الجمهورية الجزائرية الديمقراطية الشعبية

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جامعة 8 ماي 1945قالمة
كلية الرياضيات و الإعلام الآلي و علومالمادة
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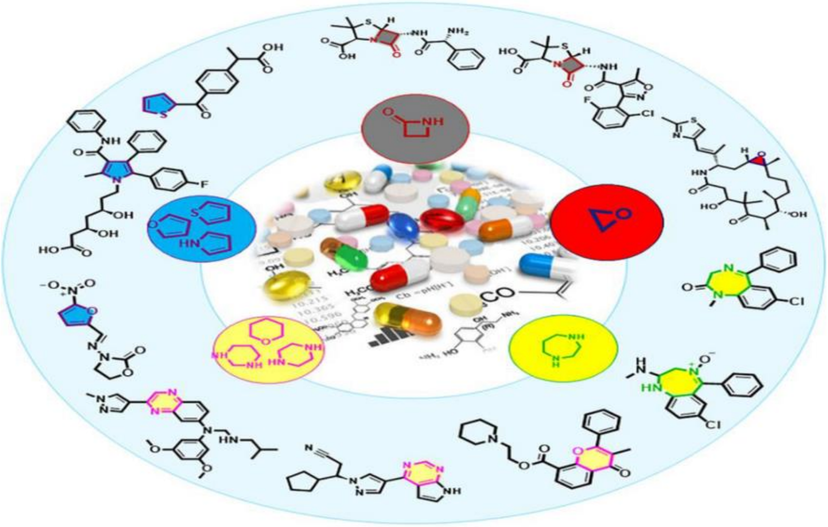
POLYCOPY COURSE

Heterocyclic Chemistry



Designed for students of Master 1 physical chemistry

Dr. SERIDI Saida

2025

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Course Objectives

This *Heterocyclic Chemistry* course, intended for first-year Master's students in physical chemistry, aims to deepen the knowledge acquired in organic chemistry by focusing on a crucial class of compounds: heterocycles.

Heterocyclic compounds play a key role in many fields of application, particularly in medicinal chemistry, agrochemicals, materials science, and biotechnology. The presence of one or more heteroatoms (mainly nitrogen, oxygen, or sulfur) in a cyclic structure gives these molecules unique chemical reactivity and functional diversity.

The course is designed to:

- Familiarize students with the rules of heterocyclic nomenclature;
- Study the main methods for the synthesis and transformation of five- and six-membered rings;
- Understand the influence of heteroatoms on chemical reactivity;
- Explore the structure and reactivity of fused heterocyclic systems;
- Highlight the biological and industrial significance of these compounds through real-world applications.

Introduction

The *Heterocyclic Chemistry* module is a fundamental component of advanced training in the Master's program in physical chemistry. It offers students the opportunity to enhance their background in organic chemistry by exploring in depth a class of compounds that are ubiquitous in both natural and synthetic systems: heterocycles.

Heterocyclic compounds are characterized by the presence of at least one non-carbon atom — such as nitrogen, oxygen, or sulfur — within a cyclic structure. This architecture confers distinctive chemical and physical properties, making heterocycles indispensable in various scientific and technological fields.

The importance of heterocycles is particularly evident in:

- **Pharmaceutical chemistry**, where more than 60% of marketed drugs contain one or more heterocyclic rings due to their strong affinity for biological targets;
- **Materials science**, where heterocycles are essential in designing organic semiconductors, dyes, sensors, and smart materials;
- **Biochemistry**, where they are found in DNA bases, coenzymes, vitamins, and alkaloids;
- **Agrochemistry**, where they are key structural components in many insecticides, herbicides, and fungicides.

This course will enable students to:

- Master the **nomenclature** and **classification** of heterocycles;
- Understand the main synthetic pathways and **reactivity mechanisms** of five- and six-membered rings as well as fused ring systems;
- Analyze the **structure–reactivity relationships** based on the nature of the heteroatoms;
- Investigate **real-life applications**, especially in drug design and molecular innovation.

Studying heterocycles is therefore a critical skill for every organic chemist, physical chemist, or pharmaceutical scientist, and it represents a foundational element in research and development across healthcare, materials, and biotechnology sectors.

Chapter I: Introduction (history, basis of nomenclature, therapeutic value)

I-1 Introduction:

Heterocyclic compounds represent a vast family of cyclic organic molecules that play a central role in organic chemistry, biochemistry, and pharmacology. These compounds are characterized by the presence of at least one heteroatom (an atom other than carbon) in their cyclic structure, with the most common heteroatoms being nitrogen (N), oxygen (O), and sulfur (S). Their importance is such that they constitute nearly half of all known organic compounds to date.

From a structural perspective, heterocycles exhibit remarkable diversity. They are primarily classified into saturated systems (such as piperidine or tetrahydrofuran), unsaturated systems (like pyridine or furan), and aromatic systems (including pyrrole or thiophene). This structural variety extends further with fused systems, where the heterocyclic ring is combined with one or more benzene rings, giving rise to structures such as quinoline, isoquinoline, or indole.

In nature, heterocycles are omnipresent. They form the backbone of many essential biomolecules: nucleic acid bases (adenine, guanine, thymine, cytosine), vitamins (such as vitamin B3 or PP), alkaloids (like nicotine or morphine), and numerous secondary metabolites. Their biological importance explains why they are privileged targets in pharmaceutical research.

The industrial applications of heterocycles are equally impressive. Approximately 60% of commercial drugs contain at least one heterocyclic core. Major therapeutic classes such as antibiotics (penicillins), anticancer agents (5-fluorouracil), or antivirals (acyclovir) are based on heterocyclic structures. Their utility also extends to agrochemicals (pesticides, herbicides), dyes, and functional materials.

From a chemical standpoint, heterocycles exhibit rich and varied reactivity, influenced by the nature of the heteroatom, the degree of unsaturation, and electronic effects. Their study helps elucidate key concepts such as aromaticity, inductive and mesomeric effects, and donor-acceptor interactions.

This course aims to systematically explore this fascinating family of compounds. We will cover:

1. The classification and nomenclature of heterocycles
2. Their structural and electronic properties
3. Classical and modern synthesis methods
4. Their characteristic reactivity
5. Their main applications in medicinal chemistry and materials science

The objective is to provide students with a thorough understanding of these molecular systems, from their fundamental aspects to their practical applications, while developing the ability to design appropriate synthesis strategies. The study of heterocycles thus serves as an essential bridge between fundamental organic chemistry and its most modern applications.

I-2- Classification of heterocyclic compounds

Heterocyclic compounds can be systematically classified into two fundamental categories based on their structural and electronic characteristics: aliphatic heterocyclic compounds and aromatic heterocyclic compounds. The aliphatic heterocycles encompass cyclic amines, cyclic amides, cyclic ethers, and cyclic thioethers, with those lacking double bonds being specifically termed saturated heterocycles (figure 1).

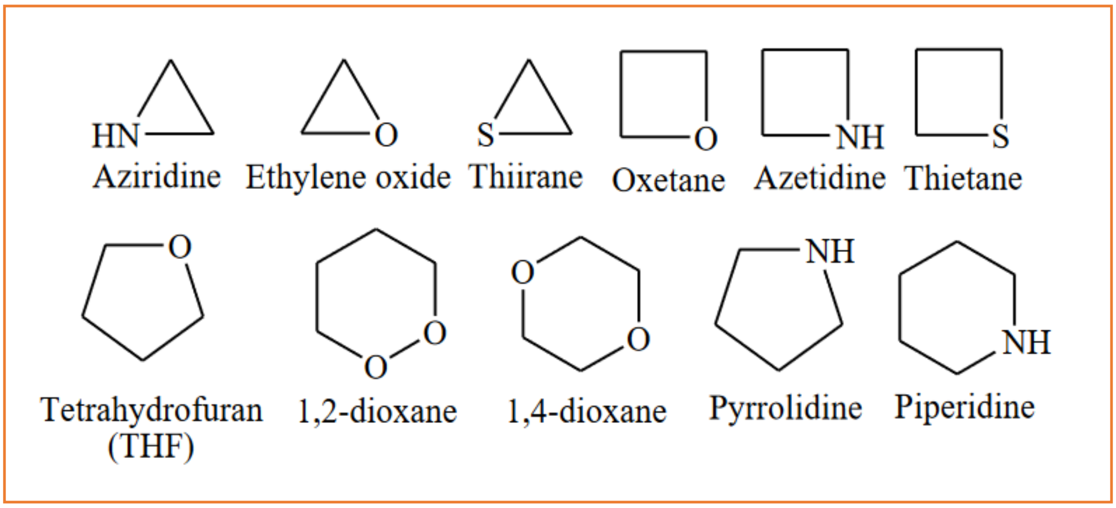


Figure 1. Examples of aliphatic heterocyclic compounds.

In contrast, aromatic heterocyclic compounds (figure 2) represent benzene analogs that adhere to Hückel's rule of aromaticity - these systems must possess a cyclic, planar structure with conjugated π-electrons and satisfy the $(4n+2)\pi$ electron count requirement (where n is typically 0, 1, or 2). This fundamental classification based on electronic structure and aromatic character provides a crucial framework for understanding the diverse properties and reactivities exhibited by different classes of heterocyclic compounds in both natural and synthetic contexts. The distinction between aliphatic and aromatic heterocycles is particularly significant as it directly influences their chemical behavior, stability, and potential applications in pharmaceutical and materials science.

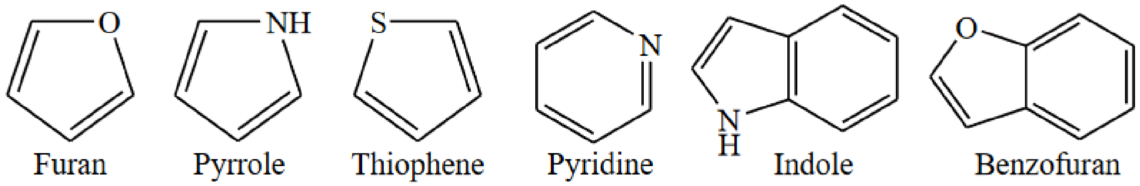


Figure 2. Examples of aromatic heterocyclic compounds.

I- 3- Nomenclature of Heterocyclic compounds

Heterocyclic compounds are named using two principal approaches: trivial nomenclature and systematic nomenclature. While the systematic method follows standardized IUPAC rules, the majority of heterocyclic compounds in both scientific literature and common usage are referred to by their well-established trivial names. This dual naming convention reflects the historical development of heterocyclic chemistry, where many important compounds were discovered and named before formal naming systems were established. The trivial names, though not systematic, remain widely used due to their simplicity and long-standing convention in chemical communications, while the systematic nomenclature provides a more rigorous and descriptive naming framework for these important organic structures.

I- 3-1 Trivial Method of Nomenclature:

In the early development of organic chemistry, heterocyclic compounds were typically named according to three key factors: their natural occurrence, the circumstances of their initial isolation, or distinctive physical/chemical properties. Many names reflected the natural sources from which these compounds were first obtained, creating an etymological connection to their origins. A classic example is "picoline" (figure 3) - this term originates from its isolation from coal tar, with the name derived from the Latin word "pictus" meaning "tarry" or "pitch-like." This historical naming convention resulted in numerous trivial names that persist in modern chemical nomenclature, serving as linguistic artifacts that reveal both the compound's discovery history and the early methodologies of chemical investigation. These source-based names often provide insight into 19th century laboratory practices when natural product isolation was a primary route to discovering new heterocyclic systems.

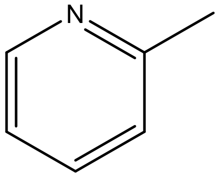


Figure 3. Picoline.

Heterocyclic compounds were also named on the basis of their characteristic properties. For example, pyrrole (figure 4); which is basic in nature; the name of pyrrole was originated from the Greek word for fiery red because of characteristic color which the compound gives with pine splint dipped in hydrochloric acid.

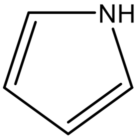


Figure 4. Pyrrole.

The trivial nomenclature system played a pioneering role in the historical development of heterocyclic chemistry, serving as the first method for naming these important compounds. While this approach laid crucial foundations, it suffers from inherent limitations - most notably its inability to convey structural information about the compounds. Despite these shortcomings, approximately sixty trivial names have endured and gained official recognition within the IUPAC nomenclature system. These sanctioned trivial names maintain particular importance as they frequently serve as root names for constructing more systematic nomenclature, especially for complex polycyclic systems and their derivatives. As illustrated in Figure 5, many fundamental heterocyclic compounds continue to be primarily identified by their traditional trivial names, demonstrating the lasting impact of this early naming convention even within modern systematic nomenclature practices. The persistence of these recognized trivial names represents a unique intersection between historical terminology and contemporary chemical nomenclature standards.

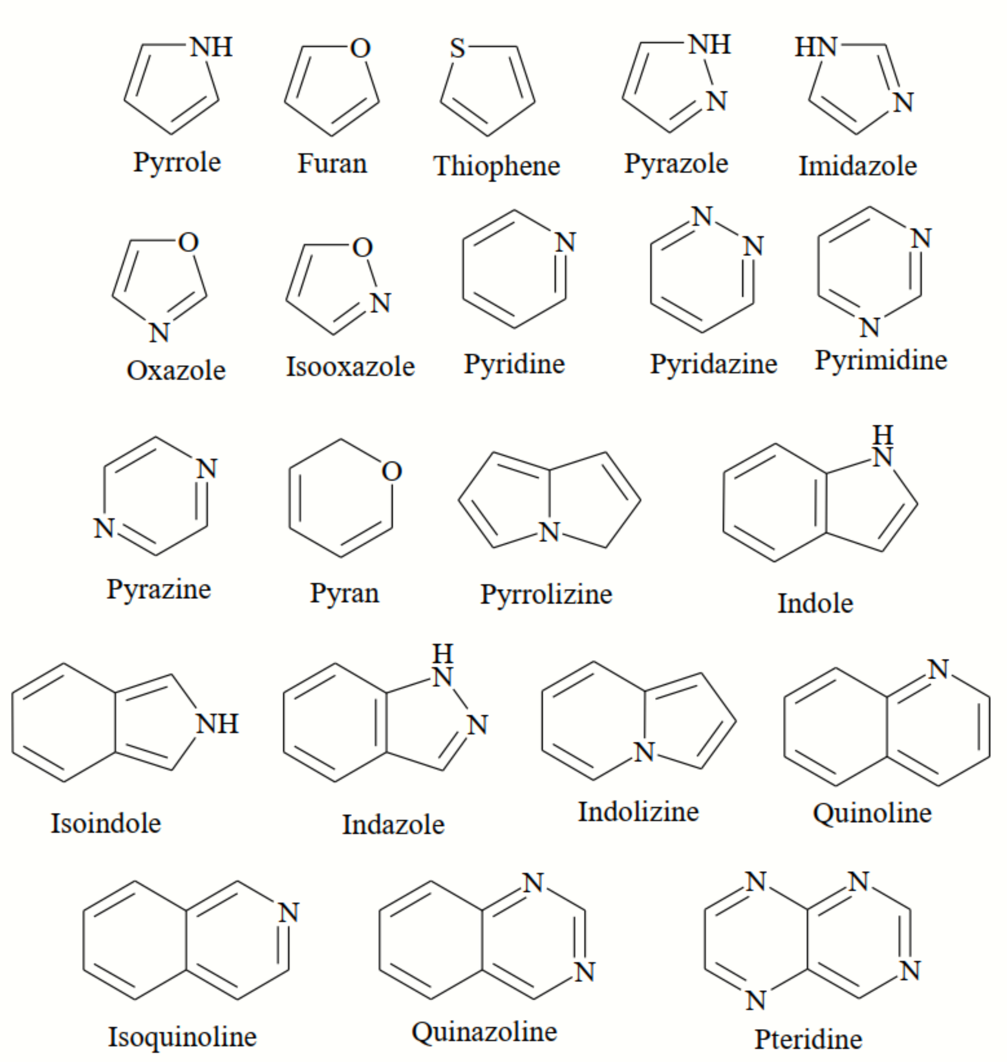


Figure 5. Some heterocyclic compounds with recognized trivial names

I-3-2 Systematic method of nomenclature:

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

Name : Prefix + Stem + Suffix

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

1. In this nomenclature the nomenclature of heterocyclic compounds are assigned by combining 'prefix' (that indicate the heteroatom present) with 'stem' (that indicate the ring size as well as the saturation and unsaturation in the ring) and 'suffixes'. The common prefixes are shown in Table 1. It should be noted that final 'a' is dropped when prefix is followed by vowel.

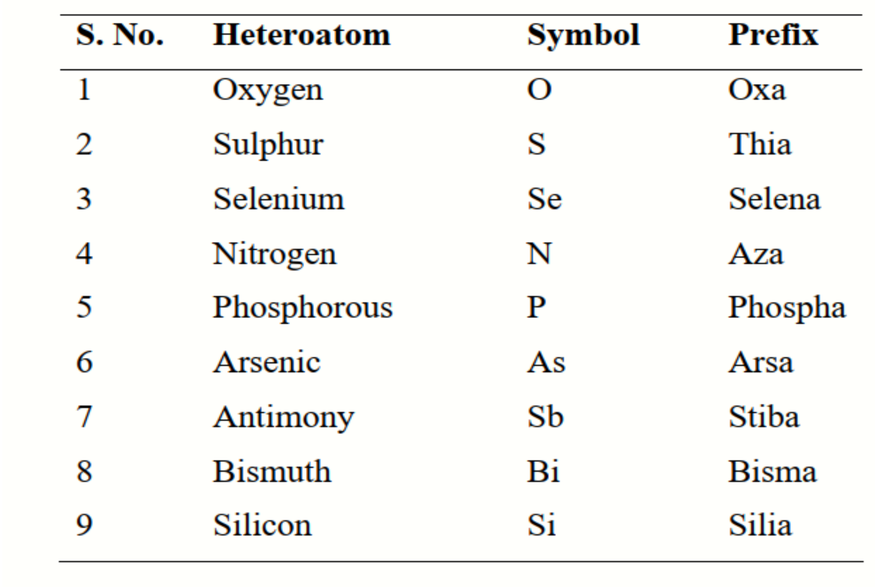
2. Nomenclature of heterocyclic compound starts with the heteroatom appears first in the table 1.

3. If more than two different heteroatoms are present in any heterocyclic compound the prefixes are listed in order in which they are appear in above table (Table 1).
4. If there are two or more than two hetero atoms of same types are present in a heterocyclic compound they are indicated by di-, tri- etc.

5. The position of saturated atom is numerically indicated with prefix '*H-*' as a part of the name of the ring system. It should be noted that where, there is a choice of numbering, the indicated position is given the lowest possible number.

6. The size of a monocyclic ring (three to ten membered rings) is indicated by stem. The common 'stem' nomenclature is given in Table 2.

Table 1. Hantzsh-Widman system: common pefixes.



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

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

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

Some examples of heterocyclic compounds with systematic nomenclature are shown in figure 6.

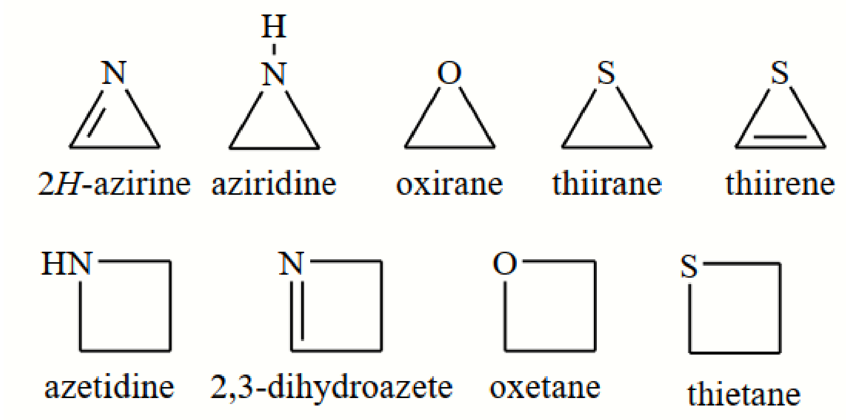
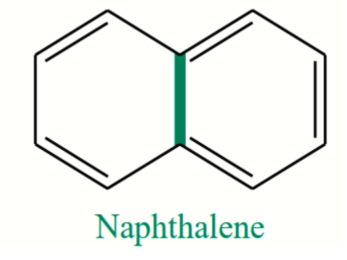


Figure 6. Examples of some heterocyclic compounds with systematic names.

I-3-3 Nomenclature of fused ring systems

Fusion: This term is used to describe the process of joining two separate rings with the maximum number of non-cumulative double bonds via two atoms and one common bond.

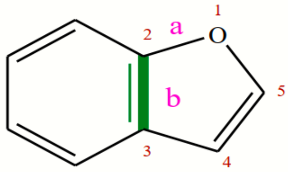
- **Ortho-fused rings**: are those rings that have only two common atoms and one bond, example; Naphthalene.



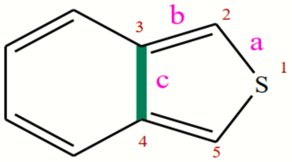
1- Nomenclature of benzofused compounds :

The nomenclature of benzene-fused heterocyclic systems follows well-established rules. When a benzene ring is condensed with either a monocyclic heterocycle (containing five or more atoms) or a heterobicyclic system, the naming convention employs the prefix "benzo" followed by a bracketed letter specifying the fusion position, then the name of the heterocycle (whether trivial, IUPAC, or modified replacement name). Certain common heterobicyclic systems are exceptions to this rule as they possess recognized trivial names. For example, the designations benzo[b]furan and benzo[c]quinoline perfectly illustrate this nomenclature system. The bracketed letter, determined according to the standard numbering of the heterocycle, indicates the exact fusion position, with bond "a" corresponding to the one immediately following the heteroatom in the clockwise direction.

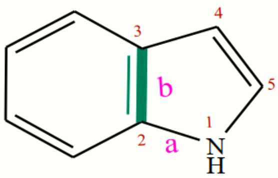
Example :



Benzo[*b*]furan



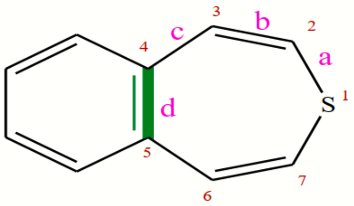
Benzo[*c*]thiophene



Benzo[*b*]pyrrole
Indole

- There is an exception to the two ring systems in which a benzene ring is fused to a hetero ring (which doesn't have a known common name) may be named by prefixing numbers indicating the positions of the hetero atoms to benzo followed by the name of the heterocyclic component.

  • Numbering is assigned according to priority order of the hetero atoms i.e. O < S < N.



Benzo[*d*]thiepine

2-Nomenclature of fused heterocyclic compounds:

Naming a fused heterocyclic system composed of two monoheterocyclic units or benzoheterocycles (e.g. chromene) fused with another hetrocycle ring is based upon considering one system as the parent (base) and the second is considered as substituent.

Name: name of minor ring [number, number-letter] name of major ring.

- The name of the minor ring is derived by writing a contracted prefix for the substituent ring present. In an attached component prefix the terminal ‘e’ is changed to ‘o’ with exception of:

Furo	From Furan
Imidazo	From Imidazole
Thieno	From Thiophene
pyrido	From Pyridine
Pyrimido	From Pyrimidine
Quino	From Quinoline
Isoquino	From Isoquinoline

The **numbers** indicate which atoms in the minor ring are common to the major ring (fusion sites in minor ring).

- **The order of the numbers indicates which atom of the minor ring is encountered closest to** atom **1** in the major numbering system (i.e. these numbers may be written in ascending or descending order e.g.2,3 or 3,2)

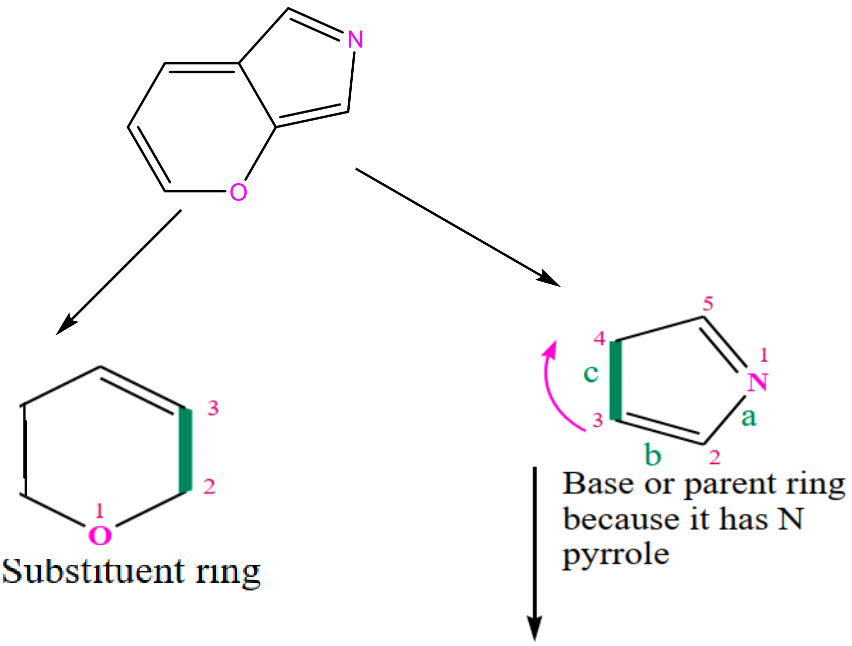
- The **letter** defines the position of attachment of the minor ring to the major ring (fusion sites in base component).

- Finally, a suffix indicates the name of the base ring is written.

The numbering system for the whole fused system is not the same as the numbers in the square brackets (i.e. there are three numbering systems; one for minor ring, one for major ring and the third is for the system as a whole).

- **Priority order of component ring systems:** Selection of a parent component or attached component is based on the following rules which are applied in order:

Rule1: One ring only contains N, Choose it

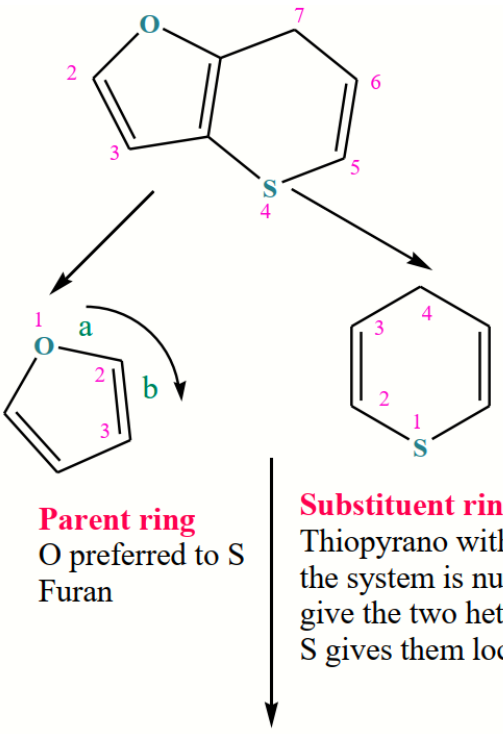


Substituent ring

Base or parent ring because it has N pyrrole

pyrano[2,3-*c*]pyrrole

Rule 2: No, Nitrogen, oxa then thia

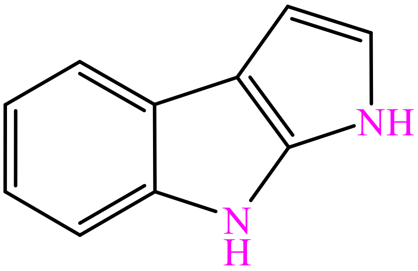


Parent ring
O preferred to S
Furan

Substituent ring
Thiopyrano with one satrated C that take locant 7 when the system is numbered as a whole (starting from O to give the two heteroatoms locants 1,4 while starting from S gives them locants 1,5)

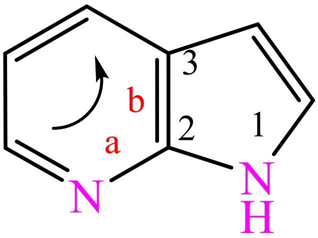
7*H*-Thiopyrano[3,2-*b*]furan

Rule 3: One consists of two or more rings, choose it



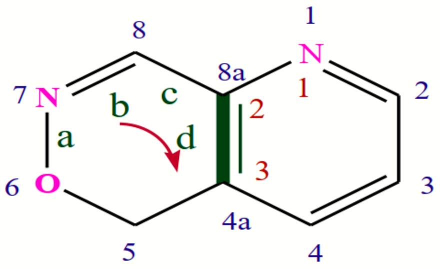
pyrrolo[2,3-*b*]indole

Rule 4: Two rings of different size, choose the larger



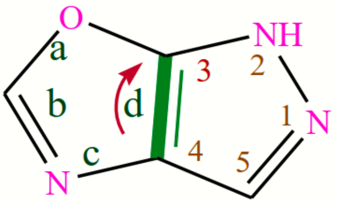
1*H*-pyrrolo[2,3-*b*]pyridine

Rule 5: Choose the one with more heteroatoms

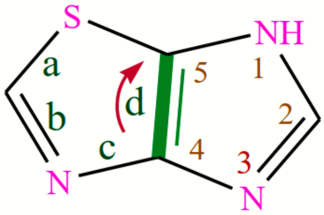


5*H*-Pyrido[2,3-*d*][1,2]oxazine
(Oxazine preferred to pyridine)

Rule 6: Same number of heteroatoms, choose oxa > thia > aza

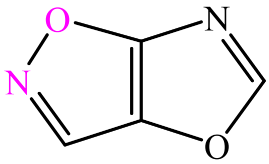


1*H*-Pyrazolo[4,3-*d*][1,3]oxazole
(O & N preferred to N only)

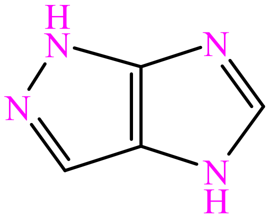


1*H*-Imidazo[4,5-*d*][1,3]thiazole

Rule 7: Same number of heteroatoms, same oxa, thia, aza, then choose lower numbering

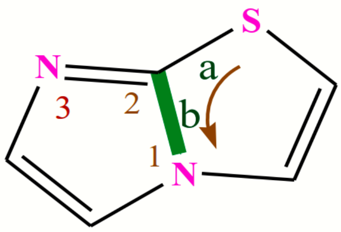


oxazolo[5,4-*d*]isoxazole



1,4-dihydroimidazo[4,5-*c*]pyrazole

Rule 8: If a position of fusion is occupied by a heteroatom the name of the component rings to be used are so chosen as both to contain the heteroatom.



Imidazo[2,1-*b*][1,3]thiazole

I-4 Therapeutic Value of Heterocyclic Compounds

1-4-1. Definition of Heterocycles

Heterocyclic compounds are cyclic structures that contain, in addition to carbon atoms, **at least one heteroatom** such as **nitrogen (N)**, **oxygen (O)**, or **sulfur (S)**. These atoms significantly influence the electronic, steric, and biological properties of the molecule.

1-4-2. Importance of Heterocycles in Medicinal Chemistry

Heterocycles are a cornerstone of **pharmaceutical chemistry**. Their presence in drugs is justified by:

- ✓ their ability to **mimic natural structures** (nucleobases, coenzymes, etc.);
- ✓ their capacity to **interact specifically** with biological targets (enzymes, receptors, DNA);
- ✓ their role in improving **pharmacokinetic properties** (solubility, stability, bioavailability).

1-4-3. Biological Activities of Heterocycles

Heterocyclic compounds are known to exhibit a wide range of biological activities:

- **Antibacterial** (e.g., β-lactams)
- **Antiviral** (e.g., nucleoside analogs)
- **Antifungal** (e.g., imidazoles)
- **Anticancer** (e.g., indole and triazole derivatives)
- **Anti-inflammatory** (e.g., pyrazolines, oxazoles)
- **Antihypertensive and cardiovascular** (e.g., pyridine derivatives)

1-4-4. Structure–Activity Relationship (SAR)

The therapeutic properties of heterocycles strongly depend on:

- the **type of heterocyclic ring** (5- or 6-membered, aromatic or non-aromatic);
- the **nature and position of substituents** on the ring;
- the ability to form **hydrogen bonds** or **π–π interactions** with the target.

I-5 Some Spectroscopic Properties of Some Heteroaromatic Systems

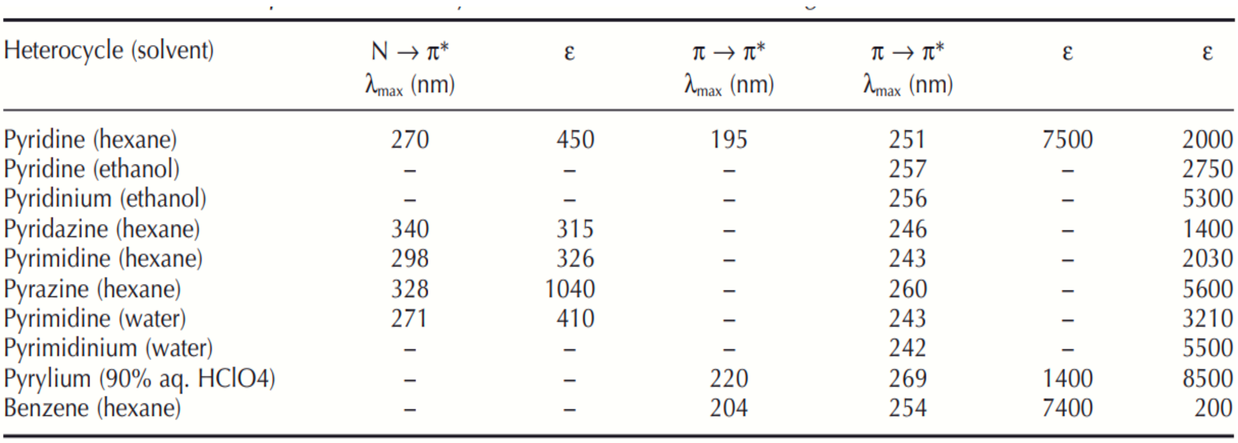
Spectroscopic techniques lie at the core of chemical research and analysis. However, detailed data such as the specific chemical shift of a proton in pyridine or the exact UV absorption maximum of indole are of direct importance mainly to those actively engaged in such experimental investigations. These values contribute little to the broader understanding of heteroaromatic reactivity. Nonetheless, the ultraviolet and infrared spectra of heteroaromatic compounds are consistent with their aromatic nature. Spectroscopic methods—particularly ultraviolet/visible (UV/Vis) and nuclear magnetic resonance (NMR) spectroscopy—are especially valuable for evaluating aromatic character, determining the position of tautomeric equilibria, and detecting transient, non-isolable intermediates.

I-5-1 Ultraviolet/Visible (Electronic) Spectroscopy

The simple unsubstituted heterocyclic systems show a wide range of electronic absorption, from the simple 200 nm band of furan, for example, to the 340 nm maximum shown by pyridazine. As is true for benzenoid compounds, the presence of substituents that can conjugate causes profound changes in electronic absorption, but the many variations possible are outside the scope of this section.

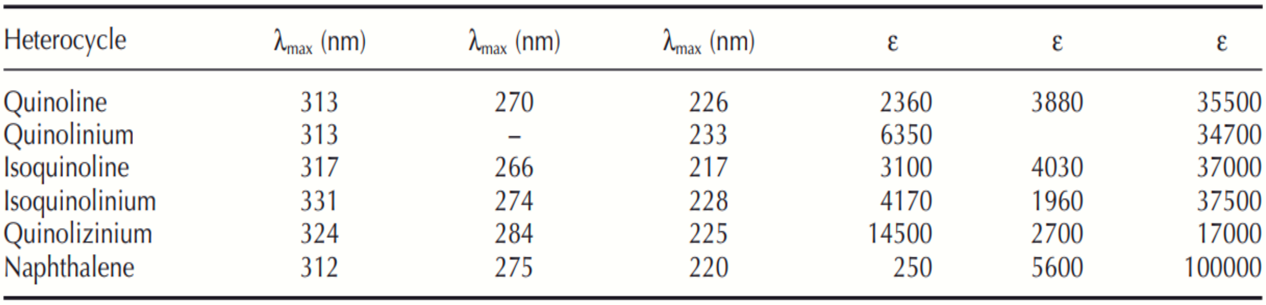
The UV spectra of the monocyclic azines show two bands, each with fine structure: one occurs in the relatively narrow range of 240 – 260 nm and corresponds to the π → π* transitions, analogous with the π → π* transitions in the same region in benzene (see Table 3). The other band occurs at longer wavelengths, from 270 nm in pyridine to 340 nm in pyridazine and corresponds to the interaction of the heteroatom lone pair with aromatic π electrons, the n → π* transitions, which of course cannot occur in benzene. The absorptions due to n → π* transitions are very solvent dependent, as is exemplified in Table 3 by the case of pyrimidine. With pyridine, this band is only observed in hexane solution, for in alcoholic solution the shift to shorter wavelengths results in masking by the main π → π* band. Protonation of the ring nitrogen naturally quenches the n → π* band by removing the heteroatom lone pair; protonation also has the effect of considerably increasing the intensity of the π → π* band, without changing its position significantly, the experimental observation of which has diagnostic utility

Table 3: Ultraviolet spectra of monocyclic azines (fine structure not given)



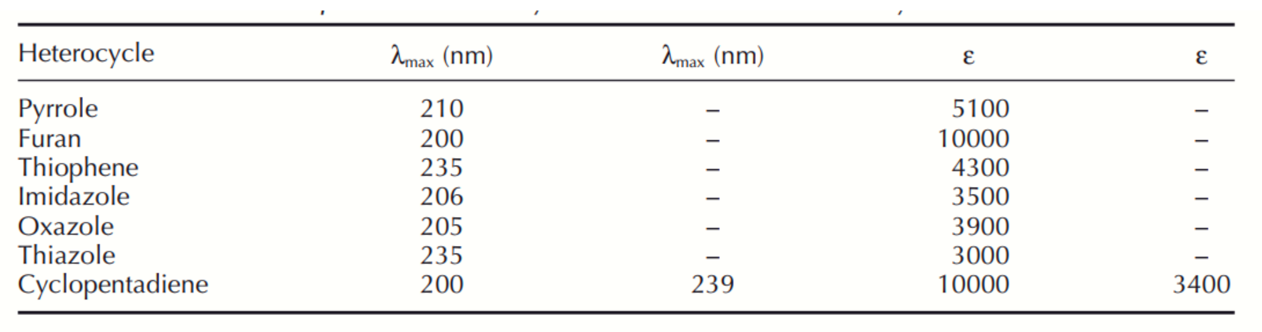
Heterocycle (solvent)	N → π* λ_{max} (nm)	ε	π → π* λ_{max} (nm)	π → π* λ_{max} (nm)	ε	ε
Pyridine (hexane)	270	450	195	251	7500	2000
Pyridine (ethanol)	–	–	–	257	–	2750
Pyridinium (ethanol)	–	–	–	256	–	5300
Pyridazine (hexane)	340	315	–	246	–	1400
Pyrimidine (hexane)	298	326	–	243	–	2030
Pyrazine (hexane)	328	1040	–	260	–	5600
Pyrimidine (water)	271	410	–	243	–	3210
Pyrimidinium (water)	–	–	–	242	–	5500
Pyrylium (90% aq. HClO4)	–	–	220	269	1400	8500
Benzene (hexane)	–	–	204	254	7400	200

Table 4: Ultraviolet spectra of bicyclic azines (fine structure not given)



Heterocycle	λ_{max} (nm)	λ_{max} (nm)	λ_{max} (nm)	ε	ε	ε
Quinoline	313	270	226	2360	3880	35500
Quinolinium	313	–	233	6350		34700
Isoquinoline	317	266	217	3100	4030	37000
Isoquinolinium	331	274	228	4170	1960	37500
Quinolizinium	324	284	225	14500	2700	17000
Naphthalene	312	275	220	250	5600	100000

Table 5: Ultraviolet spectra of monocyclic five-membered heterocycles.

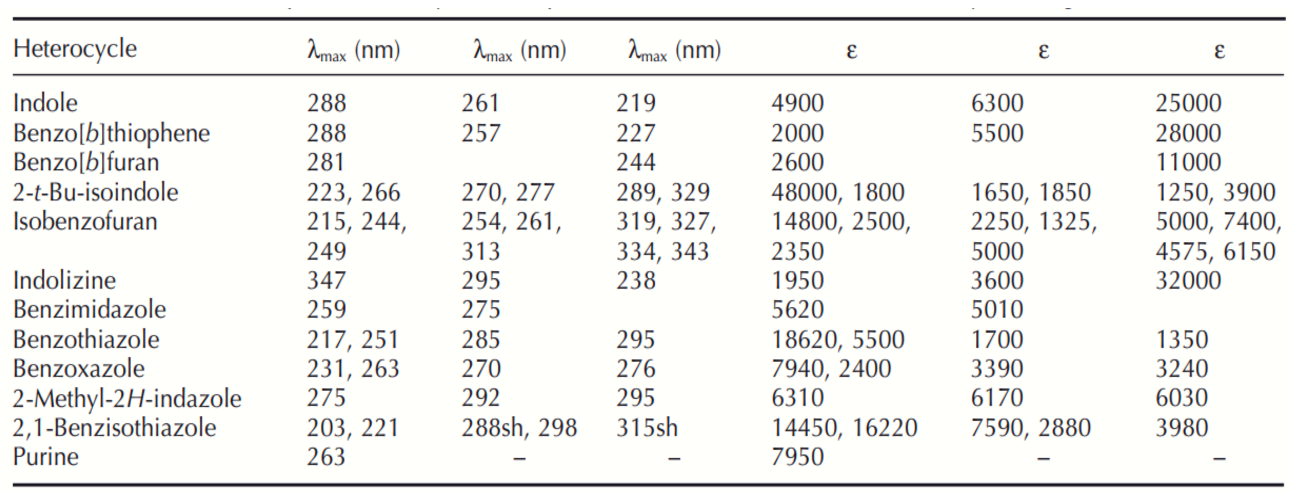


Heterocycle	λ_{max} (nm)	λ_{max} (nm)	ε	ε
Pyrrole	210	–	5100	–
Furan	200	–	10000	–
Thiophene	235	–	4300	–
Imidazole	206	–	3500	–
Oxazole	205	–	3900	–
Thiazole	235	–	3000	–
Cyclopentadiene	200	239	10000	3400

The bicyclic azines have much more complex electronic absorption, and the n → π* and π → π* bands overlap; being much more intense, the latter mask the former. Broadly, however, the absorptions of the bicyclic azines resemble that of naphthalene (Table 4).

The UV spectra of the simple five - membered heteroaromatic systems all show just one medium - to – strong low - wavelength band with no fine structure. Their absorptions have no obvious similarity to that of benzene, and no detectable n → π* absorption, not even in the azoles, which contain a pyridine - like nitrogen (Tables 5 and 6).

Table 6: Ultraviolet spectra of bicyclic compounds with five-membered heterocyclic rings



Heterocycle	λ_{max} (nm)	λ_{max} (nm)	λ_{max} (nm)	ε	ε	ε
Indole	288	261	219	4900	6300	25000
Benzo[*b*]thiophene	288	257	227	2000	5500	28000
Benzo[*b*]furan	281		244	2600		11000
2-*t*-Bu-isoindole	223, 266	270, 277	289, 329	48000, 1800	1650, 1850	1250, 3900
Isobenzofuran	215, 244, 249	254, 261, 313	319, 327, 334, 343	14800, 2500, 2350	2250, 1325, 5000	5000, 7400, 4575, 6150
Indolizine	347	295	238	1950	3600	32000
Benzimidazole	259	275		5620	5010	
Benzothiazole	217, 251	285	295	18620, 5500	1700	1350
Benzoxazole	231, 263	270	276	7940, 2400	3390	3240
2-Methyl-2*H*-indazole	275	292	295	6310	6170	6030
2,1-Benzisothiazole	203, 221	288sh, 298	315sh	14450, 16220	7590, 2880	3980
Purine	263	–	–	7950	–	–

I-5-2 Nuclear Magnetic Resonance (NMR) Spectroscopy

The chemical shifts of protons attached to, and in particular of the carbons in, heterocyclic systems, can be taken as relating to the electron density at that position, with lower fields corresponding to electron - deficient carbons. For example, in the 1H spectrum of pyridine, the lowest - field signals are for the α- protons (Table 7), the next lowest is that for the γ- proton and the highest - field signal corresponds to the β- protons, and this is echoed in the corresponding 13C shifts (Table 8). A second generality relates to the inductive electron withdrawal by the heteroatom – for example it is the hydrogens on the α- carbons of pyridine that are at lower field than that at the γ- carbon, and it is the signals for protons at the α- positions of furan that are at lower field than those at the β- positions. Protons at the α- positions of pyrylium cations present the lowest - field 1H signals. In direct contrast, the chemical shifts for *C*- protons on electron - rich heterocycles, such as pyrrole, occur at much higher fields. Coupling constants between 1,2 - related (*ortho*) protons on heterocyclic systems vary considerably. Typical values round six - membered systems show smaller values closer to the heteroatom(s). In five -membered heterocycles, altogether smaller values are typically found, but again those involving a hydrogen closer to the heteroatom are smaller, except in thiophenes, where the larger size of the sulfur atom influences the coupling constant. The magnitude of such coupling constants reflects the degree of double – bond character (bond fixation) in a particular C – C bond.

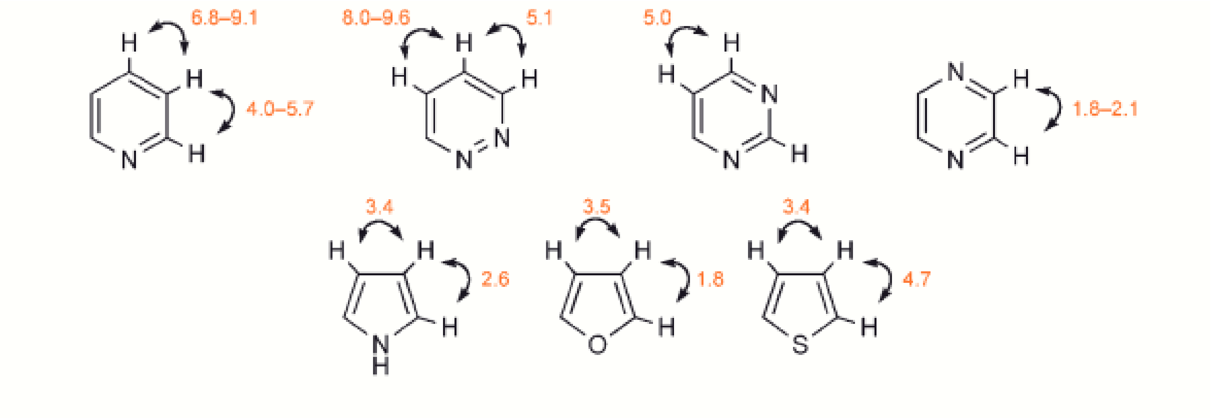
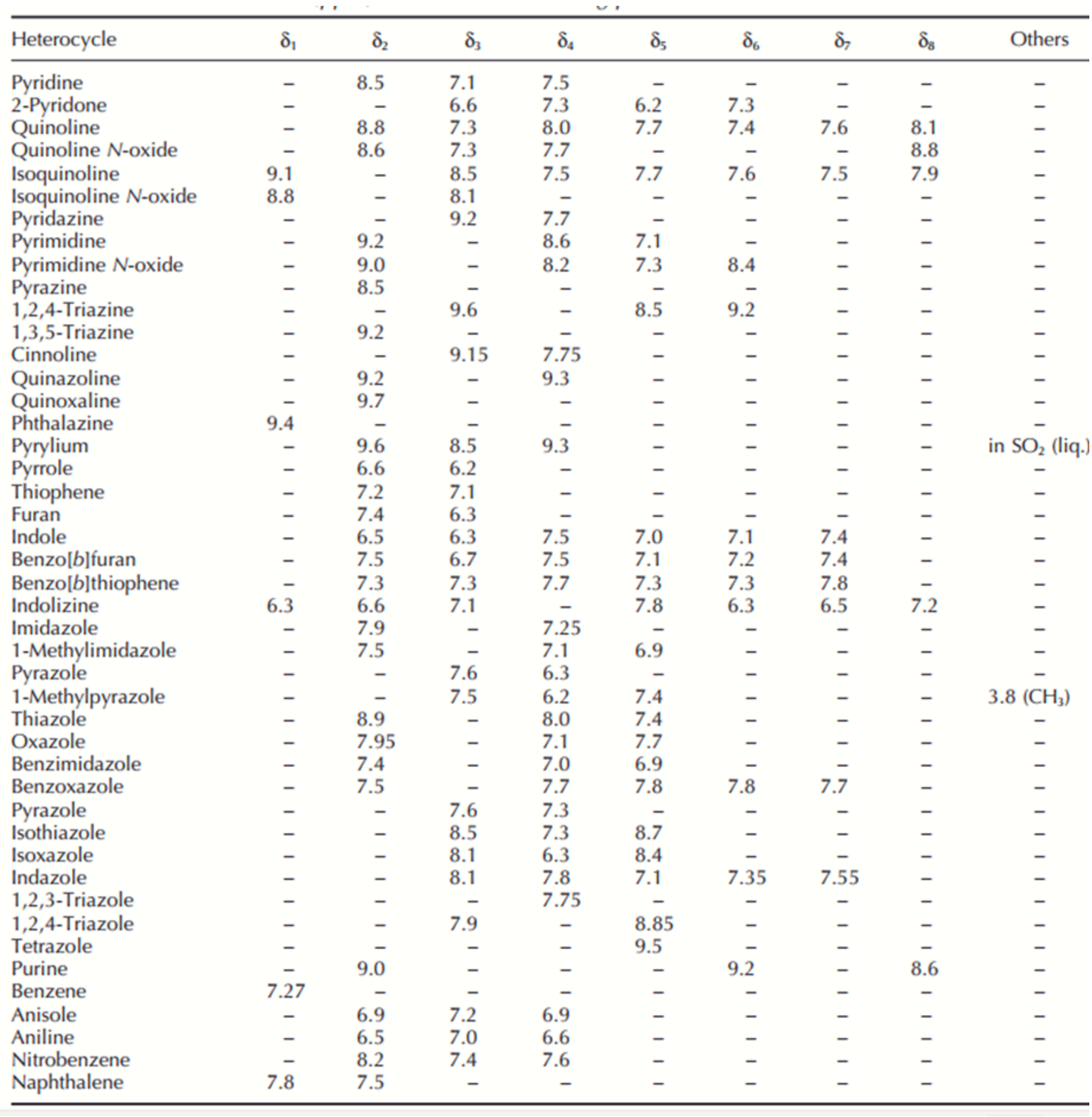
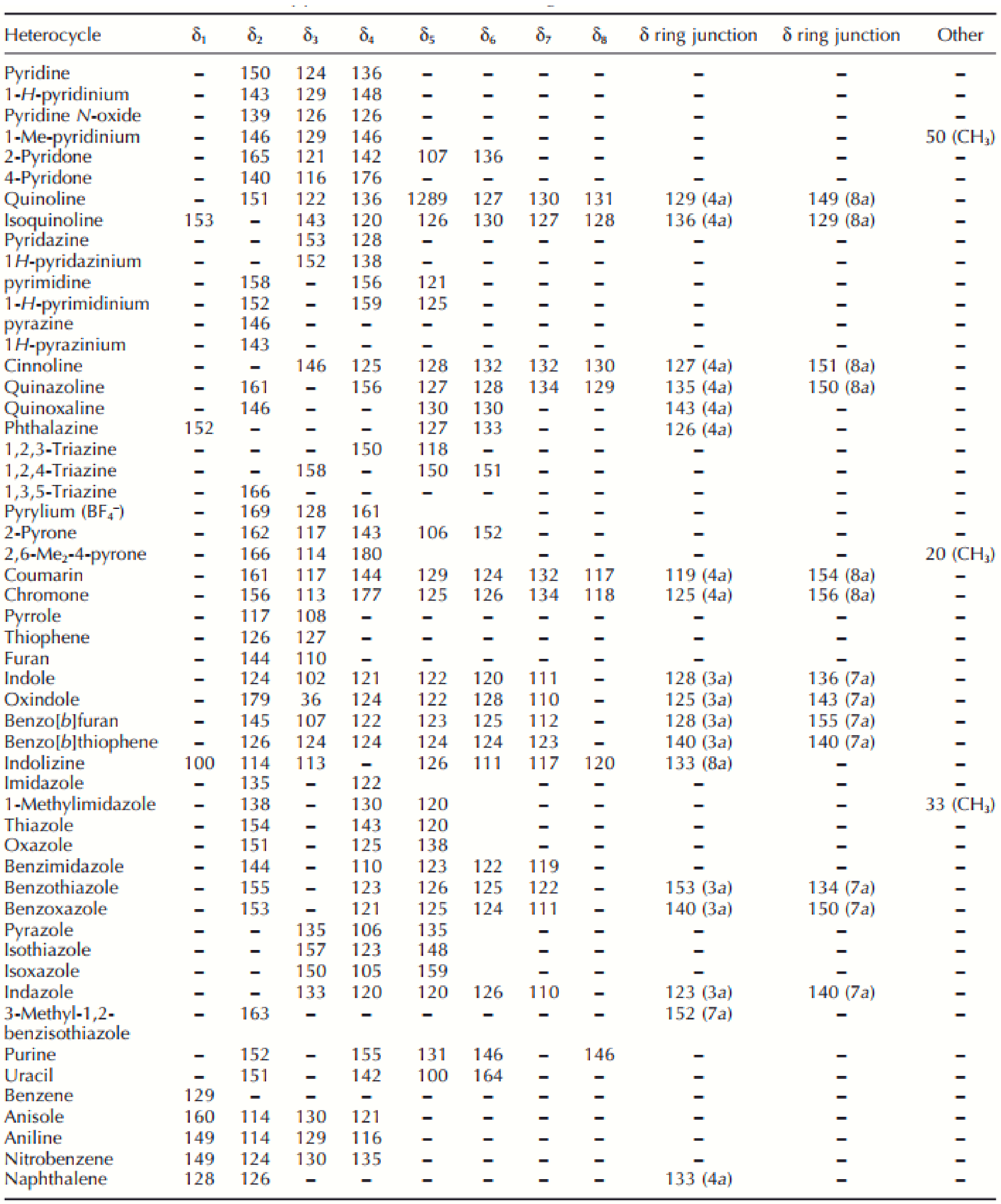


Table 7: ^{1}H chemical shifts (ppm) for heteroaromatic ring protons



Heterocycle	δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	Others
Pyridine	–	8.5	7.1	7.5	–	–	–	–	–
2-Pyridone	–	–	6.6	7.3	6.2	7.3	–	–	–
Quinoline	–	8.8	7.3	8.0	7.7	7.4	7.6	8.1	–
Quinoline *N*-oxide	–	8.6	7.3	7.7	–	–	–	8.8	–
Isoquinoline	9.1	–	8.5	7.5	7.7	7.6	7.5	7.9	–
Isoquinoline *N*-oxide	8.8	–	8.1	–	–	–	–	–	–
Pyridazine	–	–	9.2	7.7	–	–	–	–	–
Pyrimidine	–	9.2	–	8.6	7.1	–	–	–	–
Pyrimidine *N*-oxide	–	9.0	–	8.2	7.3	8.4	–	–	–
Pyrazine	–	8.5	–	–	–	–	–	–	–
1,2,4-Triazine	–	–	9.6	–	8.5	9.2	–	–	–
1,3,5-Triazine	–	9.2	–	–	–	–	–	–	–
Cinnoline	–	–	9.15	7.75	–	–	–	–	–
Quinazoline	–	9.2	–	9.3	–	–	–	–	–
Quinoxaline	–	9.7	–	–	–	–	–	–	–
Phthalazine	9.4	–	–	–	–	–	–	–	–
Pyrylium	–	9.6	8.5	9.3	–	–	–	–	in SO_2 (liq.)
Pyrrole	–	6.6	6.2	–	–	–	–	–	–
Thiophene	–	7.2	7.1	–	–	–	–	–	–
Furan	–	7.4	6.3	–	–	–	–	–	–
Indole	–	6.5	6.3	7.5	7.0	7.1	7.4	–	–
Benzo[*b*]furan	–	7.5	6.7	7.5	7.1	7.2	7.4	–	–
Benzo[*b*]thiophene	–	7.3	7.3	7.7	7.3	7.3	7.8	–	–
Indolizine	6.3	6.6	7.1	–	7.8	6.3	6.5	7.2	–
Imidazole	–	7.9	–	7.25	–	–	–	–	–
1-Methylimidazole	–	7.5	–	7.1	6.9	–	–	–	–
Pyrazole	–	–	7.6	6.3	–	–	–	–	–
1-Methylpyrazole	–	–	7.5	6.2	7.4	–	–	–	3.8 (CH_3)
Thiazole	–	8.9	–	8.0	7.4	–	–	–	–
Oxazole	–	7.95	–	7.1	7.7	–	–	–	–
Benzimidazole	–	7.4	–	7.0	6.9	–	–	–	–
Benzoxazole	–	7.5	–	7.7	7.8	7.8	7.7	–	–
Pyrazole	–	–	7.6	7.3	–	–	–	–	–
Isothiazole	–	–	8.5	7.3	8.7	–	–	–	–
Isoxazole	–	–	8.1	6.3	8.4	–	–	–	–
Indazole	–	–	8.1	7.8	7.1	7.35	7.55	–	–
1,2,3-Triazole	–	–	–	7.75	–	–	–	–	–
1,2,4-Triazole	–	–	7.9	–	8.85	–	–	–	–
Tetrazole	–	–	–	–	9.5	–	–	–	–
Purine	–	9.0	–	–	–	9.2	–	8.6	–
Benzene	7.27	–	–	–	–	–	–	–	–
Anisole	–	6.9	7.2	6.9	–	–	–	–	–
Aniline	–	6.5	7.0	6.6	–	–	–	–	–
Nitrobenzene	–	8.2	7.4	7.6	–	–	–	–	–
Naphthalene	7.8	7.5	–	–	–	–	–	–	–

Table 8: ^{13}C chemical shifts (ppm) for heteroaromatic ring carbons



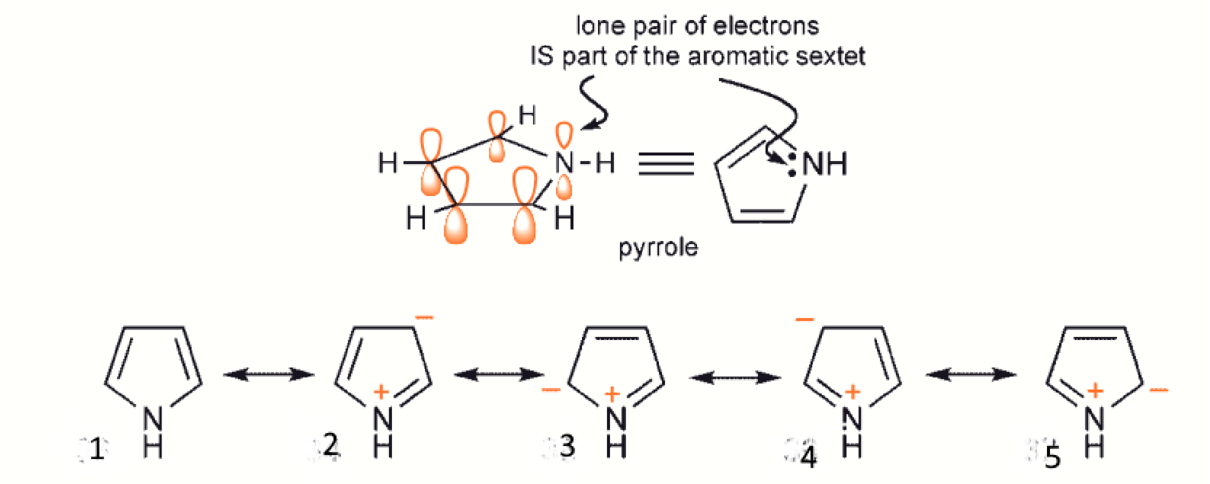
Heterocycle	δ_1	δ_2	δ_3	δ_4	δ_5	δ_6	δ_7	δ_8	δ ring junction	δ ring junction	Other
Pyridine	–	150	124	136	–	–	–	–	–	–	–
1-*H*-pyridinium	–	143	129	148	–	–	–	–	–	–	–
Pyridine *N*-oxide	–	139	126	126	–	–	–	–	–	–	–
1-Me-pyridinium	–	146	129	146	–	–	–	–	–	–	50 (CH_3)
2-Pyridone	–	165	121	142	107	136	–	–	–	–	–
4-Pyridone	–	140	116	176	–	–	–	–	–	–	–
Quinoline	–	151	122	136	1289	127	130	131	129 (4a)	149 (8a)	–
Isoquinoline	153	–	143	120	126	130	127	128	136 (4a)	129 (8a)	–
Pyridazine	–	–	153	128	–	–	–	–	–	–	–
1*H*-pyridazinium	–	–	152	138	–	–	–	–	–	–	–
pyrimidine	–	158	–	156	121	–	–	–	–	–	–
1-*H*-pyrimidinium	–	152	–	159	125	–	–	–	–	–	–
pyrazine	–	146	–	–	–	–	–	–	–	–	–
1*H*-pyrazinium	–	143	–	–	–	–	–	–	–	–	–
Cinnoline	–	–	146	125	128	132	132	130	127 (4*a*)	151 (8*a*)	–
Quinazoline	–	161	–	156	127	128	134	129	135 (4*a*)	150 (8*a*)	–
Quinoxaline	–	146	–	–	130	130	–	–	143 (4*a*)	–	–
Phthalazine	152	–	–	–	127	133	–	–	126 (4*a*)	–	–
1,2,3-Triazine	–	–	–	150	118	–	–	–	–	–	–
1,2,4-Triazine	–	–	158	–	150	151	–	–	–	–	–
1,3,5-Triazine	–	166	–	–	–	–	–	–	–	–	–
Pyrylium (BF_4^-)	–	169	128	161			–	–	–	–	–
2-Pyrone	–	162	117	143	106	152	–	–	–	–	–
2,6-Me_2-4-pyrone	–	166	114	180			–	–	–	–	20 (CH_3)
Coumarin	–	161	117	144	129	124	132	117	119 (4*a*)	154 (8*a*)	–
Chromone	–	156	113	177	125	126	134	118	125 (4*a*)	156 (8*a*)	–
Pyrrole	–	117	108	–	–	–	–	–	–	–	–
Thiophene	–	126	127	–	–	–	–	–	–	–	–
Furan	–	144	110	–	–	–	–	–	–	–	–
Indole	–	124	102	121	122	120	111	–	128 (3*a*)	136 (7*a*)	–
Oxindole	–	179	36	124	122	128	110	–	125 (3*a*)	143 (7*a*)	–
Benzo[*b*]furan	–	145	107	122	123	125	112	–	128 (3a)	155 (7*a*)	–
Benzo[*b*]thiophene	–	126	124	124	124	124	123	–	140 (3*a*)	140 (7*a*)	–
Indolizine	100	114	113	–	126	111	117	120	133 (8*a*)	–	–
Imidazole	–	135	–	122			–	–	–	–	–
1-Methylimidazole	–	138	–	130	120		–	–	–	–	33 (CH_3)
Thiazole	–	154	–	143	120		–	–	–	–	–
Oxazole	–	151	–	125	138		–	–	–	–	–
Benzimidazole	–	144	–	110	123	122	119	–	–	–	–
Benzothiazole	–	155	–	123	126	125	122	–	153 (3*a*)	134 (7*a*)	–
Benzoxazole	–	153	–	121	125	124	111	–	140 (3*a*)	150 (7*a*)	–
Pyrazole	–	–	135	106	135		–	–	–	–	–
Isothiazole	–	–	157	123	148		–	–	–	–	–
Isoxazole	–	–	150	105	159		–	–	–	–	–
Indazole	–	–	133	120	120	126	110	–	123 (3*a*)	140 (7*a*)	–
3-Methyl-1,2-benzisothiazole	–	163	–	–	–	–	–	–	152 (7*a*)	–	–
Purine	–	152	–	155	131	146	–	146	–	–	–
Uracil	–	151	–	142	100	164	–	–	–	–	–
Benzene	129	–	–	–	–	–	–	–	–	–	–
Anisole	160	114	130	121	–	–	–	–	–	–	–
Aniline	149	114	129	116	–	–	–	–	–	–	–
Nitrobenzene	149	124	130	135	–	–	–	–	–	–	–
Naphthalene	128	126	–	–	–	–	–	–	133 (4*a*)	–	–

Chapter 2 Synthesis and Reactivity of Five-Membered Rings

II-1 Structure of Five - Membered Heteroaromatic Systems

II-1 1 Structure of Pyrrole

Pyrrole is isoelectronic with the cyclopentadienyl anion but remains electrically neutral due to the greater nuclear charge of the nitrogen atom. The presence of nitrogen in the ring also disrupts radial symmetry, resulting in pyrrole lacking five equivalent resonance structures. Instead, it exhibits one structure without charge separation (structure 33) and two pairs of equivalent resonance forms with charge separation, reflecting an electron density shift away from the nitrogen atom. These resonance forms do not contribute equally; their relative significance follows the order: 33 > 35, 37 > 34, 36.

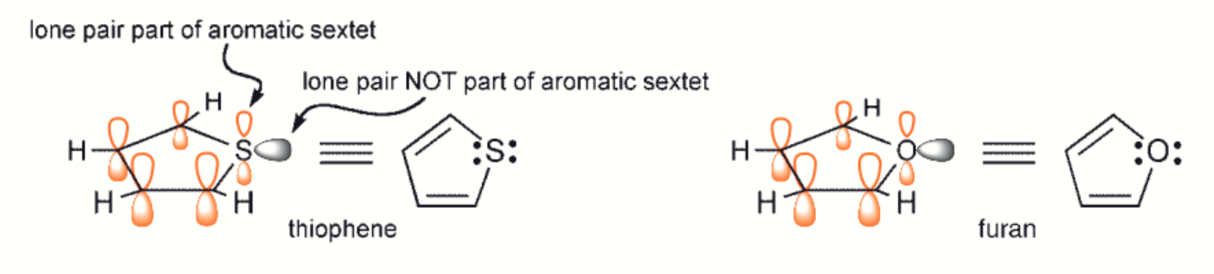


Structure of pyrrole; resonance contributors (mesomeric structures)

Resonance in pyrrole results in partial negative charges on the carbon atoms and a partial positive charge on the nitrogen. At the same time, nitrogen exerts its usual inductive effect, pulling electron density toward itself and away from the carbon atoms. Thus, the overall electron distribution in pyrrole reflects a balance between these two opposing effects—resonance and induction—with the mesomeric (resonance) effect likely dominating. This leads to a net dipole moment oriented away from the nitrogen atom. Bond length measurements support this interpretation: the bond between positions 3 and 4 is noticeably longer than the 2,3 and 4,5 bonds, yet still shorter than a typical single bond between sp^2-hybridized carbons. This is consistent with the influence of the polarized resonance structures (2–5). The tendency for electron density to shift away from nitrogen and toward the ring carbons explains why five-membered heterocycles like pyrrole are often described as "electron-rich" or "π-excessive."

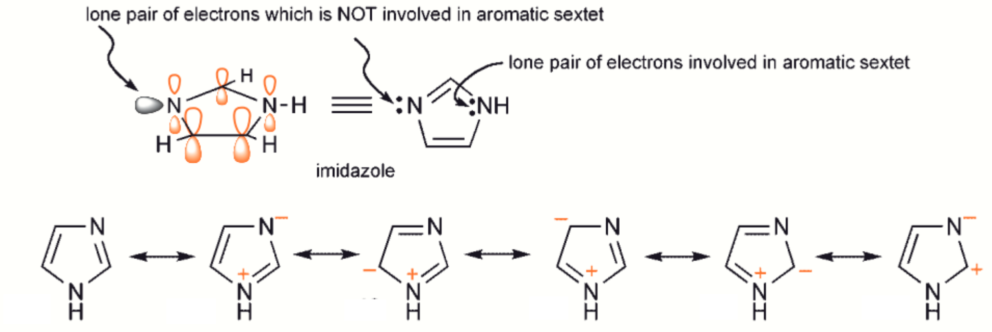
II-1-2 Structures of Thiophene and Furan

The structures of thiophene and furan are closely analogous to that discussed in detail for pyrrole above, except that the NH is replaced by S and O, respectively. A consequence is that the heteroatom in each has one lone pair as part of the aromatic sextet, as in pyrrole, but also has a second lone pair that is not involved, and is located in sp2 hybrid orbital in the plane of the ring. Mesomeric forms exactly analogous to those (above) for pyrrole can be written for each, but the higher electronegativity of both sulfur and oxygen means that the polarised forms, with positive charges on the heteroatoms, make a smaller contribution. The decreased mesomeric electron drift away from the heteroatoms is insufficient, in these two cases, to overcome the inductive polarisation towards the heteroatom (The dipole moments of tetrahydrothiophene (1.87 D) and tetrahydrofuran (1.68 D), both directed toward the heteroatom, are in any case larger than that of pyrrolidine.) and the net effect is that the dipoles are directed towards the heteroatoms in thiophene and furan.



II-1-3 Structures of Azoles

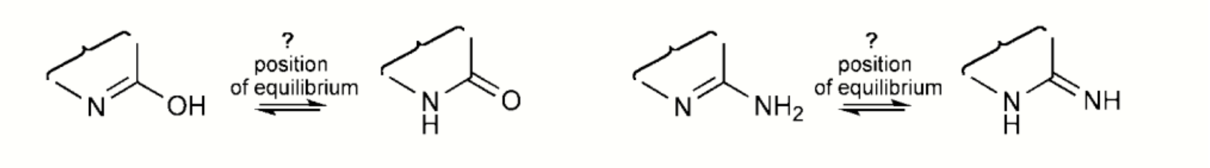
The 1,3 - and 1,2 - azoles, five - membered rings with two heteroatoms, present a fascinating combination of heteroatom types – in all cases, one heteroatom must be of the five - membered heterocycle (pyrrole, thiophene, furan) type and one of the imine type, as in pyridine; imidazole with two nitrogen atoms illustrates this best.



Structure of imidazole; resonance contributors (mesomeric structures)

II-2 Tautomerism in Heterocyclic Systems

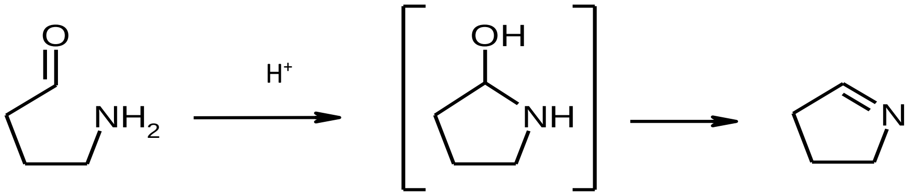
A topic that has garnered significant research attention over the years is the precise structural determination of heterocyclic molecules capable of tautomerism—such as the pyridinol/pyridone system. In general, when an oxygen atom is positioned on a carbon atom α or γ to a nitrogen atom, two tautomeric forms are possible; the same principle applies to amino groups.



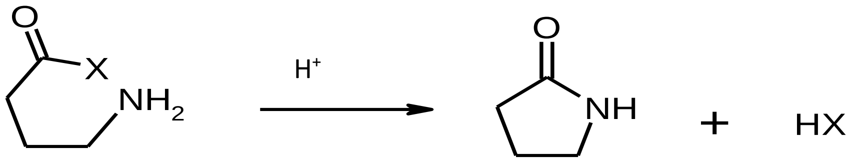
To summarize, heterocycles with oxygen atoms at the α or γ position typically favor the carbonyl tautomer, whereas amino-substituted heterocycles almost always exist in their amino form. In the case of sulfur analogues, the preferred tautomer depends on ring size: six-membered rings tend to stabilize the thione form, while five-membered rings usually adopt the thiol form. Identifying the correct tautomeric form is especially critical for purine and pyrimidine bases in DNA and RNA, as their ability to form hydrogen bonds—particularly through carbonyl oxygen atoms—is essential for accurate base pairing.

II-3 Reactions of Carbonyl Compounds

- Aldehydes and Ketones undergo addition reactions
- Acids and their derivatives undergo substitution reactions

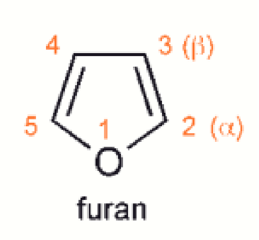


Aldehyde or Ketone



Acid, ester, acid halide, anhydride, amides!!!

Furan



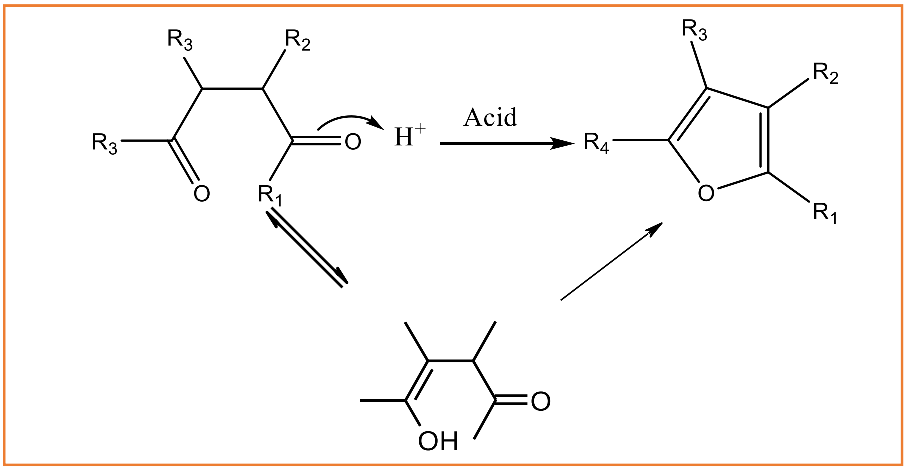
Furan-containing natural products are commonly found in various plants, marine organisms, and microorganisms, and often exhibit notable biological activities. Examples include:

- **Furano-terpenoids**: Found in essential oils and known for antimicrobial or anti-inflammatory properties.
- **Angelicin**: A furocoumarin with phototoxic activity used in dermatology.
- **Psoralen**: Another furan-containing compound used in PUVA therapy for skin conditions.
- **Furanolactones**: Such as khellin, used in traditional medicine.
- **Marine furanosesquiterpenes**: Isolated from soft corals and sponges, with cytotoxic or anticancer properties.

II-4- Synthesis of Furan

II-4-1- Paal-Knorr furan synthesis

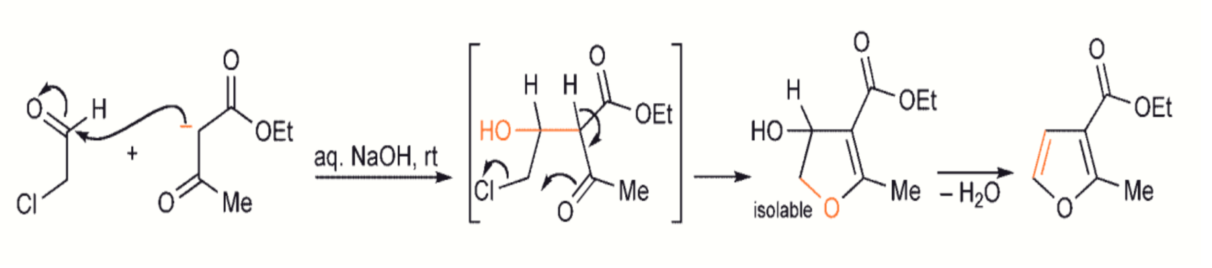
This method involves the cyclization of 1,4-diketones in the presence of an acid used as a catalyst, such as sulfuric acid, phosphorus pentoxide, or zinc chloride.



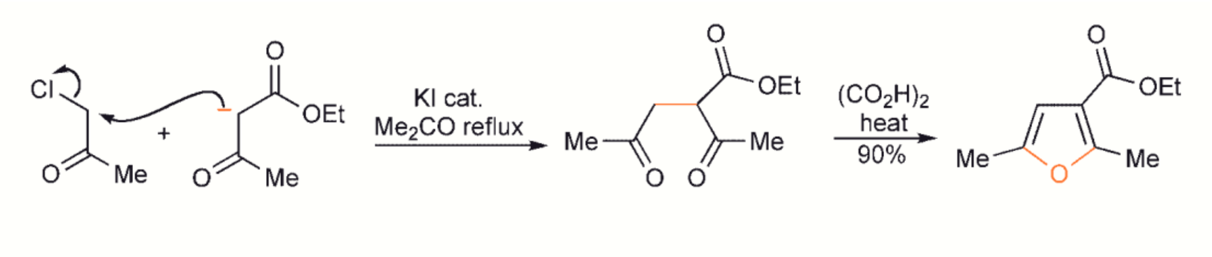
Scheme1. Paal-Knorr furan synthesis.

II-4-2 Feist-Benary Furan Synthesis

This reaction involves the **condensation of α-haloketones** with **β-dicarbonyl compounds** (such as β-ketoesters) in the presence of a base, leading to the formation of **substituted furan rings**.

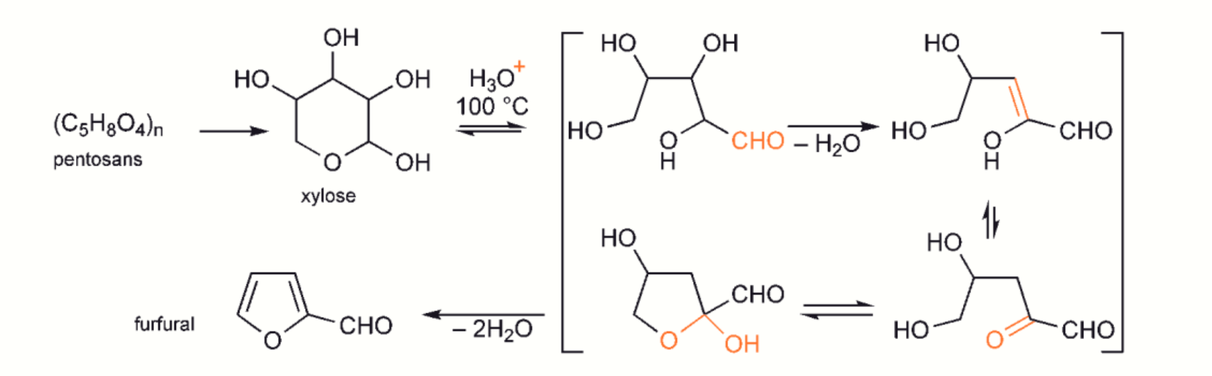


It is important to distinguish this synthesis from the alkylation of a 1,3 - dicarbonyl enolate with a 2 - haloketone, with displacement of halide, producing a 1,4 - dicarbonyl unit for subsequent ring closure;170 presumably the difference lies in the greater reactivity of the carbonyl group (aldehyde in the example) in the Feist – Benary sequence.



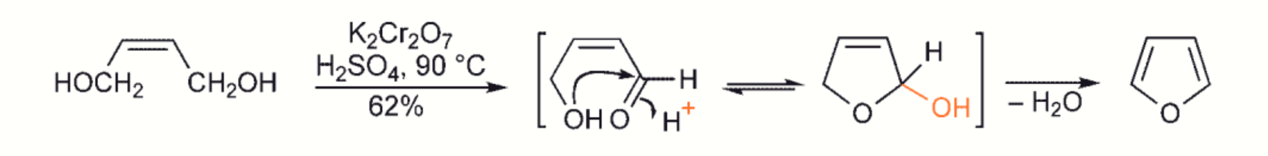
II-4-3 From Sugars

Furfural is obtained by the dehydration of pentoses. It undergoes decarboxylation in the presence of $CaCO_3$ at 625°C to produce furan.



II-4-4- From C_4O Compounds

There is a range of furan syntheses that have one aspect in common – the precursor of the aromatic furan has: (i) four carbons, (ii) an oxygen at a terminus and (iii) two degrees of unsaturation located somewhere in the five - atom sequence. Treatment (often acid) of the precursor generates the furan, by a sequence of isomerisations, a ring closure and an elimination (often of water). The simplest example here is the oxidation of *cis*- but - 2 - ene - 1,4 - diol, which gives furan *via* the hydroxy -aldehyde – the two degrees of unsaturation being the carbonyl and carbon – carbon double bonds.



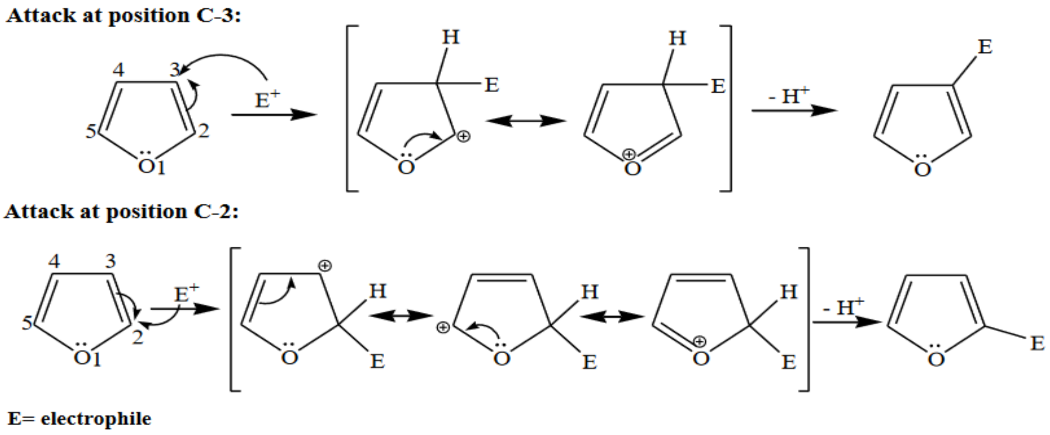
II-5 Properties of Furan

1- Physical Properties of Furan: Furan is colorless liquid. Its boiling point is 31.4° C. It has an odor similar to Chloroform. Furan is insoluble in ether but soluble in most of the organic solvents.

2- Chemical Properties of Furan: furan is an aromatic compound and more reactive than benzene. Because of the aromatic nature, furan gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

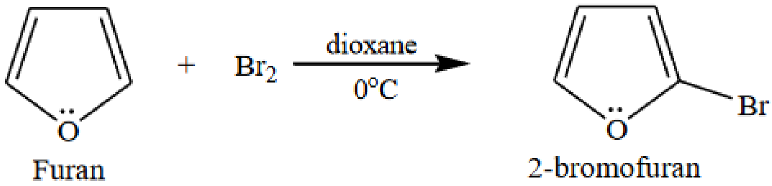
3- Electrophilic Substitution Reactions of Furan

Furan undergoes electrophilic substitution reactions at position C-2.



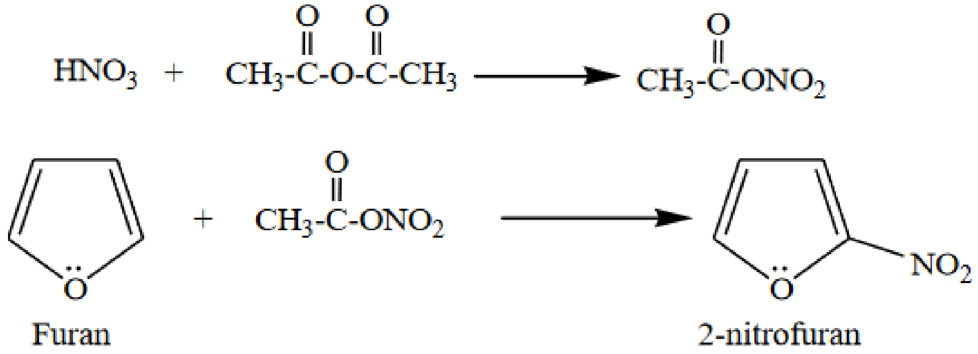
3-1 Halogenation

Furan reacts with halogens [X_2 (X_2 = Cl_2, Br_2 and I_2)] to give 2- halofuran. For example, reaction of bromine with Furan gives 2-bromofuran.



3-2 Nitration

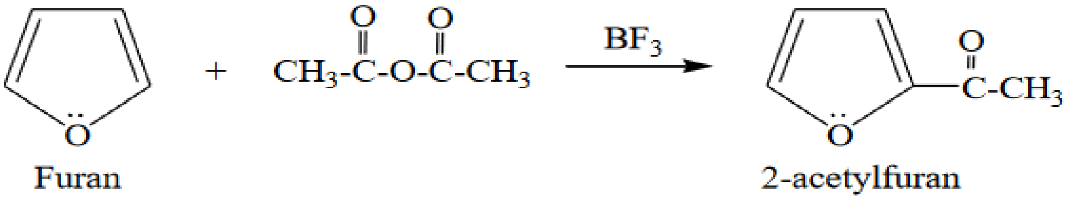
Nitration of furan is achieved by reacting it with HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $–NO_2$ acts as an electrophile.



$$HNO_3 + CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}CH_3 \longrightarrow CH_3\text{-}\overset{\overset{O}{\|}}{C}\text{-}ONO_2$$

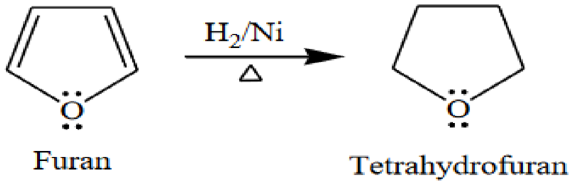
3-3 Friedel-Crafts Acylation

Reaction of furan with acetic anhydride in presence of BF3 gives 2-acetylfuran.



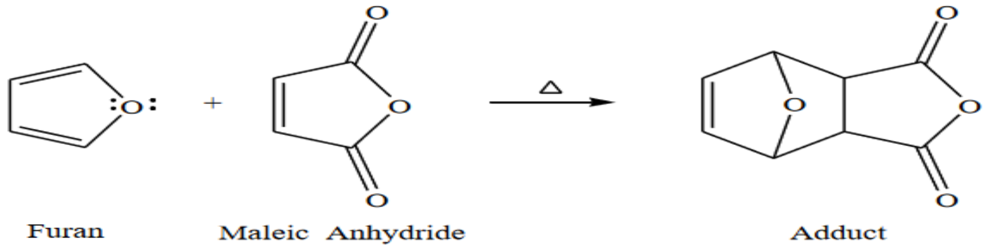
3-4 Reduction

On catalytic hydrogenation of furan, the tetrehydrofuran (THF) is obtained. THF is used as a solvent in place of ether in the Grignard reactions.



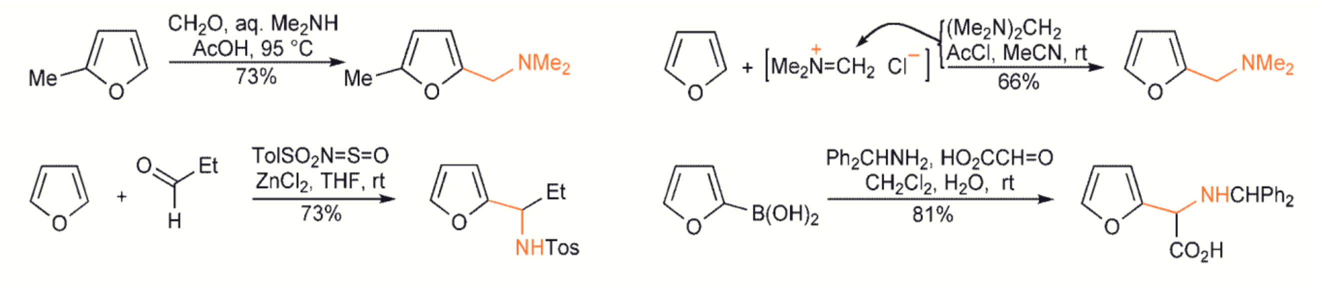
3-5 Diels-Alder Reaction

Furan is the only heterocyclic compound which undergoes Diels-Alder reaction. Diels-Alder reaction is a cycloaddtion reaction of 4π-system to 2π-system.



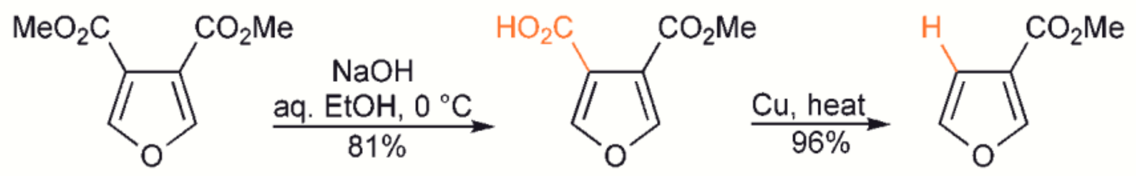
4- Condensation with Imines and Iminium Ions

Mono - alkyl - furans undergo Mannich substitution under normal conditions, but furan itself requires a preformed iminium salt for 2 - substitution. *N*- Tosyl - imines, generated *in situ* from *N*- sulfi nyl -*p*toluenesulfonamide and aldehydes, bring about tosylaminoalkylation at C - 2.43 The use of furan boronic acids allows Mannich substitutions at both α- and β- positions, with primary or secondary amine components.

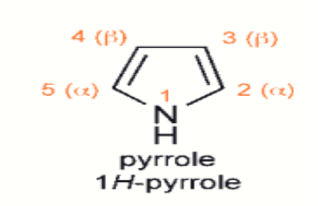


5- Furan Carboxylic Acids and Esters and Aldehydes

Save for their easy decarboxylation, furan acids (and their esters) are unexceptional. Carbon dioxide is easily lost from either α- or β- acids and presumably involves ring - protonated intermediates and a decarboxylation analogous to that of β- keto - acids, at least in those examples where copper is not utilised.

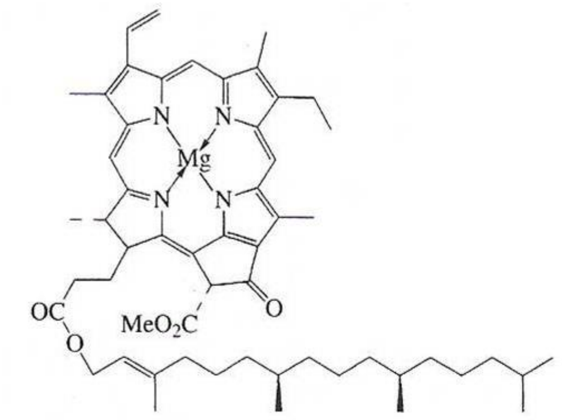


Pyrrole

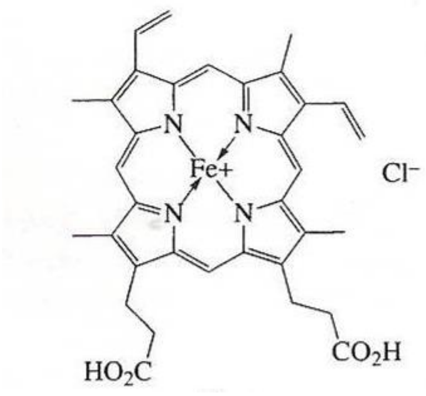


II-5-1 Importance of Pyrroles

Pyrrole is a privileged scaffold with assorted nature of biological activities. Many active compounds have been developed by amalgamation of different pharmacophores in a pyrrole ring system. Pyrroles are an active component of complex macrocycles, including the porphyrins of heme, chlorins, bacteriochlorins, chlorophyll, porphyrinogens.



Chlorophyll

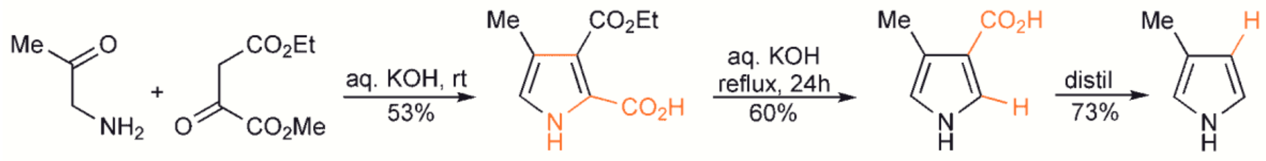


Haem (iron (II) complex)

II-5-2 Synthesis of Pyrrole

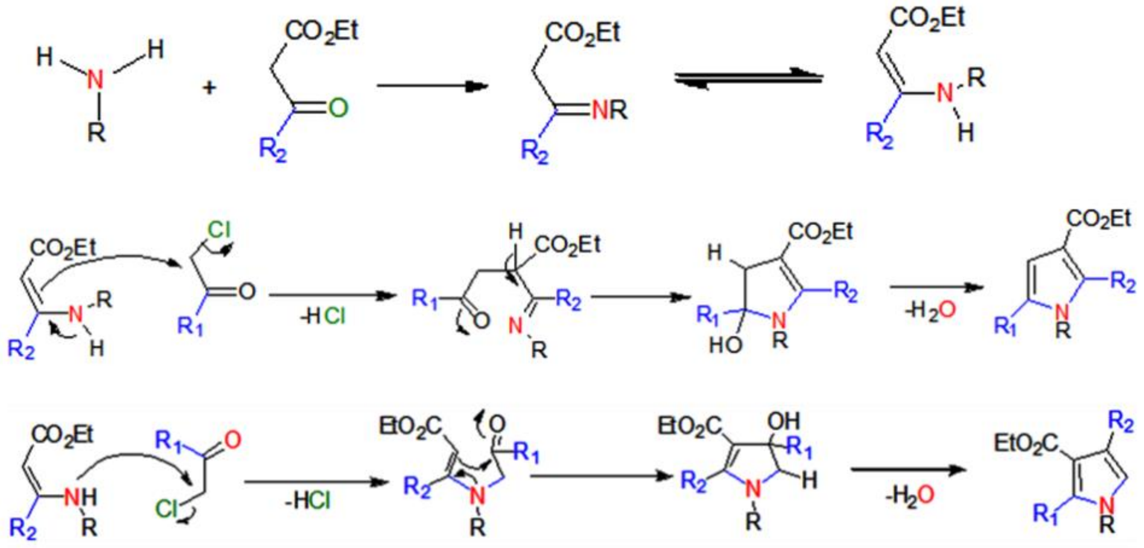
II-5-2-1 Knorr Synthesis

The original Knorr synthesis employed two equivalents of **ethyl acetoacetate**, one of which was converted to ethyl 2-oximinoacetoacetate by dissolving it in **glacial acetic acid**, and slowly adding one equivalent of saturated aqueous **sodium nitrite**, under external cooling. **Zinc** dust was then stirred in, reducing the **oxime** group to the amine.



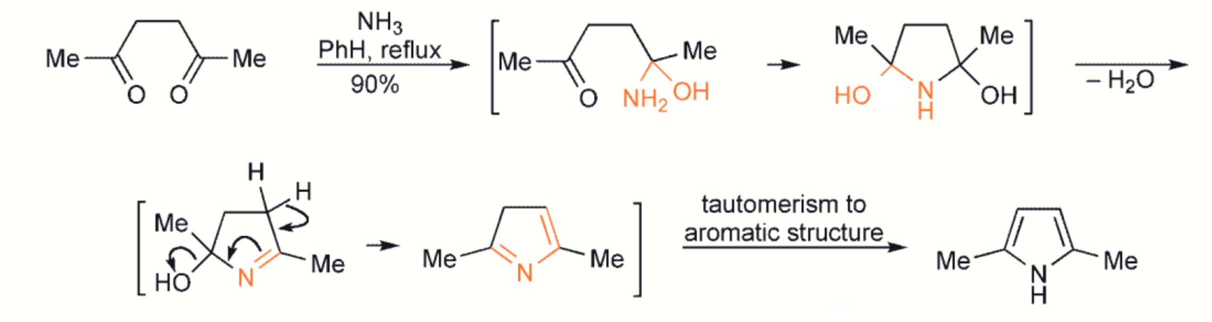
II-5-2-2 Hantzsch synthesis

This synthesis consists of condensing an α-haloketone with a β-ketone ester in the presence of ammonia or primary amines.



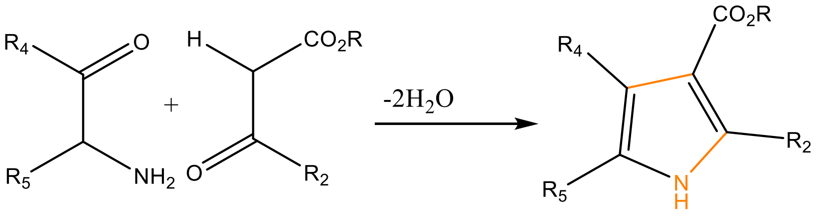
II-5-2-3 Paal-Knorr Pyrrole Synthesis

Used to synthesize **pyrroles** by the condensation of **1,4-diketones** (or their equivalents) with **primary amines** or **ammonia.**



II-5-2-4 From a- Aminocarbonyl - Compounds and Activated Ketones

α- Amino - ketones react with carbonyl compounds that have an α- methylene grouping, preferably further activated, for example by ester, as in the illustration.



II-5-3 Properties of Pyrrole

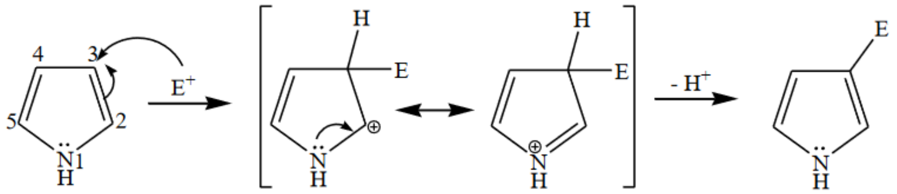
1- Physical Properties of pyrrole: Pyrrole is a colorless liquid with boiling point 131° C. It is highly sensitive to air, when pyrrole is exposed to air it turns brown and gradually resinifies. Pyrrole is slightly soluble in water but completely miscible in ether and ethanol.

2- Chemical Properties

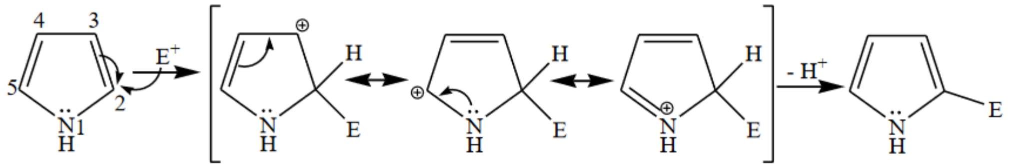
Pyrrole is an aromatic compound and more reactive than benzene. Because of the aromatic nature pyrrole gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

Pyrrole undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus, the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.

Attack at position C-3:



Attack at position C-2:



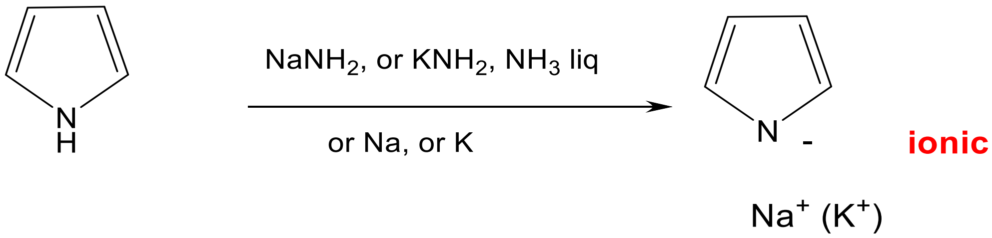
E= electrophile

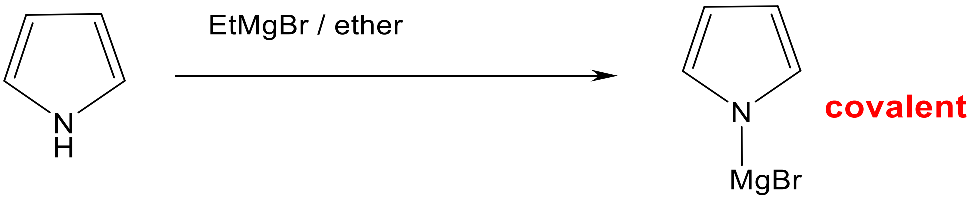
All the electrophilic substitution reactions of pyrrole occur at position C-2 and follow the similar mechanism as shown above.

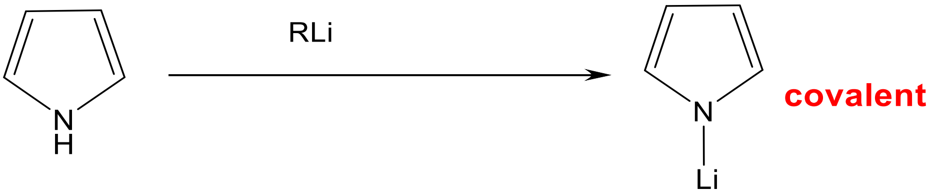
II-5-4 Reactions of Pyrrole

1- Substitution at nitrogen

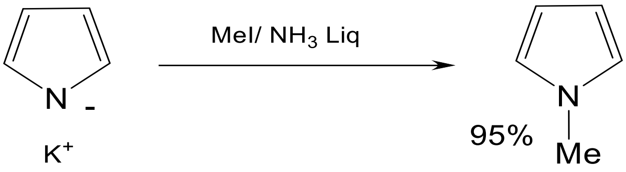
A) Metallation of Pyrrole

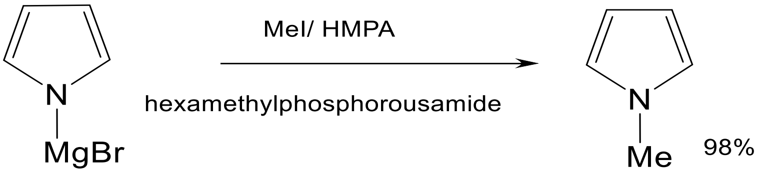


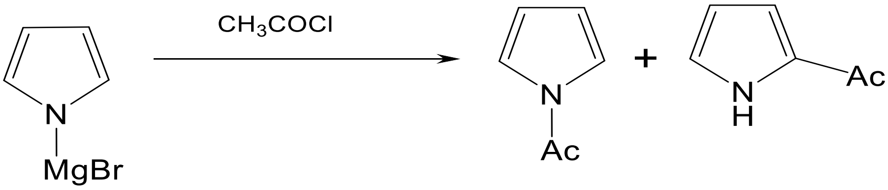


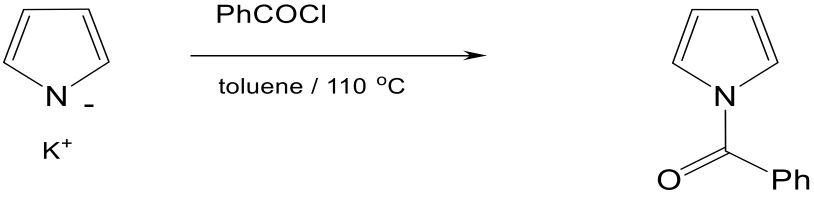


B) Formation of N-substituted Pyrrole

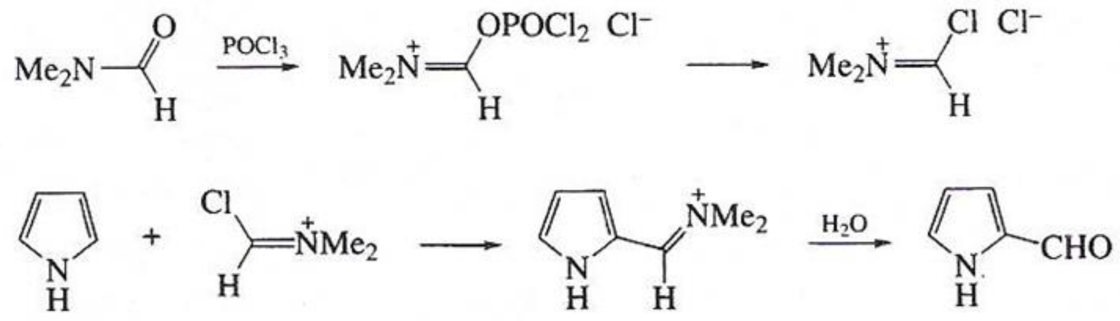




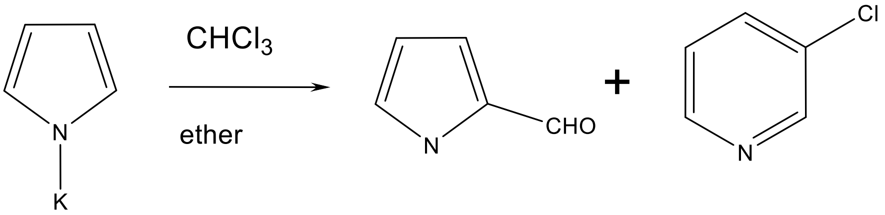




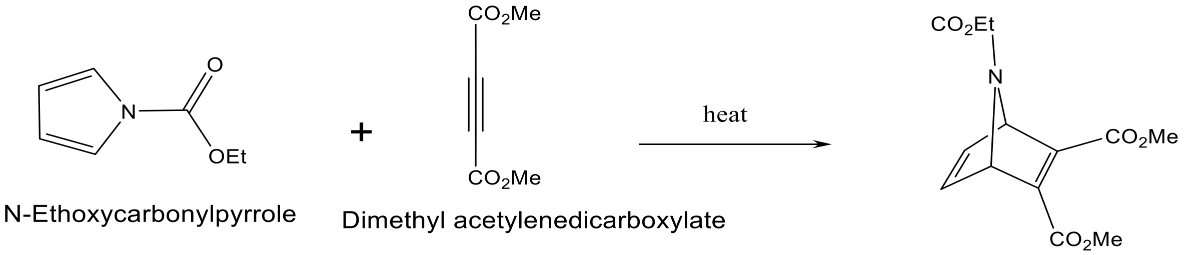
2- The Vilsmeier Haack reaction



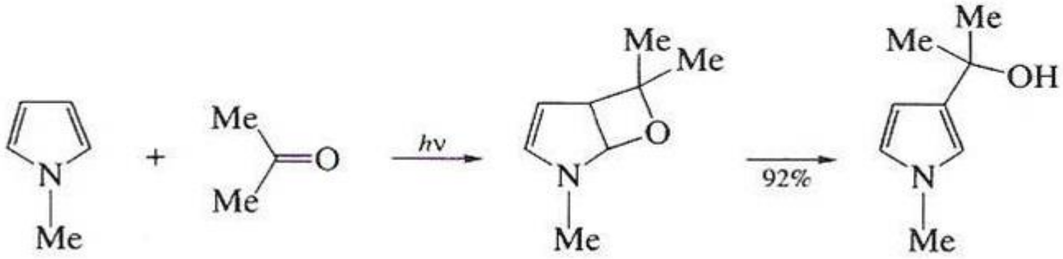
3- Reimer-Tieman Reaction



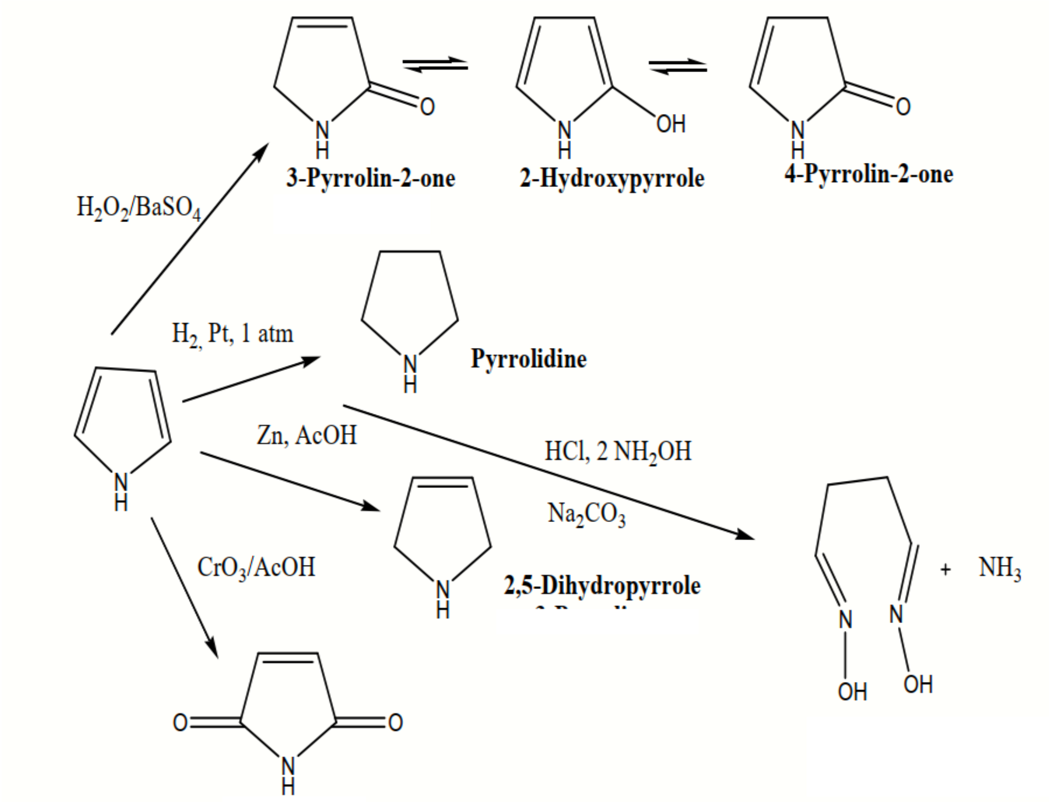
4- Diels-Alder Reactions of Pyrrole



4-1 [2 +2] Cycloaddition

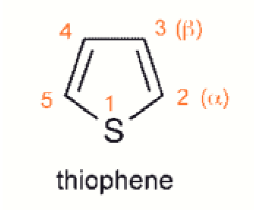


5- Other reaction



Scheme.2 Other reaction of Pyrrole.

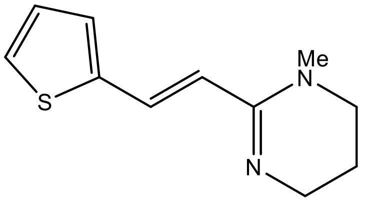
Thiophene



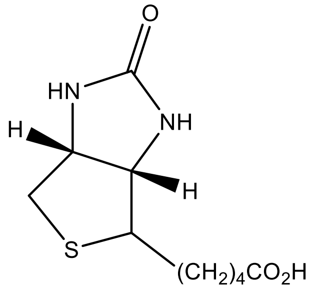
thiophene

II-6 Importance of Thiophene

- **Pyrantal (1),** is a broad-spectrum anthelmintic agent effective against pinworm and hookworm.
- **Bioten (2)**(Vitamin H), occurs in yeast and egg Thiophene also occurs in organic conducting polymers.



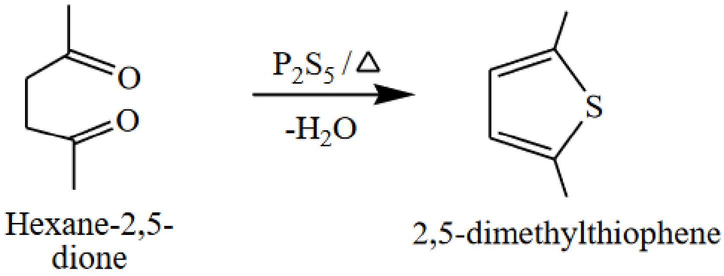
1



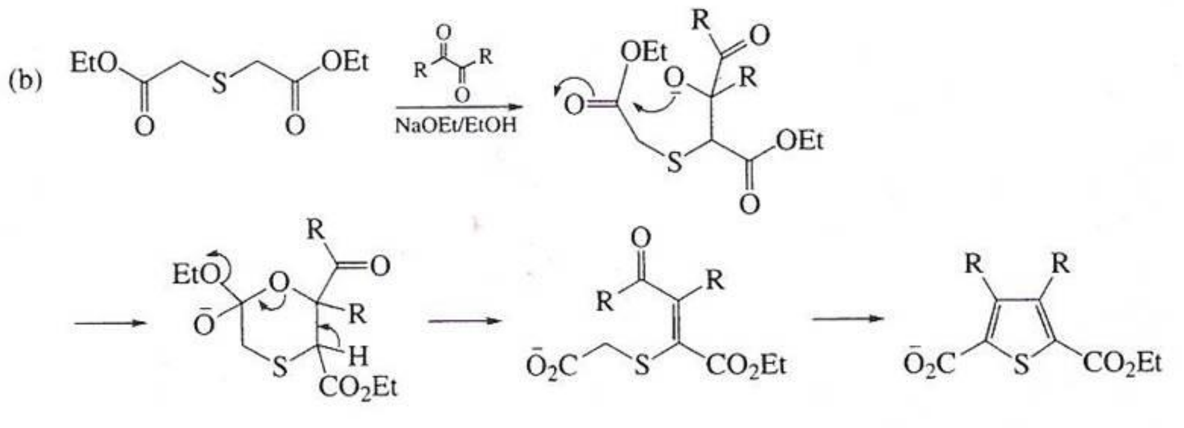
2

II-6-1 Synthesis of Thiophene

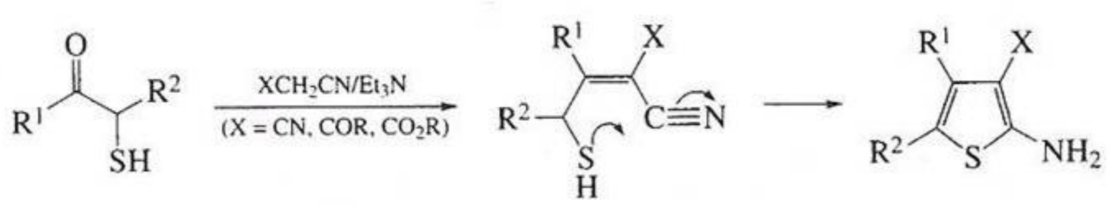
II-6-1-1 Paal Synthesis



II-6-1-2 The Hinzberg Synthesis



II-6-1-3 The Gewald Synthesis

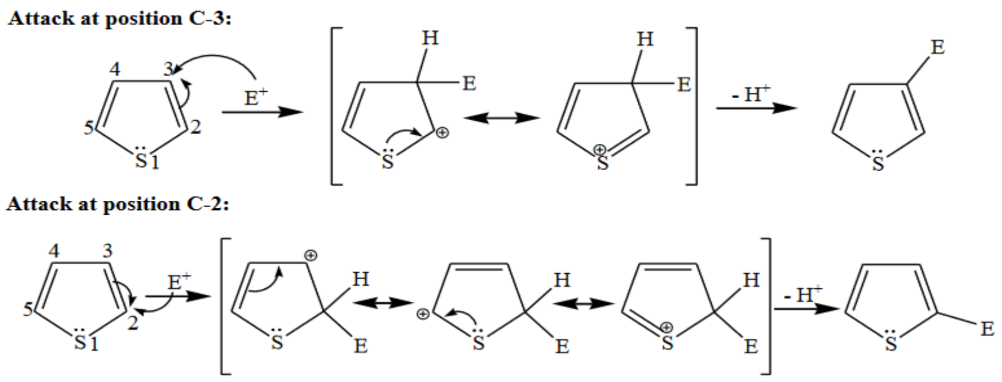


II-6-2 Properties of Thiophene

1- Physical Properties of thiophene: Thiophene is colorless liquid. Boiling point of thiophene is 357 K. It smells like benzene. It is soluble in alcohol and ether but insoluble in water.

2- Chemical Properties of thiophene: Thiophene is an aromatic compound and more reactive than benzene. Because of the aromatic nature, thiophene gives all characteristic reactions (electrophilic substitution reactions) of aromatic compounds such as halogenation, nitration, sulphonation, Friedel-Crafts reactions etc.

Similar to pyrrole and furan; thiophene also undergoes electrophilic substitution at the position C-2. Approach of the electrophile at position C-2 leads the formation of three resonating structures; however, only two resonating structures are obtained when the electrophile approaches at position C-3. Thus, the intermediate obtained by the approach of electrophile at position C-2 is more stable than the intermediate obtained by the approach of electrophile at position C-3. This is the reason that electrophilic attack occurs at position C-2. Following mechanism is suggested for the electrophilic attack at position C-2.

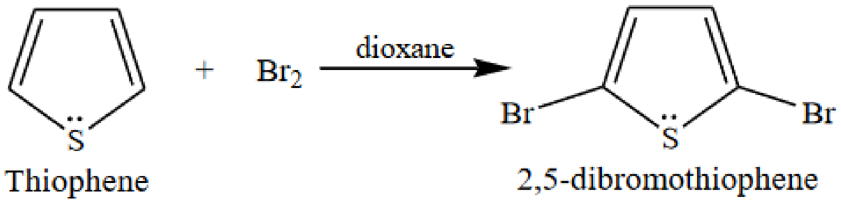


E= electrophile

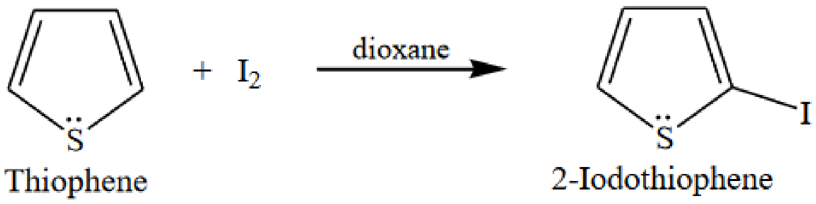
II-6-3 Reactions of Thiophene

II-6-3 1- Electrophilic Substitution Reactions of Thiophene:

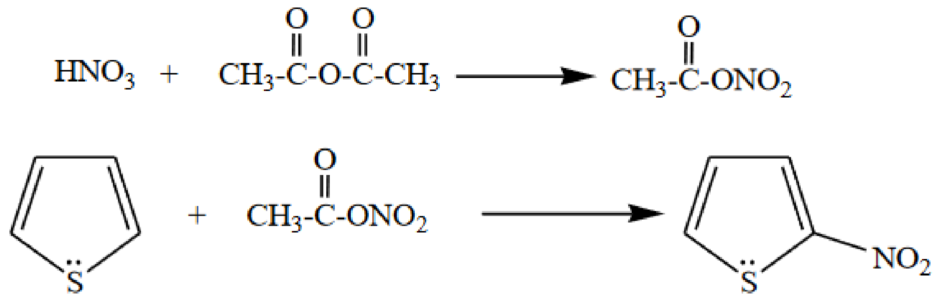
II-6-3-1-1 Halogenation: Thiophene reacts with halogens [X_2 ($X_2 = Cl_2$, Br_2 and I_2)] to give 2-halothiophene. For example, reaction of bromine with Thiophene in absence of any halogen carrier gives 2,5-dibromothiophene.



However, Iodination of thiophene in presence of yellow mercuric oxide gives 2-iodothiophene.



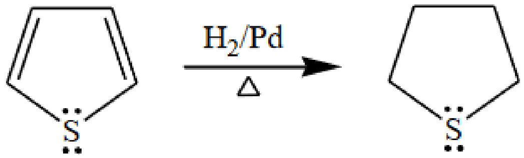
II-6-3-1-2 Nitration: 2-Nitrothiophene is obtained when nitration of thiophene is performed by reacting it with fuming HNO_3 in acetic anhydride. The reaction of HNO_3 and acetic anhydride resulted acetyl nitrate in which $–NO_2$ acts as an electrophile.



$$HNO_3 + CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH_3 \longrightarrow CH_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}ONO_2$$

Thiophene 2-nitrothiophene

II-6-3-1-3 Friedel-Crafts Acylation: Reaction of thiophene with acetic anhydride in presence of H_3PO_4 gives 2-acetylthiophene.



Thiophene Tetrahydrothiophene

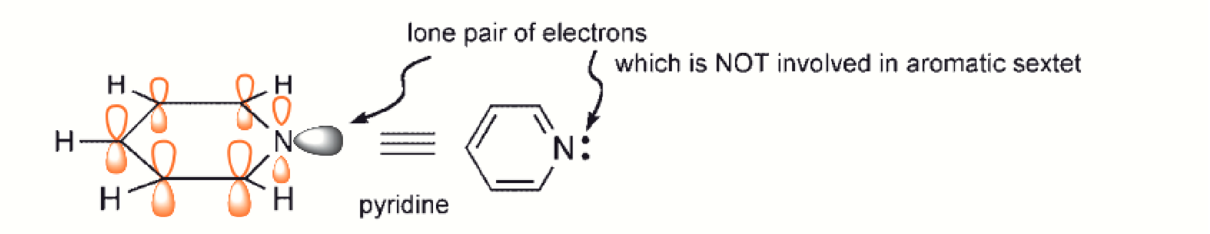
Chapter 3 Synthesis and reactivity of 6-membered rings

III-1 Structure of Six - Membered Heteroaromatic Systems

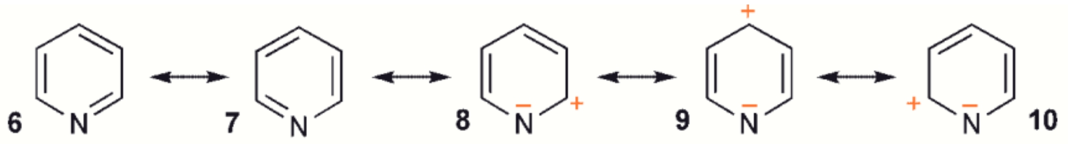
Six-membered aromatic heterocycles play a fundamental role in organic chemistry due to their exceptional chemical stability and wide-ranging applications in pharmaceuticals, agrochemicals, and materials science. Their aromatic nature, resulting from delocalized π-electrons, combined with the presence of one or more heteroatoms such as nitrogen, oxygen, or sulfur, imparts unique electronic properties that influence both their synthesis and reactivity. These heterocycles, including pyridine, pyrimidine, pyrazine, and others, serve as essential building blocks in the design of bioactive molecules and functional materials. This chapter explores the main synthetic strategies used to construct these compounds, including classical and modern approaches, and examines their characteristic chemical reactivity, which is closely linked to the electronic influence of the heteroatoms within the aromatic system.

III-1-1 Structure of Pyridine

The structure of pyridine is completely analogous to that of benzene, being related by replacement of CH by N. The key differences are: (i) the departure from perfectly regular hexagonal geometry caused by the presence of the heteroatom, in particular the shorter carbon – nitrogen bonds, (ii) the replacement of a hydrogen in the plane of the ring with an unshared electron pair, likewise in the plane of the ring, located in an sp2 hybrid orbital and not at all involved in the aromatic π- electron sextet; it is this nitrogen lone pair which is responsible for the basic properties of pyridines, and (iii) a strong permanent dipole, traceable to the greater electronegativity of nitrogen compared with carbon.



It is important to realise that the electronegative nitrogen causes inductive polarisation, mainly in the σ- bond framework, and additionally stabilises those polarised mesomeric contributors in which nitrogen is negatively charged – **8**, **9**, and **10** – which, together with contributors **6** and **7**, which are strictly analogous to the Kekulé contributors to benzene, represent pyridine. The polarised contributors also imply a permanent polarisation of the π- electron system.

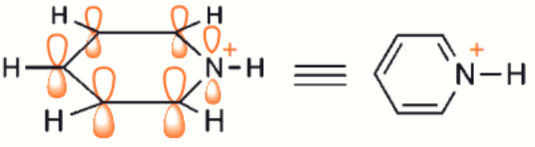


Structure of pyridine; resonance contributors (mesomeric structures)

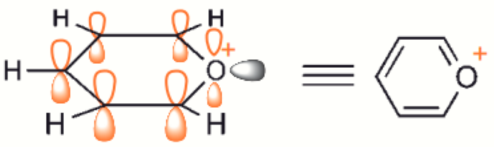
The polarisations resulting from inductive and mesomeric effects are in the same direction in pyridine, resulting in a permanent dipole towards the nitrogen atom. This also means that there are fractional positive charges on the carbons of the ring, located mainly on the α- and γ-positions. It is because of this general electron - deficiency at carbon that pyridine and similar heterocycles are referred to as 'electron - poor', or sometimes 'π- deficient'. A comparison with the dipole moment of piperidine, which is due wholly to the induced polarisation of the σ-skeleton, gives an idea of the additional polarisation associated with distortion of the π- electron system.

III-1-2 Structure of Pyridinium and Related Cations

Electrophilic addition to the pyridine nitrogen generates pyridinium ions, the simplest being 1*H*- pyridinium formed by addition of a proton. 1*H*- Pyridinium is actually isoelectronic with benzene, the only difference being the nuclear charge of nitrogen, which makes the system, as a whole, positively charged. Thus pyridinium cations are still aromatic, the diagram making clear that the system of six p orbitals required to generate the aromatic molecular orbitals is still present, though the formal positive charge on the nitrogen atom severely distorts the π- system, making the α- and γ- carbons in these cations carry fractional positive charges which are higher than in pyridine, the consquence being increased reactivity towards nucleophiles. Electron density at the pyridinium β- carbons is also reduced relative to these carbons in pyridines.

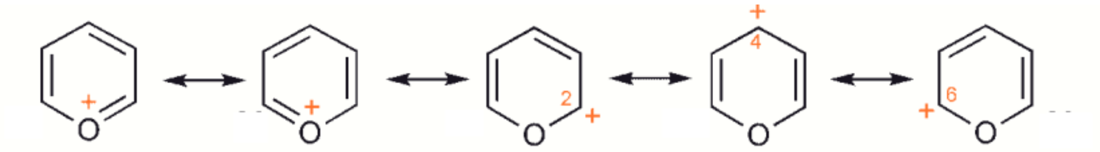


1*H*-pyridinium cation



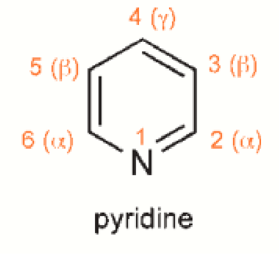
pyrylium cation

In the pyrylium cation, the positively charged oxygen also has an unshared electron pair, in an sp2 orbital in the plane of the ring, exactly as in pyridine. Once again, a set of resonance contributors, makes clear that this ion is strongly positively charged at the 2 -, 4 - and 6 - positions; in fact, because the more electronegative oxygen tolerates positive charge much less well than nitrogen, the pyrylium cation is certainly a less stabilised system than a pyridinium cation.



Structure of pyrylium cation; resonance contributors (mesomeric structures)

Pyridine

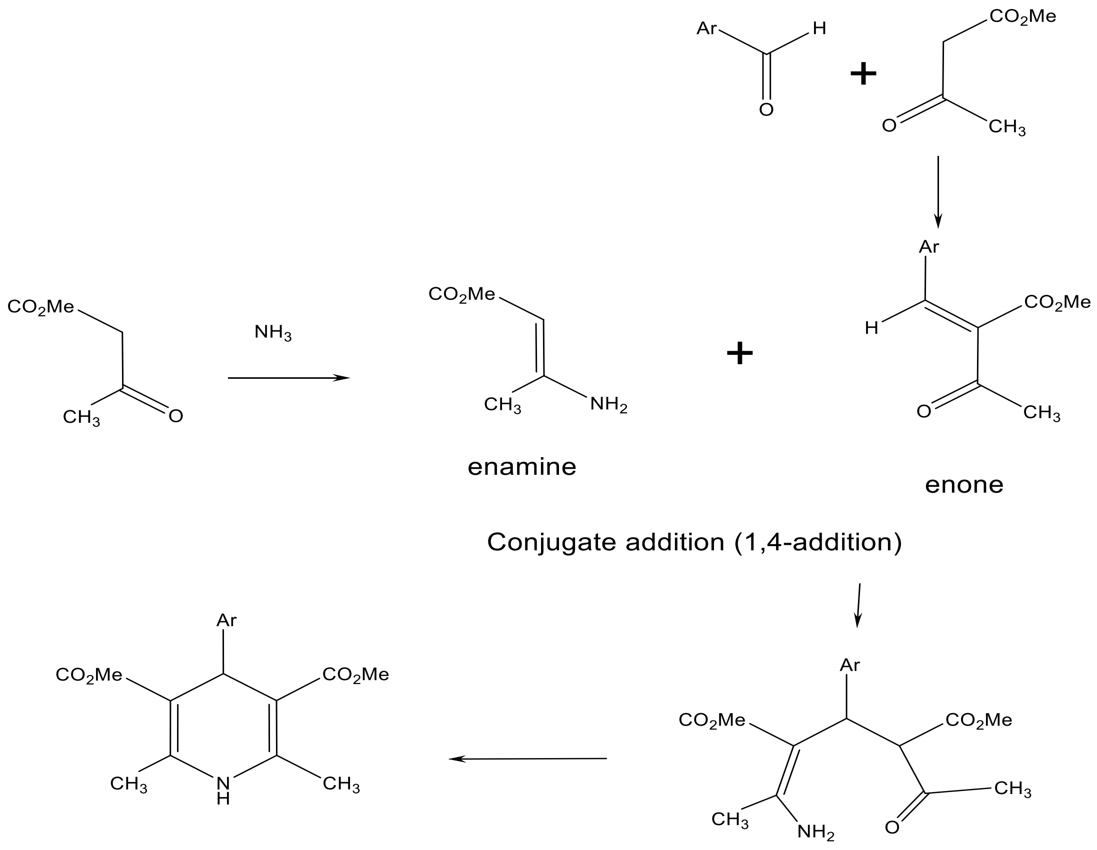


Pyridine and its simple derivatives are stable and relatively unreactive liquids, with strong penetrating odours that are unpleasant to some people. They are much used as solvents and bases, especially pyridine itself, in reactions such as *N*- and *O*- acylation and - tosylation. Pyridine and the three monomethyl pyridines (picolines) are completely miscible with water. Pyridine was first isolated, like pyrrole, from bone pyrolysates: the name is constructed from the Greek for fire, ‘pyr, and the suffix ‘idine’, which was at the time being used for all aromatic bases – phenetidine, toluidine, etc. Pyridine and its simple alkyl derivatives were for a long time produced by isolation from coal tar, in which they occur in quantity. In recent years this source has been displaced by synthetic processes: pyridine itself, for example, can be produced on a commercial scale in 60 – 70% yields by the gas -phase high - temperature interaction of crotonaldehyde, formaldehyde, steam, air and ammonia over a silica – alumina catalyst. Processes for the manufacture of alkyl - pyridines involve reaction of acetylenes and nitriles over a cobalt catalyst.

III-2 Synthesis of pyridine

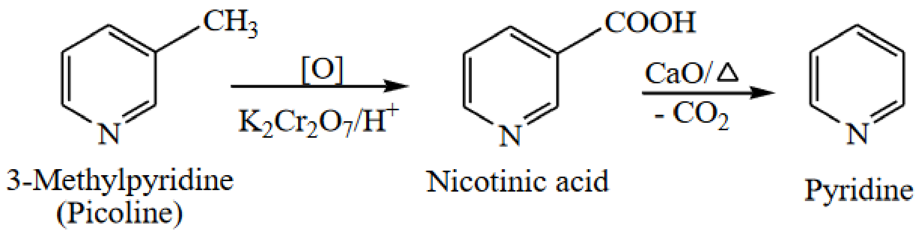
III-2-1- The Hantzsch Synthesis

The Hantzsch synthesis is a reaction involving an aldehyde, such as formaldehyde, with two equivalents of a β-keto ester, such as ethyl acetoacetate, and a nitrogen donor such as ammonia or ammonium acetate. This reaction leads to the formation of a dihydropyridine, which, upon oxidation (using HNO_3, Ce(IV), or a quinone), yields a symmetrically substituted pyridine. The reaction is typically carried out in water or ethanol as solvent, at a pH of around 8.5, which is maintained by the presence of ammonia.



III-2-2- From Picoline:

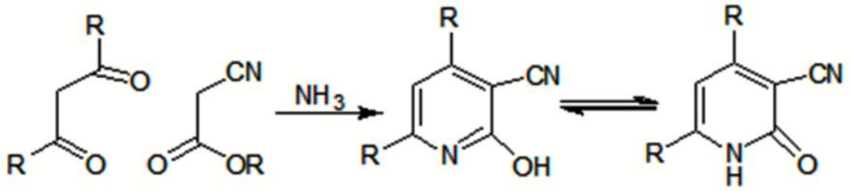
Beta-picoline on oxidation with potassium dichromate and sulphuric acid gives nicotinic acid, which on decarboxylation with calcium oxide gives pyridine.



III-2-3 Guareschi-Thorpe Synthesis

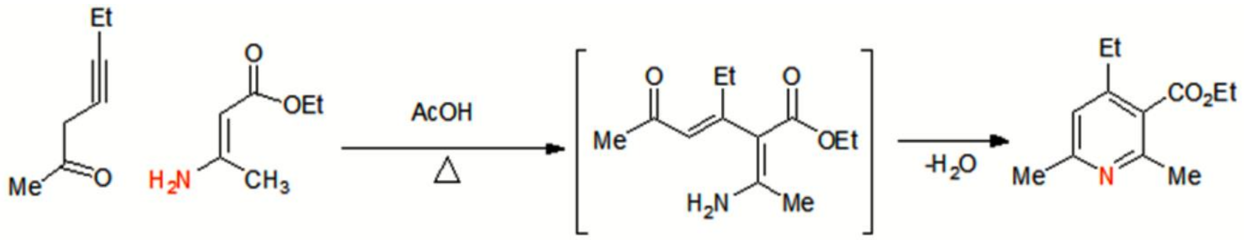
(From 1,3-dicarbonyl Compounds)

The general reaction is as follows:

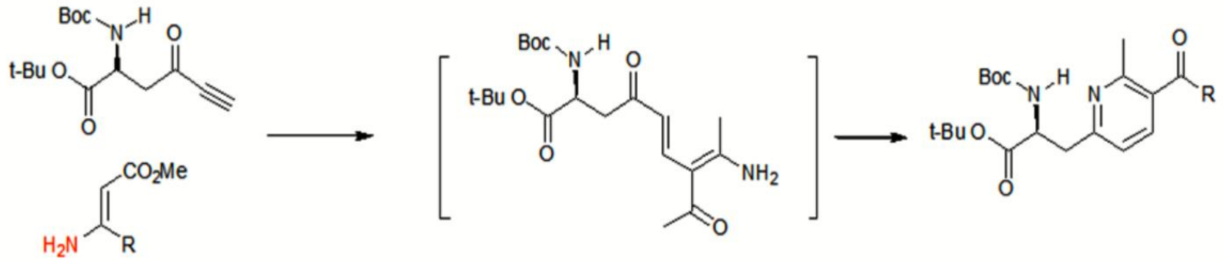


III-2-4 Bohlmann-Rahtz synthesis

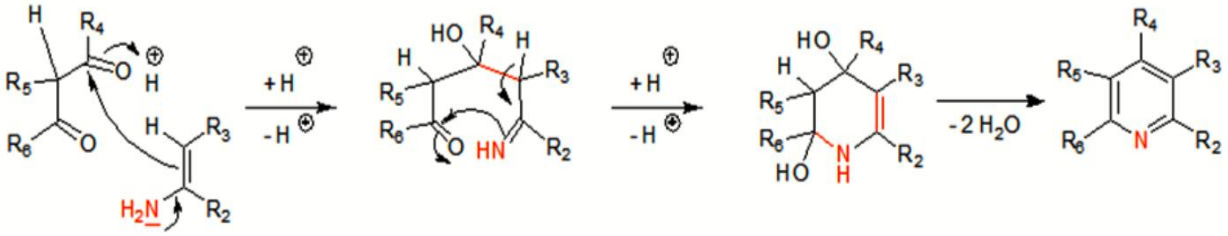
In 1957, Bohlmann and Rahtz reported the preparation of 2,3,6-trisubstituted pyridines. The reaction mechanism is based on a Michael addition between an acetylenic ketone and an enamine, leading to the formation of a γ-aminoketone (which can be isolated). This intermediate is then heated to a temperature above 120 °C to promote cyclodehydration, thereby yielding the pyridine.



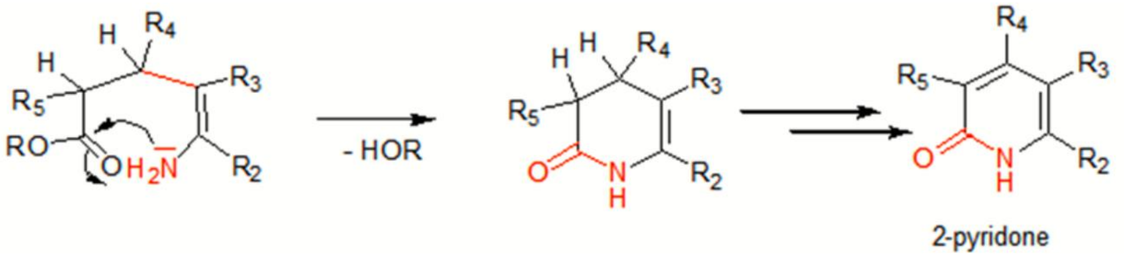
Recently, this synthesis has attracted considerable attention. Baldwin was able to synthesize α-amino acids substituted with heterocycles using this method. The alkynyl ketone adds to the 3-aminocrotonate ester to give the Michael product. Thermolysis then leads to pyridyl-β-alanine.



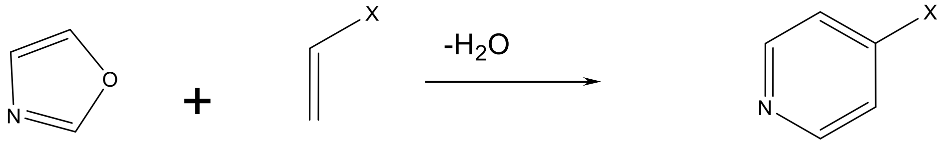
In general, Baldwin's synthesis follows the protocol of a reaction between a 1,3-dicarbonyl compound and an enamine.

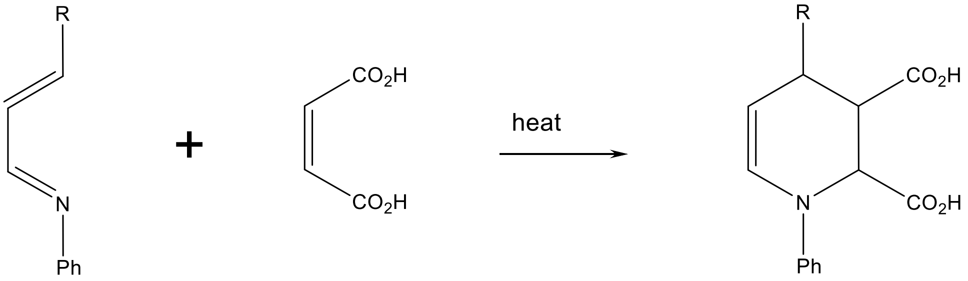


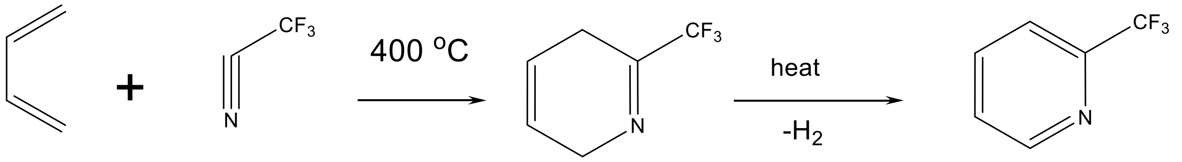
If R_6 = OR, the product obtained is a 2-pyridone.

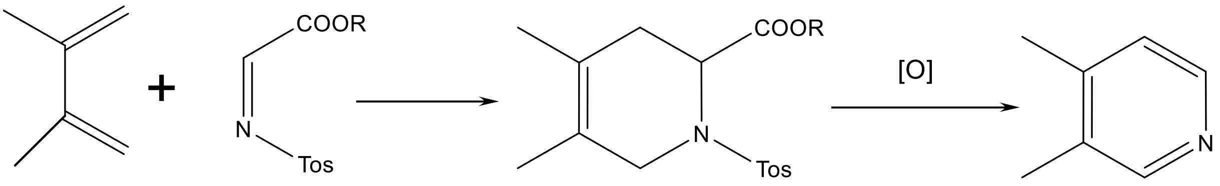


III-2-5 Diels–Alder Reaction







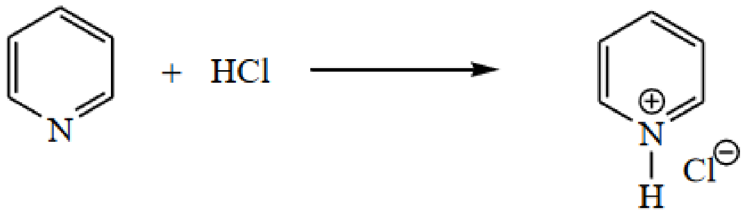


III-3 Properties of Pyridine

III-3-1- Physical Properties of Pyridine: Pyridine is a colour less liquid. Its boiling point is 115.5° C. It has a characteristic unpleasant odor. It is soluble in water and most organic solvents.

III-3-2- Chemical properties of Pyridine: Chemical properties of pyridine are discussed as follow:

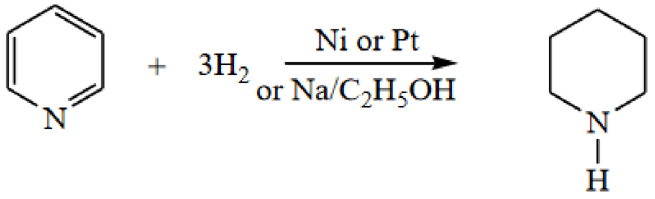
2-a. Basic character of pyridine: Pyridine is basic in nature. Its pKb is 8.75. It reacts with strong acids to form salts.



Pyridine Pyridinium Chloride

The basic nature of pyridine is due to the freely available lone pair of electrons in sp2 hybridized orbital pyridine, which does not participate in the formation of delocalized π -molecular orbital.

2-b. Reduction: Under catalytic hydrogenation of pyridine hexahydropyridine is formed. It is also known as Piperidine.

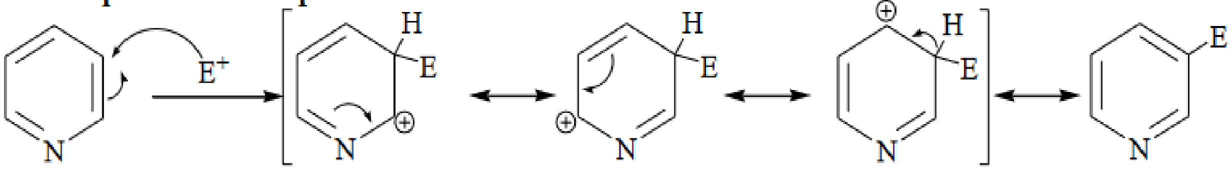


Pyridine Piperidine

3- Electrophilic Substitution

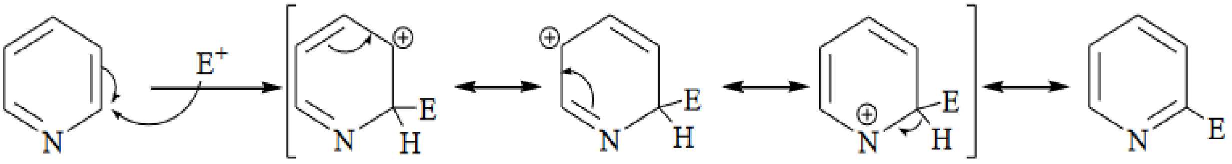
Pyridine is million times less reactive than benzene. **Nitration (less than 5%, Chlorination in moderate yield, Bromination in a good yield).** 3-position is usually attacked preferably.

Electrophilic attack at position C-3



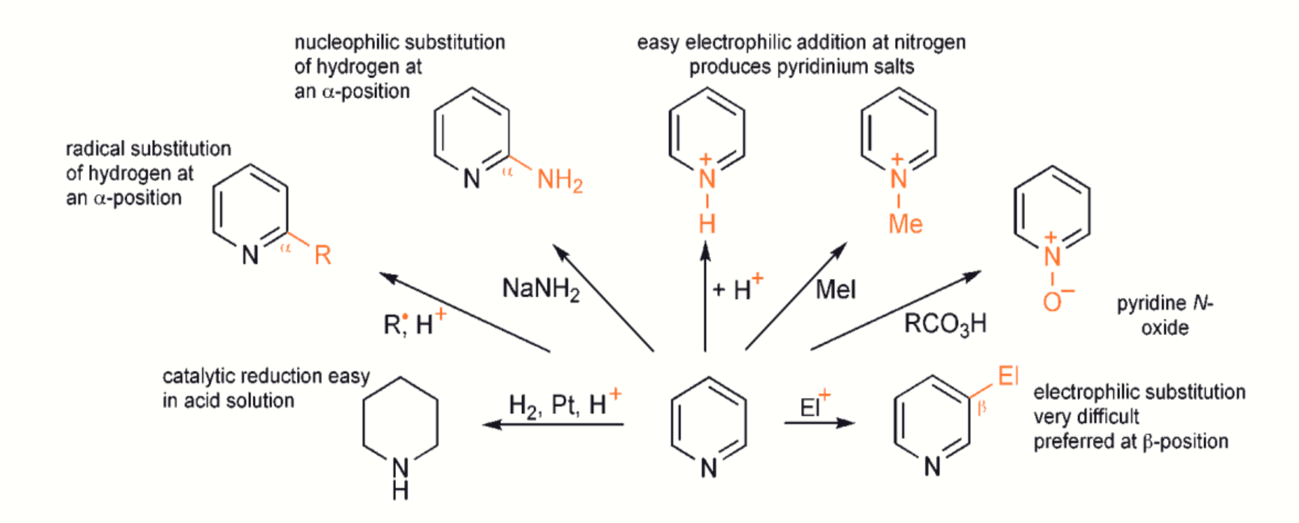
I II III

Electrophilic attack at position C-2



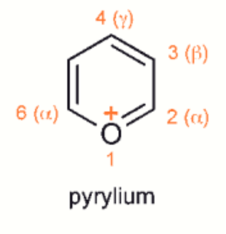
IV V VI

III-3-3- Typical reaction of pyridine

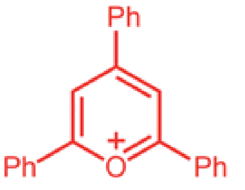


Typical reactions of pyridine

Pyrylium



Pyrylium salts are a type of six-membered cationic heterocycles with one positively charged oxygen atom. Compounds with pyrylium salts exhibit excellent absorption,fluorescence, and electron transfer properties, and thus have been widely applied as light emitters, photocatalysts, and sensitizers. pyrylium salts were widely employed for the convenient synthesis of diverse heterocyclic compounds.

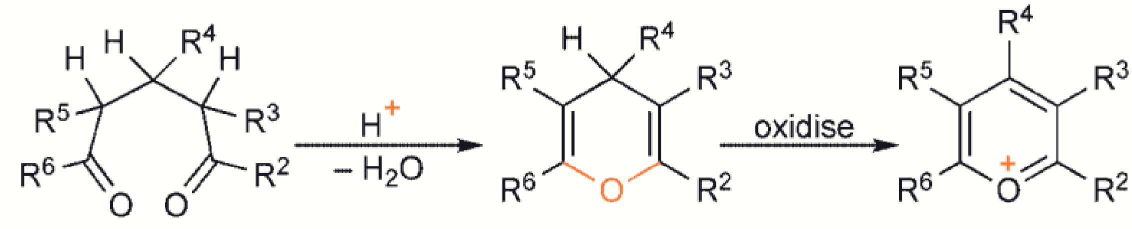


Pyrylium salt

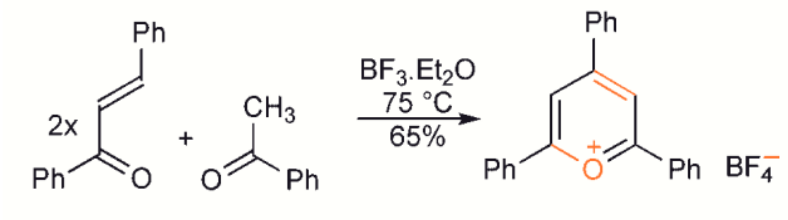
III-4 Synthesis of pyrylium

III-4-1- From 1,5-dicarbonyl compounds

These compounds are obtained by cyclization of 1,5-dicarbonyl compounds followed by oxidation.

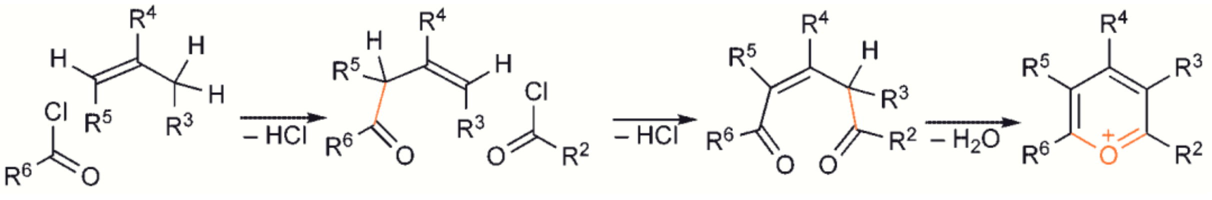


Mono - enolisation of a 1,5 - diketone, then the formation of a cyclic hemiacetal, and its dehydration, produces 4*H*- pyrans, which require only hydride abstraction to arrive at the pyrylium oxidation level. The diketones are often prepared *in situ* by the reaction of an aldehyde with two moles of a ketone (compare Hantzsch synthesis) or of a ketone with a previously prepared conjugated ketone – a chalcone in the case of aromatic ketones/aldehydes. It is the excess chalcone that serves as the hydride acceptor in this approach.



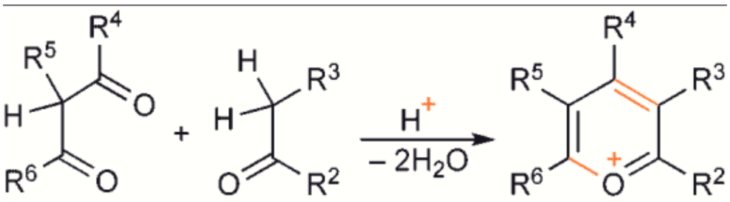
III-4- 2- Alkene acylation

Alkenes can be diacylated with an acid chloride or anhydride, generating an unsaturated 1,5 – dicarbonyl compound, which then cyclizes with loss of water.

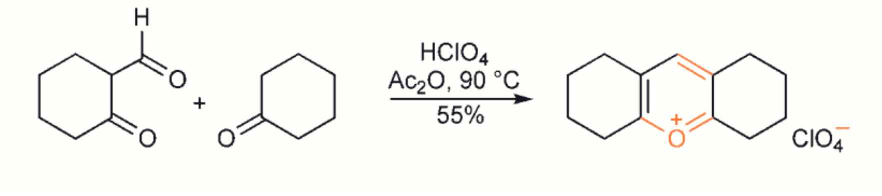


III-4-3- From 1,3-dicarbonyl compounds

The acid - catalysed condensation of a ketone with a 1,3 - dicarbonyl compound, with dehydration *in situ* produces pyrylium salts.

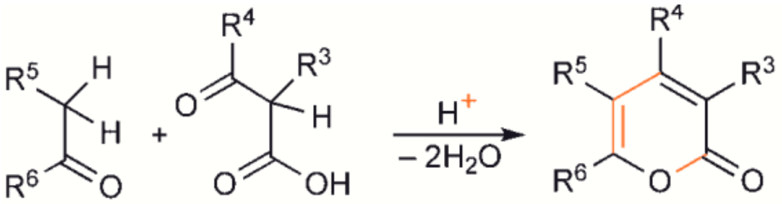


Aldol condensation between a 1,3 - dicarbonyl component and a ketone with an α- methylene, under acidic, dehydrating conditions, produces pyrylium salts. It is likely that the initial condensation is followed by a dehydration before the cyclic hemiacetal formation and loss of a second water molecule. The use of the bis - acetal of malondialdehyde, as a synthon for malondialdehyde, is one of the few ways available for preparing α- unsubstituted pyryliums



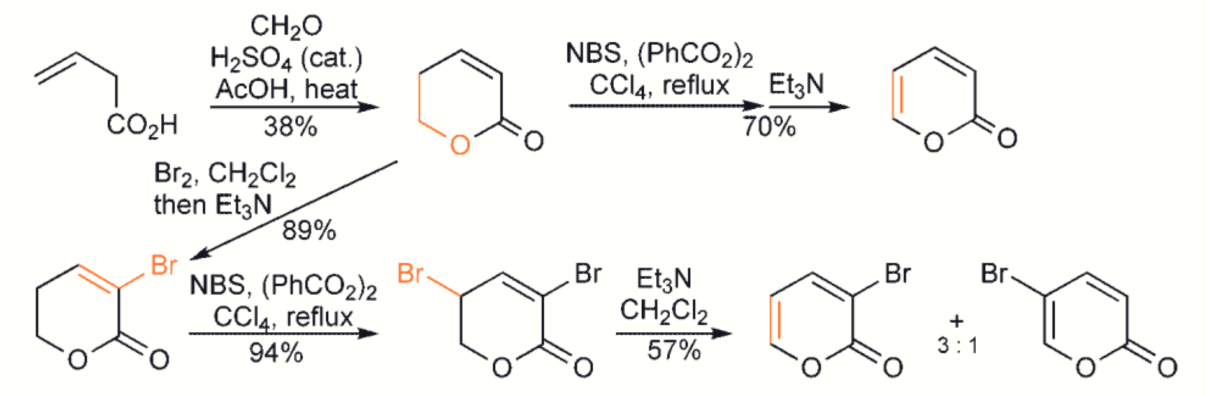
III-5- Synthesis of 4-pyrones

The classical general method for constructing 2 - pyrones is that based on the cyclising condensation of a 1,3 - keto(aldehydo) - acid with a second component that provides the other two ring carbons.



III-5- 1 Other Methods

2 - Pyrone itself can be prepared *via* Prin's alkylation of but - 3 - enoic acid with subsequent lactonisation, giving 5,6 - dihydro - 2 - pyrone, which, *via* allylic bromination and then dehydrobromination, is converted into 2 - pyrone. Alternative manipulation of the dihydropyrone affords a convenient synthesis of a separable mixture of the important 3 - and 5 - bromo - 2 – pyrones.

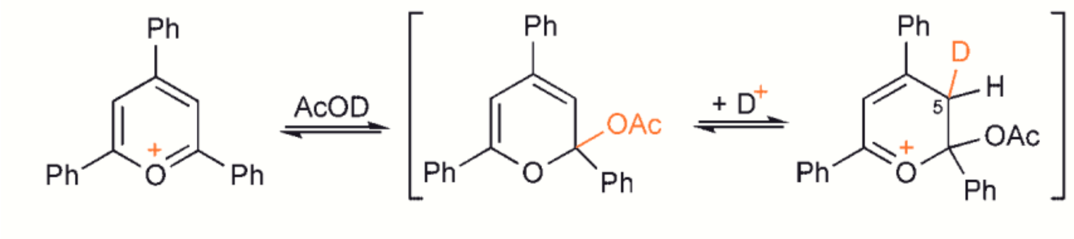


III-6 - Reactions of Pyrylium Cations

III-6-1 Reactions with Electrophilic Reagents

1- Proton Exchange

2,4,6 - Triphenylpyrylium undergoes exchange at the 3 - and 5 - positions in hot deuterioacetic acid, but the process probably involves, not protonation of the pyrylium cation, but formation of an equilibrium concentration of an addict, with acetate added to C - 2, allowing enol ether protonation and thus exchange.

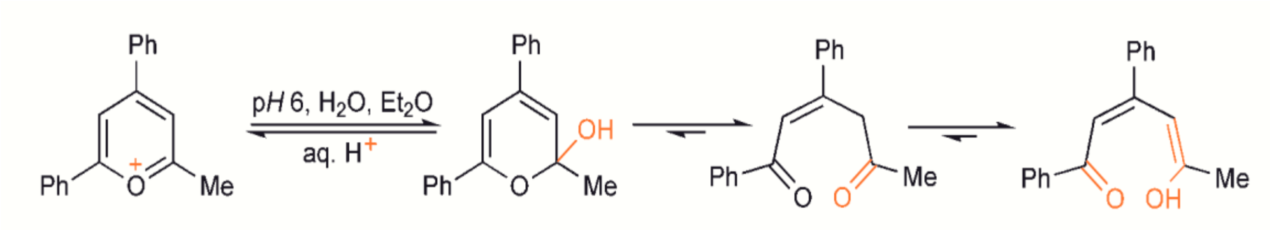


III-6-2 Addition Reactions with Nucleophilic Reagents

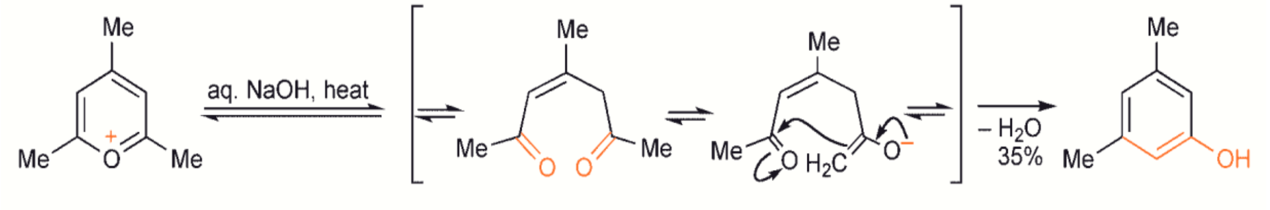
Pyrylium salts usually add nucleophiles at a carbon adjacent to the oxygen, and such reactions are analogous with those of *O*- protonated carbonyl compounds.

1- Water and Hydroxide Ion

The degree of susceptibility of pyrylium salts to nucleophilic attack varies widely: pyrylium cation itself is even attacked by water at 0 ° C, whereas 2,4,6 - trimethylpyrylium is stable in water at 100 ° C. Hydroxide anion, however, adds very readily to C - 2 in all cases. The reaction of 2 - methyl - 4,6 - diphenylpyrylium is typical:8 the immediate 2 - hydroxy - 2*H*- pyran, which is a cyclic enol hemiacetal, is in equilibrium with a dominant concentration of the acyclic tautomer, reached probably *via* a proton - catalysed process, since methoxide adducts remain cyclic.9 Treatment of such acyclic unsaturated diketones with acid regenerates the original pyrylium salt

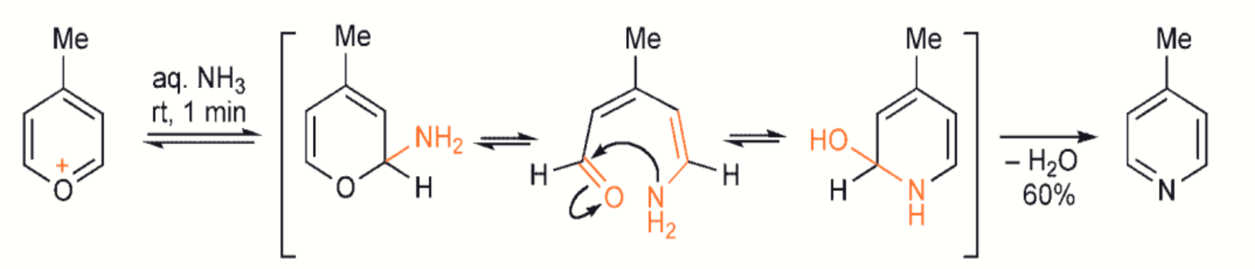


With pyryliums carrying α- alkyl groups, more vigorous alkaline treatment leads to an alternative closure, producing arenes, for example reaction of 2,4,6 - trimethylpyrylium with warm alkali causes a subsequent cyclising aldol condensation of the acyclic intermediate to give 3,5 - dimethylphenol.



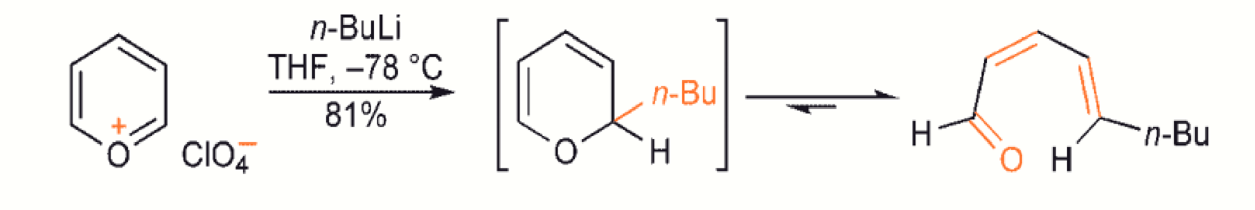
2- Ammonia and Primary and Secondary Amines

Ammonia and primary amines react with pyrylium salts to give pyridines and *N*- alkyl - or *N*-aryl – pyridinium salts, respectively.11 The transformation represents a good method for preparing the nitrogen heterocycles, providing the pyrylium salt can be accessed in the first place. The initial adduct exists as one of a number of ring - opened tautomeric possibilities,12 depending upon conditions; it is probably an amino - dienone that recloses to give the nitrogen heterocycle.



3 Organometallic Addition

Organometallic addition takes place at an α- position, or occasionally at C - 4 when the α-positions are substituted and C - 4 is unsubstituted15 or when organocuprates are used.16 The initial 2*H*- pyrans undergo electrocyclic ring opening (and more rapidly than the comparable cyclohexadiene/hexatriene transformation17) affording dienones or dienals with retention of geometrical integrity.



Chapter 4 Synthesis and reactivity of fused heterocyclic rings (indole, quinoline, isoquiniline; etc.)

IV-1 Introduction

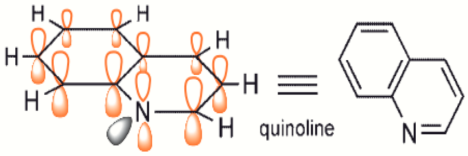
Fused heterocyclic compounds, particularly those containing nitrogen atoms such as indole, quinoline, and isoquinoline, represent a cornerstone of heterocyclic chemistry due to their widespread occurrence in natural products, pharmaceuticals, and materials science. These structures, composed of two or more rings sharing common atoms, often exhibit enhanced electronic conjugation and unique reactivity profiles, making them valuable scaffolds in medicinal chemistry and synthetic organic chemistry.

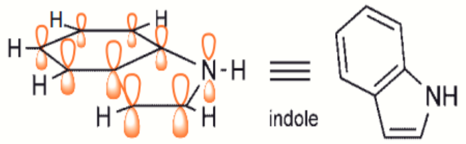
The indole nucleus, found in the amino acid tryptophan and numerous alkaloids, is notable for its biological activity and ease of functionalization. Quinoline and isoquinoline systems are similarly prominent, serving as frameworks for antimalarial, anticancer, and antimicrobial agents. Their fused ring nature endows them with significant rigidity and electronic properties that influence their chemical reactivity and interactions with biological targets.

This chapter provides a comprehensive overview of the synthetic strategies employed to construct these fused heterocycles, including classical methods such as the Fischer indole synthesis and Skraup synthesis, as well as modern catalytic and multicomponent approaches. Additionally, the chapter explores the reactivity patterns typical of these systems, including electrophilic substitution, metal-catalyzed coupling reactions, and nucleophilic additions, with emphasis on structure–reactivity relationships and synthetic utility.

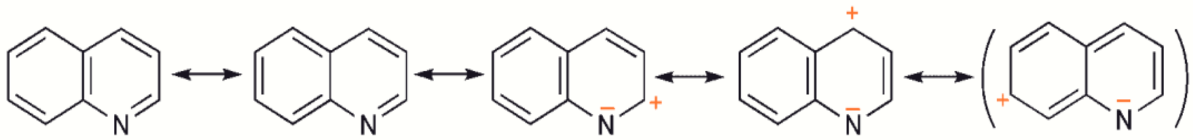
IV-2 Structures of Bicyclic Heteroaromatic Compounds

Once the concepts of the structures of benzene, naphthalene, pyridine and pyrrole, as prototypes, have been assimilated, it is straightforward to extrapolate to those systems which combine two (or more) of these types, thus quinoline is like naphthalene, only with one of the rings a pyridine, and indole is like pyrrole, but with a benzene ring attached.

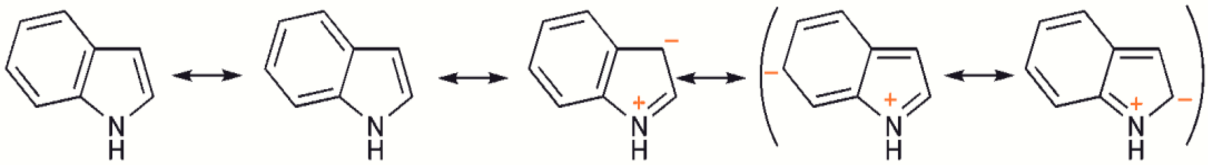




Resonance representations must take account of the pattern established for benzene and the relevant heterocycle. Contributors in which both aromatic rings are disrupted make a very much smaller contribution and are shown in parentheses.

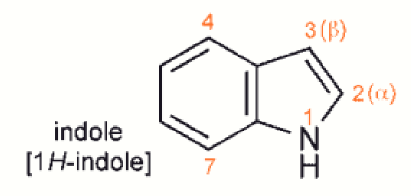


Structure of quinoline; resonance contributors (mesomeric structures)



Structure of indole; resonance contributors (mesomeric structures)

Indole



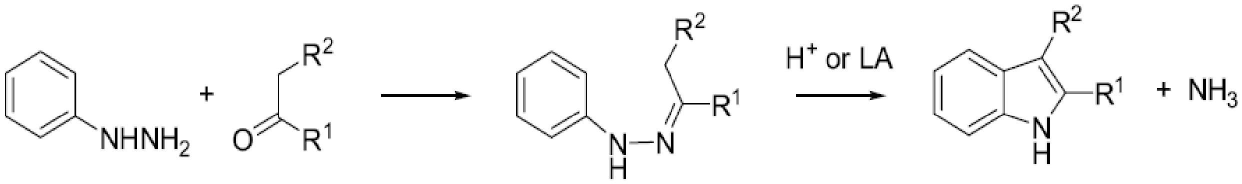
Indole is an aromatic heterocyclic organic compound with formula C_8H_7N. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five membered nitrogen containing pyrrole ring. Chemistry of Indole was developed with the study of the dye indigo. Indigo can be converted to Isatin and then to Oxindole. Indole was first synthesized in 1866, when Adolf von Baeyer reduced Oxindole to Indole using zinc dust. The name Indole is a combined name of the words indigo and oleum, since Indole was first isolated by treatment of the indigo dye with oleum.

Indole is widely distributed in the natural environment and can be produced by a variety of bacteria. As an intercellular signal molecule, it regulates various aspects of bacterial physiology.

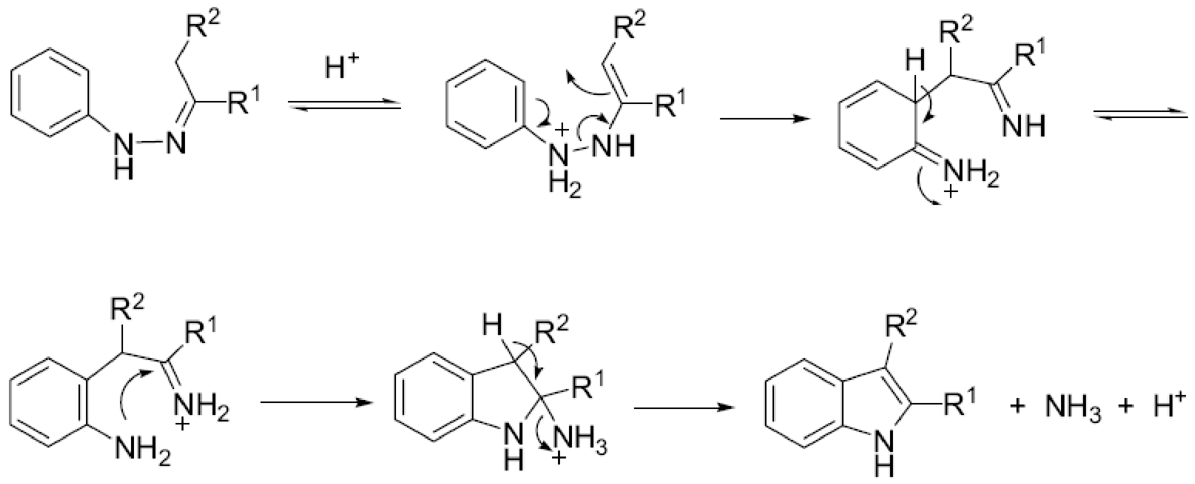
IV-3 Synthesis of Indole

IV-3-1The Fisher-Indole synthesis

The Fischer indole synthesis is a reaction discovered by Hermann Emil Fischer (Nobel Prize in 1902). The Fischer indole synthesis involves the addition of phenylhydrazine to a ketone or aldehyde under acidic conditions.
It is one of the oldest methods for the synthesis of substituted indoles. Although this method is not ideal for preparing unsubstituted indole, it is commonly used to produce indole derivatives substituted at positions 2 and/or 3, particularly in the synthesis of antimigraine drugs of the triptan class.

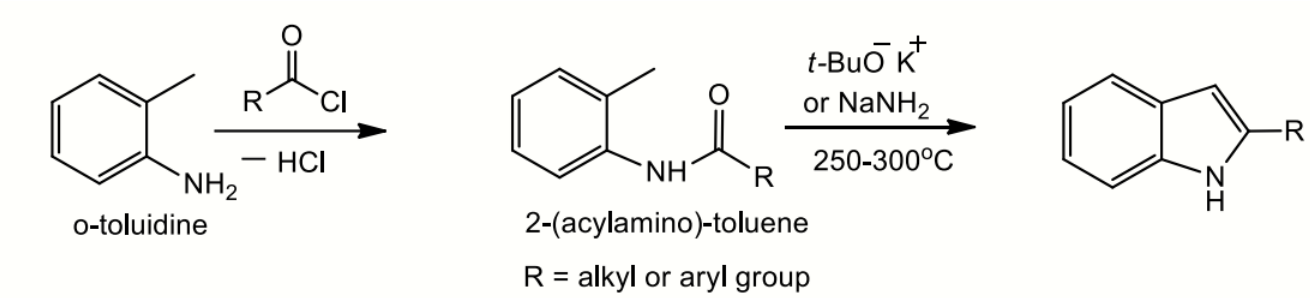


Mechanism



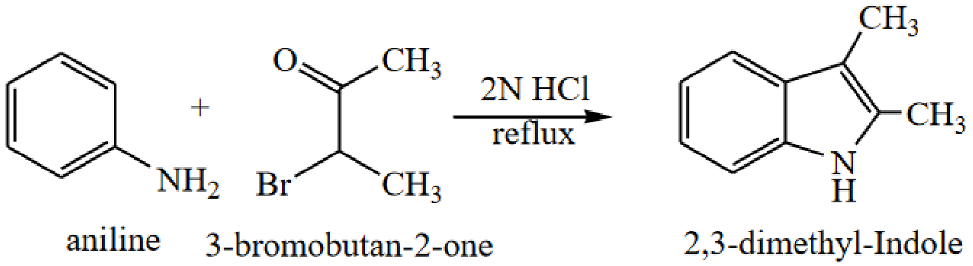
IV-3-2 Madelung Synthesis:

The base-catalyzed cyclization of 2-(acylamino) toluenes typically requires very harsh conditions, such as treatment with sodium amide or potassium tert-butoxide at temperatures ranging from 250 to 300 °C. This method is generally limited to the synthesis of simple indoles, like 2-methylindole, and is unsuitable for substrates containing sensitive functional groups.

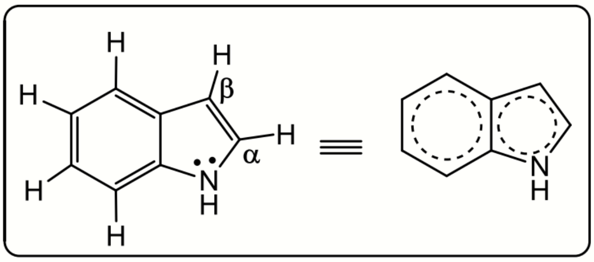


IV-3-3 The Bischler's synthesis

This method involves the reaction of an aryl amine and α - halooketone or α-haloaldehyde in presence of zinc chloride under thermal or heating condition. The reaction is shown as follow.



IV-4 Reactions of Indole

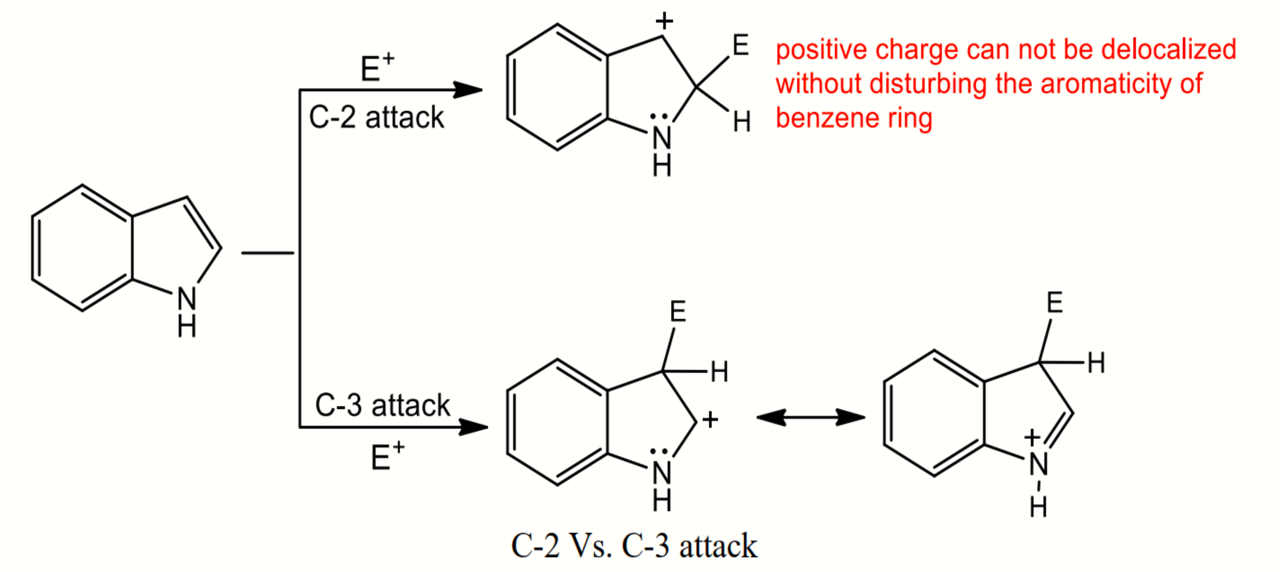


The fusion of a benzene ring to the 2,3-positions of a pyrrole ring gives rise to one of the most significant heterocyclic frameworks in organic chemistry: the indole ring system.

- **Aromaticity**: Indole is a planar, aromatic molecule that complies with Hückel's rule (4n+2) πelectrons. All atoms within the structure are sp^2 hybridized, each contributing a p-orbital that overlaps to form a delocalized π-system containing 10 electrons—eight from the carbon atoms and two from the nitrogen lone pair.
- **Resonance**: The indole structure is best described as a resonance hybrid of several canonical forms.
- **Reactivity**: Being a π-excessive, electron-rich heterocycle, indole primarily undergoes electrophilic substitution reactions.
- **Comparative Reactivity**: Despite its electron-rich character, indole is significantly less reactive toward electrophiles than monocyclic heterocycles such as pyrrole or furan.

IV-4-1 Electrophilic Substitution Reactions

The pyrrole ring in indole is very electron rich, in comparison to the benzene ring, therefore, electrophile's attack always takes place in the five-membered ring, except in special circumstances.

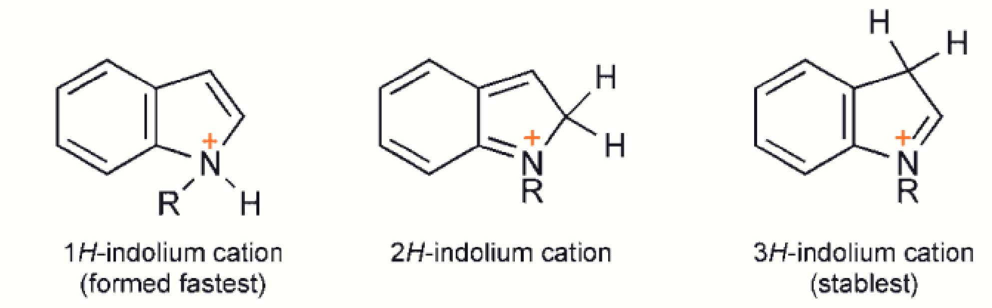


C-2 Vs. C-3 attack

The preferred site of electrophilic substitution is C-3, because the cation formed by the C-3 attack of electrophile is more stable than that of the C-2 attack. In case of C-3 attack, transition intermediate formed has positive charge adjacent to N atom that can be stabilized by the delocalization of lone pair of electrons of nitrogen. Whereas, the positive charge of transition intermediate formed by the C-2 attack, cannot be stabilized without disturbing aromaticity of benzene ring. If C-3 position is occupied, then electrophilic substitution takes place at C-2 and if both of them are occupied then electrophile attacks at C-6 position.

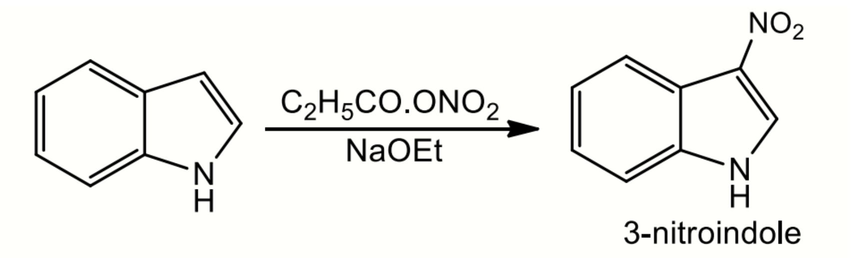
1- Protonation: Indole is a very weak base pKa -3.5. The nitrogen atom of indole gets easily protonated even in water (at pH = 7) giving 1*H*-indolium cation. However, thermodynamically most stable cation is formed by the protonation of C-3 rather than N.

3-protonated cation (3 *H*-indolium cation) retains full benzene aromaticity (in contrast to the 2 - protonated cation) with delocalisation of charge over the nitrogen and α carbon.

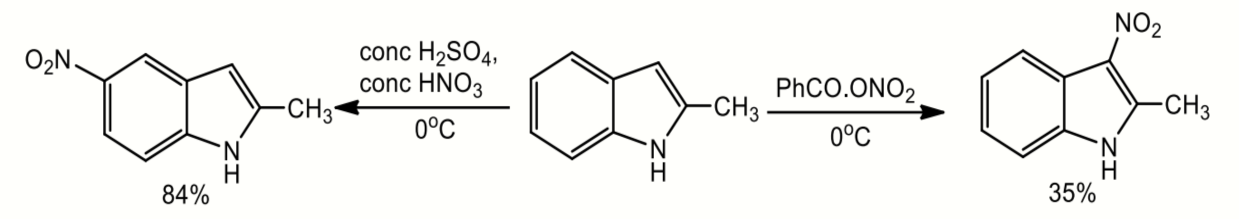


2- Nitration:

Common nitrating reagent, mixture of acids (H_2SO_4 + HNO3) leads to acid-catalysed polymerisation of indole. Therefore, nitration of indole is carried out using non-acidic nitrating agent such as benzoyl nitrate and ethyl nitrate.

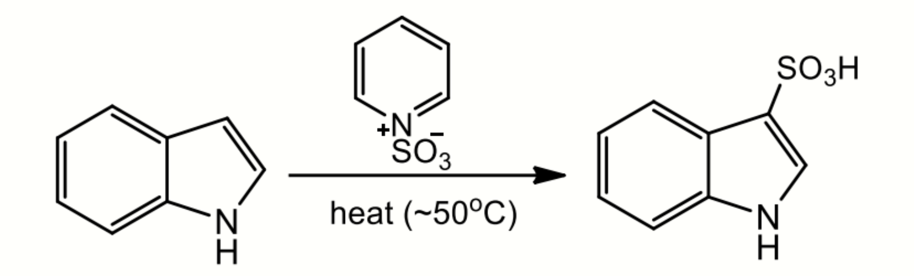


Nitration of **2-Methylindole** with benzoyl nitrate gives a 3-nitro derivative however, nitration under acidic conditions using nitric/sulfuric acids gives C-5 –NO2 substituted product.



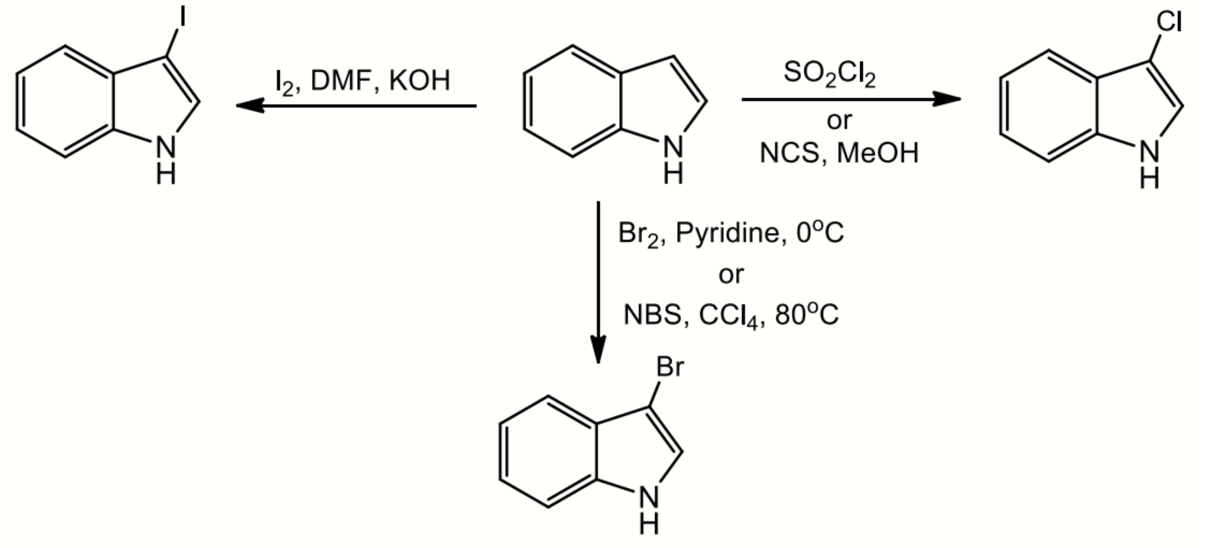
3- Sulphonation

Sulfonation of indole, at C-3, is performed using the pyridine–sulfur trioxide complex in hot pyridine.



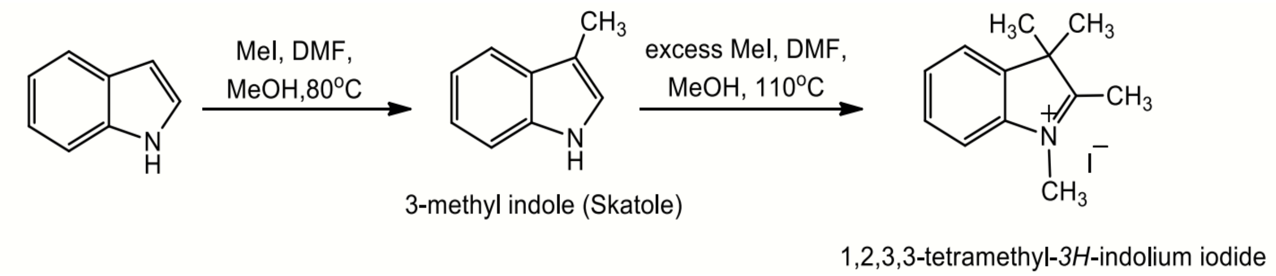
4- Halogenation

3-Halo- and 2-halo-indoles are unstable therefore, must be utilised immediately after their preparation.



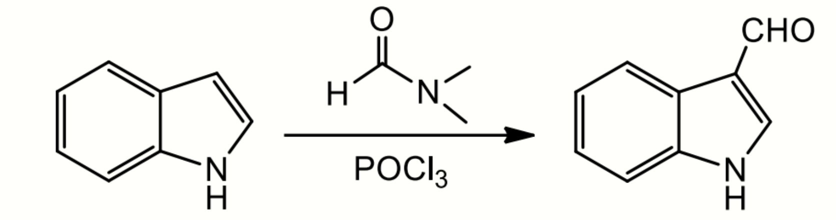
5-Alkylation

Indoles do not react with alkyl halides at room temperature. Indole itself begins to react with methyliodide in dimethylformamide at about 80°C, to give main product 3-methyl indole (skatole). As the temperature is increased, further methylation takes place resulting in 1,2,3,3-tetramethyl-3*H*-indolium iodide.

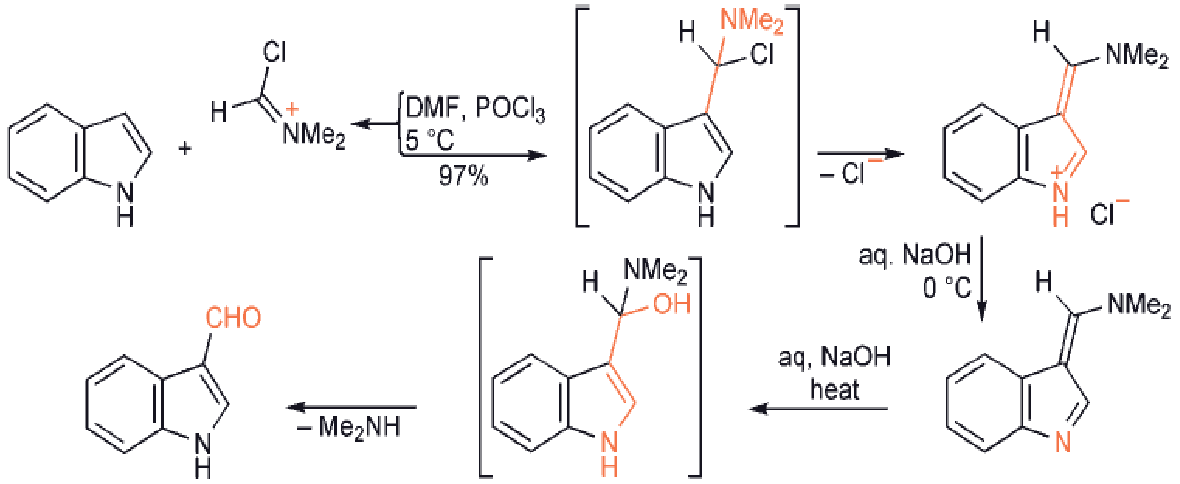


6- The Vilsmeier Haack reaction

The Vilsmeier reaction is a very efficient method for the formylation of electron rich aromatic rings by the use of acid chloride (POCl3) and DMF. Indoles can be readily formylated to 3-formyl-indoles via Vilsmeier reaction. Even indoles carrying an electron-withdrawing group at the 2-position, for example ethyl indole-2-carboxylate, undergo smooth Vilsmeier 3-formylation.



Mechanism



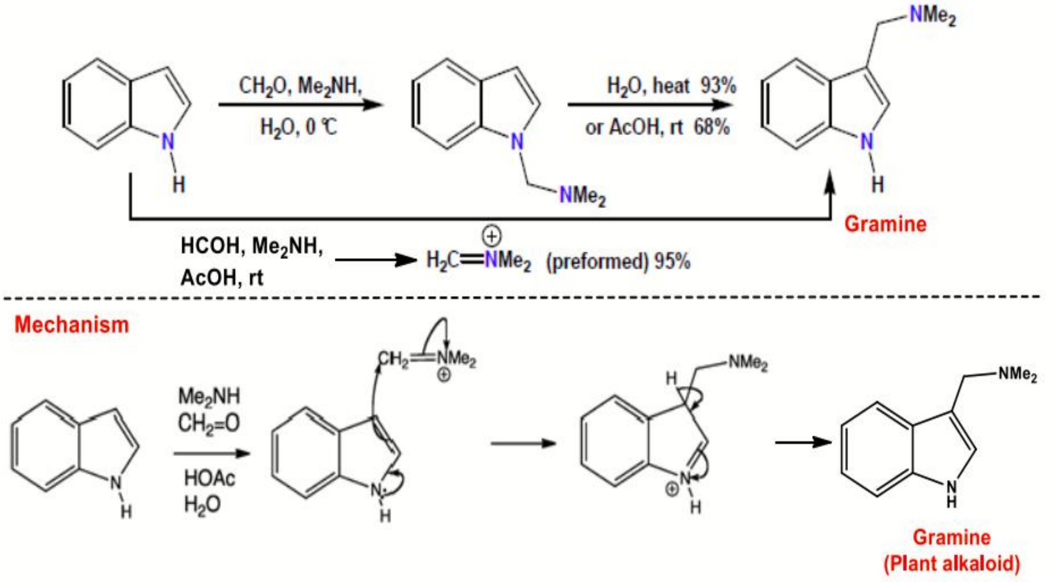
7- Reactions with Iminium Ions: Mannich Reactions

Indole reacts with a mixture of formaldehyde and dimethylamine at 0 °C under neutral conditions to form N-substituted dimethylaminomethyl indole.

- At elevated temperatures or in acidic media such as acetic acid, this intermediate undergoes rearrangement into the thermodynamically more stable 3-(dimethylaminomethyl)indole, known as **gramine**.

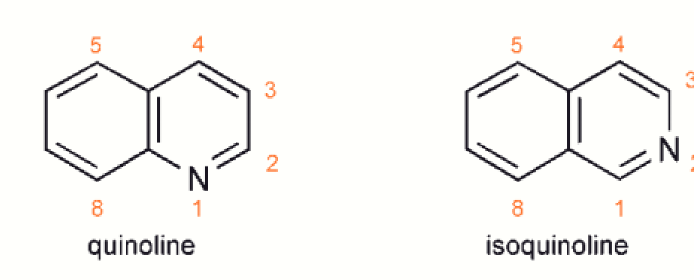
- **Gramine** can also be synthesized directly in high yield by reacting indole with formaldehyde and dimethylamine in acetic acid.

- This transformation represents a valuable example of the Mannich reaction, as gramine serves as a key intermediate for the preparation of various 3-substituted indole derivatives.



Quinolines and Isoquinoline

Quinoline is a high - boiling liquid; isoquinoline is a low - melting solid; each has a sweetish odour. Both bases have been known for a long time: quinoline was first isolated from coal tar in 1834, isoquinoline from the same source in 1885. Shortly after the isolation of quinoline from coal tar, it was also recognized as a pyrolytic degradation product of cinchonamine, an alkaloid closely related to quinine, from which the name quinoline is derived; the word quinine, in turn, derives from *quina*, a Spanish version of a local South American name for the bark of quinine - containing Cinchona species

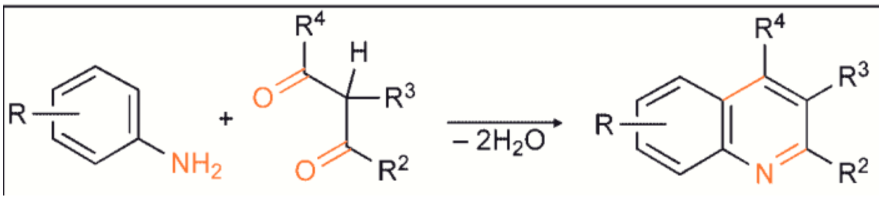


IV-5-1 Synthesis of Quinolines and Isoquinolines

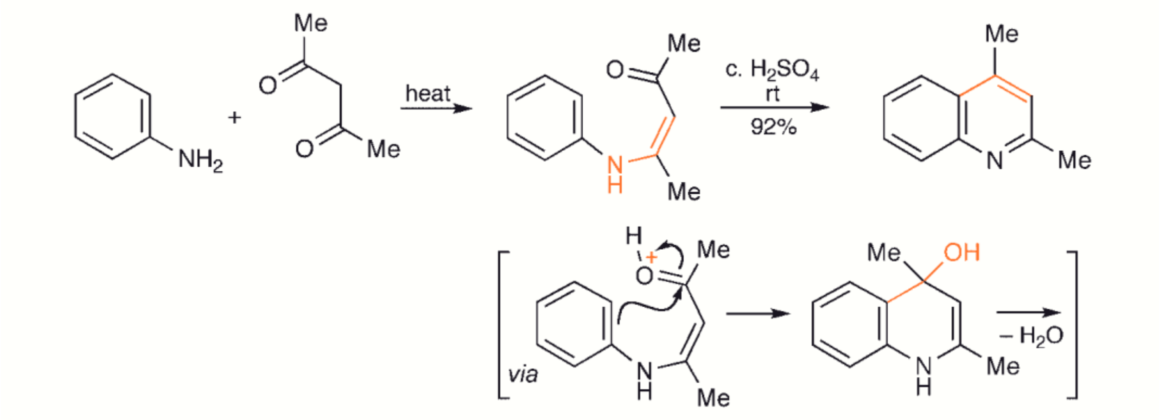
IV-5-1-1 Ring Syntheses

The more generally important approaches to quinoline and isoquinoline compounds from non – heterocyclic precursors are summarised in this section.

Anilines react with 1,3 - dicarbonyl compounds to give intermediates which can be cyclised with acid.

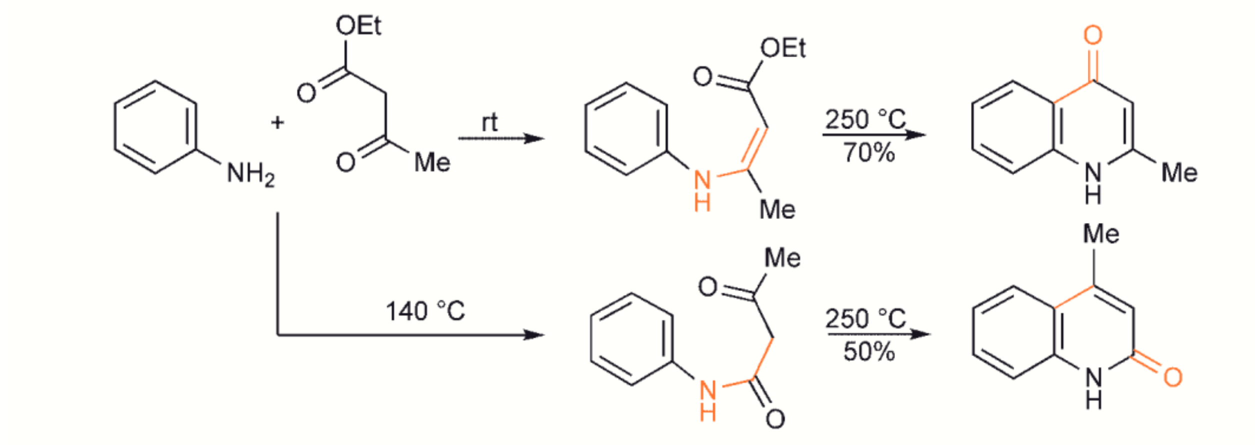


Condensation of a 1,3 - dicarbonyl compound with an arylamine gives a high yield of a β-amino - enone, which can then be cyclised with concentrated acid. Mechanistically, the cyclisation step is an electrophilic substitution by the *O*- protonated amino - enone, followed by loss of water to give the aromatic quinoline.

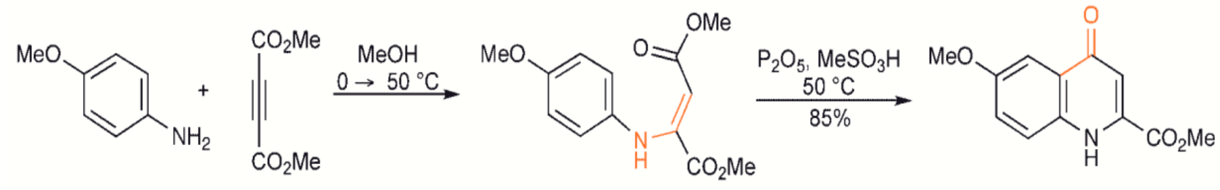


IV-5-1-2 Conrad – Limpach – Knorr Reaction

If the 1,3 - dicarbonyl component is at the 1,3 - keto acid oxidation level, then the product is a quinolone. Anilines and β- keto esters react at lower temperatures to give the kinetic product, a β- aminoacrylate, cyclisation of which gives a 4 - quinolone. At higher temperatures, β- keto acid anilides are formed and cyclisation of these affords 2 - quinolones.

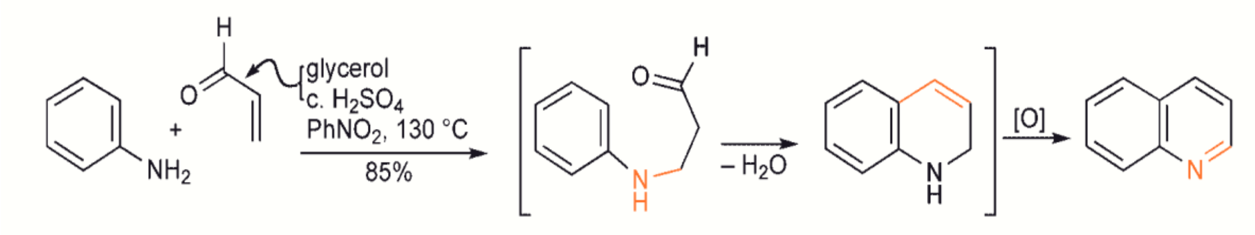


β- Aminoacrylates, for cyclisation to 4 - quinolones, are also available *via* the addition of anilines to acetylenic esters, or by displacement of ethoxy from ethoxymethylenemalonate (EtOCH = C(CO$_2$Et)$_2$.



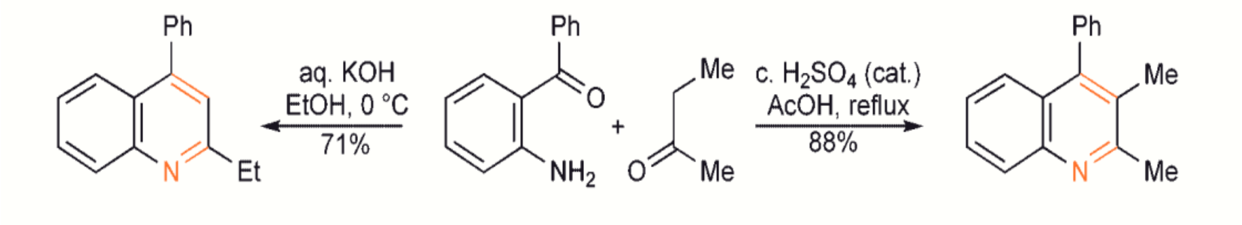
IV-5-1-3 The Skraup Synthesis

In this extraordinary reaction, quinoline is produced when aniline, concentrated sulfuric acid, glycerol and a mild oxidising agent are heated together.111 The reaction has been shown to proceed *via* dehydration of the glycerol to acrolein, to which aniline then adds in a conjugate fashion. Acid - catalysed cyclisation produces a 1,2 - dihydro - quinoline, finally dehydrogenated by the oxidising agent – the corresponding nitrobenzene or arsenic acid have been used classically. The Skraup synthesis is best for the ring synthesis of quinolines unsubstituted on the hetero- ring.



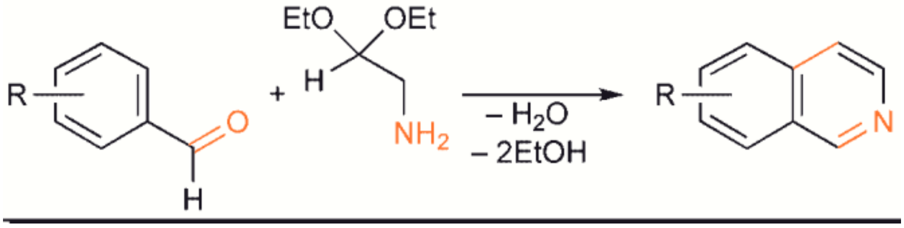
IV-5-1-4 The Friedl ä nder Synthesis

This route has been used extensively for the synthesis of substituted quinolines. In the original sequence, an *ortho*- acyl - arylamine is condensed with a ketone or aldehyde (which must contain an α- methylene group) by base or acid catalysis to yield the quinoline. The orientation of condensation depends on the regioselectivity of enolate or enol formation. Control of regiochemistry can be obtained by using a removable phosphonate, to direct enolisation, as in $RCOCH_2P(O)(OMe)_2$. 2 - Substituted quinolines can be obtained regioselectively from methyl ketones using pyrrolidine as catalyst



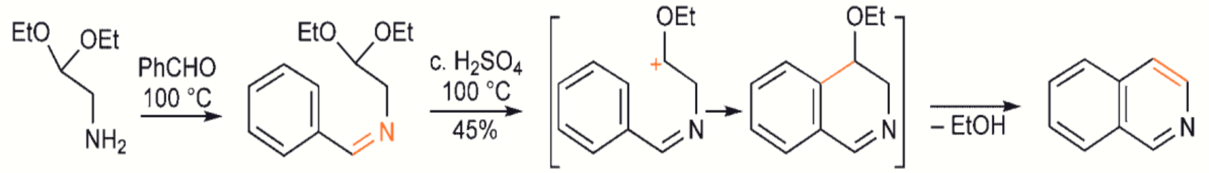
IV-5-1-5 Isoquinolines from Aryl - aldehydes and Aminoacetal

Aromatic aldehydes react with aminoacetal (2,2 - diethoxyethanamine) to generate imines that can be cyclised with acid to isoquinolines carrying no substituents on the heterocyclic ring.



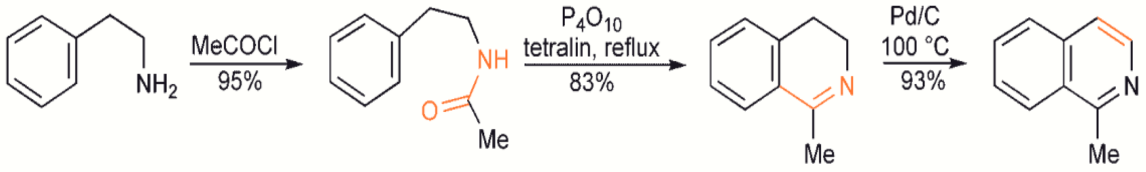
IV-5-1-6 The Pomeranz – Fritsch Synthesis

This synthesis is normally carried out in two stages. Firstly, an aryl aldehyde is condensed with aminoacetal to form an aryl - aldimine. This stage proceeds in high yield under mild conditions. Secondly, the aldimine is cyclised by treatment with strong acid; hydrolysis of the imine competes and reduces the efficiency of this step and for this reason trifluoroacetic acid with boron trifluoride is a useful reagent. The second step is similar to those in the Combes and Skraup syntheses, in that the acid initially protonates, causing elimination of ethanol and the production of a species that can attack the aromatic ring as an electrophile. Final elimination of a second mole of alcohol completes the process.



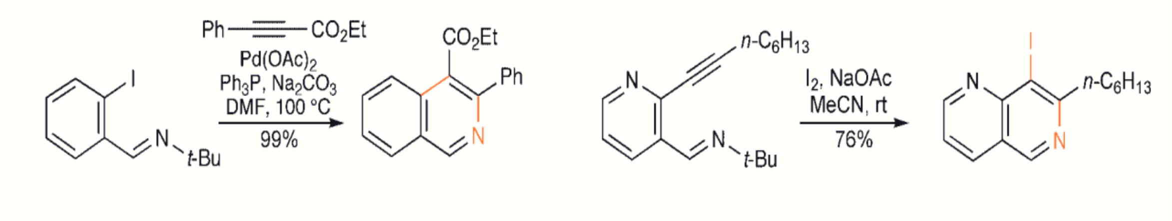
IV-5-1-7 The Bischler – Napieralski Synthesis

In the classical process, a 2 - aryl - ethanamine reacts with a carboxylic acid chloride or anhydride to form an amide, which can be cyclised, with loss of water, to a 3,4 - dihydro - isoquinoline, then readily dehydrogenated to the isoquinoline using, for example, palladium, sulfur or diphenyl disulfide. Common cyclisation agents are phosphorus pentoxide, often with phosphoryl chloride, and phosphorus pentachloride. The electrophilic intermediate is very probably an imino chloride, or imino phosphate; the former have been isolated and treated with Lewis acids when they are converted into isonitrilium salts, which cyclise efficiently to 3,4 - dihydroisoquinolines.



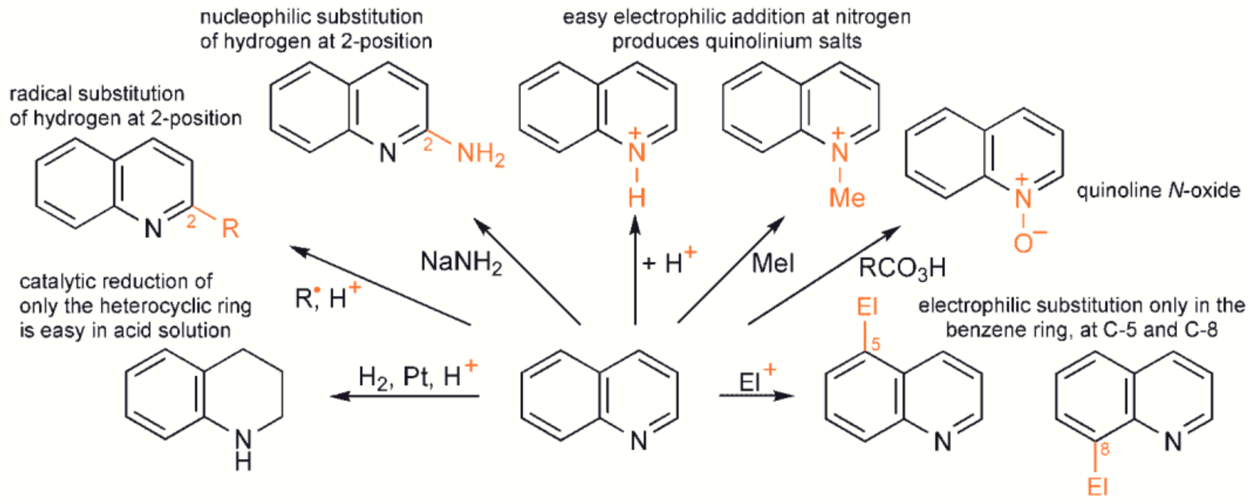
IV-5-1-8 Isoquinolines from ortho- Alkynyl - Araldehyde - Imines

ortho- Iodo - araldehyde imines react directly with internal alkynes, using palladium (0) catalysis, generating isoquinolines in which the original nitrogen substituent has been lost as isobutene; the scheme shows one of many examples of this important process.



IV-5-2 Typical reactions of quinoline

Quinoline and isoquinoline, the two possible structures in which a benzene ring is annelated to a pyridine ring, represent an opportunity to examine the effect of fusing one aromatic ring to another. Clearly, both the effect that the benzene ring has on the reactivity of the pyridine ring, and *vice versa*, as well as comparison with the chemistry of naphthalene must be considered. Firstly, it will be clear from the discussion of pyridine with electrophiles that, of the two rings, electrophilic substitution favours the benzenoid ring, rather than the pyridine ring. Regioselectivity, which in naphthalene favours an α- position, is mirrored in quinoline/isoquinoline chemistry by preferred substitution at the 5 - and 8 - positions. It should be noted that such substitutions usually involve attack on the species formed by electrophilic addition (often protonation) at the nitrogen, which has the effect of further discouraging (preventing) attack on the heterocyclic ring.

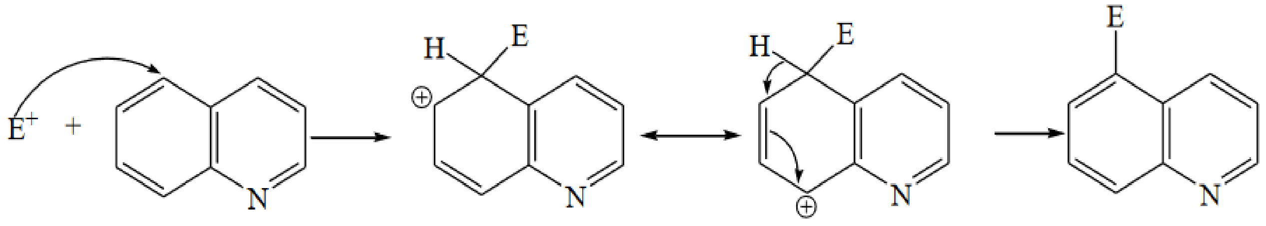


Typical reactions of quinoline (isoquinoline is very similar)

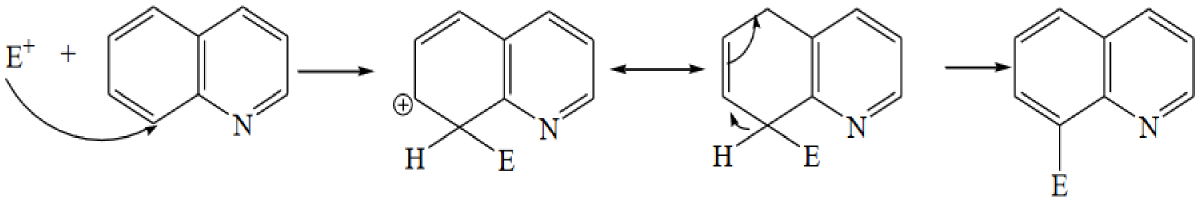
IV-5-2-1 Electrophilic substitution

Out of the two fused rings in quinoline, the carbocyclic (benzene) ring is relatively more electron rich and resembles benzene ring while the nitrogen containing ring (less electron rich) resembles with pyridine ring. Therefore, the electrophilic substitution in quinoline takes place more readily at benzene ring (at position 5 and 8 of benzene ring) rather than the pyridine ring. Thus, if both the positions in benzene ring are vacant than mixture of substituted product is obtained. The general mechanism of electrophilic substitution on quinoline is shown below.

a. At position 5

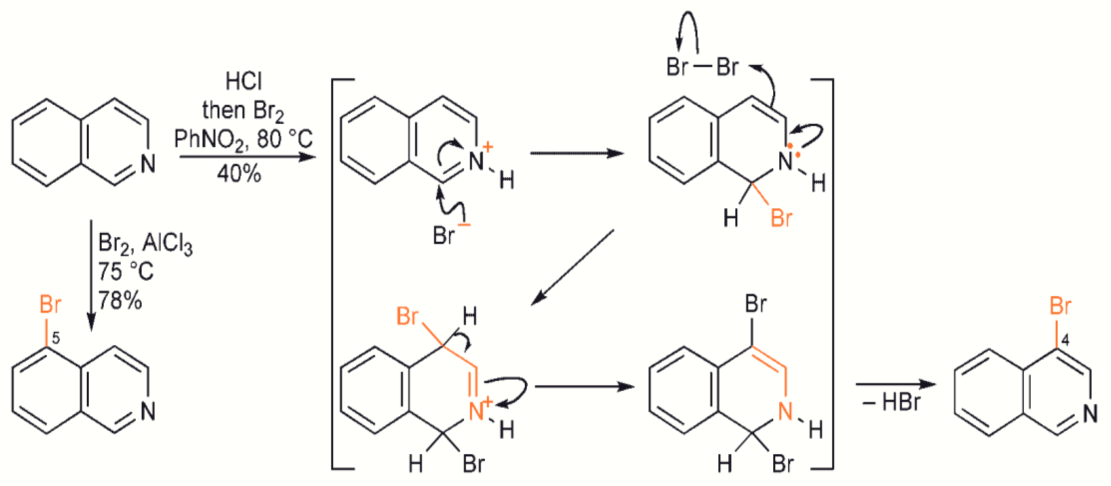


b. At position 8



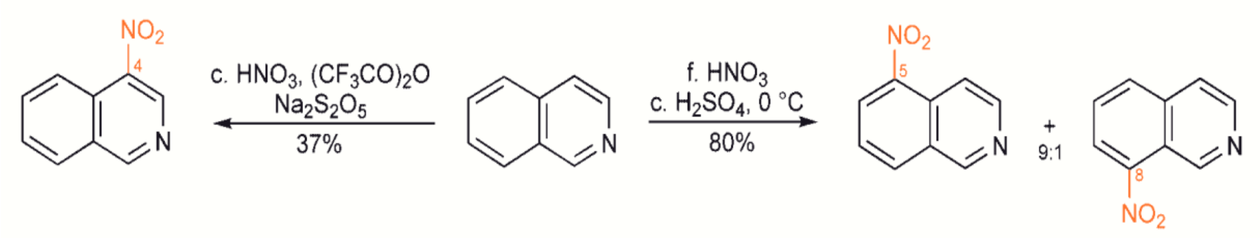
1- Halogenation

Ring substitution of quinoline and isoquinoline by halogens is rather complex, products depending on the conditions used.7 In concentrated sulfuric acid, quinoline gives a mixture of 5 - and 8 - bromo derivatives; comparably, isoquinoline is efficiently converted into the 5 - bromo - derivative in the presence of aluminium chloride,8 or with *N*- bromosuccinimide in concentrated sulfuric acid. Introduction of halogen to the hetero - rings occurs under remarkably mild conditions in which halide addition to a salt initiates the sequence. Thus, treatment of quinoline or isoquinoline hydrochlorides with bromine produces 3 - bromoquinoline and 4 - bromoisoquinoline, respectively, as illustrated below for the latter.



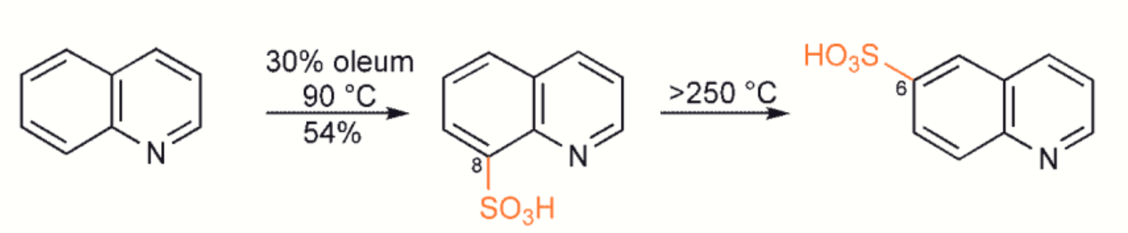
2- Nitration

The positional selectivity for proton exchange is partly mirrored in nitrations, quinoline gives approximately equal amounts of 5 - and 8 - nitro - quinolines, whereas isoquinoline produces almost exclusively the 5 - nitro - isomer; mechanistically the substitutions involve nitronium ion attack on the N- protonated heterocycles. Nitration in the pyridine ring, at a position β to the heteroatom, can be achieved viathe Baake – Katritzky protocol. 7 - Nitroisoquinoline can be obtained by nitration of 1,2,3,4, - tetrahydroisoquinoline and then dehydrogenation of the hetero ring with potassium nitrosodisulfonate.



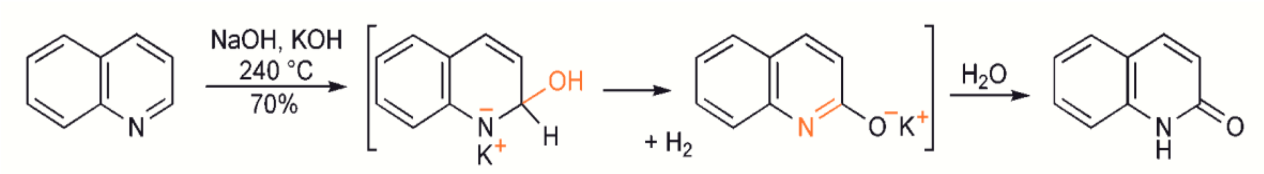
3- Sulfonation

Sulfonation of quinoline gives largely the 8 - sulfonic acid, whereas isoquinoline affords the 5 - acid. Reactions at higher temperatures produce other isomers, under thermodynamic control, for example both quinoline 8 - sulfonic acid and quinoline 5 - sulfonic acid are isomerised to the 6 - acid.



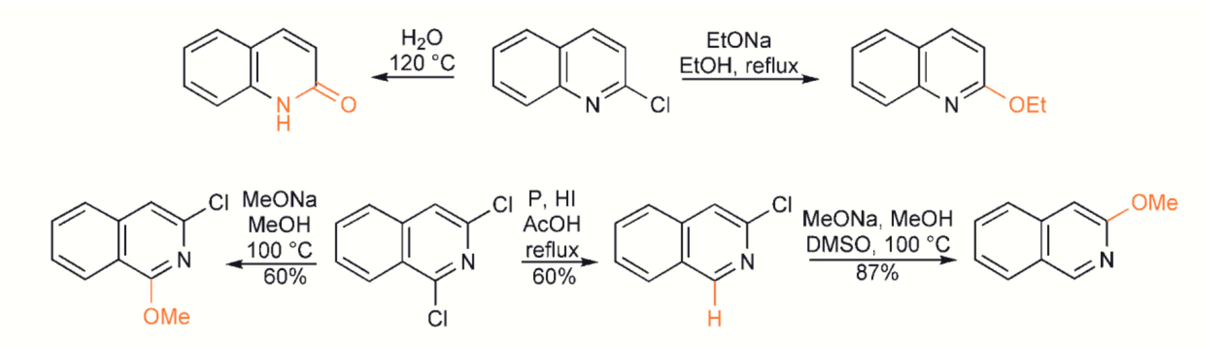
4- Hydroxylation

Both quinoline and isoquinoline can be directly hydroxylated with potassium hydroxide at high temperature with the evolution of hydrogen. 2 - Quinolone (carbostyril) and 1 -isoquinolone (isocarbostyril) are the isolated products.

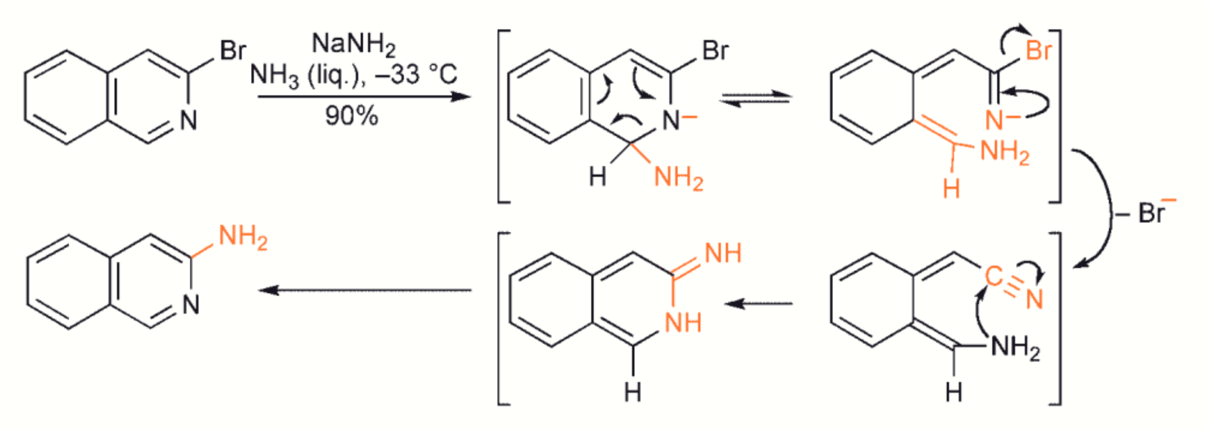


5- Nucleophilic Substitution with Displacement of Good Leaving Groups

The main principle here is that halogen on the homocyclic rings of quinoline and isoquinoline, and at the quinoline - 3 - and the isoquinoline - 4 positions, behaves as would a halo - benzene. In contrast, 2 - and 4 - halo -quinolines and 1 - halo - isoquinolines have the same susceptibility as α- and γ- halopyridines. 3 - Halo - isoquinolines are intermediate in their reactivity to nucleophiles.

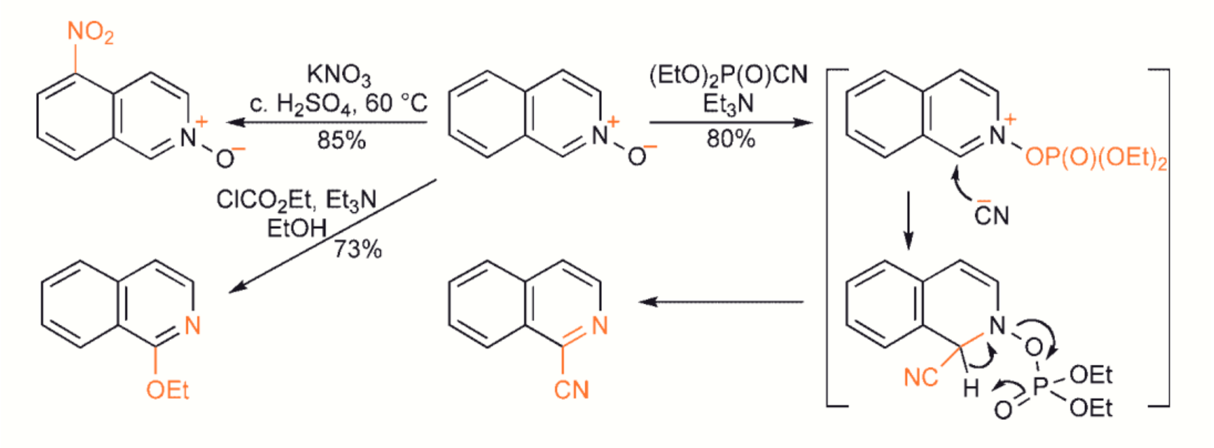


An apparent exception to the relative unreactivity of 3 - halo - isoquinolines is provided by the reaction of 3 - bromoisoquinoline with sodium amide. Here, a different mechanism, known by the acronym ANRORC (**A**ddition of **N**ucleophile, **R**ing **O**pening and **R**ing **C**losure), leads to the product, apparently of direct displacement, but in which a switching of the ring nitrogen to become the substituent nitrogen, has occurred.



IV-5- Quinoline and Isoquinoline *N*- Oxides

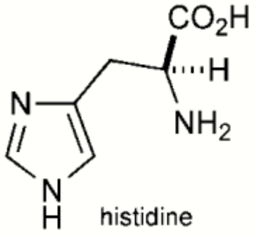
N- Oxide chemistry in these bicyclic systems largely parallels the processes described for pyridine *N*- oxide, with the additional possibility of benzene ring electrophilic substitution, for example mixed acid nitration of quinoline *N*- oxide takes place at C - 5 and C - 8 *via* the *O*-protonated species, but at C - 4 at lower acid strength; nitration of isoquinoline *N*- oxide takes place at C - 5.Diethyl cyanophosphonate converts quinoline and isoquinoline *N*- oxides into the 1 - and 2 - cyano - heterocycles in high yields in a process which must have *O*- phosphorylation as a first step, and in which the elimination of diethylphosphate may proceed *via* a cyclic transition state; trimethylsilyl cyanide and diazabicycloundecene effect the same transformation. A chloroformate and an alcohol convert the *N*- oxides into ethers, as illustrated below for isoquinoline *N*- oxide, a chloroformate and a Grignard reagent produce 2 - substituted quinolines, and a chloroformate then an isonitrile produce 2 - carbamoyl - 1,2 - dihydro - isoquinolines.

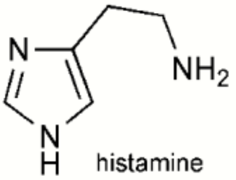


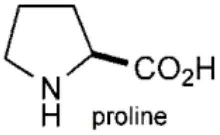
Chapter 5 Applications to the synthesis of compounds of biological interest

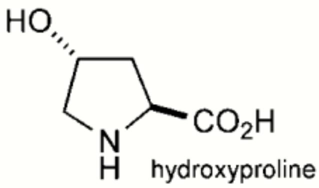
V-1 Heterocyclic Amino Acids and Related Substances

There are four amino acids, amongst the 20 that make up proteins, that have an aromatic side - chain, and of these, two have a heteroaromatic side - chain – histidine, with an imidazole, and tryptophan, with an indole. Both of these are amongst the 'essential amino acids ', i.e. they need to be part of the diet since they cannot be biosynthesised by human beings. Decarboxylation of histidine produces the hormone histamine. Proline is the only heterocyclic DNA- coded α- amino acid – it is based on pyrrolidine; hydroxyproline is an essential component of collagen, the fibrous structural protein that supports tissues and is the main component of cartilage.

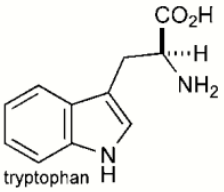

histidine

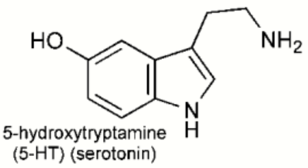

histamine

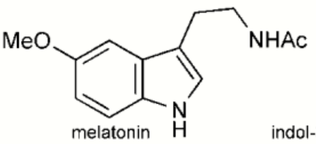

proline

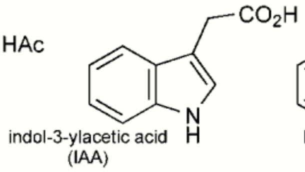

hydroxyproline

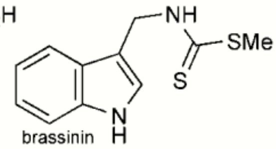
Decarboxylated tryptophan is called tryptamine. The phenol, 5 - hydroxytryptamine (5 - HT or serotonin) and histamine are important neurotransmitters (33.2). *N*- Acetyl - 5 - methoxytryptamine, known as melatonin, is produced by the pineal gland, a pea - sized gland at the base of the brain. It is involved in controlling the natural daily cycle of hormone release in the body – the circadian rhythm. The secretion of melatonin is triggered by the dark and is suppressed by natural daylight, therefore controlling periods of sleepiness and wakefulness. Indol - 3 - ylacetic acid (IAA) is an auxin – a plant growth stimulant. Brassinin, isolated from turnips, is a phytoalexin – one of a group of compounds produced by plants as a defense mechanism against attack by microorganisms.


tryptophan

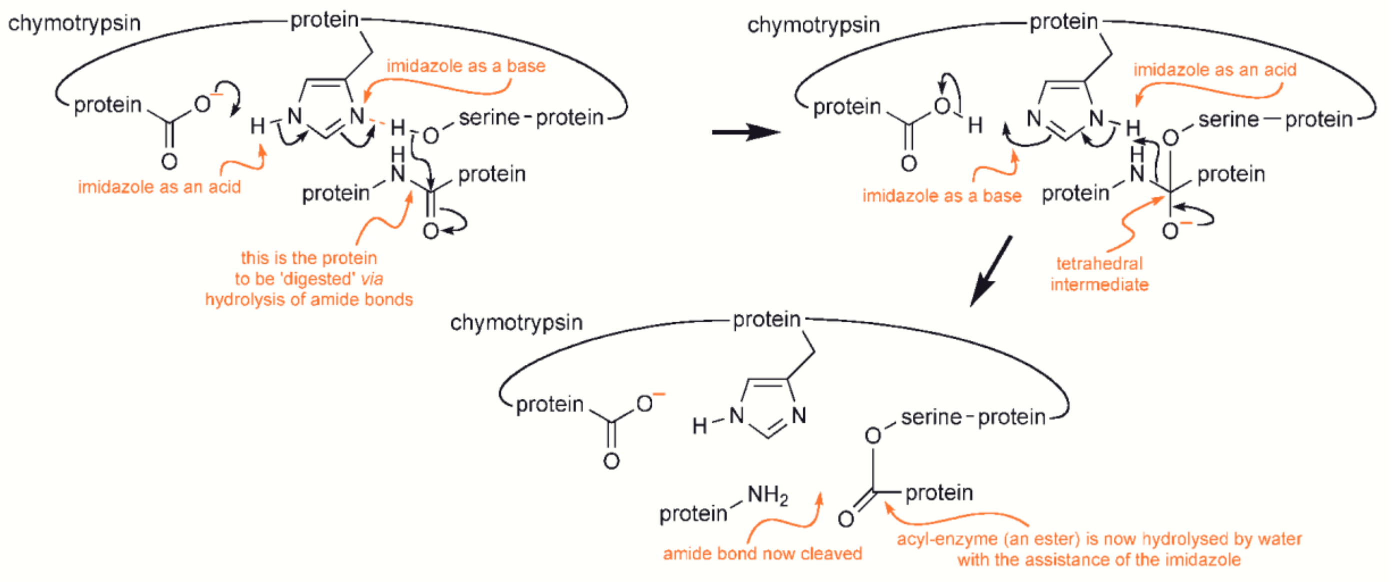

5-hydroxytryptamine
(5-HT) (serotonin)


melatonin


indol-3-ylacetic acid
(IAA)


brassinin

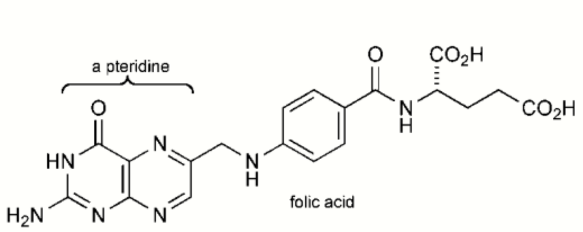
The ability of an imidazole to act as both an acid (*N*- hydrogen) and a base (the imine nitrogen) is put to good use in the active sites of several enzymes in which the imidazole rings of appropriately placed histidines effectively 'shuffle' protons from one place to another. One example is the digestive enzyme chymotrypsin, which brings about the hydrolysis of protein amide groups in the small intestine: the enzyme provides a 'proton' at one site, while it accepts a 'proton' at another, making use of the ambiphilic character of the imidazole ring to achieve this. Effectively, the imidazole activates a serine alcoholic hydroxyl by removing the proton as the oxygen attacks the amide bond. Subsequently, that same proton is delivered to the cleaving amide nitrogen as the tetrahedral intermediate breaks down.



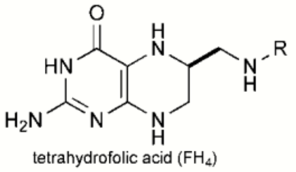
The role of histidine in chymotrypsin hydrolysis of peptides

V-2 Enzyme Co - Factors; Heterocyclic Vitamins; Co - Enzymes

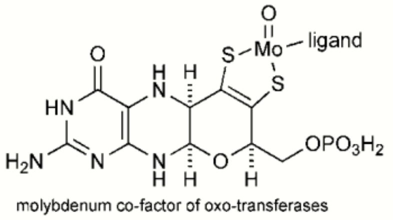
Many enzymes require a component, other than the protein portion, for their catalytic activity – a co - factor. If the co - factor is removed, the remaining protein (apoenzyme) has no catalytic activity. A co - factor that is firmly bound to the apoenzyme is termed a prosthetic group and most contain a metal centre. A co – factor that is bound loosely to the apoenzyme and can be readily separated from it is called a co - enzyme. Co - enzymes play a critical role in the catalysis. Vitamins are substances essential for a healthy life; humans must ingest vitamins *via* their diet because there is no mechanism for their biosynthesis in the body. There are 14 vitamins – the name was coined when the first vitamin chemically identified (vitamin B1 in 1910) turned out to be an amine – a *vit*al *amin*e. A typical vitamin is folic acid, a complex molecule in which the functionally important unit is the bicyclic pyrazino [2,3 -*d*] pyrimidine (pteridine) ring system, and its arylaminomethyl substituent. Folic acid is converted in the body into tetrahydrofolic acid (FH4) which is crucial in carrying one - carbon units, at various oxidation levels, for example in the biosynthesis of purines, and is mandatory for healthy development of the foetus during pregnancy. Other essential co - factors that contain pteridine units must and can be biosynthesised in humans – without them we cannot survive – and are incorporated into oxygen – transfer enzymes based on molybdenum, in which the metal is liganded by a complex ene - dithiolate.



folic acid



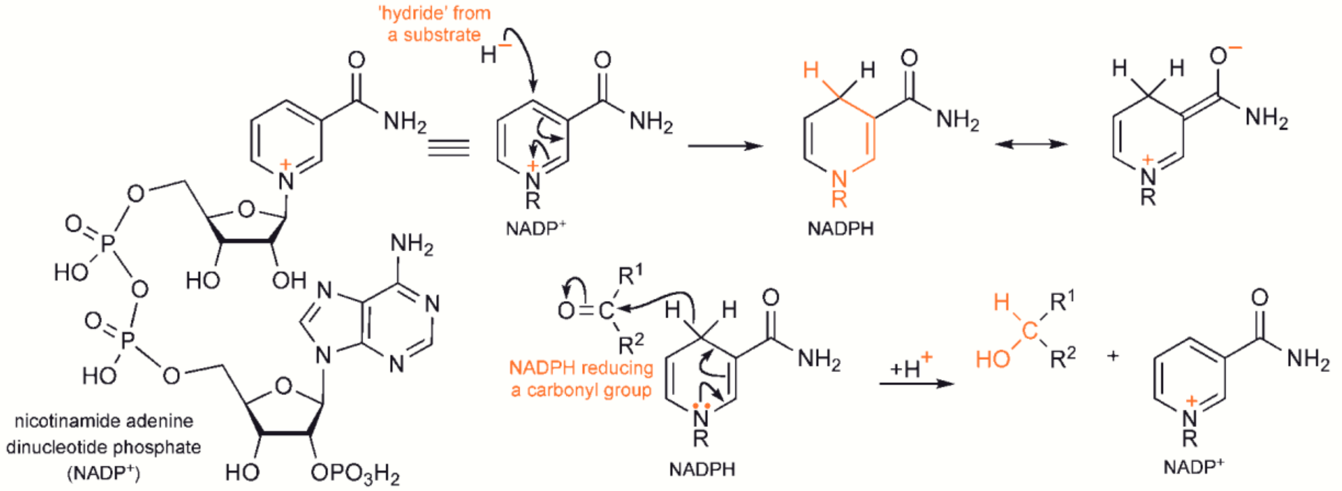
tetrahydrofolic acid (FH_4)



molybdenum co-factor of oxo-transferases

V-3 Niacin (Vitamin B3) and Nicotinamide Adenine Dinucleotide Phosphate (NADP+)

Nicotinamide adenine dinucleotide phosphate (NADP+) is a large complicated co - enzyme, but the significant part for its role in oxidation/reduction processes is the pyridinium ring – to understand the mechanism one can think of it as simply an *N*- alkyl pyridinium salt of nicotinamide. The positively charged nitrogen acts as an electron sink and allows this co - enzyme to accept two electrons and a proton, i.e. effectively, hydride. In line with typical pyridinium reactivity, the hydride adds at a γ- position, thus producing a 1,4 - dihydropyridine (NADPH), the process being feasible because NADPH is a stabilised 1,4 - dihydropyridine in which the ring nitrogen is conjugated to the carbonyl of the 3 - substitutent (Hantzsch synthesis). In the reverse sense, NADPH is a vital reducing agent in biosynthesis – it is nature' s sodium borohydride. The rationale for the reverse process is the regain of aromaticity in the co -enzyme product – a pyridinium ion.

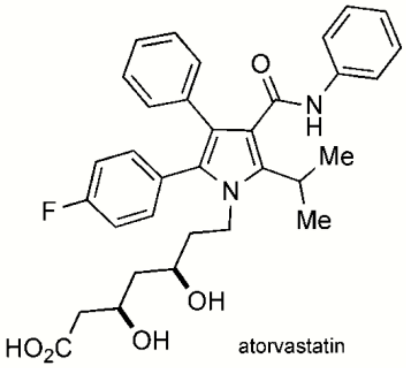


The role of a pyridinium ion and a 1,4-dihydropyridine in enzyme-catalysed oxidation and reduction processes

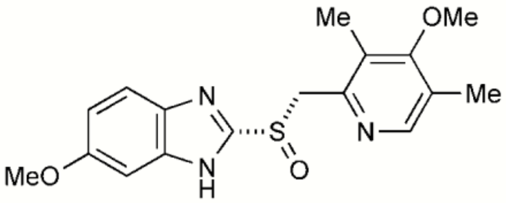
V-4 Heterocycles in Medicine

Heterocyclic compounds are fundamental to modern medicine due to their wide range of biological activities and structural versatility. These compounds, which contain rings with at least one non-carbon atom (such as nitrogen, oxygen, or sulfur), are commonly found in the core structures of many therapeutic agents. Their ability to interact selectively with enzymes, receptors, and nucleic acids makes them essential in the development of drugs targeting various diseases.

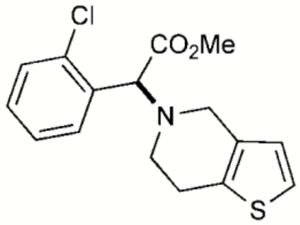
Among the ten top-selling prescription drugs by global revenue, seven are small-molecule heterocyclic compounds. These include atorvastatin (Lipitor), a statin used to lower cholesterol; esomeprazole (Nexium), a proton pump inhibitor for reducing gastric acid; clopidogrel (Plavix), an antiplatelet agent used to prevent blood clots; olanzapine (Zyprexa) and risperidone (Risperdal), both antipsychotics used in the treatment of schizophrenia; amlodipine (Norvasc), an antihypertensive; and quetiapine (Seroquel), prescribed for schizophrenia and bipolar disorder. Of the remaining three drugs, two are biologics—modified polypeptides: darbepoetin alfa (Aranesp) and etanercept (Enbrel). The only non-heterocyclic small molecule among the top ten is seretide (Advair), an anti-asthmatic composed of a steroid and a β-agonist.



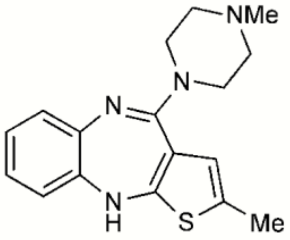
atorvastatin



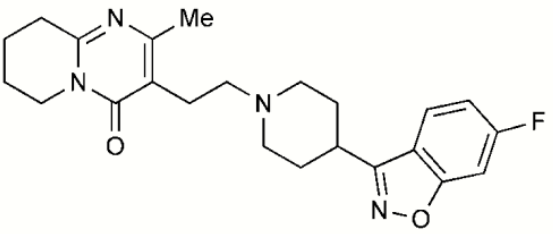
esomeprazole ((*S*)-omeprazole)



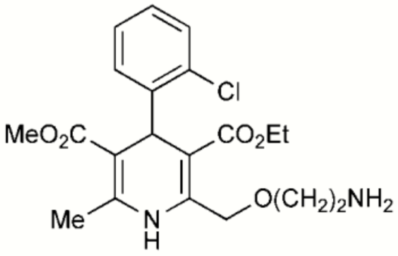
clopidogrel



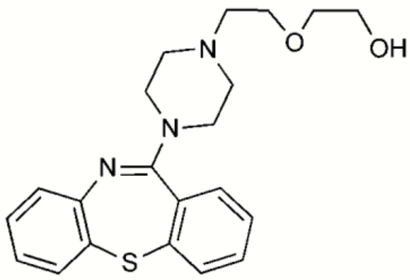
olenzapine



risperidone



amlodipine

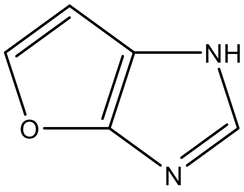


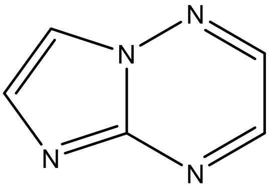
quetiapine

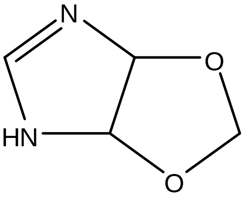
Problems

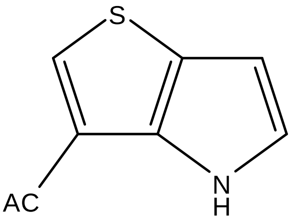
Nomenclature of Heterocycles

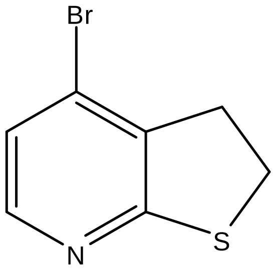
A) Name the following compounds

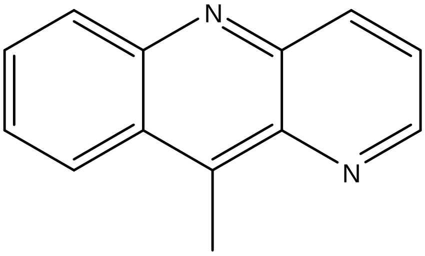


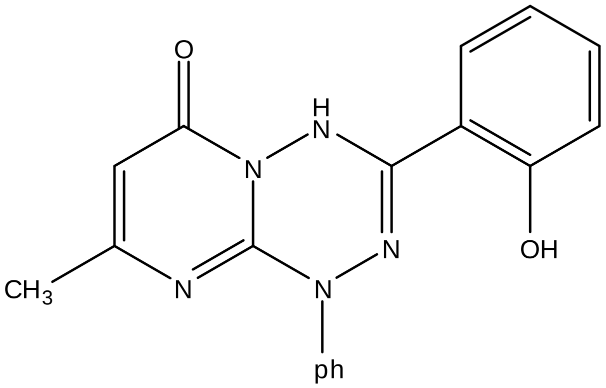


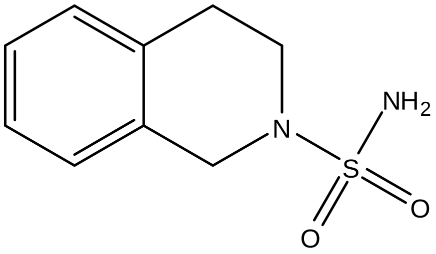


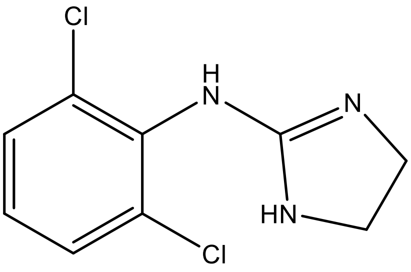






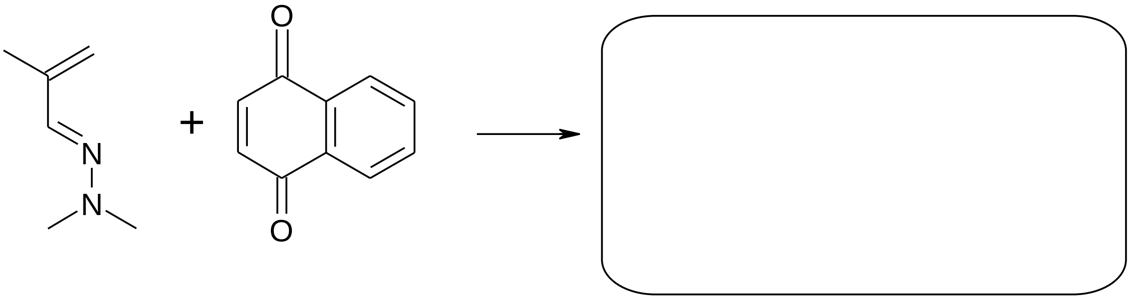






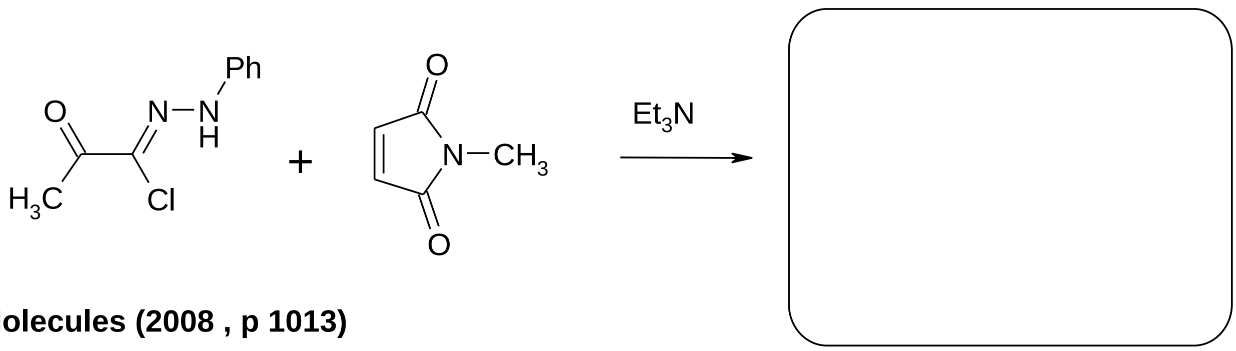
B) Complete the following equations:

1)



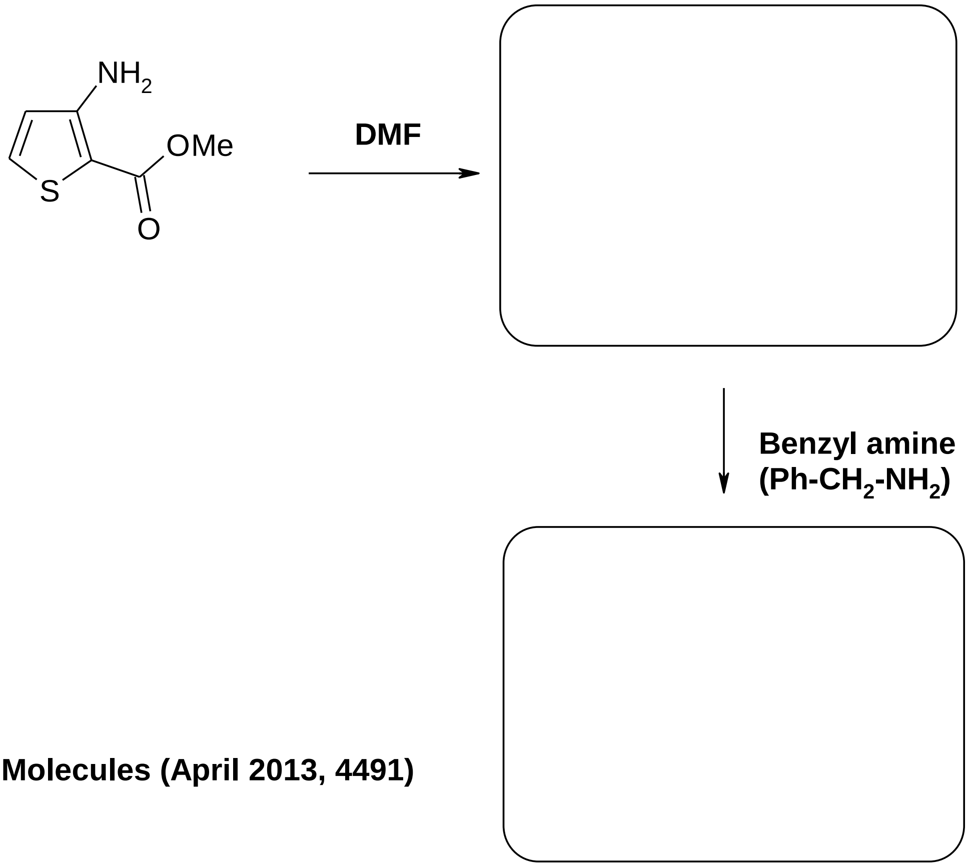
Molecules (2002 , p 918)

2)



Molecules (2008 , p 1013)

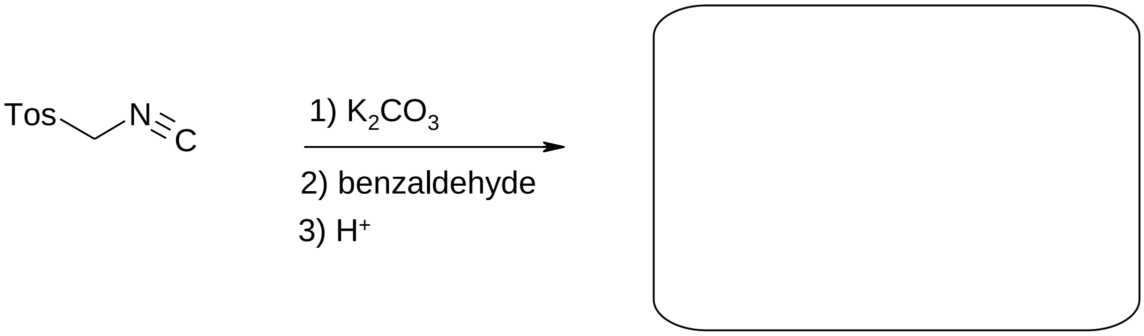
3)



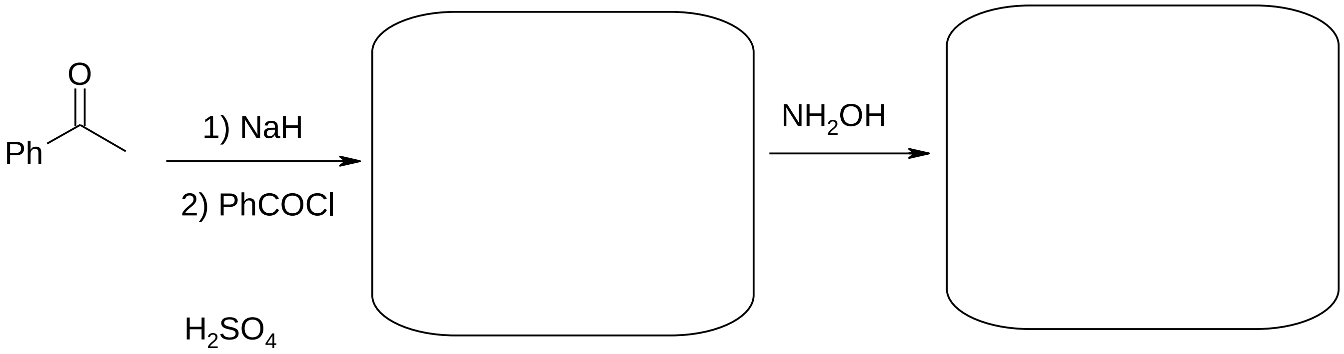
Molecules (April 2013, 4491)

Heterocyclic compound

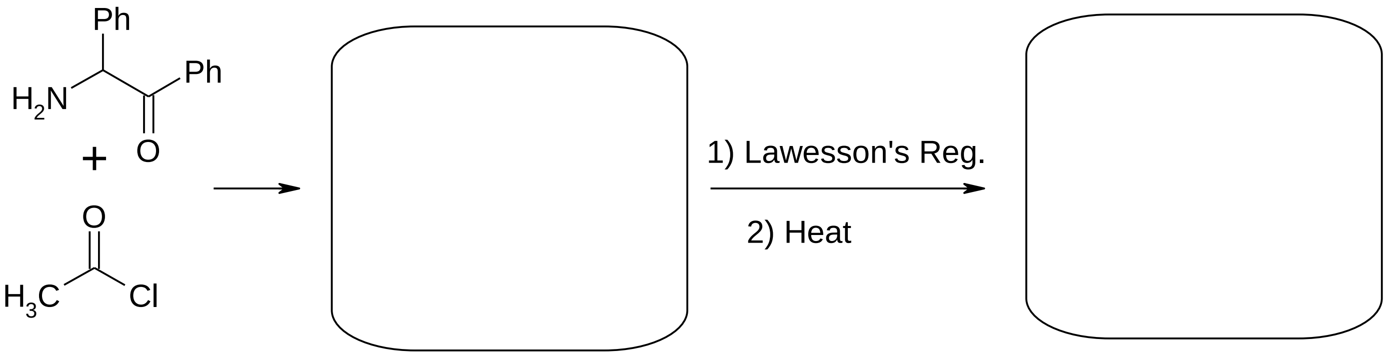
4)



5)

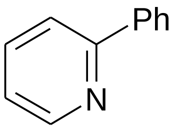


6)



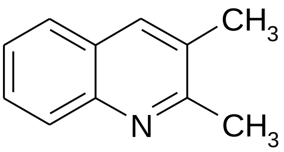
3) How can you prepare the following compounds

A)



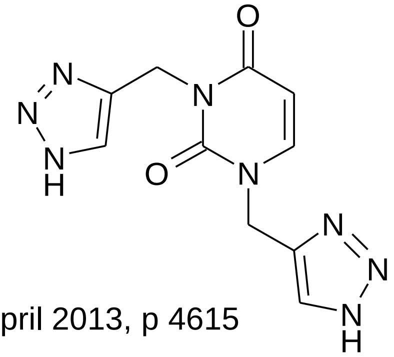
starting from 2-pyrone

B)

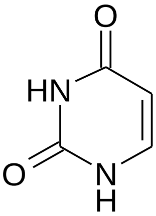


starting from 2-nitrobenzaldehyde and any other reagent

C)



starting from



Molecules april 2013, p 4615

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