Heterocyclic Chemistry

Dr. Ayad

Recommended reading

- Essential of organic chemistry for student of pharmacy – Paul M. Dewick
- Organic Chemistry – Morrison & Boyd
- Heterocyclic Chemistry – Stephen J. Clark
- Heterocyclic Chemistry - Alan R. Katritzky

Introduction

- Heterocycles contain one or more heteroatoms in a ring

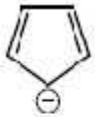
carbocycle heterocycles – X, Y, Z are usually O, N or S

- Heterocycles are important and a large proportion of natural products contain them
- Many pharmaceuticals and agrochemicals contain at least one heterocyclic unit
- Heterocyclic systems are important building-blocks for new materials possessing interesting electronic, mechanical or biological properties

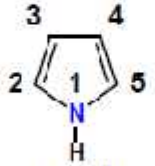
Classification – Unsaturated / Saturated

Classification – Aromatic Five-Membered

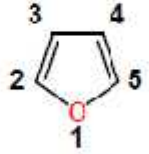
Isoelectronic carbocycle



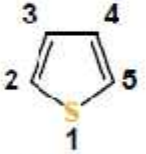
Heterocycles



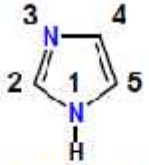
pyrrole



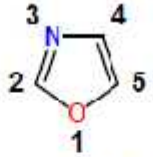
furan



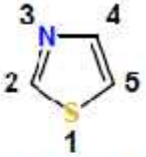
thiophene



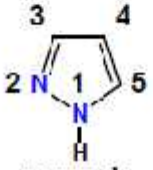
imidazole



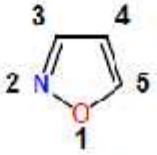
oxazole



thiazole

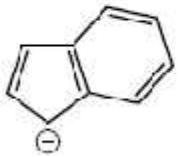


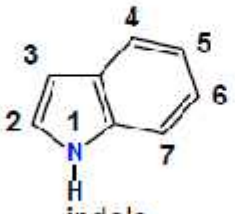
pyrazole



isoxazole

isothiazole





indole

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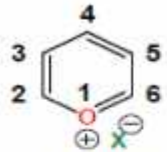
Classification – Aromatic Six-Membered

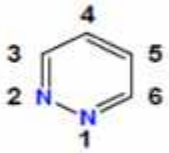
Isoelectronic carbocycle

Heterocycles

pyridine

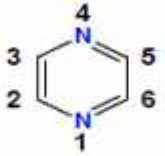


pyrylium

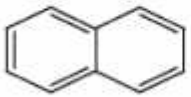


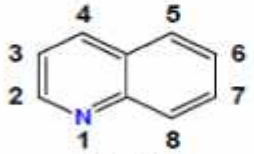
pyridazine

pyrimidine

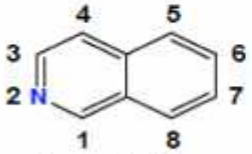


pyrazine





quinoline

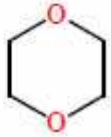


isoquinoline

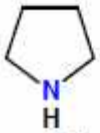
Saturated

ethylene oxide

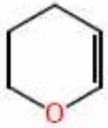
THF



1,4-dioxan

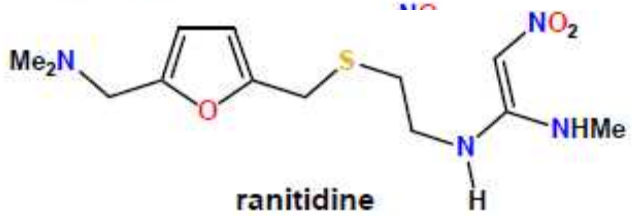


pyrrolidine



dihydropyran

Bioactive Furans, Pyrroles and Thiophenes

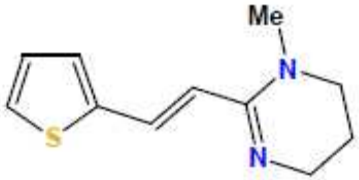


ranitidine

- Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H_2-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers

ketorolac

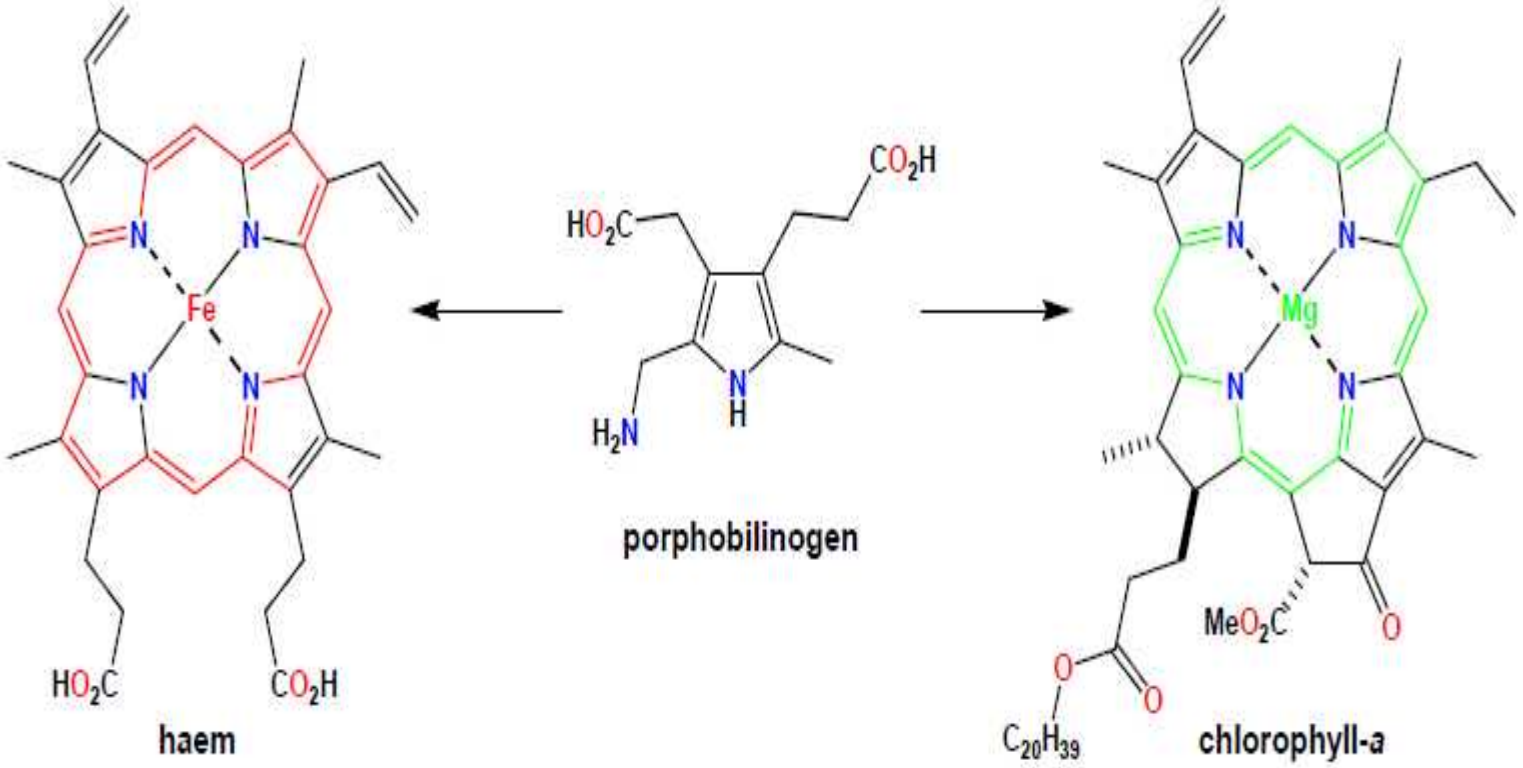
- Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug



banminth

- Pyrantel (Banminth®, Phibro) is an anthelminthic agent and is used to treat worms in livestock

Porphyrin is an important cyclic tertrapyrrole that is the core structure of heme and chlorophyll.

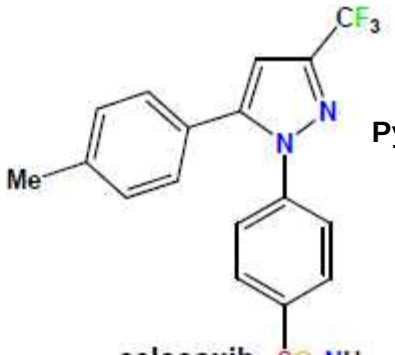


- The pigment haem is found in the oxygen carrier haemoglobin
- Chlorophyll-*a* is responsible for photosynthesis in plants
- Both haem and chlorophyll-*a* are synthesised in cells from porphobilinogen

1,2-Azoles – Bioactive 1,2-Azoles

Isoazole

leflunomide



Pyrazole

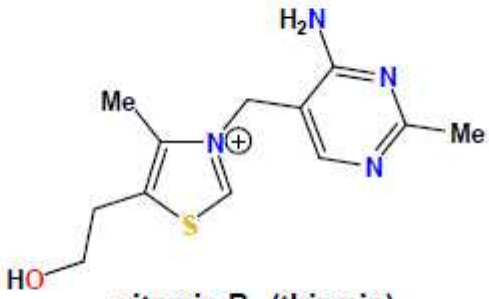
celecoxib SO_2NH_2

- Leflunomide (Arava®, Sanofi-Aventis) inhibits pyrimidine synthesis in the body and is used for the treatment of rheumatoid arthritis and psoriatic arthritis
- Celecoxib (Celebrex®, Pfizer) is a non-steroidal anti-inflamatory (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms
- Celecoxib is a COX-2 inhibitor, blocking the cyclooxygenase-2 enzyme responsible for the production of prostaglandins. It is supposed to avoid gastrointestinal problems associated with other NSAIDs, but side effects (heart attack, stroke) have emerged

1,3-Azoles – Bioactive 1,3-Azoles

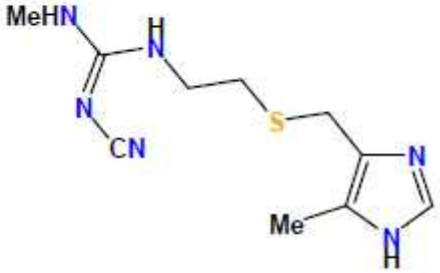
O-methylhalfordinol

Oxazole



vitamin B_1 (thiamin)

Thiazole



cimetidine

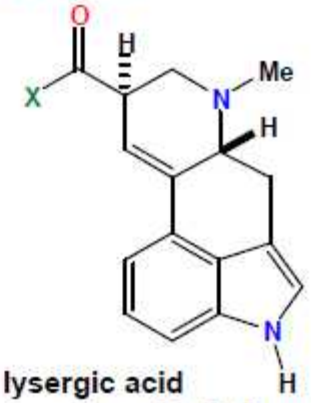
Imidazole

- *O*-Methylhalfordinol is a plant-derived alkaloid
- Vitamin B1 (thiamin) is essential for carbohydrate metabolism. Deficiency leads to beriberi, a disease which is characterised by nerve, heart and brain abnormalities
- Cimetidine (Tagamet®, GSK) is an H_2-receptor antagonist which reduces acid secretion in the stomach and is used to treat peptic ulcers and heartburn

Indoles – Bioactive Indoles

tryptophan

sumatriptan



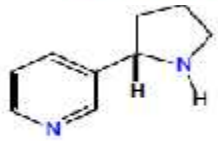
X = OH lysergic acid

X = NEt_2 *lysergic acid diethyamide* (LSD)

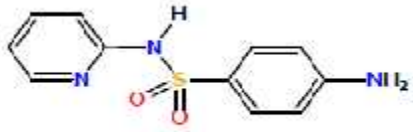
- Tryptophan is one of the essential amino acids and a constituent of most proteins
- Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS
- LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural product of the ergot fungus

5-hydroxytryptamine (serotonin)

Bioactive Pyridines

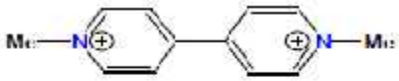


nicotine

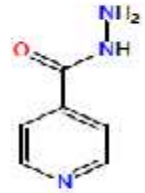


sulphapyridine

- Nicotine is pharmacologically active constituent of tobacco – toxic and addictive
- Sulphapyridine is a sulfonamide anti-bacterial agent – one of the oldest antibiotics



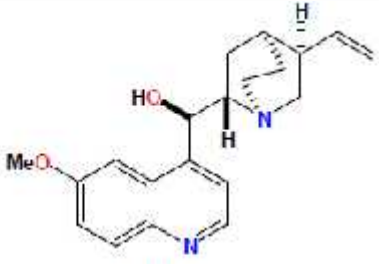
paraquat



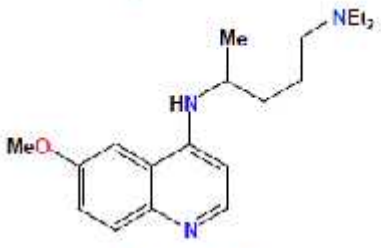
isoniazide

- Paraquat is one of the oldest herbicides – toxic and non-selective
- Isoniazide has been an important agent to treat tuberculosis – still used, but resistance

Bioactive Quinolines/Isoquinolines

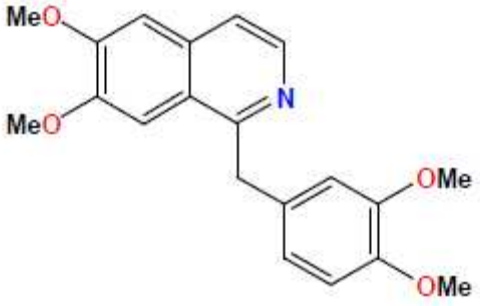


quinine



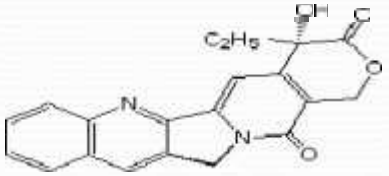
chloroquine

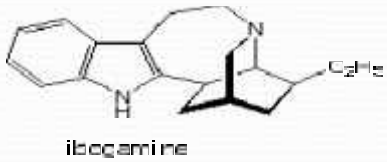
- Quinine is an anti-malarial natural product isolated from the bark of the *Cinchona* tree
- Chloroquine is a completely synthetic anti-malarial drug that has the quinoline system found in quinine – parasite resistance is now a problem

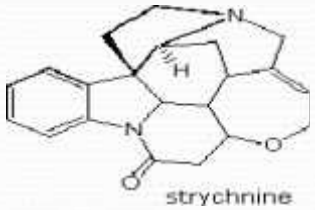


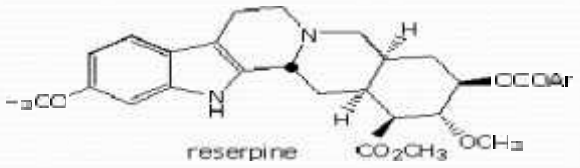
papaverine

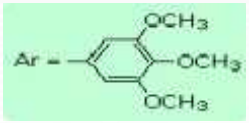
Heterocyclic structures are found in many natural products. Examples of some nitrogen compounds, known as alkaloids . Camptothecin is a quinoline alkaloid which inhibits the DNA enzyme topoisomerase I. Reserpine is an indole alkaloid, which has been used for the control of high blood pressure and the treatment of psychotic behavior. Ajmaline and strychnine are also indole alkaloids, the former being an antiarrhythmic agent and latter an extremely toxic pesticide. The neurotoxins saxitoxin and tetrodotoxin both have marine origins and are characterized by guanidiniun moieties. Aflatoxin B_1 is a non-nitrogenous carcinogenic compound produced by the Aspergillus fungus.

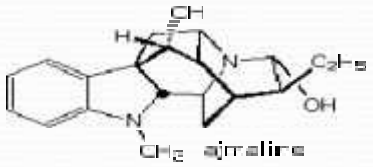


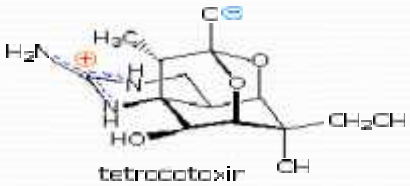




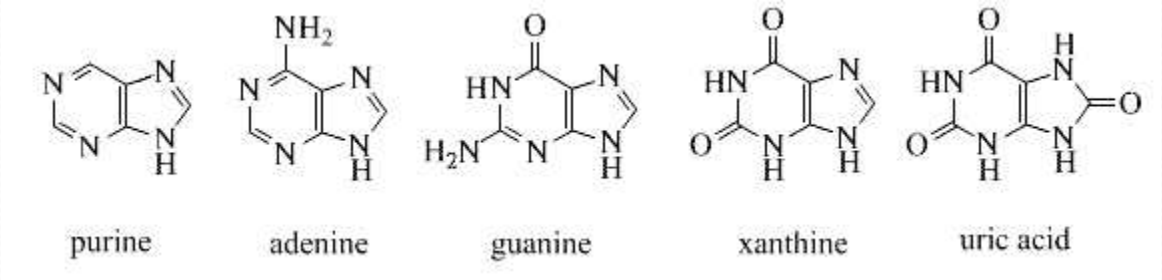




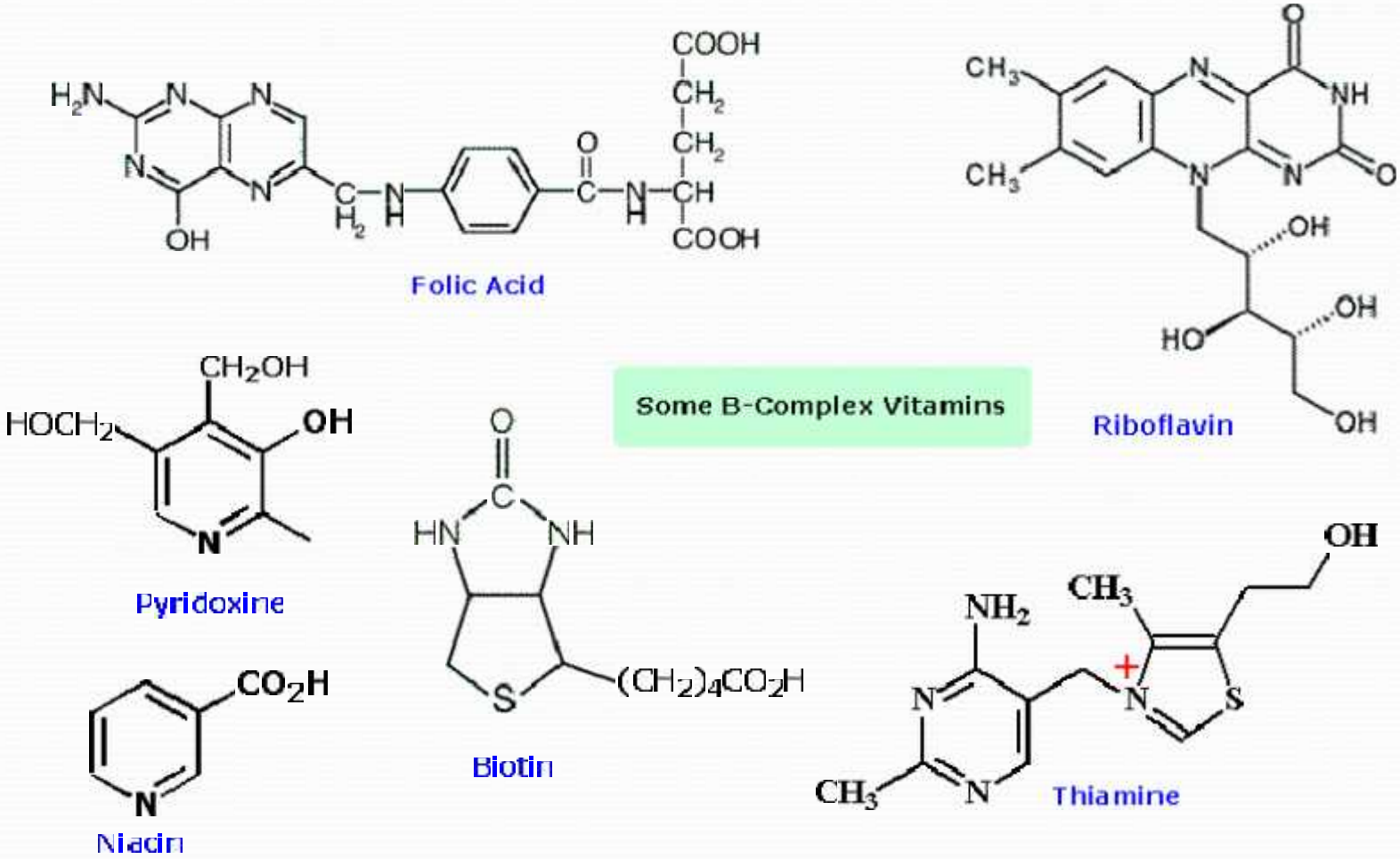




Derivatives of the simple fused ring heterocycle purine constitute an especially important and abundant family of natural products. The amino compounds adenine and guanine are two of the complementary bases that are essential components of DNA. Structures for these compounds are shown in the following diagram. Xanthine and uric acid are products of the metabolic oxidation of purines. Uric acid is normally excreted in the urine; an excess serum accumulation of uric acid may lead to an arthritic condition known as gout.



Sulfur heterocycles are found in nature, but to a lesser degree than their nitogen and oxygen analogs. Two members of the B-vitamin complex, biotin and thiamine, incorporate such heterocyclic moieties. These are shown together with other heterocyclic B-vitamins in the following diagram



Heterocycle Synthesis

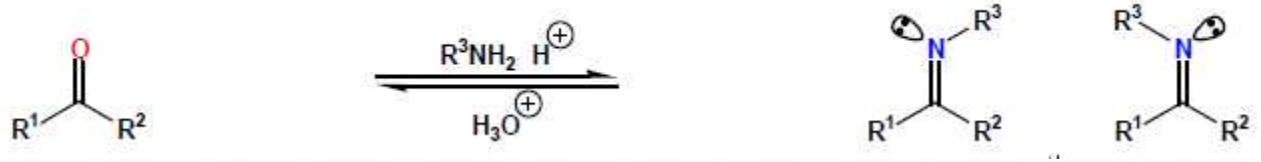
- Heterocycle synthesis requires:

  C–O or C–N bond formation using imines, enamines, acetals, enols, enol ethers

  C–C bond formation using enols, enolates, enamines

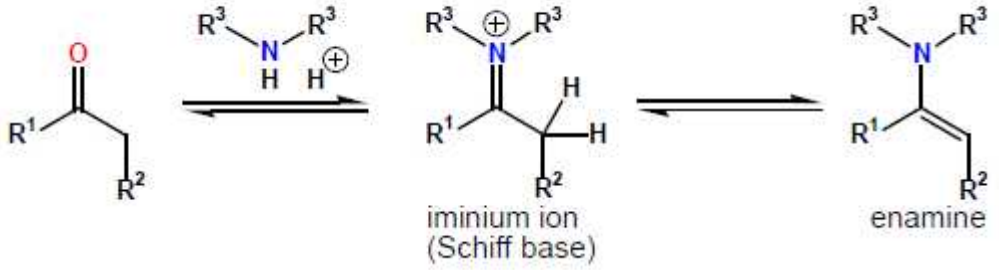
Functional Group Chemistry

Imine Formation



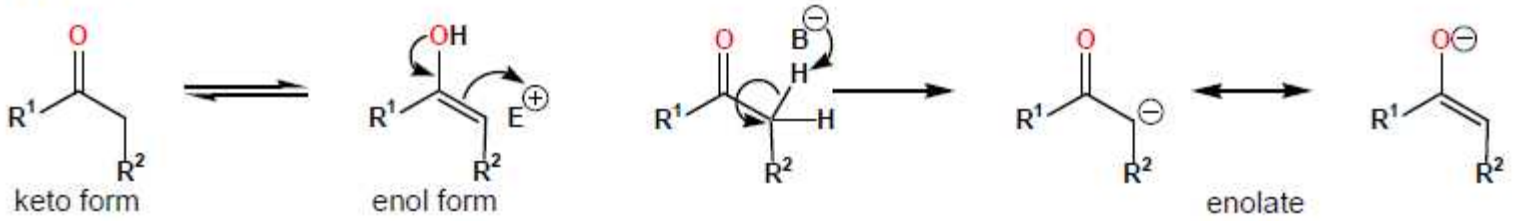
- Removal of water is usually required to drive the reaction to completion
- If a dialkylamine is used, the iminium ion that is formed can't lose a proton and an enamine is formed

Enamines



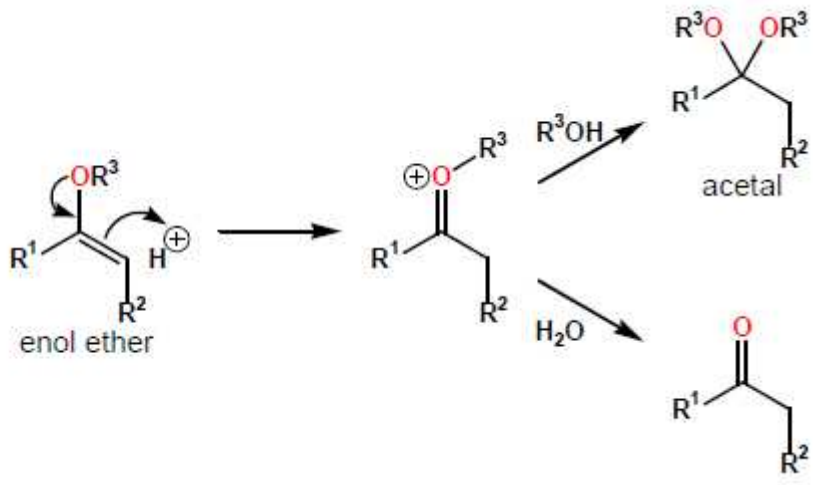
Functional Group Chemistry

Enols and Enolates



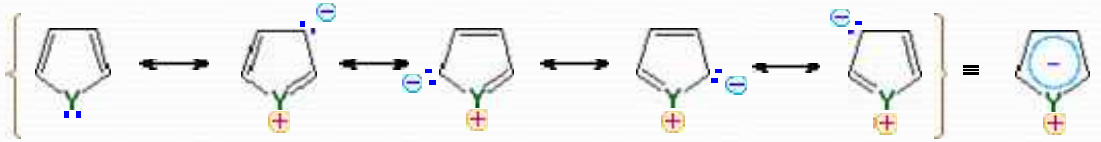
- The enol form is favoured by a conjugating group R^2 e.g. CO_2R, COR, CN, NO_2 etc.
- Avoid confusing enols (generated under neutral/acidic conditions) with enolates (generated under basic conditions)
- Enolates are nucleophilic through *C* or *O* but react with *C* electrophiles through *C*

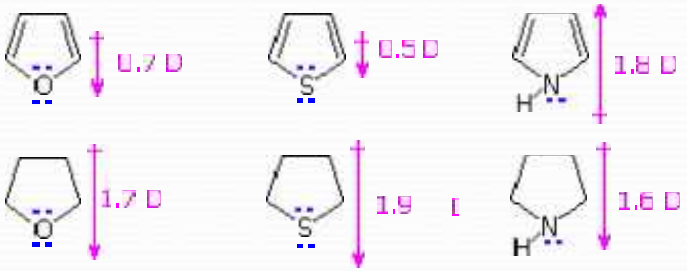
Enol Ethers



Furans, Pyrroles and Thiophenes – Structure

It is the "aromatic" unsaturated compounds, furan, thiophene and pyrrole that require our attention. In each case the heteroatom has at least one pair of non-bonding electrons that may combine with the four π-electrons of the double bonds to produce an annulene having an aromatic sextet of electrons. This is illustrated by the resonance description at the top of the following diagram. The heteroatom Y becomes sp^2-hybridized and requires a positive charge as its electron pair is delocalized around the ring. An easily observed consequence of this delocalization is a change in dipole moment compared with the analogous saturated heterocycles, which all have strong dipoles with the heteroatom at the negative end. As expected, the aromatic heterocycles have much smaller dipole moments, or in the case of pyrrole a large dipole in the opposite direction. An important characteristic of aromaticity is enhanced thermodynamic stability, and this is usually demonstrated by relative heats of hydrogenation or heats of combustion measurements. By this standard, the three aromatic heterocycles under examination are stabilized, but to a lesser degree than benzene. Additional evidence for the aromatic character of pyrrole is found in its exceptionally weak basicity (pK_a *ca.* 0) .



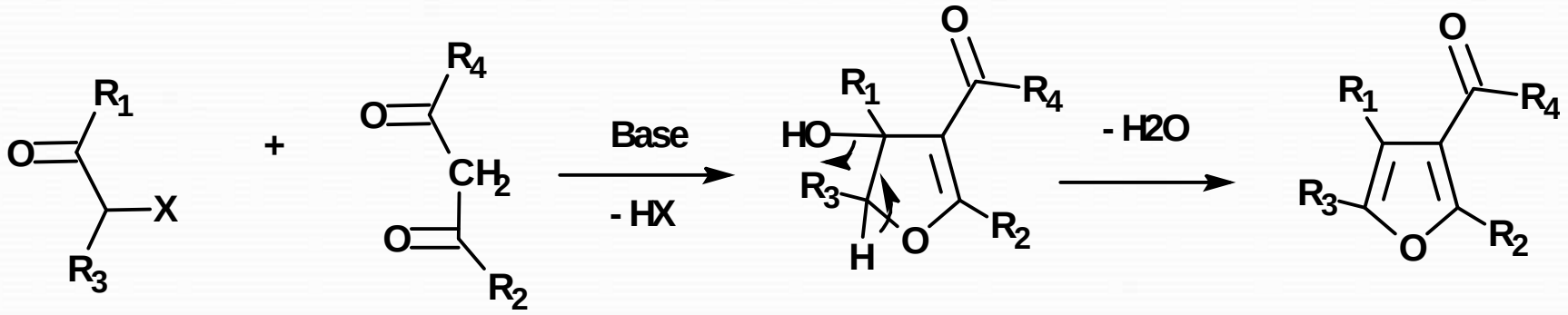


Stabilization Energies

Benzene	Furan	Thiophene	Pyrrole
38	16	11	16

kcal/mole from heats of combustion

Feist - Benary synthesis of furane



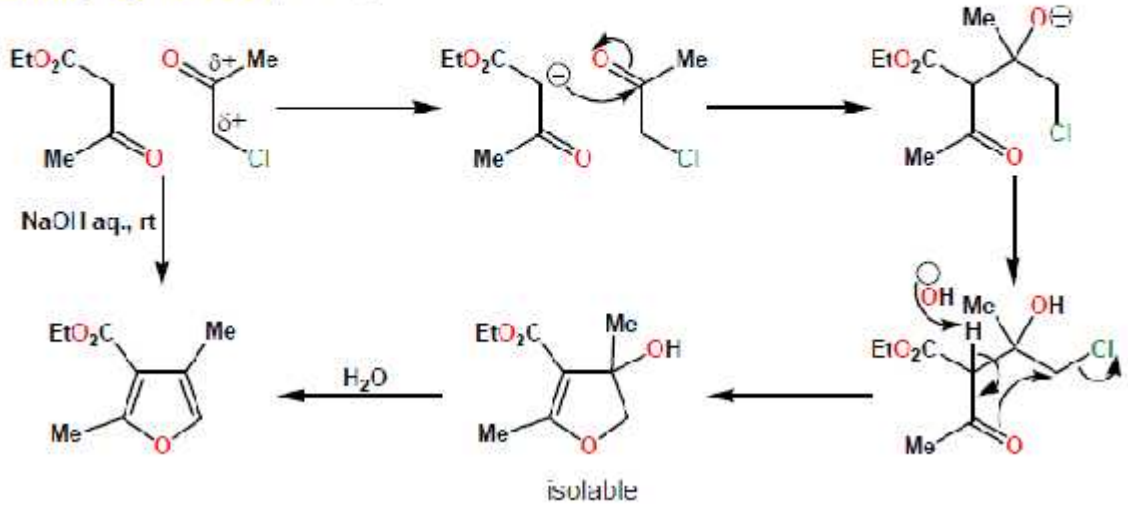
~J=halogen ketone =J=dicarbonyl

X = Cl, Br, I

Base = NaOH, amine, pyridine

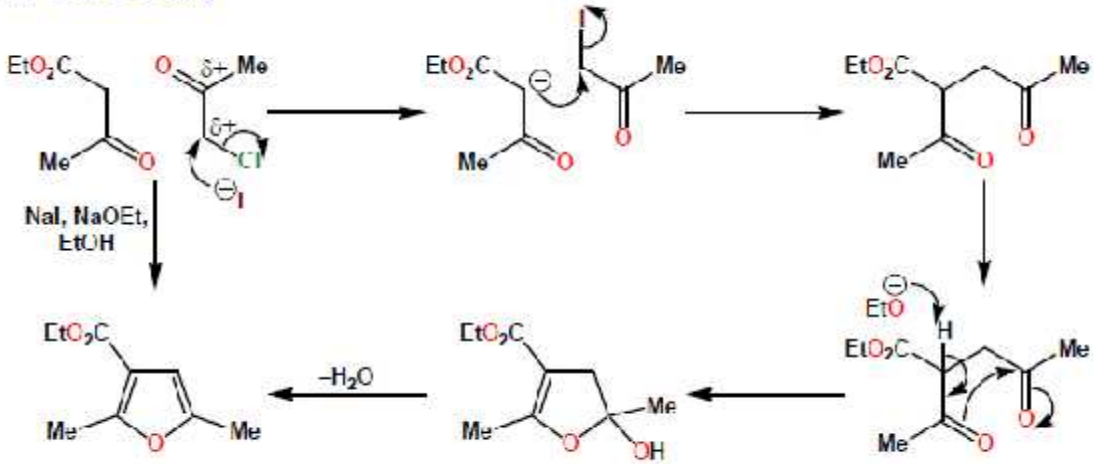
Furans – Synthesis

Feist-Benary Synthesis ("3+2")



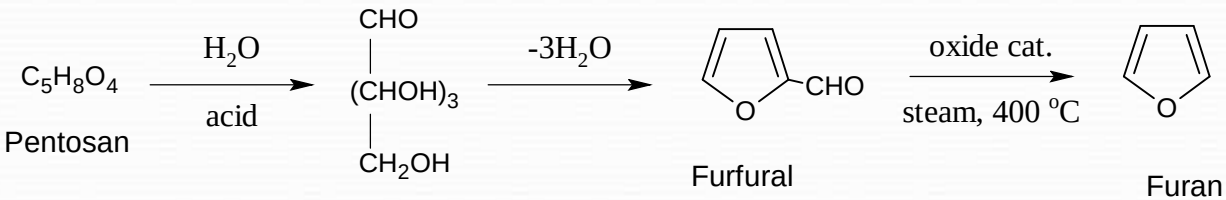
The **Feist-Benary synthesis** is an organic reaction between α-halogen ketones and β-dicarbonyl compounds to substituted furan compounds. This condensation reaction is catalyzed by amines such as ammonia and pyridine.

Modified Feist-Benary



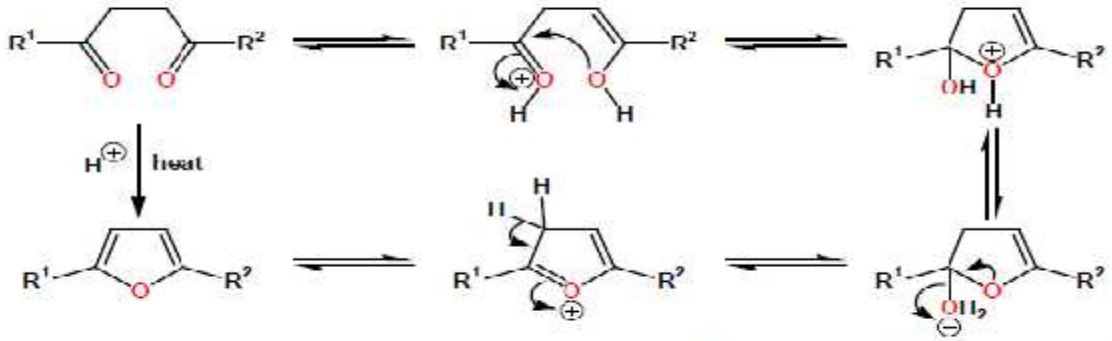
Furans – Synthesis

Furan is most readily preparead by decarbonylation (elimination of CO_2) of furfural.

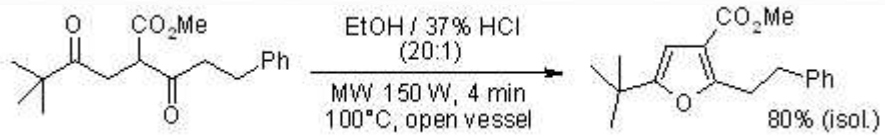


Furans – Synthesis

Paal Knorr Synthesis

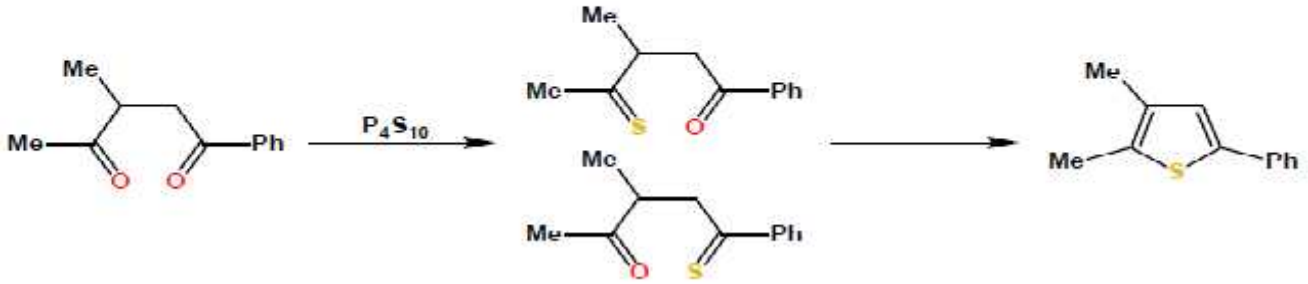


- The reaction is usually reversible and can be used to convert furans into 1,4-diketones
- A trace of acid is required – usually TsOH (p-$MeC_6H_4SO_3H$)

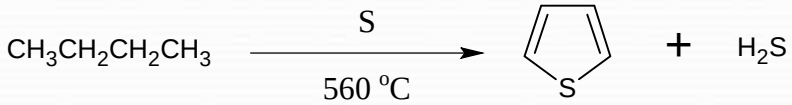


Thiophenes – Synthesis

Synthesis of Thiophenes by Paal Knorr type reaction ("4+1")



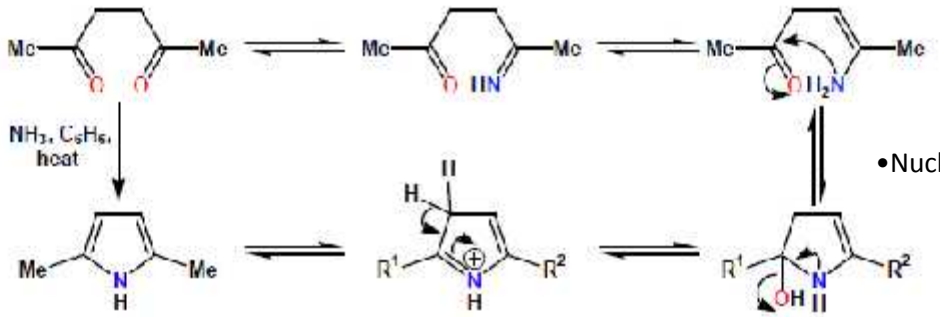
Thiophene can prepared on an industerial scale by the high temperature reaction between n-butane and sulfur.



n- Butane Thiophene

Pyrroles – Synthesis

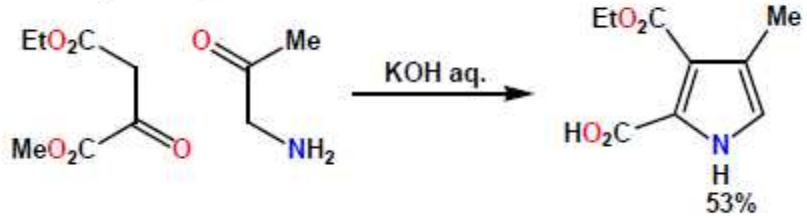
Paal Knorr Synthesis ("4+1")



•Nucleophilic addition

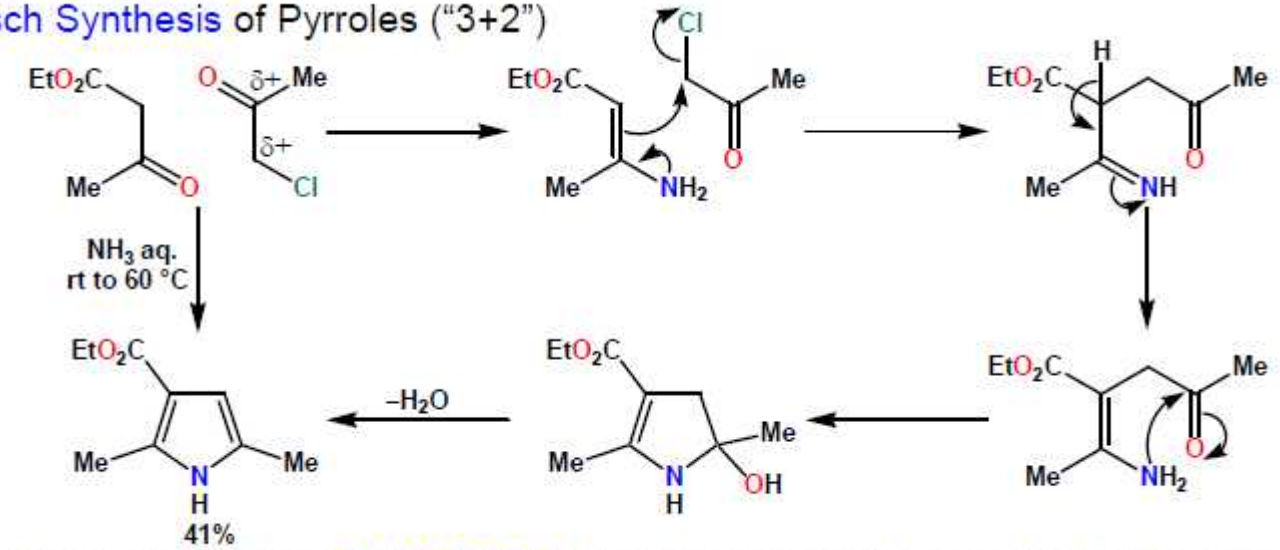
• Ammonia or a primary amine can be used to give the pyrrole or *N*-alkyl pyrrole

Knorr Pyrrole Synthesis ("3+2")



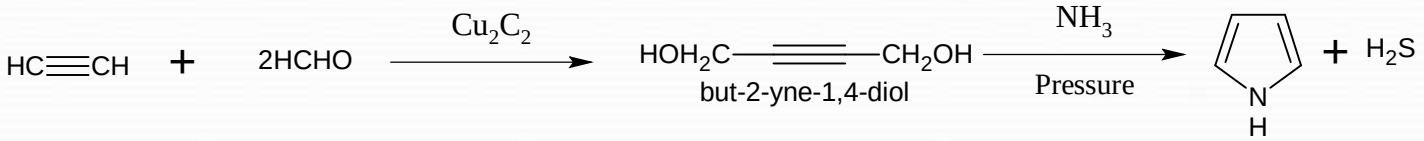
•Reaction of α-amino ketone with a β- ketoester

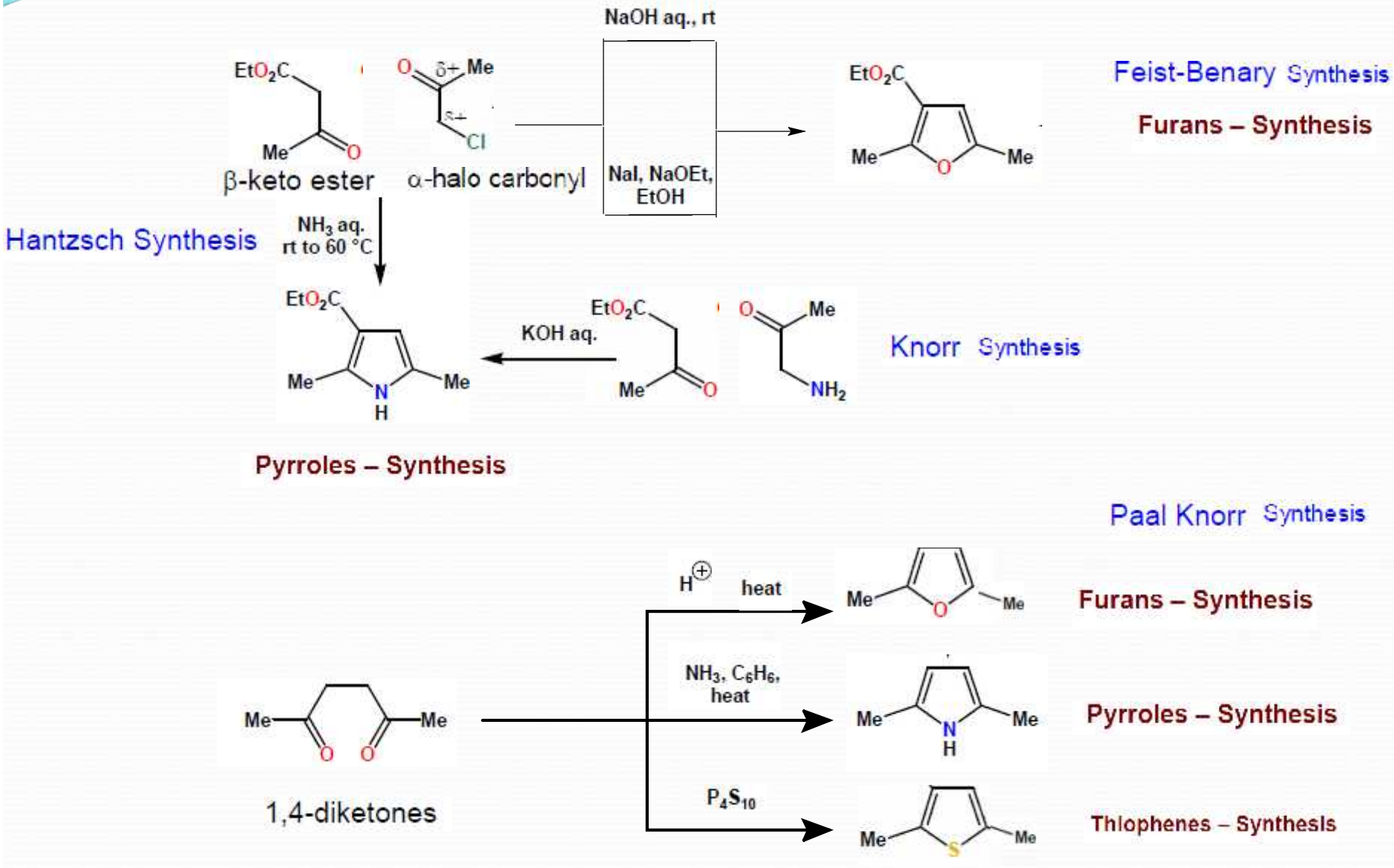
Hantzsch Synthesis of Pyrroles ("3+2")



- A modified version of the Feist-Benary synthesis and using the same starting materials: an α-halo carbonyl compound and a β-keto ester

Pyrrole can be synthesized as shown bellow




NaOH aq., rt
β-keto ester
α-halo carbonyl
NaI, NaOEt, EtOH
Feist-Benary Synthesis
Furans – Synthesis
Hantzsch Synthesis
NH3 aq. rt to 60 °C
KOH aq.
Knorr Synthesis
Pyrroles – Synthesis
Paal Knorr Synthesis
heat
Furans – Synthesis
NH3, C6H6, heat
Pyrroles – Synthesis
P4S10
Thiophenes – Synthesis
1,4-diketones