Al-Mustaqbal College University
Department of Pharmacy

Organic Chemistry

Second stage

LEC:1

Dr. Sabrean Farhan Jawad

Heterocycles

Ring compounds with elements other than carbon in the ring. The most common elements to appear in heterocyclic compounds are oxygen, nitrogen and sulfur.

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

The aromatic heterocycles are similar to other aromatic compounds.

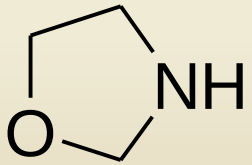
Heterocyclic Nomenclature

Replacement nomenclature (IUPAC recommended 1957)

Oxygen	oxa
Sulfur	thia
Nitrogen	aza

Lowest number assigned to the hetero atom with the highest precedence: O > S > N

thiacyclobutane



1-oxa-3-azacyclopentane

Hantzsch-Widman (1888)

Suffixes

	ring with nitrogen		ring without nitrogen	
Ring members	unsat'd	sat'd	unsat'd	sat'd
3	-irine	-iridine	irene	irine
4	ete	etidine	ete	etane
5	ole	olidine	ole	olane
6	ine	perhydro__ine	in	ane
7	epine	perhydro__epine	epin	epane

You must know the * names

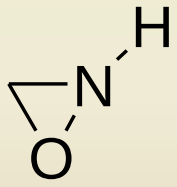
* oxirane
ethylene oxide
oxacyclopropane

* thiirane
ethylene sulfide
thiacyclopropane

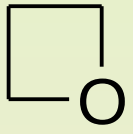
* aziridine
ethylene imine
azacyclopropane

diazirane

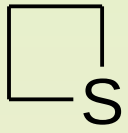
1-azirine



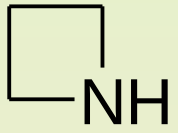
oxaziridine
oxazacyclopropane



oxetane
oxacyclobutane



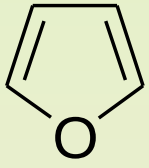
thietane
thiacyclobutane



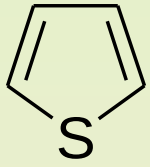
azetidine
azacyclobutane

azete
azacyclobutadiene

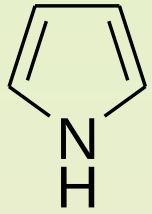
1-azetine
1-azacyclobutene



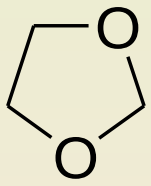
* furan
oxole
oxacyclopentandiene



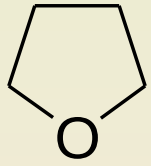
* thiophene
thiole
thiacyclopentandiene



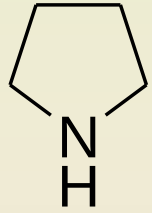
* pyrrole



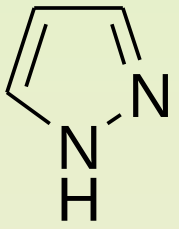
1,3-dioxolane
1,3-dioxacyclopentane



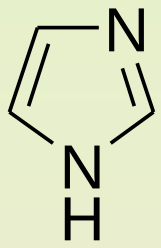
* tetrahydrofuran



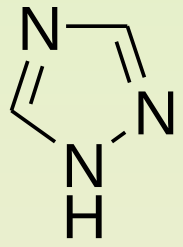
* pyrrolidine
azacyclopentane



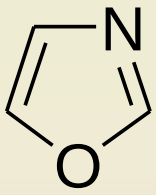
pyrazole



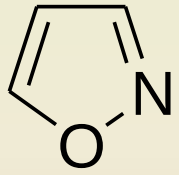
imidazole



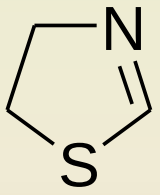
1,2,4-triazole



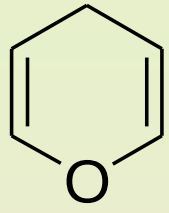
oxazole



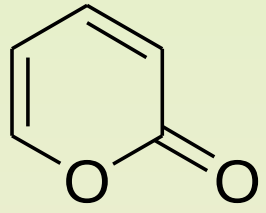
isooxazole



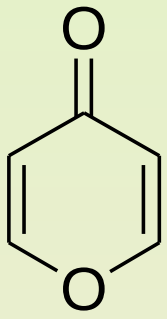
thiazole



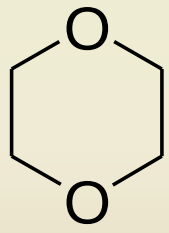
4-hydropyran



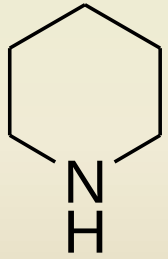
2-pyrone



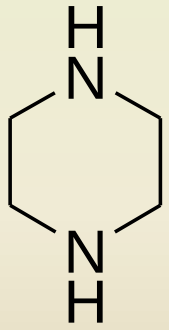
4-pyrone



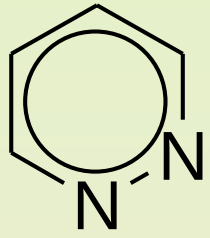
* 1,4-dioxane



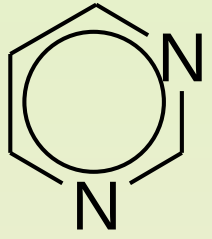
* piperidine



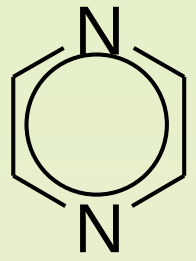
piperazine



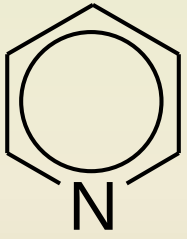
pyridazine



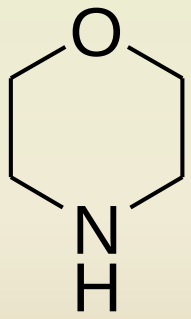
pyrimidine



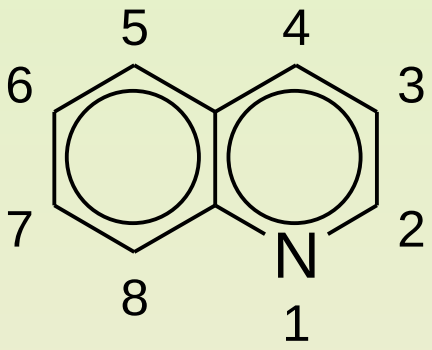
pyrazine



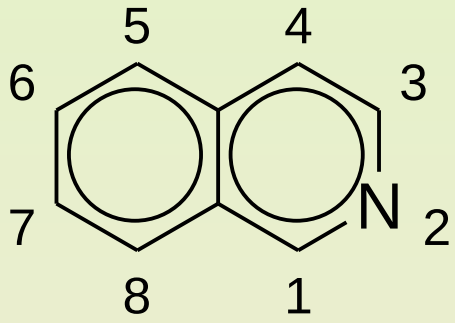
* pyridine



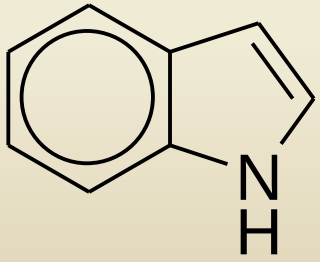
* morpholine



* quinoline



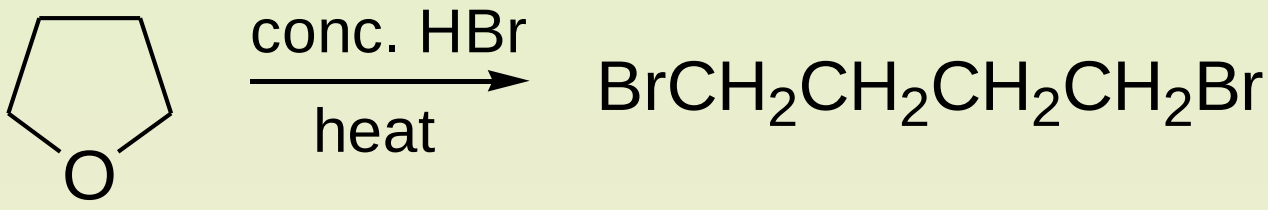
* isoquinoline



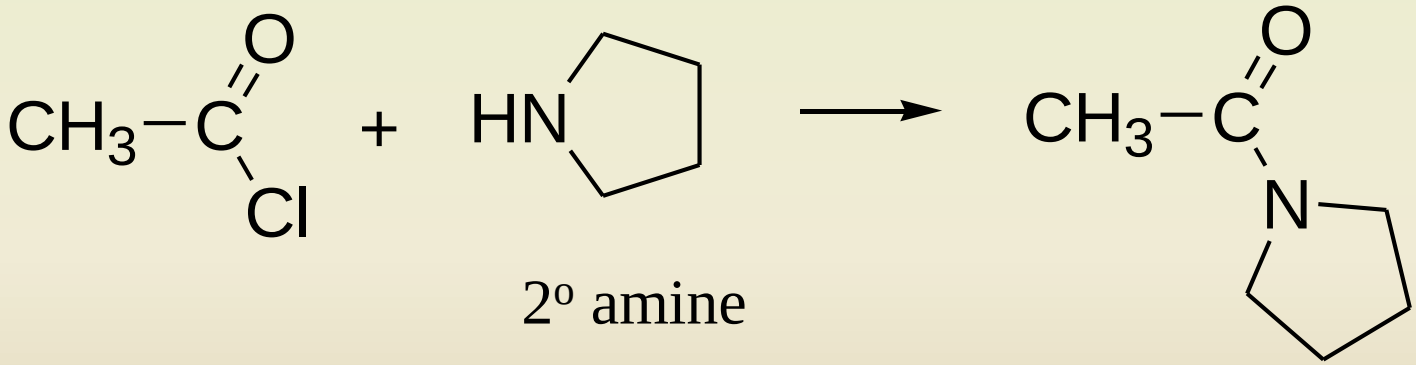
* indole

Aliphatic heterocyclics, chemistry

Ethers



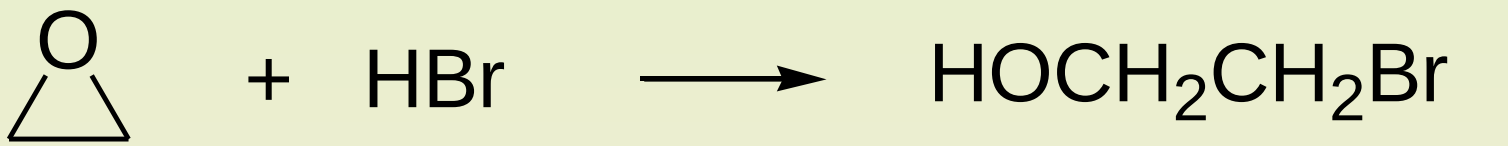
Amines

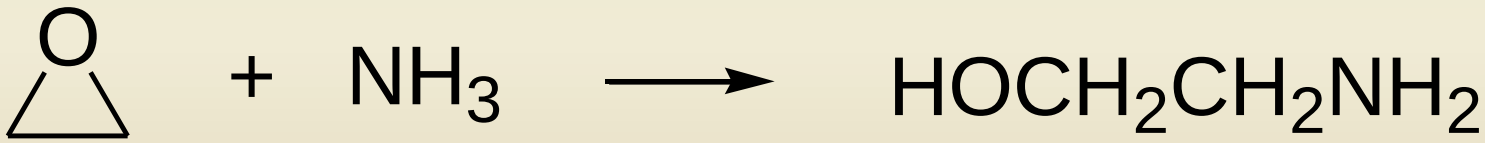


2° amine

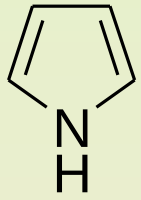
sulfides

Three-membered rings undergo additions due to angle strain, eg. epoxides

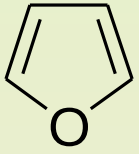




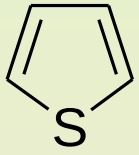
Aromatic heterocycles



pyrrole

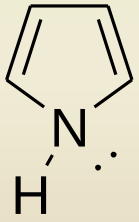


furan



thiophene

Aromatic! EAS very, very reactive
resonance stabilization energy ~ 22-28 Kcal/mole

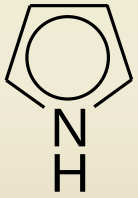


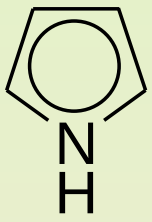
sp^2 6 pi electrons

no unshared pair on Nitrogen

very weak base

$K_b = 10^{-14}$



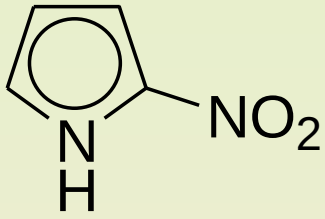


pyrrole

strong acids → polymer!

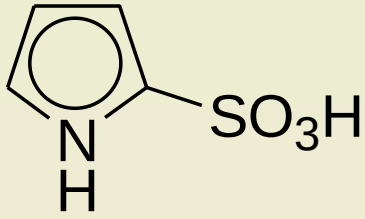
$CH_3CO_2^-NO_2^+$

$(CH_3CO)_2O$, 5°C →

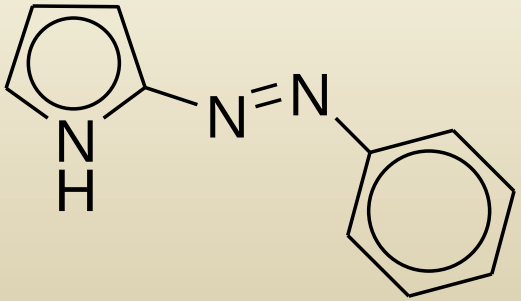


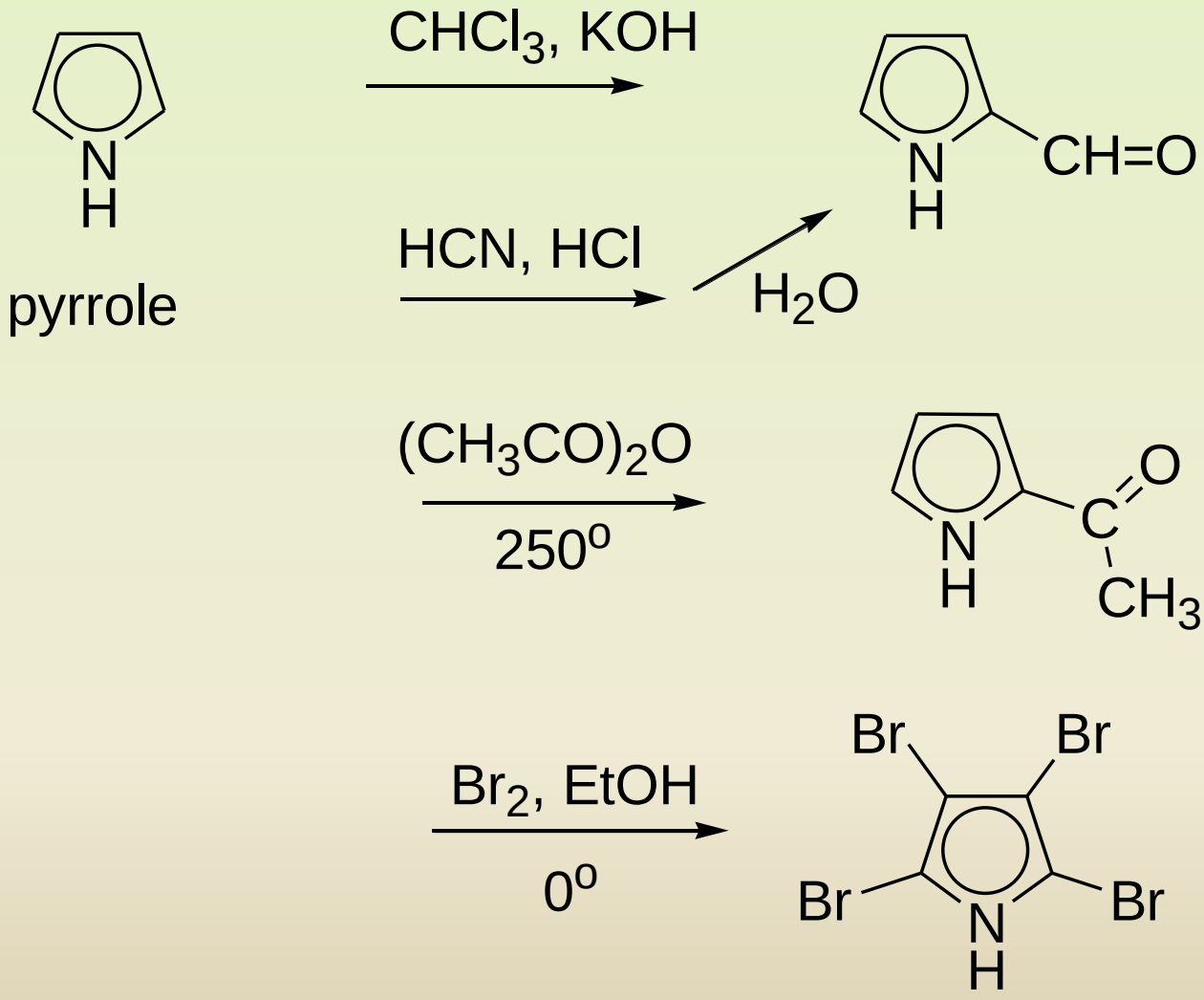
SO_3

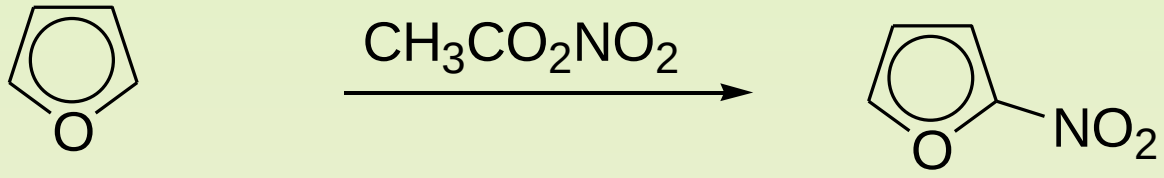
pyridine, 90° →



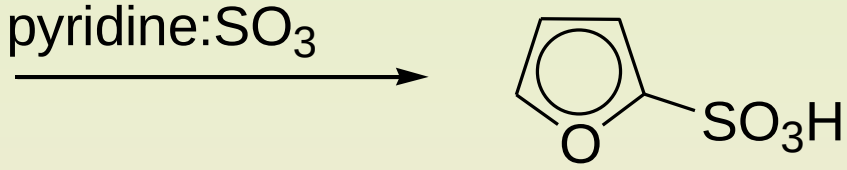
$C_6H_5^-N_2^+Cl^-$ →

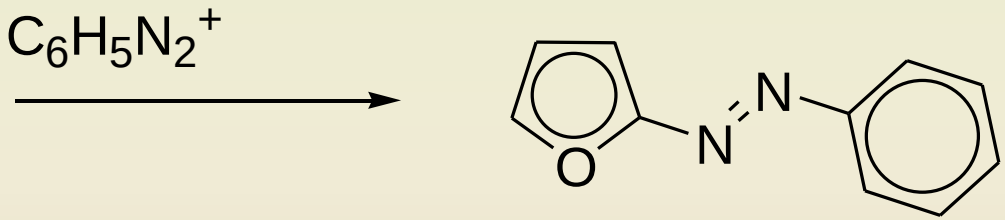


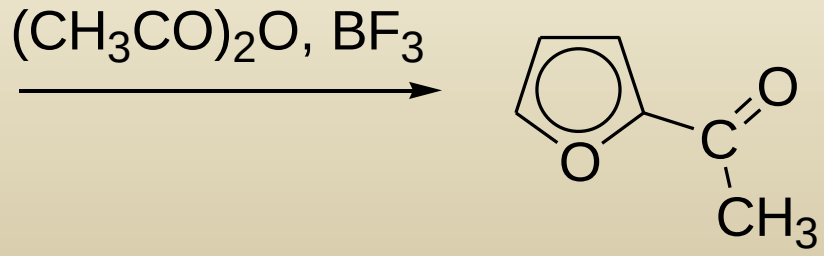

CHCl3, KOH
N
H
pyrrole
CH=O
HCN, HCl
H2O
(CH3CO)2O
250o
O
C
CH3
Br2, EtOH
0o
Br

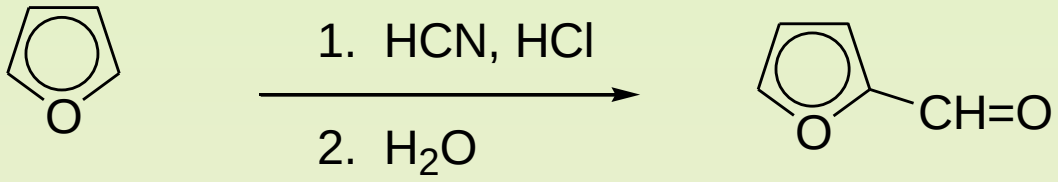

$CH_3CO_2NO_2$
O
O
NO_2

furan

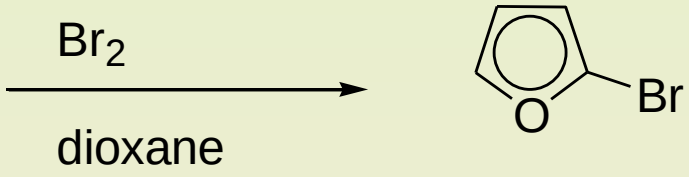

pyridine:SO_3
O
SO_3H

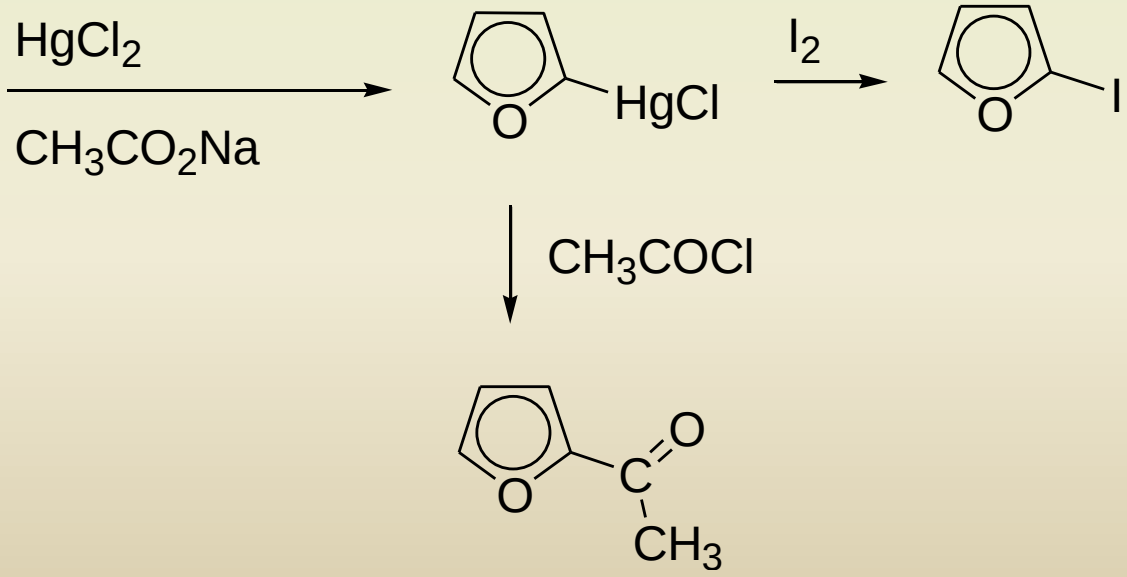

$C_6H_5N_2^+$
O
N
N


$(CH_3CO)_2O$, BF_3
O
O
C
CH_3

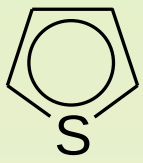

1. HCN, HCl
2. H2O
O
CH=O

furan

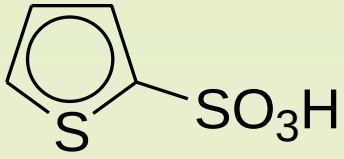

Br2
dioxane
O
Br


HgCl2
CH3CO2Na
O
HgCl
I2
O
I
CH3COCl
O
O
C
CH3

less reactive, can use acids

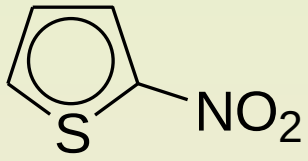


H_2SO_4

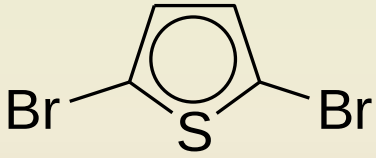


$CH_3CO_2NO_2$

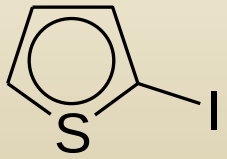
$(CH_3CO)_2O$



Br_2, benzene

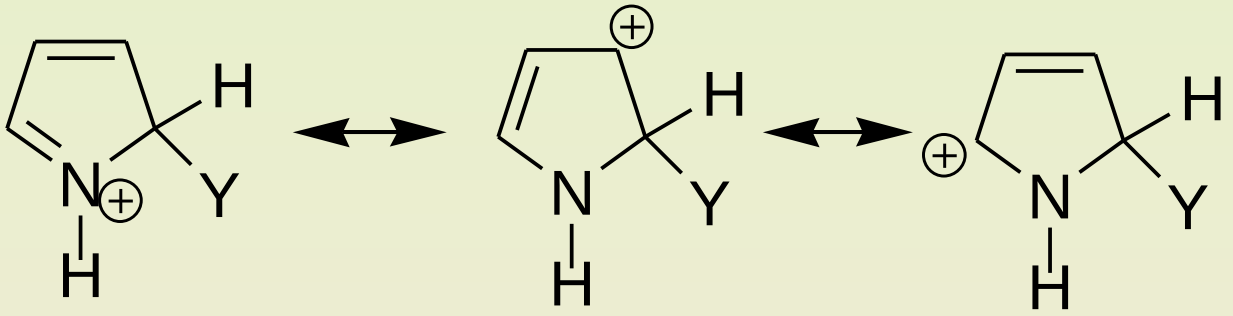


I_2, HgO

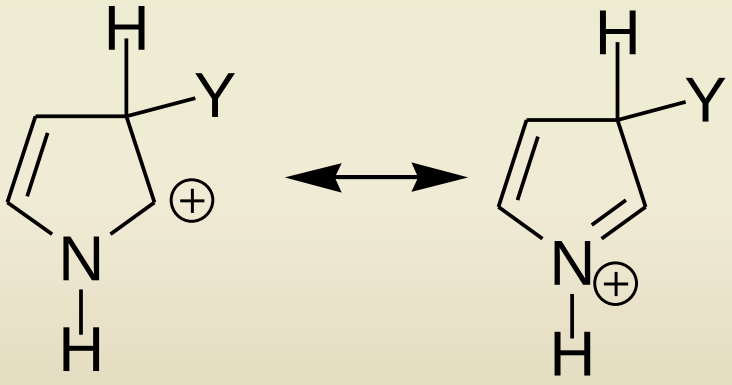


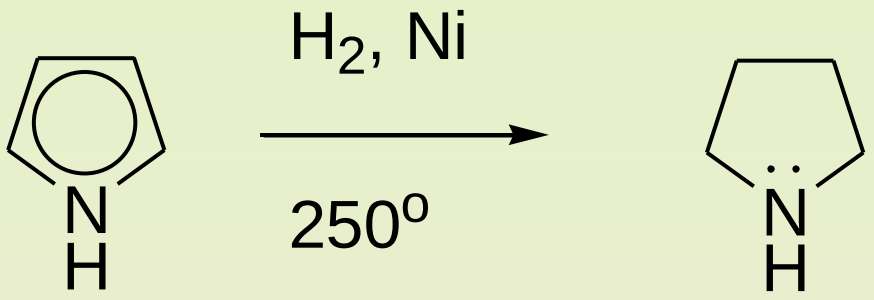
Why EAS → 2-position?

2-



3-

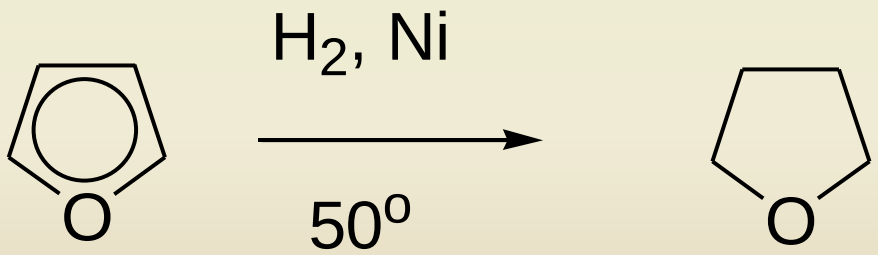




Kb = 10^{-14}

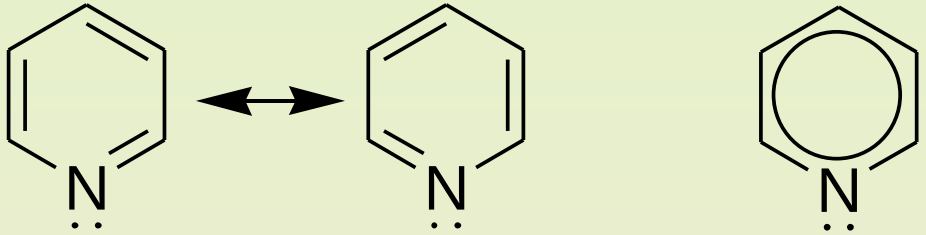
Kb = 10^{-3}

2^{o} amine



THF

Pyridine

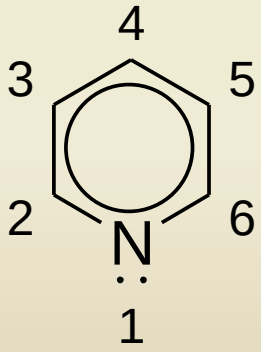


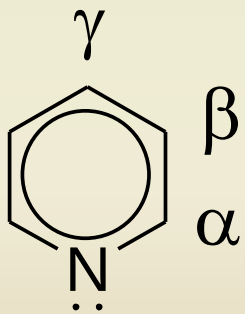
6 pi electrons,

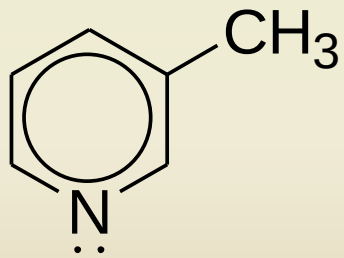
sp^2, flat

aromatic, resonance stabilization energy ~ 23 Kcal/mole

$Kb = 2.3 \times 10^{-9}$





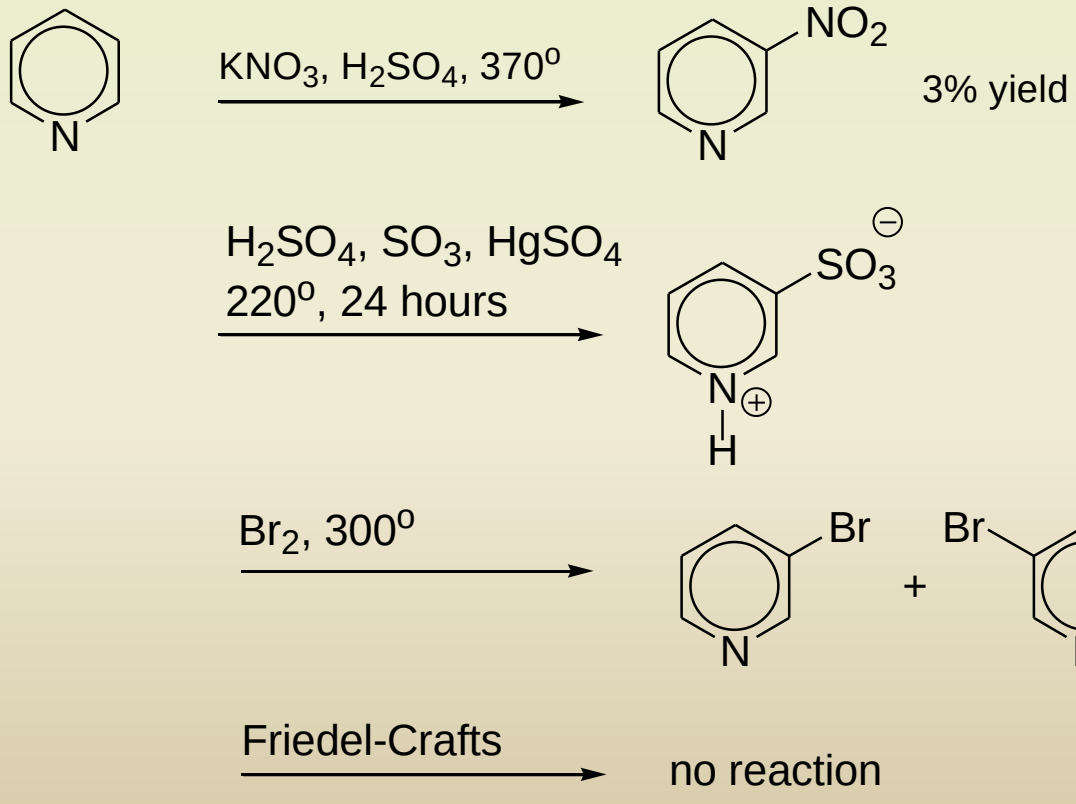


β-picoline

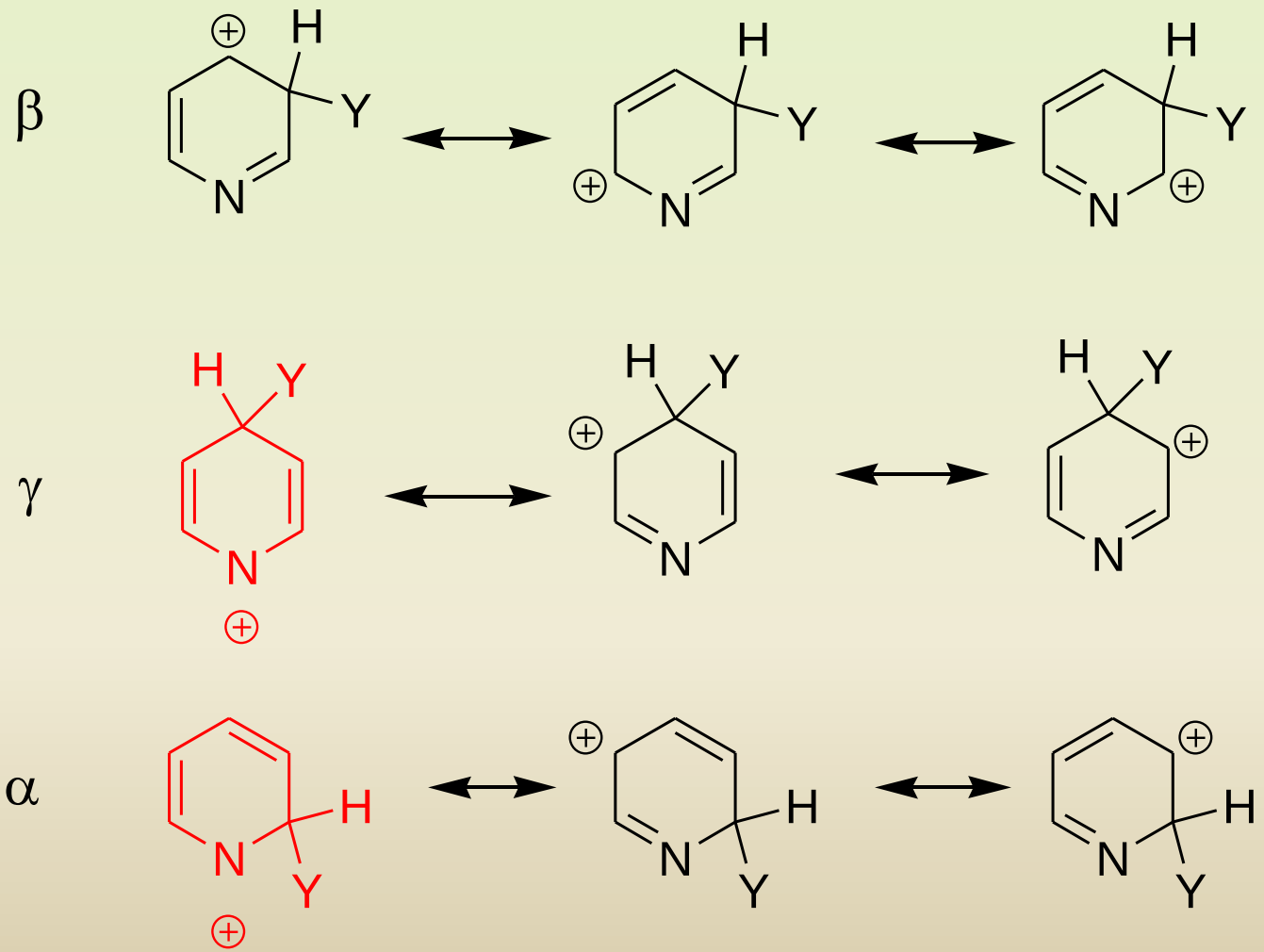
Pyridine important solvent & base (~ 3° amine)

Reactions:

1) EAS (much less reactive than benzene ~ nitro)

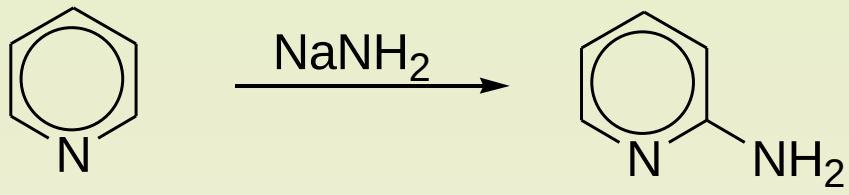


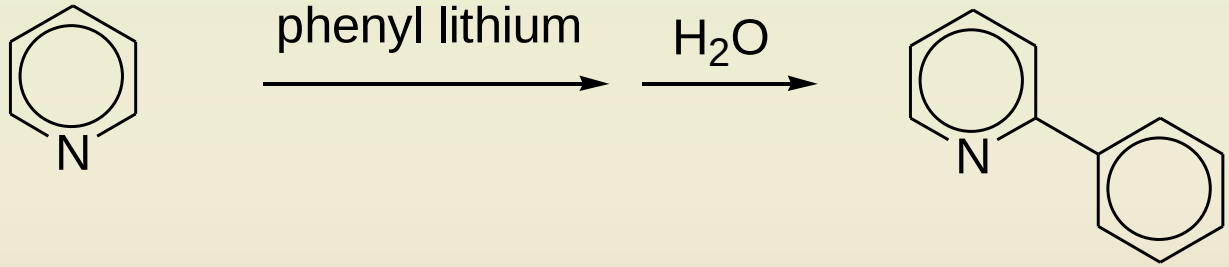
Deactivated to EAS due to electronegativity of Nitrogen
Directs beta due to destabilization of alpha and gamma

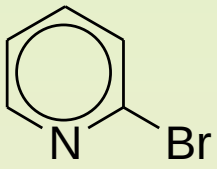


Pyridine, reactions

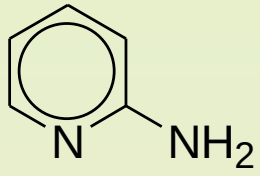
2) Nucleophilic aromatic substitution

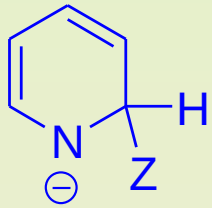


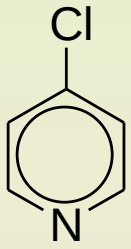




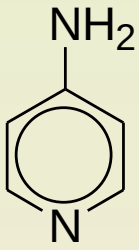
NH_3, 200^o

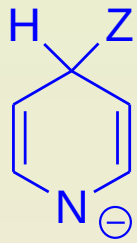


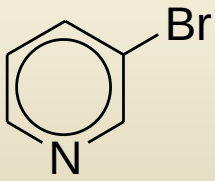




NH_3, 200^o







NH_3, 200^o

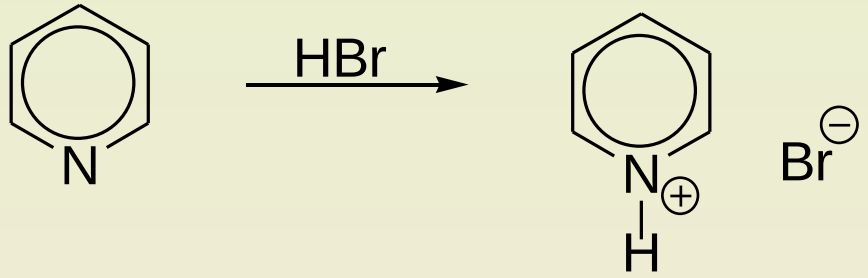
NR

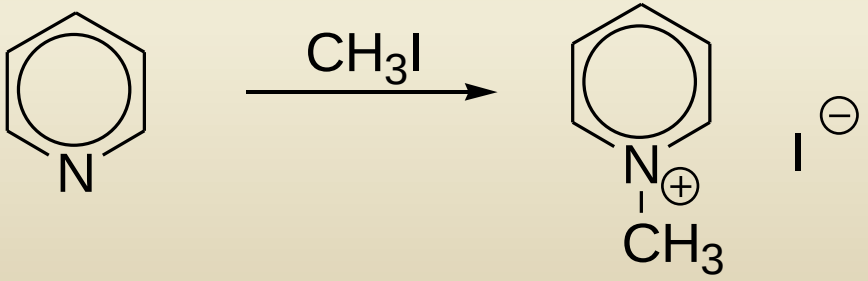
activated to nucl. arom. subts.
directs alpha & gamma

Pyridine, reactions

3) As base

$Kb = 2.3 \times 10^{-9}$

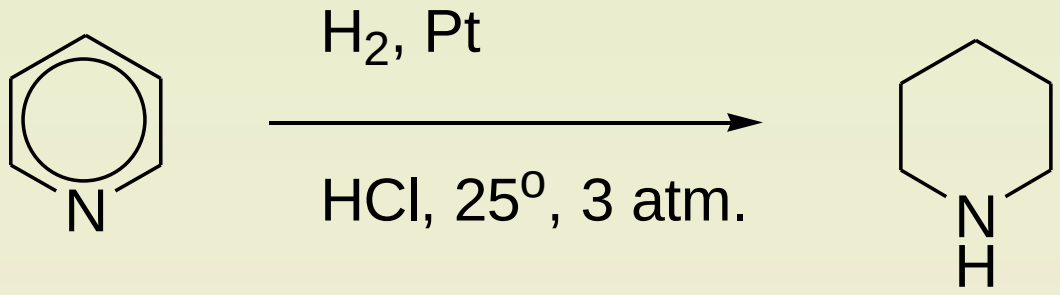




4^o salt

Pyridine, reactions

4) reduction

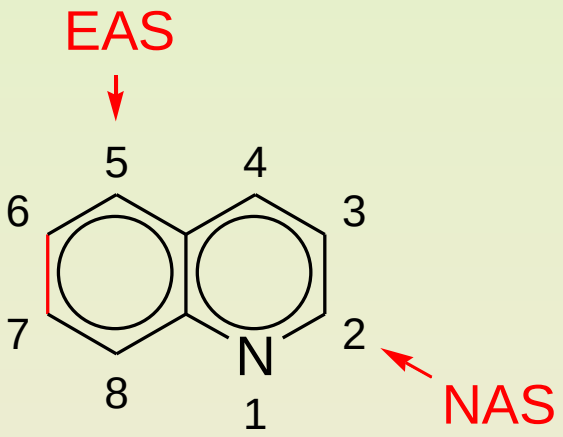


piperidine

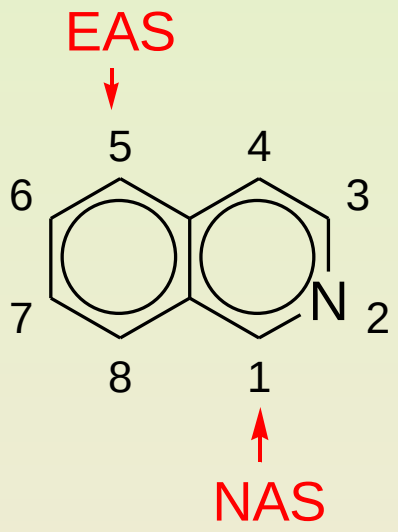
Kb = 2 X 10^{-3}

aliphatic 2^{o} amine

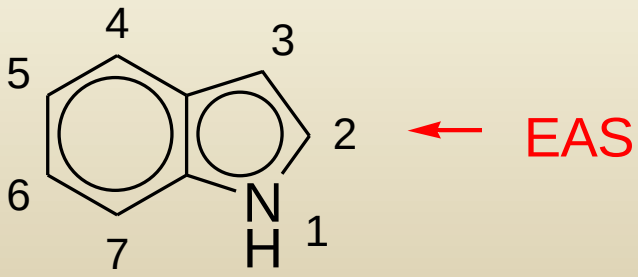
Polynuclear Heteroaromatics



quinoline

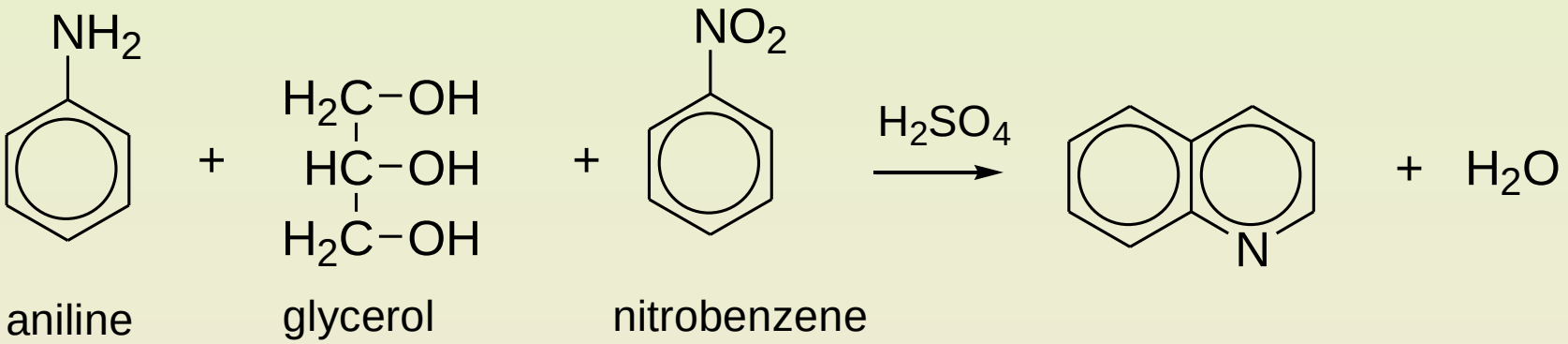


isoquinoline



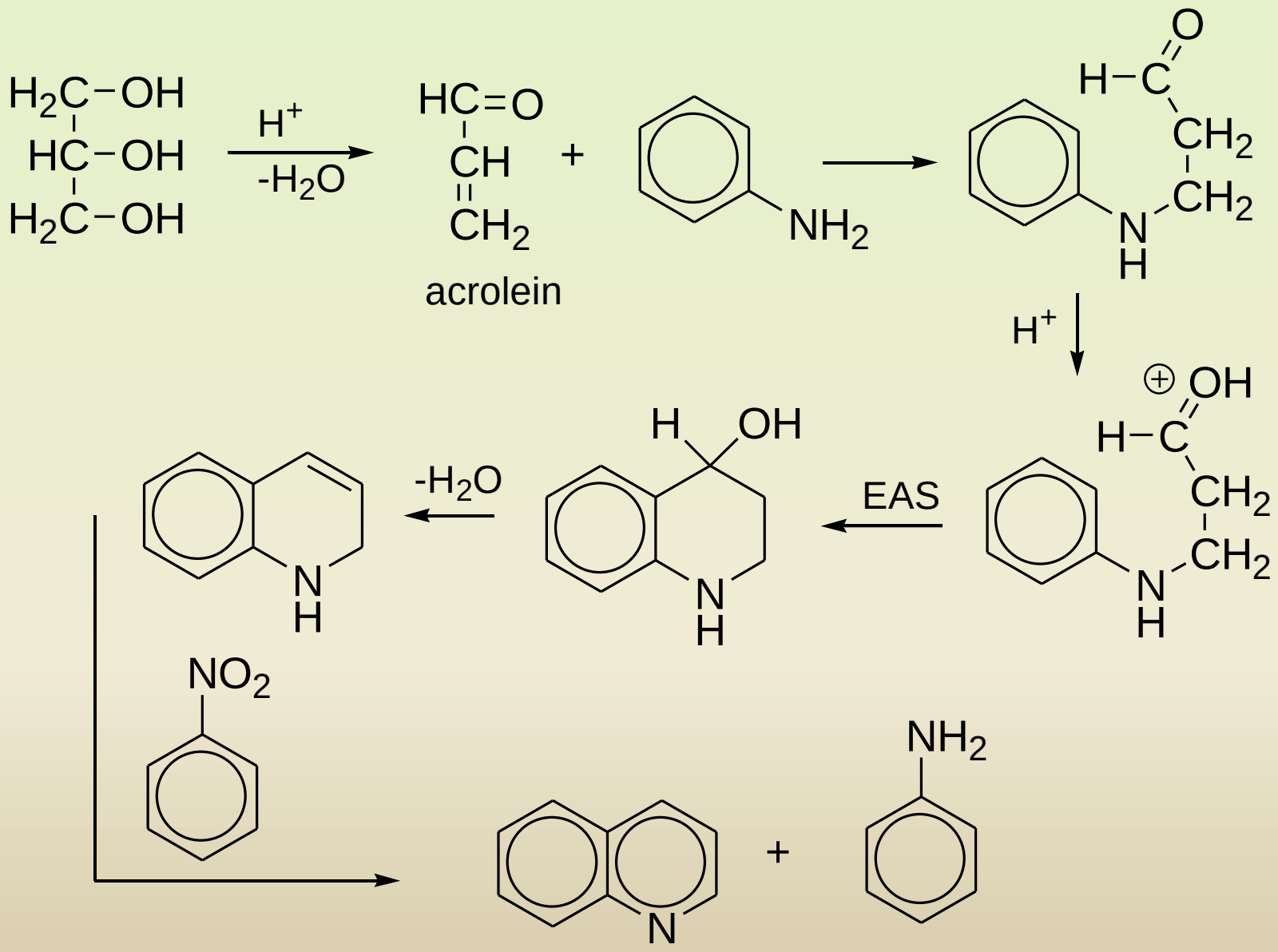
indole

Skraup synthesis of quinoline



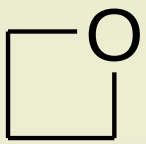
aniline glycerol nitrobenzene

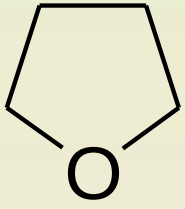
The nitrobenzene is not only the solvent, but is also one of the reactants.

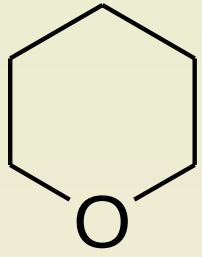

H2C−OH
HC−OH
H2C−OH
H+
-H2O
HC=O
CH
CH2
acrolein
+
NH2
O
H−C
CH2
CH2
N
H
H+
⊕OH
H−C
CH2
CH2
N
H
EAS
H
OH
N
H
-H2O
N
H
NO2
NH2
+
N

Heterocycles as you would expect!

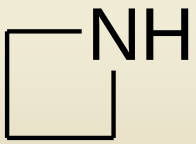
angle strain

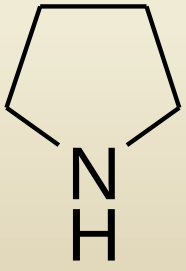


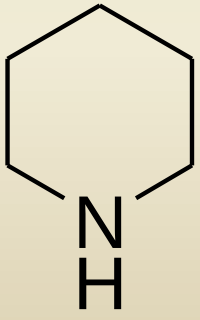




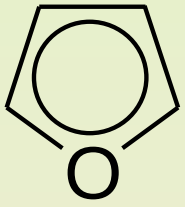
ethers

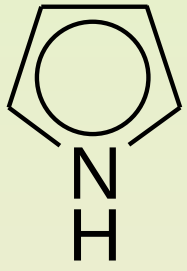


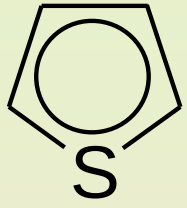




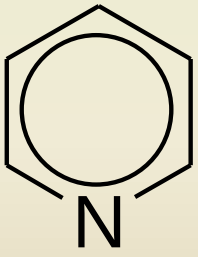
amines



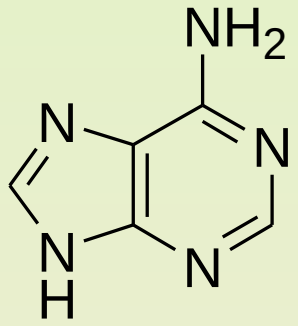




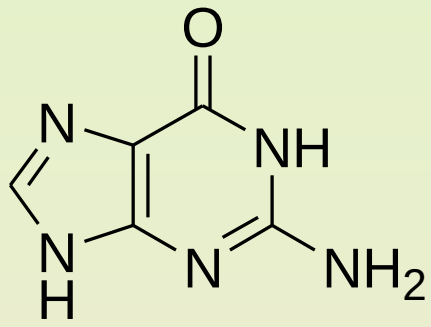
EAS



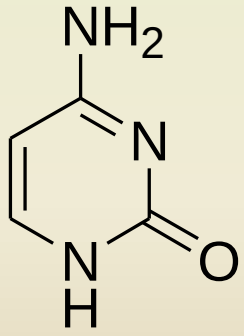
nucleophilic aromatic substitution



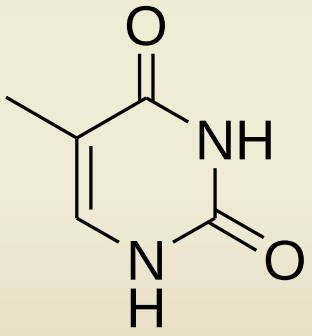
adenine



guanine



cytosine



thymine