Int. J. Curr.Res.Chem.Pharma.Sci. 1(9): (2014):88–120

INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN CHEMISTRY AND PHARMACEUTICAL SCIENCES

(p-ISSN: 2348-5213: e-ISSN: 2348-5221)
www.ijcrcps.com

Review Article

REVIEW IN CYCLIC COMPOUNDS WITH HETEROATOM

DR. NAGHAMMAHMOODALJAMALI

Ph.D ., Assist. Professor in Organic Chemistry , Chemistry Department .,College of Education .,IRAQ.
Corresponding Author: dr.nagham_mj@yahoo.com

Abstract

In this survey., all types of cyclic compounds (aliphatic and aromatic) which containing one or more heteroatoms like (sulfur , nitrogen , oxygen , selenium ,….)- various Membered Rings ,methods of preparations , reactions , stability , strain of angle ,some of applications , comparison of stability , nomenclature .

Keywords: types of cycles , hetero atom ,heteroaromatic , organometallic .

Introduction

Cyclic Compounds With Heteroatom

Compounds classified as heterocyclic probably constitute the largest and most varied family of organic compounds. After all, every carbocyclic compound, regardless of structure and functionality, may in principle be converted into a collection of heterocyclic analogs by replacing one or more of the ring carbon atoms with a different element. Even if we restrict our consideration to oxygen, nitrogen and sulfur (the most common heterocyclic elements), the permutations and combinations

Hetero Aromatic Systems

This includes heteroannulenes, which comply with the HÜCKEL rule, i.e. which possess *(4n* + 2) ^•-electrons delocalized over the ring. The most important group of these compounds derives from annulene (benzene). They are known as *heteroarenes,* e.g.((furan, thiophene, pyrrole, pyridine, and the pyrylium and thiinium ions)). As regards stability and reactivity, they can be compared to the correspondingbenzenoid.

The antiaromatic systems, i.e. systems possessing *4n* delocalized electrons, e.g. oxepin, azepine, thiepin, azocine, and 1,3-diazocine, as well as the corresponding annulenes, are, by contrast, much less stable and very reactive.

The classification of heterocycles as heterocycloalkanes, heterocycloalkenes, heteroannulenes and Heteroaromatics allows an estimation of their stability and reactivity. In some cases, this can also beapplied to inorganic heterocycles[1-5]. For instance, borazine, a colorless liquid, bp 55°C, is classifiedas a heteroaromatic system.

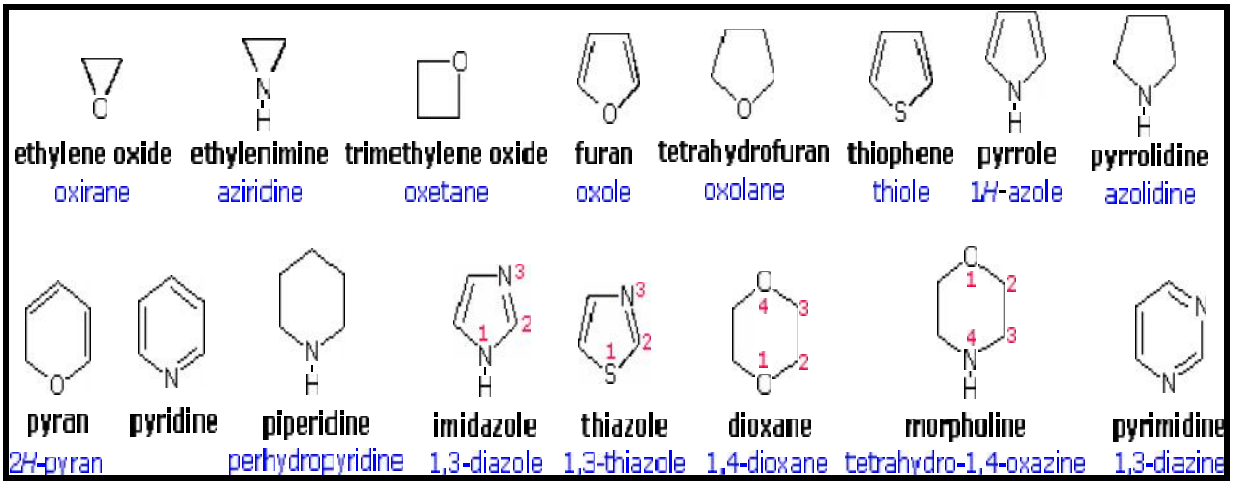
Heterocyclic Compounds

A cyclic organic compound containing all carbon atoms in ring formation is referred to as a *carbocyclic compound.* If at least one atom other than carbon, forms a part of the ring system then it is designated as a *heterocyclic* compound[6-8]. Nitrogen, oxygen and sulfur are the most common heteroatoms.

Nomenclature:

Devising a systematic nomenclature system for heterocyclic compounds presented a formidable challenge, which has not been uniformly concluded.

Many heterocycles, especially amines, were identified early on, and received trivial names which are still preferred. Some monocyclic compounds of this kind are shown in the following chart, with the common (trivial) name in bold and a systematic name based on the Hantzsch-Widman system given beneath it in blue. The rules for using this system will be given later. For most students, learning these common names will provide an adequate nomenclature background.



An easy to remember, but limited, nomenclature system makes use of an elemental prefix for the heteroatom followed by the appropriate carbocyclic name. A short list of some common prefixes is given in the following table, priority order increasing from right to left. Examples[5-10]. of this nomenclature are: ethylene oxide = oxacyclopropane, furan = oxacyclopenta-2,4-diene, pyridine = azabenzene, and morpholine = 1-oxa-4-azacyclohexane.

Element	oxygen	sulfur	selenium	nitrogen	phosphorous	silicon	boron
Valence	II	II	II	III	III	IV	III
Prefix	Oxa	Thia	Selena	Aza	Phospha	Sila	Bora

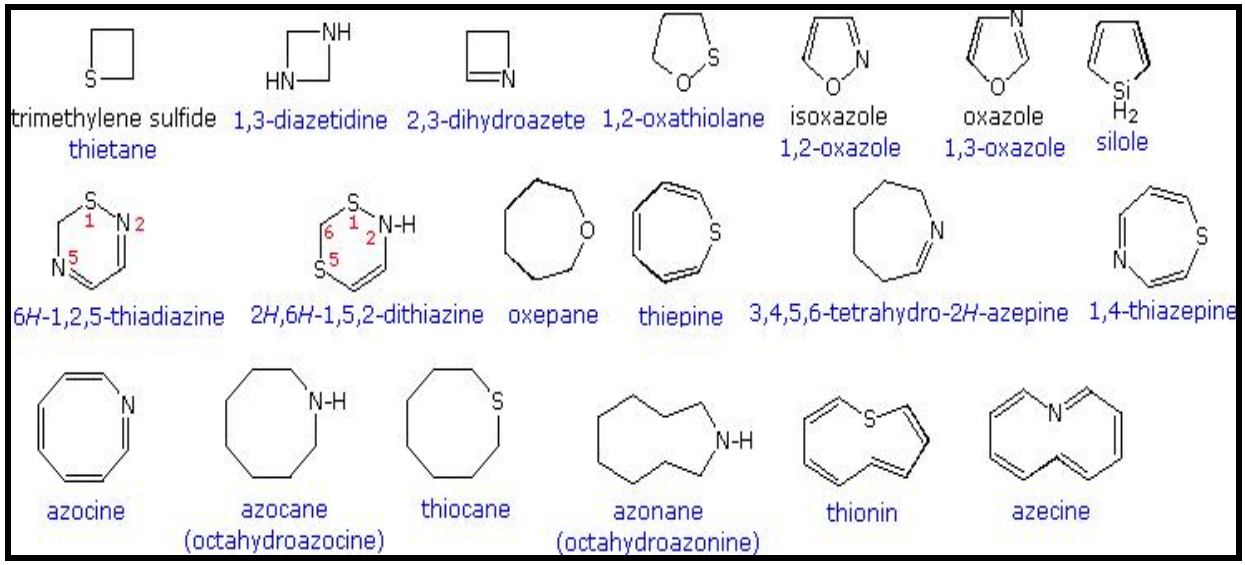
The Hantzsch-Widman system provides a more systematic method of naming heterocyclic compounds that is not dependent on prior carbocyclic names. It makes use of the same hetero atom prefix defined above (dropping the final "a"), followed by a suffix designating ring size and saturation. As outlined in the following table, each suffix consists of a ring size root (blue) and an ending intended to designate the degree of unsaturation in the ring. In this respect, it is important to recognize that the saturated suffix applies only to completely saturated ring systems, and the unsaturated suffix applies to rings incorporating the maximum number of non-cumulated double bonds. Systems having a lesser degree of unsaturation require an appropriate prefix, such as "dihydro"or "tetrahydro".

Ring Size	3	4	5	6	7	8	9	10
Suffix Unsaturated Saturated	irene irane	ete etane	ole olane	ine inane	epine epane	ocine ocane	onine onane	ecine ecane

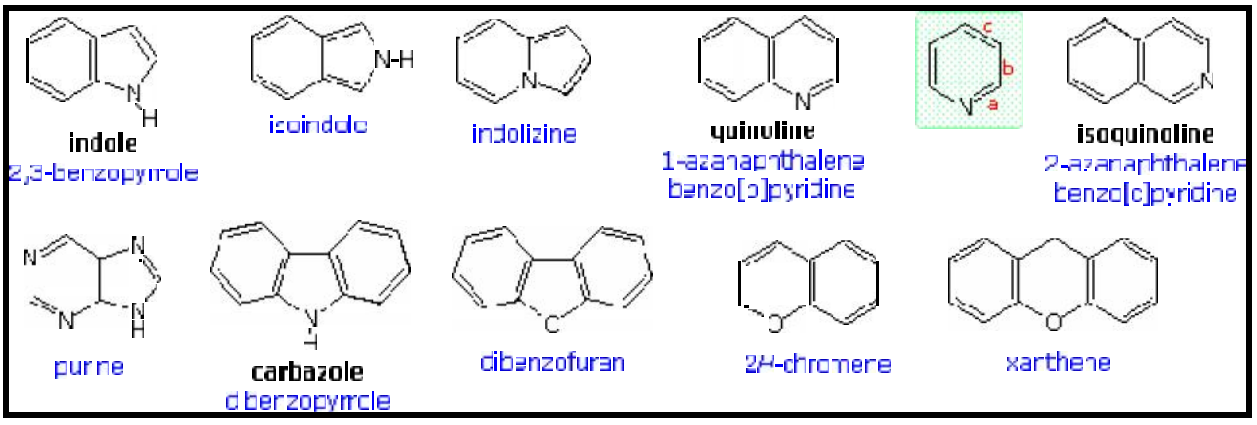
Despite the general systematic structure of the Hantzsch-Widman system, several exceptions and modifications have been incorporated to accommodate conflicts with prior usage. Some examples are:

• The terminal "e" in the suffix is optional though recommended.
• Saturated 3, 4 & 5-membered nitrogen heterocycles should use respectively the traditional "iridine", "etidine" & "olidine" suffix.
• Unsaturated nitrogen 3-membered heterocycles may use the traditional "irine" suffix.
• Consistent use of "etine" and "oline" as a suffix for 4 & 5-membered unsaturated heterocycles is prevented by their former use for similar sized nitrogen heterocycles.
• Established use of oxine, azine and silane for other compounds or functions prohibits their use for pyran, pyridine and silacyclohexane respectively.

Examples of these nomenclature rules are written in blue, both in the previous diagram and that shown below. Note that when a maximally unsaturated ring includes a saturated atom, its location may be designated by a "#*H* " prefix to avoid ambiguity, as in pyran and pyrrole above and several examples below. When numbering a ring with more than one heteroatom, the highest priority atom is #1 and continues in the direction that gives the next priority atom the lowest number.



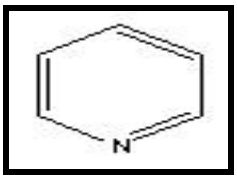
All the previous examples have been monocyclic compounds. Polycyclic compounds incorporating one or more heterocyclic rings are well known. A few of these are shown in the following diagram. As before, common names are in black and systematic names in blue. The two quinolines illustrate another nuance of heterocyclic nomenclature. Thus, the location of a fused ring may be indicated by a lowercase letter which designates the edge of the heterocyclic ring involved in the fusion, as shown by the pyridine ring in the green shaded box.



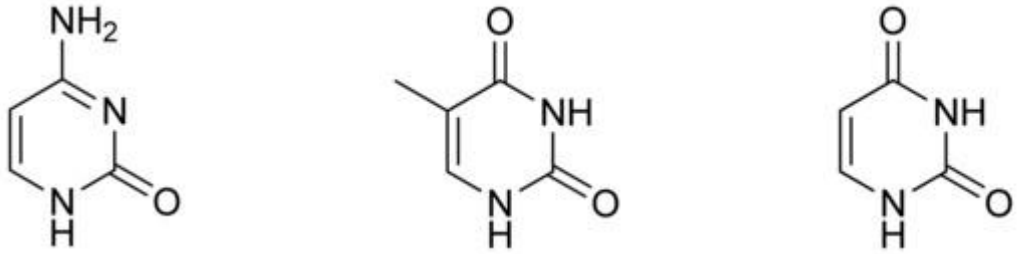
Incorporation of an oxygen, a nitrogen, a sulfur, or an atom of a related element into an organic ring structure in place of a carbon atom gives rise to a heterocyclic compound. Since the heterocyclic atom must form more than one bond in order to be incorporated into a ring structure, halogens do not form heterocyclic compounds although they may be substituents on a heterocyclic ring structure.

Heterocyclic compounds, like polycyclic ring compounds[11-14], are usually known by non-systematic names.

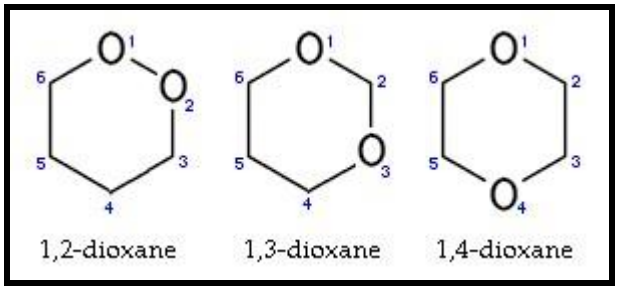
They may be either simple aromatic rings or non-aromatic rings. Some examples are pyridine (C_5H_5N), pyrimidine ($C_4H_4N_2$) and dioxane ($C_4H_8O_2$).



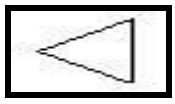
Pyridine (C_5H_5N)



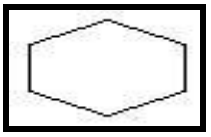
Three Pyrimidines ($C_4H_4N_2$) - Cytosine, Thymine, and Uracil



Note that compounds such as cyclopropane, an anaesthetic with explosive properties, and cyclohexane, a solvent, are not heterocyclic, they are merely cycloalkanes. The suffix *-cyclic* implies a ring structure, while *hetero-* refers to an atom other than carbon.



Cyclopropane



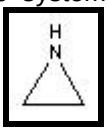
Cyclohexane

Heterocyclic chemistry is the chemistry branch dealing exclusively with synthesis, properties and applications of heterocyclics especially vital to drug design.

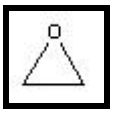
Three-Membered Rings

Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing one heteroatom are generally stable. Those with two heteroatoms are more likely to occur as reactive intermediates. Common 3-membered heterocyclics[1-5] are:

- One N: Aziridine; Azirane; Dimethyleneimine; Ethyleneimine; Ethylimine
- One O: Ethylene Oxide, generally known as epoxides. The systematic name is oxirane. The unsaturated ring system is an oxirene (generally unstable).
- One S: Thiirane; Ethylene Sulfide, generally known as an episulfide.



Aziridine



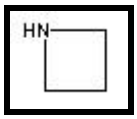
Ethylene Oxide, Oxirane

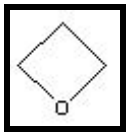
Ethylene Sulfide, Thiirane

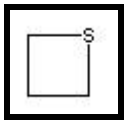
Four-Membered Rings

Azetidine, oxetane, and thietane—the four-membered rings containing, respectively, nitrogen, oxygen, and sulfur atoms—are prepared by nucleophilic displacement reactions such as those used to prepare the corresponding three-membered rings

- One N: Azetidine; Trimethylene Imine
- One O: Oxetane; 1,3-Epoxypropane; 1,3-Propylene Oxide; Trimethylene Oxide; Cyclooxabutane; Oxacyclobutane
- One S: Thietane; Trimethylene Sulfide





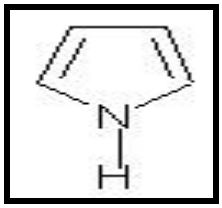


Trimethylene Imine, Azetidine 1,3-Epoxypropane, Oxetane Trimethylene Sulfide, Thietane

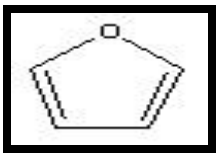
Five-Membered Rings

With heterocyclics containing five atoms, the unsaturated compounds are frequently more stable because of aromaticity.

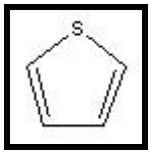
- With one heteroatom:
- With N: Pyrrole (aromatic), dihydropyrrole and tetrahydropyrrole
- With O: Furan (aromatic), dihydrofuran and tetrahydrofuran
- With S: Thiophene (aromatic), dihydrothiophene and tetrahydrothiophene
- With As: Arsole and analogues
- With two heteroatoms:
- One N and one or more of N,S,O: the azoles
- Two S: Dithiolane



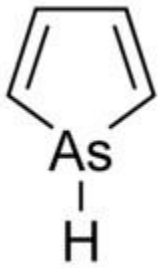
Pyrrole



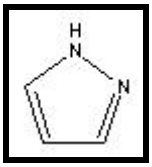
Furan



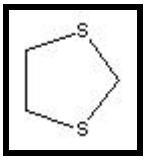
Thiophene



Arsole



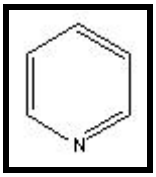
1,2-Diazole, Pyrazole



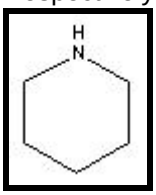
1,3-Dithiolane

Six-Membered Rings

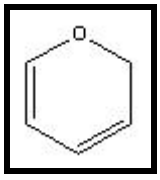
- With one heteroatom:
- With N: Pyridine, Piperidine
- With O: Pyran
- With S: Thiane
- With two heteroatoms:
- Two N: Pyridazine, Pyrimidine, Pyrazine are the 1,2-, 1,3-, and 1,4- isomers, respectively.
- Two N: Piperazine
- One N and one O: Oxazine, Morpholine
- One N and one S: Thiazine
- Two S: Dithiane - 1,2-, 1,3- and 1,4- isomers, respectively
- Two O: Dioxane - 1,2-, 1,3- and 1,4- isomers, respectively.



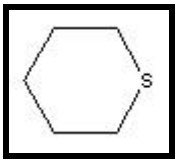
Pyridine



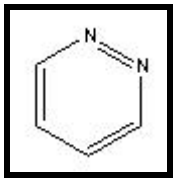
Piperidine



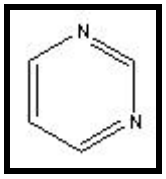
Pyran



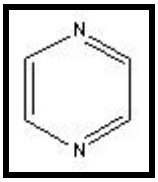
Tetrahydrothiopyran, Thiane



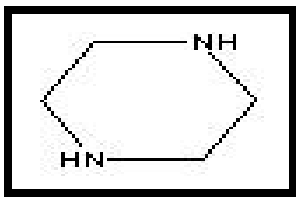
1,2-Diazine, Pyridazine



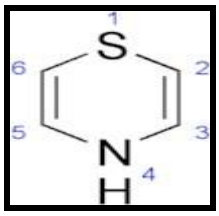
1,3-Diazine, Pyrimidine



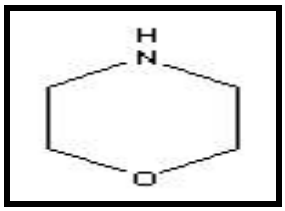
1,4-Diazine, Pyrazine



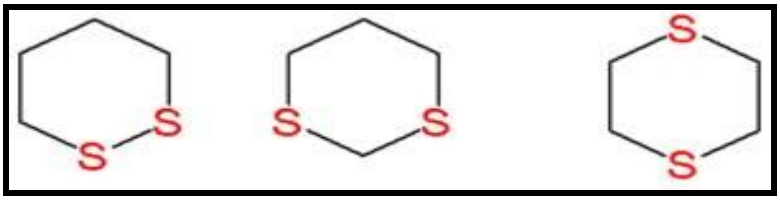
Piperazine



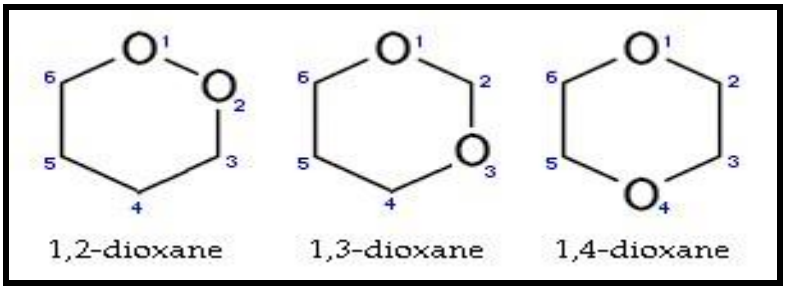
Thiazine



Morpholine, Oxazine



1,2-dithiane 1,3-dithiane 1,4-dithiane

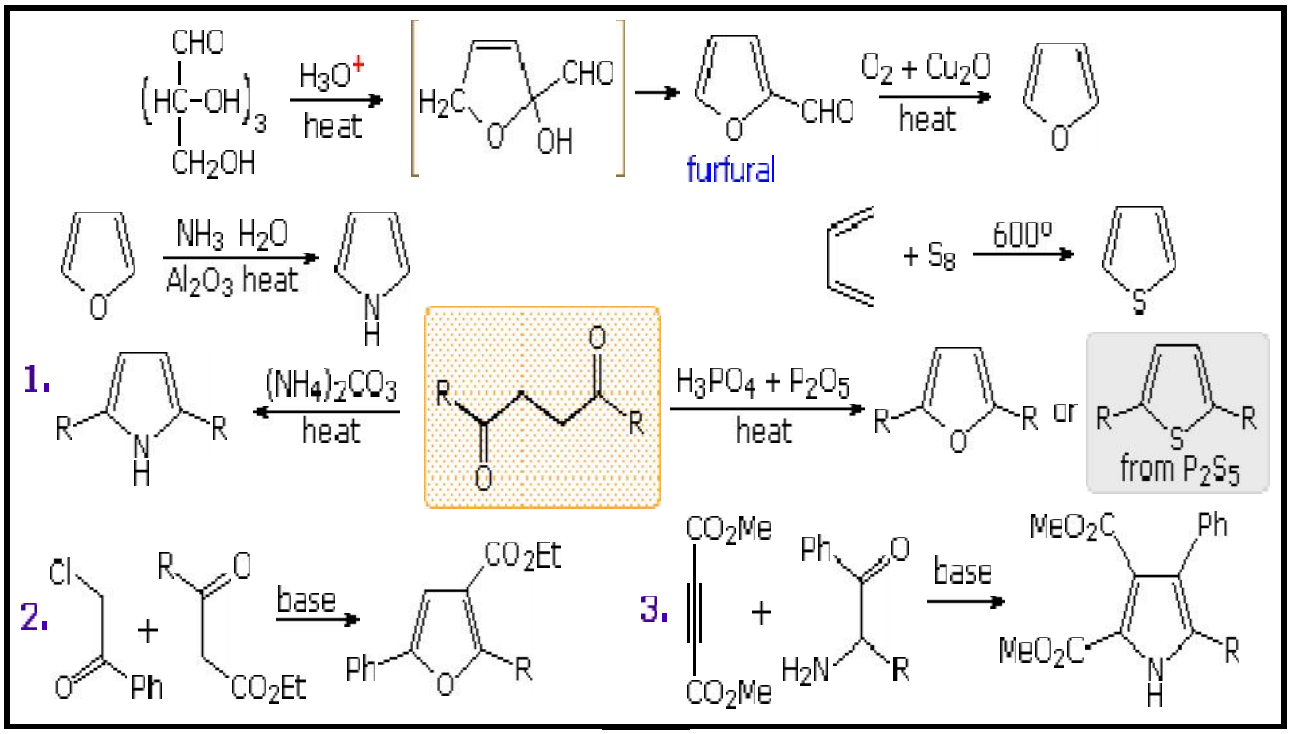


Five-Membered Rings :

Preparation :

Commercial preparation of furan proceeds by way of the aldehyde, furfural, which in turn is generated from pentose containing raw materials like corncobs, as shown in the uppermost equation below. Similar preparations of pyrrole and thiophene are depicted in the second row equations. Equation 1 in the third row illustrates a general preparation of substituted furans, pyrroles and thiophenes from 1,4-dicarbonyl compounds, known as the Paal-Knorr synthesis. Many other procedures leading to substituted heterocycles[15-20]. of this kind have been devised. Two of these are shown in reactions 2 and 3. Furan is reduced to tetrahydrofuran by palladium-catalyzed hydrogenation. This cyclic ether is not only a valuable solvent, but it is readily converted to 1,4-dihalobutanes or 4-haloalkylsulfonates, which may be used to prepare pyrrolidine and thiolane.

Dipolar cycloaddition reactions often lead to more complex five-membered heterocycles.



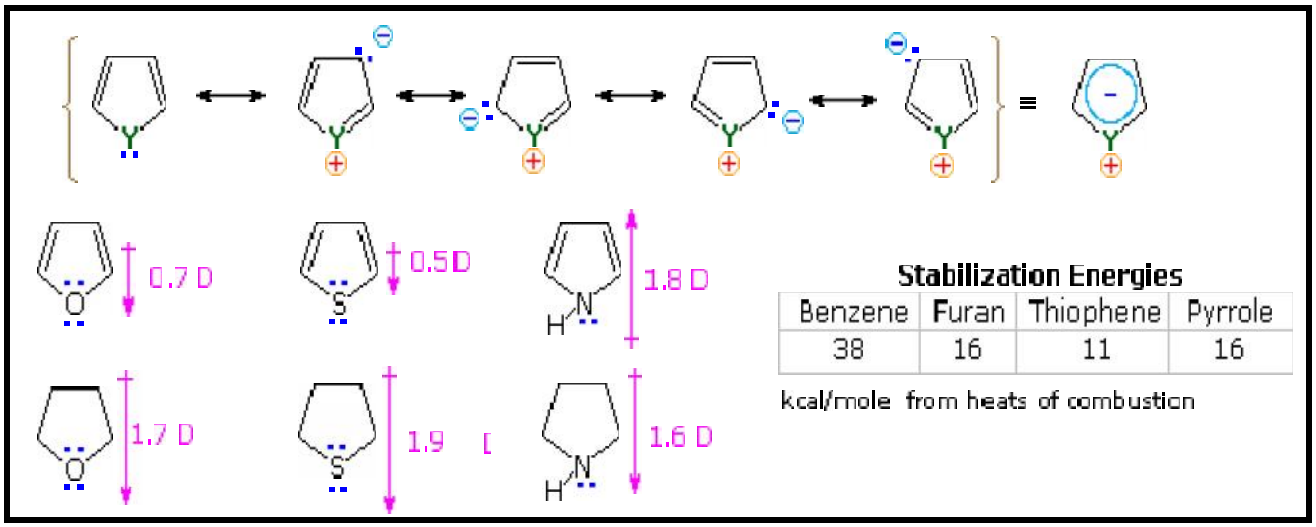
Indole is probably the most important fused ring heterocycle in this class. By clicking on the above diagram three examples of indole synthesis will be displayed. The first proceeds by an electrophilic substitution of a nitrogen-activated benzene ring. The second presumably takes place by formation of a dianionic species in which the $ArCH_2()$ unit bonds to the deactivated carbonyl group. Finally, the Fischer indole synthesis is a remarkable sequence of tautomerism, sigmatropic rearrangement, nucleophilic addition, and elimination reactions occurring subsequent to phenylhydrazone formation. This interesting transformation involves the oxidation of two carbon atoms and the reduction of one carbon and both nitrogen atoms.

Reactions:

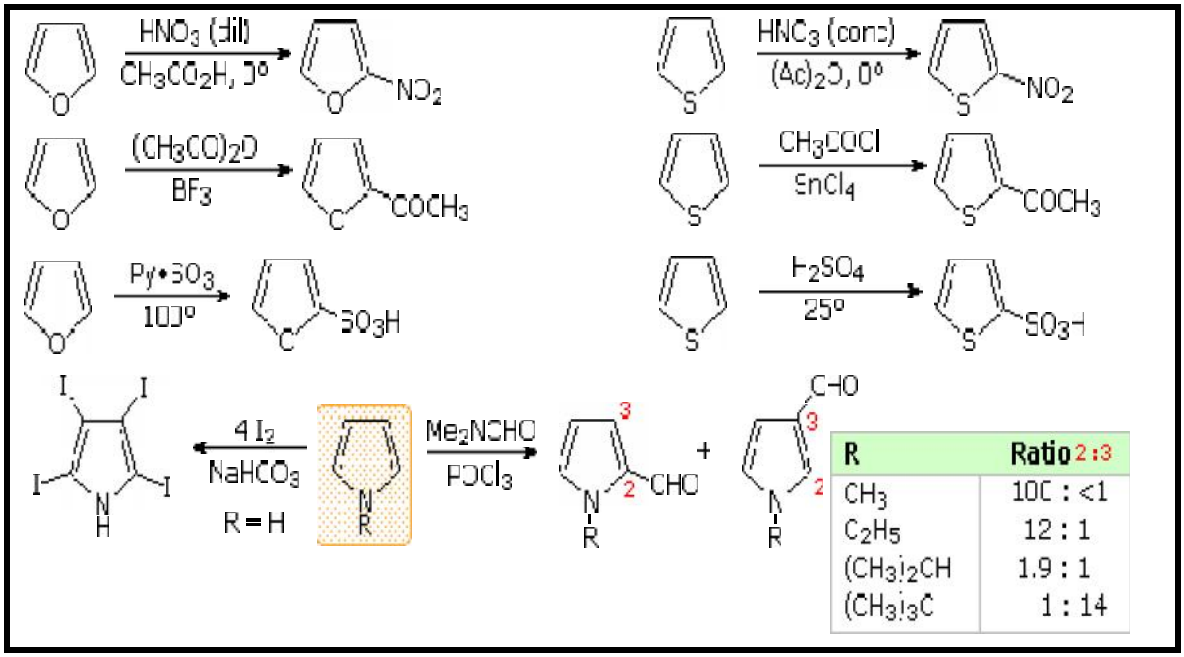
The chemical reactivity of the saturated members of this class of heterocycles: tetrahydrofuran, thiolane and pyrrolidine, resemble that of acyclic ethers, sulfides, and 2º-amines, and will not be described here. 1,3-Dioxolanes and dithiolanes are cyclic acetals and thioacetals. These units are commonly used as protective groups for aldehydes and ketones, and may be hydrolyzed by the action of aqueous acid.

It is the "aromatic" unsaturated compounds[21-28]., furan, thiophene and pyrrole that require our attention. In each case the heteroatom has at least one pair of non-bonding electrons that may combine with the four π-electrons of the double bonds to produce an annulene having an aromatic sextet of electrons. This is illustrated by the resonance description at the top of the following diagram. The heteroatom Y becomes sp^2-hybridized and acquires a positive charge as its electron pair is delocalized around the ring. An easily observed consequence of this delocalization is a change in dipole moment compared with the analogous saturated heterocycles, which all have strong dipoles with the heteroatom at the negative end. As expected, the aromatic heterocycles have much smaller dipole moments, or in the case of pyrrole a large dipole in the opposite direction. An important characteristic of aromaticity is enhanced thermodynamic stability, and this is usually demonstrated by relative heats of hydrogenation or heats of combustion measurements. By this standard, the three aromatic heterocycles under examination are stabilized, but to a lesser degree than benzene.

Additional evidence for the aromatic character of pyrrole is found in its exceptionally weak basicity (pK_a *ca.* 0) and strong acidity (pK_a = 15) for a 2º-amine. The corresponding values for the saturated amine pyrrolidine are: basicity 11.2 and acidity 32.

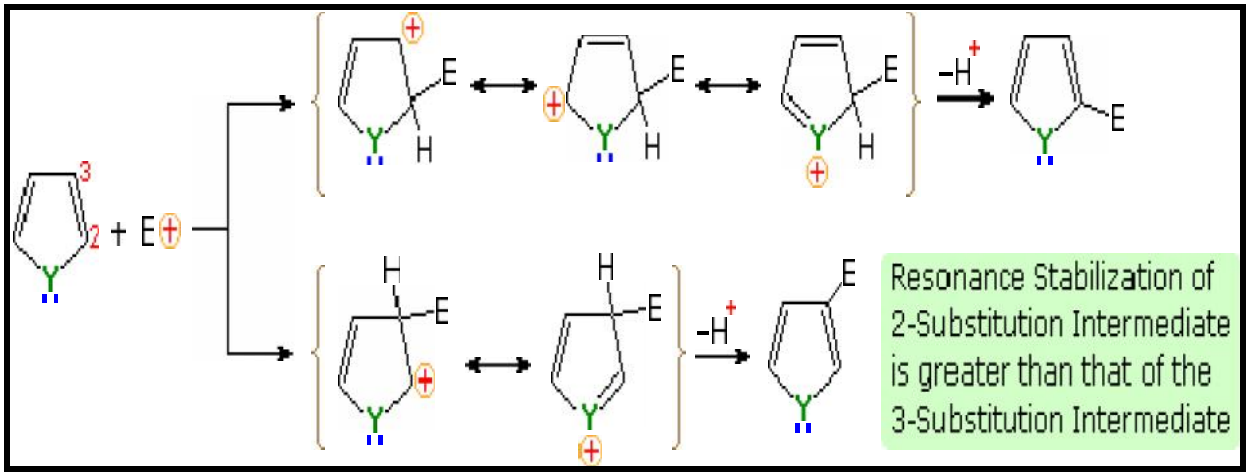


Another characteristic of aromatic systems, of particular importance to chemists, is their pattern of reactivity with electrophilic reagents. Whereas simple cycloalkenes generally give addition reactions, aromatic compounds tend to react by substitution. As noted for benzene and its derivatives, these substitutions take place by an initial electrophile addition, followed by a proton loss from the "onium" intermediate to regenerate the aromatic ring. The aromatic five-membered heterocycles all undergo electrophilic substitution, with a general reactivity order: pyrrole>> furan >thiophene> benzene. Some examples are given in the following diagram. The reaction conditions show clearly the greater reactivity of furan compared with thiophene. All these aromatic heterocycles react vigorously with chlorine and bromine, often forming polyhalogenated products together with polymers. The exceptional reactivity of pyrrole is evidenced by its reaction with iodine (bottom left equation), and formation of 2-acetylpyrrole by simply warming it with acetic anhydride (no catalyst).



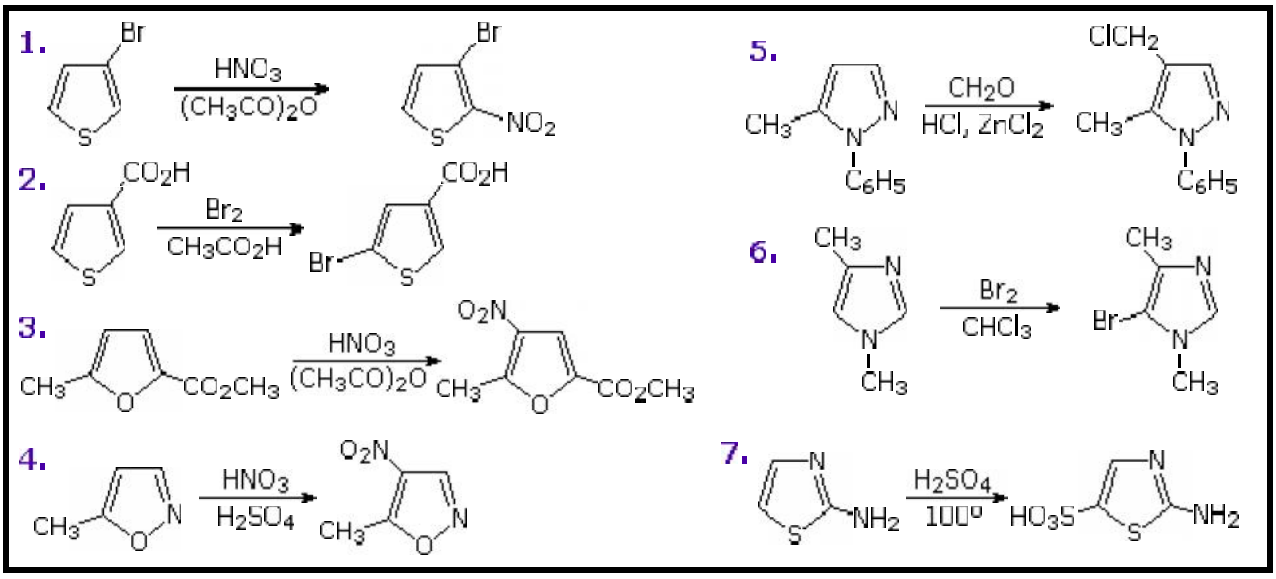
There is a clear preference for substitution at the 2-position (α) of the ring, especially for furan and thiophene. Reactions of pyrrole require careful evaluation, since N-protonation destroys its aromatic character. Indeed, N-substitution of this 2º-amine is often carried out prior to subsequent reactions. For example, pyrrole reacts with acetic anhydride or acetyl chloride and triethyl amine to give N-acetylpyrrole. Consequently, the regioselectivity of pyrrole substitution is variable, as noted by the bottom right equation.

An explanation for the general α-selectivity of these substitution reactions is apparent from the mechanism outlined below. The intermediate formed by electrophile attack at C-2 is stabilized by charge delocalization to a greater degree than the intermediate from C-3 attack. From the Hammond postulate we may then infer that the activation energy for substitution at the former position is less than the latter substitution.



Functional substituents influence the substitution reactions of these heterocycles in much the same fashion as they do for benzene. Indeed, once one understands the ortho-para and meta-directing character of these substituents, their directing influence on heterocyclic ring substitution is not difficult to predict. The following diagram shows seven such reactions. Reactions 1 & 2 are 3-substituted thiophenes, the first by an electron donating substituent and the second by an electron withdrawing group. The third reaction has two substituents of different types in the 2 and 5- positions.

Finally, examples 4 through 7 illustrate reactions of 1,2- and 1,3-oxazole, thiazole and diazole. Note that the basicity of the sp^2-hybridized nitrogen in the diazoles is over a million times greater than that of the apparent sp^3-hybridized nitrogen, the electron pair of which is part of the aromatic electron sextet.

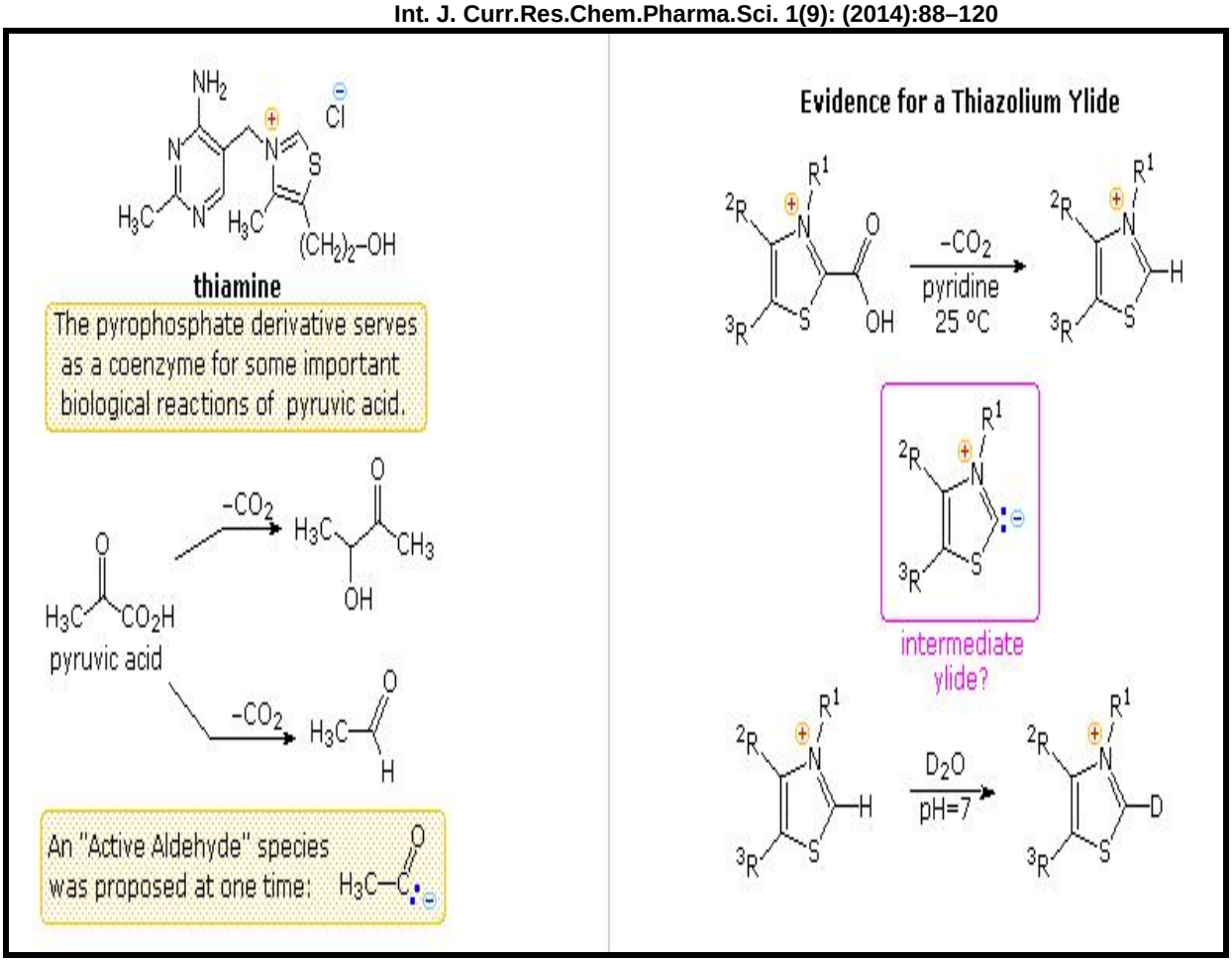


Other possible reactions are suggested by the structural features of these heterocycles. For example, furan could be considered an enol ether and pyrrole an enamine. Such functions are known to undergo acid-catalyzed hydrolysis to carbonyl compounds and alcohols or amines. Since these compounds are also heteroatom substituted dienes, we might anticipate Diels-Alder cycloaddition reactions with appropriate dienophiles. These possibilities will be illustrated above by clicking on the diagram. As noted in the upper example, furans may indeed be hydrolyzed to 1,4-dicarbonyl compounds, but pyrroles and thiophenes behave differently. The second two examples, shown in the middle, demonstrate typical reactions of furan and pyrrole with the strong dienophile maleic anhydride. The former participates in a cycloaddition reaction; however, the pyrrole simply undergoes electrophilic substitution at C-2. Thiophene does not easily react with this dienophile.

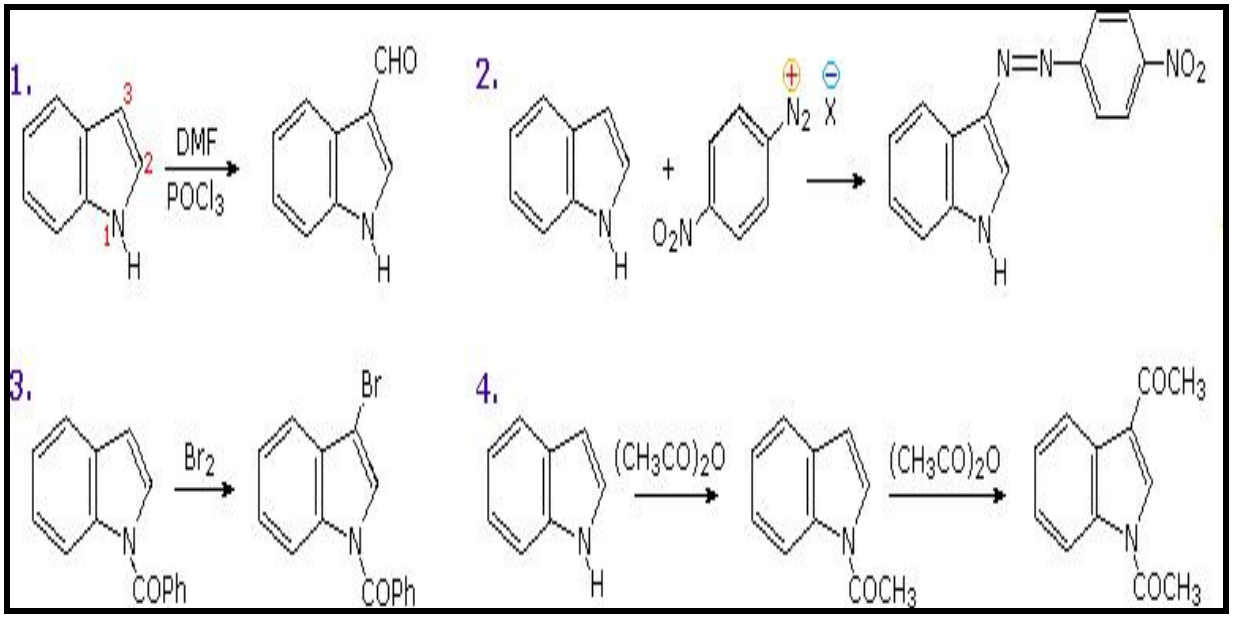
The bottom line of the new diagram illustrates the remarkable influence that additional nitrogen units have on the hydrolysis of a series of N-acetylazoles in water at 25 ºC and pH=7. The pyrrole compound on the left is essentially unreactive, as expected for an amide, but additional nitrogens markedly increase the rate of hydrolysis. This effect has been put to practical use in applications of the acylation reagent 1,1'-carbonyldiimidazole (Staab's reagent).

Another facet of heterocyclic chemistry was disclosed in the course of investigations concerning the action of thiamine (following diagram). As its pyrophosphate derivative, thiamine is a coenzyme for several biochemical reactions, notably decarboxylations of pyruvic acid to acetaldehyde and acetoin. Early workers speculated that an "active aldehyde" or acyl carbanion species was an intermediate in these reactions. Many proposals were made, some involving the aminopyrimidine moiety, and others, ring-opened hydrolysis derivatives of the thiazole ring, but none were satisfactory. This puzzle was solved when R. Breslow (Columbia) found that the C-2 hydrogen of thiazolium salts was unexpectedly acidic (pK_a*ca*. 13), forming a relatively stable ylide conjugate base. As shown, this rationalizes the facile decarboxylation of thiazolium-2-carboxylic acids and deuterium exchange at C-2 in neutral heavy water.

Appropriate thiazolium salts catalyze the conversion of aldehydes to acyloins in much the same way that cyanide ion catalyzes the formation of benzoin from benzaldehyde, the benzoin condensation. By clicking on the diagram, a new display will show mechanisms for these two reactions. Note that in both cases an acyl anion equivalent is formed and then adds to a carbonyl function in the expected manner. The benzoin condensation is limited to aromatic aldehydes, but the use of thiazolium catalysts has proven broadly effective for aliphatic and aromatic aldehydes. This approach to acyloins employs milder conditions than the reduction of esters to enediol intermediates by the action of metallic sodium .



The most important condensed ring system related to these heterocycles is indole. Some electrophilic substitution reactions of indole are shown in the following diagram. Whether the indole nitrogen is substituted or not, the favored site of attack is C-3 of the heterocyclic ring. Bonding of the electrophile at that position permits stabilization of the onium-intermediate by the nitrogen without disruption of the benzene aromaticity.

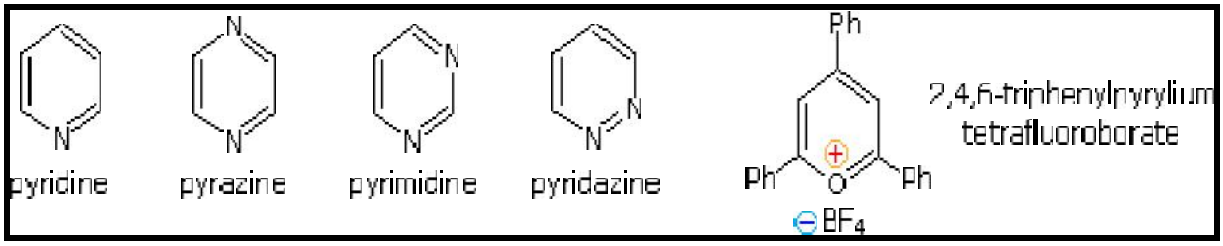


Six-Membered Rings :

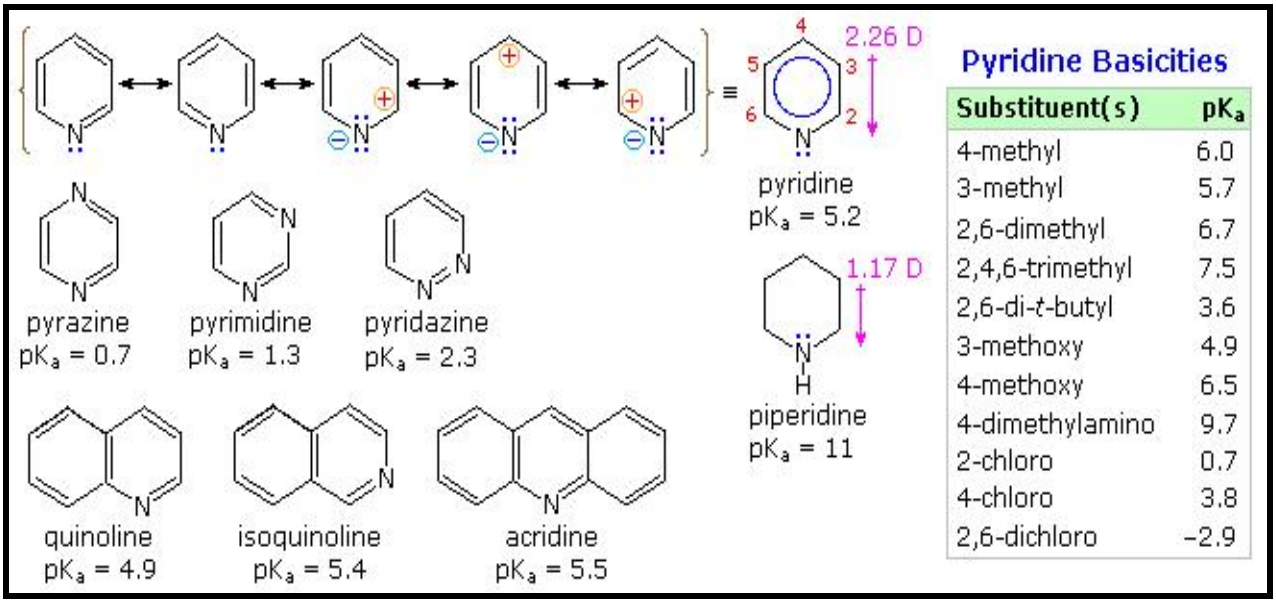
Properties :

The chemical reactivity of the saturated members of this class of heterocycles: tetrahydropyran, thiane and piperidine, resemble that of acyclic ethers, sulfides, and 2º-amines, and will not be described here. 1,3-Dioxanes and dithianes are cyclic acetals and thioacetals. These units are commonly used as protective groups for aldehydes and ketones, as well as synthetic intermediates, and may be hydrolyzed by the action of aqueous acid. The reactivity of partially unsaturated compounds depends on the relationship of the double bond and the heteroatom (*e.g.* 3,4-dihydro-2H-pyran is an enol ether).

Fully unsaturated six-membered nitrogen heterocycles, such as pyridine, pyrazine, pyrimidine and pyridazine, have stable aromatic rings. Oxygen and sulfur analogs are necessarily positively charged, as in the case of 2,4,6-triphenylpyrylium tetrafluoroborate.



From heat of combustion measurements, the aromatic stabilization energy of pyridine is 21 kcal/mole. The resonance description drawn at the top of the following diagram includes charge separated structures not normally considered for benzene. The greater electronegativity of nitrogen (relative to carbon) suggests that such canonical forms may contribute to a significant degree. Indeed, the larger dipole moment of pyridine compared with piperidine supports this view. Pyridine and its derivatives are weak bases, reflecting the sp^2 hybridization of the nitrogen. From the polar canonical forms shown here, it should be apparent that electron donating substituents will increase the basicity of a pyridine, and that substituents on the 2 and 4-positions will influence this basicity more than an equivalent 3-substituent. The pK_a values given in the table illustrate a few of these substituent effects. Methyl substituted derivatives have the common names picoline (methyl pyridines), lutidine (dimethyl pyridines) and collidine (trimethyl pyridines). The influence of 2-substituents is complex, consisting of steric hindrance and electrostatic components. 4-Dimethylaminopyridine is a useful catalyst for acylation reactions carried out in pyridine as a solvent. At first glance, the sp^3 hybridized nitrogen might appear to be the stronger base, but it should be remembered that N,N-dimethylaniline has a pK_a slightly lower than that of pyridine itself. Consequently, the sp^2 ring nitrogen is the site at which protonation occurs.



Pyridine Basicities

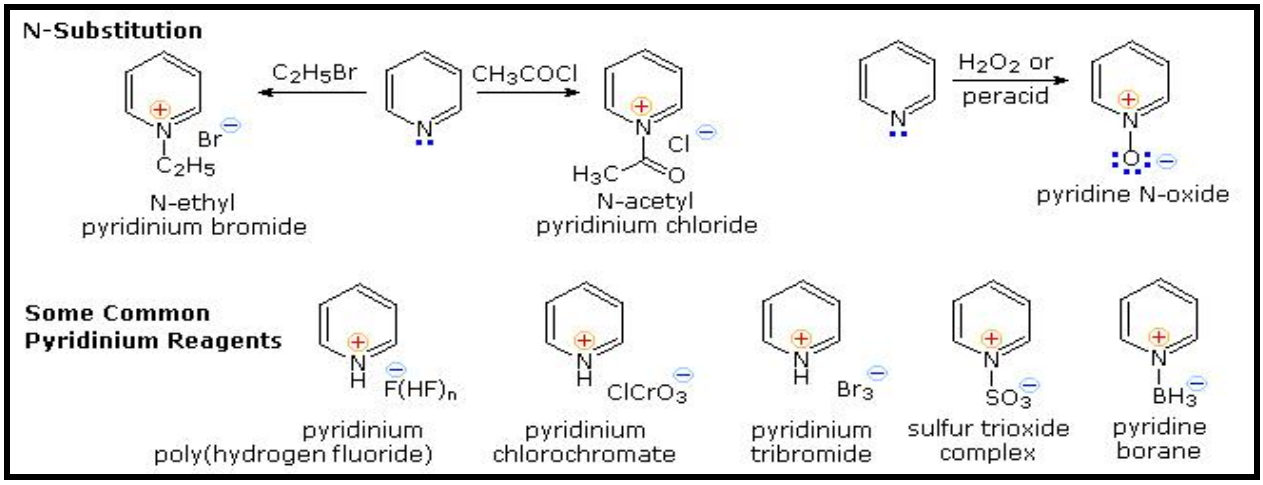
Substituent(s)	pK_a
4-methyl	6.0
3-methyl	5.7
2,6-dimethyl	6.7
2,4,6-trimethyl	7.5
2,6-di-*t*-butyl	3.6
3-methoxy	4.9
4-methoxy	6.5
4-dimethylamino	9.7
2-chloro	0.7
4-chloro	3.8
2,6-dichloro	-2.9

The diazinespyrazine, pyrimidine and pyridazine are all weaker bases than pyridine due to the inductive effect of the second nitrogen. However, the order of base strength is unexpected. A consideration of the polar contributors helps to explain the difference between pyrazine and pyrimidine, but the basicity of pyridazine seems anomalous. It has been suggested that electron pair repulsion involving the vicinal nitrogens destabilizes the neutral base relative to its conjugate acid.

Electrophilic Substitution of Pyridine

Pyridine is a modest base (pK_a=5.2). Since the basic unshared electron pair is not part of the aromatic sextet, as in pyrrole, pyridinium species produced by N-substitution retain the aromaticity of pyridine. As shown below, N-alkylation and N-acylation products may be prepared as stable crystalline solids in the absence of water or other reactive nucleophiles. The N-acyl salts may serve as acyl transfer agents for the preparation of esters and amides. Because of the stability of the pyridiniumcation, it has been used as a moderating component in complexes with a number of reactive inorganic compounds. Several examples of these stable and easily handled reagents are shown at the bottom of the diagram. The poly(hydrogen fluoride) salt is a convenient source of HF for addition to alkenes and conversion of alcohols to alkyl fluorides, pyridiniumchlorochromate (PCC) and its related dichromate analog are versatile oxidation agents and the tribromide salt is a convenient source of bromine. Similarly, the reactive compounds sulfur trioxide and diborane are conveniently and safely handled as pyridine complexes.

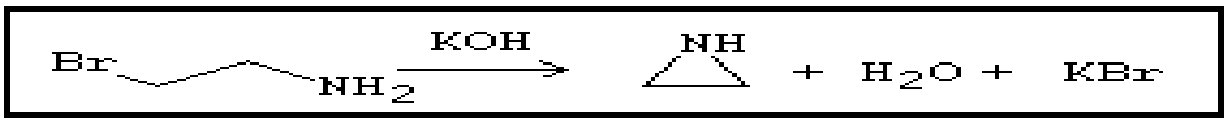
Amine oxide derivatives of 3º-amines and pyridine are readily prepared by oxidation with peracids or peroxides, as shown by the upper right equation. Reduction back to the amine can usually be achieved by treatment with zinc (or other reactive metals) in dilute acid.



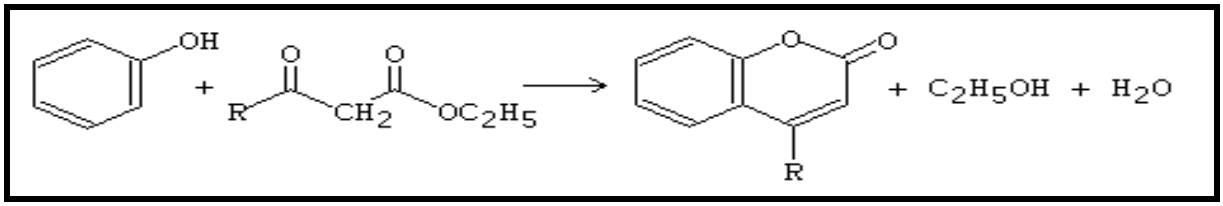
From the previous resonance description of pyridine, we expect this aromatic amine to undergo electrophilic substitution reactions far less easily than does benzene. Furthermore, as depicted above by clicking on the diagram, the electrophilic reagents and catalysts employed in these reactions coordinate with the nitrogen electron pair, exacerbating the positive charge at positions 2,4 & 6 of the pyridine ring. Three examples of the extreme conditions required for electrophilic substitution are shown on the left. Substituents that block electrophile coordination with nitrogen or reduce the basicity of the nitrogen facilitate substitution, as demonstrated by the examples in the blue-shaded box at the lower right, but substitution at C-3 remains dominant. Activating substituents at other locations also influence the ease and regioselectivity of substitution. By clicking on the diagram a second time, three examples will shown on the left. The amine substituent in the upper case directs the substitution to C-2, but the weaker electron donating methyl substituent in the middle example cannot overcome the tendency for 3-substitution. Hydroxyl substituents at C-2 and C-4 tautomerize to pyridones, as shown for the 2-isomer at the bottom left.

Pyridine N-oxide undergoes some electrophilic substitutions at C-4 and others at C-3. The coordinate covalent N–O bond may exert a push-pull influence, as illustrated by the two examples on the right. Although the positively charged nitrogen alone would have a strong deactivating influence, the negatively charged oxygen can introduce electron density at C-2, C-4 & C-6 by π-bonding to the ring nitrogen. This is a controlling factor in the relatively facile nitration at C-4. However, if the oxygen is bonded to an electrophile such as SO_3, the resulting pyridinium ion will react sluggishly and preferentially at C-3.

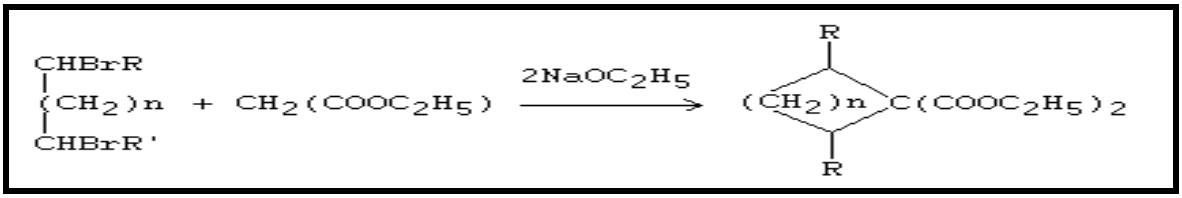
Synthesis of cyclic Compounds:
Gabriel Ethylenimine Method;
Gabriel-MarckwaldEthylenimine Synthesis:



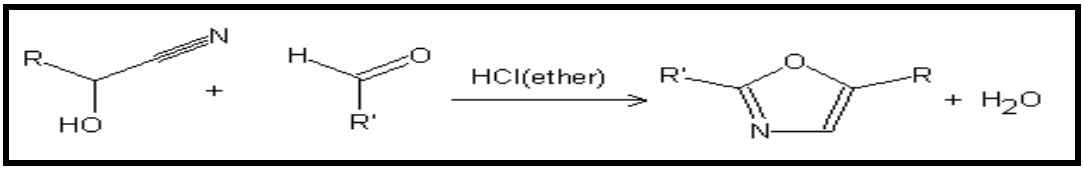
Pechmann Condensation (PechmannCoumarin Synthesis).:



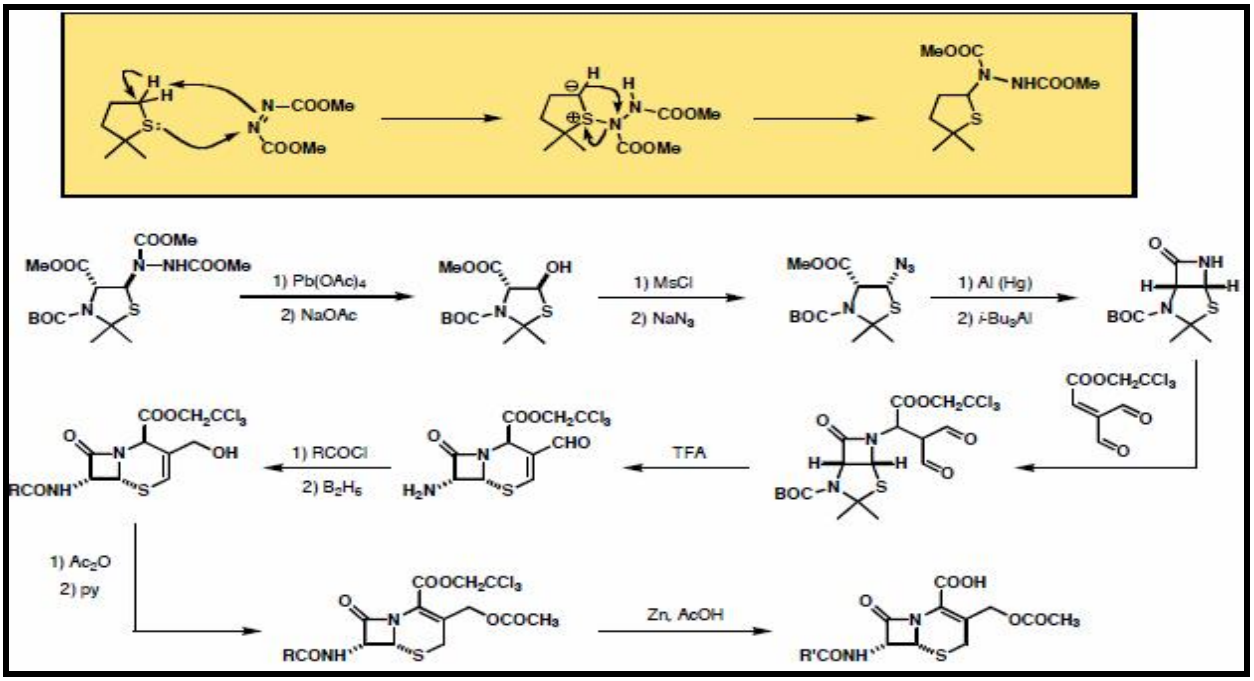
Perkin Alicyclic Synthesis.:



Fischer Oxazole Synthesis :

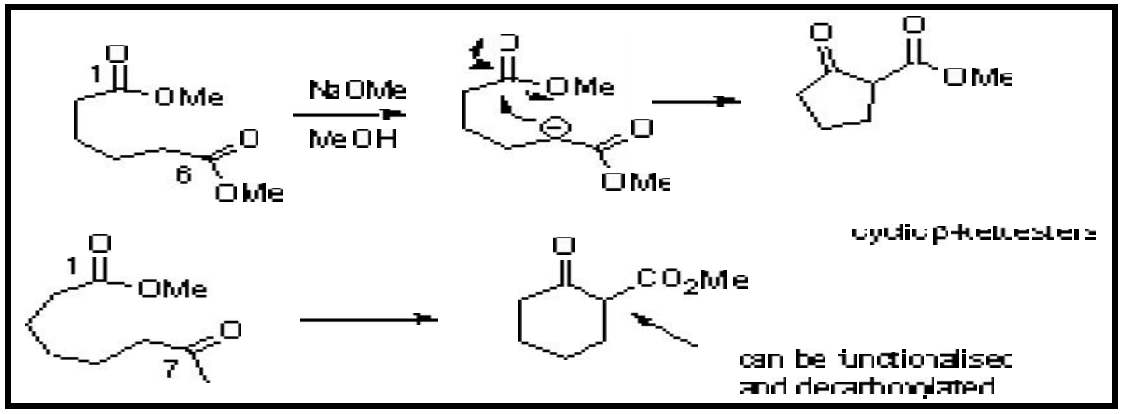


Other Methods :



IntramolecularClaisen Condensations – The Dieckmann Cyclisation :

Reaction works best with 1,6 or 1,7 diesters to give 5 or 6 membered rings.



3-membered rings :

Heterocycles with three atoms in the ring are more reactive because of ring strain. Those containing one heteroatom are, in general, stable. Those with two heteroatoms are more likely to occur as reactive intermediates.

Common 3-membered heterocycles with *one* heteroatom are:

Heteroatom	Saturated	Unsaturated
Nitrogen	Aziridine	Azirine
Oxygen	Oxirane (ethylene oxide, epoxides)	Oxirene
Sulfur	Thiirane (episulfides)	Thiirene

Those with two heteroatoms include:

Heteroatom	Saturated	Unsaturated
Nitrogen		Diazirine
Nitrogen/oxygen	Oxaziridine	
Oxygen	Dioxirane	

4-membered rings :

Compounds with one heteroatom:

Heteroatom	Saturated	Unsaturated
Nitrogen	Azetidine	Azete
Oxygen	Oxetane	Oxete
Sulfur	Thietane	Thiete

Compounds with two heteroatoms:

Heteroatom	Saturated	Unsaturated
Nitrogen	Diazetidine	
Oxygen	Dioxetane	Dioxete
Sulfur	Dithietane	Dithiete

5-membered rings:

With heterocycles containing five atoms, the unsaturated compounds are frequently more stable because of aromaticity.

Five-membered rings with *one* heteroatom:

Heteroatom	Saturated	Unsaturated
Nitrogen	*Pyrrolidine* (Azolidine is not used)	*Pyrrole* (Azole is not used)
Oxygen	*Tetrahydrofuran*(Oxolane is rare)	*Furan* (Oxole is not used)
Sulfur	Thiolane	*Thiophene* (Thiole is not used)
Boron	Borolane	Borole
Phosphorus	Phospholane	Phosphole
Arsenic	Arsolane	Arsole
Antimony	Stibolane	Stibole
Bismuth	Bismolane	Bismole
Silicon	Silolane	Silole
Tin	Stannolane	Stannole

The 5-membered ring compounds containing *two* heteroatoms, at least one of which is nitrogen, are collectively called the azoles. Thiazoles and isothiazoles contain a sulfur and a nitrogen atom in the ring. Dithiolanes have two sulfur atoms.

Heteroatom	Saturated	Unsaturated (and partially unsaturated)
Nitrogen/nitrogen	*Imidazolidine* *Pyrazolidine*	*Imidazole* (Imidazoline) *Pyrazole* (Pyrazoline)
Nitrogen/oxygen	Oxazolidine Isoxazolidine	Oxazole (Oxazoline) Isoxazole
Nitrogen/sulfur	Thiazolidine Isothiazolidine	Thiazole (Thiazoline) Isothiazole
Oxygen/oxygen	Dioxolane	
Sulfur/sulfur	Dithiolane	

A large group of 5-membered ring compounds with *three* heteroatoms also exists. One example is dithiazoles that contain two sulfur and a nitrogen atom.

Heteroatom	Saturated	Unsaturated
3 × Nitrogen		Triazoles
2 × Nitrogen / 1 × oxygen		Furazan Oxadiazole
2 × Nitrogen / 1 × sulfur		Thiadiazole
1 × Nitrogen / 2 × sulfur		Dithiazole

Five-member ring compounds with *four* heteroatoms:

Heteroatom	Saturated	Unsaturated
4 × Nitrogen		Tetrazole

With 5-heteroatoms, the compound may be considered inorganic rather than heterocyclic. Pentazole is the all nitrogen heteroatom unsaturated compound.

6-membered rings:

Six-membered rings with a *single* heteroatom:

Heteroatom	Saturated	Unsaturated
Nitrogen	*Piperidine* (Azinane is not used)	*Pyridine* (Azine is not used)
Oxygen	Oxane	*Pyran* (2*H*-Oxine is not used)
Sulfur	Thiane	*Thiopyran* (2*H*-Thiine is not used)
Silicon	Salinane	Siline
Germanium	Germinane	Germine
Tin	Stanninane	Stannine
Boron	Borinane	Borinine
Phosphorus	Phosphinane	Phosphinine
Arsenic	Arsinane	Arsinine

With *two* heteroatoms:

Heteroatom	Saturated	Unsaturated
Nitrogen / nitrogen	*Piperazine*	Diazines
Oxygen / nitrogen	*Morpholine*	Oxazine
Sulfur / nitrogen	*Thiomorpholine*	Thiazine
Oxygen / oxygen	Dioxane	Dioxine
Sulfur / sulfur	Dithiane	Dithiine

With three heteroatoms:

Heteroatom	Saturated	Unsaturated
Nitrogen		Triazine
Oxygen	Trioxane	
Sulfur	Trithiane	

With four heteroatoms:

Heteroatom	Saturated	Unsaturated
Nitrogen		Tetrazine

The hypothetical compound with six nitrogen heteroatoms would be hexazine.

7-membered rings:

With 7-membered rings, the heteroatom must be able to provide an empty pi orbital (e.g., boron) for "normal" aromatic stabilization to be available; otherwise, homoaromaticity may be possible. Compounds with one heteroatom include:

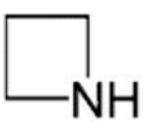
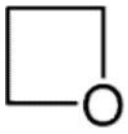
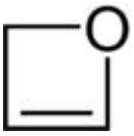
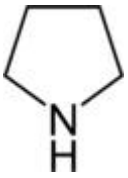
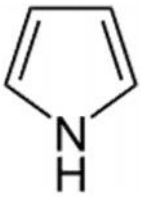
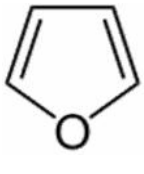
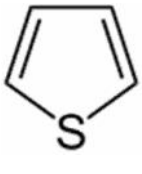
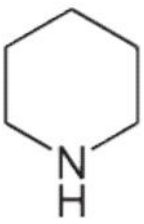
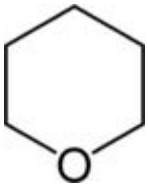
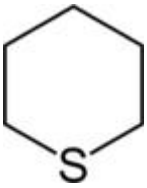
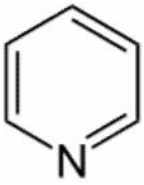
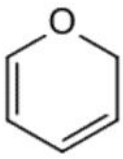
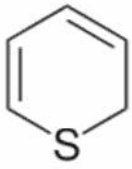
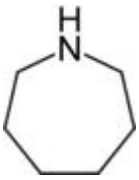
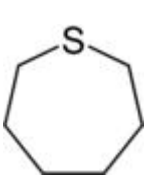
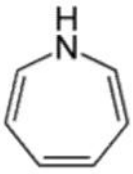
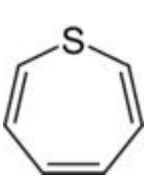
Heteroatom	Saturated	Unsaturated
Nitrogen	Azepane	Azepine
Oxygen	Oxepane	Oxepine
Sulfur	Thiepane	Thiepine

Those with two heteroatoms include:

Heteroatom	Saturated	Unsaturated
Nitrogen	Homopiperazine	Diazepine
Nitrogen/sulfur		Thiazepine

8-membered rings:

Heteroatom	Saturated	Unsaturated
Nitrogen	Azocane	Azocine
Sulfur		

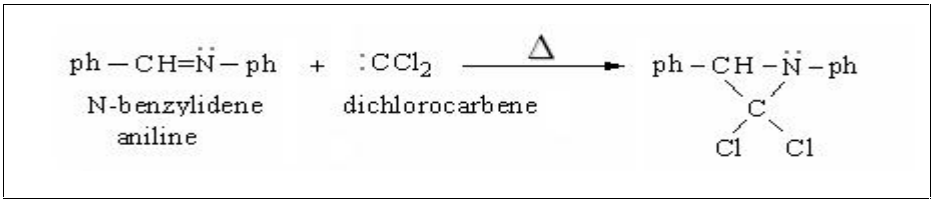
	Saturated			Unsaturated		
Heteroatom	Nitrogen	Oxygen	Sulfur	Nitrogen	Oxygen	Sulfur
	Aziridine	Oxirane	Thiirane	Azirine	Oxirene	Thiirene
3-Atom Ring						
	Azetidine	Oxetane	Thietane	Azete	Oxete	Thiete
4-Atom Ring						
	Pyrrolidine	Oxolane	Thiolane	*Pyrrole*	*Furan*	*Thiophene*
5-Atom Ring						
	Piperidine	Oxane	Thiane	*Pyridine*	*Pyran*	*Thiopyran*
6-Atom Ring						
	Azepane	Oxepane	Thiepane	Azepine	Oxepine	Thiepine
7-Atom Ring						

Fused rings

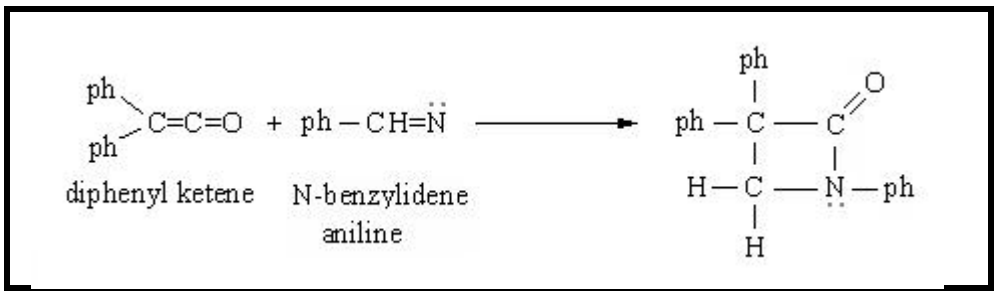
Heterocyclic rings systems [1-3 , 28]that are formally derived by fusion with other rings, either carbocyclic or heterocyclic, have a variety of common and systematic names. For example, with the benzo-fused unsaturated nitrogen heterocycles, pyrrole provides indole or isoindole depending on the orientation. The pyridine analog is quinoline or isoquinoline. For azepine, benzazepine is the preferred name.

Heterocyclic compounds are organic chemical substances that consist of molecules containing one or more rings of atoms with at least one atom being an element other than carbon. The class includes many compounds of biological importance, such as nucleic acids and certain vitamins, hormones, and pigments. Also included are industrially significant pharmaceuticals, pesticides, herbicides, dyestuffs, plastics, and most hallucinogens. Ordinary organic compounds have a backbone of carbon atoms, which are bonded to one another and to hydrogen or other atoms, or both. Joining a chain of carbon atoms together results in a ring, or cyclic compound. In heterocyclic compounds, one or more of the carbon atoms in the ring is replaced by the atom (called a hetero-atom) of another element. The hetero-atoms are most frequently oxygen, nitrogen, or sulfur. As in hydrocarbons, the heterocyclic ring atoms may be saturated (held together by single bonds) or unsaturated (one or more bonds are double or triple). Heterocyclic rings may also be aromatic (having alternating single and double bonds). Many of the naturally occurring heterocycles are aromatic. The geometry of the carbon atom predisposes it to most readily form rings containing five or six members. The best known of the simple heterocyclic compounds are pyridine, pyrrole, furan, and thiophenePyrrole is a common aromatic heterocycle with five members, in which the hetero-atom is nitrogen. Both the plant pigment chlorophyll and the red pigment of blood, hemoglobin, contain pyrrole nuclei. Many of the aromatic heterocyclic compounds consist of a heterocycle[26-30]. fused to a benzene ring. Several natural and synthetic pigments, such as indigo and the phthalocyanins, are derived from fused rings containing pyrrole nuclei, as is the amino acid tryptophan. Vinyl pyrrolidone, a pyrrolidine derivative, is the basis for water-soluble polymers that are used as blood plasma extenders, and are incorporated into many cosmetic products, such as hair sprays. Five-membered, oxygen-containing heterocycles occur widely in nature, especially in many simple sugars. A particular way of treating carbohydrates, which are polymers (long-chain molecules) of simple sugars, produces furfural, a derivative of furan whose hetero-atom is oxygen. Produced commercially from corncobs and oat husks, furfural is used as an industrial solvent and to make phenol-furfural resins. The compound can be chemically reduced to give furfuryl alcohol, which can be polymerized to make heat- and alkali-resistant resins that are used to line chemical plants. The simplest six-membered heterocycles are pyridine, with the hetero-atom nitrogen, and pyran, with an oxygen hetero-atom. The pyridine ring occurs in many natural substances, such as vitamin B_6 (pyridoxine) and nicotine. Commercially important pyridine derivatives include the weedkillerparaquat and vinylpyridine, a starting material for some synthetic rubbers. Several important pharmaceuticals also contain the pyridine nucleus. Fused rings (i.e., those that share a carbon atom) of pyridine form the basis of some important alkaloids (e.g., quinine and morphine). Fused tetrahydropyran nuclei occur in a number of important natural products, such as vitamin E (tocopherol) and the anthocyanin pigments, which produce the reds and blues of many flowers. There exist several exceptions to the trend towards five- or six-member rings. One such substance, ethylene oxide, is a three-membered heterocycle consisting of two carbon atoms and one oxygen atom. It is produced by partial oxidation of ethylene. Its main use is in the manufacture of ethylene glycol, commonly employed in automobile antifreeze. The important antibiotics, the penicillins and cephalosporins, all contain four-membered heterocycles with nitrogen as the hetero-atom. Many heterocyclic compounds contain more than one hetero-atom in a single ring[1-5 , 28]., and in many cases, the hetero-atoms are the same. Imidazole, with two nitrogen atoms in a five-membered ring, is an important constituent of the amino acid histidine. The thiazole ring with one sulfur and one nitrogen atom occurs in vitamin B1 (thiamine), penicillins, and a number of other drugs. Six-membered rings containing two nitrogen atoms—uracil, thymine, and cytosine—are important components of nucleic acids. The pyrimidine ring occurs in barbiturate drugs. Dioxan, a heterocyclic ether, contains two oxygen atoms and is important industrially as a solvent. Fused rings may contain several hetero-atoms. The purine bases adenine and guanine, found in nucleic acids, contain four nitrogen atoms in a ring, as does the alkaloid caffeine. Riboflavin, another of the B-group vitamins, has three fused rings and contains four-ring nitrogen atoms.

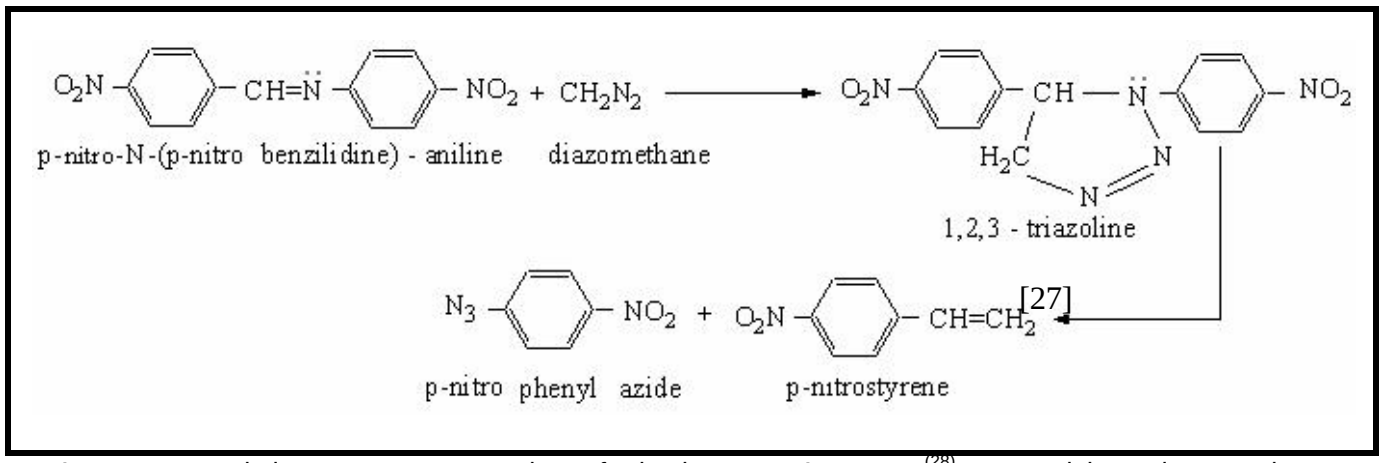
Dichloro carbine added to N-benzylidene aniline to give the corresponding dichloroaziridine



Staudinger [20 ,28] reported the formation of 1,3,3,4 – tetraphenyl-2- azetidinone from the reaction of diphenyl ketene with N-benzylidineanilines



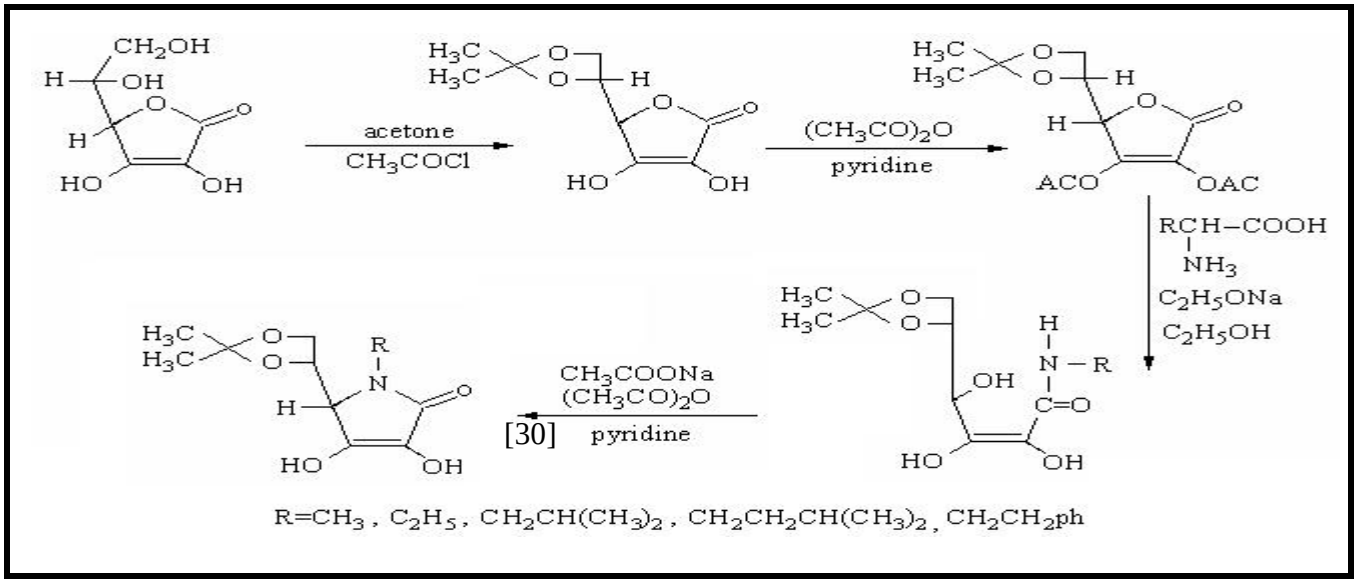
The reaction of diazomethane[37] with p-nitro -N- (p-nitro benzylidene) aniline gave compound via 1,3 –dipolar cycloaddition

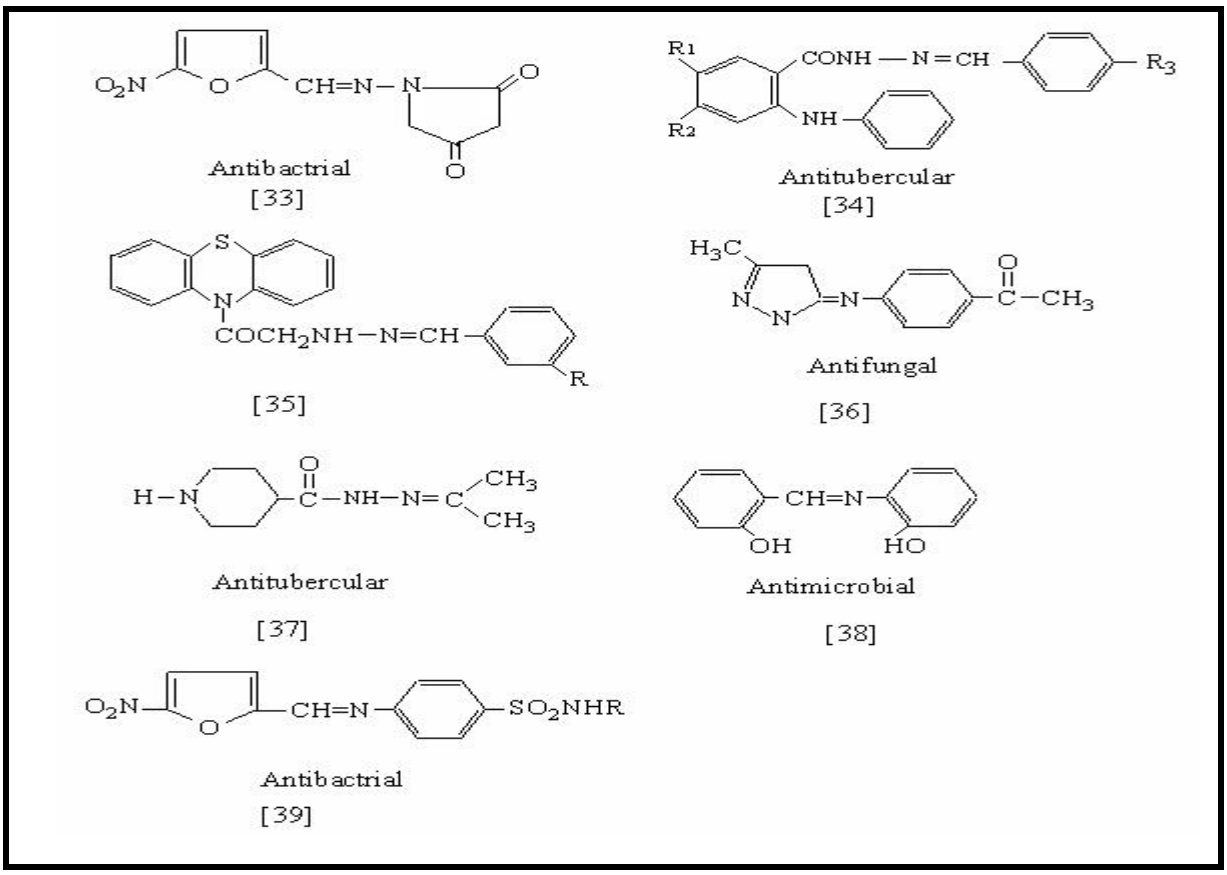


Azasugars or imine sugars are analog of simple sugars such as glucose in which the ring oxygen of the ring has been replaced by an amino group .

Azasugars[28] can modulate glucoproteineprosses by strongly interfering with glycohydrolysis as well as glyosyl transfers involved in a wide range of important biological processes .

Hassan synthesized azasugar derivatives

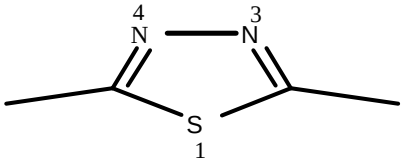


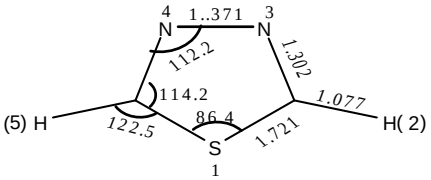


Thiadiazole is one of a class of organic heterocyclic[1-5]. compounds containing a five member diunsaturated ring structure composed of two nitrogen atoms at position (3 and 4) and one sulfur atom at position (1).

Most of published work on the four thiadiazoles has been on the 1, 3, 4-thiadiazoles. Physical, theoretical, and spectroscopic properties have been reviewed [1,2, 3,4].

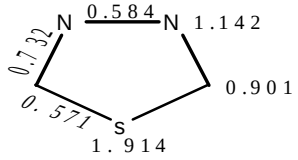
Bak et.al. made a careful analysis of the microwave spectrum of 1,3,4-thiadiazole, they could determine the structure of the molecule .





According to microwave spectroscopy, the π-electron delocalization decrease in the order: 1,2,5-thiadiazole > thiophene > 1,3,4-thiadiazole > 1,2,5-oxadiazole.

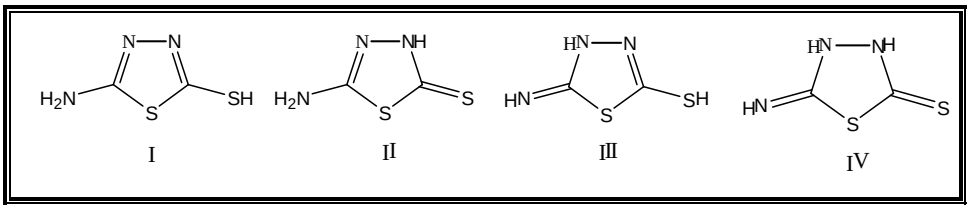
Zahradnik and Kouteckymade a series of studies and found that the calculated bond orders show a larger π-electron delocalization in the 1,2,5 than in the 1,3,4 isomer, in agreement with the results .The formal double bonds have a lower bond order in the 1,2,5 than in the 1,3,4-isomer, whereas the reverse is true for the formal single bonds.



U.V spectral features have been investigated, the parent molecule absorbs at 229nm, and substituents with lone pairs cause bathochromic shifts

The aromatic thiadiazole nucleus is associated with a variety of pharmacological actions, such as fungicidal, controlling blood pressure and can affect central nervous systemThese activities are probably due to the presence of the -N=C-S- moiety. Furthermore, a great number of variously substituted 1,3,4-thiadiazoles have been synthesized and tested for their different activities

2-Amino-5-mercapto-1,3,4-thiadiazole is capable of existing in four tautomeric form:



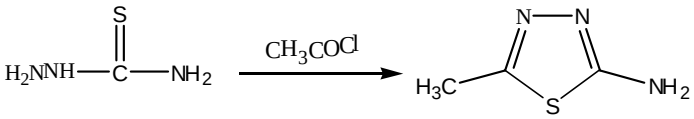
In the literature[46-51], amino-mercapto-1,3,4-thiadiazole, is described under different chemical names because of the differences in chemical terminology. However, in order to obtain a fuller understanding of the literature, the various terms are listed below.

AMT stands for 2-amino-5-mercapto-1,3,4-thiadiazole, which also found under the chemical names of 5-amino-1,3,4-thiadiazole-2-thiol, 1,3,4-thiadiazole-2(3H)-thion-5-amino, 2-amino-1,3,4-thiadiazole-5-thiol and 2-mercapto-5-amino-1,3,4-thiadiazole. It should be noted that all have the same general formula $C_2H_3N_3S_2$.

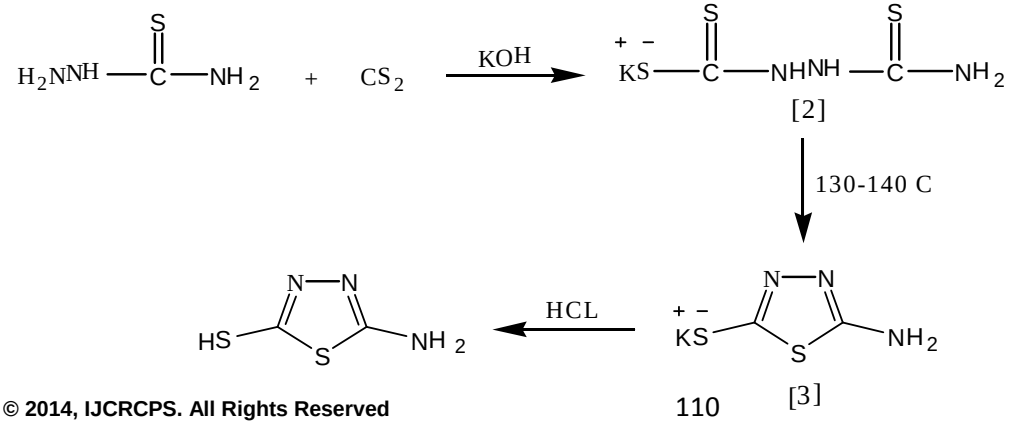
AMT is a white-yellowish powdered crystalline solid, with a molecular weight of 133.19g/mol, melt at 227Cº.

Synthesis of 1, 3, 4-thiadiazole derivatives

Since thiadiazoles have a variety of potential biological activities and utilities as technologically useful materials, a number of methods for the preparation have been developed. Many synthesis of 1,3,4-thiadiazoles proceed from thiosemicarbazide or substituted thiosemicarbazide,for example thiosemicarbazide itself was shown to cyclize directly to 2-amino-5-methyl-1,3,4-thiadiazole through the reaction with acetyl chloride:

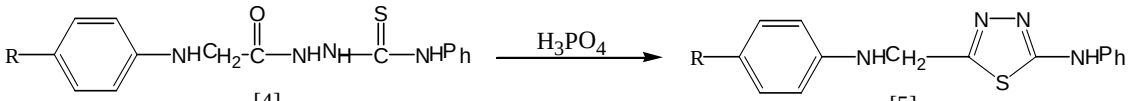


This simple route to 2-amino-5-substituted-1,3,4-thiadiazoles seems to be quite general. A useful preparative method for 2-amino-5-mercapto-1,3,4-thiadiazole was developed , which showed that when thiosemicarbazide is treated with carbon disulfide and potassium hydroxide, the potassium salt of thiosemicarbazide-4-dithiocarboxylic acid was formed. Heating to 140Cº causes cyclization to the salt of 2-amino-5-mercapto-1,3,4-thiadiazole [28]:



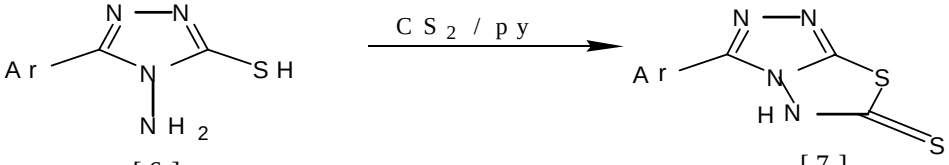
[1] [2] [3]

Hiremarth synthesized a series of 2-amino-5-[4‘-(substituted)anilino]-methyl-1,3,4-thiadiazole through cyclocondensation of thiosemicarbazide derivatives with phosphoric acid.



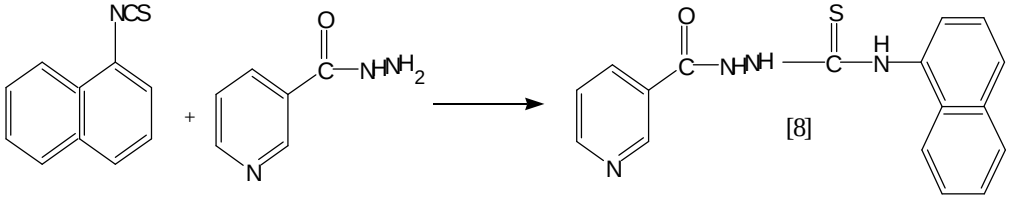
[4] [5]

Mohan prepared 3-aryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole-6(5H)-thiones by the reaction of 3-aryl-4-amino-5-mercapto-1,2,4-triazoles with CS_2 in the presence of pyridine.

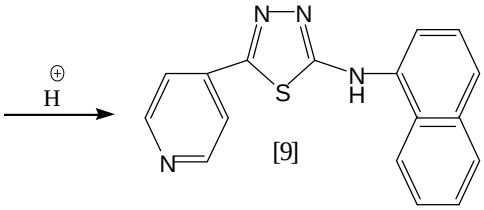


[6] [7]

Zamani synthesized new 1,3,4-thiadiazole derivative , bearing pyridyl and 1-naphthyl rings, using 1,4-disubstituted thiosemicarbazide: Ar = *p*-ClC$_6$H$_4$, *p*-NO$_2$C$_6$H$_4$, *p*-PhC$_6$H$_4$

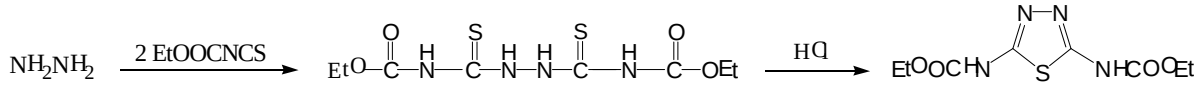


[8]



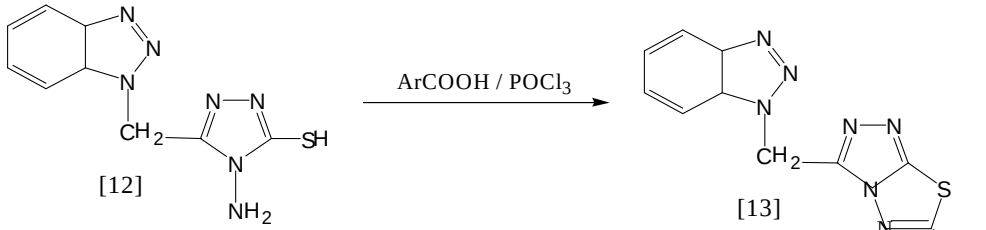
[9]

Kurzer and Seckerfound that the use of reactants incorporating free hydrazine group provided a versatile route to substituted 1,3,4-thiadiazoles. They reported various approaches, employing the prototype hydrazine itself and some of its simple congeners:



[10] [11]

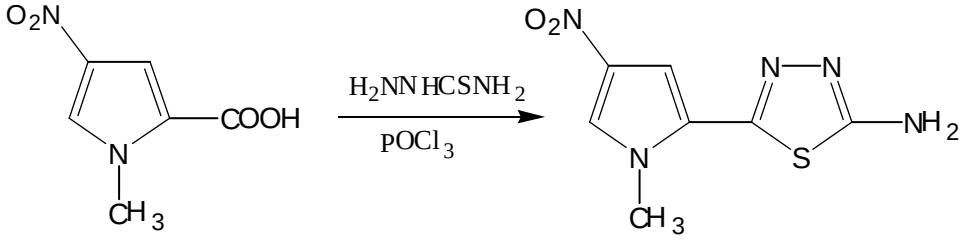
El-Khawass synthesized a series[1-6] of 6-substituted -3-[1-(1H-benzotriazole)methyl]-1,2,4-triazolo[3,4-b][1,3,4]thiadiazolesfrom condensation of the 1-(4-amino-4H-1,2,4-triazole-3-thion-5-yl)methyl-1H- benzotriazole [12] with carboxylic acids in the presence of phosphorus oxychloride:



[12] [13]

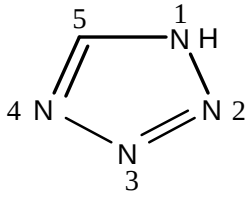
Ar = C_6H_5 , *p*-$CH_3C_6H_4$, *p*-BrC_6H_4

Shafiee e found that the reaction of 1-methyl-4-nitropyrrol-2-carboxylic acid. with phosphorus oxychloride and thiosemicarbazide afforded 2-amino-5-(1-methyl-4-nitro-2-pyrrolyl)-1,3,4-thiadiazole



[14] [15]

Tetrazole is one of a class of organic heterocyclic compounds containing a five member diunsaturated ring structure composed of four nitrogen atoms and one carbon. The simplest member of tetrazole family is tetrazole itself, white to yellow crystalline solids with a weak characteristic odor; melts at 156Cº.

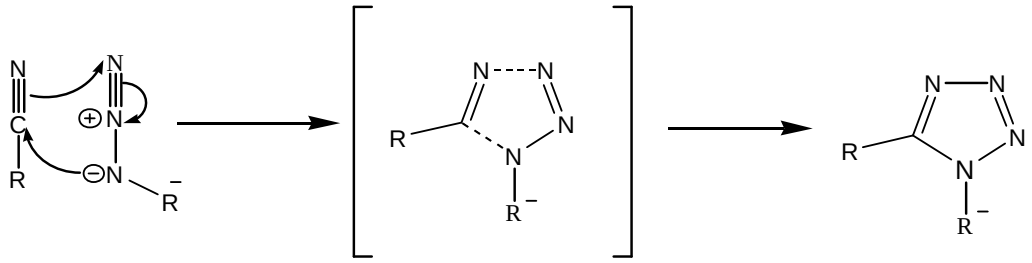


Synthesis of tetrazoles

Tetrazoles[1-6 , 28] are an increasingly popular heterocyclic with wide range of applications. The discovery of the pharmacological and biological properties of tetrazoles initiated an enormous development in tetrazole chemistry over the last 40 years

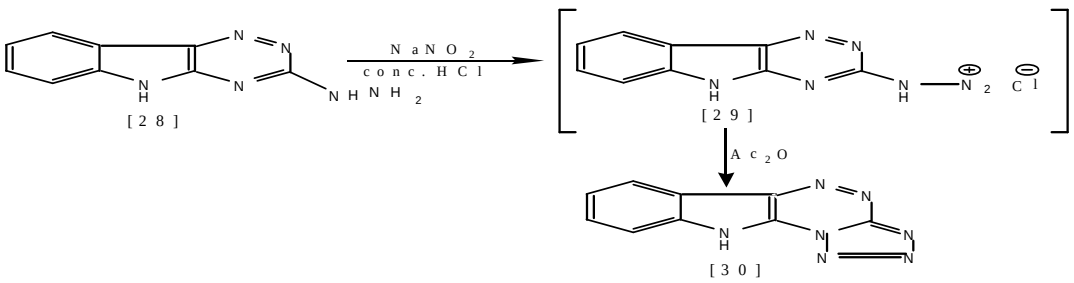
Tetrazole derivatives show fungicidal and antiviral activity. In addition to their various biological properties, tetrazoles also serve as precursors for the synthesis of further interesting heterocycles.

The most direct method to form tetrazoles is via [2+3] cycloaddition of azides and nitrile.

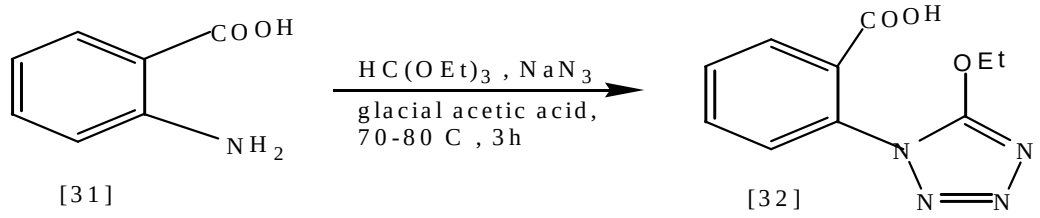


: [2+3] cycloaddition of an organic azide and an organic nitrile

Abdel-Latif found that the reaction of 3-hydrazino[1,2,4]triazino[5,6-b]indole with nitrous acid afforded the diazonium which could be cyclized with acetic anhydride to 10H-tetrazolo[5‘,1‘:3,4][1,2,4]triazino[5,6-b]indol .

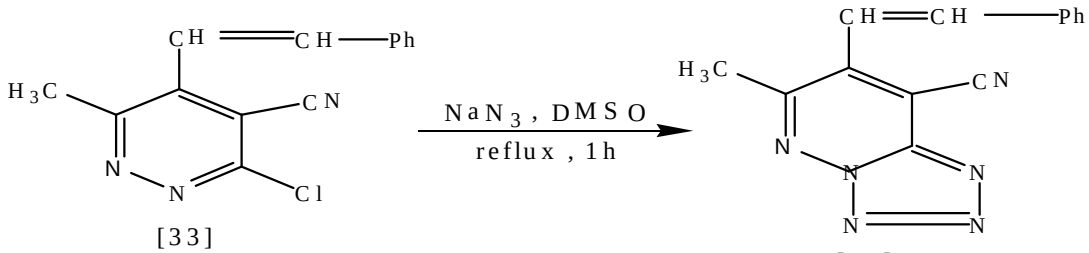


Several methods[28-30] for the synthesis of 1-monosubstituted tetrazoles have been reported. Heterocyclization of primary amines with triethylorthoformate and sodium azide seems to be the most convenient method. It is applicable to the synthesis of tetrazoles, using aliphatic, aromatic and heterocyclic amines of different structure. For example, anthranilic acid was found to react with triethylorthoformate and sodium azide (70-80Cº,3h) giving 1-(*o*-carboxyphenyl)tetrazole



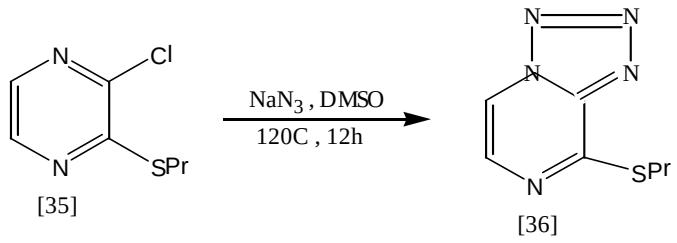
[31] [32]

El-Gaby prepared 6-methyl-7-styryl-tetrazolo[1,5-b]pyridazin-8-carbonitrile as novel compound by reaction of 3-chloro-4-cyano-6-methyl-5-styrylpyridazine with sodium azide in dimethylsulfoxide:



[33] [34]

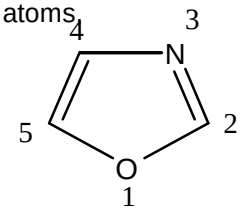
Young found that the reaction of 2-chloro-3-thiopropylpyrazine with sodium azide in DMSO gave 8-propylthiotetrazolo[1,5-a] pyrazine .



[35] [36]

Oxazoles:

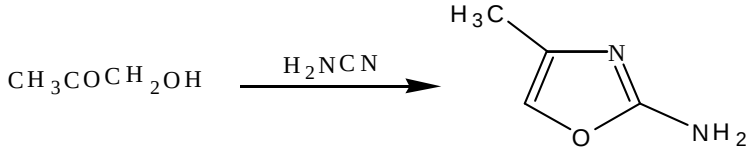
Oxazole[1 , 28] is a heterocyclic organic compound, azafuran, with a five –member ring molecular structure, C_3H_3ON, containing three carbon atoms, one oxygen atom, and one nitrogen atom. It is a clear to yellowish liquid with a pyridine like odor



Oxazole and its derivatives are used as building block for biochemical and pharmaceutical as well as in other industrial applications such as pesticides, dyes, fluorescent brightening agents, textile auxiliaries and plastics. The oxazole molecules are planar with conjugated π-electron sextets in cyclic system

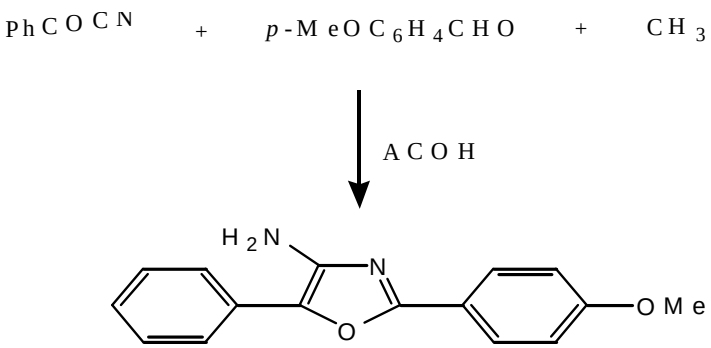
The growing literature demonstrates that the oxazole derivatives are becoming of great interest, this is primarily due to the large number of uses of oxazoles in many diverse areas.

Crank and Foulis found that 2-amino-4-methyl oxazole was obtained in high yield by the reaction between hydroxyacetone and cyanamide.



[37]

Lakhan and Singh found the reaction[12-16] of benzoyl cyanide with anisaldehyde in equimolar amounts in the presence excess of anhydrous ammonium acetate in glacial acetic acid affords 4-amino-2-*p*-methoxyphenyl-5-phenyloxazole :



[38]

A strategy to build oxazole is the closure of the chain Z-C-N-C-C-O upon attack of nucleophilic O-atom on an elecrophilic C-atom with Z as a leaving group:

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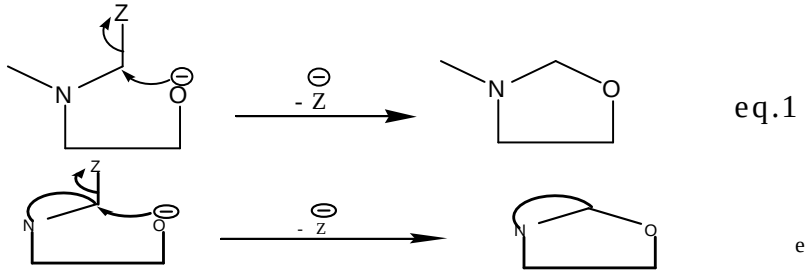
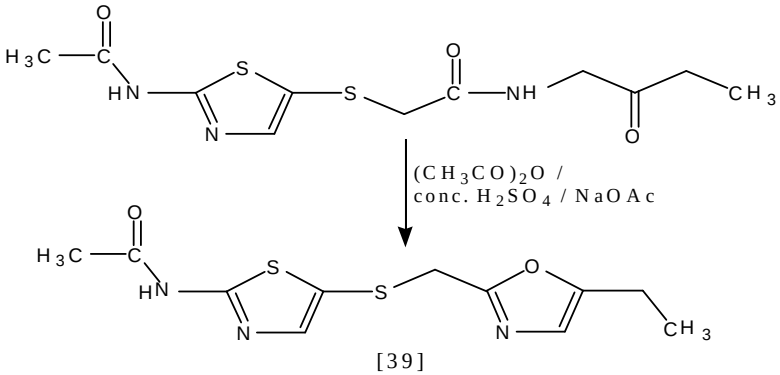
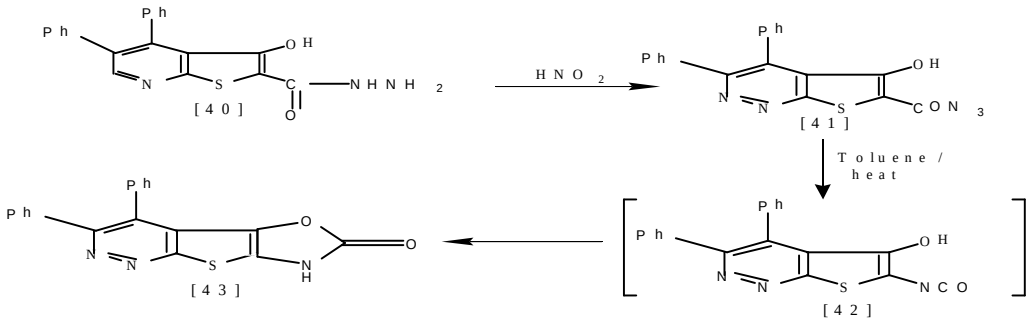


Kim et.al.synthesized the 2,5-disubstituted oxazole by cyclodehydration of [[2-acetylamino-5-thiazolyl]thio]-N-(2-oxobutyl)acetamide using acetic anhydride and conc. sulfuric acid:

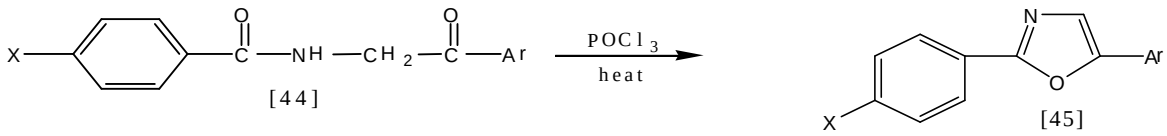


[39]

Bakhite et.al. found that the treatment of the carbohydrazide with sodium nitrite in glacial acetic acid produced the carboazide derivative which then refluxed in dry toluene to furnish oxazolo[5‘,4‘:4,5]thieno[2,3-c]pyridazine via the isocyanate intermediate:

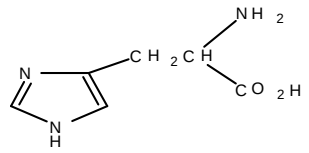


Balaban prepared a series of 2[4-(4-halobenzenesulphonyl)phenyl]-5- aryloxazoles through cyclization of 2-aza-1-[4-(4-halobenzensulphonyl)- phenyl]-4-aryl-1,4-butanedione under the action of phosphorus oxychloride:

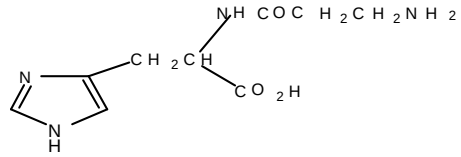


Imidazole[28-30] is a heterocyclic compound of five member diunsaturated ring structure, it is an azapyrrole, composed of three carbon atoms and two nitrogen atoms, the two nitrogen atoms being separated by one carbon atom. It is an important ring system, for many substances of biological and chemical interest. The parent substance was first obtained from glyoxal and ammonia, for this reason it was named glyoxaline, this name is almost obsolete and imidazole or iminazole is greatly preferred.

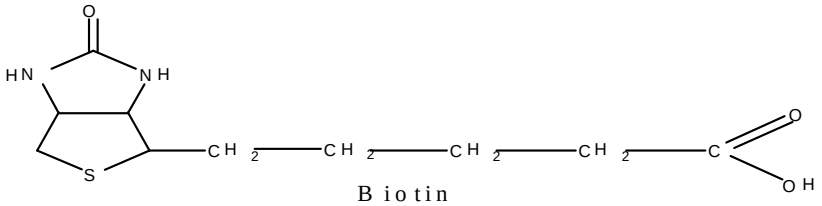
Imidazole nucleus forms the main structure of some well-known components of human organisms such as the essential amino acid histidine; carnosine, a constituent of mammalian muscle; and biotin(vitamin H), a coenzyme for several enzymes that transport carboxyl units in tissue and plays an integral role in gluconeogenesis, lipogenesis, and fatty acid synthesis. This ring is also found in the purine units of DNA and RNA.



histidine

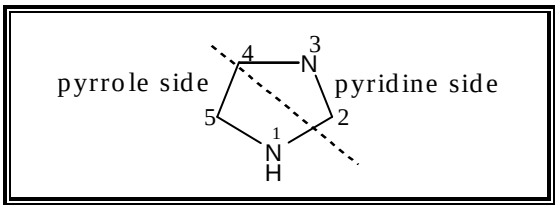


carnosine



Biotin

Imidazole is an aromatic compound because it is cyclic, planar and associated with 6π-electrons; one from each carbon, one from the "pyridine″ nitrogen, and two from the "pyrrole″ nitrogen:



The nonbonding electrons on N-1 are part of the π-cloud because they are in *p*-orbitals, while the nonbonding electrons on N-3 are in sp^2 orbital, perpendicular to the *p*-orbitals. This leaves the pyridine-type nitrogen with an unshared electron pair and confer on it basic and nucleophilic properties.

The imidazole[1-6] hydrogen atom in imidazole is tautomeric, and in practice, the two nitrogen atoms are indistinguishable.

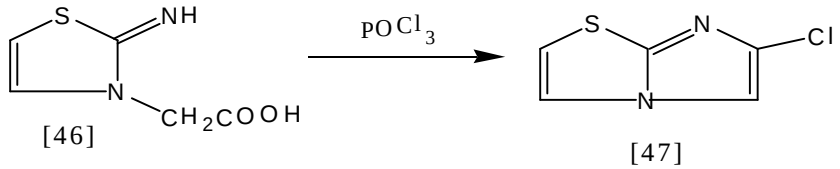
The pk_a of the imidazole ring (pk_a = 6.8) is close to neutrality, therefore it can exist in both the protonated and unprotonated forms at physiological PH (PH = 7.3). This is one of the reasons why histidine, the imidazole containing amino acid, is an important component of serine protease enzymes: these are family of closely related enzymes that contain uniquely reactive serine residue at the active site. They are called protease because they catalyze the hydrolysis of peptide bonds in polypeptides and proteins.

The simplest member of the imidazole family is imidazole itself, colorless to pale yellow crystalline solids with a weak amine like odor, boil at 256Cº.

Synthesis of imidazoles[21-28]

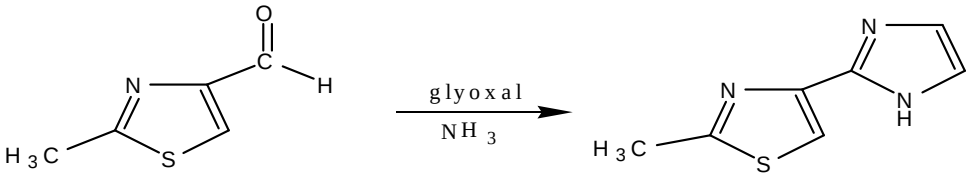
The considerable biological importance of the group of compounds incorporating an imidazole nucleus has stimulated much work on this hetero cycle.

Paolini and Lendvayfound that the reaction of 3-carboxymethyl-2-iminothiazoline and $POCl_3$ gives 6-chloroimidazo[2,1-b]thiazoline , some of the synthesized compounds showed anti-inflammatory and antihypertensive activity:



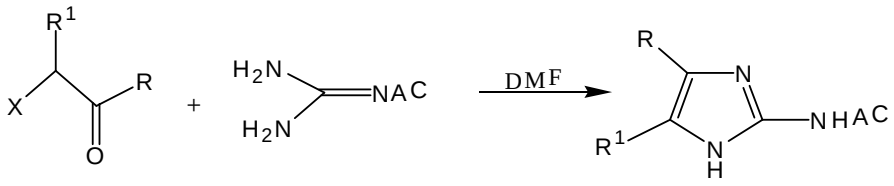
[46] [47]

Shafiee and Shahocinisynthesized 2-(2-methyl-4-thiazolyl)imidazole from the reaction of readily available 2-methyl-4-formylthiazole with glyoxal and ammonia in ethanol:



[48] [49]

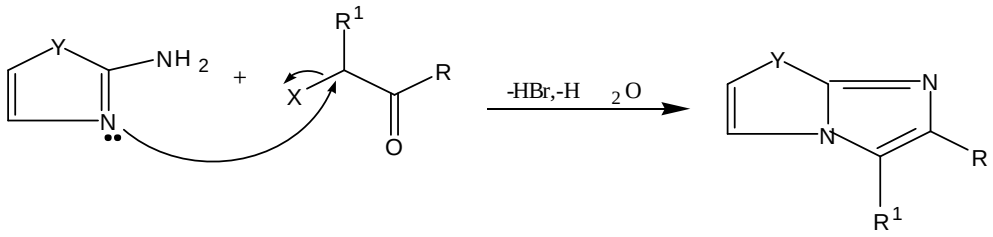
Little and Webber have observed that when α-haloketones were stirred, at room temperature in DMF, with excess of N-acetylguanudine , the corresponding 4,5-disubstituted N-(1H-imidazol-2-yl)acetamide was formed:



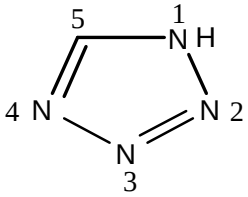
[50]

On the other hand, the reaction of α-bromoketones with urea derivative give the corresponding imidazolone derivatives.

Various ring systems containing the $–C(NH_2)$-N- moiety as a part of the ring have been found to condense with α-bromoketones to yield condensed imidazo-heterocyclic systems; the ring nitrogen attacks the CH_2Br unit rather than the primary exocyclic amino group:



Tetrazole[28-30] is one of a class of organic heterocyclic compounds containing a five member diunsaturated ring structure composed of four nitrogen atoms and one carbon. The simplest member of tetrazole family is tetrazole itself, white to yellow crystalline solids with a weak characteristic odor; melts at 156Cº.



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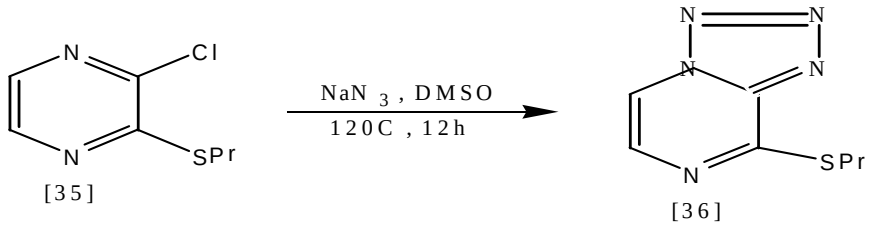

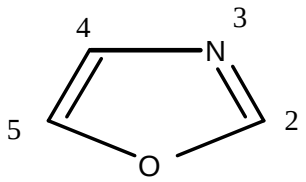

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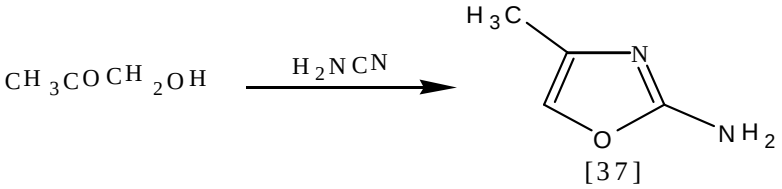

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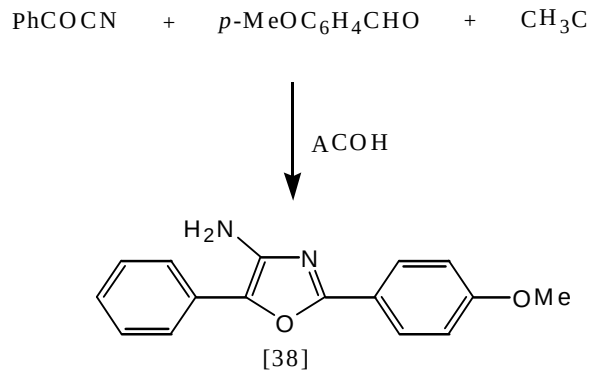

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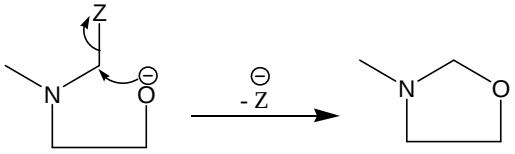

eq.1

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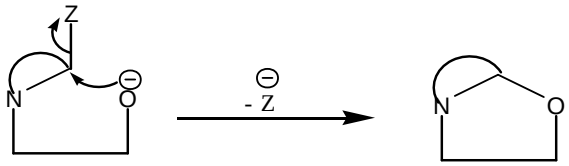

eq.2

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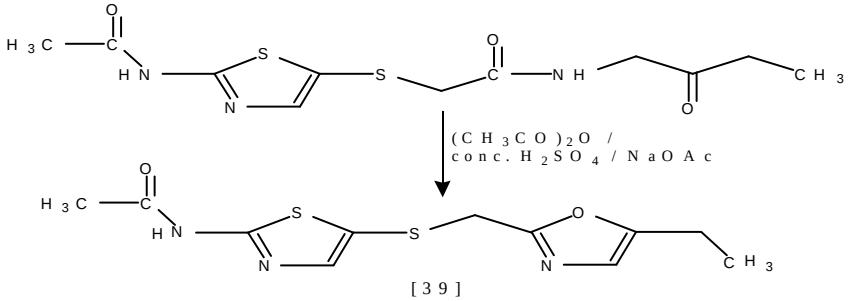

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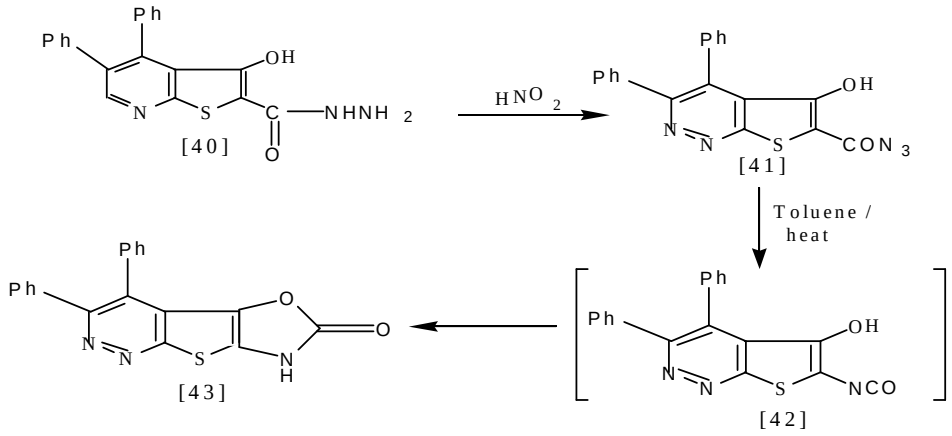

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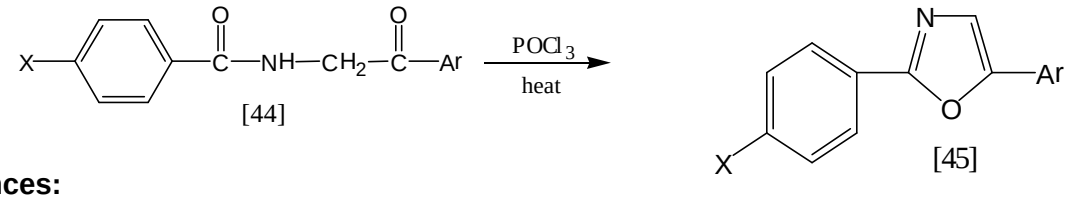

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