

Course Summary

Introduction

- Definition of terms and classification of heterocycles
- Functional group chemistry: imines, enamines, acetals, enols, and sulfur-containing groups

Intermediates used for the construction of aromatic heterocycles

- Synthesis of aromatic heterocycles
- Carbon–heteroatom bond formation and choice of oxidation state
- Examples of commonly used strategies for heterocycle synthesis

Five-membered aromatic heterocycles

- General properties, structure and reactivity of pyrroles, furans and thiophenes
- Methods and strategies for the synthesis of five-membered heteroaromatics
- Electrophilic substitution reactions of pyrroles, furans and thiophenes
- Strategies for accomplishing regiocontrol during electrophilic substitution

1,2 and 1,3-Azoles

- Structure and reactivity of 1,2- and 1,3-azoles
- Synthesis and reactions of imidazoles, oxazoles and thiazoles
- Synthesis and reactions of pyrazoles, isoxazoles and isothiazoles

Indoles

- Comparison of electronic structure and reactivity of indoles to that of pyrroles
- Fisher and Bischler indole syntheses
- Reactions of indoles with electrophiles
- Mannich reaction of indoles to give 3-substituted indoles (gramines)
- Modification of Mannich products to give various 3-substituted indoles

Pyridines

- General properties, electronic structure
- Synthesis of pyridines
- Electrophilic substitution of pyridines
- Nucleophilic substitution of pyridines
- Metallation of pyridines

Pyridine derivatives

- Structure and reactivity of oxy-pyridines, alkyl pyridines, pyridinium salts, and pyridine *N*-oxides

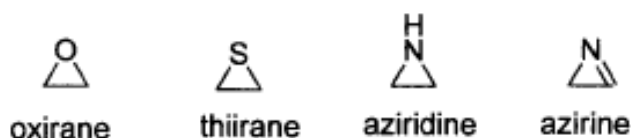
Quinolines and isoquinolines

Quinolines and isoquinolines

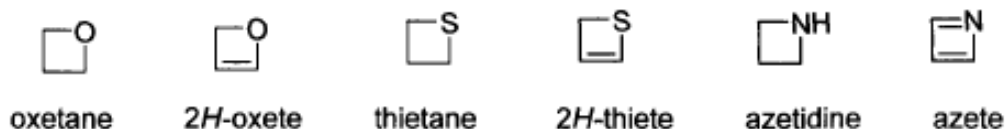
- General properties and reactivity compared to pyridine
- Electrophilic and nucleophilic substitution quinolines and isoquinolines
- General methods used for the synthesis of quinolines and isoquinolines

Heterocyclic Chemistry

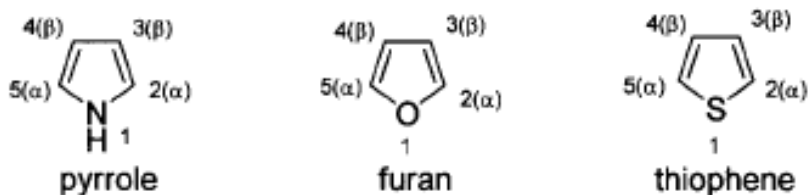
Heterocycles, as the name suggests, are cyclic compounds containing one or more heteroatoms such as N, O, S, P, Si, B, and Se. They may be further divided into aromatic heterocycles and saturated heterocycles. Heterocycles can be named by the size of their rings. Therefore, they may be classified as three-, four-, five-, six-, and seven-membered heterocycles, and so on. The most frequently encountered three-membered heterocycles are oxirane, thiirane, aziridine, and azirine.



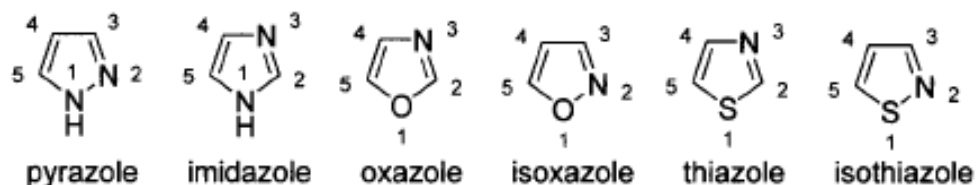
Four-membered heterocycles include oxetane, 2*H*-oxete, thietane, 2*H*-thiete, azetidine, and azetine. In drug discovery, oxetanes and azetidines are increasingly incorporated into drugs to modulate biological and physical properties and expand intellectual property space.



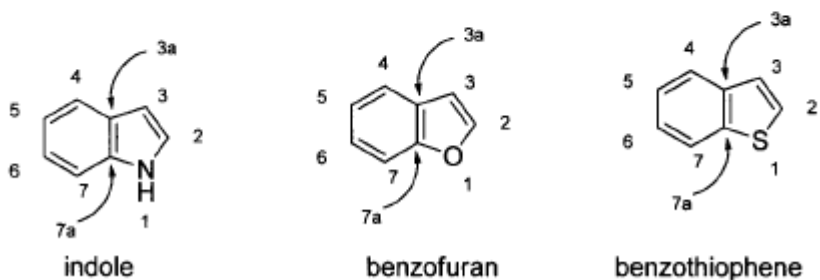
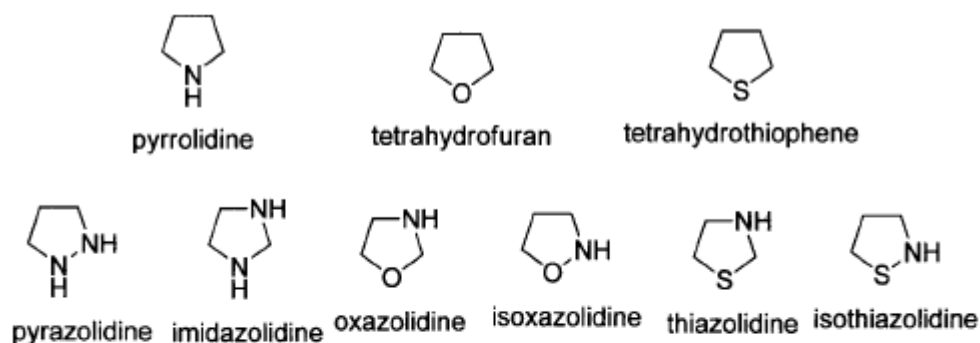
Five- and six-membered heterocycles are of utmost importance to both life and drug discovery. The most common five-membered heterocycles with one heteroatom are pyrrole, furan, and thiophene.



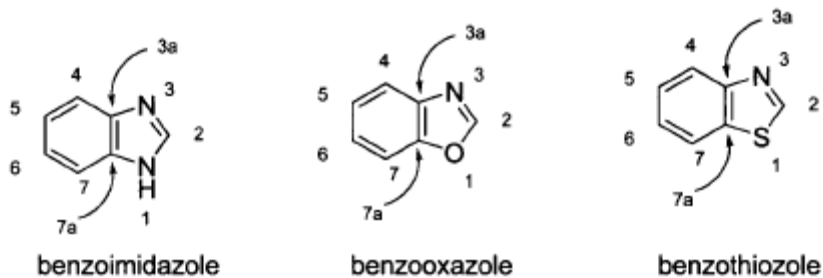
Popular five-membered heterocycles with two heteroatoms include pyrazole, imidazole, oxazole, isoxazole, thiazole, and isothiazole.



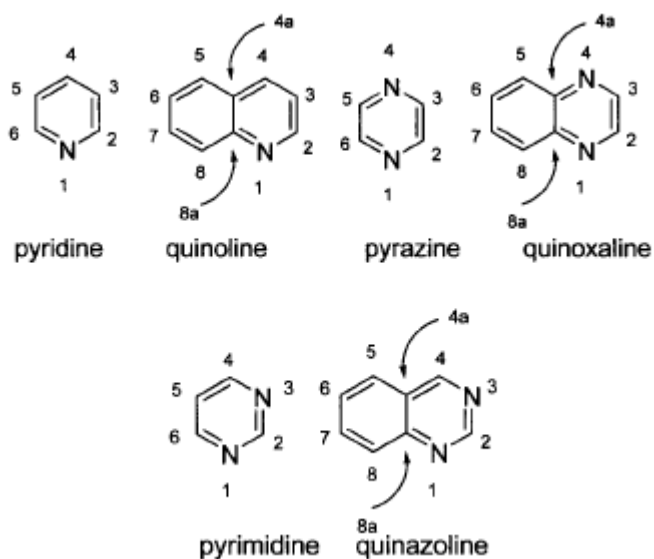
All these aromatic heterocycles have corresponding saturated heterocycles. Among those, pyrrolidines, tetrahydrofurans, and oxazolidines are more frequently encountered in drug discovery.



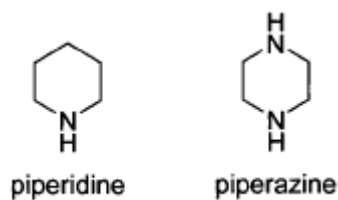
Some of the important benzene-fused five-membered heterocycles are indole, benzofuran, benzothiophene, benzimidazole, benzoxazole, and benzothiazole. The numbering of these heterocycles is shown below:



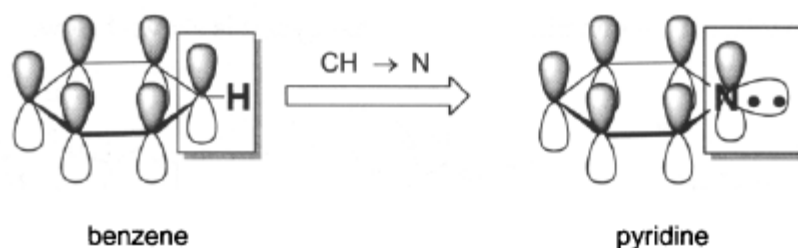
Chief among the six-membered heterocycles, pyridine and its benzene-fused derivative quinoline are most ubiquitous. Pyrazine and its benzene-fused analogue, quinoxaline, also play an important role in heterocyclic chemistry.



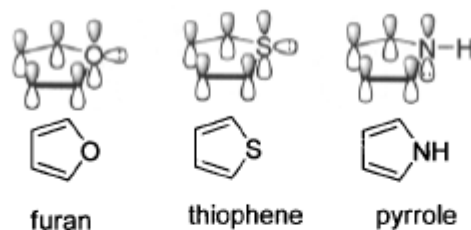
Their corresponding saturated derivatives, often encountered in drug discovery, are piperidine and piperazine.



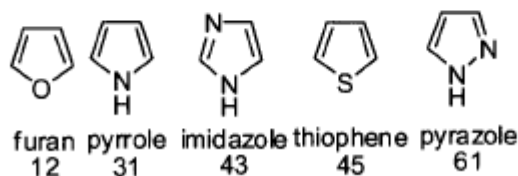
Aromaticity of Heterocycles

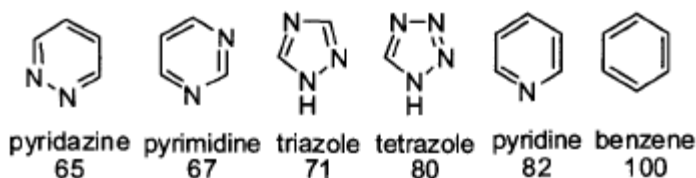


According to Hückel's rule of aromaticity, a cyclic ring molecule is aromatic when the number of its π -electrons equals $4n + 2$, where n is zero or any positive integer. The most common aromatic compound is benzene, which has $4 + 2 = 6$ π electrons. Pyridine, an electron-deficient aromatic heterocycle, also has 6 π -electrons. Compared with benzene, pyridine has an additional lone pair of electrons on the nitrogen atom after it contributes a pair of electrons to the 6 π -electrons that give it aromaticity. These lone pair electrons are responsible for much of pyridine's unique physical and chemical properties. In contrast, furan, an electron-excessive aromatic heterocycle with 6 π -electrons, differs from both benzene and pyridine. The oxygen atom has two lone pairs of electrons, one of which contributes to the 6 π -electrons to achieve aromaticity. The second pair of electrons is located in an sp^2 hybrid orbital in the plane of the furan ring. Thiophene is similar to furan in its aromaticity, although thiophene is more "aromatic" because the S atom is larger than the O atom.



The relative aromaticity of common heterocycles is shown below:



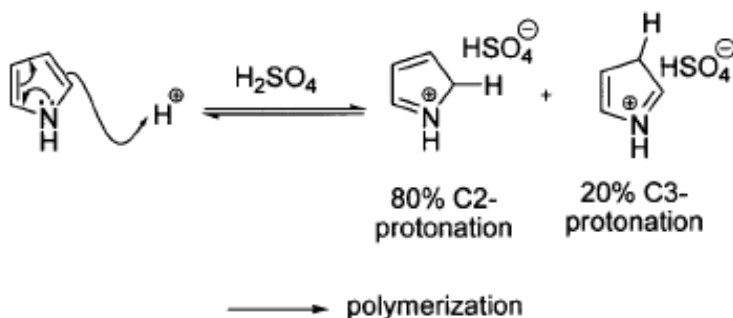


Pyrrole, also an aromatic heterocycle with 6 π -electrons, is probably the most unique of all among the aromatic heterocycles. Different from furan and thiophene, the nitrogen atom on the pyrrole ring has only one lone pair of electrons, which contributes to the 6 π -electrons to achieve aromaticity. As a consequence, although pyrrole is also an electron-excessive aromatic heterocycle like furan and thiophene, it has many characteristics of its own. For instance, it is probably the most reactive as a nucleophile among all aromatic heterocycles. In addition, pyrrole's conjugation effect outweighs the nitrogen's inductive effect in the contributing dipole moment, with the partial positive charge resting at the nitrogen atom.

Reactivity of the Pyrrole Ring

Protonation

The pyrrole nitrogen atom ($pK_a = -3.80$)¹ is only weakly basic; pyrrole loses its aromaticity when protonated because the lone pair electrons are involved in the aromatic sextet. When treated with a strong acid such as sulfuric acid, the protonation does not occur at the nitrogen atom, but most of the protonation takes place at C2 (80%), and 20% of the protonation takes place at C3 (20%).



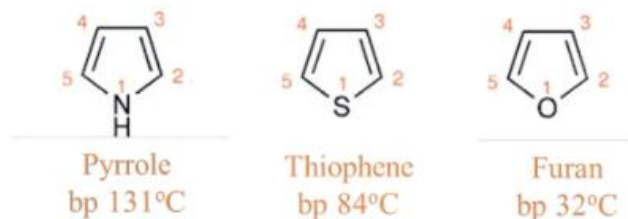
Pyrrole, Furan and Thiophene



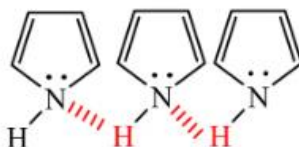
Introductions

- The main reason for the study of pyrrole came from the work on the structure of hemoglobin, the blood respiratory pigment, and the chlorophyll, the green photosynthetic pigment of plants.
- Thiophene is found in plants in association with polyacetylenes with which they are biogenetically closely linked.
- Furan occurs widely in secondary plant metabolites, especially in terpenoids.
- Unsubstituted pyrrole, furan, and thiophene are usually obtained from petroleum.

- **Pyrrole, thiophene and furan** are colorless liquids of boiling points **131°C, 84°C and 32°C** respectively.



- **Pyrrole** has a relatively high boiling point as compared to furan and thiophene, this is due to the presence of intermolecular hydrogen bonding in pyrrole.

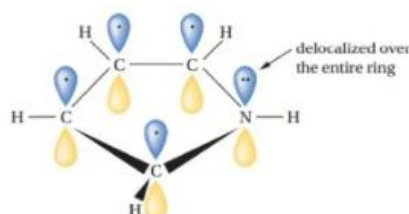
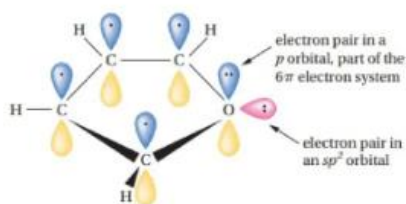


Structure and Aromaticity

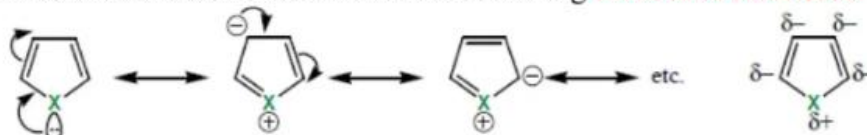
- **Pyrrole, furan and thiophene are aromatic** because:
 - 1) They fulfill the criteria for aromaticity, the extent of delocalization of the nonbonding electron pair is decisive for the aromaticity.
 - 2) The order of aromatic character of these three heterocycles compared to benzene is as follows:

Benzene > Thiophene > pyrrole > Furan

This order is consistent with the *resonance Energies and* order of the *electronegativity values* (oxygen : 3.44 , nitrogen : 3.04 and thiophene : 2.56).



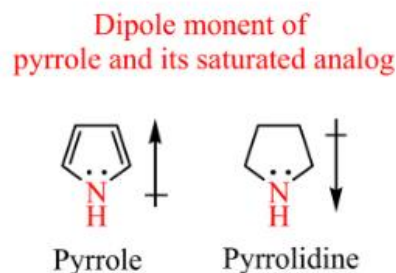
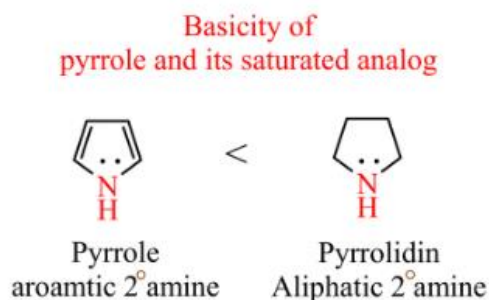
- 3) They tend to react by **electrophilic substitution** due appearance of **-ve** charge on carbon atoms due to delocalization as shown in the following **resonance structures**.



- In comparison to benzene the order of reactivity in electrophilic substitution is as follows: **Pyrrole > Furan > Thiophene > Benzene**
- Electrophilic substitution** on **furan** requires **very mild, non acidic conditions** (acids may induce polymerization or ring opening), however, for **thiophene** the acidity is less critical since it is stable to **aqueous mineral acids** but not to **100 % strong acids** or **Lewis acids** such as AlCl_3 .
- Regioselectivity:** The **2 & 5 (α) positions** are more reactive than **3 & 4 (β) Positions**, as in pyrrole the intermediate results from electrophilic attack at C2 can be stabilized by three resonance structures while the intermediate results from the attack C3 is only stabilized by two resonance structures.

Evidence of aromatic character in pyrrole

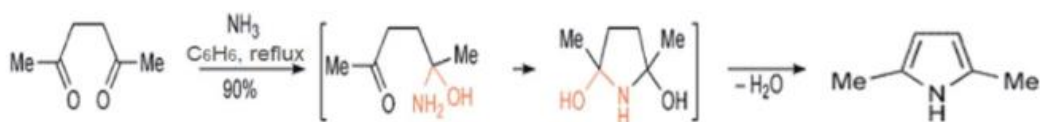
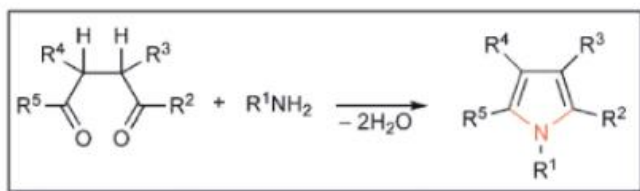
- All ring bonds are intermediates between single and double bonds.
- It tends to react by electrophilic substitution.
- It shows **lower basicity and higher acidity** as a secondary amine compared to **pyrrolidine**, due to the nitrogen lone pair's involvement in the aromatic sextet. This reversal in dipole moment causes protonation at carbon atoms rather than nitrogen.



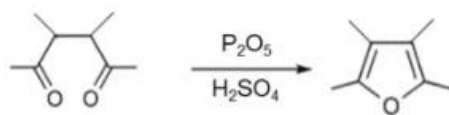
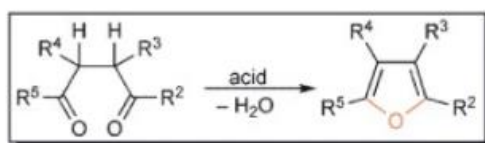
Synthesis of Pyrrole, Furan and Thiophene

1) From 1,4-dicarbonyl compounds (Paal-Knorr Synthesis)

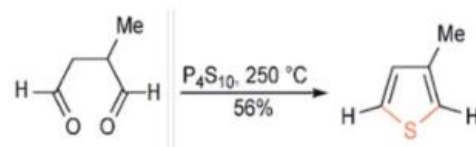
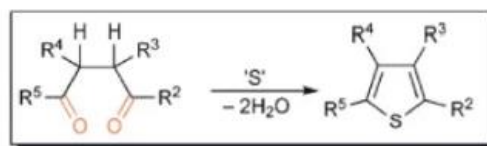
Pyrrol: 1,4-Dicarbonyl compounds can be dehydrated, with ammonia (NH₃) or amines, to form pyrrole.



Furan: 1,4-Dicarbonyl compounds can be dehydrated, with acids, to form furans.

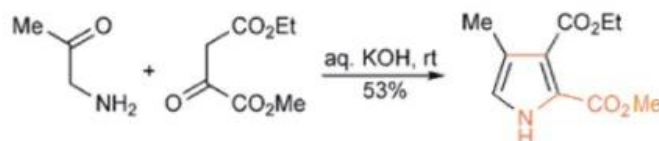
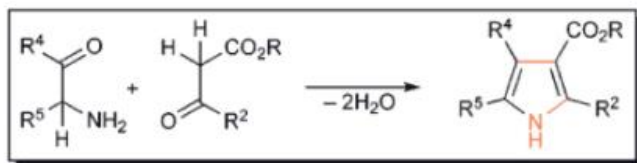


Thiophene: 1,4 - Dicarbonyl compound with a source of sulfide, traditionally phosphorus sulfides, to form thiophenes.

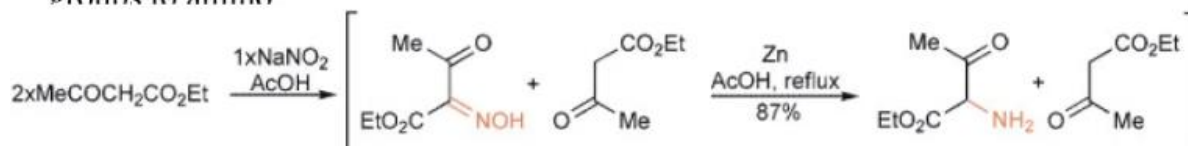


2) Knorr synthesis of Pyrrole

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

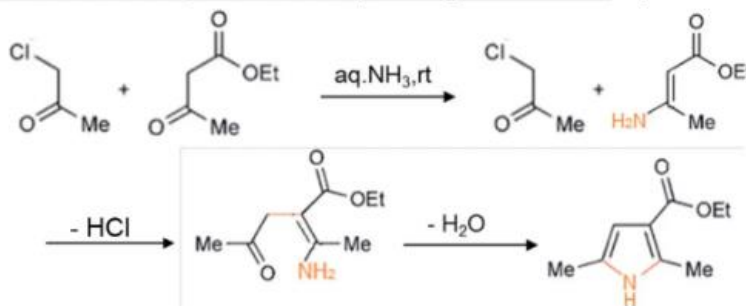


- A way of avoiding the difficulty of handling α - aminocarbonyl compounds is to prepare them in the presence of the second component, with which they are to react. **Zinc - acetic acid** or **sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$)** can be used to reduce oximino groups to amino groups



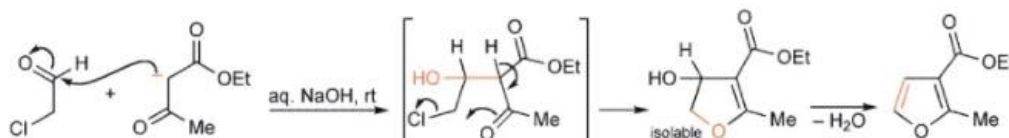
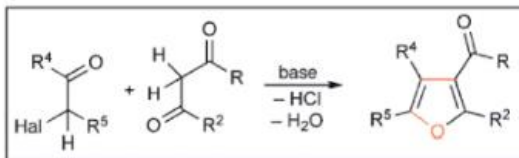
3) The Hantzsch Synthesis of Pyrrole

α - Halo-carbonyl compounds react with 1,3 - dicarbonyl compounds in the presence of ammonia to give pyrrole.



4) The Feist-Benary Synthesis of Furan

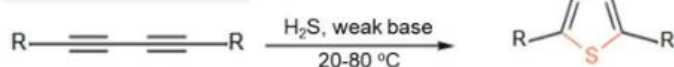
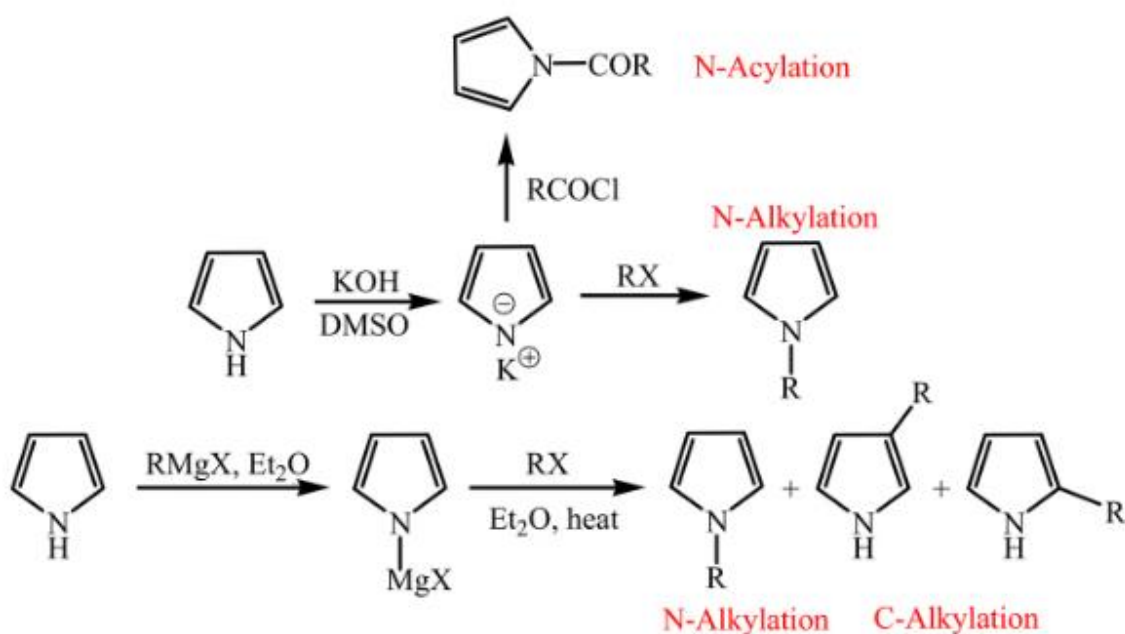
α - Halo - carbonyl compounds react with 1,3-dicarbonyl compounds in the presence of a base (not ammonia) to give furans.



Reactions

1) Alkylation and acylation of Pyrrole and *N*-metallated Pyrrole

- Due to participation of N lone pair in aromaticity, pyrrole has exceptionally strong acidic properties for a secondary amine for instance it can react with strong bases or Grignard reagent or potassium metal in inert solvents, and with sodium amide in liquid ammonia, to give salt like metallated compounds.
- These derivatives can be used to **alkylate or acylate pyrrole**, the position of substitution may be the nitrogen, the α - or the β -carbon depending on type of metallic cation and the polarity of solvent used as shown below:

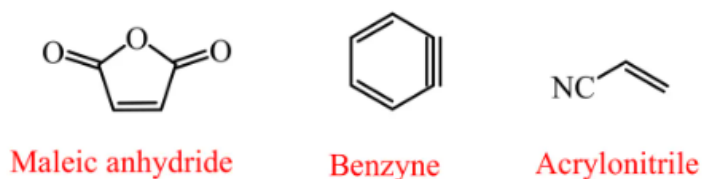


2) Cycloaddition reactions (Diels Alder Reaction)

- **Cycloaddition reaction** is one in which two reactants add together with formation of 2 new C-C bonds at the same time to give a cyclic product e.g. **Diels-Alder reaction**.
- **Diels-Alder reaction** involves addition of a compound containing a double or a triple bond (2π e it is Called **dienophile**) across the 1,4-position of a conjugated system (4π e, **1,3-diene**), with the formation of a six membered ring.



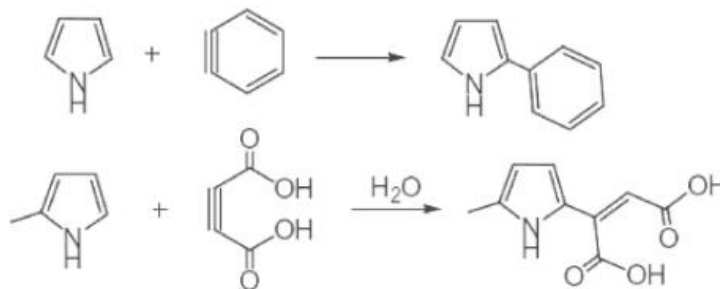
- The heterocyclic compounds can react as a **1,3-diene** in **Diels-Alder reaction** with reactive dienophiles (e.g. maleic anhydride, or benzyne) or with less reactive dienophiles (e.g. acrylonitrile) in presence of catalyst.



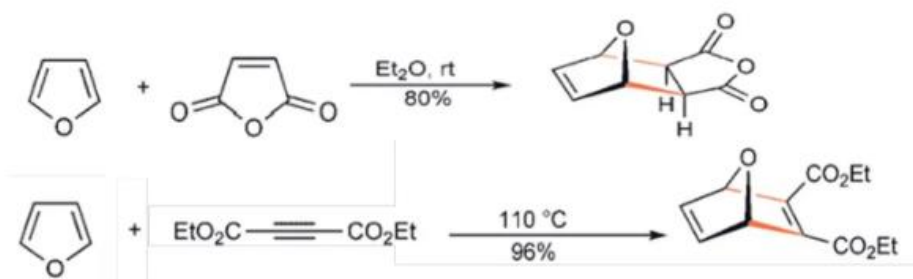
- The diene can be activated by E.D.g while the dienophile by E.W.g.
- Thus N-alkyl pyrrole and N-amino pyrrole are more reactive than pyrrole itself in Diels-Alder reaction but less reactive than furan (the least aromatic 5- membered heterocycle thus the most reactive in addition) .
- The order of reactivity in Diels-Alder reaction is as follows which is the reverse of aromaticity order:



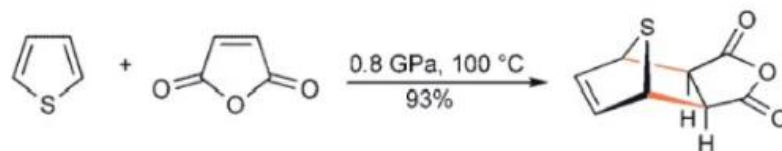
Pyrrole generally do not undergo easily Diels-Alder reaction but the typical reaction is α -substitutive addition.



Furan

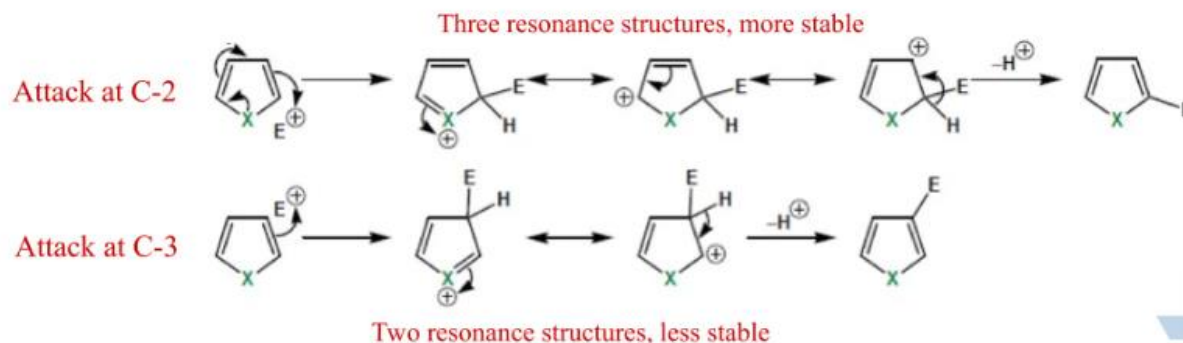


Thiophene

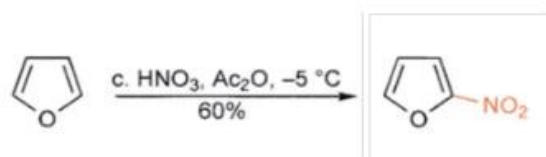
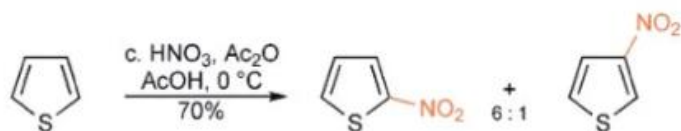
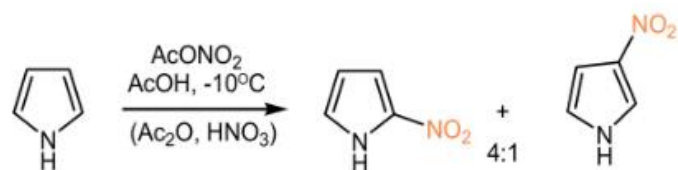


3) Electrophilic Substitution reactions

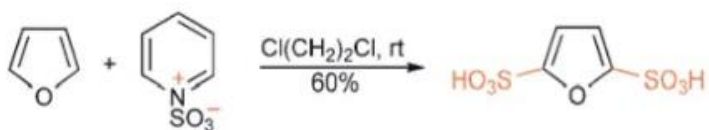
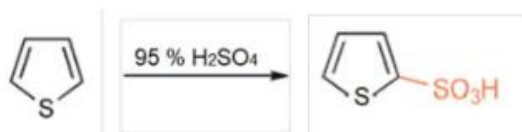
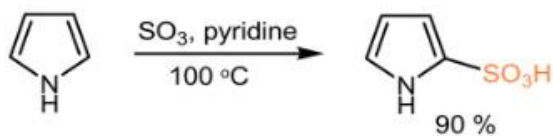
- Electrophilic substitution normally occurs at a carbon atoms.
- Also it occurs preferentially at C-2 (the position next to the heteroatom) rather than at C-3 (if position 2- is occupied it occurs at position 3).
- This is due to attack at C-2 gives more stable intermediate (it is stabilized by three resonance structure) than the intermediate resulted from C-3 attack (it is stabilized by two resonance structure).



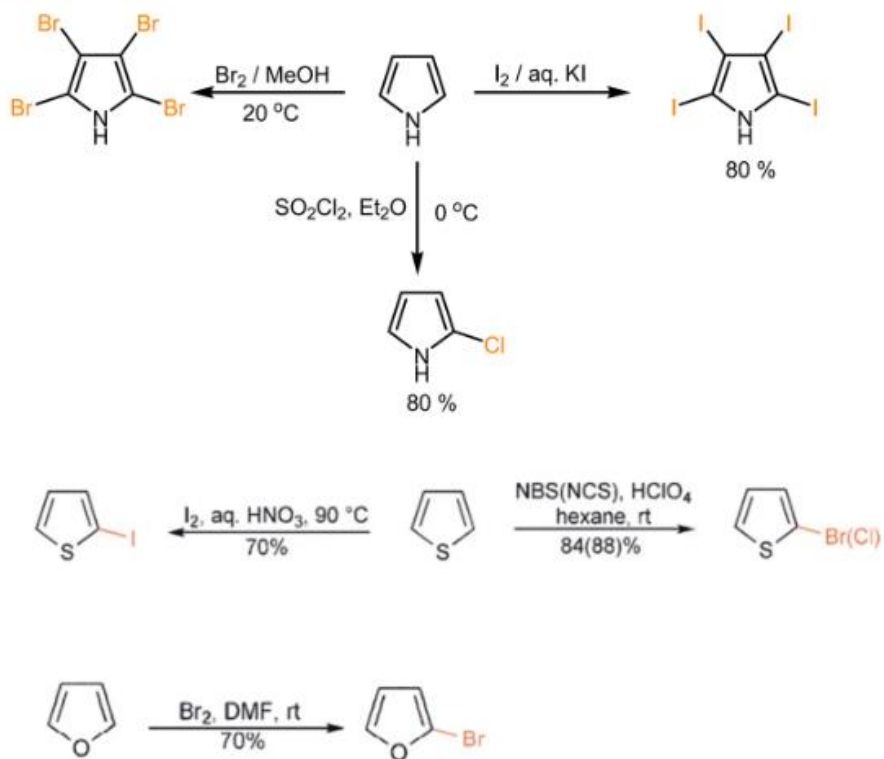
1) Nitration



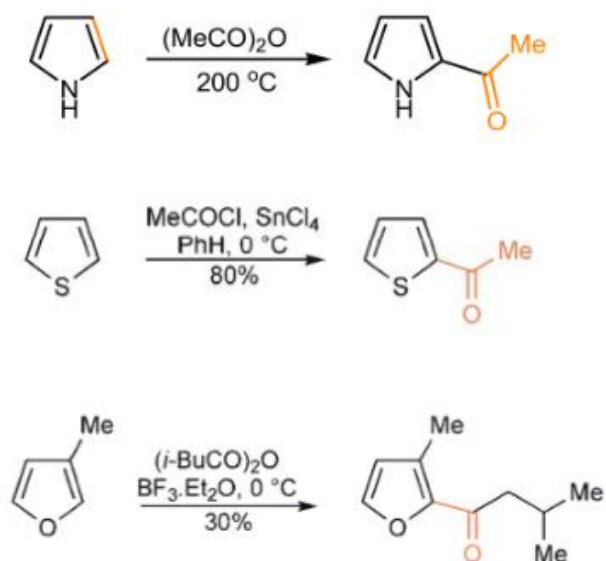
2) Sulfonation



3) Halogenation

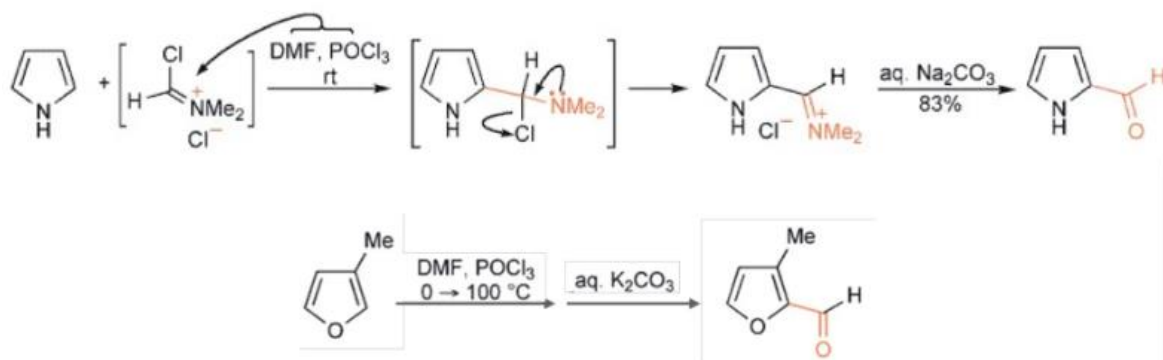


4) Friedel-Crafts Acylation (C-acylation)



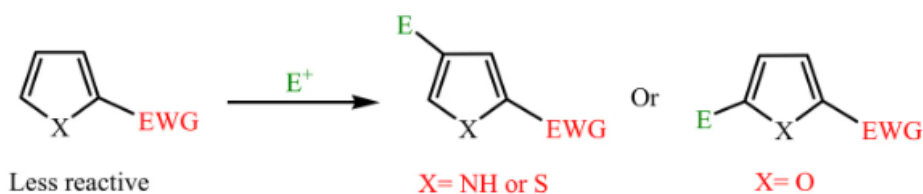
5) Vilsmeier acylation

Formylation of pyrrole and furan by reacting it with dimethylformamide/phosphoryl chloride.

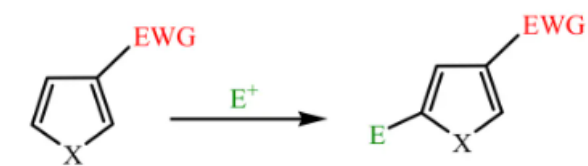


Second Electrophilic Substitution

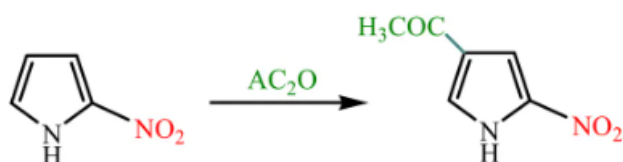
A) Monosubstituted with Electro Withdrawing group



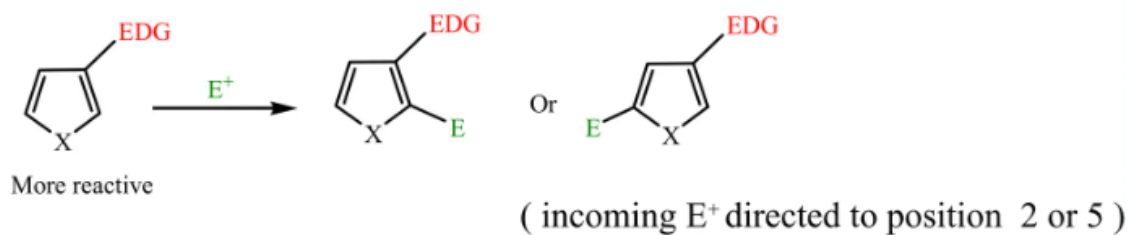
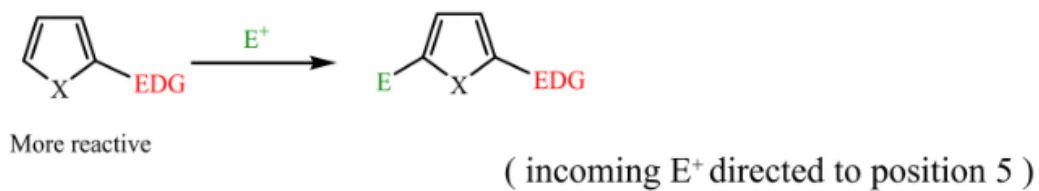
(incoming E⁺ directed to position 4 or 5)



(incoming E⁺ directed to position 5)

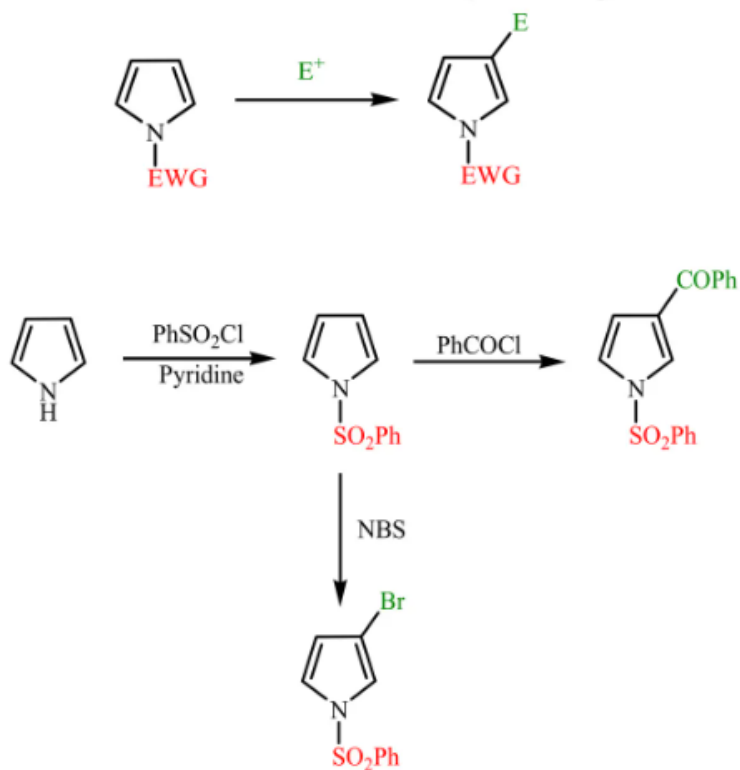


B) Monosubstituted with Electro Donating group

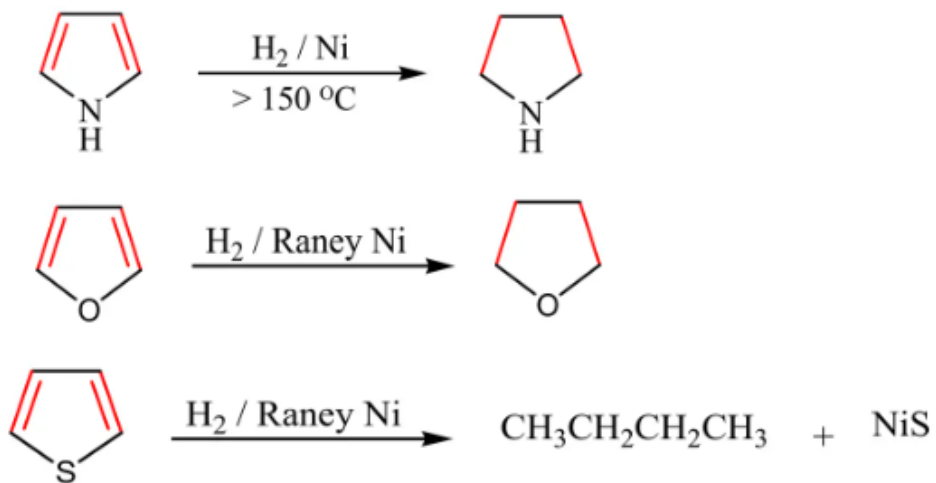


C) N-substituted pyrrole with electron withdrawing group

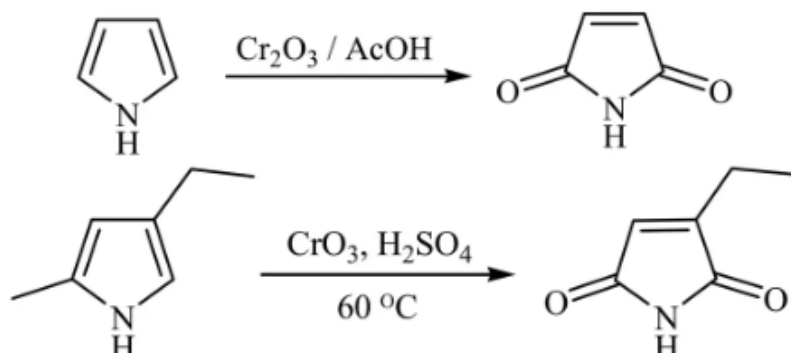
(incoming E⁺ directed to position 3)



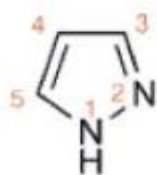
4) Reduction Reaction



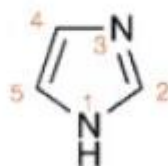
5) Oxidation Reaction



Pyrazole and Imidazole

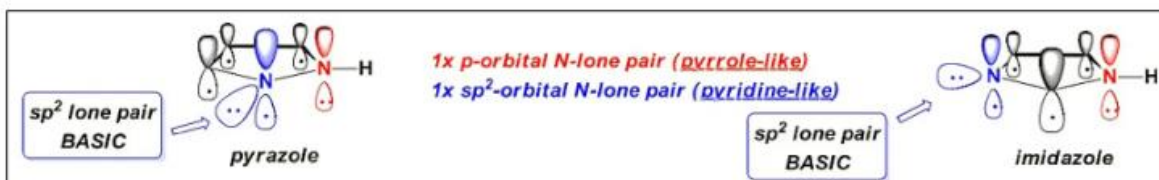
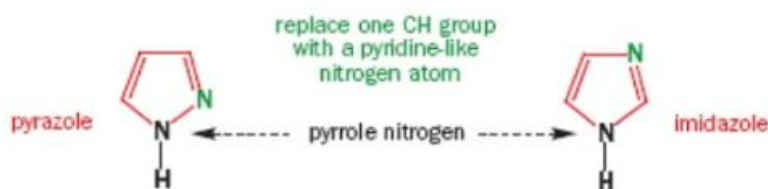


Pyrazole



Imidazole

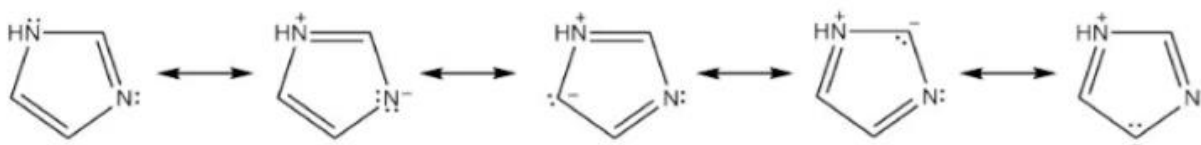
Introduction



Only **one nitrogen** atom can contribute two electrons to the aromatic sextet. It is the nitrogen with the hydrogen (**red**) and it is described as pyrrole-like nitrogen. While the **second nitrogen** which has no hydrogen (**blue**) is described as pyridine-like.

Resonance Structure of Imidazole

- The lone pair on pyrrole-like nitrogen is delocalized round the ring while that on the pyridine-like nitrogen is localized in sp^2 orbital on nitrogen. Thus these compounds have properties intermediate between those of pyrrole and pyridine.

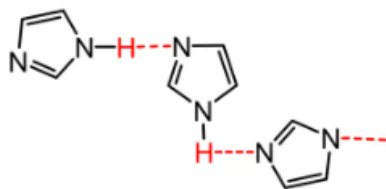


Physical properties of imidazole and pyrazole

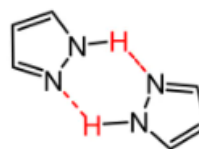
Solubility

- Imidazole and pyrazole are water soluble solids and insoluble in aprotic solvent.
- They have very much higher boiling points than pyridine: 256 and 187 °C respectively, this difference is due to imidazole has an extensive hydrogen bonding than pyrazole thus imidazole molecules can exist as oligomers, consequently more energy is required to break these bonds to bring the molecules from one phase to another.
- On the other hand pyrazole molecules can form dimers only thus lesser energy is required to break these molecules.

Imidazole molecules as a polymer



Pyrazole molecules as a dimer



- N-substituted imidazole and pyrazole have lower boiling and melting points than the unsubstituted compounds due to inability to form H-bonds.

Basicity

- Imidazole is a stronger base than pyrazole or pyridine and of course pyrrole. Thus imidazole and pyrazole are more stabilized than pyrrole in acidic medium.

Basicity order: Imidazole > Pyridine > Pyrazole > Pyrrole

This can be explained as follows:

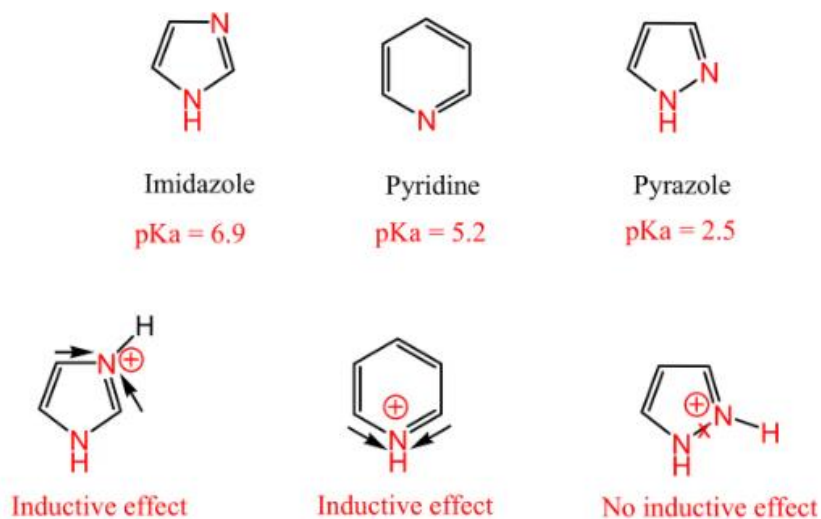
- i) Pyrrole is not basic because the lone pair on the only nitrogen is needed to complete the aromatic π system and protonation if occurs at all occurs at carbon rather than on nitrogen and the resulting cation is not aromatic.



- ii) Imidazole has two nitrogen atoms and on protonation the positive charge can be delocalized over them but although in pyridine its l.p. is available for protonation as it is not involved in maintaining aromaticity, it has only has one nitrogen on which to stabilize the positive charge thus it is less basic than imidazole.

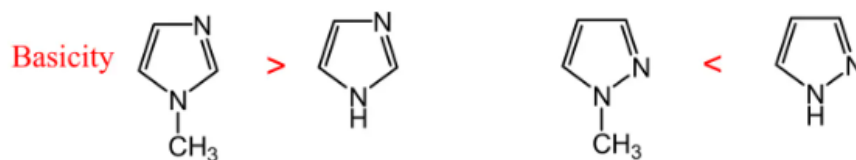


iii) Pyrazole is much weaker base than imidazole and pyridine although it also have two nitrogen atoms as in case of imidazole. This difference is due to the fact that the positive charge in pyrazolium ion is less stabilized than in the imidazolium ion and pyridinium ion.



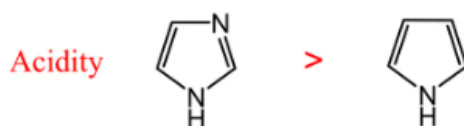
Basicity

- Generally E.D.G groups on the ring increase the basicity while E.W.G. decrease it.
- N-methyl imidazole is more basic than imidazole itself.
- However, N-methylpyrazole is less basic than pyrazole which can be attributed to steric hindrance effect which cause difficulty in accessing the lone pair of electron by the proton.



Acidity

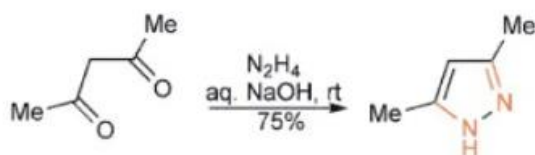
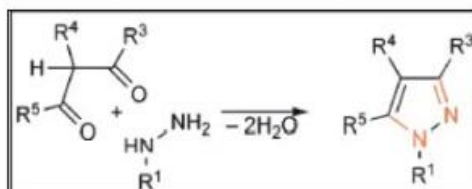
- Imidazoles unsubstituted in the 1-position are weak acids. Its acidity is greater than that of pyrrole and equals that of pyrazole.
- Thus imidazole and pyrazole are **amphoteric substances**.



Synthesis of pyrazole and imidazole

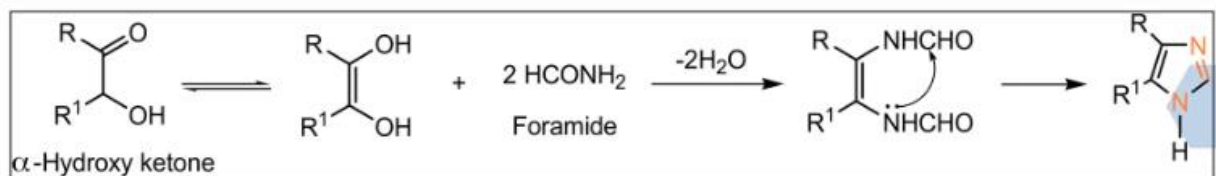
Pyrazole

- From 1,3 - Dicarbonyl Compounds and Hydrazines.



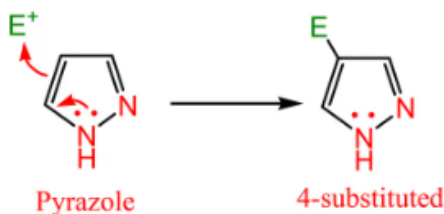
Imidazole

- From α -Hydroxy ketone and Formamide.



Reactions

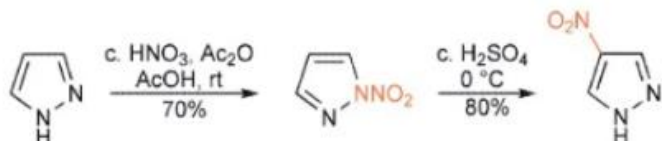
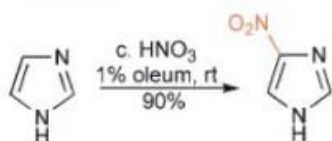
- Diazoles are less reactive than 5-membered heterocycles with one heteroatom (pyrrole and its analogs) in electrophilic aromatic substitution due to the inductive electron-withdrawing effect of the second heteroatom.
- However, they are more reactive than pyridine due to delocalization of the lone pair of electrons on the N-atom make the C- atoms bear negative charges while in pyridine the N- atom exerts inductive electron withdrawing effect only.
- The orientation in pyrazole, is at the 4-position due to the deactivation effect of the pyridine-like nitrogen.



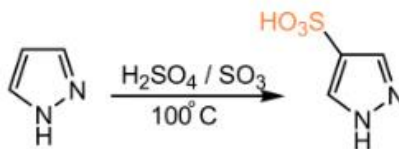
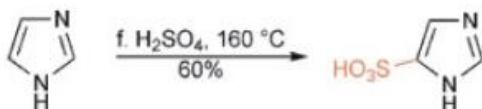
- The orientation in imidazole, is at 4 or 5-position.

Electrophilic Substitution Reactions

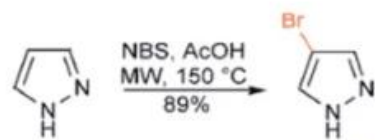
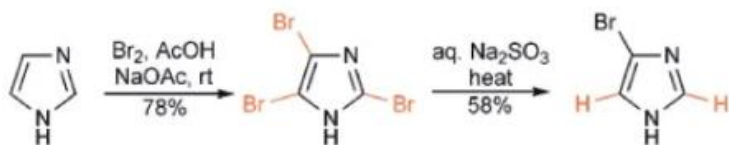
1) Nitration



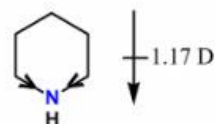
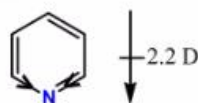
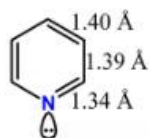
2) Sulfonation



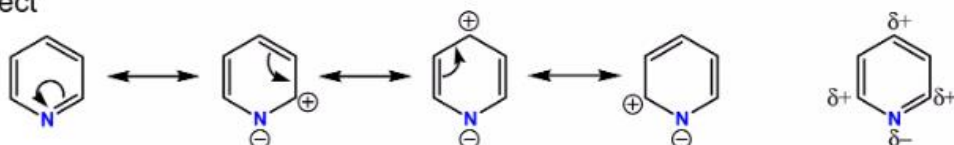
3) Halogenation



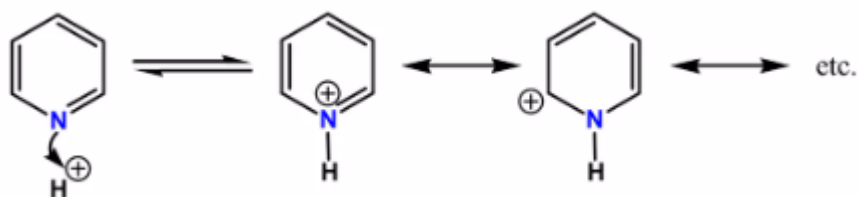
Pyridines – Structure



- Isoelectronic with and analogous to benzene
- Stable, not easily oxidised at C, undergoes substitution rather than addition
- -I Effect (inductive electron withdrawal)
- -M Effect

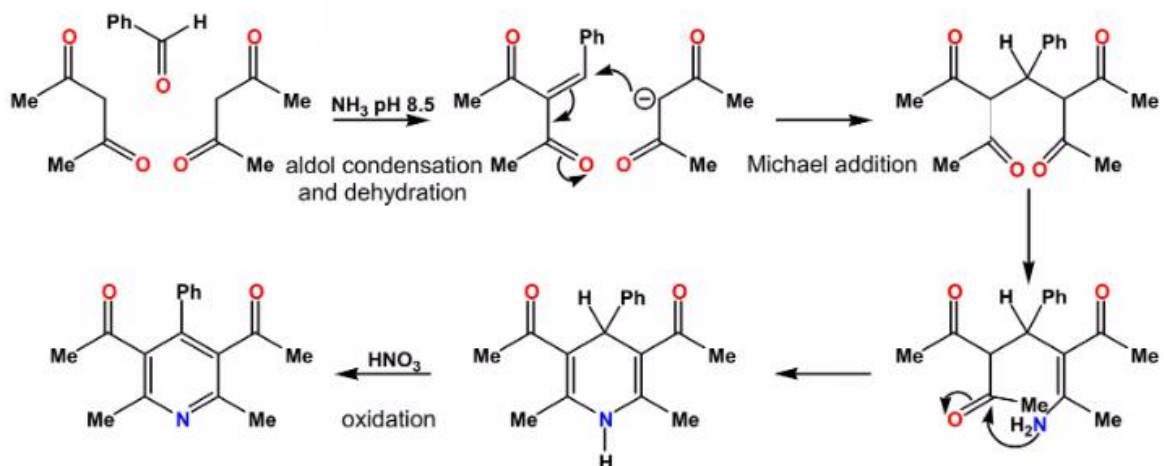


- Weakly basic – $pK_a \sim 5.2$ in H_2O (lone pair is **not** in aromatic sextet)
- Pyridinium salts are also aromatic – ring carbons are more δ^+ than in parent pyridine



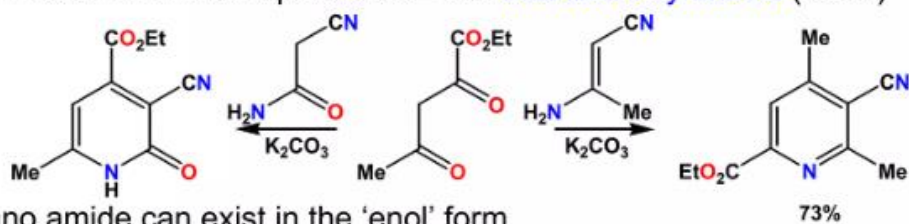
Pyridines – Synthesis

The Hantzsch synthesis ("5+1")



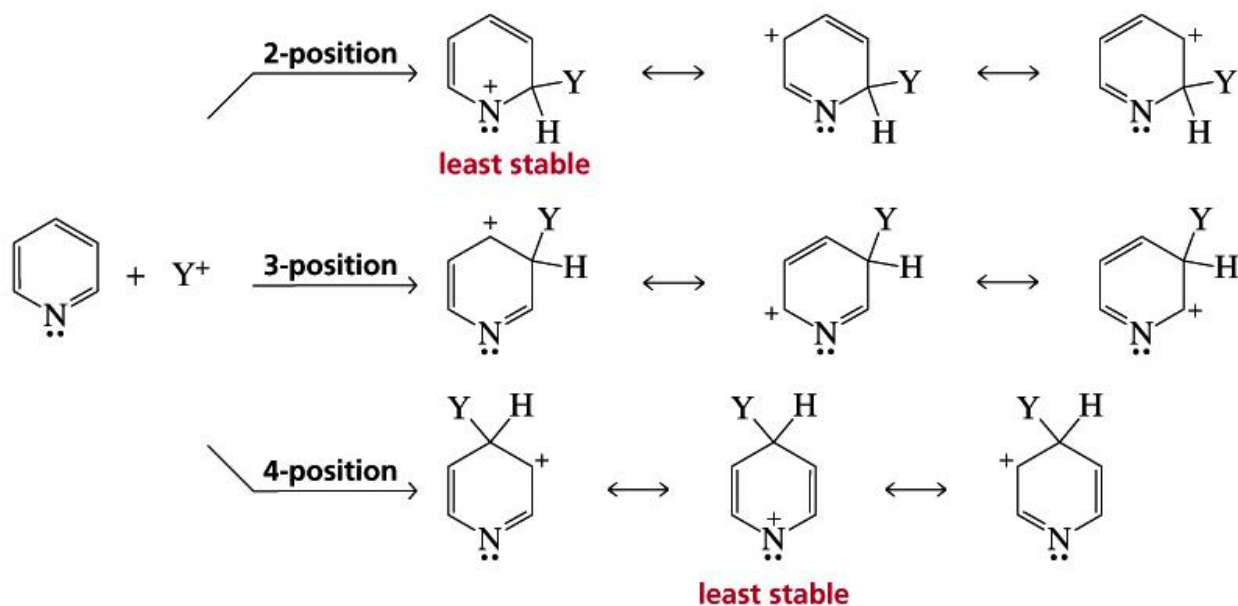
- The reaction is useful for the synthesis of symmetrical pyridines
- The 1,5-diketone intermediate can be isolated in certain circumstances
- A separate oxidation reaction is required to aromatise the dihydropyridine

From Enamines or Enamine Equivalents – the Guareschi synthesis ("3+3")



- The β -cyano amide can exist in the 'enol' form

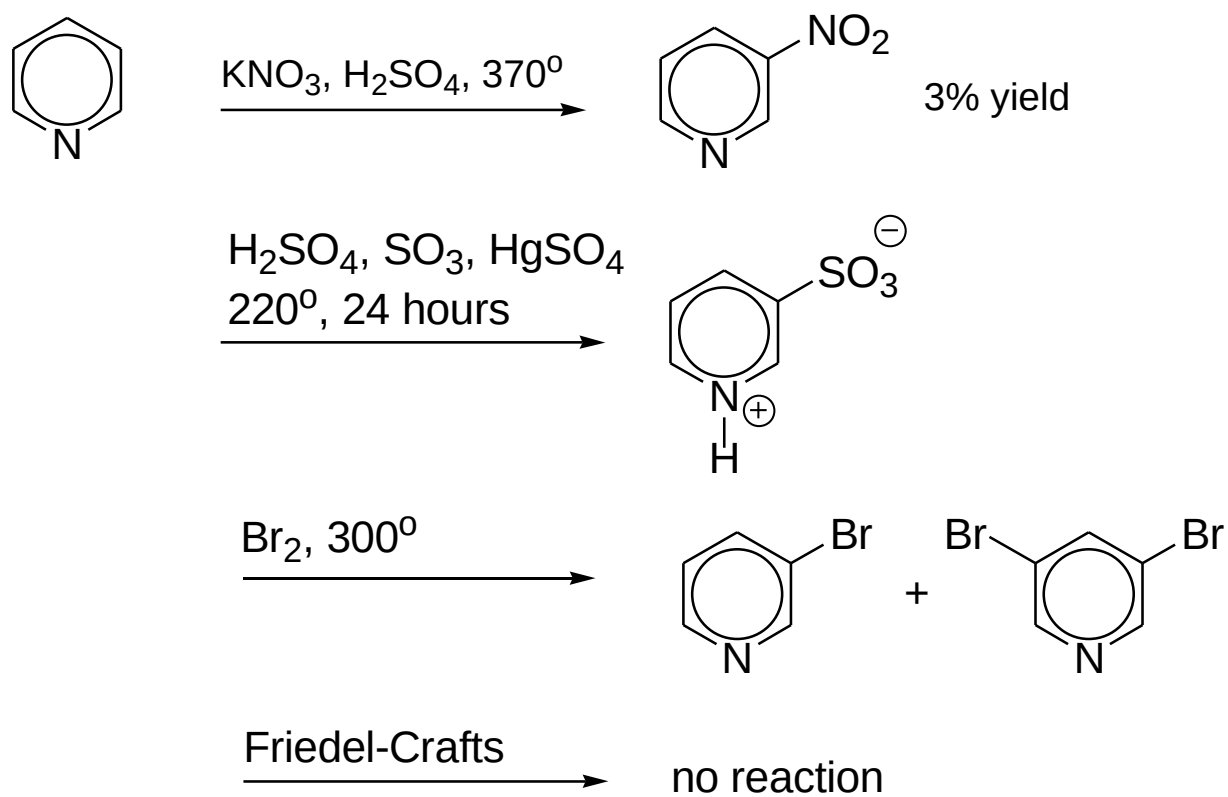
Pyridines – Electrophilic Reactions



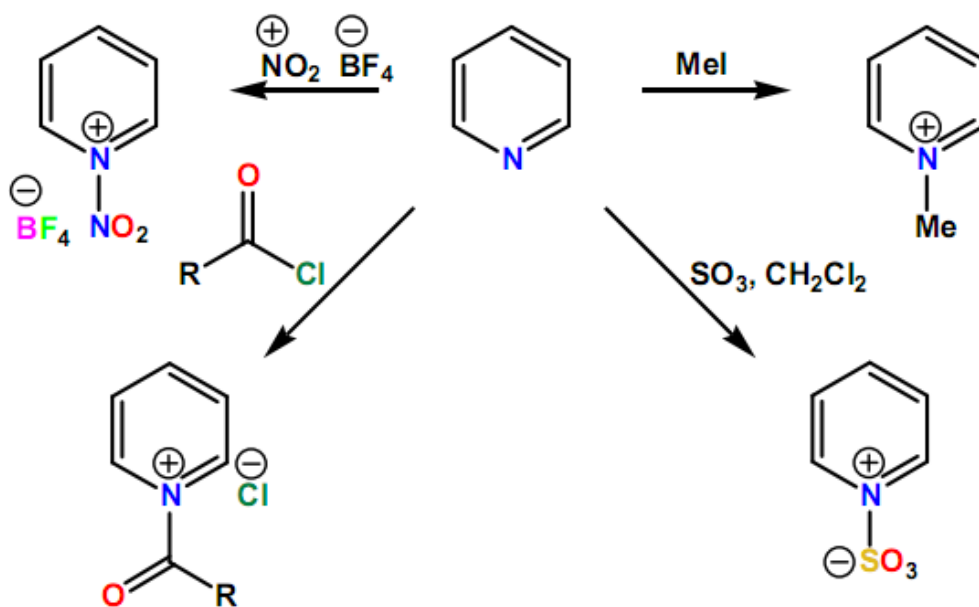
Pyridine important solvent & base ($\sim 3^\circ$ amine)

Reactions:

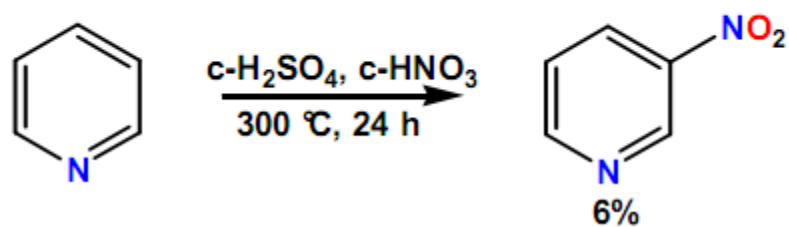
1) EAS (much less reactive than benzene $\sim$ nitro)



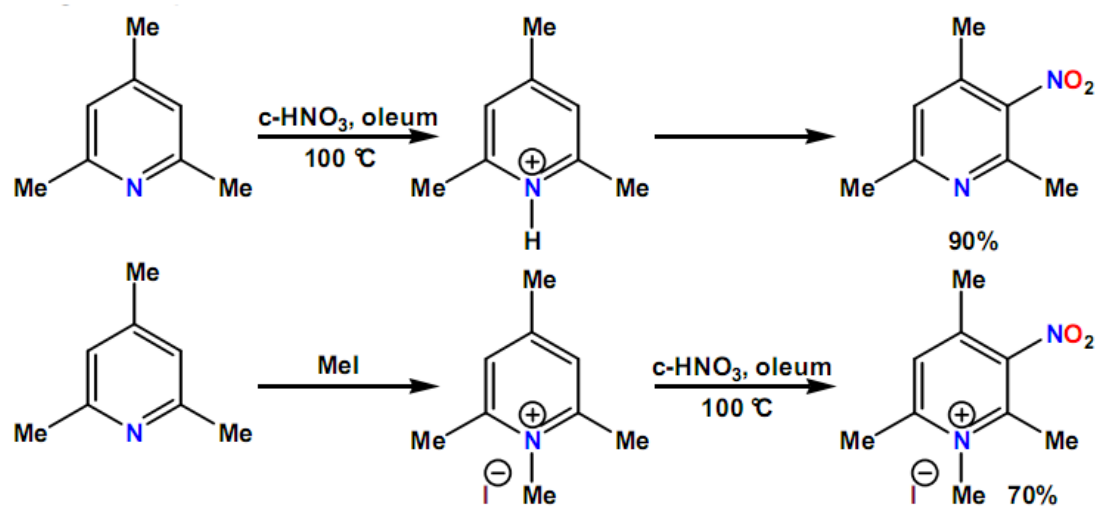
N Substitution



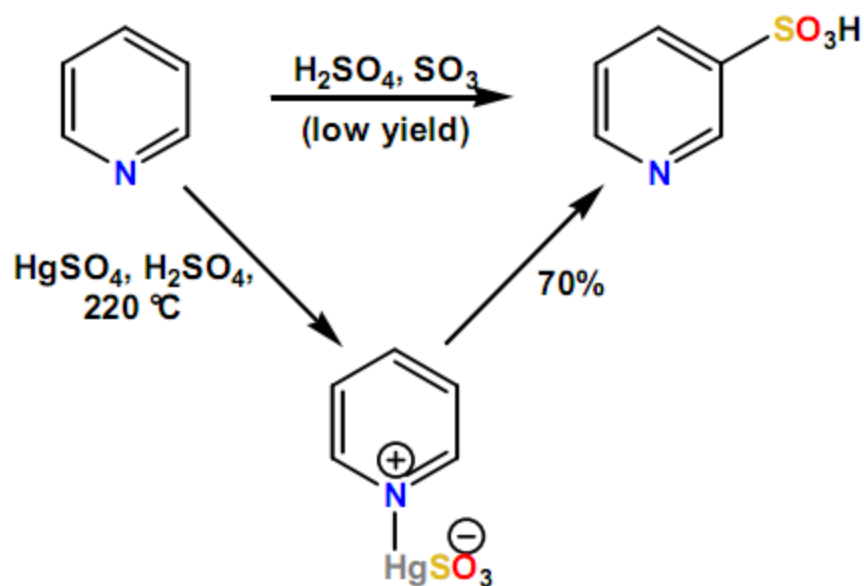
Nitration of Pyridine



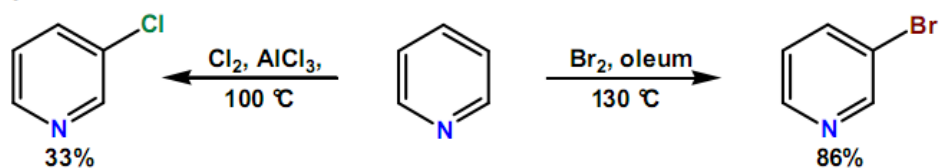
Friedel-Crafts reactions are not usually possible on free pyridines



Sulfonation of Pyridine

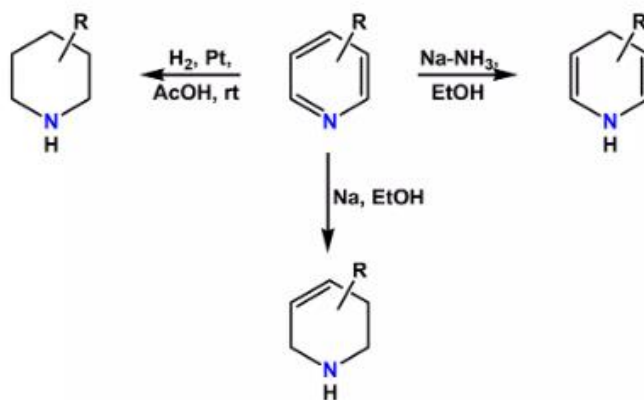


Halogenation of Pyridine



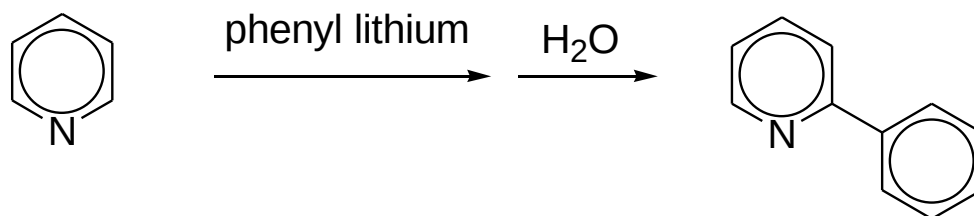
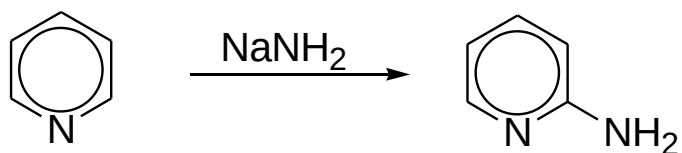
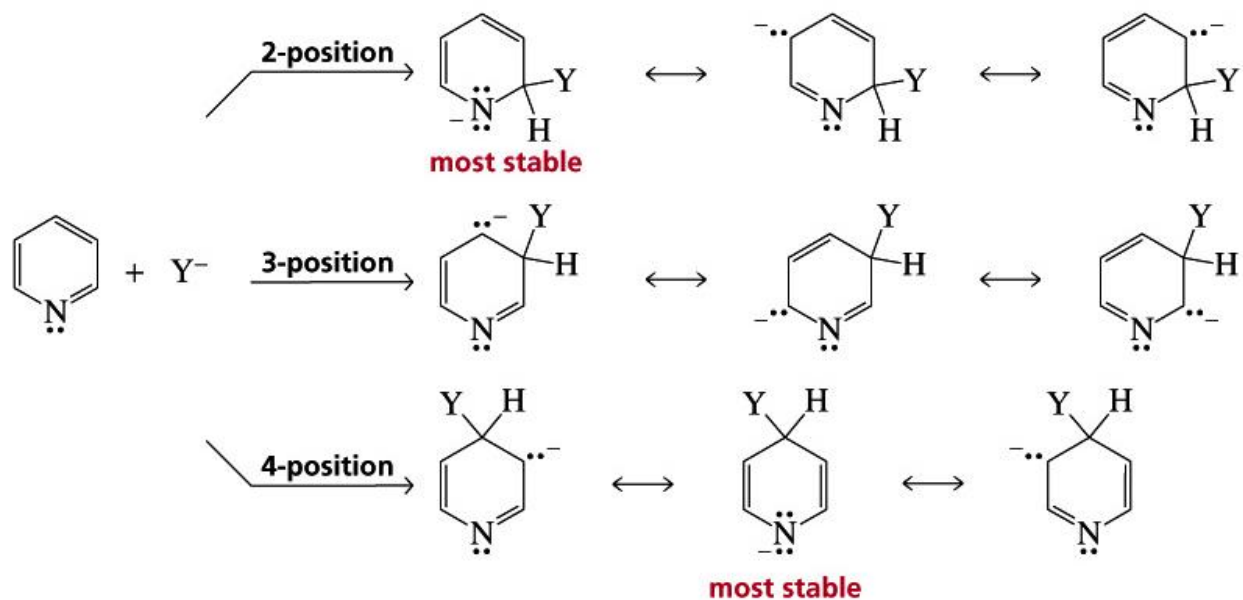
Pyridines – Reduction

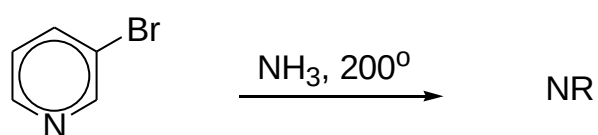
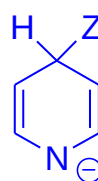
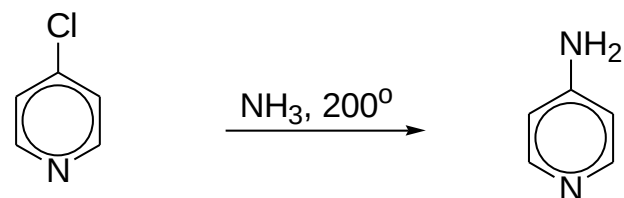
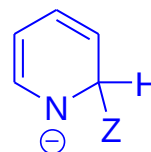
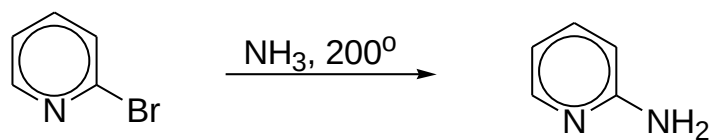
Full or Partial Reduction of Pyridines



- Pyridines generally resist oxidation at ring carbon atoms and will often undergo side-chain oxidation in preference to oxidation of the ring
- Full or partial reduction of the ring is usually easier than in the case of benzene

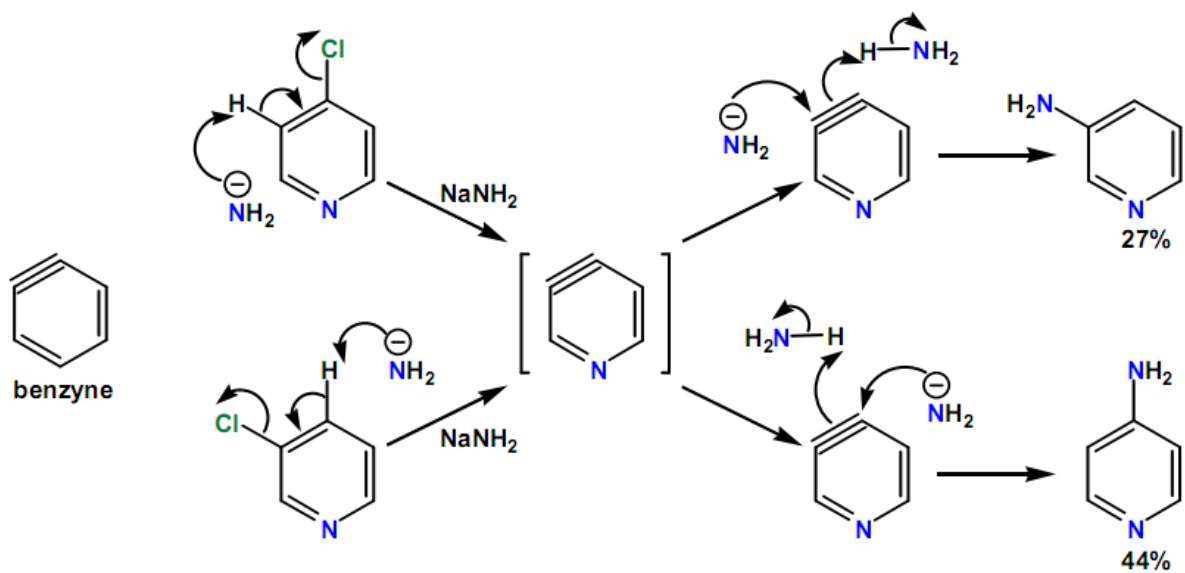
Pyridine undergoes nucleophilic aromatic substitution at C-2 and C-4





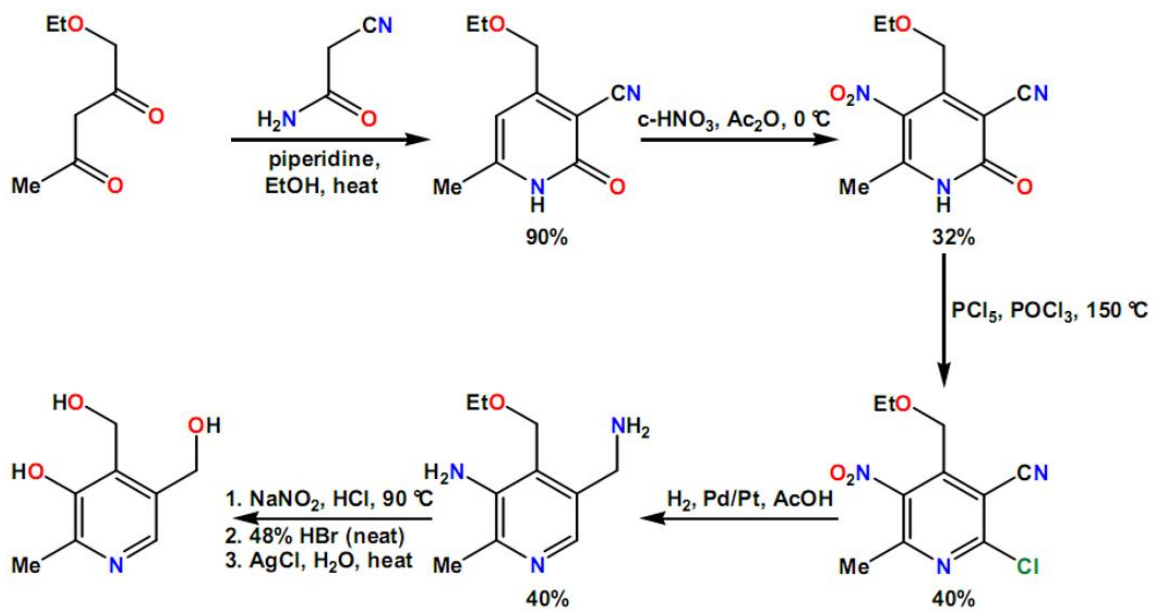
activated to nucl. arom. substs.
directs alpha & gamma

Pyridyne Formation

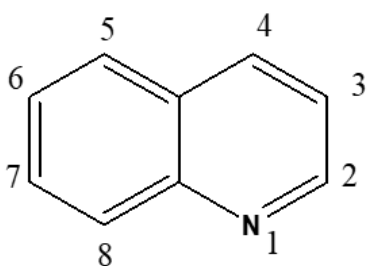


Pyridines – Synthesis of a Natural Product

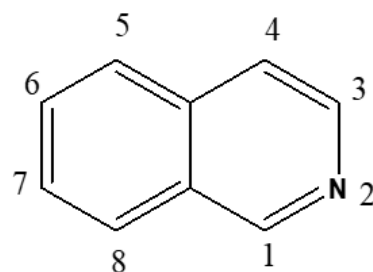
Synthesis of Pyridoxine (Vitamin B₆) Using the Guareschi Synthesis



Quinoline



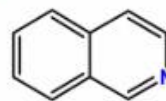
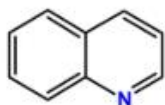
Quinoline
Benzo[b]pyridine
1-azanaphthalene



Isoquinoline
Benzo[c]pyridine
2-azanaphthalene

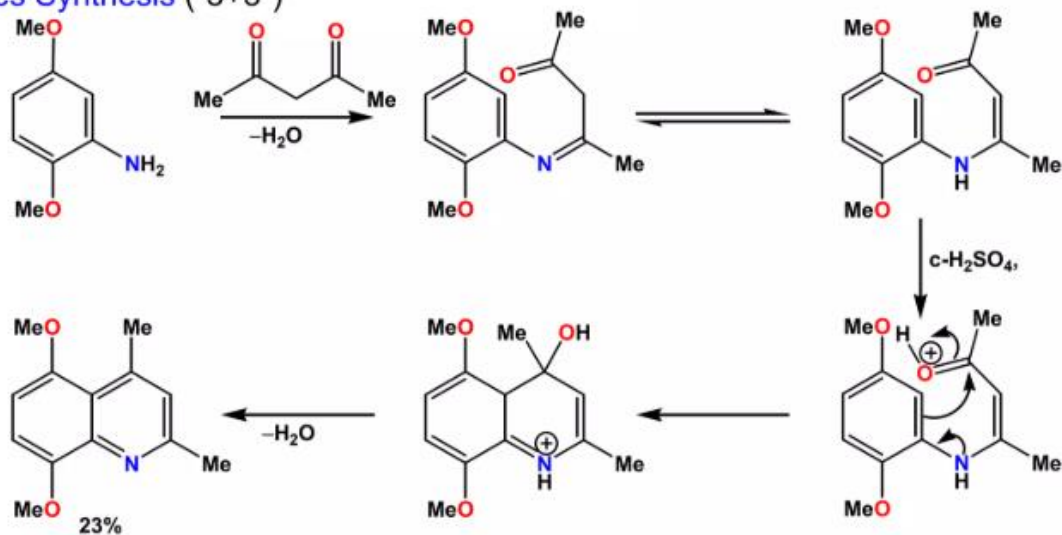
Quinolines – Synthesis

Structure



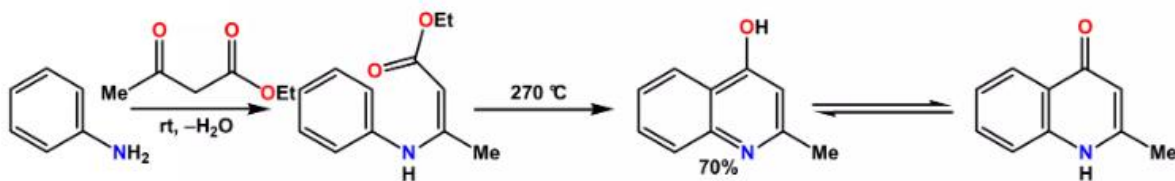
- pK_a values (4.9 and 5.4) are similar to that of pyridine
- Possess aspects of pyridine and naphthalene reactivity e.g. form *N*-oxides and ammonium salts

Combes Synthesis (“3+3”)

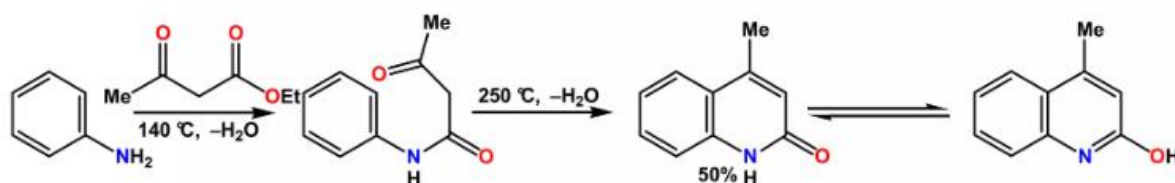


Quinolines – Synthesis

Conrad-Limpach-Knorr Synthesis ("3+3")

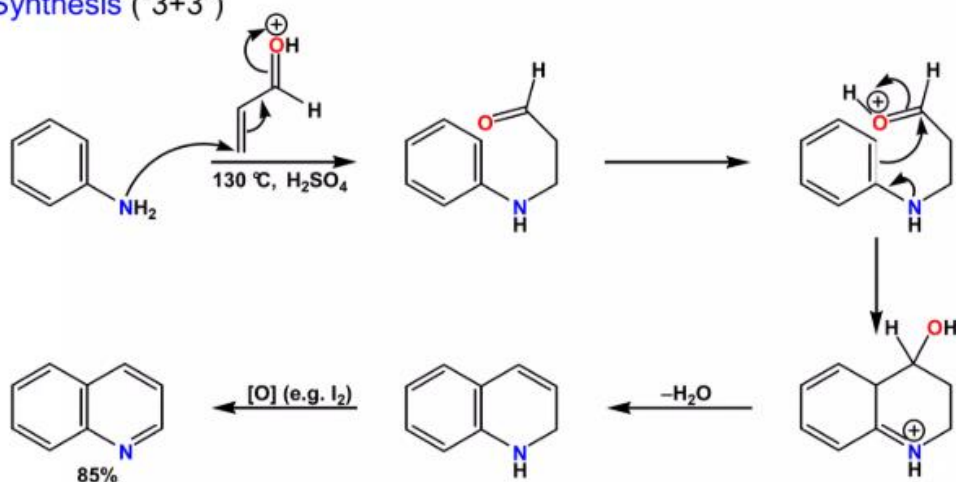


- Very similar to the [Combes synthesis](#) by a β -keto ester is used instead of a β -diketone
- Altering the reaction conditions can completely alter the regiochemical outcome



Quinolines – Synthesis

Skraup Synthesis ("3+3")

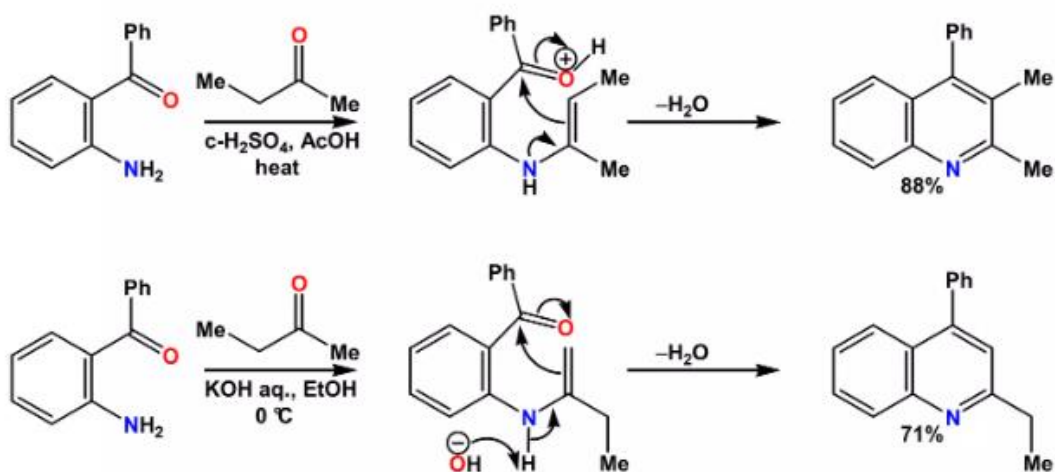


- Acrolein can be generated *in situ* by treatment of glycerol with conc. sulfuric acid
- A mild oxidant is required to form the fully aromatic system from the dihydroquinoline



Quinolines – Synthesis

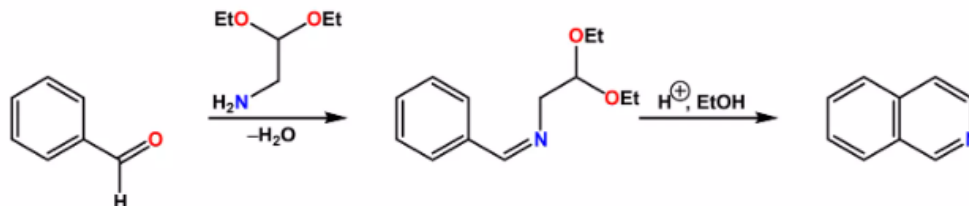
Friedlander Synthesis ("4+2")



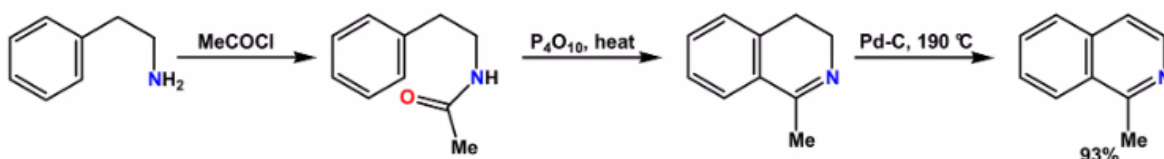
- The starting acyl aniline can be difficult to prepare
- Acidic and basic conditions deliver regioisomeric products in good yields

Isoquinolines – Synthesis

Pomeranz-Fritsch Synthesis (“3+3”)



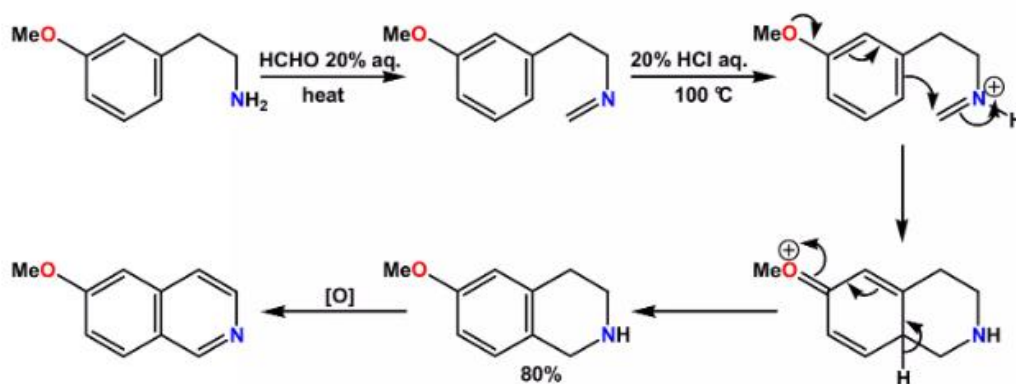
Bischler-Napieralski Synthesis (“5+1”)



- Cyclisation can be accomplished using POCl₃ or PCl₅
- Oxidation of the dihydroisoquinoline can be performed using a mild oxidant

Isoquinolines – Synthesis

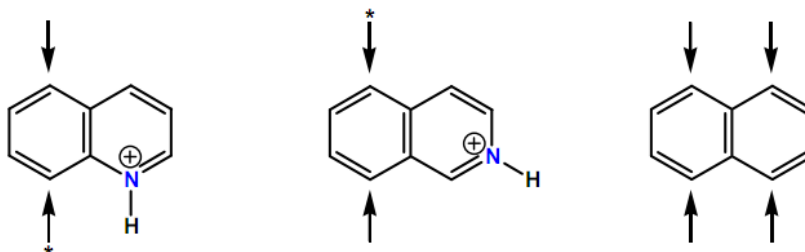
Pictet Spengler Synthesis (“5+1”)



- An electron-donating substituent on the carboaromatic ring is required
- A tetrahydroisoquinoline is produced and subsequent oxidation is required to give the fully aromatic isoquinoline

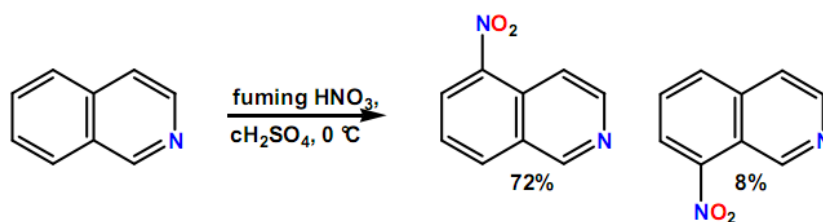
Electrophilic Reactions

Regiochemistry



- Under strongly acidic conditions, reaction occurs *via* the ammonium salt
- Attack occurs at the benzo- rather than hetero-ring
- Reactions are faster than those of pyridine but slower than those of naphthalene

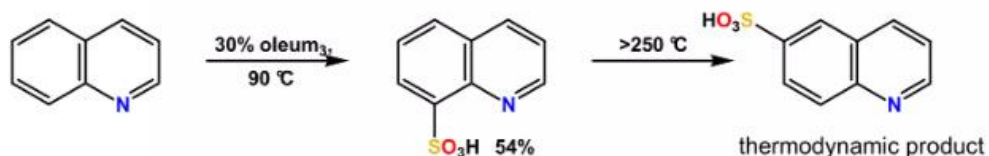
Nitration



- In the case of quinoline, equal amounts of the 5- and 8-isomer are produced

Quinolines/Isoquinolines – Electrophilic Reactions

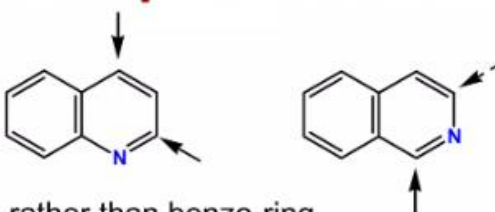
Sulfonation



- Halogenation is also possible but product distribution is highly dependent on conditions
- It is possible to introduce halogens into the hetero-ring under the correct conditions
- Friedel-Crafts alkylation/acylation is not usually possible

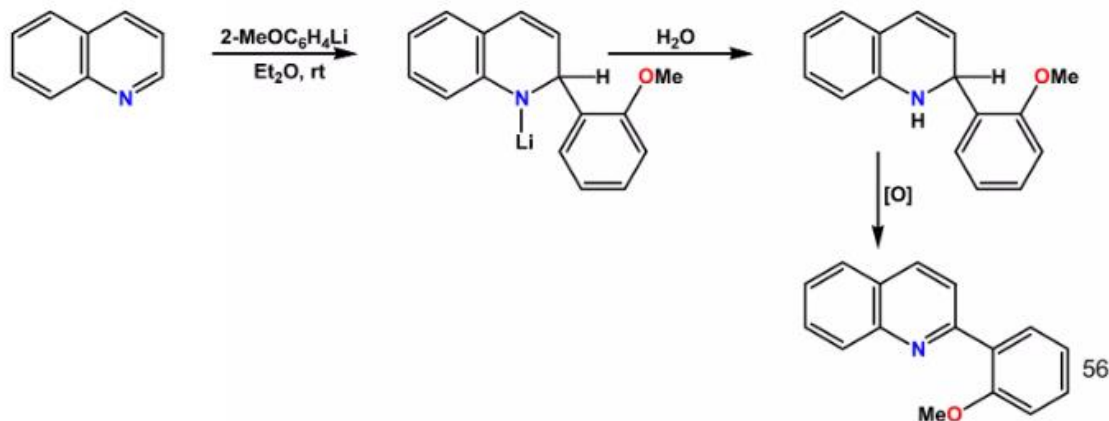
Quinolines/Isoquinolines – Nucleophilic Reactions

Regiochemistry

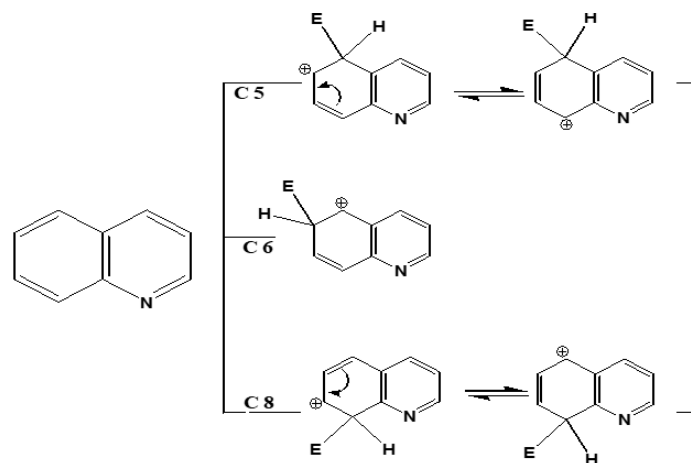


- Attack occurs at hetero- rather than benzo-ring
- They are generally more reactive than pyridines to nucleophilic attack

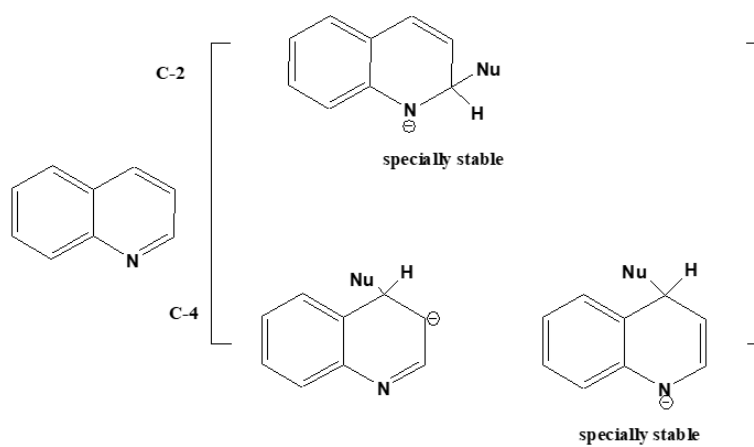
Carbon Nucleophiles

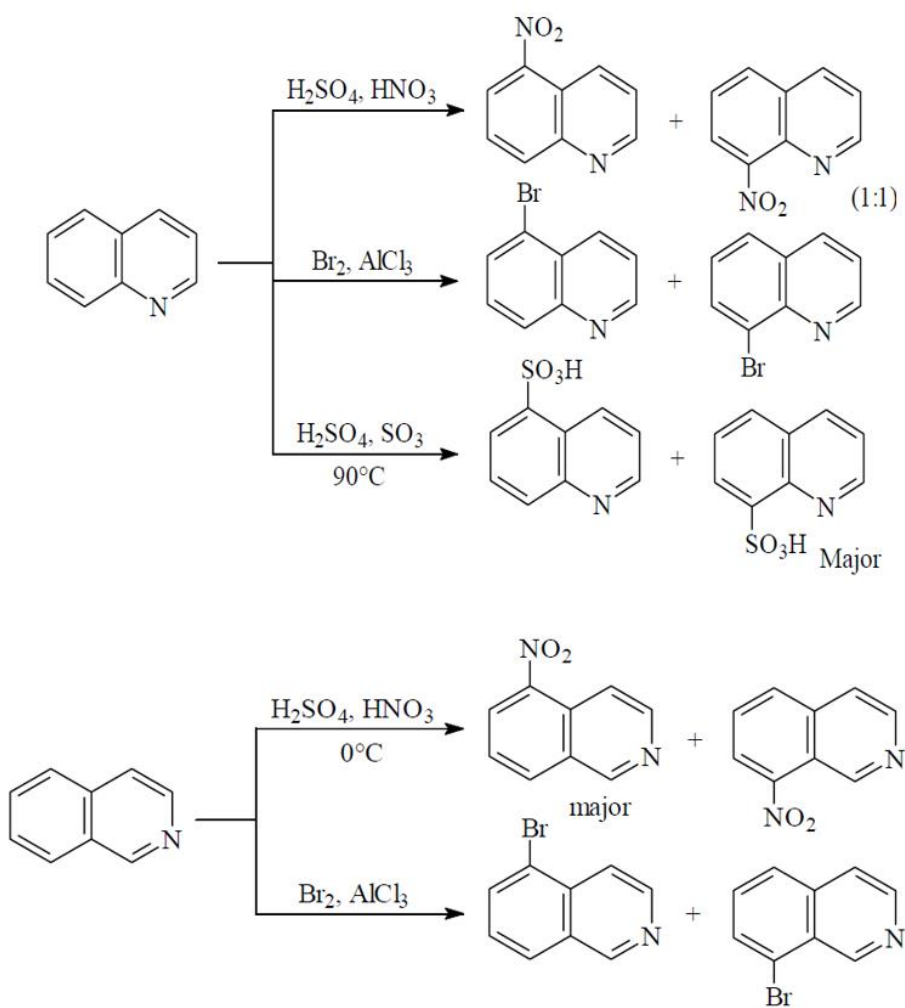


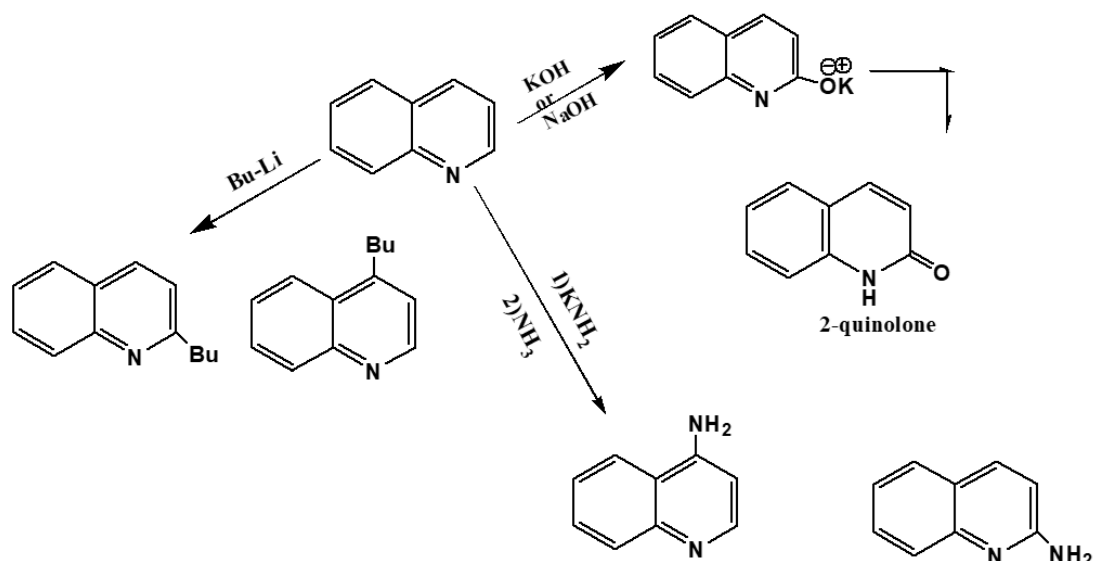
EAS



NAS

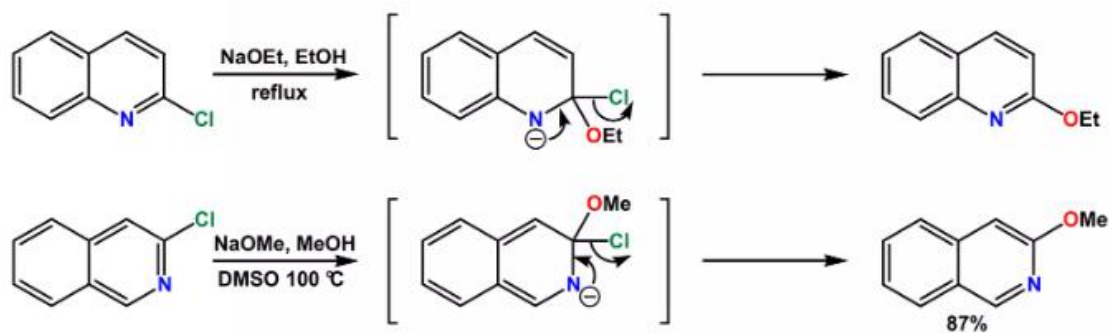




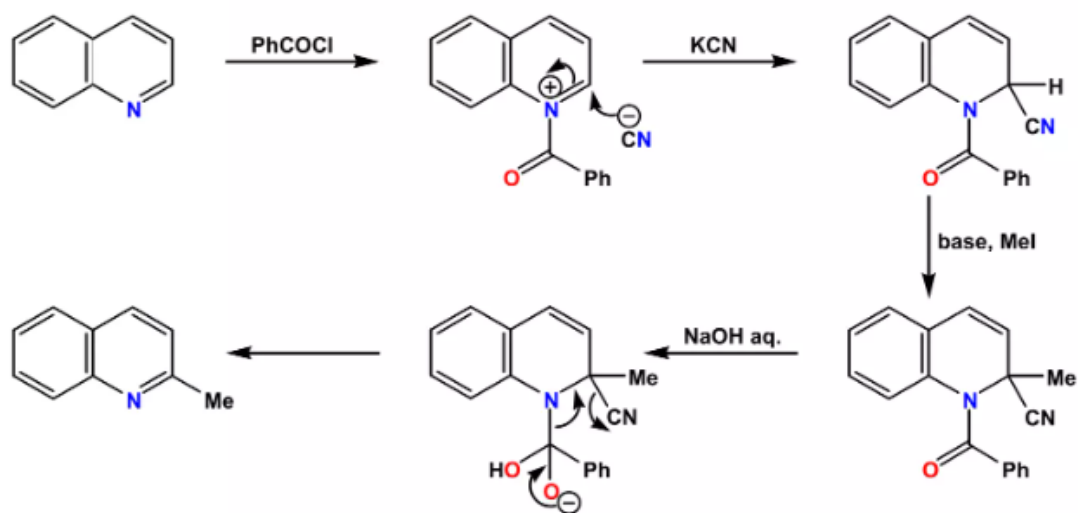


Quinolines/Isoquinolines – Nucleophilic Substitution

Displacement of Halogen

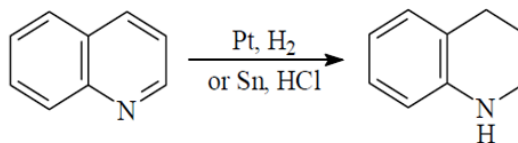
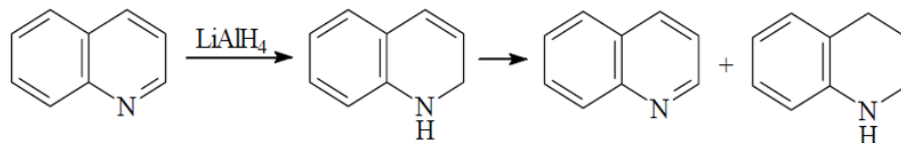


Quinolines/Isoquinolines – The Reissert Reaction

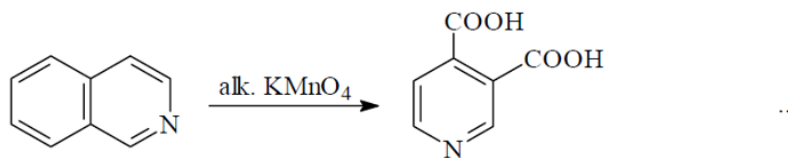
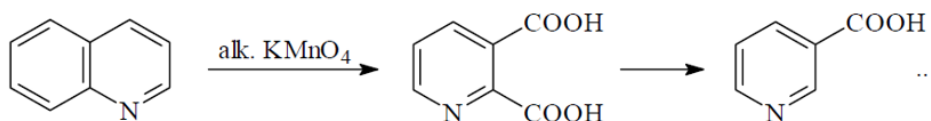


- The proton adjacent to the cyano group is extremely acidic
- The reaction works best with highly reactive alkyl halides

Reduction of quinoline

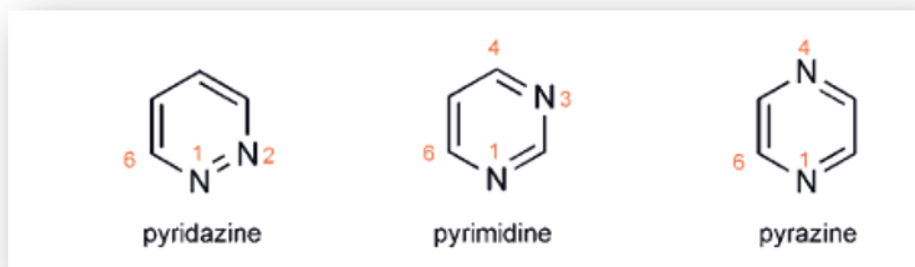


Oxidations



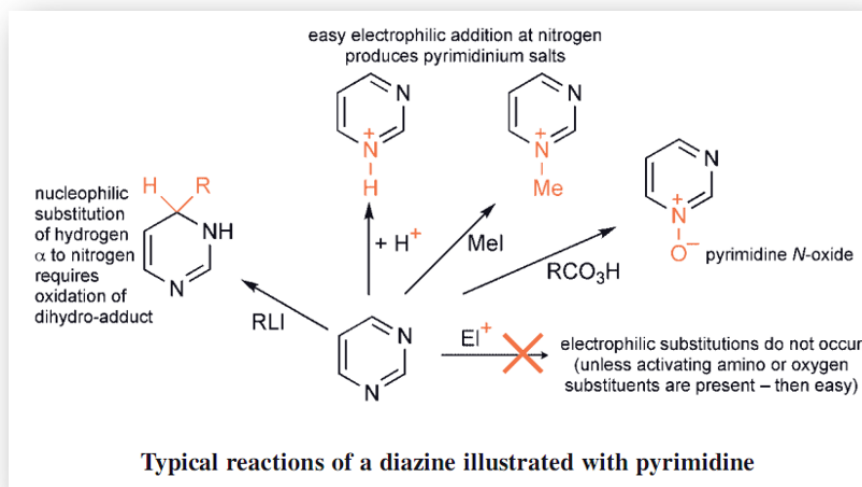
Diazines:

Pyridazine, Pyrimidine and Pyrazine

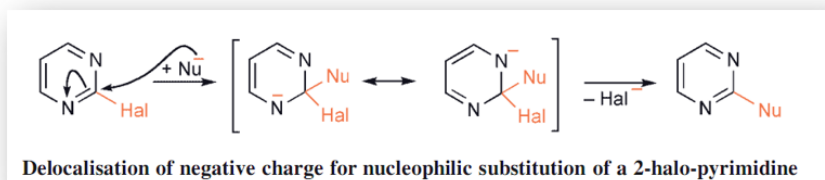


- 1- Two heteroatoms withdraw electron density from the ring carbons even more than one in pyridine
- 2- unsubstituted diazines are even more resistant to electrophilic substitution than is pyridine
- 3- diazines more easily attacked by nucleophiles than pyridine
- 4- each of the diazines is appreciably less basic than pyridine,

electrophilic additions take place at one nitrogen only, because the presence of the positive charge in the products renders the second nitrogen extremely unreactive towards a second electrophilic addition

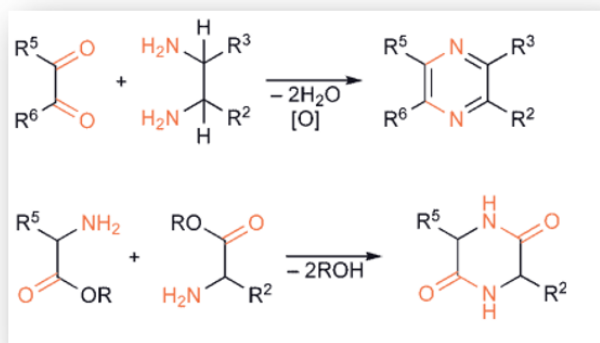


All positions on each of the diazines, with the sole exception of the 5 - position of a pyrimidine, are α and/or γ to an imine ring nitrogen and, in considering nucleophilic addition/substitution, the monohalo - diazines are more reactive than either 2 - or 4 - halo - pyridines

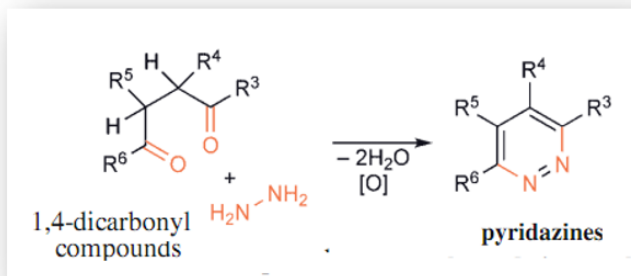


Preparation method

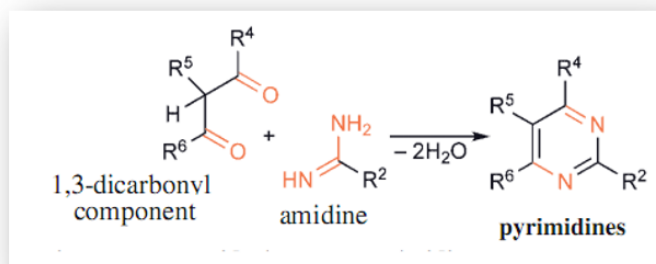
pyrazine produce from 1,2 - diamine and a 1,2 - dicarbonyl compound generate unsymmetrical, or using 2 - aminocarbonyl compounds also generates symmetrically substituted



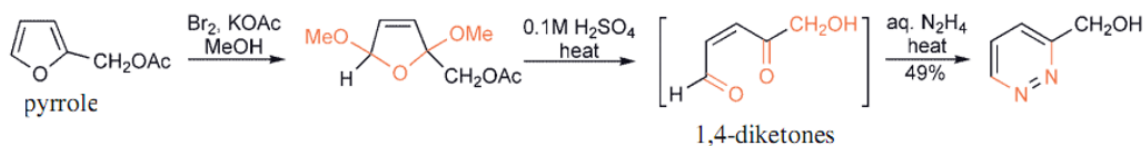
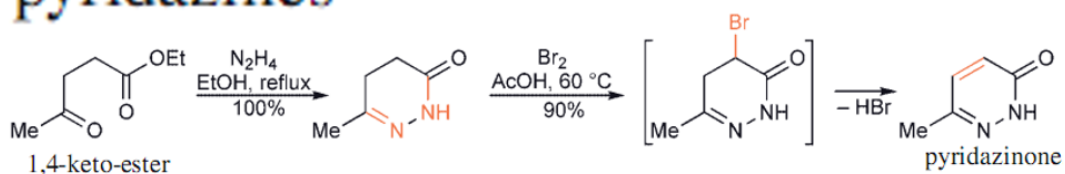
hydrazine and this in combination with 1,4 - dicarbonyl compounds readily produces dihydro - pyridazines



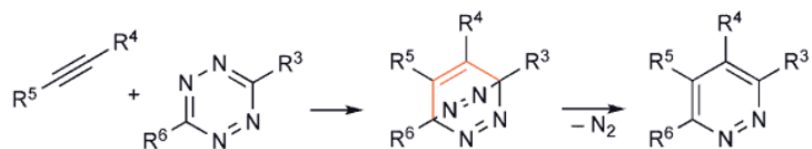
Pyrimidines result from the interaction of a 1,3 - dicarbonyl component and an amidine



pyridazines



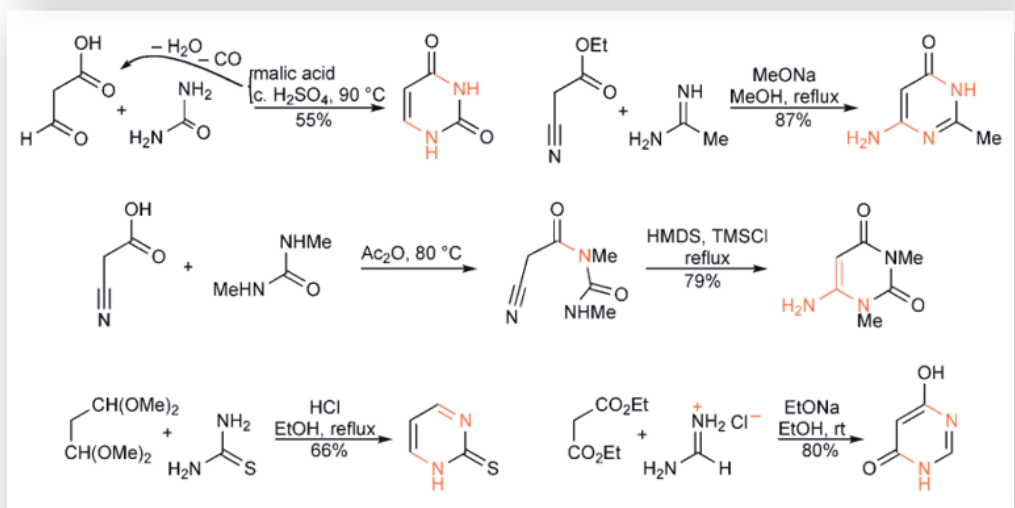
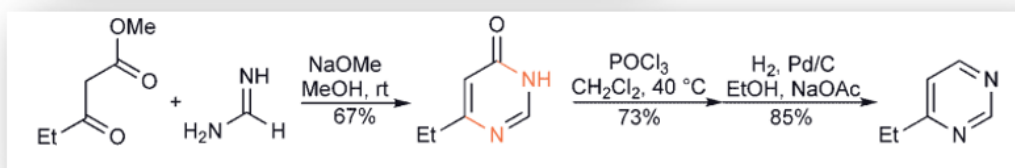
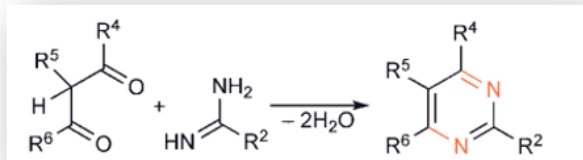
Cycloaddition of a 1,2,4,5-Tetrazine with an Alkyne with elimination of nitrogen

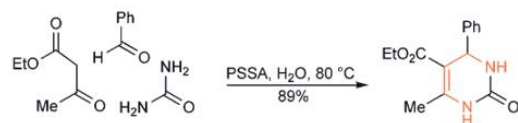


Pyrimidines

1,3-Dicarbonyl Compound and an N-C-N Fragment

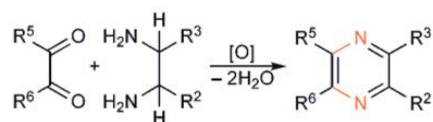
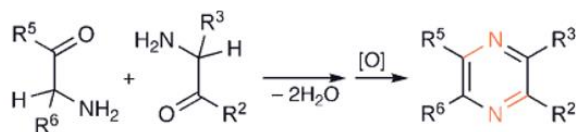
The N-C-N component – amidine, guanidine, or a urea, thiourea



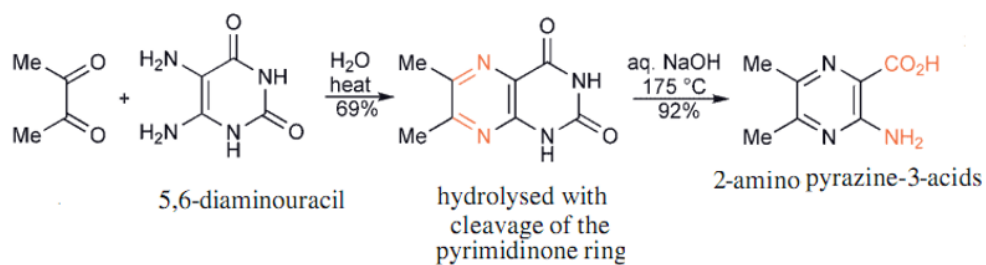
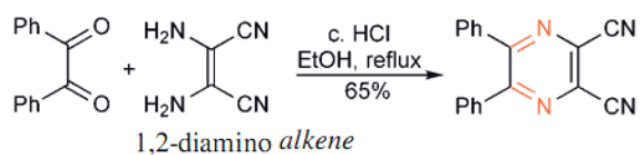
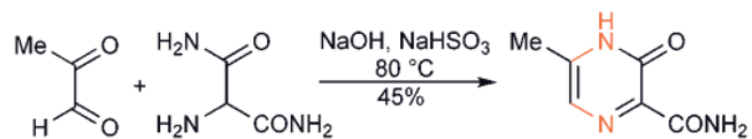
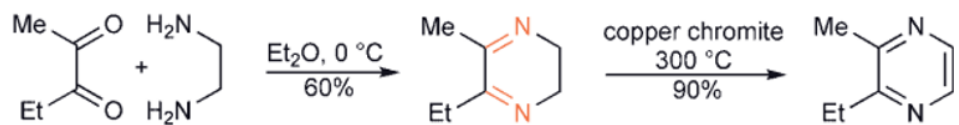


Pyrazines

Self-Condensation of a 2-Amino-Ketone

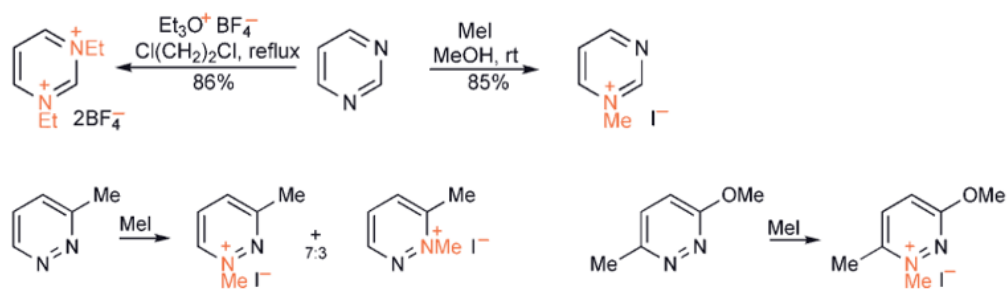


1,2-Dicarbonyl Compounds and 1,2-Diamines

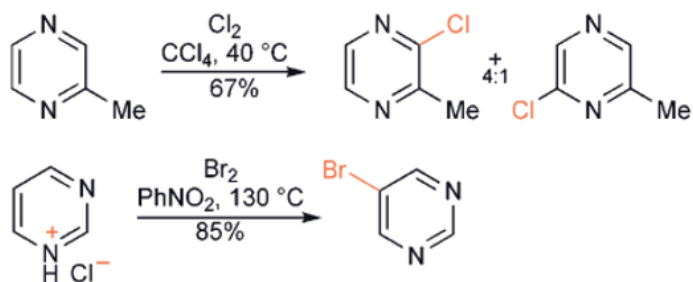


REACTIONS

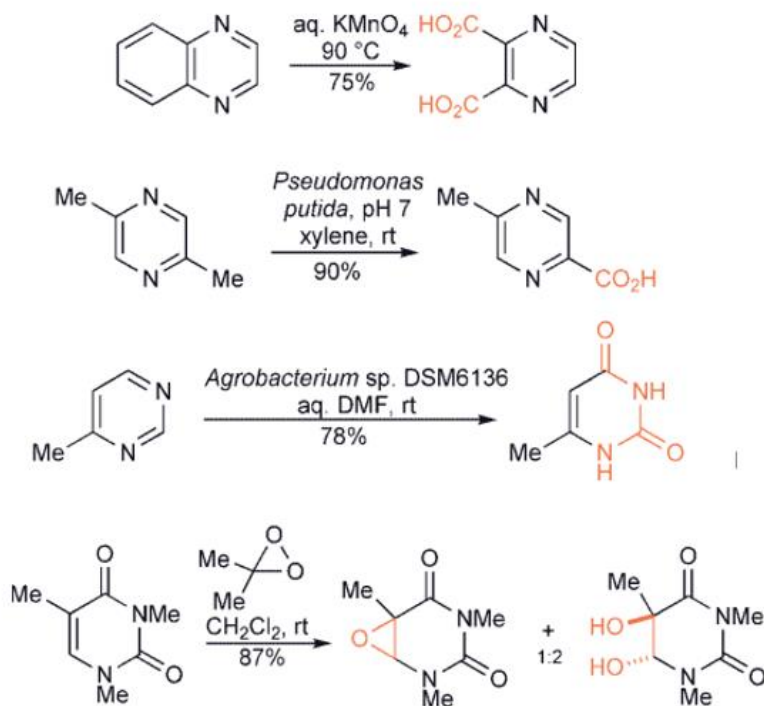
Alkylation



Substitution at Carbon



Reactions with Oxidising Agents



Nucleophilic Substitution with Displacement of Good Leaving Groups

