

## Introduction to Heterocyclic Chemistry

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Heterocycles are cyclic structures with at least one atom other than C and H. Most common heteroatoms are N, O and S. A large portion of natural products are heterocyclic compounds and some are being utilized as pharmaceuticals, agrochemicals *etc.* Heterocyclic compounds can be categorized according to their ring sizes. Examples with 3- and 4-membered rings are given in Fig. 1.

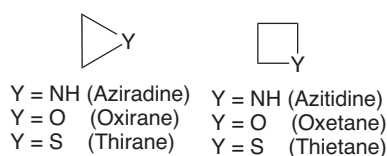


Figure 1: 3- and 4-membered heterocycles

Many 5- and 6-membered heterocycles are known but 7- and 8-membered heterocycles are uncommon. This article focuses on 5- and 6-membered compounds.

Heterocycles fall into various categories depending on the heteroatom/s present and their position/s in the ring/s, e.g.

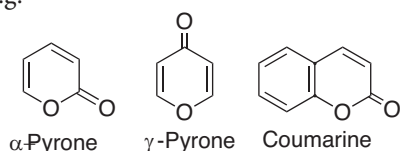


Figure 2: Oxygen containing heterocycles

There can be one, two or more heteroatoms present in a small ring system and some of the molecules are given in Fig. 3. These heterocycles can be further classified into aromatic, non-aromatic and anti-aromatic.

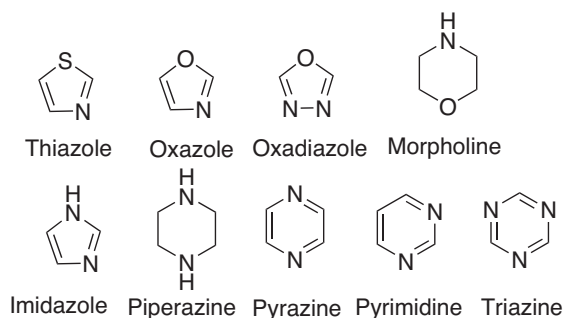


Figure 3: Heterocycles with 2 or 3 heteroatoms

If a compound is cyclic planar with  $(4n+2)$   $\pi$ -electrons, it is **aromatic**. **Anti-aromatic** compounds are cyclic planar with  $4n$   $\pi$  electrons, while all cyclic non-planar compounds become **non-aromatic**.

## Mono heterocycles with N, O and S

The 5- and 6-membered heterocycles are the most common molecules found in nature or in laboratories. All the saturated rings are non-aromatic due to loss of planarity. The ring-strain in 5- or 6 membered rings is relatively small.

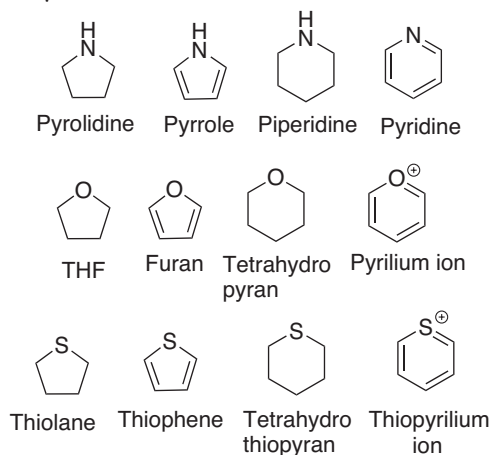


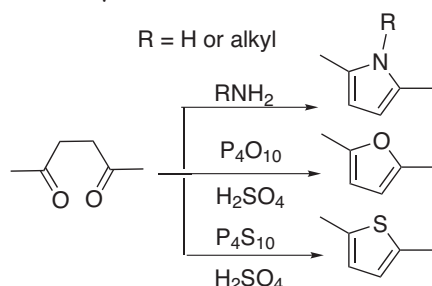
Figure 4: 5- and 6-membered heterocycles containing N, O and S

As a result, the chemical behavior of saturated 5- or 6 membered heterocycles resembles that of open-chain analogues. Piperidine is found in pepper as a flavoring agent; pyrrolidine is present in two essential amino acids, namely proline and hydroxyproline while tetrahydrofuran (THF) is commonly used as a solvent in many organic syntheses.

## Pyrrole (1), furan (2) and thiophene (3)

Pyrrole moiety is found in amino acids and in many other naturally occurring alkaloids such as chlorophyll, hemin and bilirubin. Furan and its derivatives are present

in heat-treated food and they are produced through thermal degradation of natural food items. They exist in roasted coffee, instant coffee and in cigarette smoke. Thiophenes are found in secondary metabolites of plants. These 5-membered heterocyclic compounds are **planar** with six delocalized electrons. Paal Knorr synthesis is the most common synthetic route to these molecules.

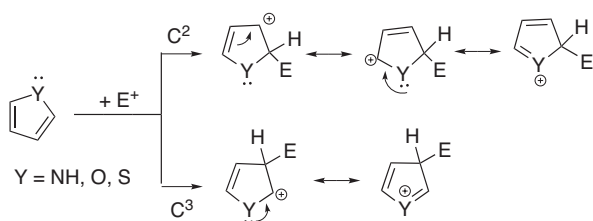


**Figure 5:** Paal Knorr synthesis of heterocycles

Out of these three, furan is the **most reactive** and **least aromatic** heterocycle as its **resonance energy (RE)** is the **lowest** due to higher electronegativity of oxygen. Higher electronegativity of oxygen does not allow its lone pair to delocalize into the ring.

	Order of aromaticity increases →			
	(2)	(1)	(3)	PhH
RE	16	22	29	36 kJ mol <sup>-1</sup>

These rings readily undergo **electrophilic substitution (ES)** reactions at carbon-2 (C<sup>2</sup>), since the electrophilic attack on C<sup>2</sup> shows extra stability with more resonance structures compared to that on C<sup>3</sup> as shown below.



**Figure 6:** Resonance structures of intermediates

**Table 1:** Reactions of 5-membered heterocycles

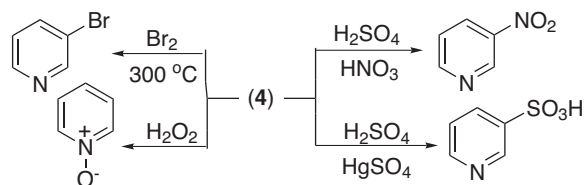
(\* thiophenes are unreactive)

Note that the tendency of electrophilic substitution decreases: (1) > (2) > (3) > PhH.

Starting material	Reaction and reagents	Product
 Y = NH, O, S	Reduction H <sub>2</sub> /Pt	
	Nitration conc. HNO <sub>3</sub> /H <sub>2</sub> SO <sub>4</sub>	
	Sulphonation H <sub>2</sub> SO <sub>4</sub> /pyridine	
	Halogenation X <sub>2</sub>	
	Alkylation EtCl/SnCl <sub>4</sub>	
	Oxidation* Cr <sub>2</sub> O <sub>3</sub>	
	Gattermann Koch* HCN/HCl/SnCl <sub>4</sub> /H <sub>2</sub> O	
	Coupling reactions* ArN <sub>2</sub> Cl/NaOH	

#### Pyridine (4)

**Pyridine** is the most important six membered heterocycle which is **aromatic** with six  $\pi$  electrons. Pyridine is **more basic** (pK<sub>b</sub>, ca. 8.8) than pyrrole. In pyrrole, the lone pair is in the delocalized electron cloud which makes it less basic than pyridine. Pyridine is less basic than aliphatic amines since the lone pair on pyridine nitrogen is *sp*<sup>2</sup> hybridized. When compared to benzene, pyridine is less reactive towards **electrophilic substitutions**, which takes place at C<sup>3</sup> (Fig. 7). An electrophile can attack C<sup>2</sup>, C<sup>3</sup> and C<sup>4</sup> positions. The attack at C<sup>3</sup> affords more resonance stabilized intermediates compared to attacks at C<sup>2</sup> and C<sup>4</sup>.



**Figure 7:** Substitution at C<sup>3</sup> & N-oxidation

Unlike 5-membered heterocycles, pyridine undergoes **addition** at nitrogen (Fig. 8). Pyridine can be a **catalyst in acylation** reactions of phenols, alcohols

and amines using acyl chlorides.

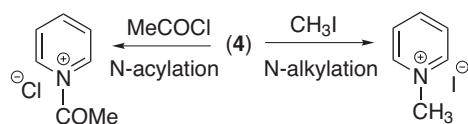


Figure 8: Acylation & alkylation of pyridine

The **nucleophilic substitution (NS)** at C<sup>2</sup> is more favorable. It can also be reduced to piperidine, and with KOH/PCl<sub>5</sub> to 2-chloro pyridine. Lithiated 4-methyl pyridine can be used to produce functionalized pyridine derivatives (Fig. 9).

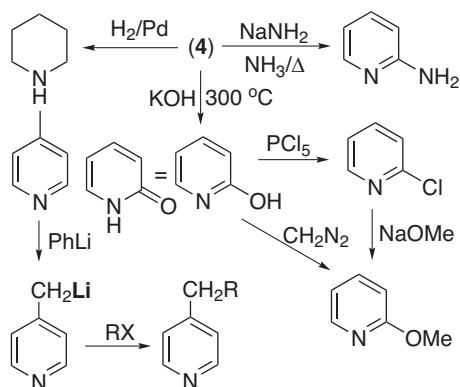


Figure 9: Some reactions of pyridine

### Diazines and Triazines

Diazines are 6-membered heterocycles containing two nitrogen atoms in the ring. There are three diazines called pyridazine, pyrimidine and pyrazine. Pyrimidine derivatives such as cytosine, thymine and uracil are some of the nucleobases present in DNA and RNA.

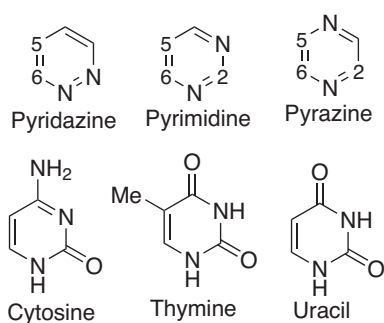


Figure 10: Diazines and some nucleic acids

1,3,5-Triazines such as cyanuric chloride, melamine and cyanuric acid can be prepared easily by trimerizing cyanogen chloride (ClCN), cyanamide (H<sub>2</sub>NCN) and urea (H<sub>2</sub>NCONH<sub>2</sub>), respectively.

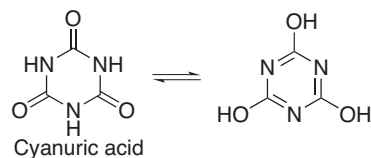
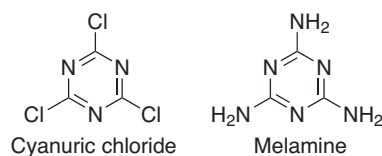


Figure 11: Triazine derivatives

Melamine has been used improperly in pet food and milk products to increase the nitrogen level. Chlorines in cyanuric chloride can be readily replaced by nucleophiles. Herbicide atrazine is produced by replacing chlorines with amines.

### Heterocycles with fused rings

The most common types of fused ring systems contain five and six membered rings (*e.g.* quinoline, benzothiofene, benzofuran indole, *etc.*). Many of these compounds are naturally available in plant materials.

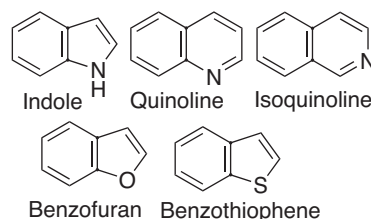


Figure 12: Heterocycles with fused rings

### Synthesis of fused heterocycles

**Indole** derivatives are the most abundant heterocycles in biologically active natural products. Phenyl hydrazine reacts with a ketone or aldehyde in the presence of an acid or a Lewis catalyst (BF<sub>3</sub>, ZnCl<sub>2</sub>) to produce indole derivatives as shown Fig. 13. This is called Fischer indole synthesis.

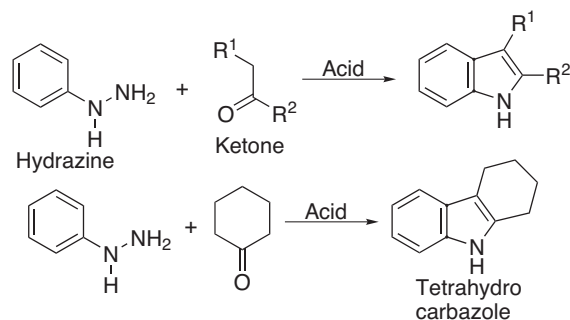


Figure 13: Fischer indole synthesis

Chemists have developed many synthetic routes to fused heterocycles using a combination of various components (e.g., aniline, disubstituted benzenes, amines, alkynes and vinyl halides). Intra-molecular Heck coupling is used to synthesize fused rings (Fig. 14).

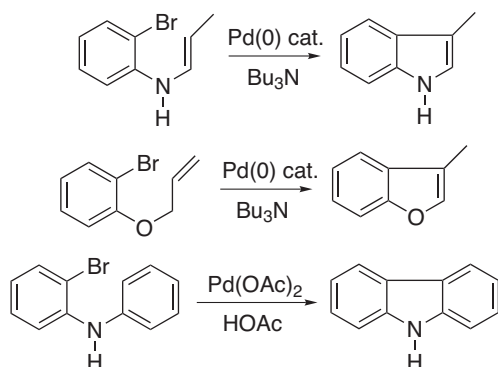


Figure 14: Heck cross coupling reactions

Benzopyridines occur in nature as alkaloids. Substituted aniline reacts with glycerol in the presence of an acid (conc.  $H_2SO_4$ ) and an oxidizing agent ( $PhNO_2$ ) to produce quinoline derivatives as shown Fig. 15.

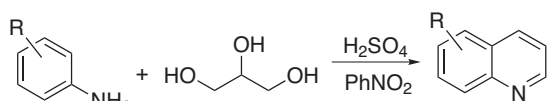


Figure 15: Skraup synthesis of quinoline

Dehydration of acyl  $\beta$ -phenylethylamine with  $POCl_3$  or  $P_4O_{10}$  yields isoquinoline.

### Reactions of fused heterocycles

**Indole (5)** undergoes electrophilic substitution reactions in the heterocyclic ring rather than in the fused benzene ring, thus, the ES readily occurs at  $C^3$ , but if the 3-position is blocked, substitution occurs at  $C^2$ . Some reactions are given in Fig. 16.

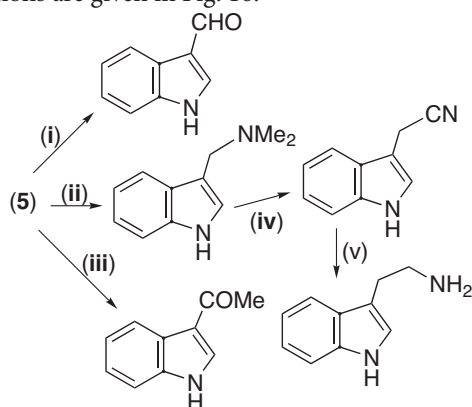


Figure 16: (i)  $DMF/POCl_3$ ; (ii)  $[Me_2N=CH_2]^+$ ; (iii)  $MeCOCl^-$ ; (iv) aq.  $NaCN$  & (v)  $LiAlH_4$

Bromination and nitration of **quinoline (6)** generate a (1:1) mixture of 5- and 8-substituted derivatives (Fig. 17).

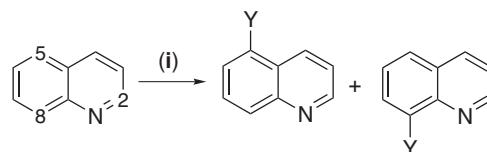


Figure 17: (i)  $Br_2/Ag_2SO_4$ ,  $Y = Br$  or (i) conc.  $H_2SO_4$  and  $HNO_3$ ,  $Y = NO_2$ .

Nitration of **isoquinoline (7)** gives 5-nitro compound as the major product (Fig. 18).

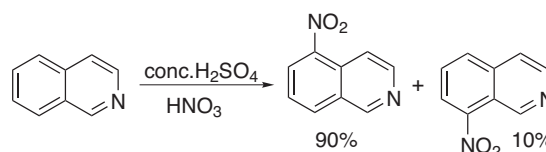


Figure 18: Nitration of isoquinoline

Some nucleophilic substitution reactions of quinoline and isoquinoline are given below.

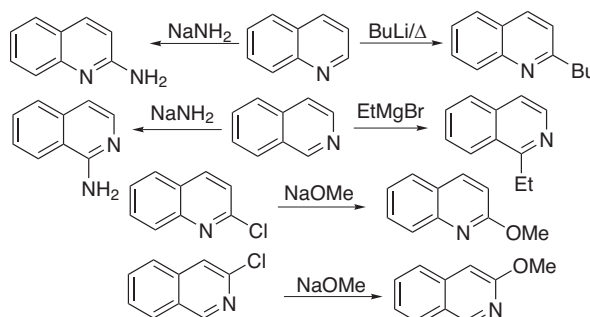
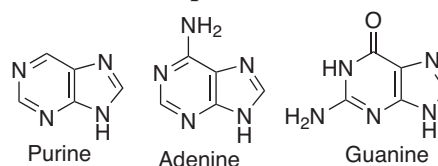


Figure 19: Nucleophilic substitution reactions of quinoline and isoquinoline

### Heterocycles as biomolecules

Among many other important biomolecules, DNA consists of two fused heterocyclic units (e.g., **adenine** and **guanine**) based on **purine**.



Some other important heterocycles include vitamins (e.g.,  $B_1$ ,  $B_2$ ,  $B_3$  and  $B_{12}$ ), pigments (e.g., bilirubin) enzyme cofactors (e.g., folic acid), amino acids (histidine, tryptophan), and hormones (e.g., melatonin).