

BOOKS

- 1) *Heterocyclic Chemistry* - J. A. Joule, K. Mills and G. F. Smith
- 2) *Heterocyclic Chemistry (Oxford Primer Series)* - T. Gilchrist
- 3) *Organic Chemistry*, Jonathan Clayden Nick Greeves Stuart Warren, 2th Edition
- 4) *Organic Chemistry Structure and Function*, K. Peter C. Vollhardt, Neil Schore, 6th Edition
- 5) *Organic Chemistry*, T. W. Graham Solomons, Craig B. Fryhle

1. HETEROCYCLIC COMPOUNDS

1.1 Classification of Heterocyclic Compounds

1.2 Non-Aromatic Heterocycles

1.2.1 Nomenclature of Non-Aromatic Compounds

1.2.2 Preparation of Heterocyclic Alkanes

1.2.3 Reactions of Epoxides

1.2.3.1 Acid-catalyzed Reactions

1.2.3.2 Base-catalyzed Reactions

1.3 Aromatic Heterocycles

1.3.1 Nomenclature of Aromatic Compounds

1.4 Six-membered aromatic heterocycles

1.4.1 Synthesis of Pyridines

1.4.2 Reactions of Pyridines

1.4.2.1 Electrophilic Substitution of Pyridines

1.4.2.2 Nucleophilic Substitution of Pyridines

1.5 Five-Membered Unsaturated Heterocycles

1.5.1 Preparation of Pyrrole, furan, and thiophene

1.5.2 Reactions of pyrrole, furan, and thiophene

1.5.2.1 Electrophilic Aromatic Substitution of pyrrole, furan, and thiophene

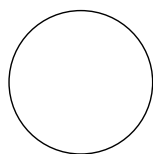
1.6 Benzo-fused Heterocycles

1. HETEROCYCLIC COMPOUNDS

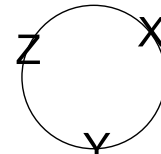
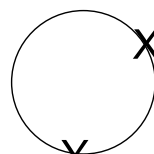
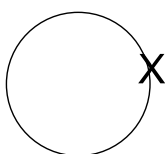
1.1 Classification of Heterocyclic Compounds

Cyclic organic compounds are carbocycles or heterocycles

- ✓ Carbocycle rings contain only carbon atoms
- ✓ Heterocycles contain one or more heteroatoms (O, N, S) in a ring



Carbocycles



Heterocycles: generally O, N, S

Heterocyclic compounds are divided into two groups as aromatic and non-aromatic.

A. Non-Aromatics:

Heterocycloalkanes, Aliphatics

- ❖ Small Ring Heterocycles
- ❖ Alkaloids
- ❖ β -lactams

B. Aromatics:

i) Five-membered Heterocycles

Pyrrrole, Furan, Thiophene and etc.

ii) Six-membered Heterocycles

Pyridine

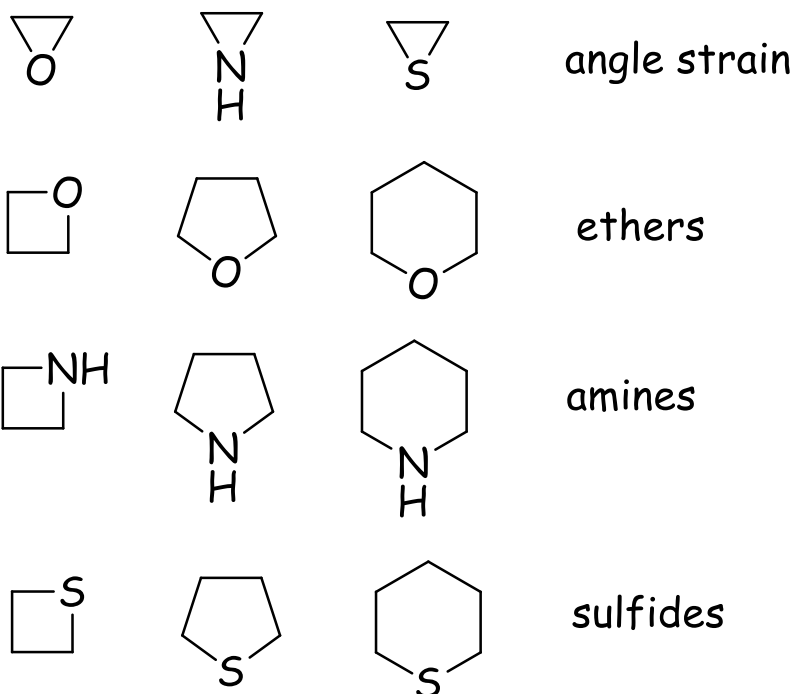
1.2 Non-Aromatic Heterocycles

The **aliphatic heterocycles** are similar to the open chain analogues, ethers, amines and sulfides

Oxacycloalkane: Oxygen-containing heterocycle

Azacycloalkane: Nitrogen-containing heterocycle

Thiacycloalkane: Sulfur-containing heterocycle



1.2.1 Nomenclature of Non-Aromatic Compounds:

Cyclic ethers can be named in several ways. One simple way is to use replacement.

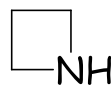
Nomenclature, in which we relate the cyclic ether to the corresponding hydrocarbon ring system and use the prefix oxa- to indicate that an oxygen atom replaces a CH_2 group. In case of nitrogen and sulfur, aza and thia prefixes are used respectively.



oxetane
oxacyclobutane



thietane
thiacyclobutane



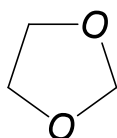
azetidine
azacyclobutane



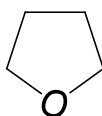
azete
azacyclobutadiene



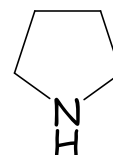
1-azetine
1-azacyclobutene



1,3-Dioxacyclopentane



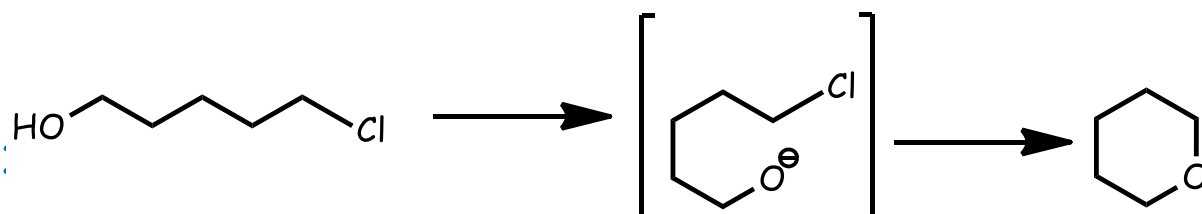
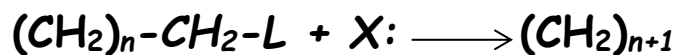
Tetrahydrofuran
oxacyclopentane



Pyrrolidine
azacyclopentane

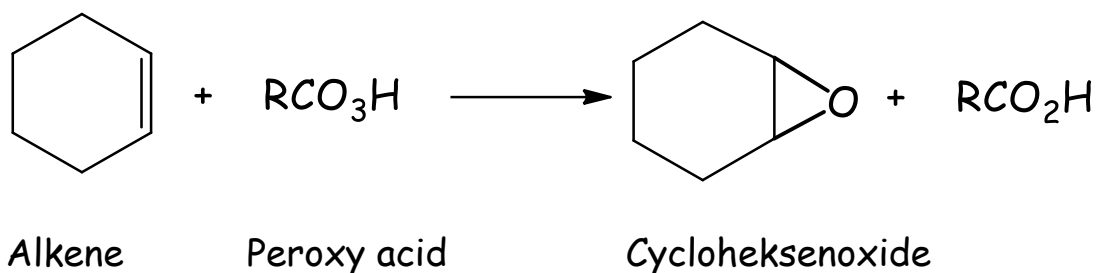
1.2.2 Preparation of Heterocyclic Alkanes

1. Intramolecular S_N2 reaction



2. Special synthesis of epoxides

Epoxides can be synthesized by the reaction of an alkene with an organic peroxy acid (RCO_3H —sometimes called simply a peracid), a process that is called epoxidation. Meta-Chloroperoxybenzoic acid (MCPBA) is one peroxy acid reagent commonly used for epoxidation.



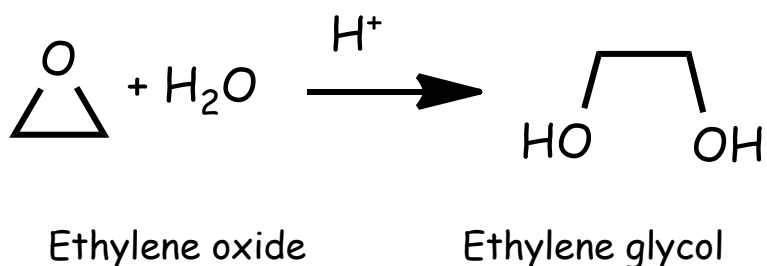
R: CH_3 , m-chlorophenyl

1.2.3 Reactions of Epoxides

The highly strained three-membered ring of epoxides makes them much more reactive toward nucleophilic substitution than other ethers.

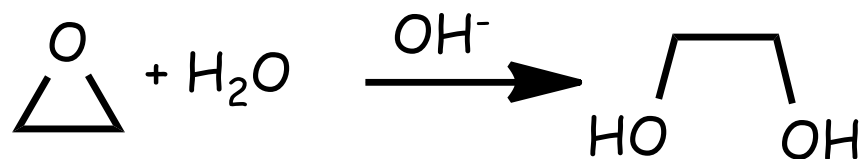
1.2.3.1 Acid-catalyzed Reactions

Acid catalysis assists epoxide ring opening by providing a better leaving group (an alcohol) at the carbon atom undergoing nucleophilic attack. This catalysis is especially important if the nucleophile is a weak nucleophile such as water or an alcohol. An example is the acid-catalyzed hydrolysis of an epoxide.

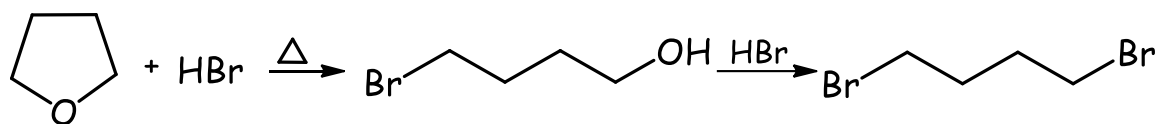


1.2.3.2 Base-catalyzed Reactions

Epoxides can also undergo base-catalyzed ring opening. Such reactions do not occur with other ethers, but they are possible with epoxides (because of ring strain), provided that the attacking nucleophile is also a strong base such as an alkoxide ion or hydroxide ion.



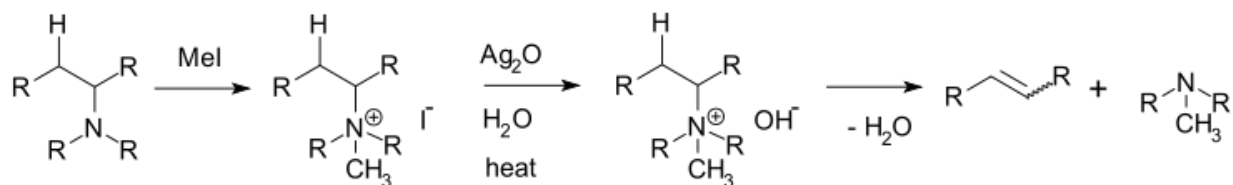
For rings larger than four, ring strain driving force is absent: Need strong acid:



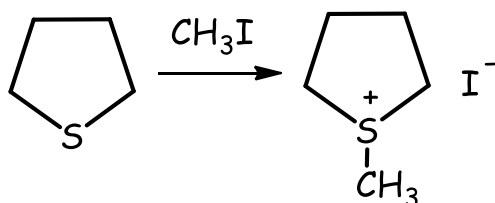
For azaheterocycloalkanes:

Acid just protonates the nitrogen to ammonium salt.

Ring opening can be done by Hofmann elimination:



For thiaheterocycloalkanes:



1.3 Aromatic Heterocyclic compounds

The **aromatic heterocycles** are similar to other aromatic compounds. All of these compounds are generally accepted as aromatic and reactivities expected for aromatic compounds.

1.3.1 Nomenclature of Aromatic Compounds:

Common names for many ring systems are accepted by the IUPAC rules:

❖ - rings with maximum double bonds

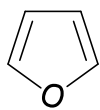
furan, pyrrole, indole, pyridine, etc.

❖ - saturated ring systems

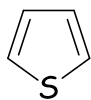
either prefixes dihydro-, tetrahydro-, perhydro-,

or in five-membered rings pyrrolidine, piperidine,

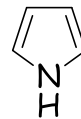
in six-membered rings piperazine, piperazine



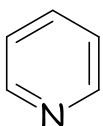
Furan
Oxacyclopentadiene



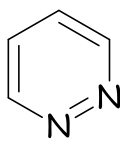
Thiophene
Thiacyclopentadiene



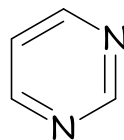
Pyrrole



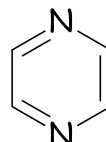
Pyridine



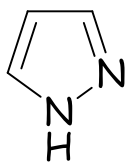
Pyridazine



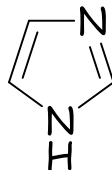
Pyrimidine



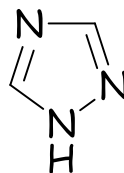
Pyrazine



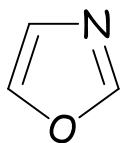
Pyrazole



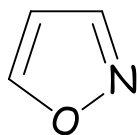
Imidazole



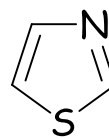
1,2,4-Triazole



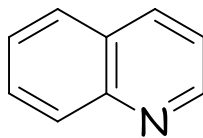
Oxazole



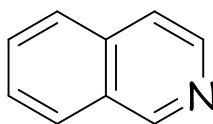
Isoxazole



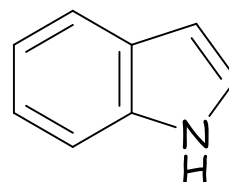
Thiazole



Quinoline



Isoquinoline

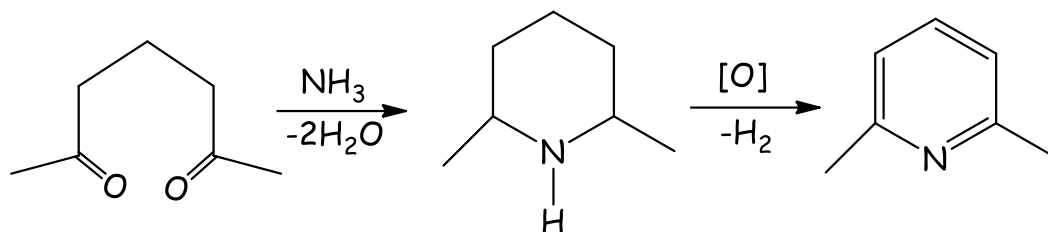


Indole

1.4 Six-membered aromatic heterocycles

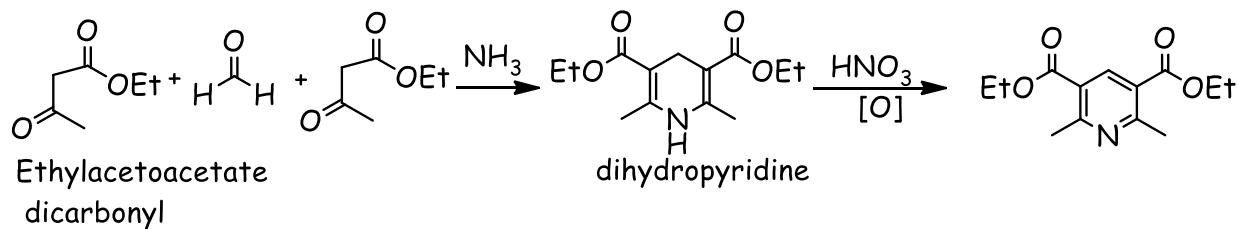
1.4.1 Synthesis of Pyridine

i) From 1,5-dicarbonyl compounds

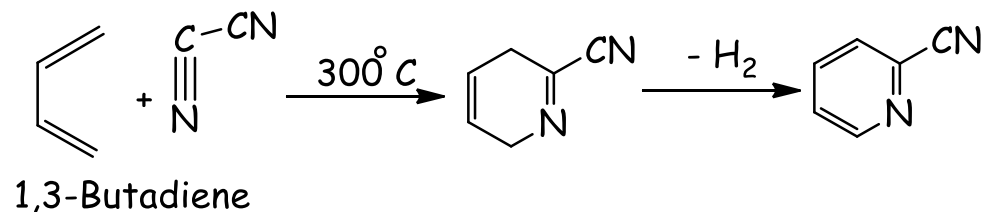


(O): HNO₃, Ce(IV), or a quinone

ii) Hantzsch Synthesis:



iii) By Diels Alder Reaction



1.4.2 Reactions of Pyridine

1.4.2.1-Electrophilic Substitution of Pyridines

Pyridine does not undergo electrolytic substitution. Aromatic electrophilic substitution on pyridine is not a useful reaction. It does not undergo nitration, sulfonation, halogenation, and Friedel-Crafts reactions or acylation or coupling with diazonium salts.

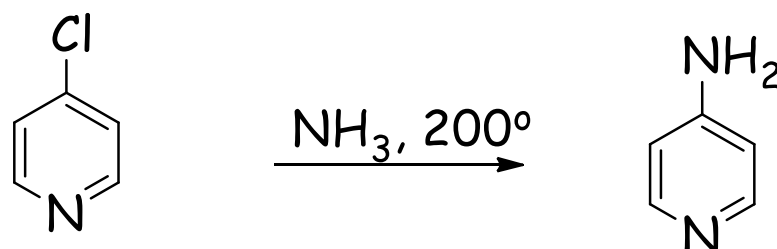
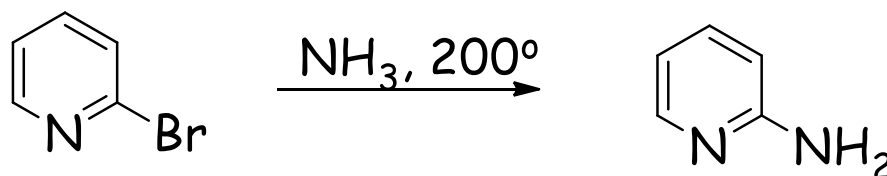
However, pyridine is relatively (to benzene) electron poor, therefore electrophilic substitution can take place only under extreme conditions (e.g. v. high temperature) and only at C3 with a low yield.

1.4.2.2-Nucleophilic Substitution of Pyridines

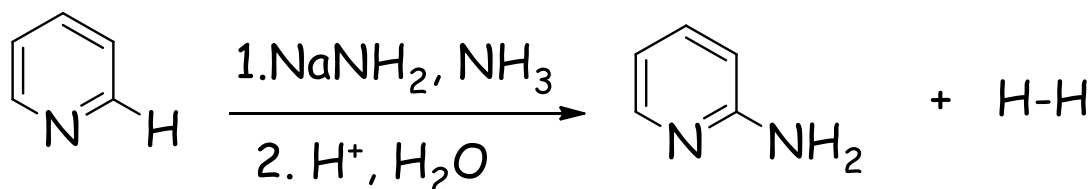
Pyridines undergo nucleophilic substitution. As we mentioned before pyridines can undergo *electrophilic* substitution only if they are activated by electron-donating substituents, but they readily undergo

nucleophilic substitution without any activation other than the ring nitrogen atom.

Pyridine is very reactive towards nucleophiles than benzene. It resembles benzene having strong electron withdrawing group (E.W.G). Pyridine undergoes nucleophilic aromatic substitution at C-2 and C-4:

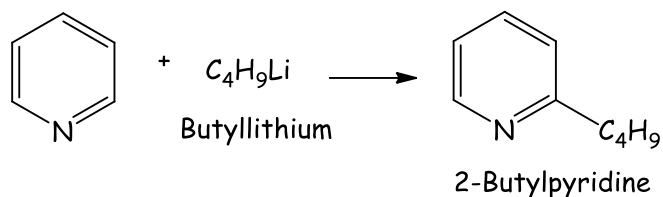


i) The Chichibabin reaction

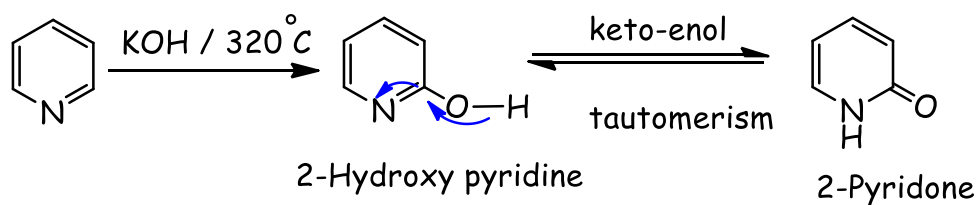


ii) **Reaction with organometallic compounds:**

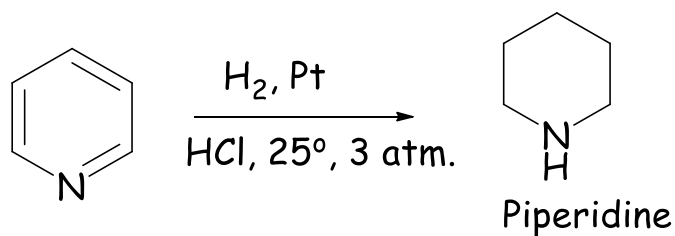
lithium reagents



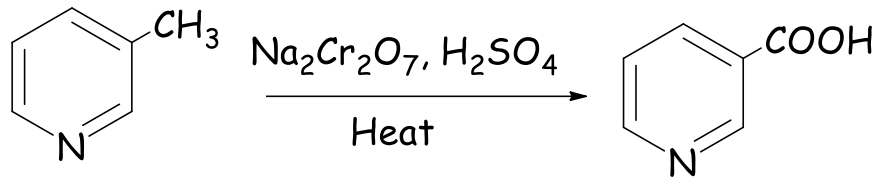
iii) **Reaction with potassium hydroxide**



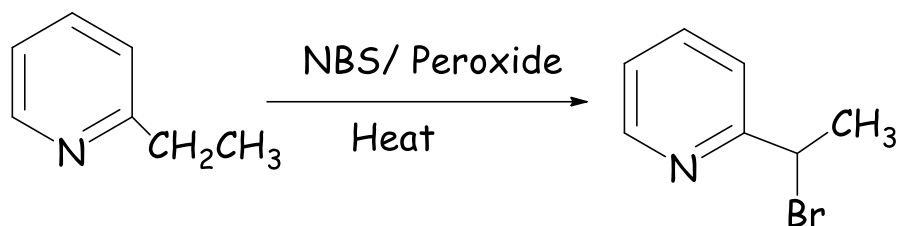
iv) **Reduction Reaction**



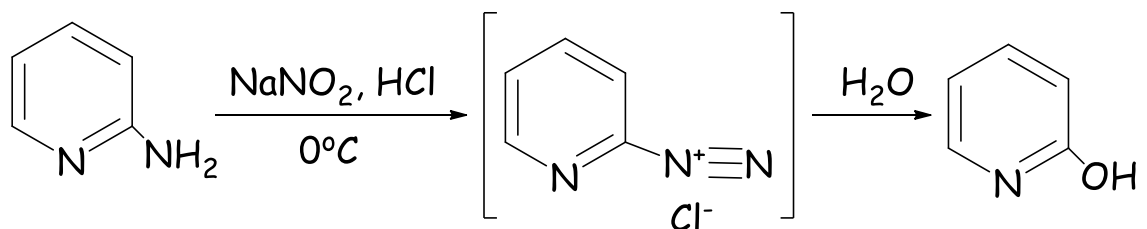
v) Oxidation of Substituted Pyridine



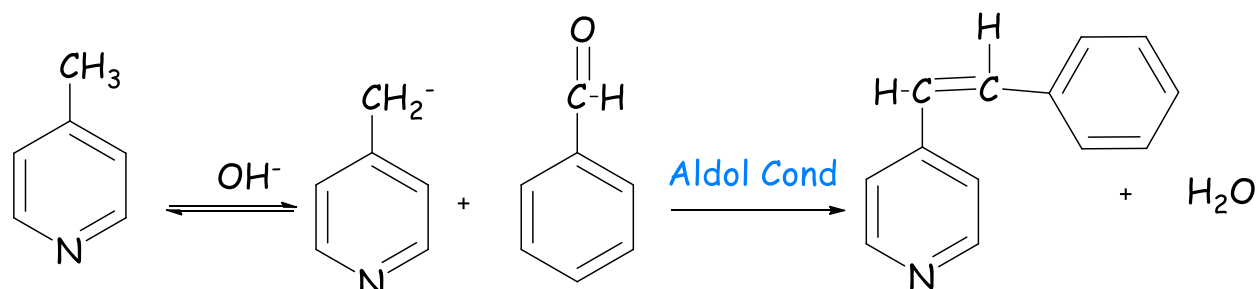
vi) Bromination of Substituted Pyridine



vii) Diazotization of Aminopyridine

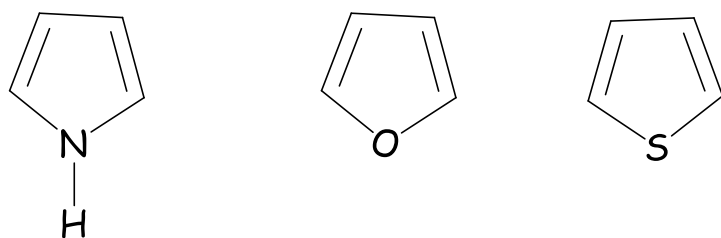


viii) Reactions of pyridine-based anionic nucleophiles



1.5 Five-Membered Unsaturated Heterocycles

Pyrrole, furan, and thiophene are common five-membered unsaturated heterocycles

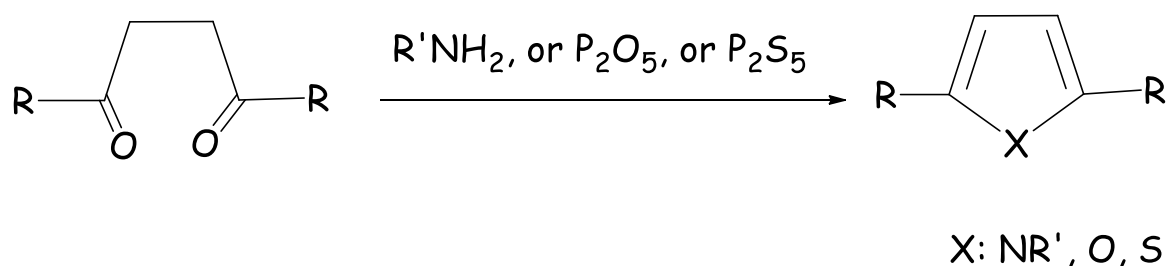


Pyrrole, furan, and thiophene

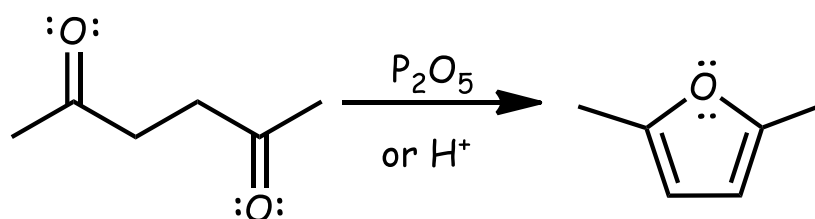
1.5 Preparation of Pyrrole, furan, and thiophene

i) Paal-Knorr synthesis of heterocyclopentadienes

Cyclization of 1,4-dicarbonyl compounds with nitrogen, sulfur, or oxygen nucleophiles gives the five-membered aromatic heterocycles pyrrole, thiophene, and furan

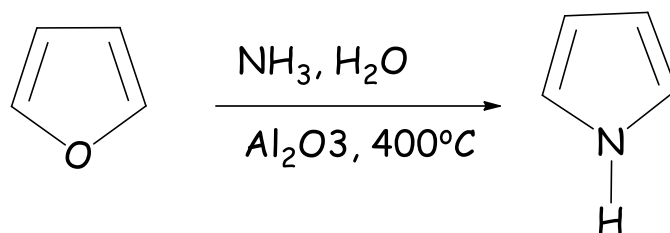


Example:



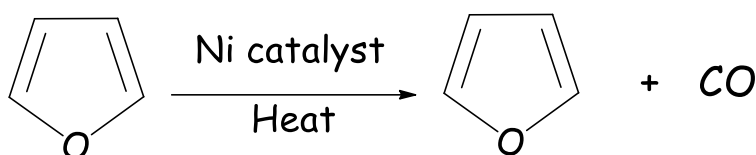
ii) Pyrrole

Commercially obtained from coal tar or by treatment of furan with ammonia over an alumina catalyst at $400^\circ C$.



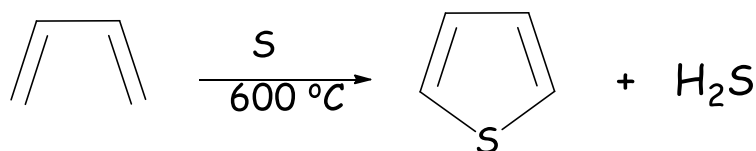
iii) Furan

Commercially obtained by removing of CO from furfural



iv) Thiophene

Commercially obtained from coal tar or by cyclization of butane or butadiene with sulfur at 600°C.



1.5.2 Reactions of Pyrrole, furan, and thiophene

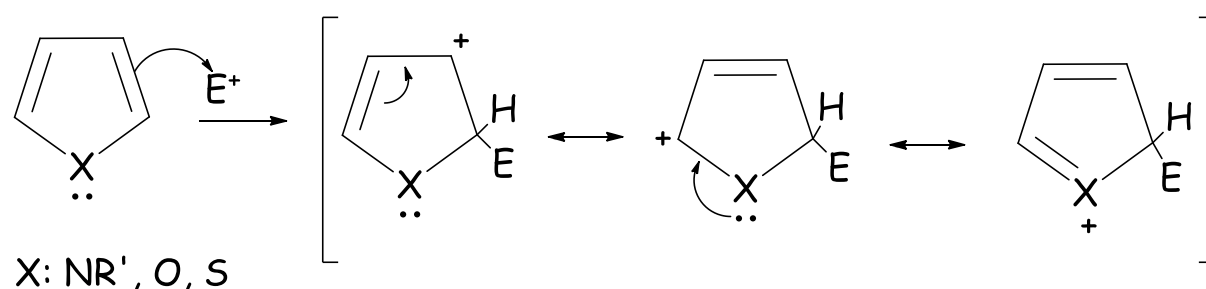
All reactions are opposite to that of pyridine. Electrophilic substitution is much easier than it is with benzene while nucleophilic substitution is more difficult.

1.5.2.1 Electrophilic Aromatic Substitution

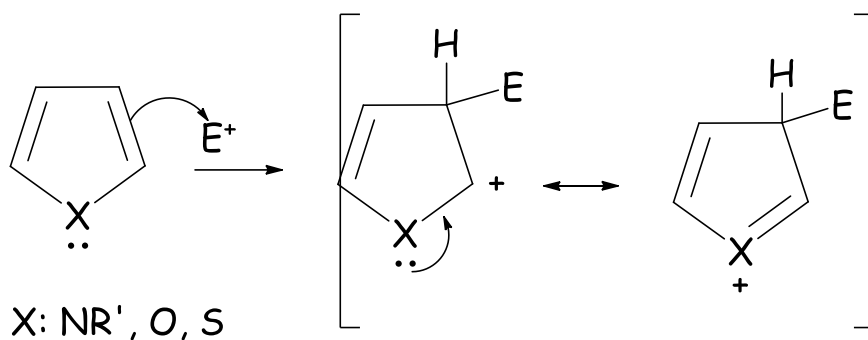
The order of reactivity is:

Pyrrole > Furan > Thiophene > Benzene

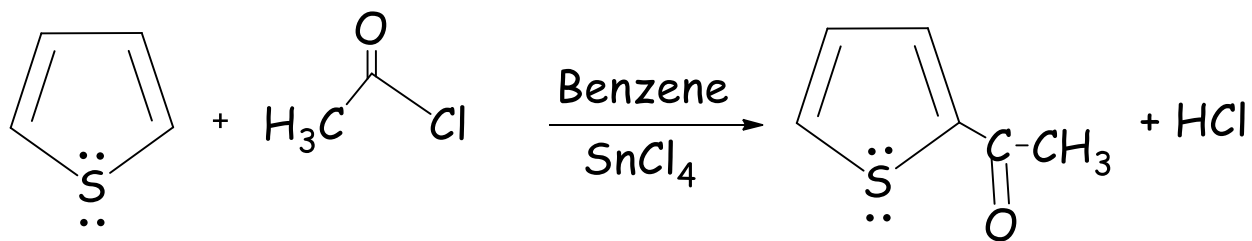
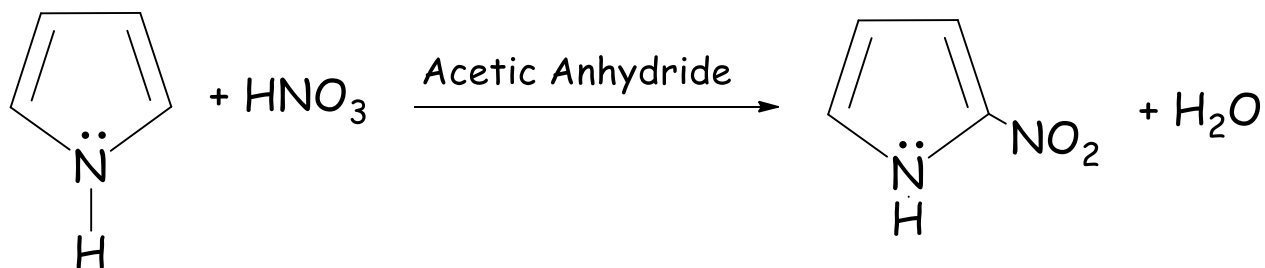
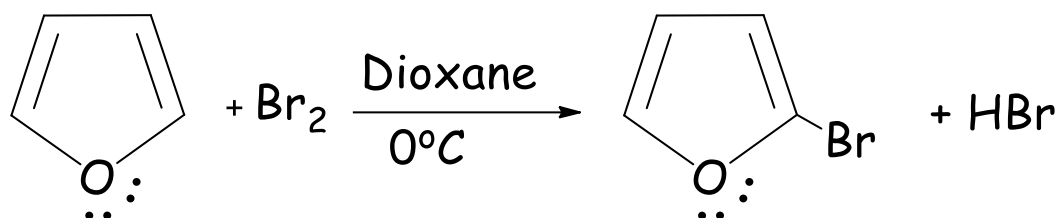
Attack at C2 is preferred generally

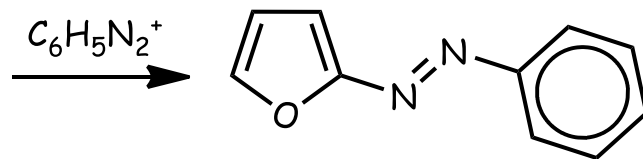
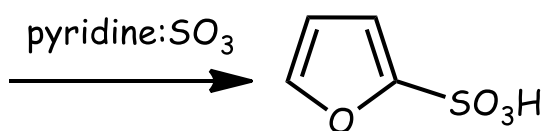
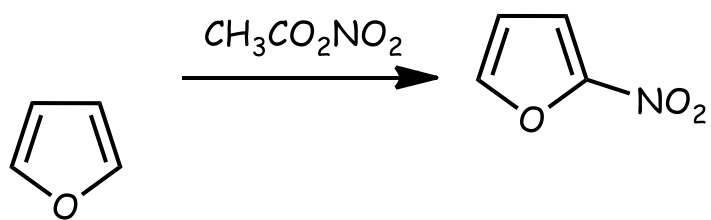
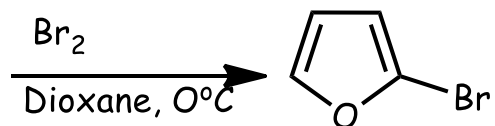
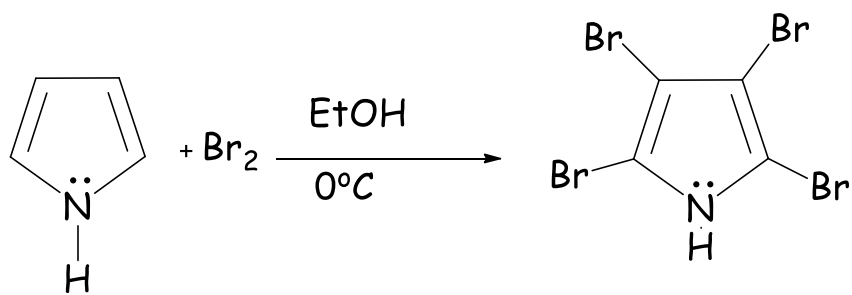
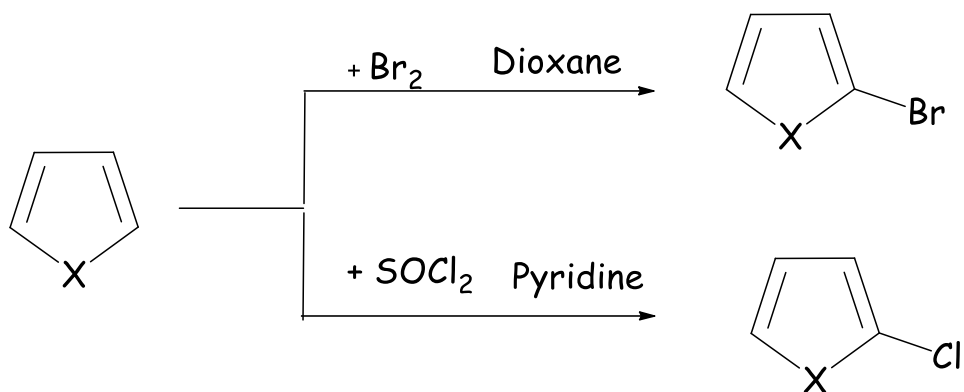


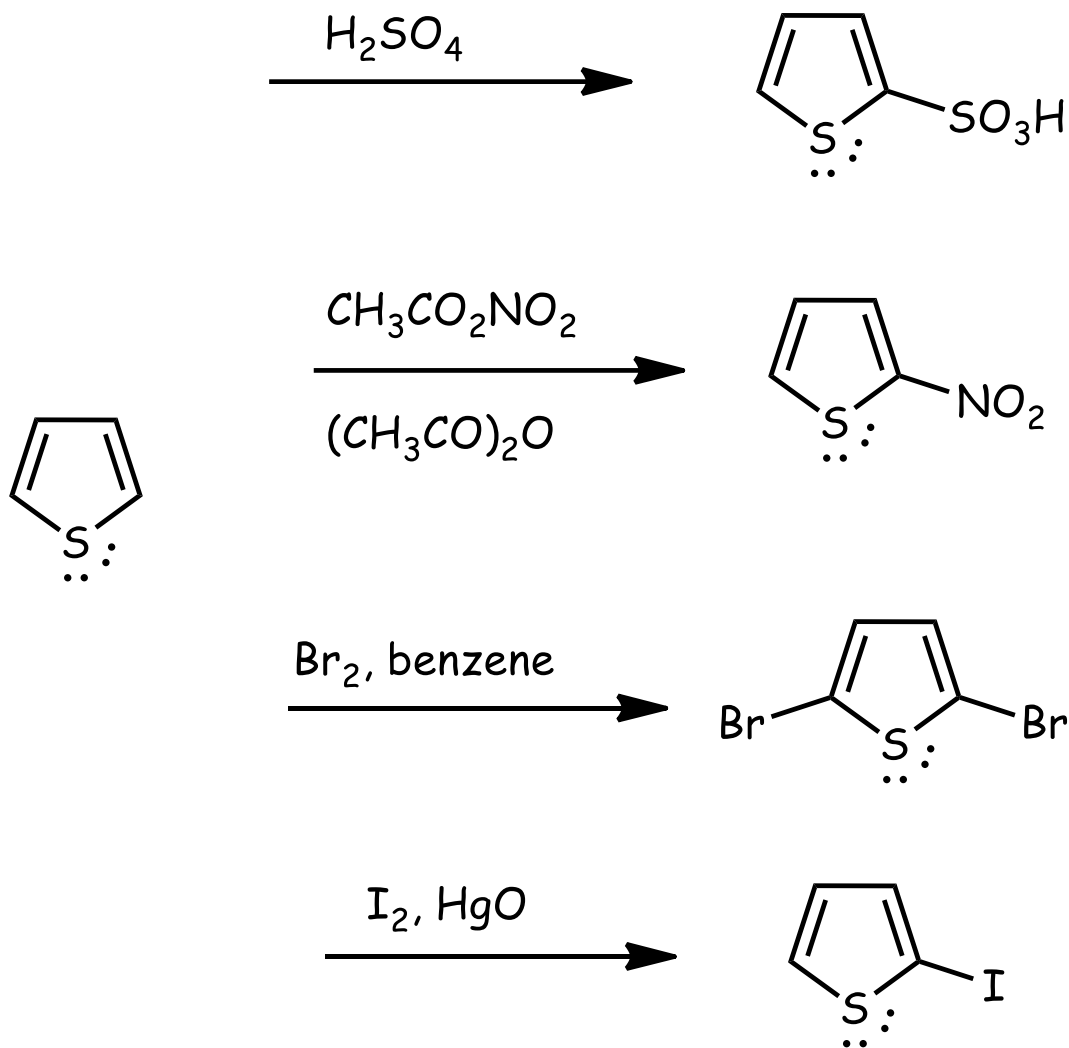
But often also attack at C3



Examples

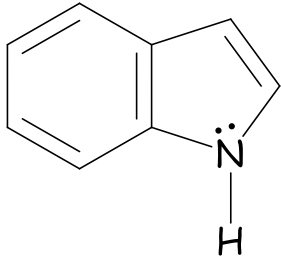




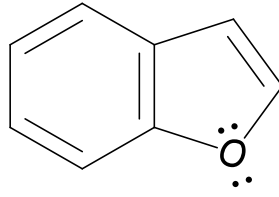


1.6 Benzo-fused heterocycles

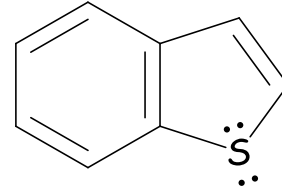
Indole, benzofuran, and benzothiophene all contain a five-membered aromatic ring fused to a benzene ring



Indole



Benzofuran



Benzothiophene