National University –SUDAN

Faculty of Clinical and Industrial Pharmacy

Second Year (**Batch-PA-14**)-Semester Four

Organic Chemistry in Pharmacy

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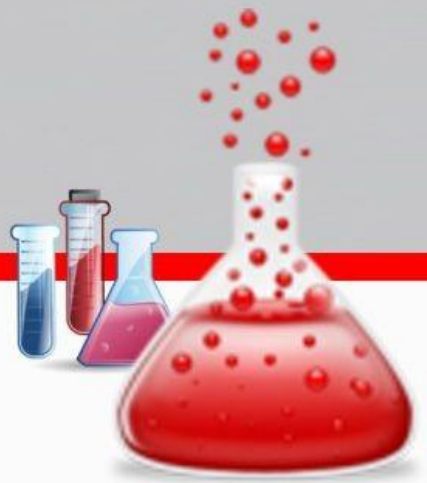
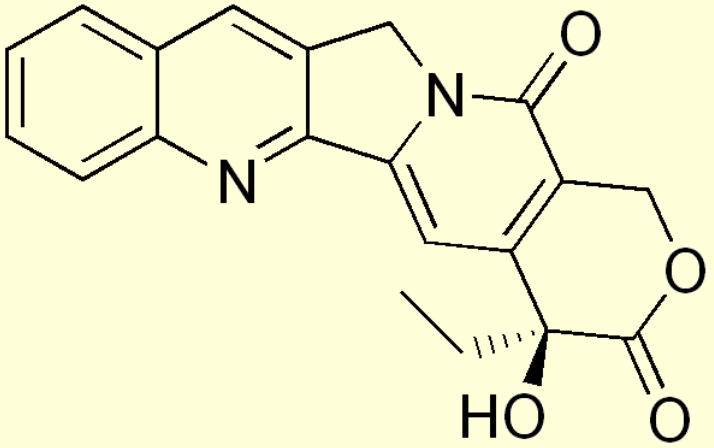
Phone Number (**00249-913714903)**

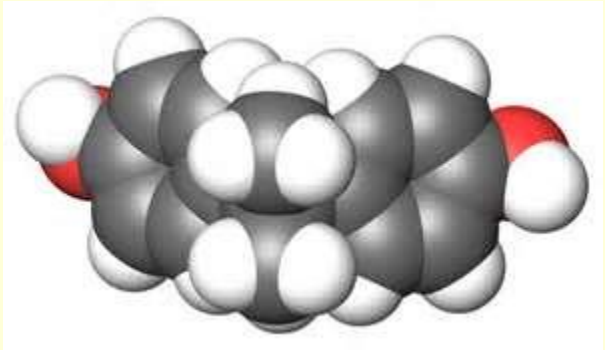


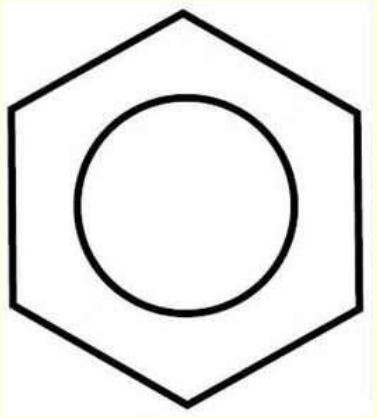
Cytotoxin- Inhibits DNA-topoisomerase enzymes



Happy Tree (China)

Aromatic and Heterocyclic Chemistry





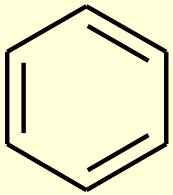
Aromatic Compounds

- Many aromatic substances have rather simple structures and contain a six-carbon unit (C_6H_5)
- Arenes = aromatic hydrocarbon
- Aromatic: refers to the level of stability for an arene

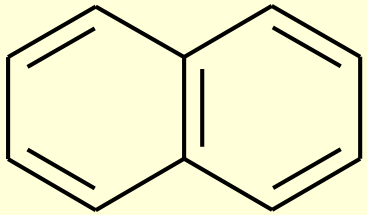
- Benzene: is the parent hydrocarbon of the class or aromatic compounds

When Is A Molecule Aromatic?

- For a molecule to be aromatic it must:
  - Be cyclic
  - Have a *p*-orbital on every atom in ring
  - Be planar
  - Posses 4n+2 p electrons (n = any integer)

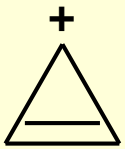


benzene

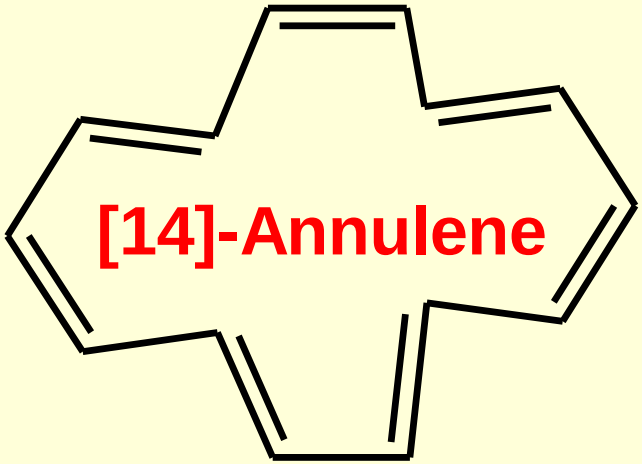


naphthalene

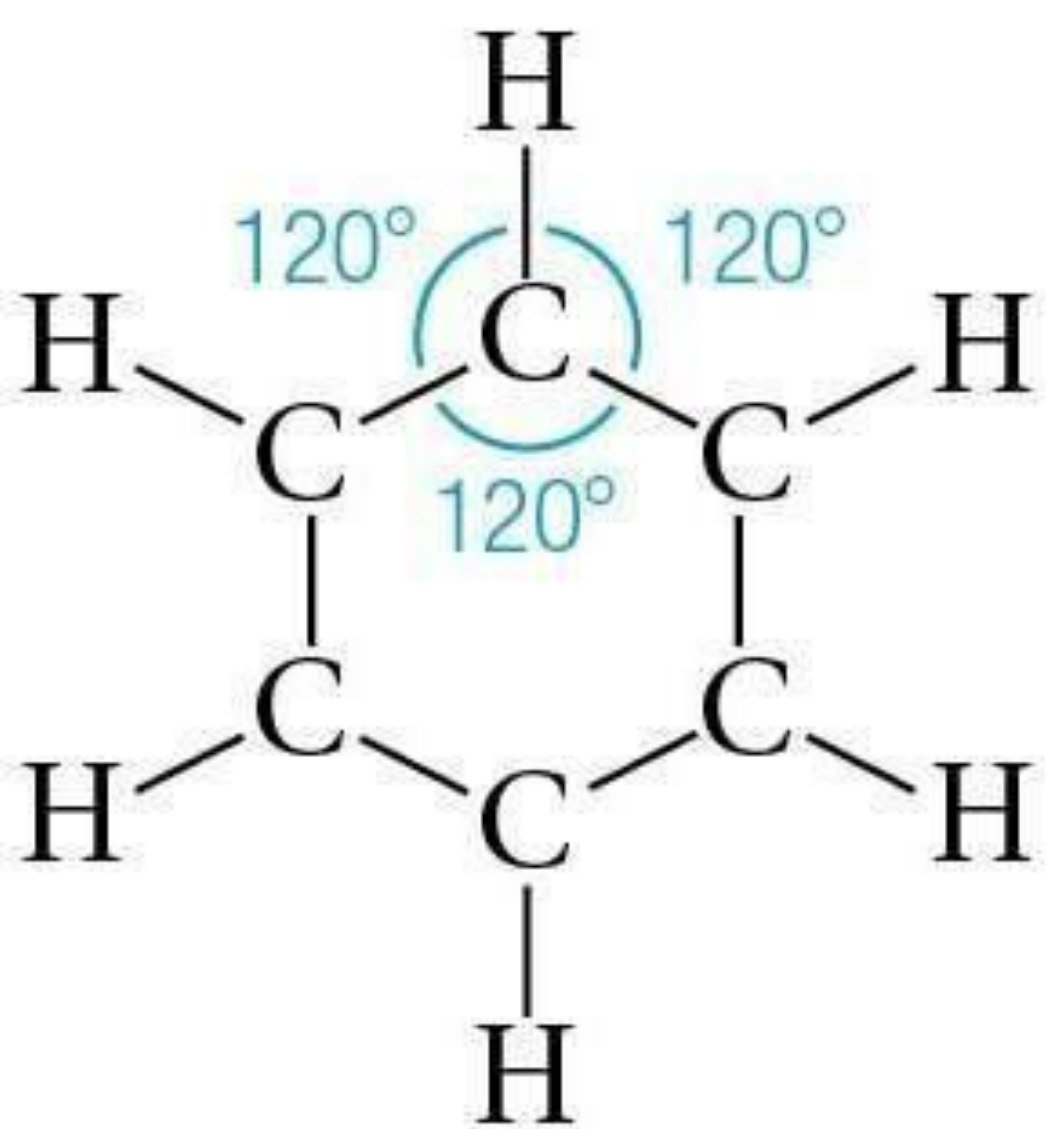
Erich Hückel



cyclopropenyl cation



Benzene C_6H_6.



Discovery of Benzene

- Isolated in 1825 by Michael Faraday who determined C:H ratio to be 1:1.
- Synthesized in 1834 by Eilhard Mitscherlich who determined molecular formula to be C_6H_6.
- Other related compounds with low C:H ratios had a pleasant smell, so they were classified as aromatic.

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Benzene properties

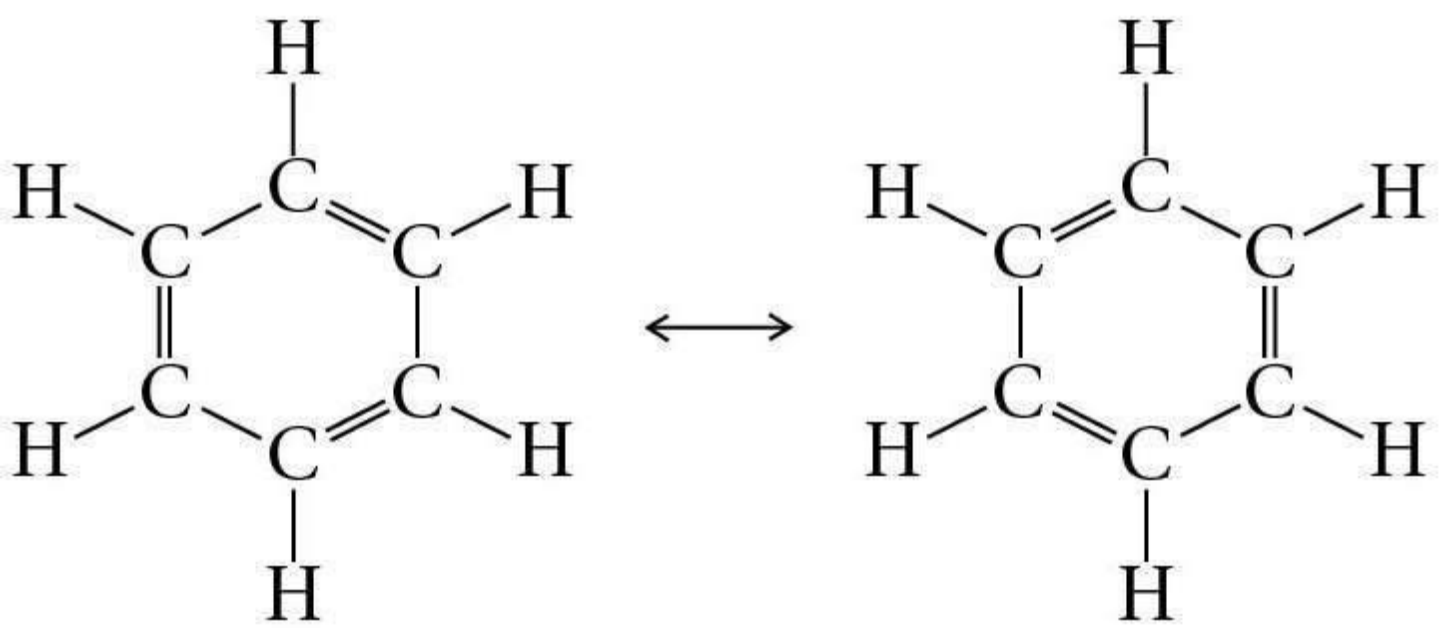
- The carbon to hydrogen ration in benzene suggest a highly unsaturated structure, however it behaves as if it were saturated.
- Does not decolorize bromine solution the way alkenes and alkynes do
- It is not easily oxidized by potassium permanganate
- Does not undergo addition reactions the same as alkenes or alkynes

Benzene

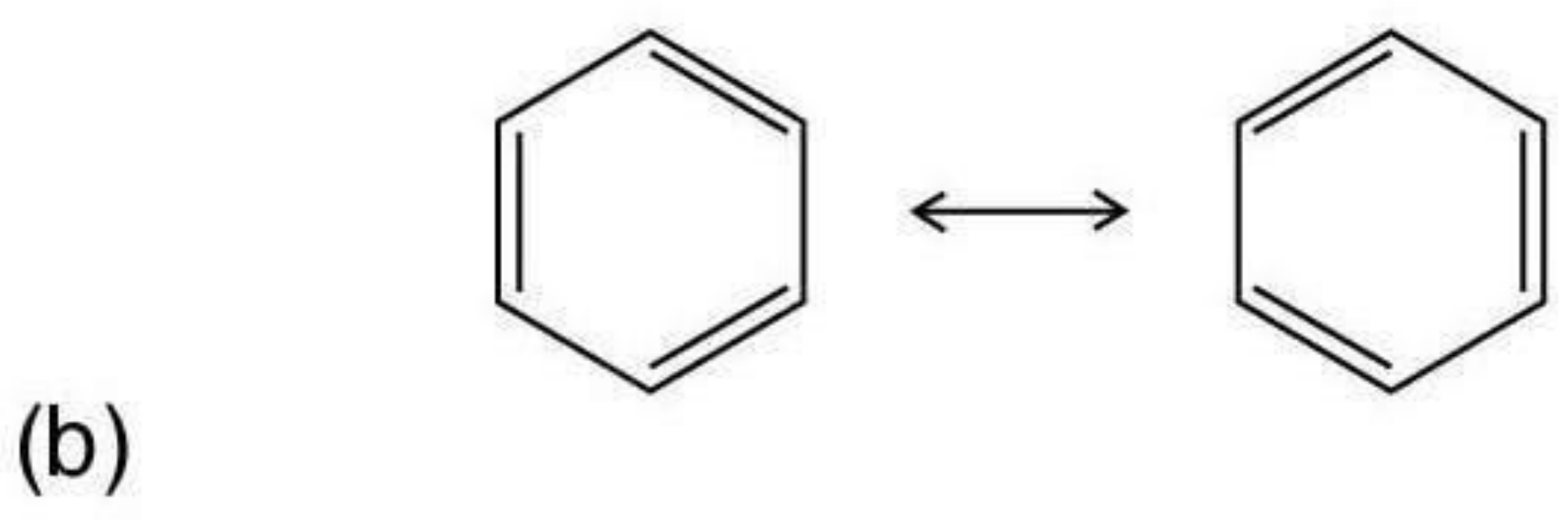
- Benzene is one of the most important commercial organic chemicals with approximately 17 billion pounds produced annually the United States alone.

Two Lewis structures for the benzene ring.

- Friedrich Kekule (1865) proposed the tetracovalence of carbon in the structure of benzene (alternating double single bonds)



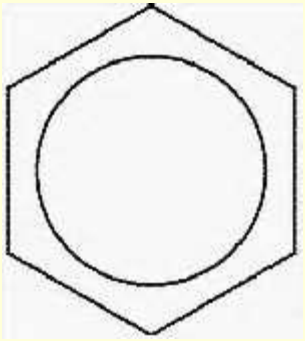
Shorthand notation for benzene rings.

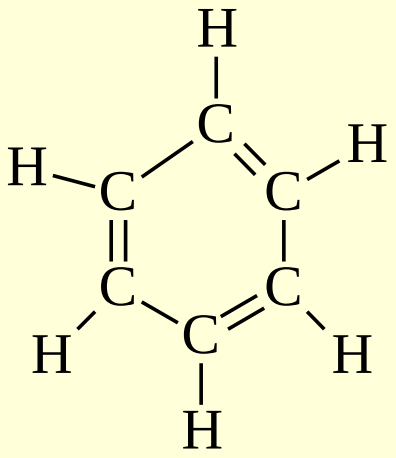


Kekulé Structure

- Proposed in 1866 by Friedrich Kekulé, shortly after multiple bonds were suggested.
- Thus benzene is often written as a circle to remind us of the delocalize nature of the electrons

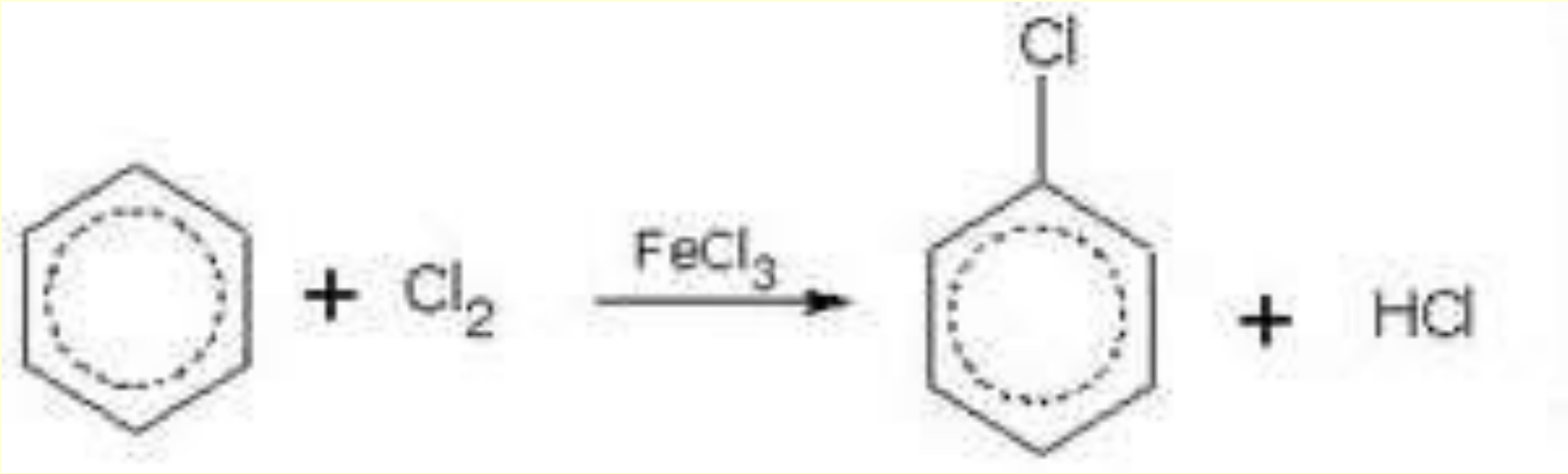
- Failed to explain existence of only one isomer of 1,2-dichlorobenzene.



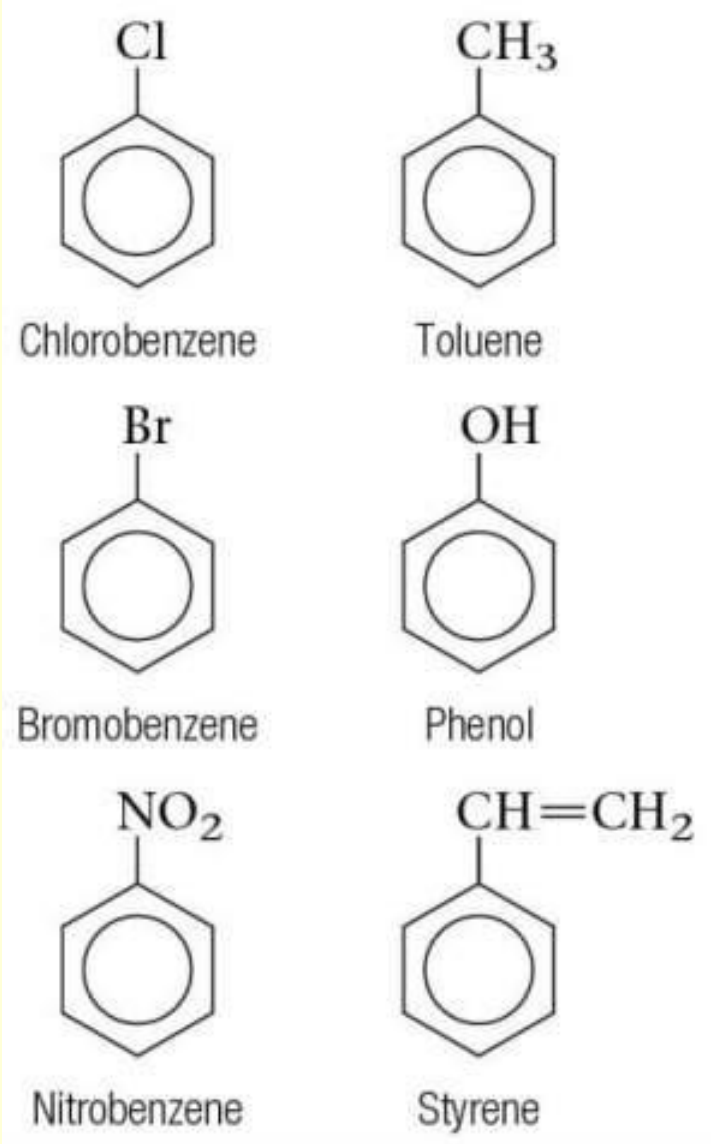


Substitution Reaction Benzene

- Benzene reacts mainly by substitution reaction



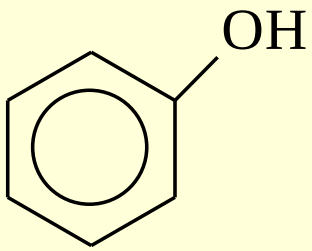
Some common mono-substituted benzene molecules



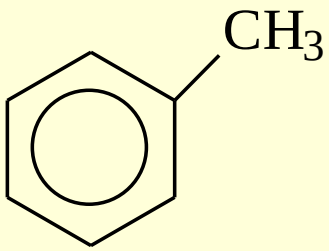
Toluene, sometimes you see this on marker pens ”contains no toluene”

Has the condensed structural formula

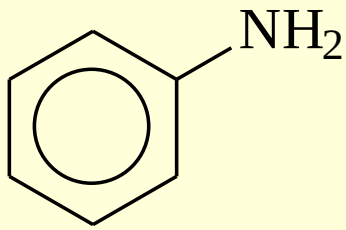
Common Names of Benzene Derivatives



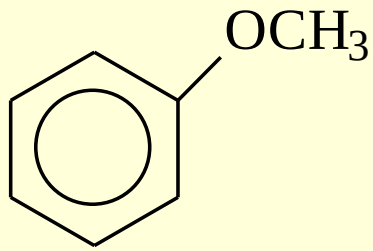
phenol



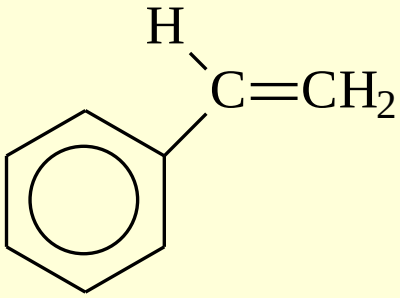
toluene



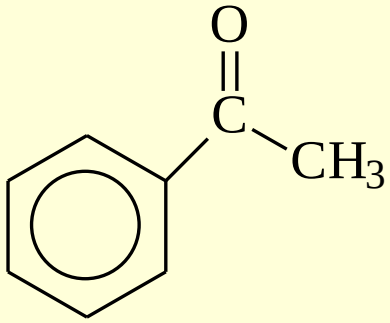
aniline



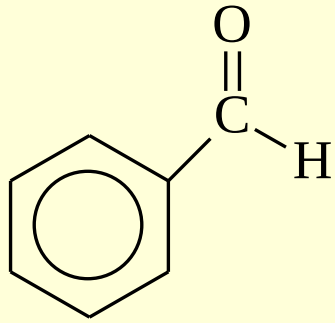
anisole



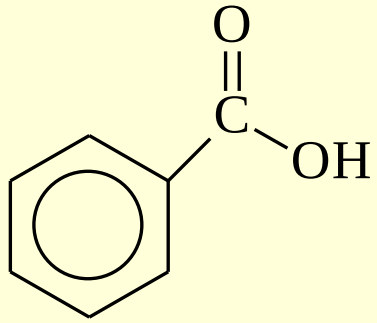
styrene



acetophenone



benzaldehyde



benzoic acid

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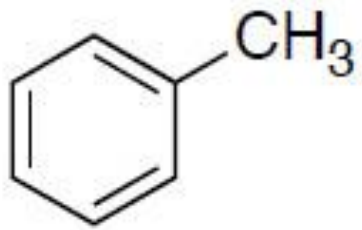
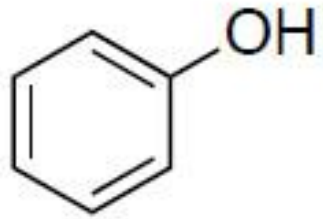
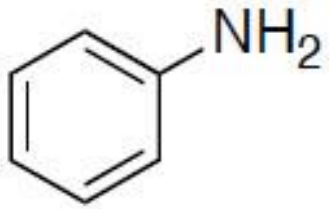


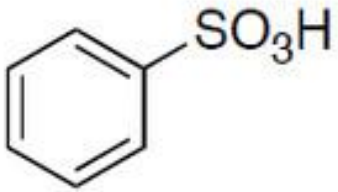
toluene



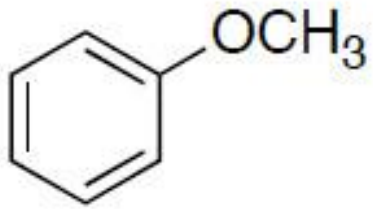
phenol



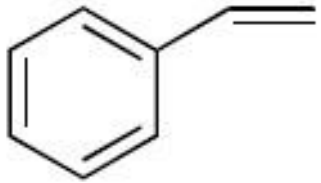
aniline



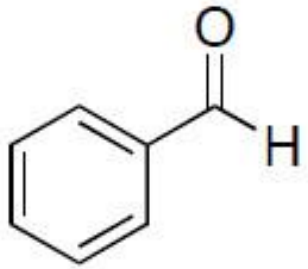
benzenesulfonic acid



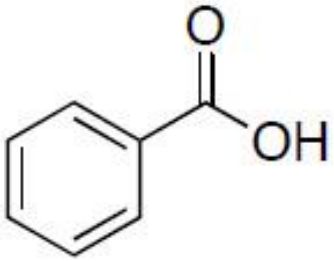
anisole



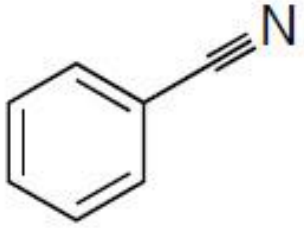
styrene



benzaldehyde



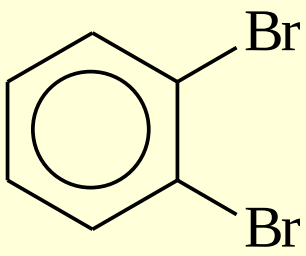
benzoic acid



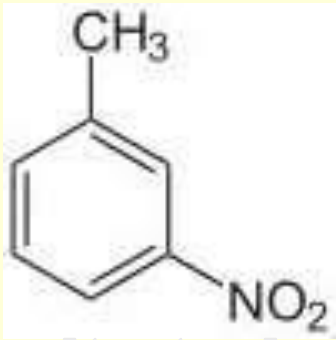
benzonitrile

Disubstituted Benzenes

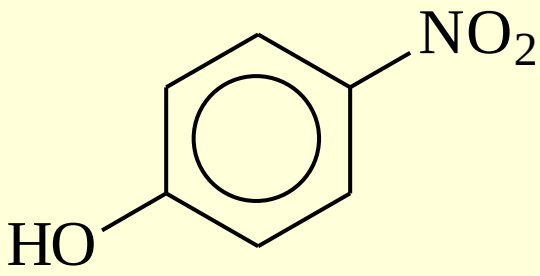
The prefixes *ortho*-, *meta*-, and *para*- are commonly used for the 1,2-, 1,3-, and 1,4-positions, respectively.



o-dibromobenzene or
1,2-dibromobenzene



m nitrotoulene



p-nitrophenol or
4-nitrophenol

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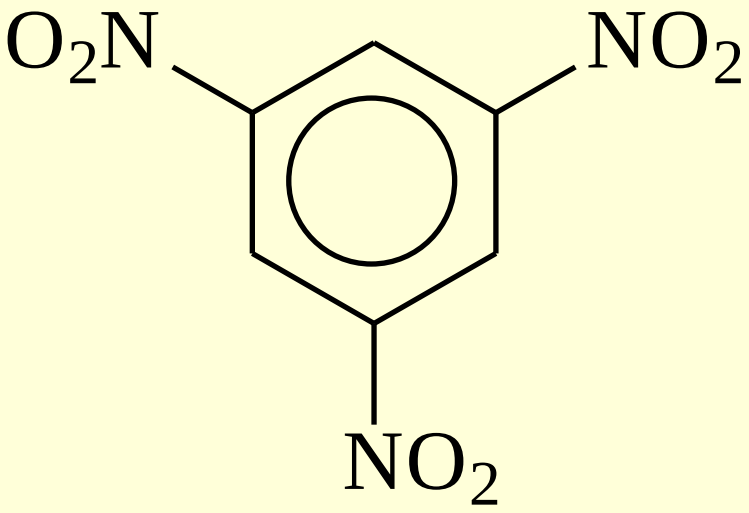
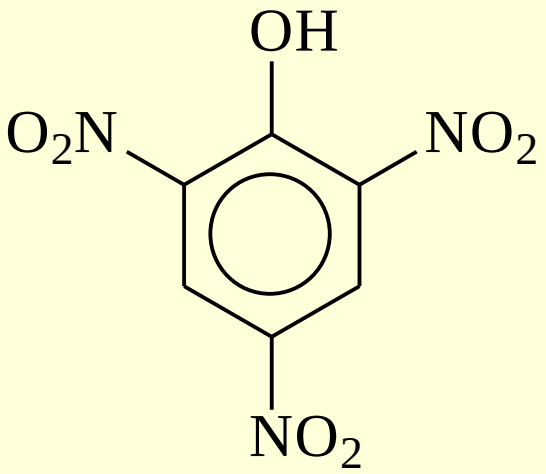
3 or More Substituents

Use the smallest possible numbers, but the carbon with a functional group is #1.



1,3,5-trinitrobenzene



2,4,6-trinitrophenol

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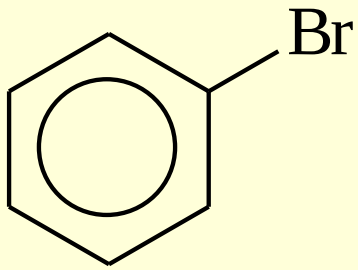
Phenyl and Benzyl

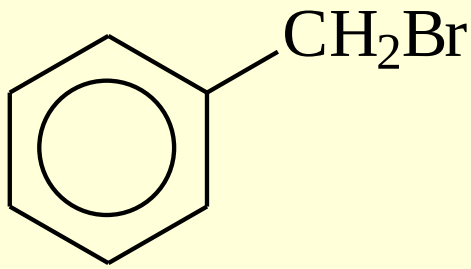
- Aromatic hydrocarbons are classified as arenes.
- The symbol Ar is used for an aryl group (just as R symbolizes alkyl group)
- Two groups with special names occur frequently in aromatic compounds: phenyl group and benzyl group

Phenyl and Benzyl

Phenyl indicates the benzene ring attachment. The benzyl group has an additional carbon.



phenyl bromide



benzyl bromide

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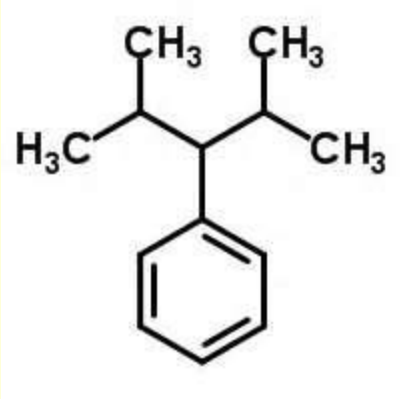
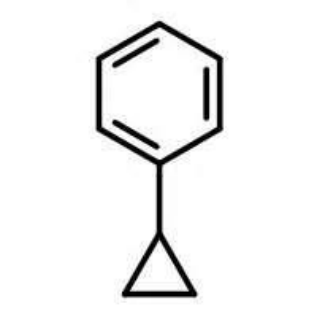
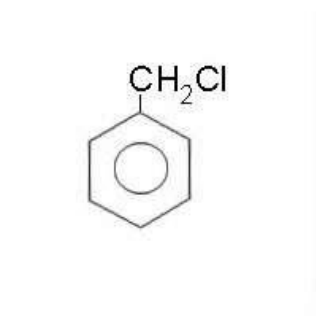
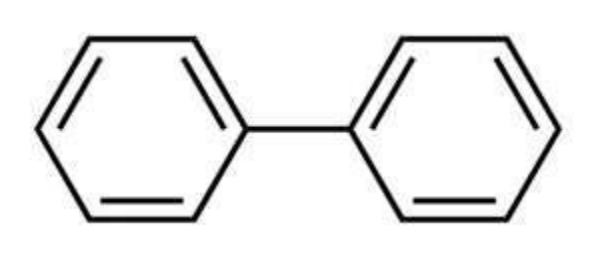




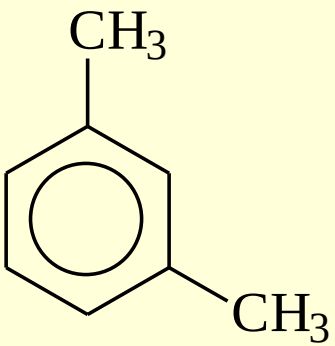
- 2, 4 dimethyl 3 phenyl pentane phenylcyclopropane



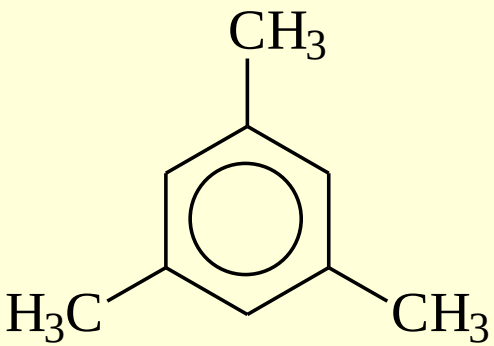


- Benzyl chloride biphenyl

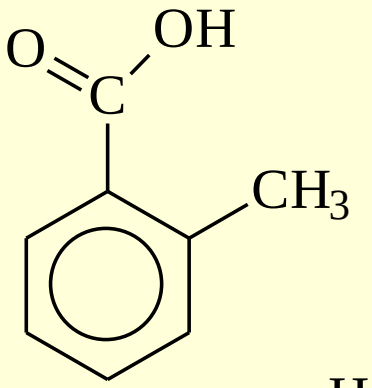
Common Names for Disubstituted Benzenes



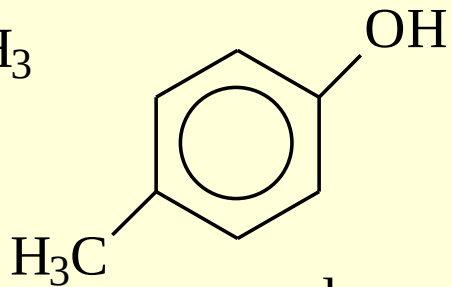
m-xylene



mesitylene



o-toluic acid



p-cresol

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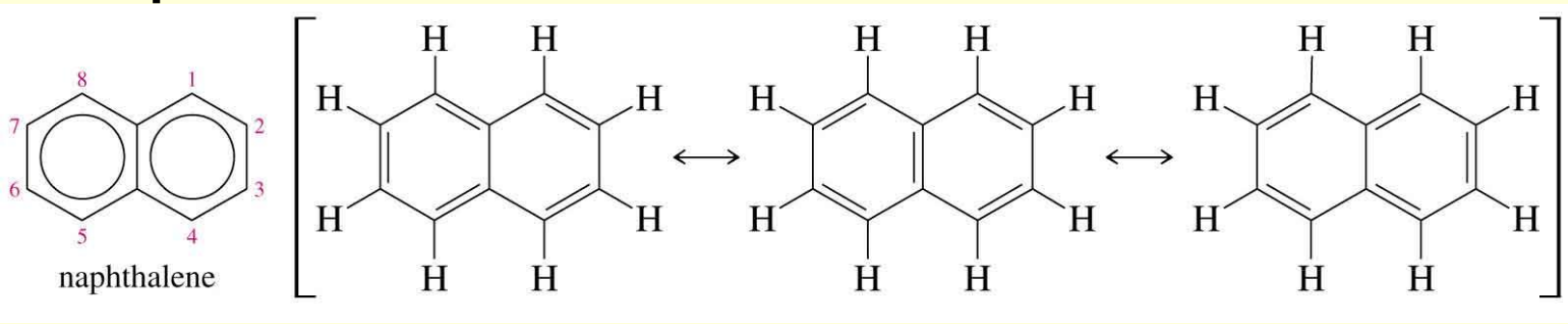
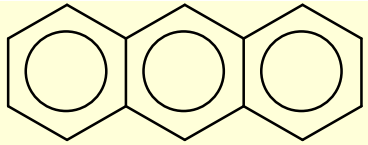
Fused Ring Hydrocarbons

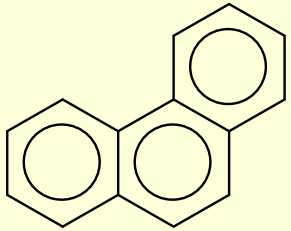
- Naphthalene



- Anthracene



- Phenanthrene



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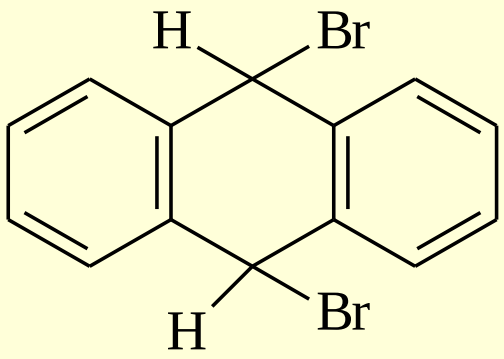
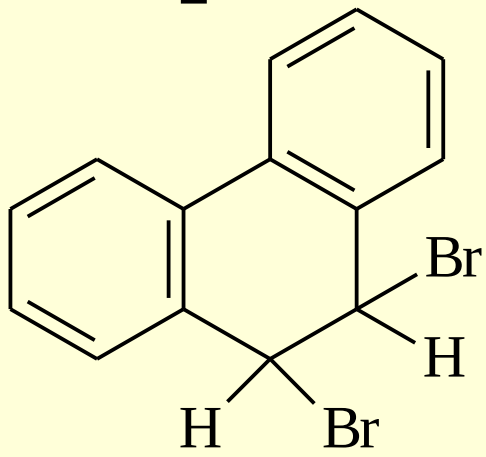
Reactivity of Polynuclear Hydrocarbons

As the number of aromatic rings increases, the resonance energy per ring decreases, so larger PAH's will add Br_2.

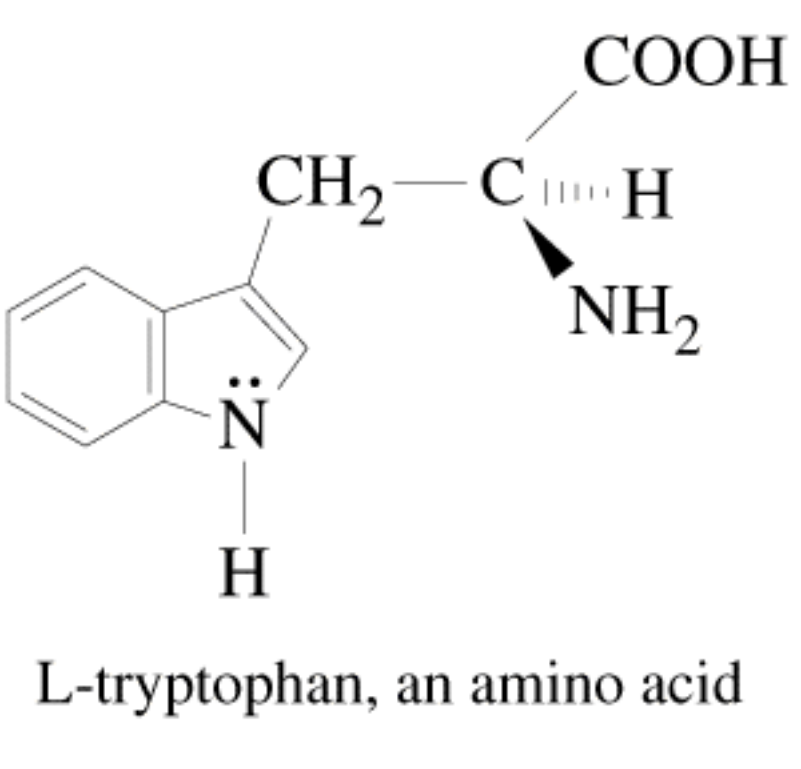




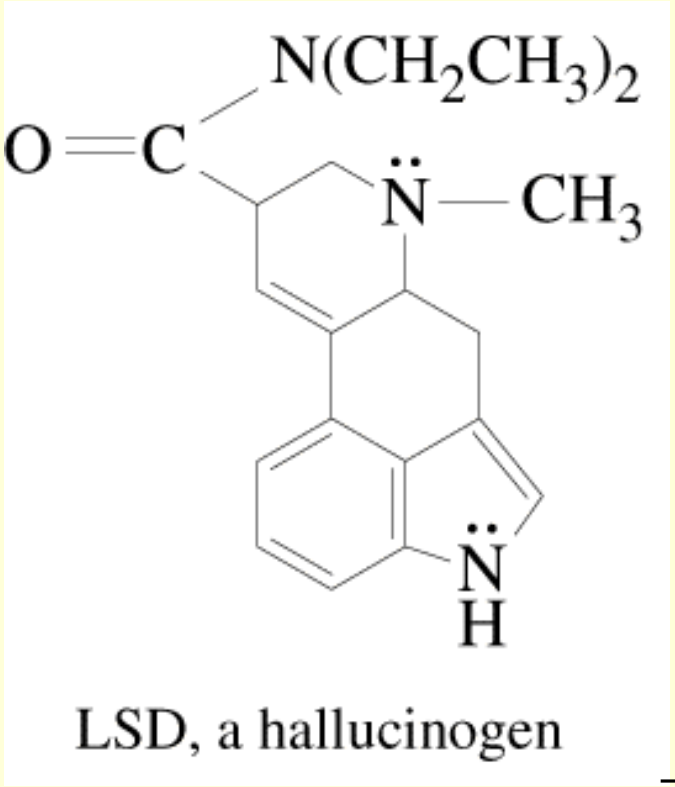
(mixture of cis and trans isomers) =>

Fused Heterocyclic Compounds

Common in nature, synthesized for drugs.



L-tryptophan, an amino acid



LSD, a hallucinogen

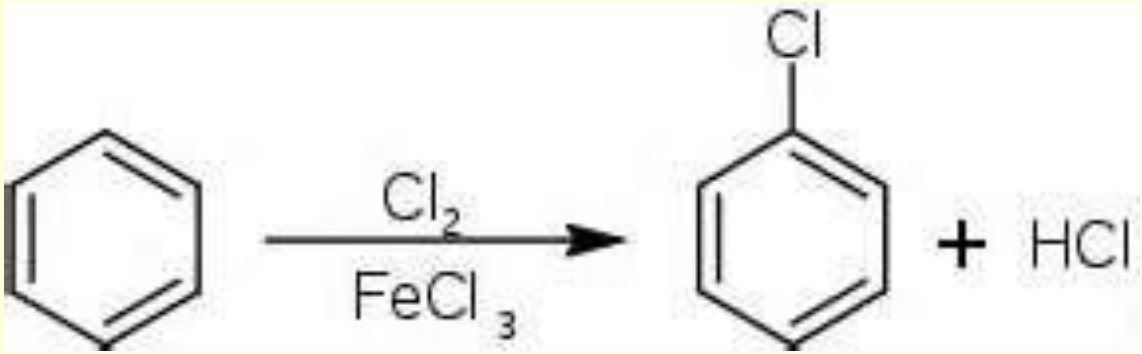
=>

Physical Properties

- Melting points: More symmetrical than corresponding alkane, pack better into crystals, so higher melting points.
- Boiling points: Dependent on dipole moment, so *ortho* > *meta* > *para*, for disubstituted benzenes.
- Density: More dense than nonaromatics, less dense than water.
- Solubility: Generally insoluble in water. =>

Electrophilic Aromatic substitution

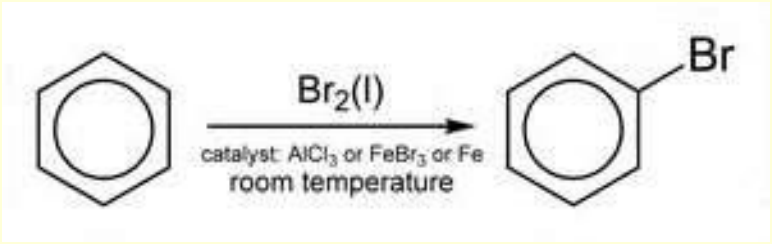
- The most common reaction of aromatic compounds involves substitution of other atoms or groups for a ring hydrogen



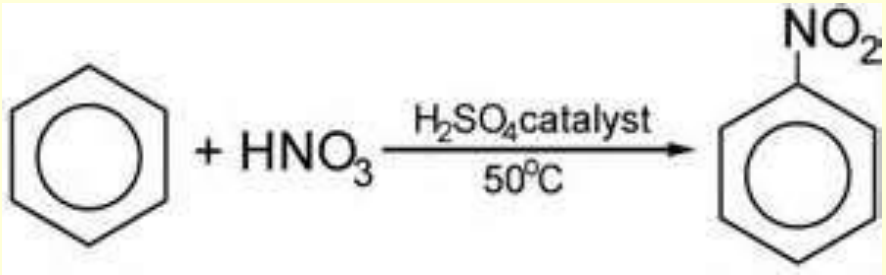
Chlorination

- $C_6H_6 + Cl_2$ ----- $C_6H_5Cl + HCl$ $FeCl_3$ is catalyst

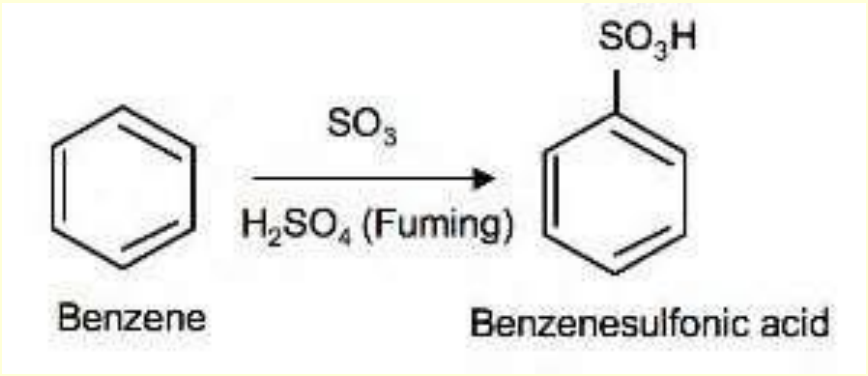
Electrophilic Aromatic substitution

- 

- bromination

- 

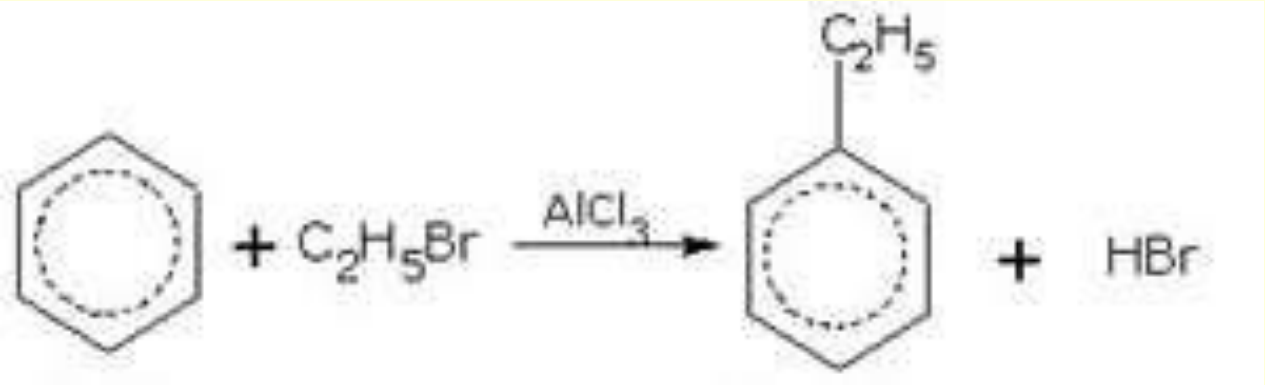
- nitration

- 

- sulfonation

Friedel-Crafts reaction

- Refers to Alkylation of aromatics
- The Friedel-Craft alkylation reaction has some limitations…it cannot be applied to an aromatic ring that already has one it a nitro or sulfonic acid group



Ortho, Para-directing and Meta-directing groups

- Substituents already present on an aromatic ring determine the position taken by a new substituent.
- Certain groups are ortho, para directing, and others are meta directing

Directing and activation effects of common functional groups (groups are listed in decreasing order of activation)

Substituent group	Name of group
-NH_2, -NHR, -NR_2	Amino
-OH, -$OHCH_3$, -OOR	Hydroxyl, alkoxy
O -NHC—R	acylamino
-CH_3, -CH_2,CH_3, -R	Alkyl
_____	_____
-F, -Cl, -Br, -I	Halo
_____	_____

all ortho, para directing

Directing and activation effects of common functional groups (groups are listed in decreasing order of activation)

Substituent group	• Name of group
O O -C-R, -C-OH	acyl, carboxy
O O -C-NH2, -C-OR	carboxamindo, carboalkoxy
O -S-OH	sulfonic acid
O -C≡N	cyano
O -N O	nitro

meta dircting

Effect of Groups on Electrophilic Aromatic Substitution

Activating: *Ortho*, *para* directors

Strongly activating

$-NH_2$ ($-NHR$, $-NR_2$)

$-OH$

Moderately activating

$-OCH_3$ ($-OC_2H_5$, etc.)

$-NHCOCH_3$

Weakly activating

$-C_6H_5$

$-CH_3$ ($-C_2H_5$, etc.)

Deactivating: *Meta* directors

$-NO_2$

$-N(CH_3)_3^+$

$-CN$

$-COOH$ ($-COOR$)

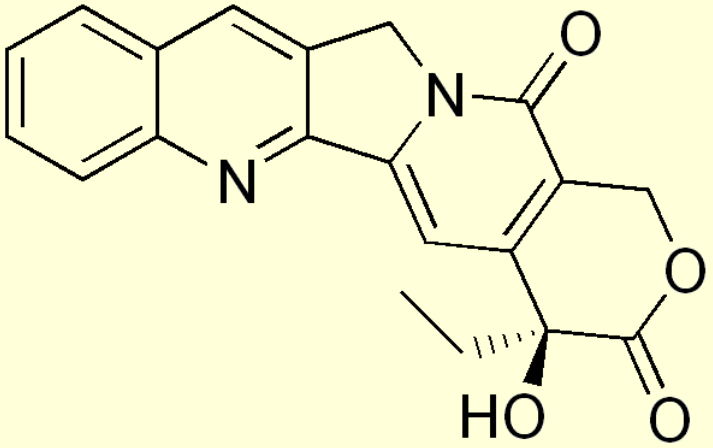
$-SO_3H$

$-CHO$, $-COR$

Deactivating: *Ortho*, *para* directors

$-F$, $-Cl$, $-Br$, $-I$

Cytotoxin- Inhibits DNA-topoisomerase enzymes



Happy Tree (China)

Heterocyclic Chemistry

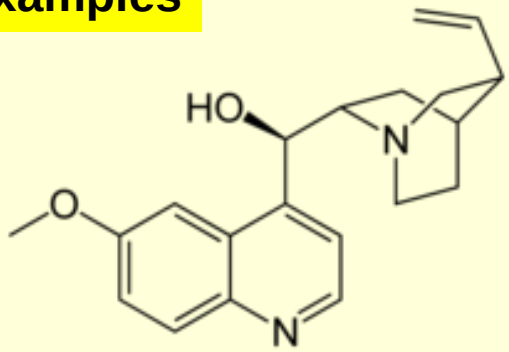
The largest class of organic compounds.

Most drugs contain herocyclic rings

Definition: **Heterocyclic compounds** are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as the heteroatom. The ring may be aromatic or non-aromatic

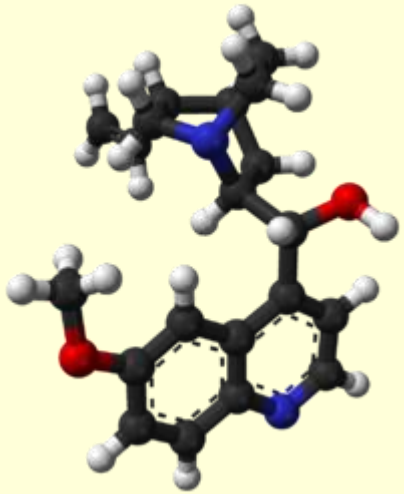
Significance – Two thirds of all organic compounds are aromatic heterocycles. Most pharmaceuticals are heterocycles.

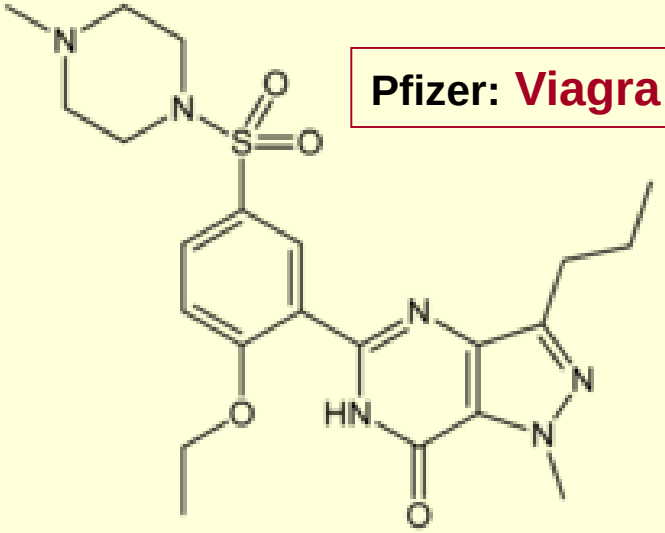
Examples



Quinine

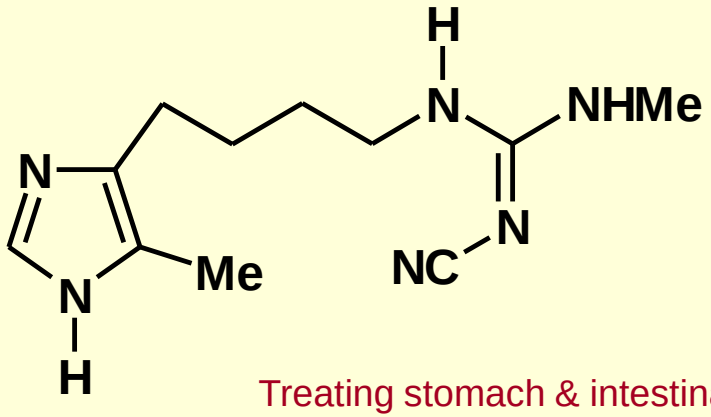
Treatment of malaria for 400 years (Peru)





Pfizer: Viagra

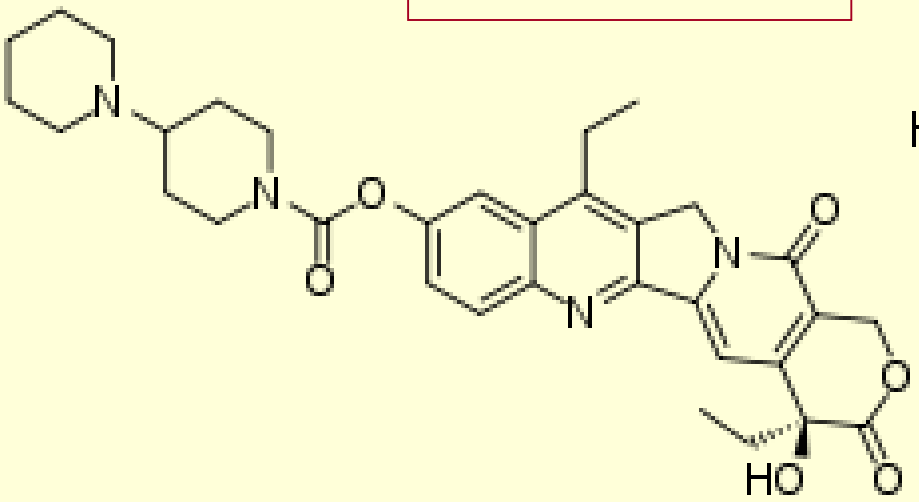
Erectile dysfunction



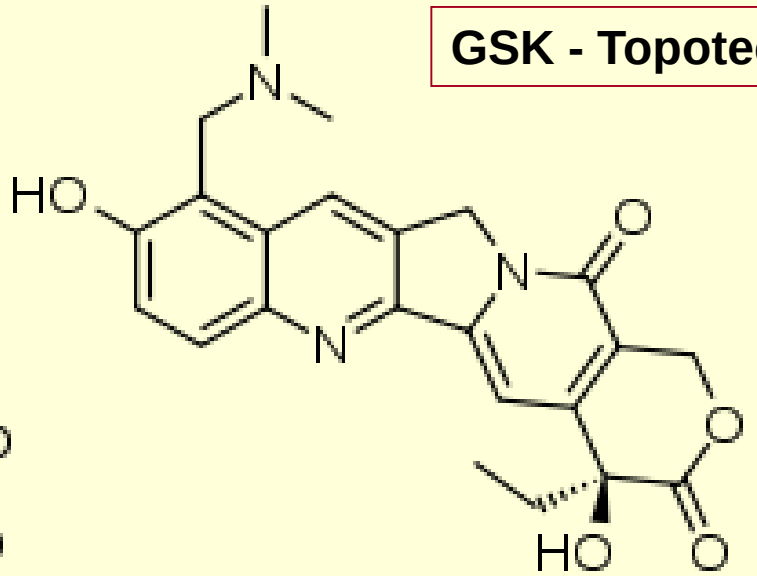
Treating stomach & intestinal ulcers

Camptothecin Analogues

Pfizer - Irinotecan



GSK - Topotecan

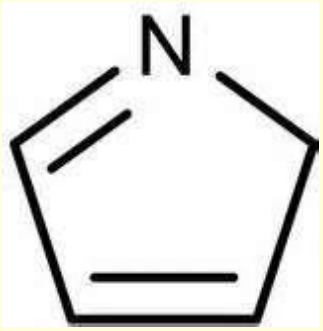


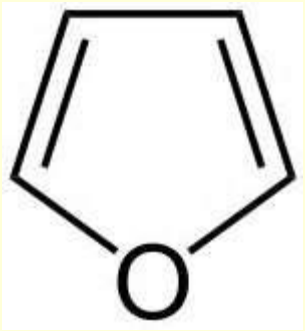
Ovarian & lung cancer

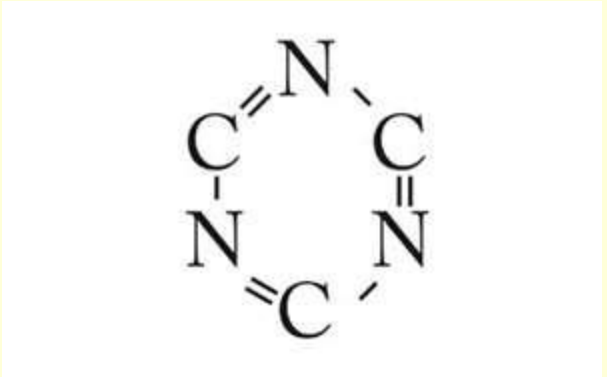
More soluble & less side-effects

Heteroatoms

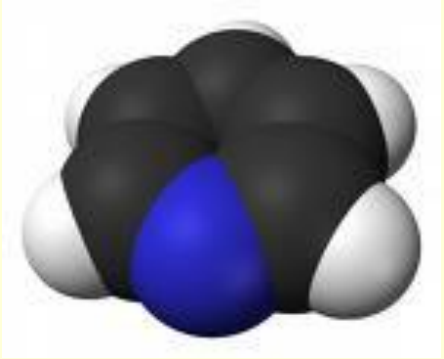
- Are atoms other than carbon or hydrogen that may be present in an organic compound.
- The most common heteroatoms are oxygen, nitrogen and sulfur

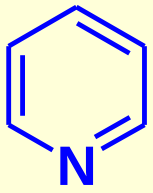




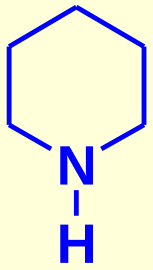


Six Membered Heterocycles: Pyridine

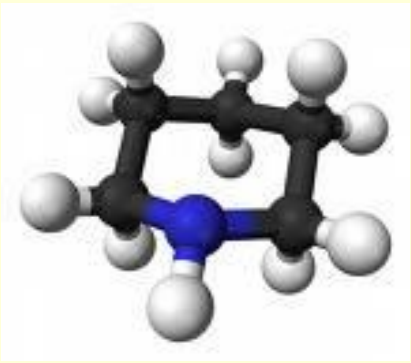




pyridine



piperidine



Pyridine replaces the CH of benzene by a N atom (and a pair of electrons)

Hybridization = sp^2 with similar resonance stabilization energy

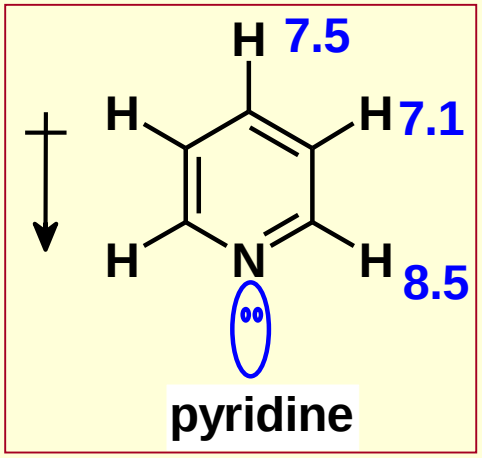
Lone pair of electrons not involved in aromaticity

Pyridinium ion: p*K*a = 5.5

Piperidine: p*K*a = 11.29

diethylamine : p*K*a = 10.28

^{1}H NMR: δ



pyridine

Pyridine is a weak base
Pyridine is π-electron deficient
Electrophilic aromatic substitution is difficult
Nucleophilic aromatic substitution is easy

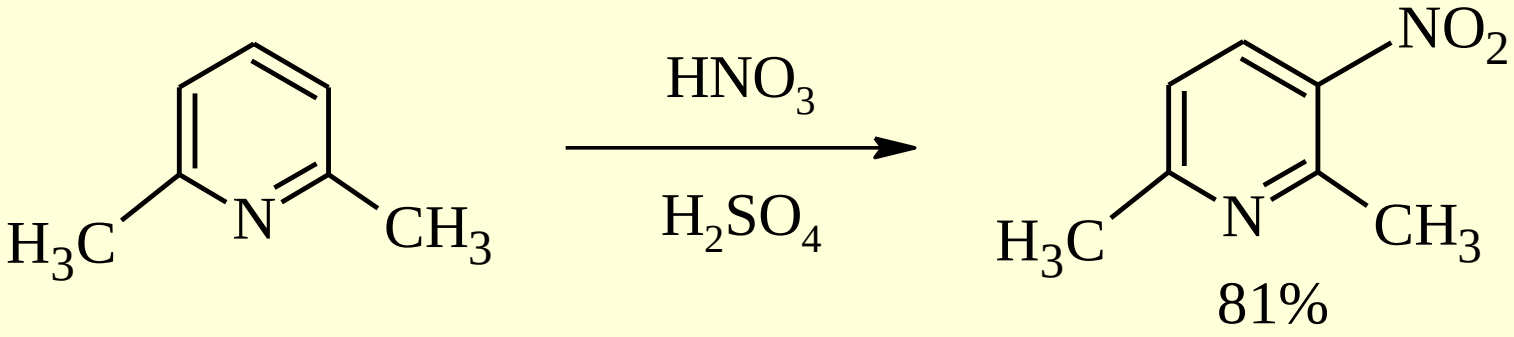
Chemistry of pyridine

Electrophilic substitution in pyridine

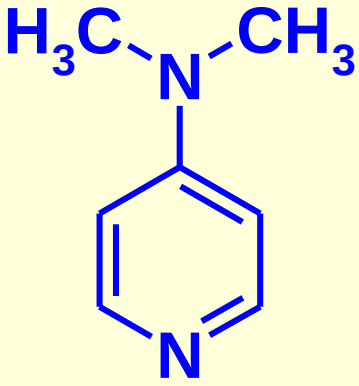
Pyridine is less active, than benzene toward electrophilic agents, because nitrogen is
more electronegative, than carbon and acts like an electron withdrawing substituent,
including the meta-directing effect.

It undergoes this reaction only under drastic conditions, ex nitration or bromination and requires high temperatures and strong acid catalyst

<u>Example:</u>

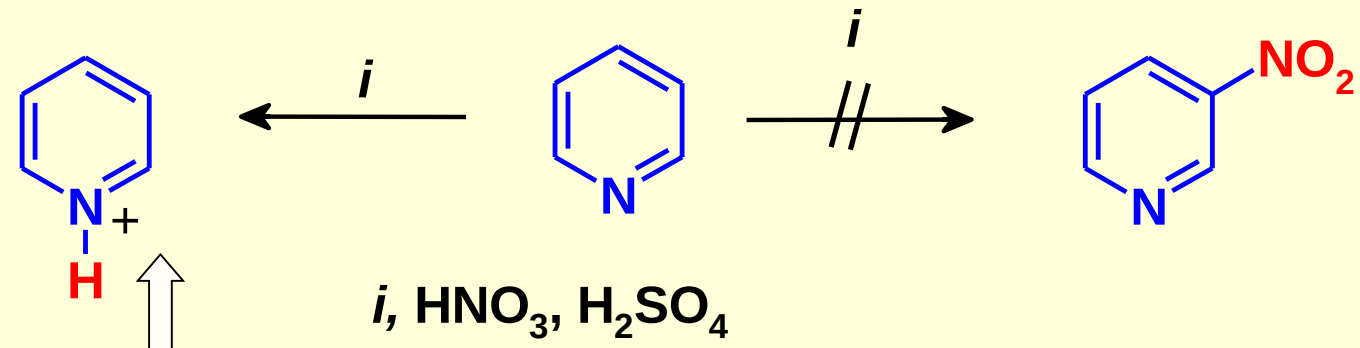


DMAP (DimethylAminoPyridine)

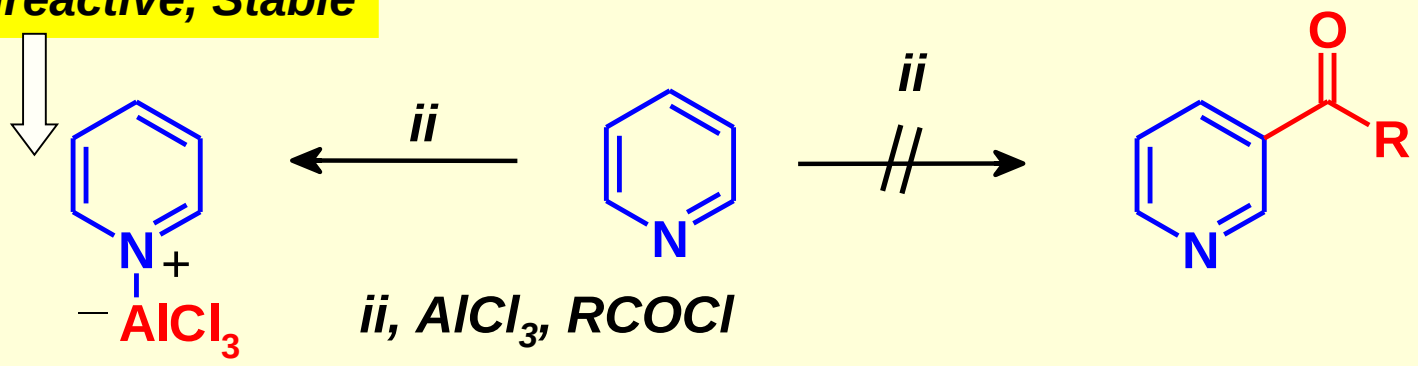


Whereas acylations "catalyzed" by pyridine are normally carried out in pyridine as the reaction solvent. Only small amounts of DMAP are required to do acylations

Attempted Electrophilic Aromatic Substitution

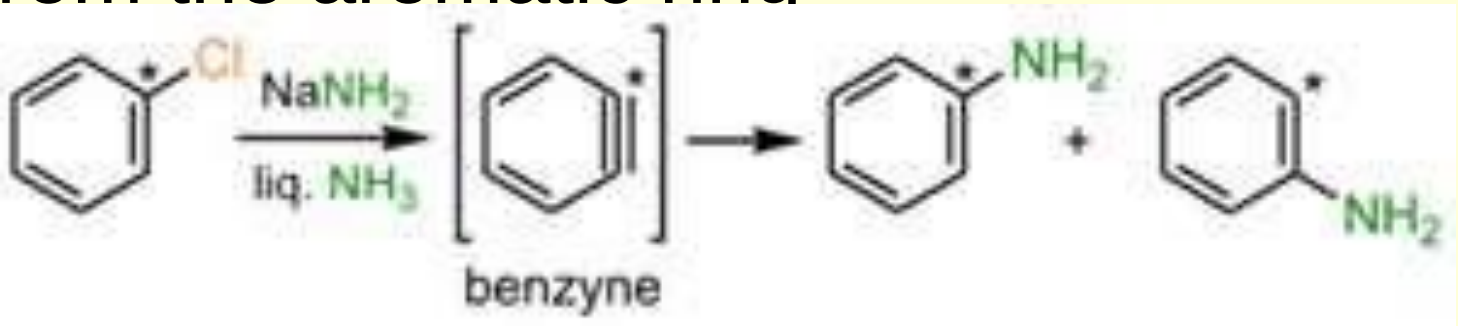


Unreactive, Stable

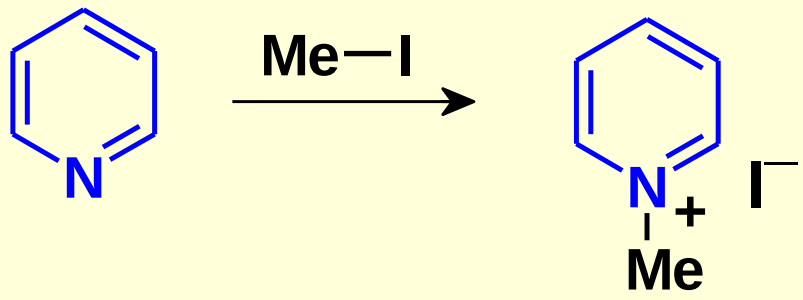


Nucleophilic aromatic substitution

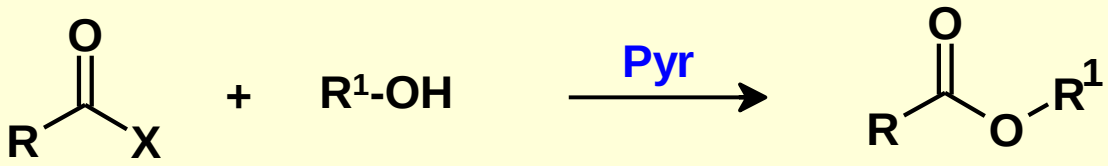
- The reaction of pyridines
- A nucleophile displaces a hydride or halide ion from the aromatic ring



Pyridine as a nucleophile

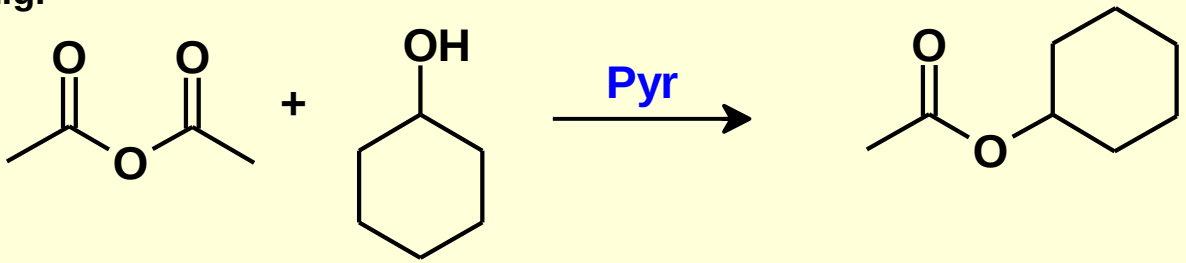


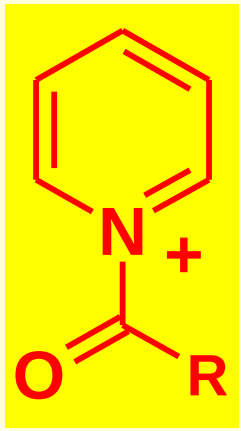
Use Pyridine as a solvent to make esters



X = OAc, Cl, Br

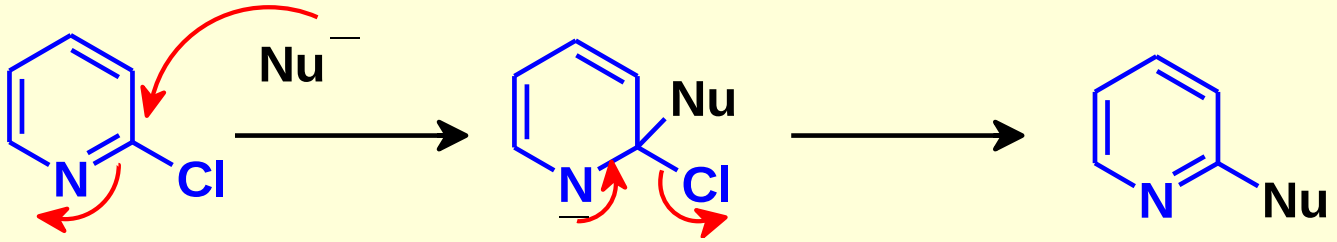
E.g.



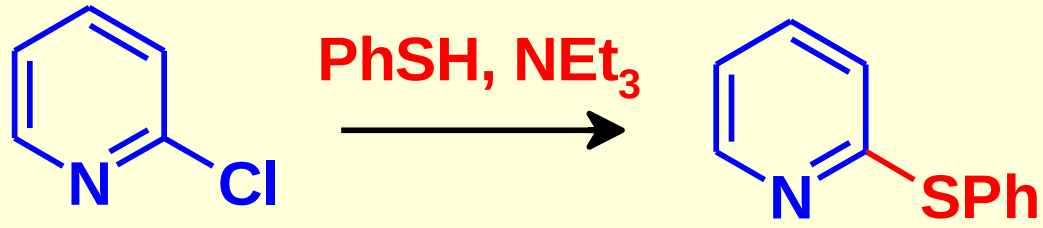


Acyl pyridinium ion
Reactive intermediate

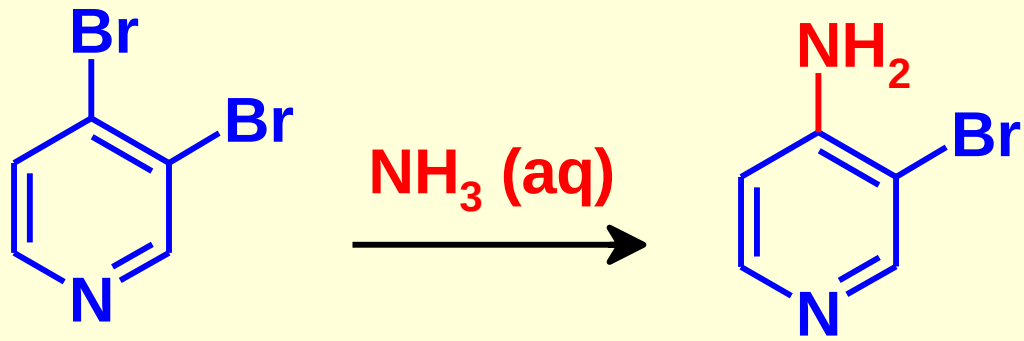
Nucleophilic Substitution at 2- and 4-positions of pyridine is most favoured



E.g.



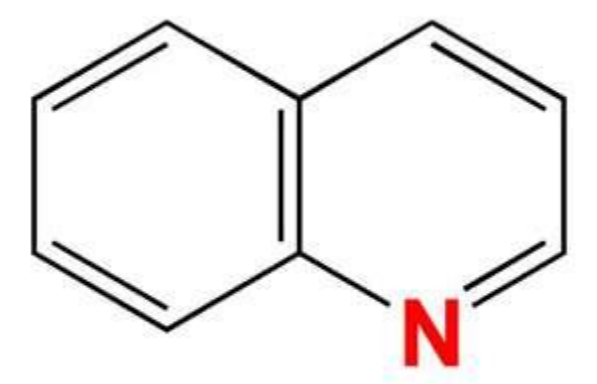
93%

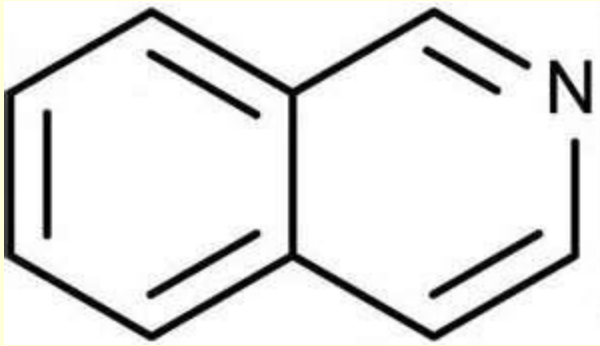


65%

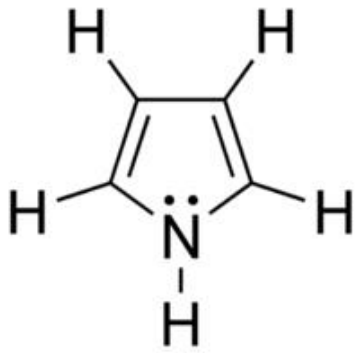
Heterocycles

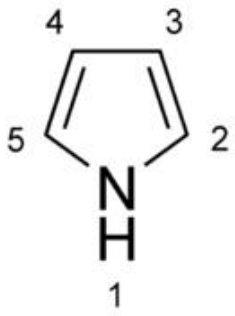
- The pyridine ring can be fused with benze rings t produce polycyclic aromatic heterocycles.
- Examples of 6-membered heterocycles include quinoline and isoquinoline

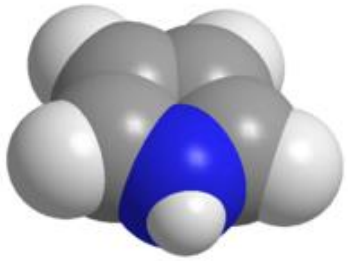




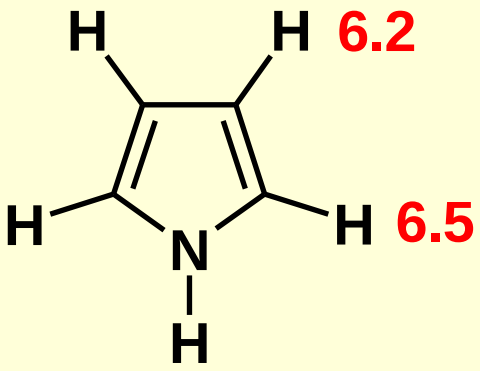
Five Membered Heterocycles: Pyrrole







^{1}H NMR: δ



Pyrrole

Aromatic: Thus, 6π electrons

Sp^2 hybridised and planar

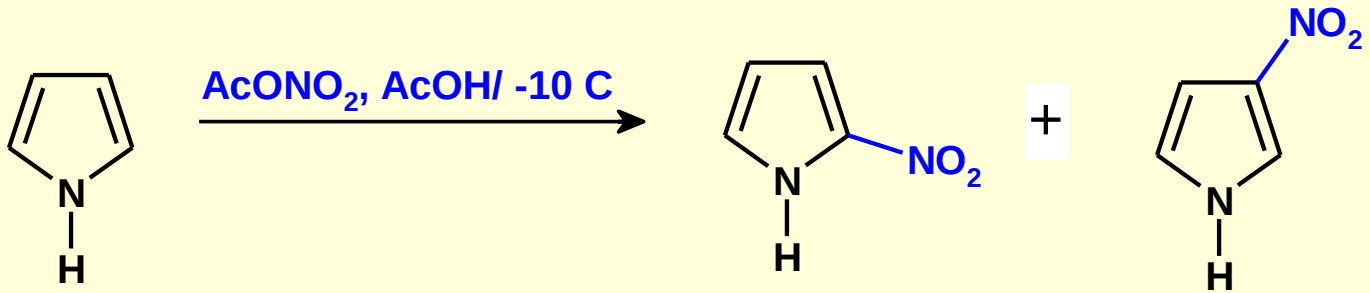
Lone pair tied up in aromatic ring

Pyrrole is π-electron excessive

Thus, Electrophilic Aromatic Substitution is Easy

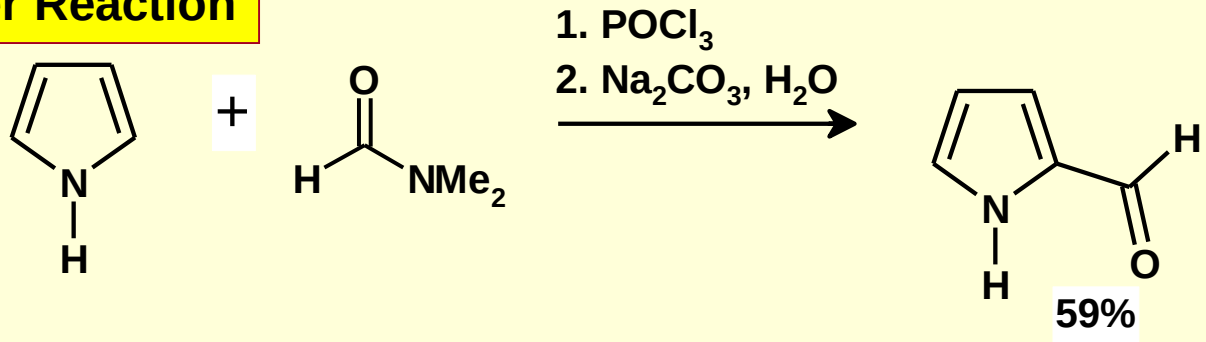
Nucleophilic Substitution is Difficult

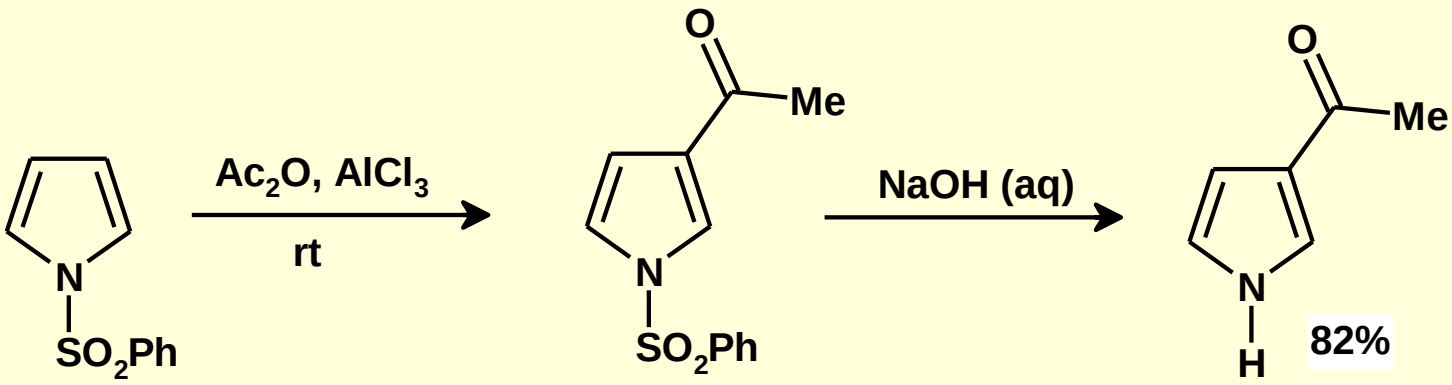
Electrophilic Aromatic Substitution preferred at the 2-position



Normal acidic nitration causes polymerization

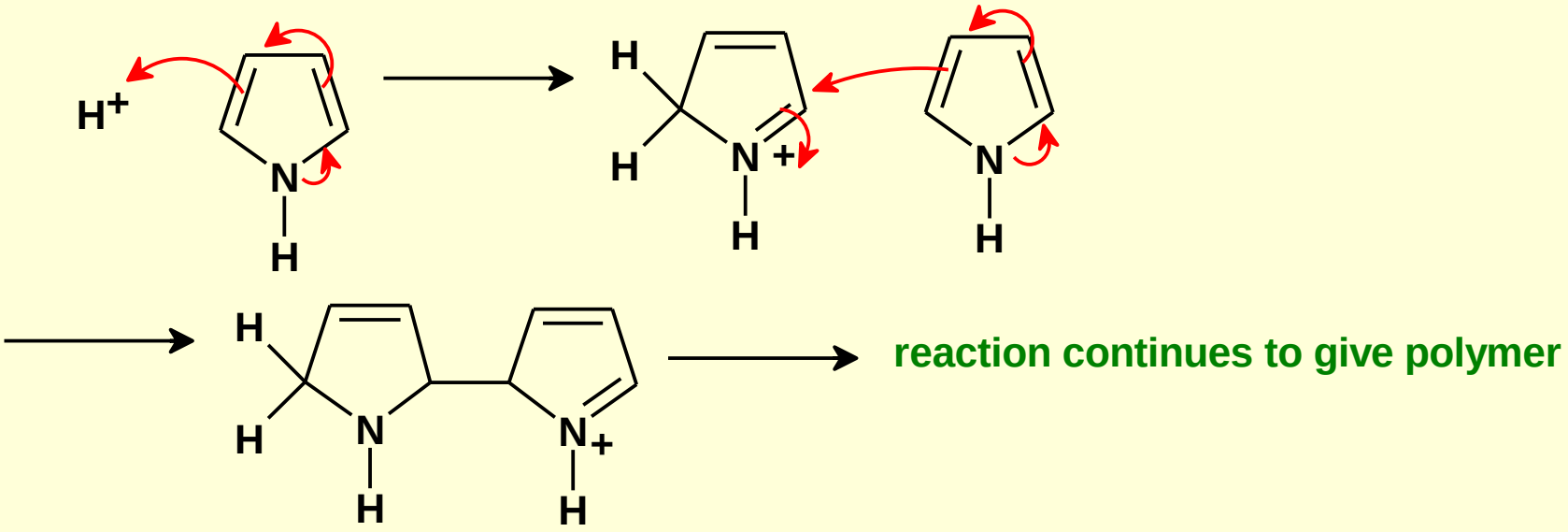
Vilsmeier Reaction





Electron-withdrawing group allows substitution at the 3-position

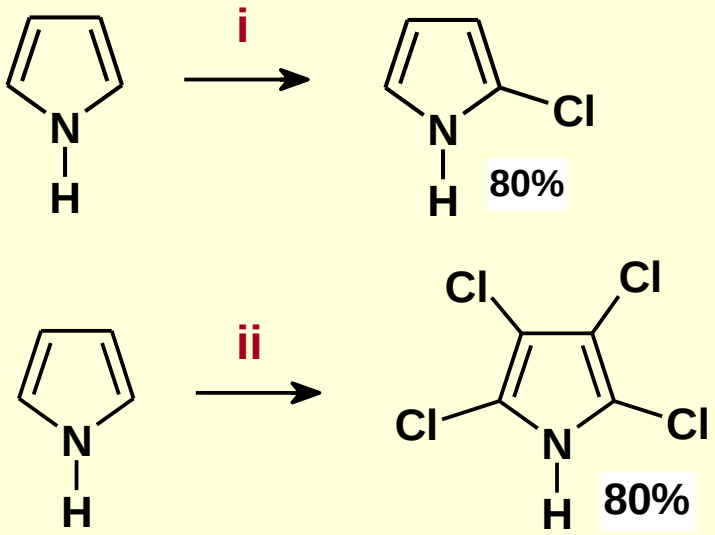
Organic Synthesis with Pyrrole should avoid strong acids



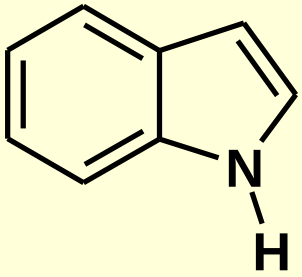
reaction continues to give polymer

i; 1 X SO_2Cl_2, Et_2O

ii; 4 X SO_2Cl_2, Et_2O



Indole



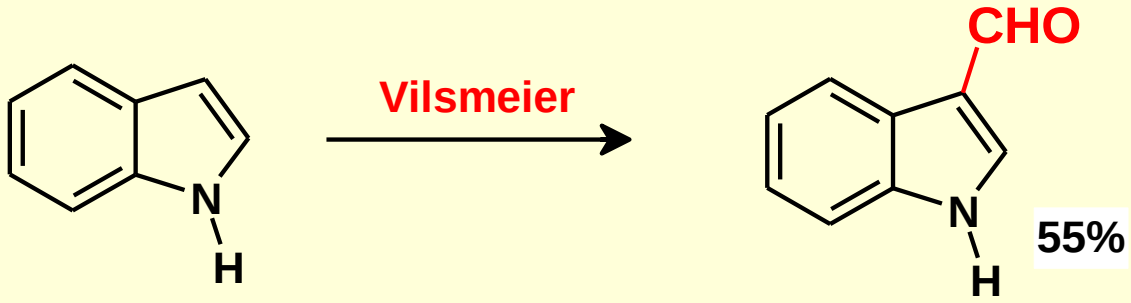
Indole

Aromatic due to 10 π-electrons

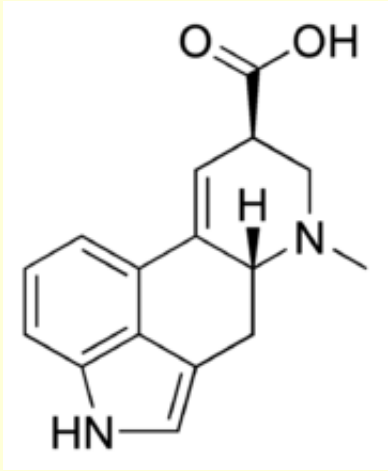
Benzene part is non-reactive

Electrophilic aromatic substitution

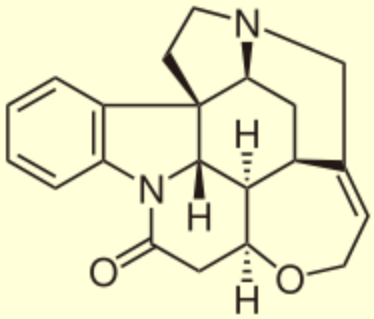
occurs at the 3-position



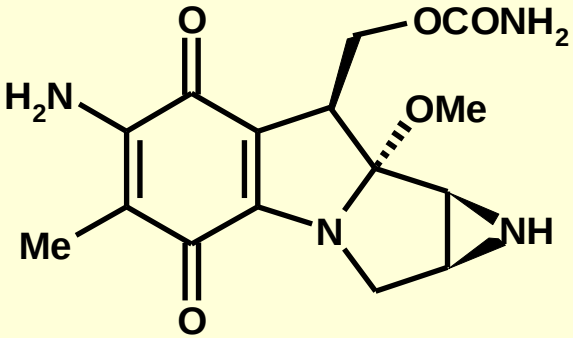
Indole Alkaloids



Lysergic acid (LSD)

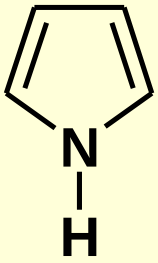


Strychnine

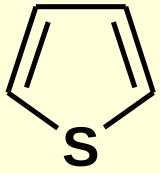


Mitomycin C

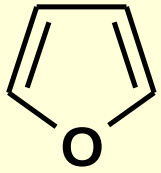
Other Five Membered Heterocycles



Pyrrole



Thiophene



Furan

Least reactive

More aromatic than Furan

The least aromatic:
The O atom is too electronegative

Less reactive than pyrrole, but substitution always at 2-position

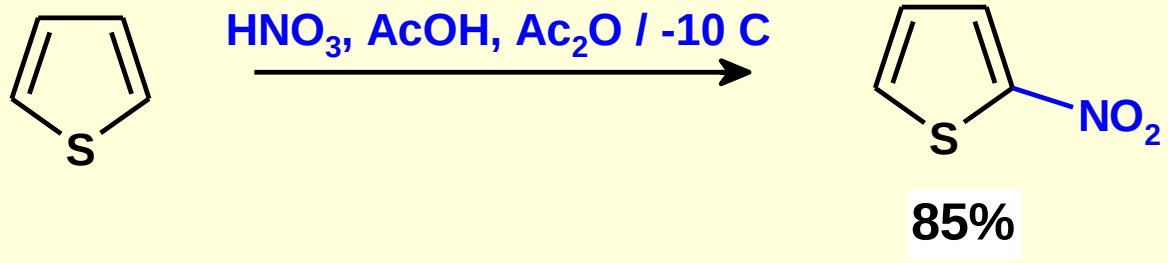
Electrophilic Substitution, not addition

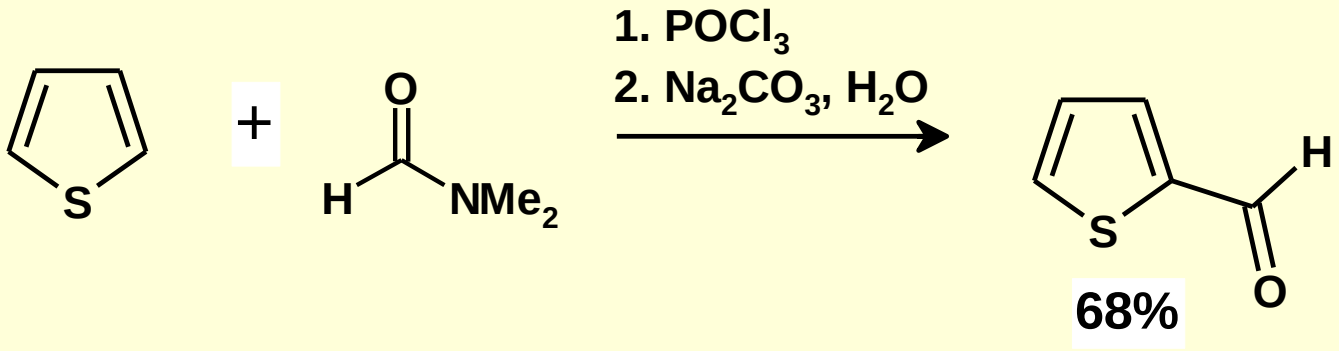
Can give addition, as well as substitution products when reacted with E^+

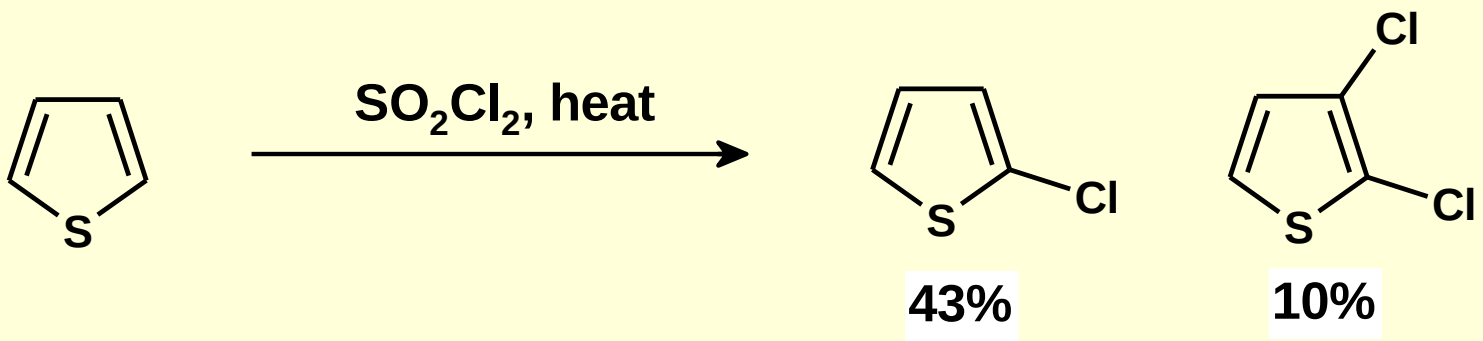
Thiophene has similar reactivity to benzene

Electrophilic Aromatic Substitution of Thiophene

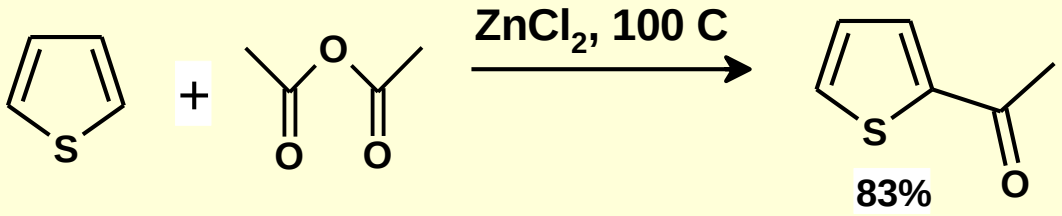
Avoid concentrated mineral acids or strong Lewis acids, e.g. $AlCl_3$



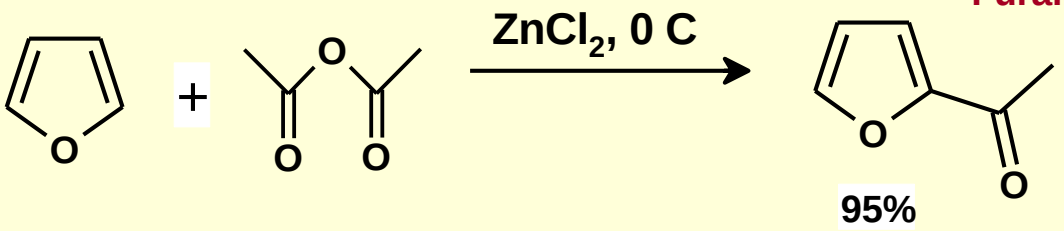


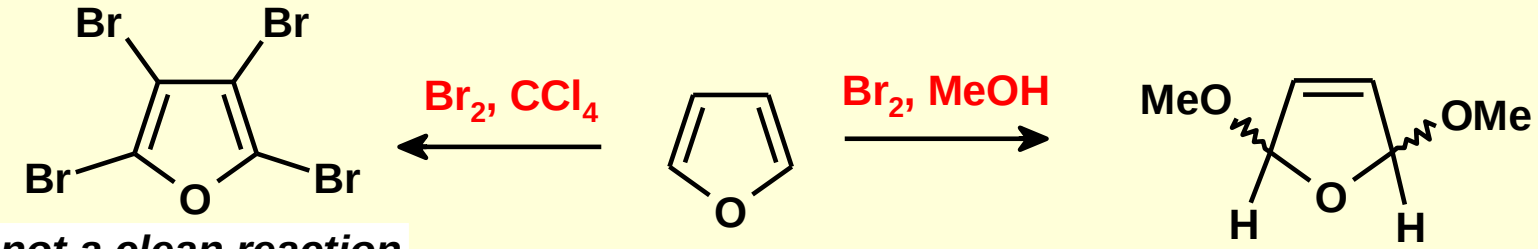


Some Reactions of Furan



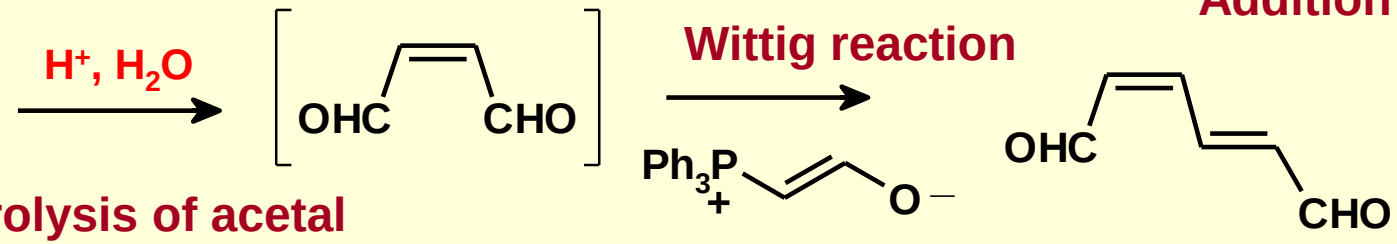
Furan is more reactive than thiophene





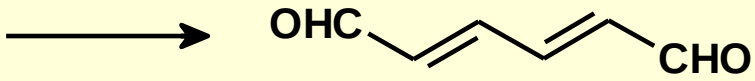
not a clean reaction

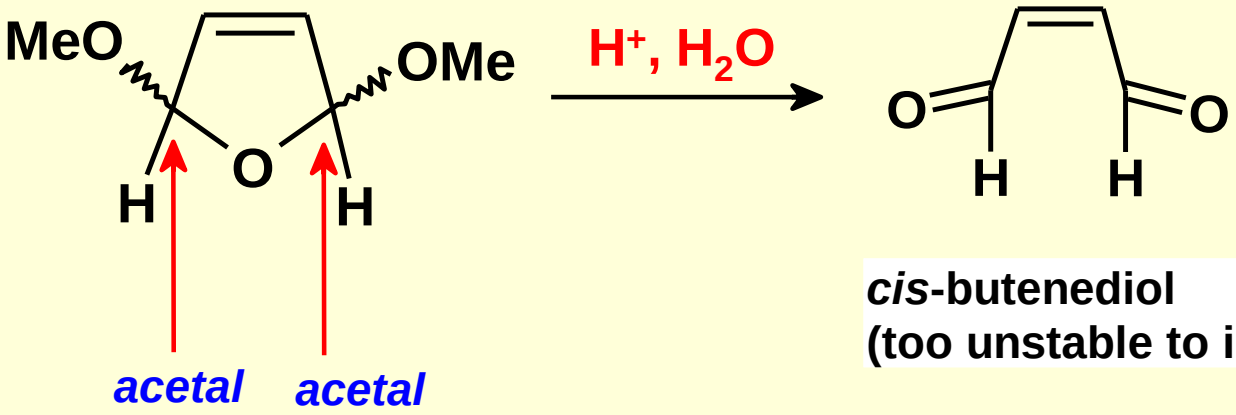
Addition product



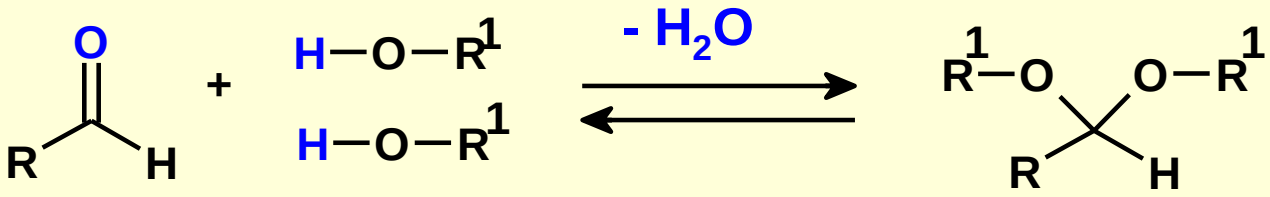
Hydrolysis of acetal

Furan is easily cleaved to dicarbonyls



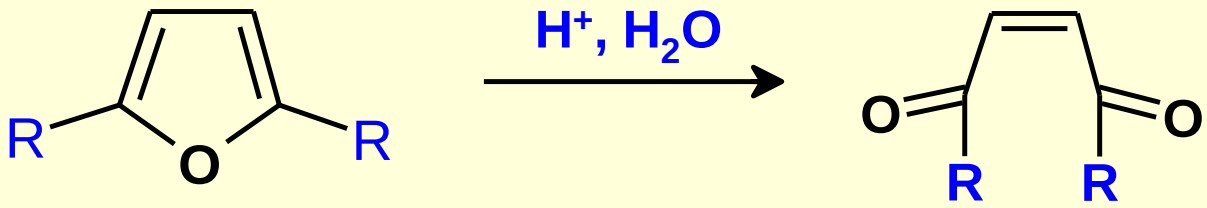


cis-butenediol
(too unstable to isolate)



aldehyde + 2 x alcohol acetal

acid-catalysed



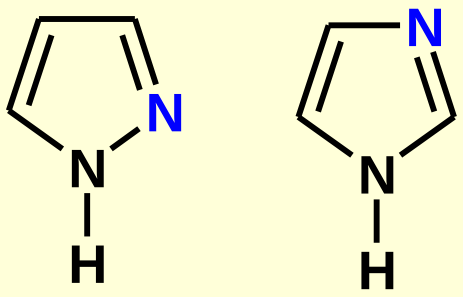
Furan is a source of 1,4-dicarbonyls in Organic Synthesis

Diels–Alder reaction

- is an organic chemical reaction (specifically, a cycloaddition) between a conjugated diene(chemical with 2 double bonds) and a substituted alkene, commonly termed the dienophile, to form a substituted cyclohexene system

Five-membered Rings with Two or More Nitrogens

Diazoles



Pyrazole

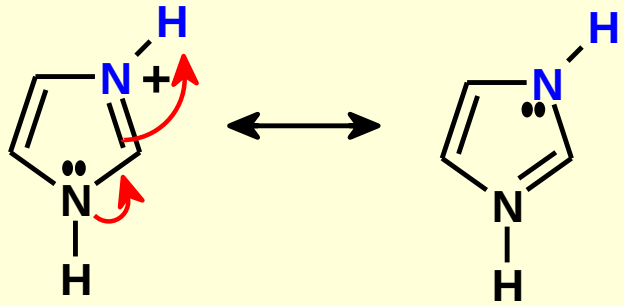
Imidazole

p*K*a = 14.5 (imidazole)

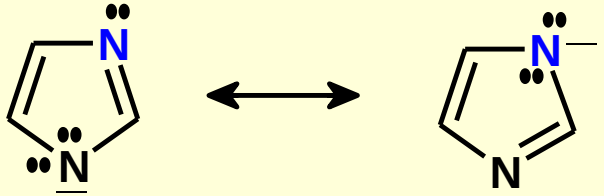
p*K*a = 16.5 (pyrrole)

Imidazole is more basic than pyridine, but more acidic than pyrrole

Imidazole + H^+ ⟶



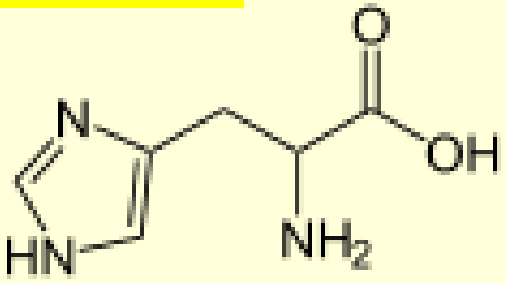
Imidazole - H^+ $\xrightarrow[-\ H_2O]{NaOH}$



Properties: ***Very stable cation and anion of imidazole is formed***

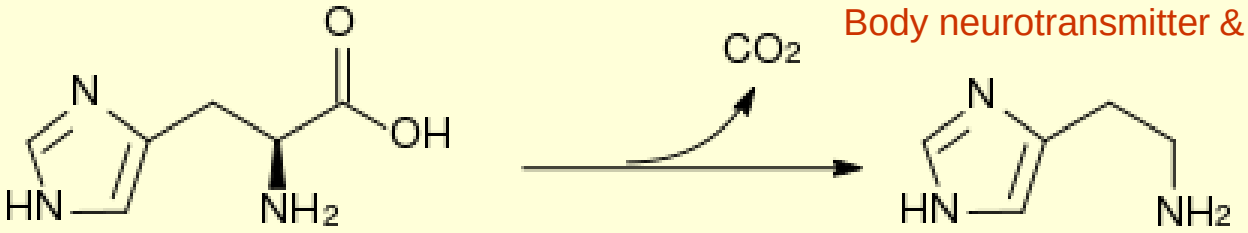
Some Natural Imidazole Compounds

Histidine



Important ligand to many metalloproteins

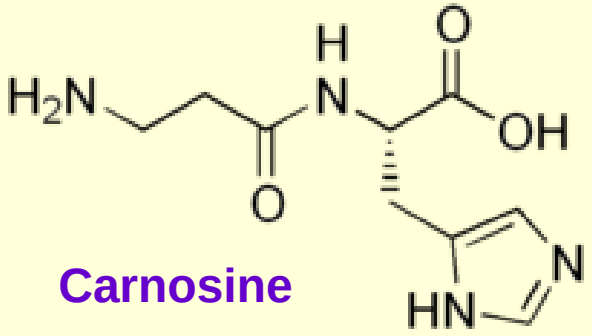
Is one of the essential amino acids.
A relatively small change in cellular pH can result in a change in its charge



Body neurotransmitter & local immune response

histamine

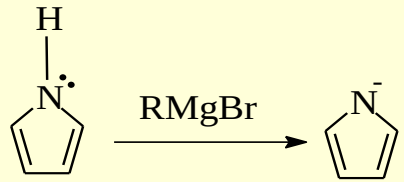
histidine carboxylase



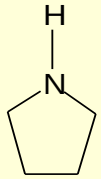
Carnosine

Dipeptide in high concentrations in the brain & muscles
- Improves social interactions & treatment of autism

Pyrrole is a stronger acid, than secondary amines, due to the aromatic stabilization of the conjugate base



$pK_a = 23$

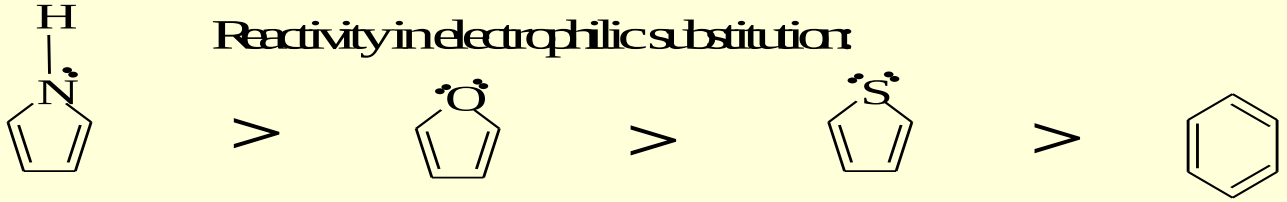


$pK_a = 44$

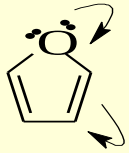
3. Chemistry of pyrrole, furan, and thiophene

All three heterocycles have an atom with at least one lone electron pair, involved to the aromatic conjugation. It is evidenced both by physical and chemical properties.

Reactivity in electrophilic substitution:



pyrrole > furan > thiophene >



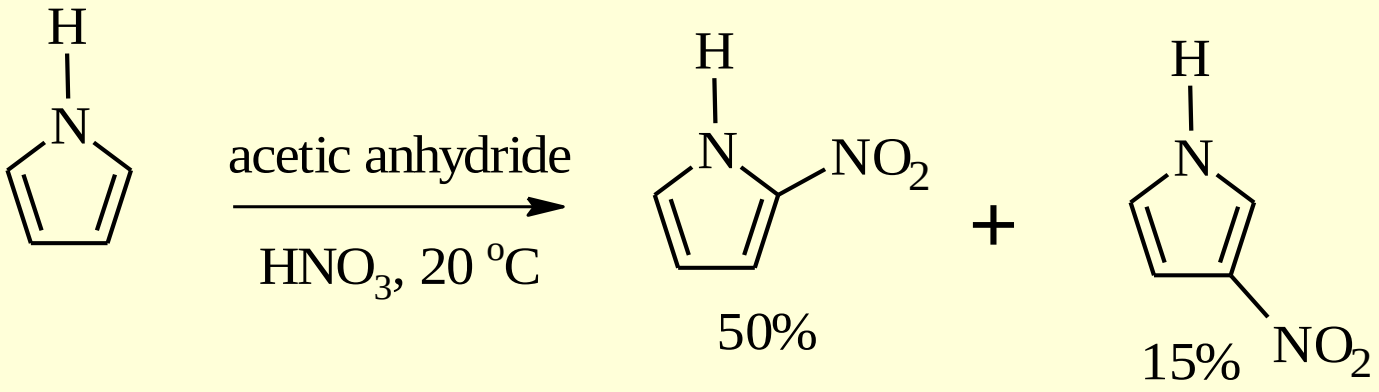
$\mu = 0.7D$

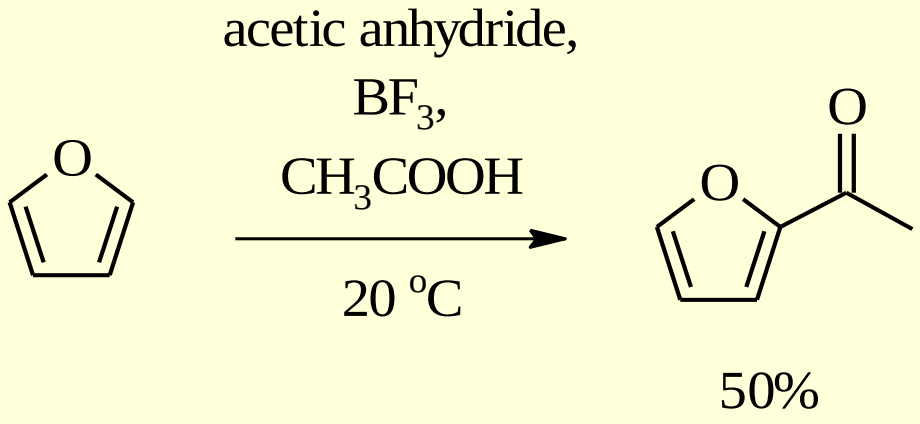
b.p. = 31.4°C

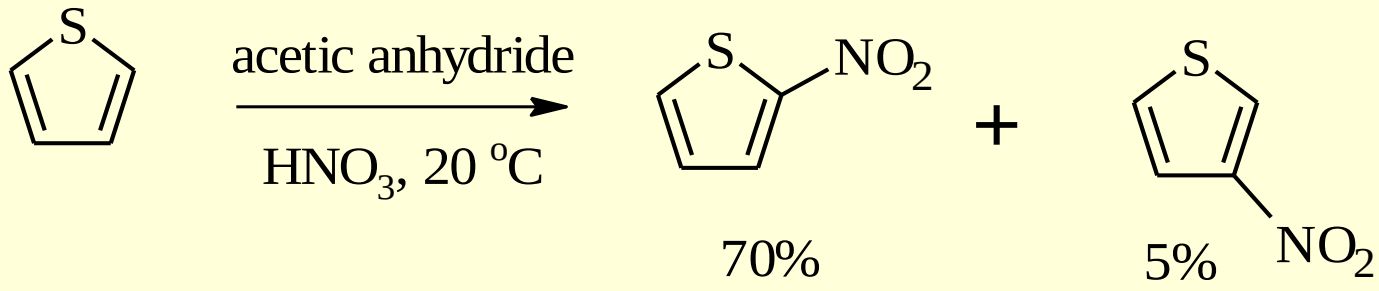
$\mu = 1.7D$

b.p. = 67°C

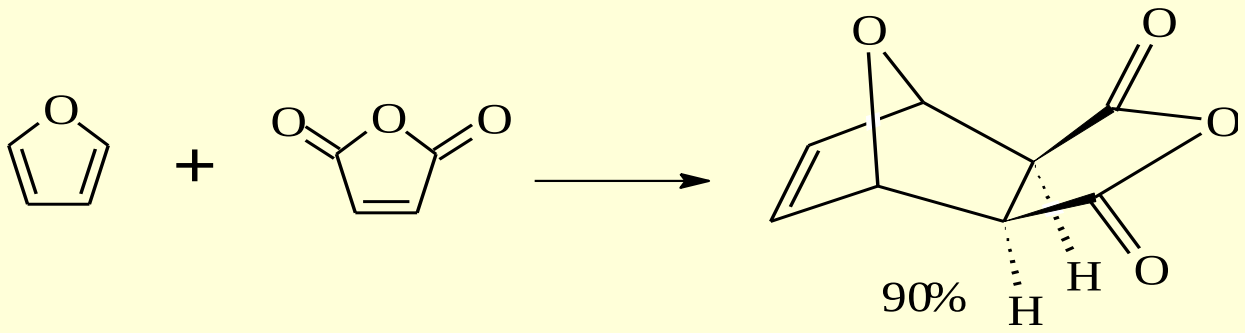
Examples:


H
N
acetic anhydride
HNO3, 20 °C
H
N
NO2
50%
+
H
N
NO2
15%

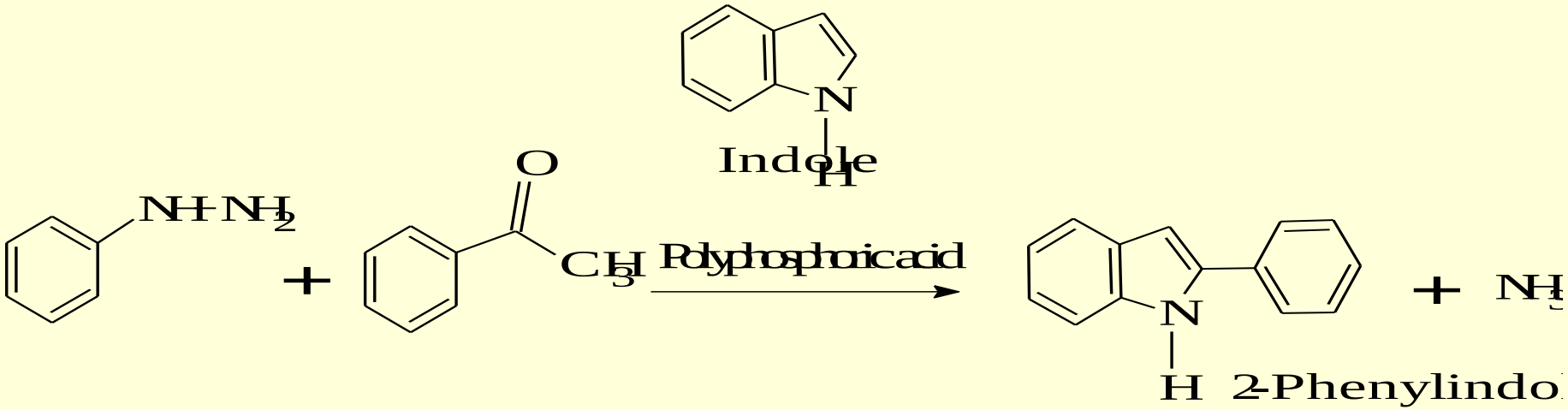

acetic anhydride,
BF3,
CH3COOH
20 °C
O
O
O
50%


S
acetic anhydride
HNO3, 20 °C
S
NO2
70%
+
S
NO2
5%

Furan is able to act as a diene in the reactions of cycloaddition

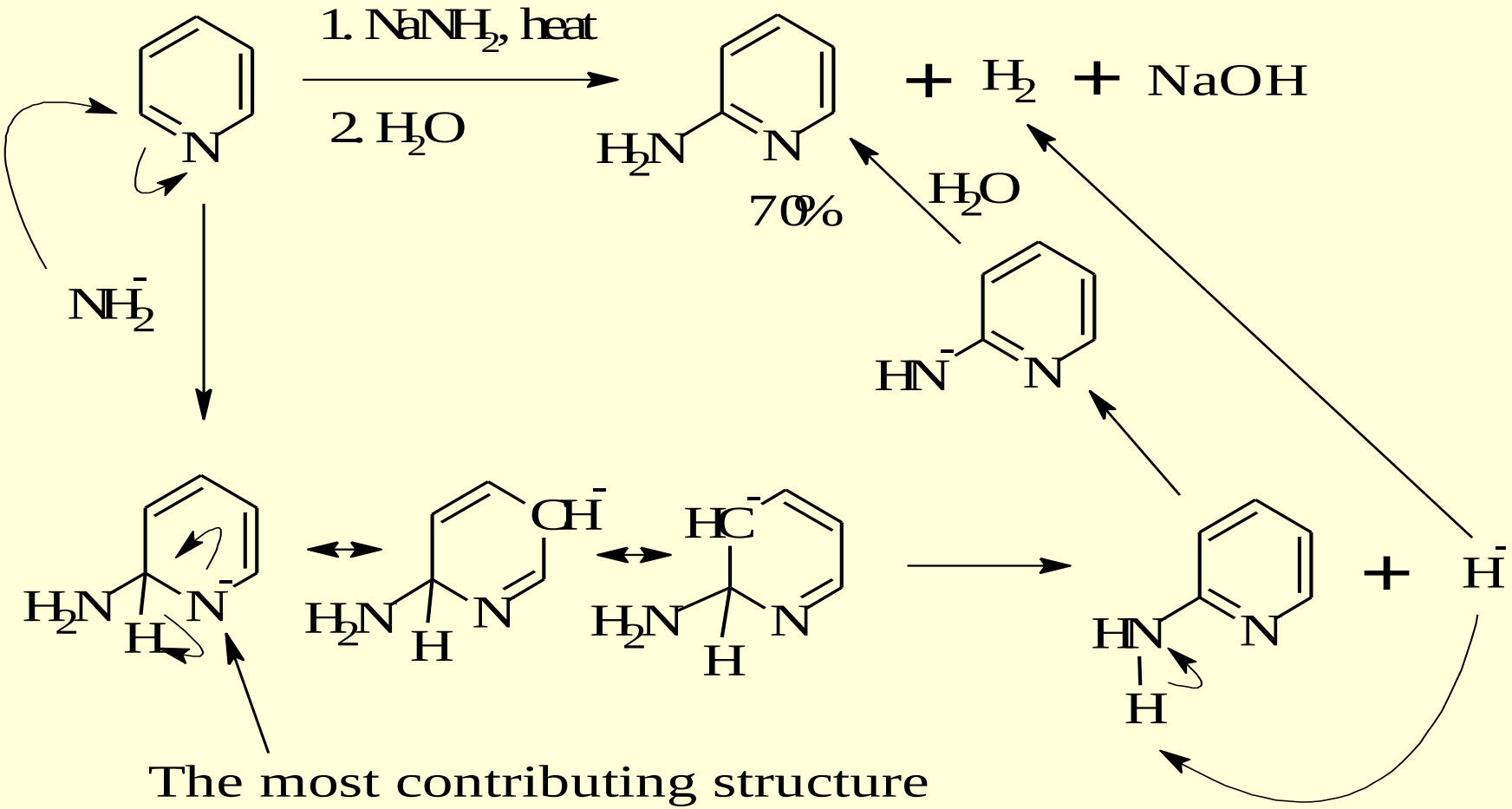


The Fisher synthesis of indoles

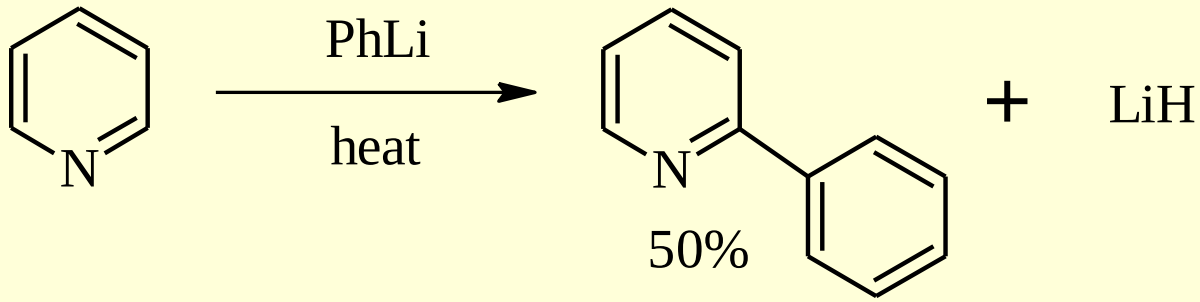


Nucleophilic substitution in pyridine

The presence of nitrogen enables pyridine to react with nucleophilic agents, like an electron withdrawing substituents enables benzene to participate in such reactions, including the ortho-directing effect.



Another example:



These reactions require very strong nucleophiles and heat, because H^- is a very weak leaving group. In ortho- or para-substituted pyridines nucleophilic substitution proceeds much easier.