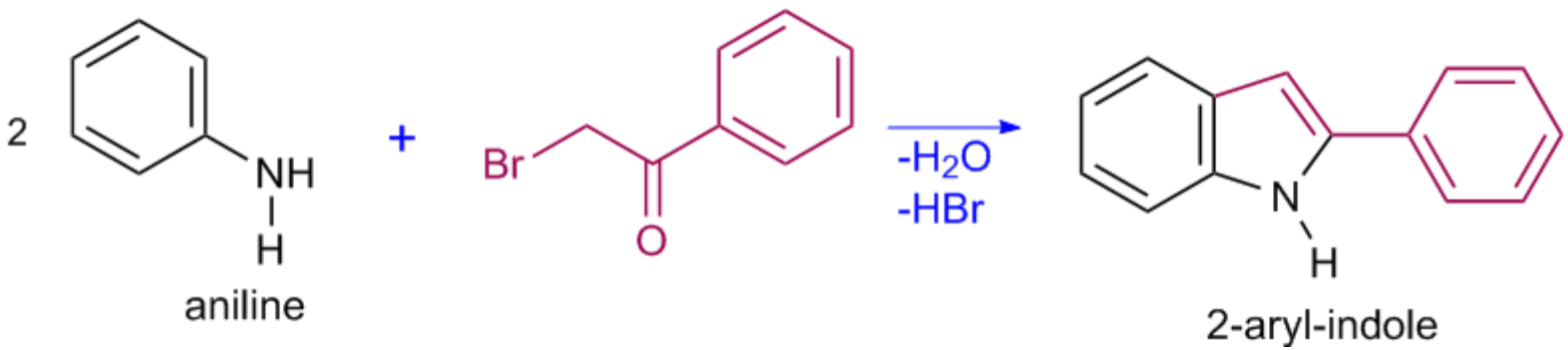




Synthesis

2. Bischler–Möhlau indole synthesis

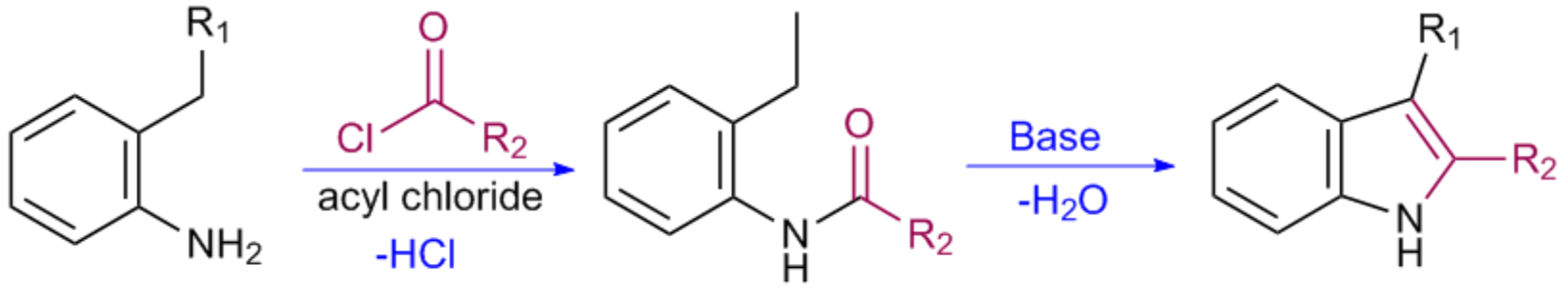
- Synthesis of a 2-aryl-indole from an α-bromo-acetophenone and excess aniline



Synthesis

3. Madelung synthesis

- Intramolecular cyclization of *N*-phenylamide using strong base at high temp.



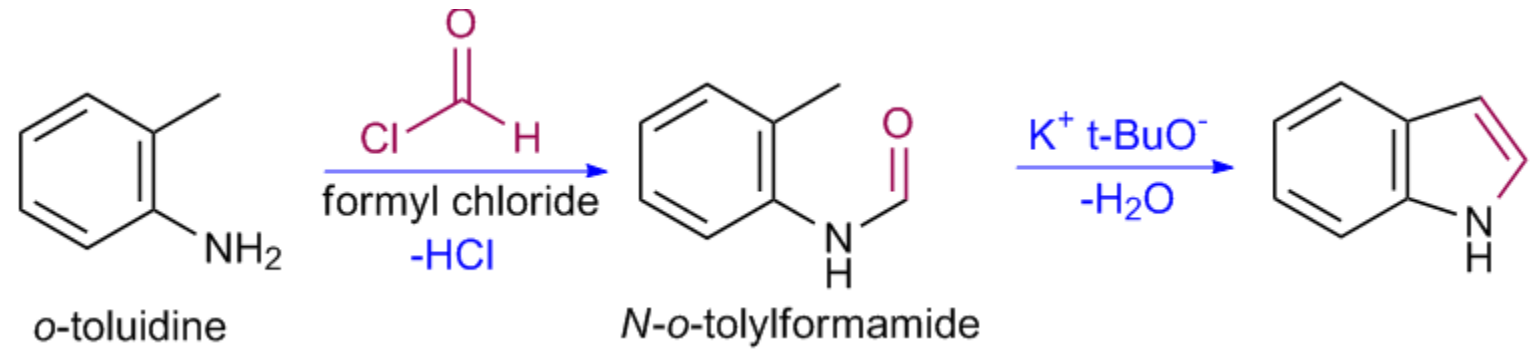
2-substituted aniline — N-phenylamide — substituted Indole

Base = BuLi, K^+ t-BuO^-, K^+ $EthO^-$, KOH

Synthesis

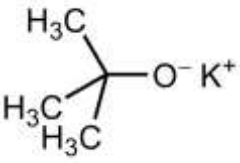
3. Madelung synthesis

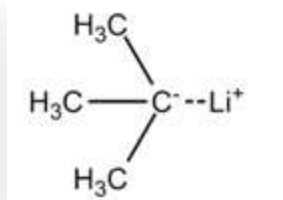
E.g.

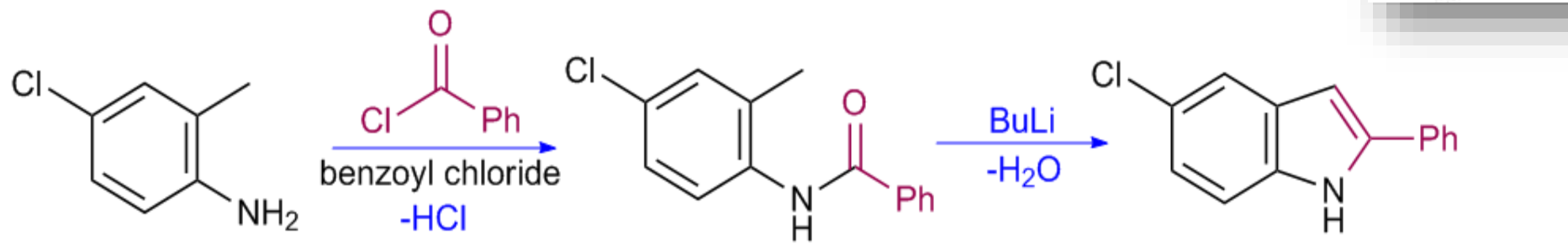


o-toluidine

N-*o*-tolylformamide







4-chloro-2-methylaniline

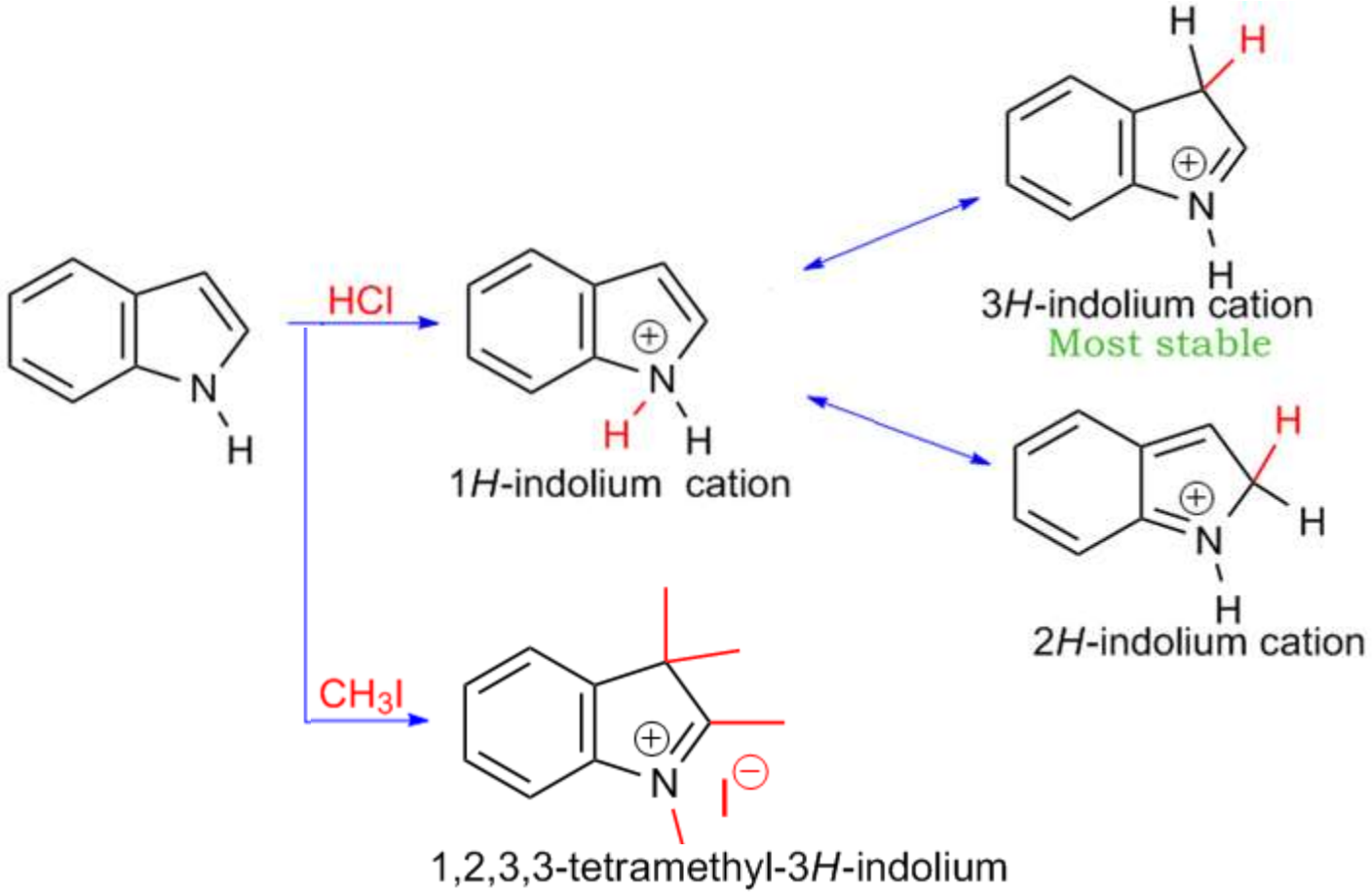
N-substituted-benzamide

5-chloro-2-phenyl-1*H*-indole

Reactions

1. Electrophilic addition to N

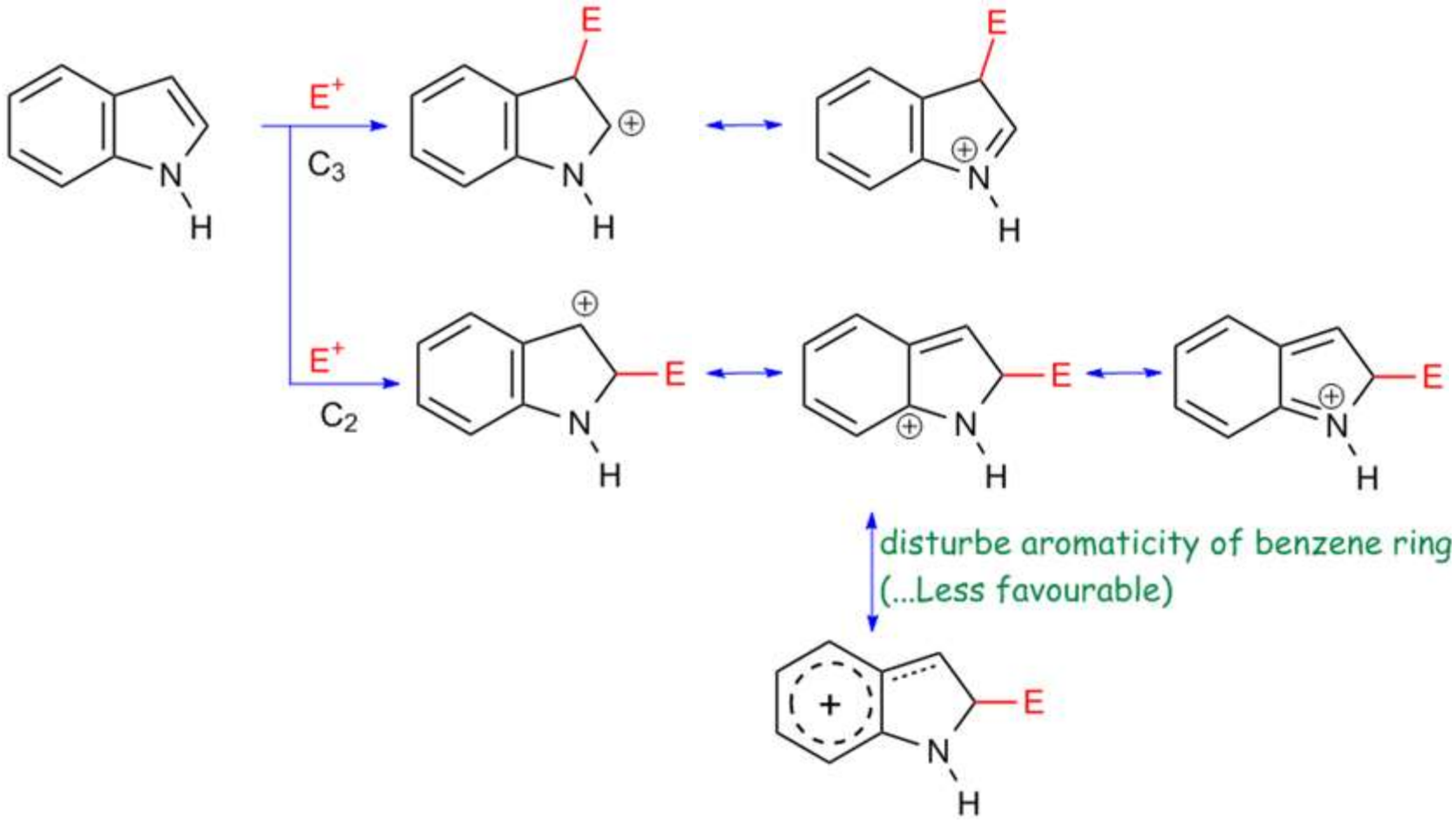
- Indoles, like pyrroles, are very weak bases



Reactions

2. Electrophilic aromatic substitution

EAS of indole favors at 3rd position

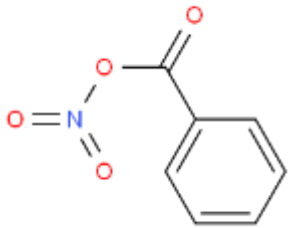


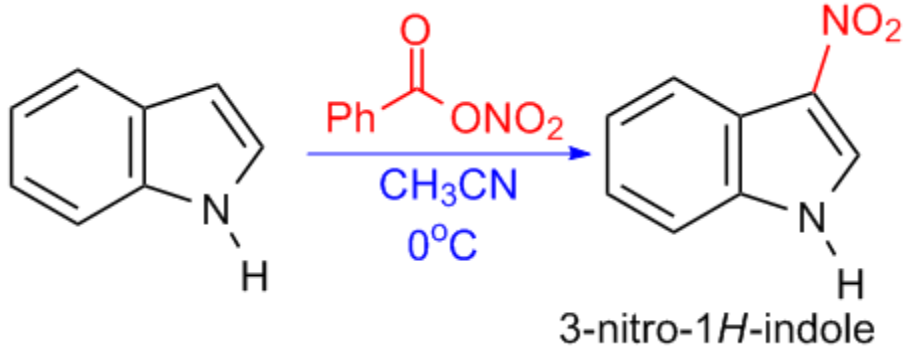
Reactions

2. Electrophilic aromatic substitution

a. Nitration

- Common nitrating agents cause acid - catalysed polymerization(high reactivity of indole).
- So indole can be nitrated using benzoyl nitrate as a *non - acidic nitrating agent.*





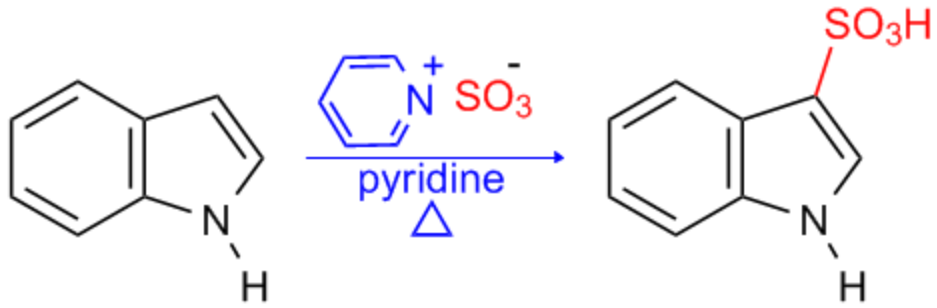
3-nitro-1*H*-indole

Reactions

2. Electrophilic aromatic substitution

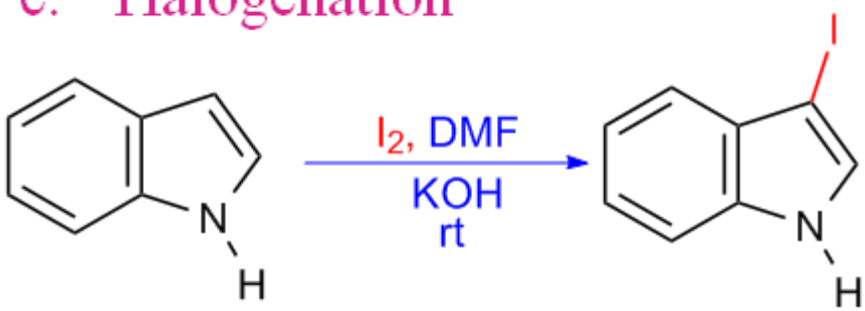
b. Sulphonation

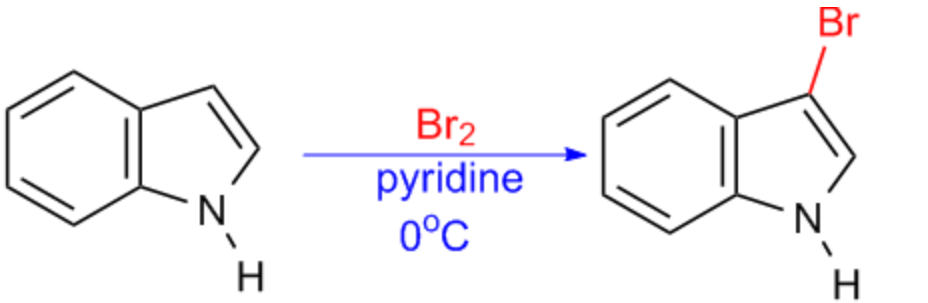
- using the pyridine – sulfur trioxide complex in hot pyridine.



1*H*-indole-3-sulfonic acid

c. Halogenation





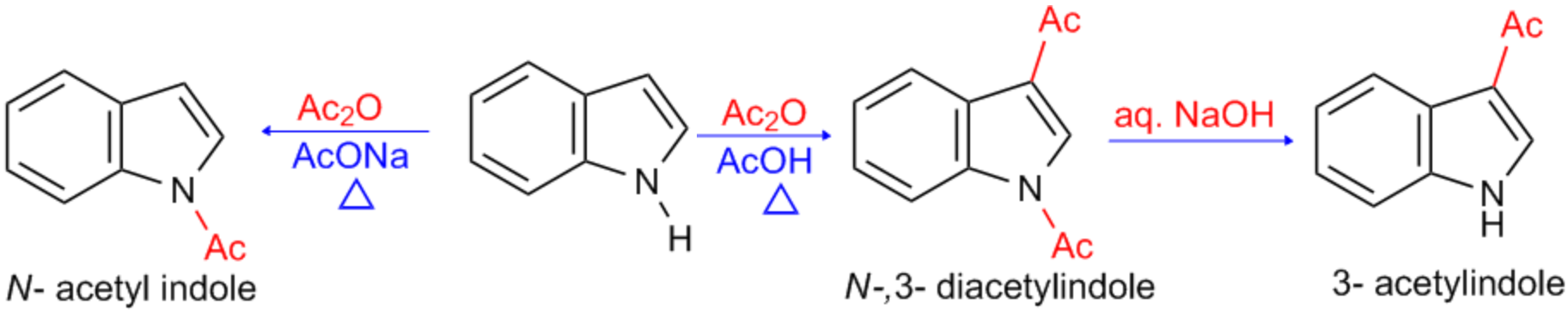
3-bromo-1*H*-indole

Reactions

2. Electrophilic aromatic substitution

e. Acylation

- acetylation in the presence of sodium acetate, affords *N*- acetyl indole.
- Indole reacts with acetic anhydride, gives 1,3 - diacetylindole predominantly, which upon HL with aqueous sodium hydroxide at room temperature gives 3 - acetylindole

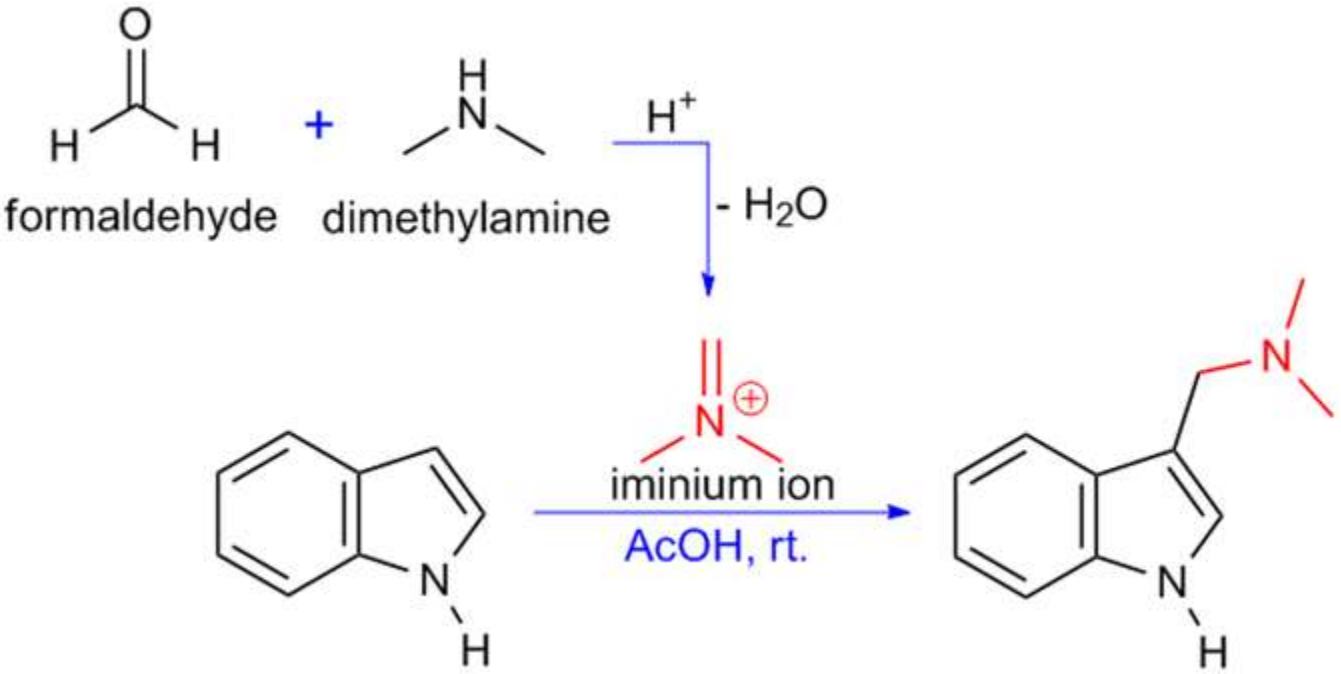


Reactions

2. Electrophilic aromatic substitution

f. Mannich reaction : reaction with Iminium Ion

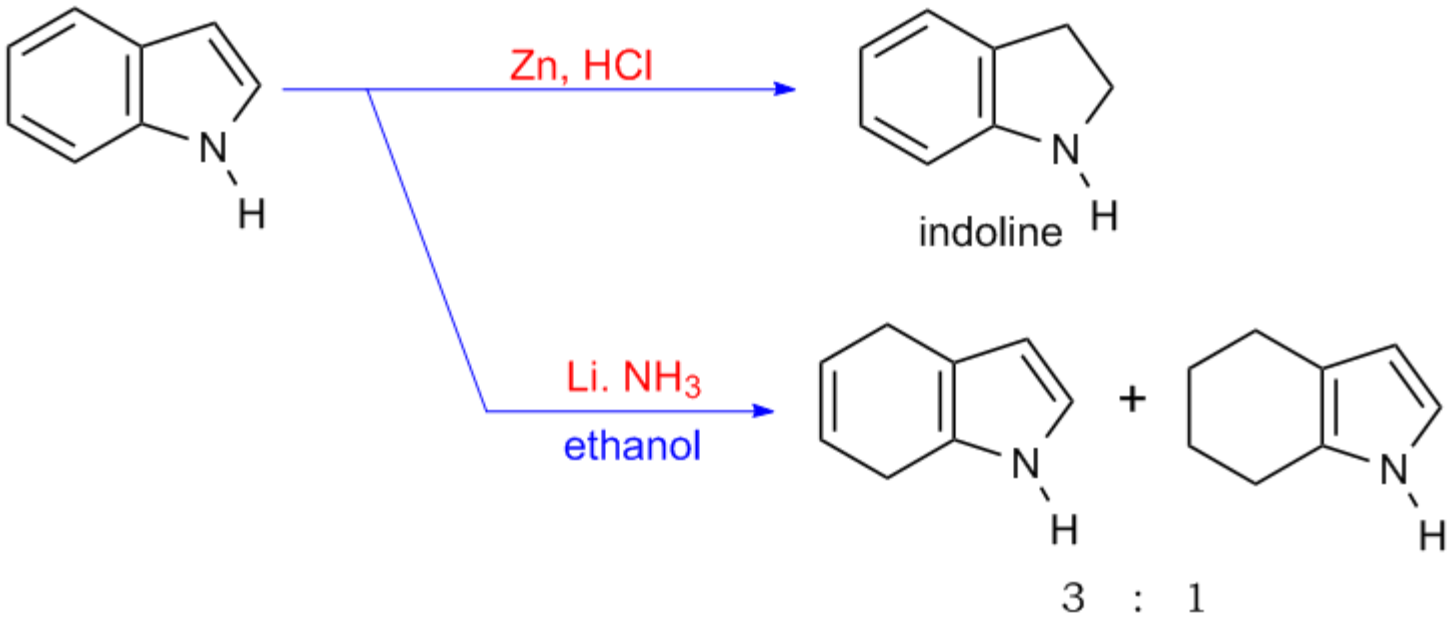
- Indole reacts with a mixture of formaldehyde and dimethylamine in acetic acid by substitution and converted into 3 – dimethyl aminomethyl indole (gramine)



Reactions

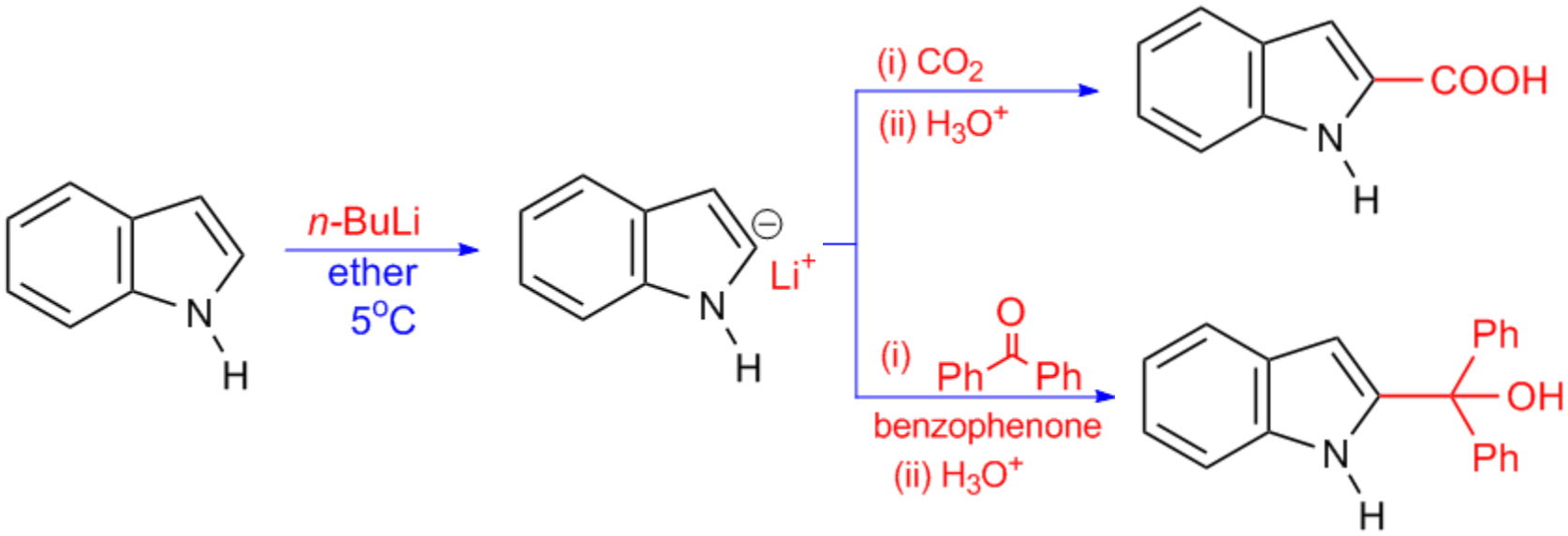
3. Reduction reactions

- Lithium/liquid ammonia reduce the benzene ring; 4,7 – dihydroindole is the main product



Reactions

4. Nucleophilic substitution



Medicinal uses

(1) Indole alkaloids :

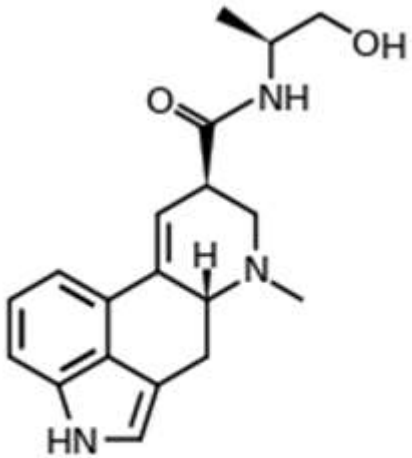
A. *Reserpine*
- antihypertensive of the late 1950s and early 1960s
- to treat agitated psychotic conditions

B. Vinca alkaloids : *Vincristine, vinblastine*
- Anticancer agent

C. Ergot alkaloids:

Ergometrine :
- to prevent bleeding after childbirth (smooth muscle constriction effect),

Ergotamine - used in migraine



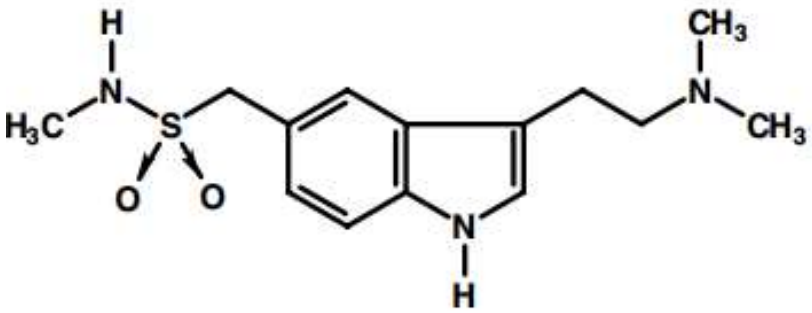
ergometrine

Medicinal uses

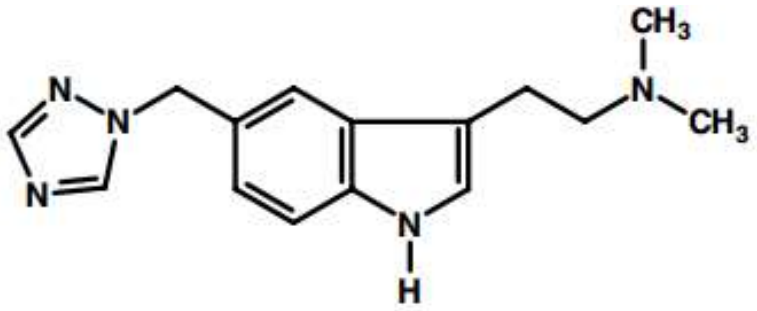
(2) TRIPTANS:

Sumatriptan, rizatriptan, naratriptan, zolmitriptan

- treatment of moderate to severe migraine and cluster headaches.
- Because of their higher affinity and selectivity for the serotonin 5-$HT_{1B/1D}$ receptors



Sumatriptan

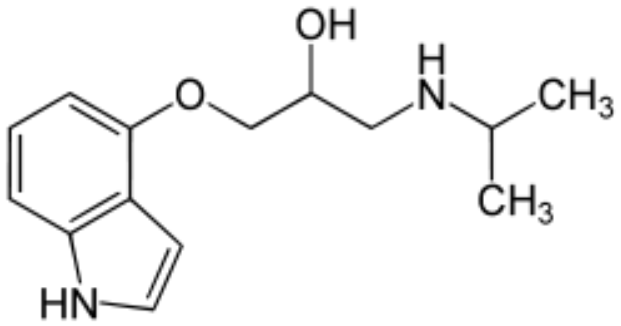


Rizatriptan

Medicinal uses

(3) *Pindolol:* Nonselective β-Blockers

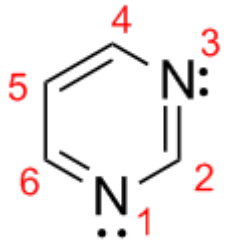
- used in the treatment of hypertension and angina pectoris.



PYRIMIDINE

Properties

1. Aromatic



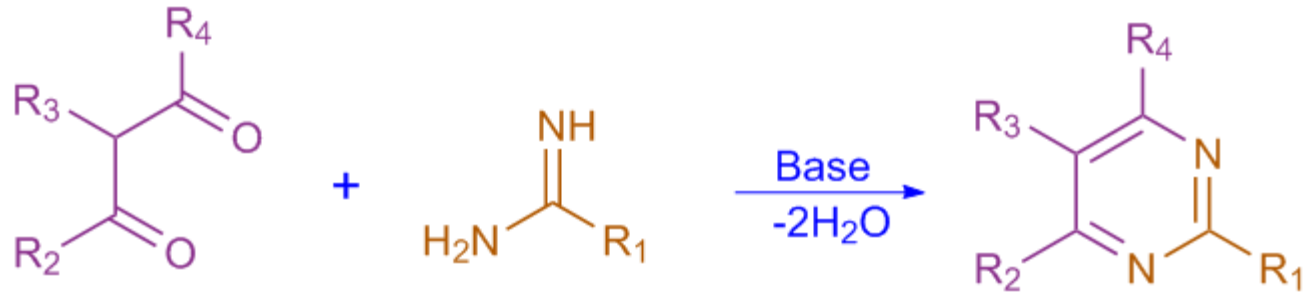
- Each atom is sp^2 hybridized , planar
- the total nu of delocalized e- are 6 (4 of four C, 2 from Ns) follows the Hückel's rule

2. Weak Base

Synthesis

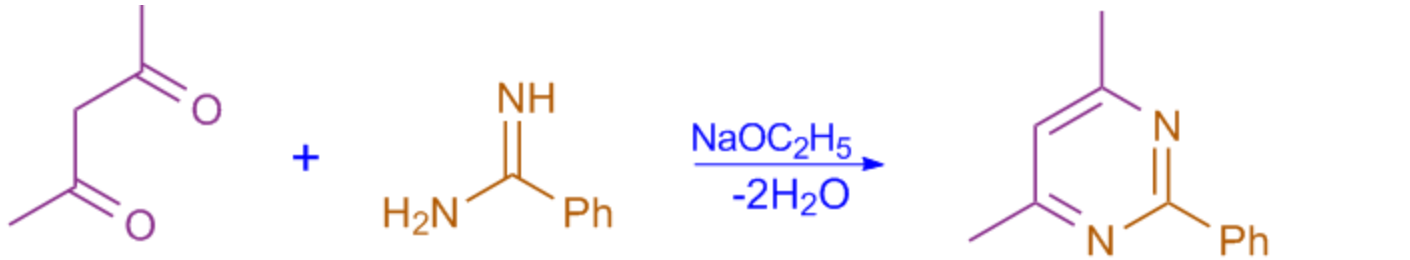
1. From 1,3 - Dicarbonyl Compound

- Combining 1,3 - dicarbonyl component with an N – C – N fragment such as a urea, an amidine or a guanidine.



1,3 - dicarbonyl compound

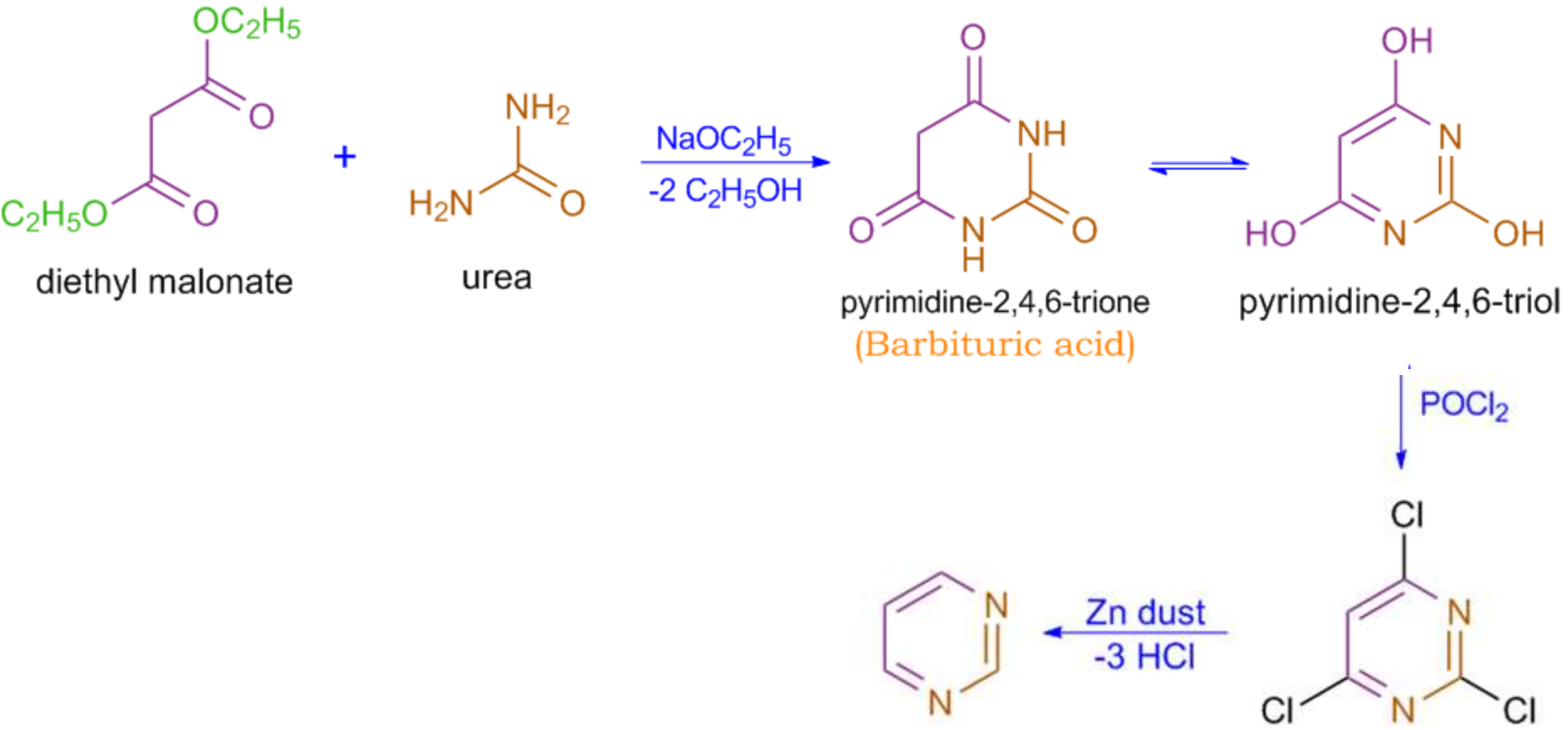
E.g.



pentane-2,4-dione benzimidamide 4,6-dimethyl-2-phenylpyrimidine

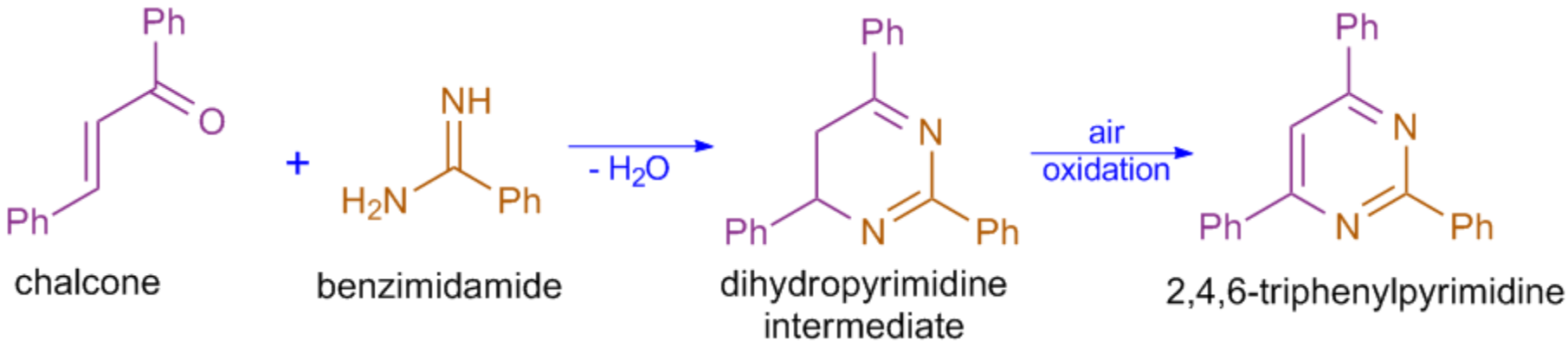
Synthesis

1. From 1,3 - Dicarbonyl Compound



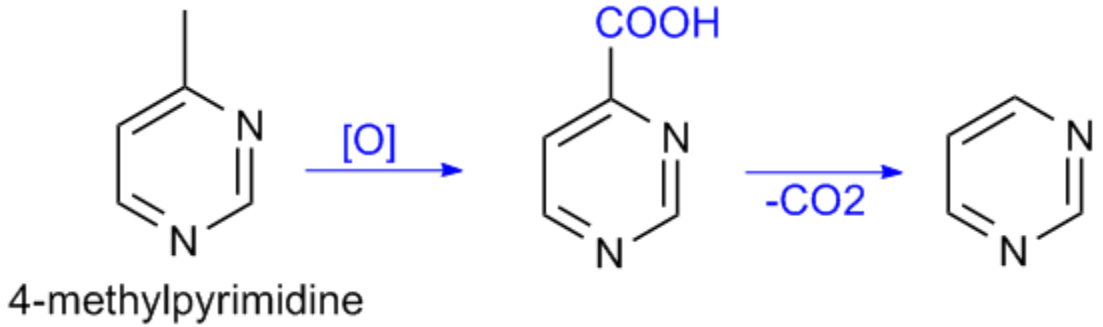
Synthesis

2. From α , β - Unsaturated Ketones



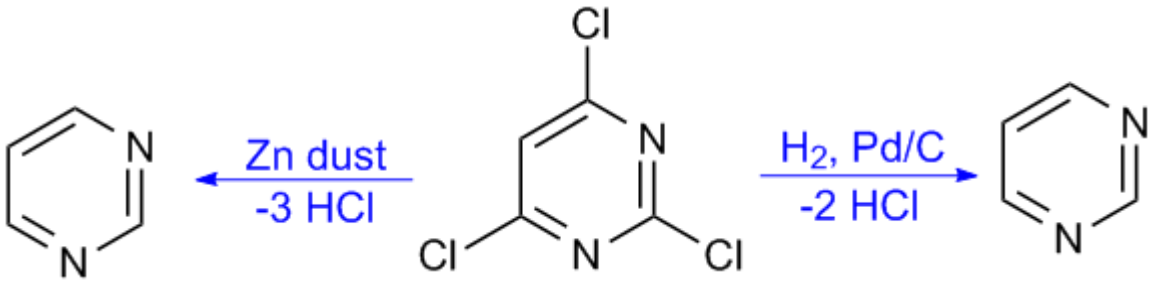
Synthesis

3. From alkyl pyrimidine



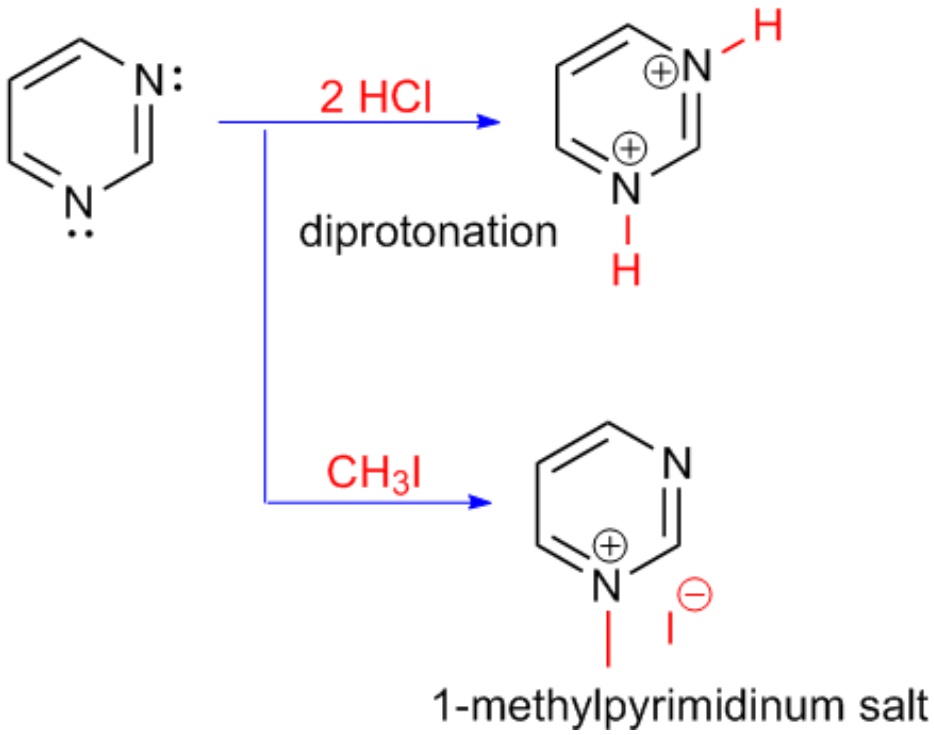
4-methylpyrimidine

4. From Chloro pyrimidine



Reactions

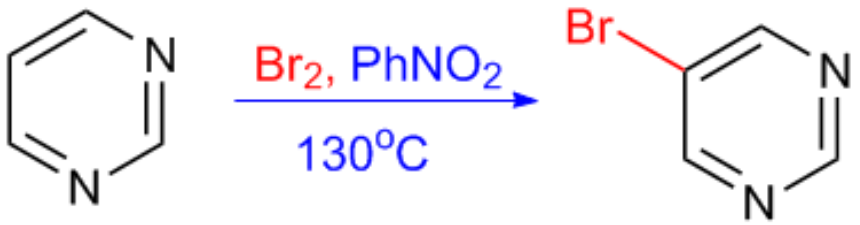
1. Electrophilic addition to N



Reactions

2. Electrophilic aromatic substitution

- Less reactive due to two N present in hetero skeletal
- Reaction is possible at 5th position, if ring is *activated by EDG.*
- no nitration *or* sulfonation



Reactions

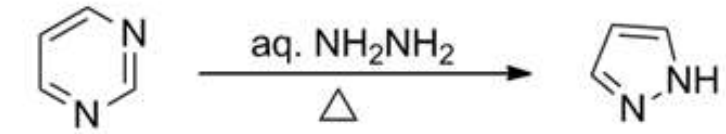
3. Nucleophilic substitution

PYRAZOLE

Synthesis

1. From pyrimidine

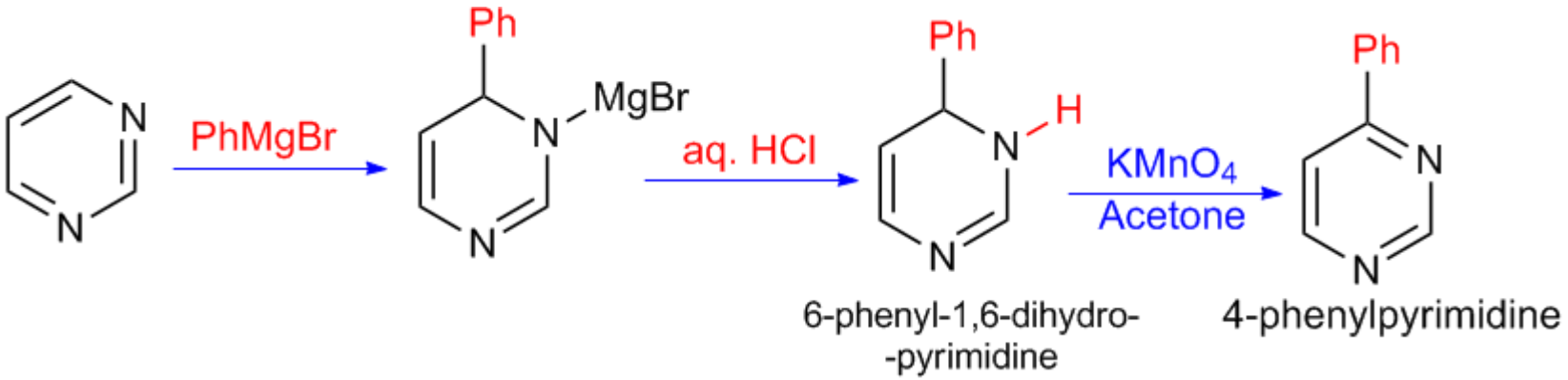
- Pyrimidine is very susceptible to nucleophilic addition.
- it reacts with hot hydrazine solution to give pyrazole.



Pyrimidine pyrazole

Reactions

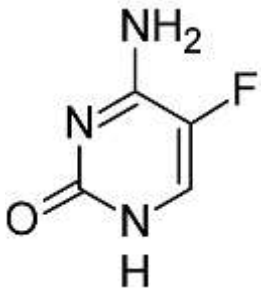
3. Nucleophilic substitution



Medicinal uses

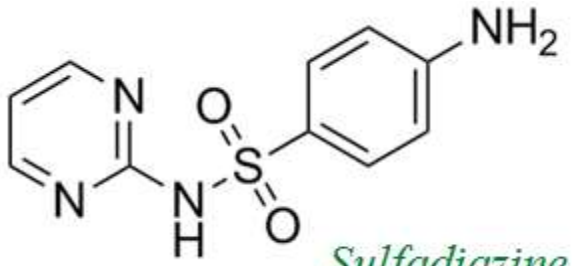
(1) *Flucytosine*

- 5-Fluorocytosine
- antifungal agent



(2) *Sulfadiazine, Sulfamethazine*

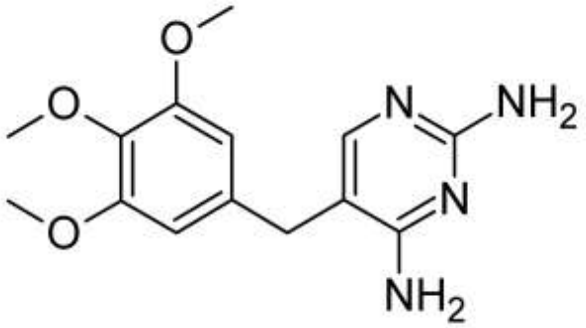
- Antibacterial agent



Sulfadiazine

(3) *Trimethoprim*

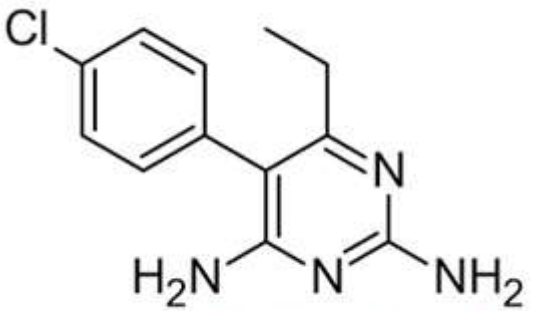
- Antibacterial agent



Medicinal uses

(4) *Pyrimethamine, Sulfadoxine*

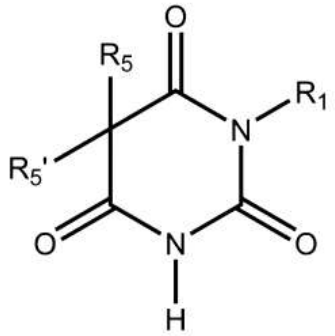
- Antimalarial drugs



Pyrimethamine

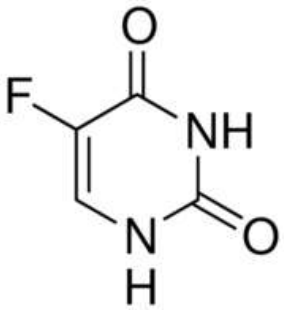
(5) Barbiturates : *Phenobarbital, Pentobarbital, Secobarbital*

- Used as Sedatives and Hypnotics



(6) Antimetabolites : *5-Fluorouracil*

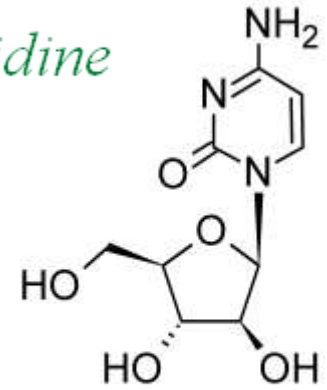
- Anticancer agent



Medicinal uses

(7) *Nucleoside Antimetabolites* : *Cytarabine, Trifluridine*

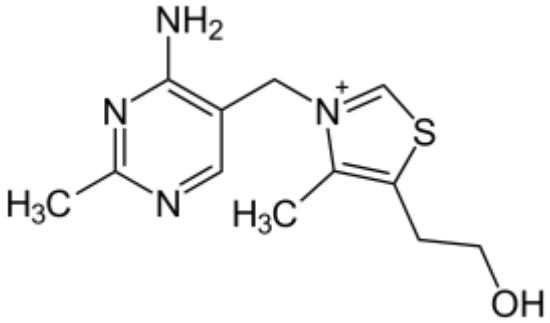
- Antiviral agent



Cytarabine

(8) *Vitamin B1 (Thiamine):*

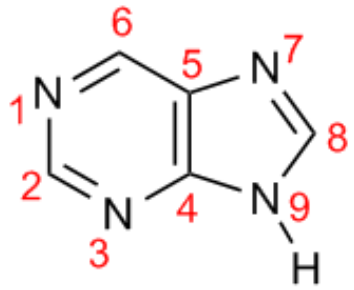
- Used in thiamine deficiency



PURINE

Properties

1. Aromatic



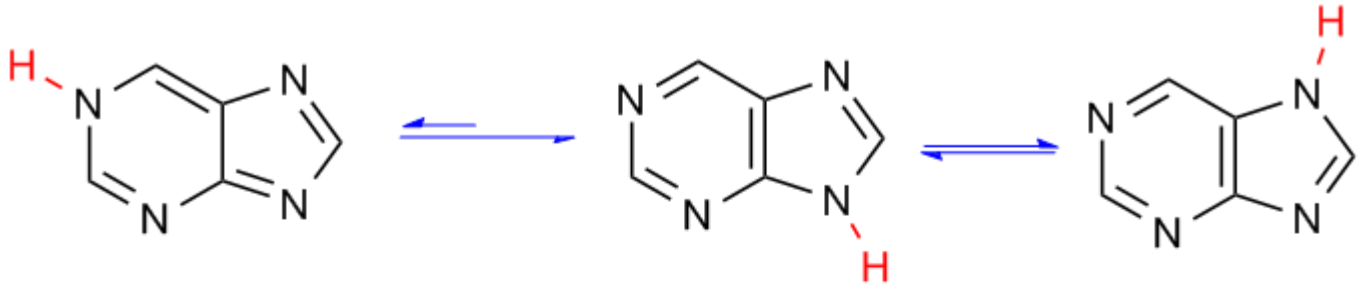
- Each atom is sp^2 hybridized , planar
- the total nu of delocalized e- are 10 (5 of five C, 3 from N_1, N_3, N_7 & 2 from N_9) follows the Hückel's rule

2. weak base

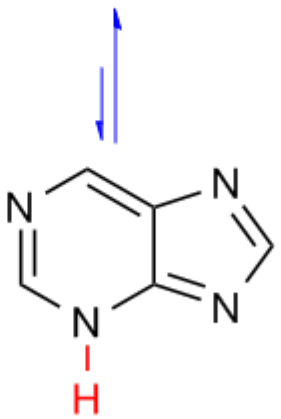
Properties

3. Tautomerism

- 7*H*- and 9*H*- tautomers are more stable



1*H*-purine ⇌ 9*H*-purine ⇌ 7*H*-purine

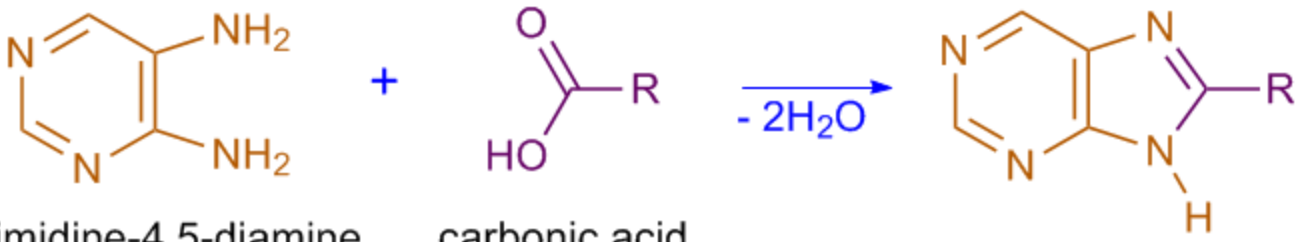


7*H*-purine

Synthesis

1. Traube Synthesis

- Synthesis of purines by heating 4,5 - diaminopyrimidines with carbonic acid / formamide

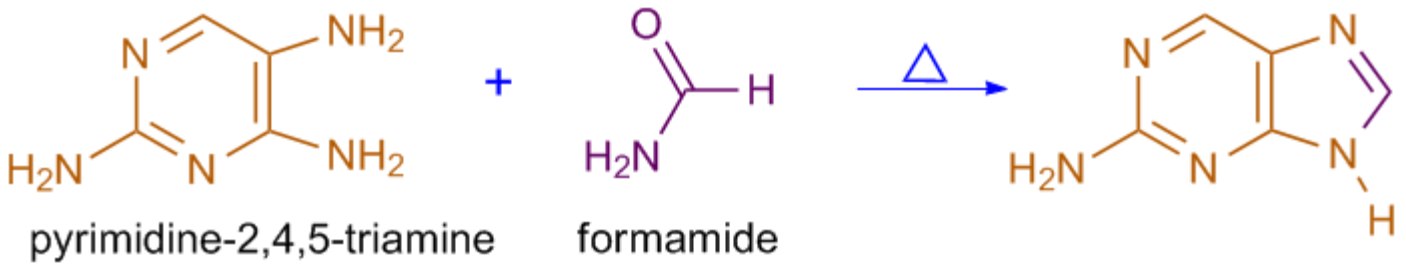


pyrimidine-4,5-diamine carbonic acid

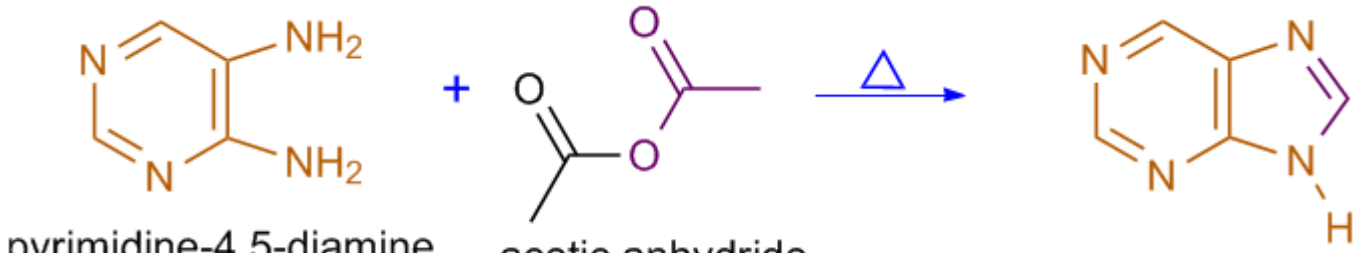
Synthesis

1. Traube Synthesis

E.g.



pyrimidine-2,4,5-triamine formamide

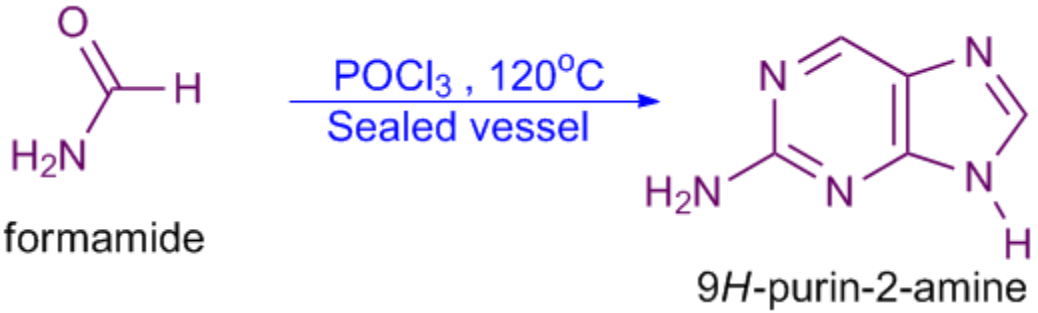


pyrimidine-4,5-diamine acetic anhydride

Synthesis

2. From formamide

- Laboratory synthesis , formamide is heated in an vessel at 120 °C

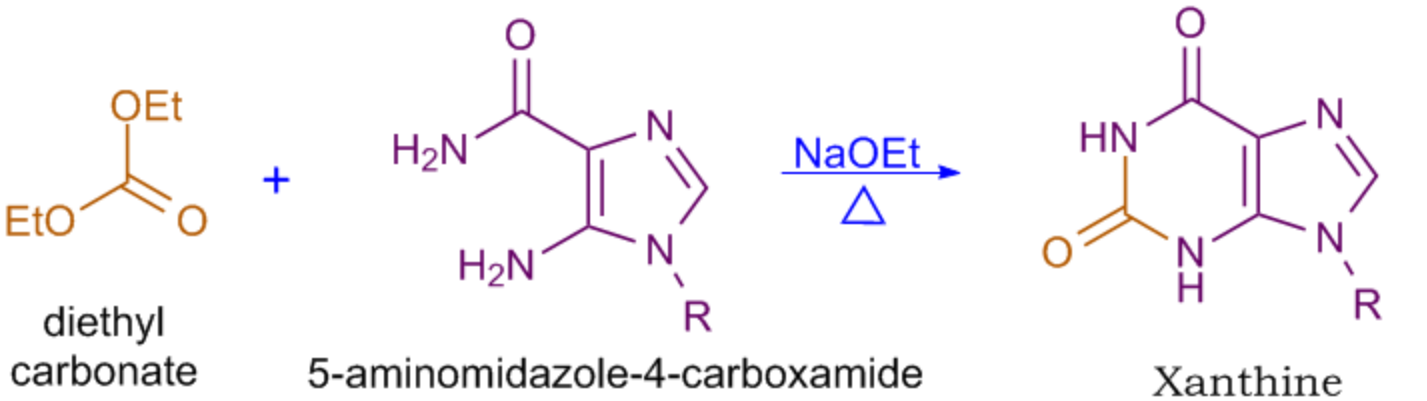


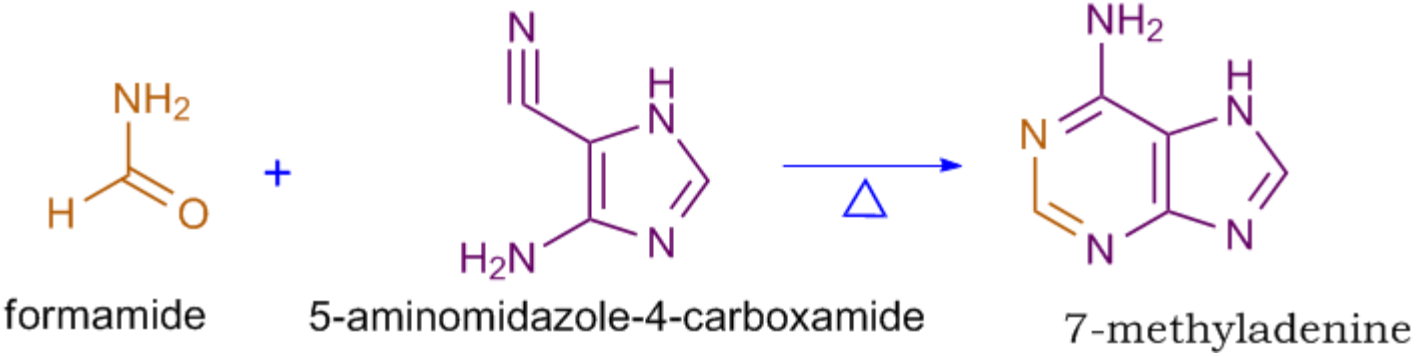
formamide

9*H*-purin-2-amine

Synthesis

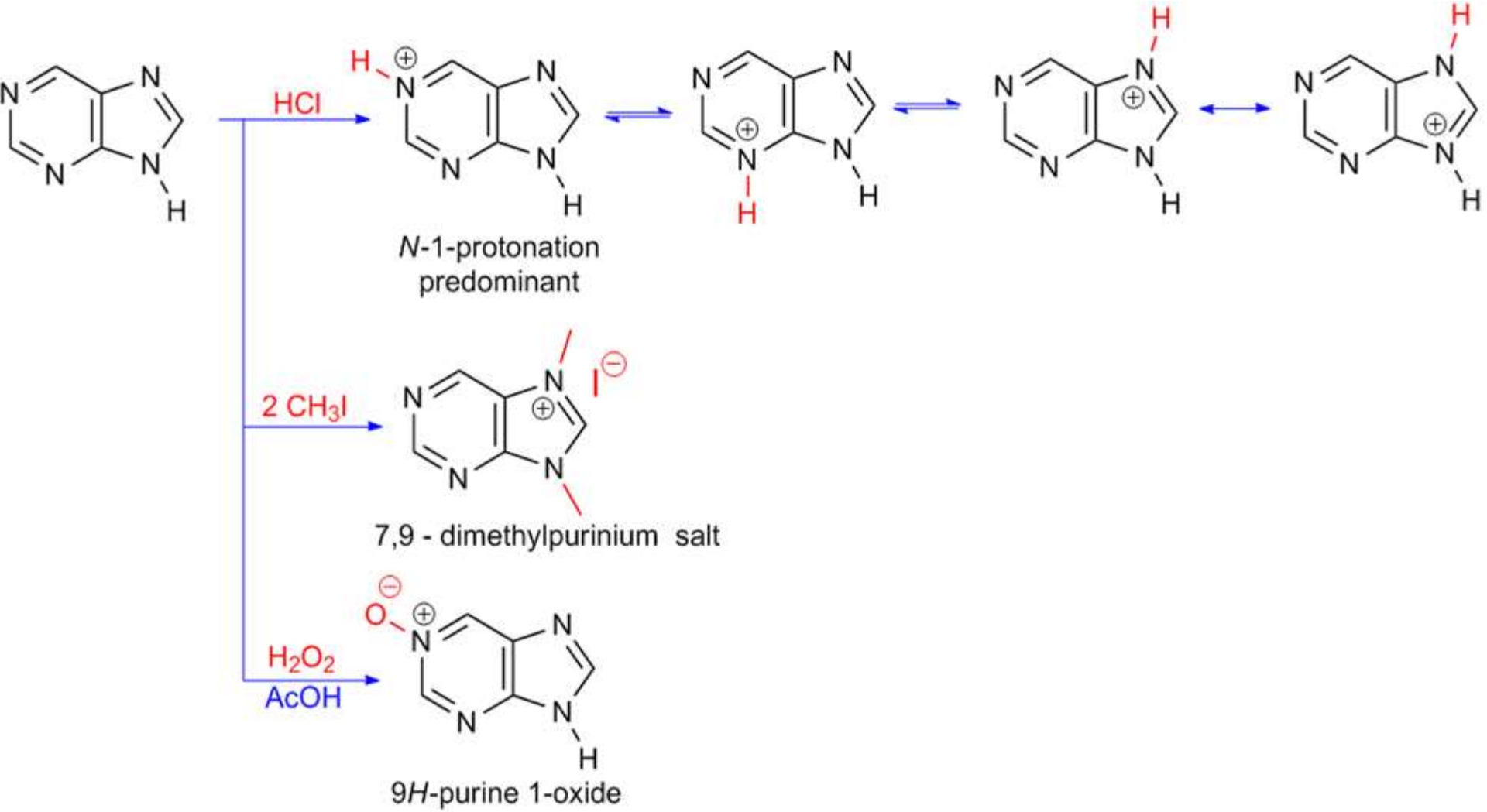
3. From substituted imidazole





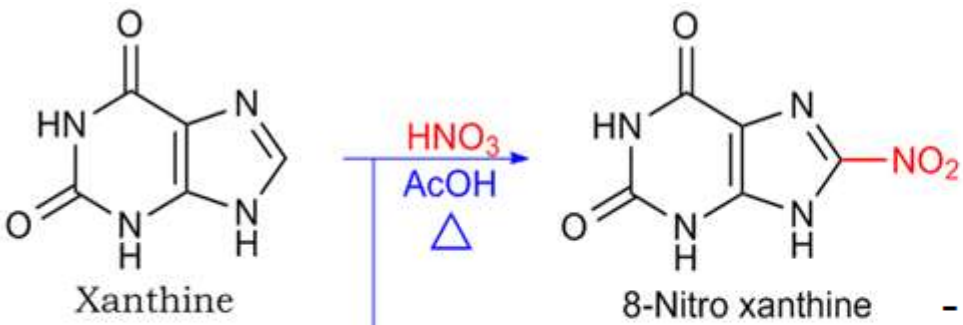
Reactions

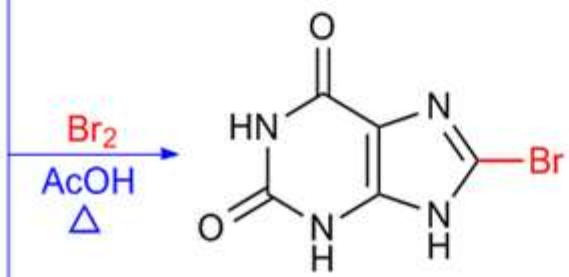
1. Electrophilic addition to N



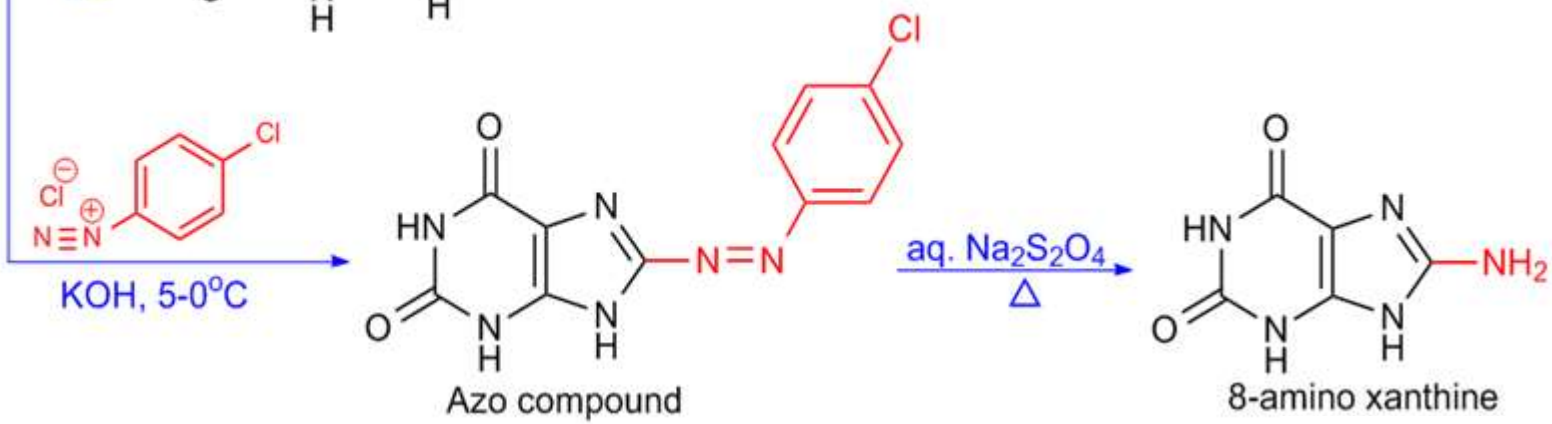
Reactions

2. Electrophilic aromatic substitution





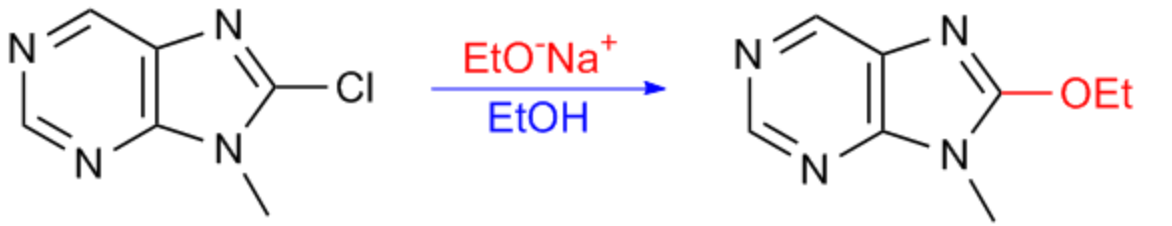
- Reaction is possible at 8th position,
- Oxy and amino derivatives react readily than non-substituted purines



Reactions

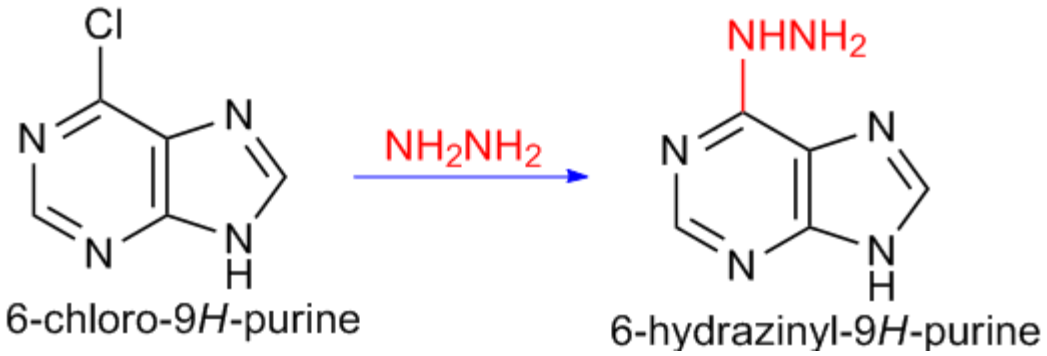
3. Nucleophilic substitution

- Nucleophilic *displacement* , where halides are the most popular leaving group



8-chloro-9-methyl-9*H*-purine

8-ethoxy-9-methyl-9*H*-purine



6-chloro-9*H*-purine

6-hydrazinyl-9*H*-purine

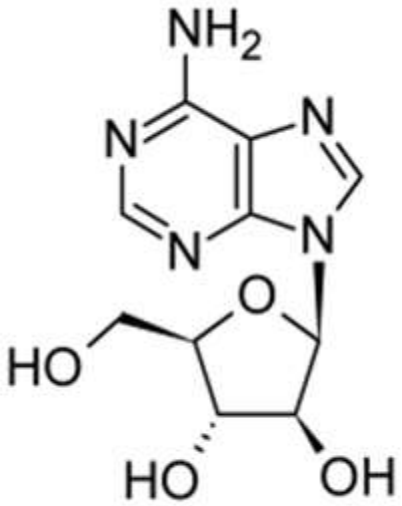
Medicinal uses

(5) Nucleoside Antimetabolites: *Acyclovir; Valacyclovir; Ganciclovir; Vidarabine*

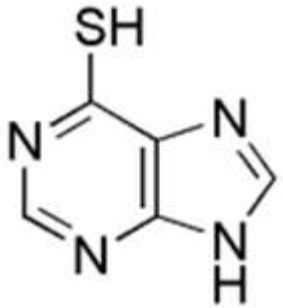
- Antiviral agent

(6) Antimetabolites : *6-Mercaptopurine, thioguanine, azathioprine*

- Anticancer agent



Vidarabine

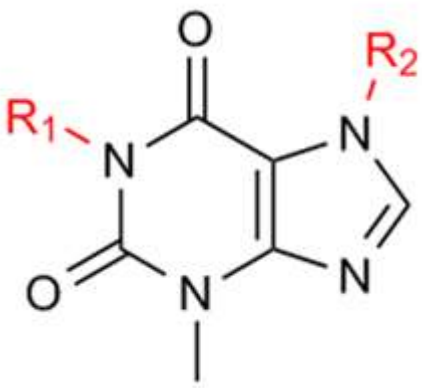


6-Mercaptopurine

Medicinal uses

(5) Methylxanthines : *Caffeine, theophylline, theobromine*

- Drugs used in bronchial Asthma
- Used as CNS stimulants



	R_1	R_2
Caffeine	$-CH_3$	$-CH_3$
Theophylline	$-CH_3$	H
Theobromine	H	$-CH_3$

End of the topic

Reference:

Heterocyclic Chemistry– R.K. Bansal
Heterocyclic Chemistry– Joule & Mills
Organic Chemistry – Mr. & Mrs. Mehta
Net Source