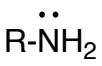
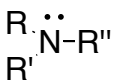
Amines (McM chapt 24)

(**R: alkyl, aryl**)

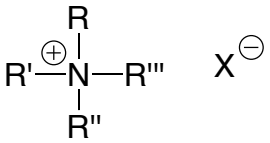


Primary amine

Secondary amine

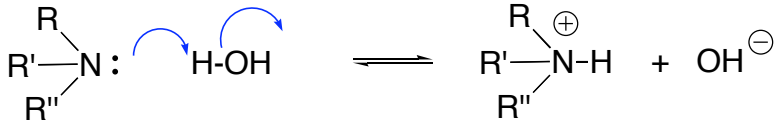


Tertiary amine



Quartenary ammonium salts

Basic compounds



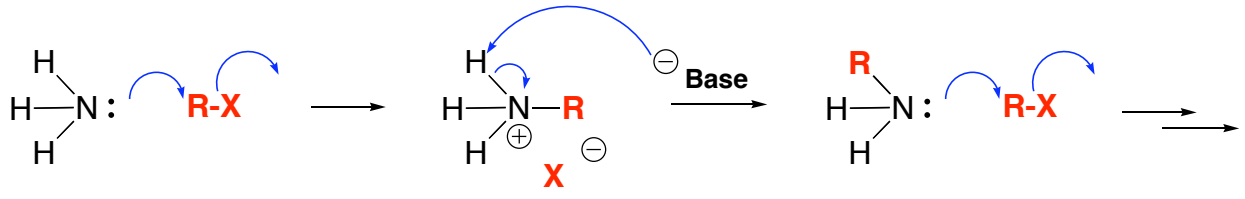
(**R: H, alkyl, aryl**)

pKa Alkylamines: ca 9-11
Arylamines: ca 4-5
(anilines)

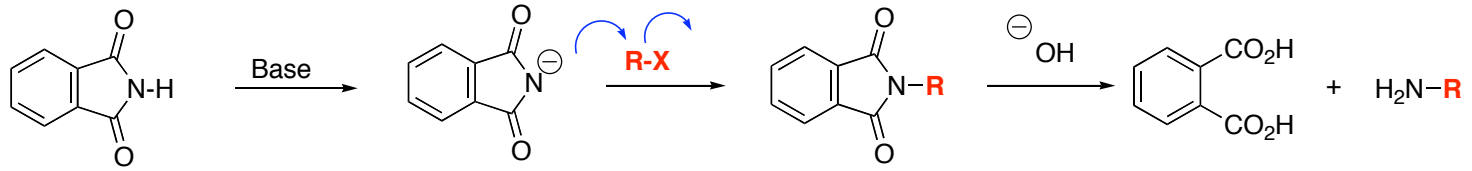
Synthesis

Known react. from KJM10xx

Alkylation (ammonia or amine, phtalimide)

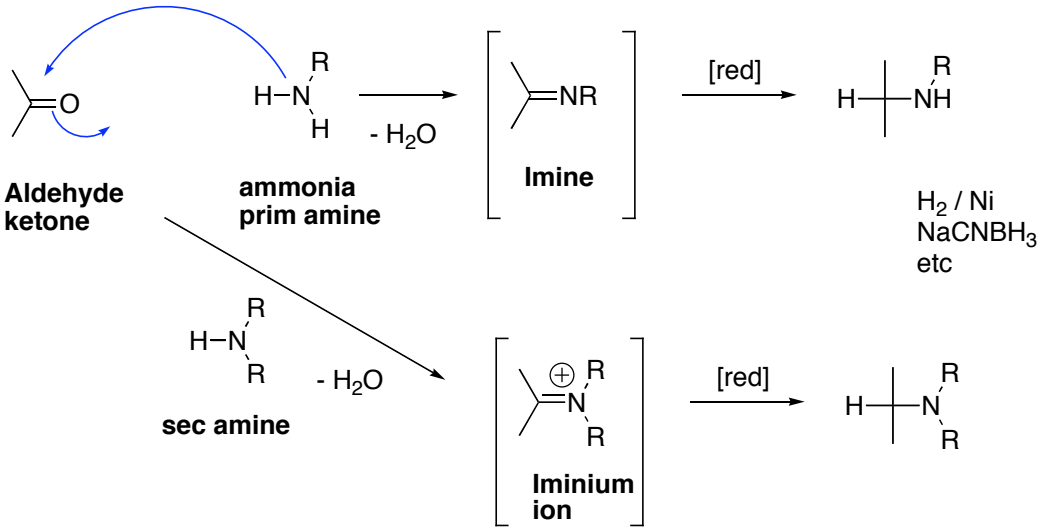


(R: H, alkyl, aryl)



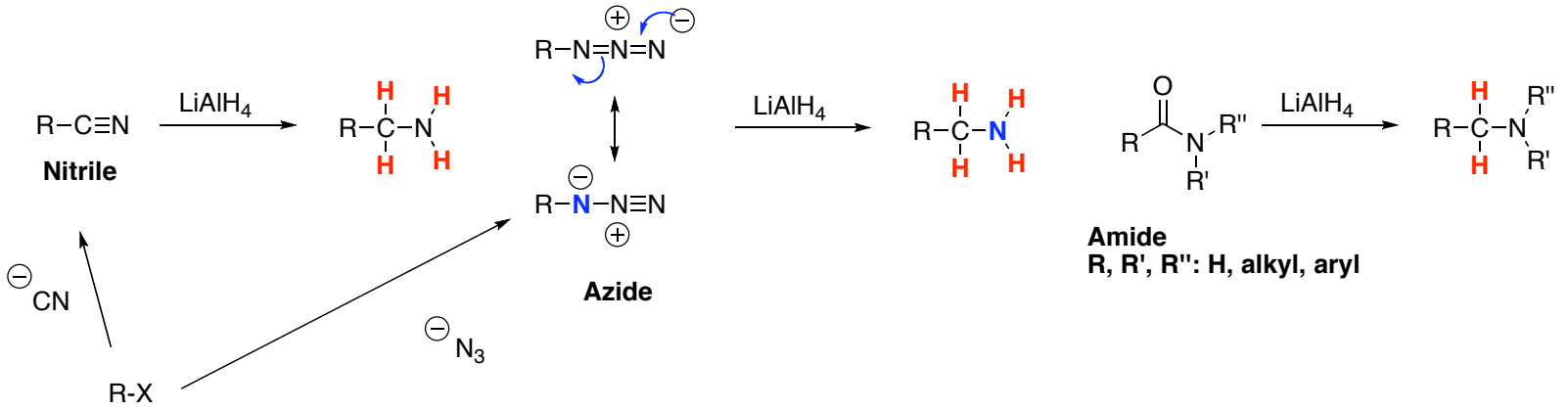
Acidity
c.f. 1,3-dicarbonyls

Reductive amination



Reductions

- **Nitriles**
- **Azides**
- **Amides**



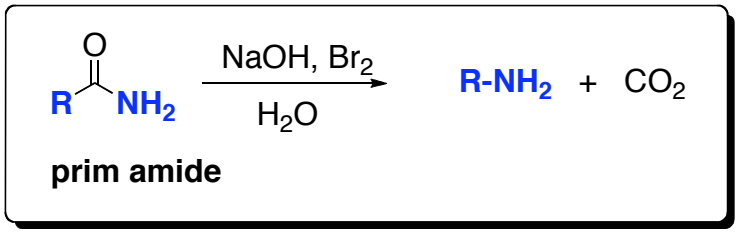
- **Aromatic nitro compounds**

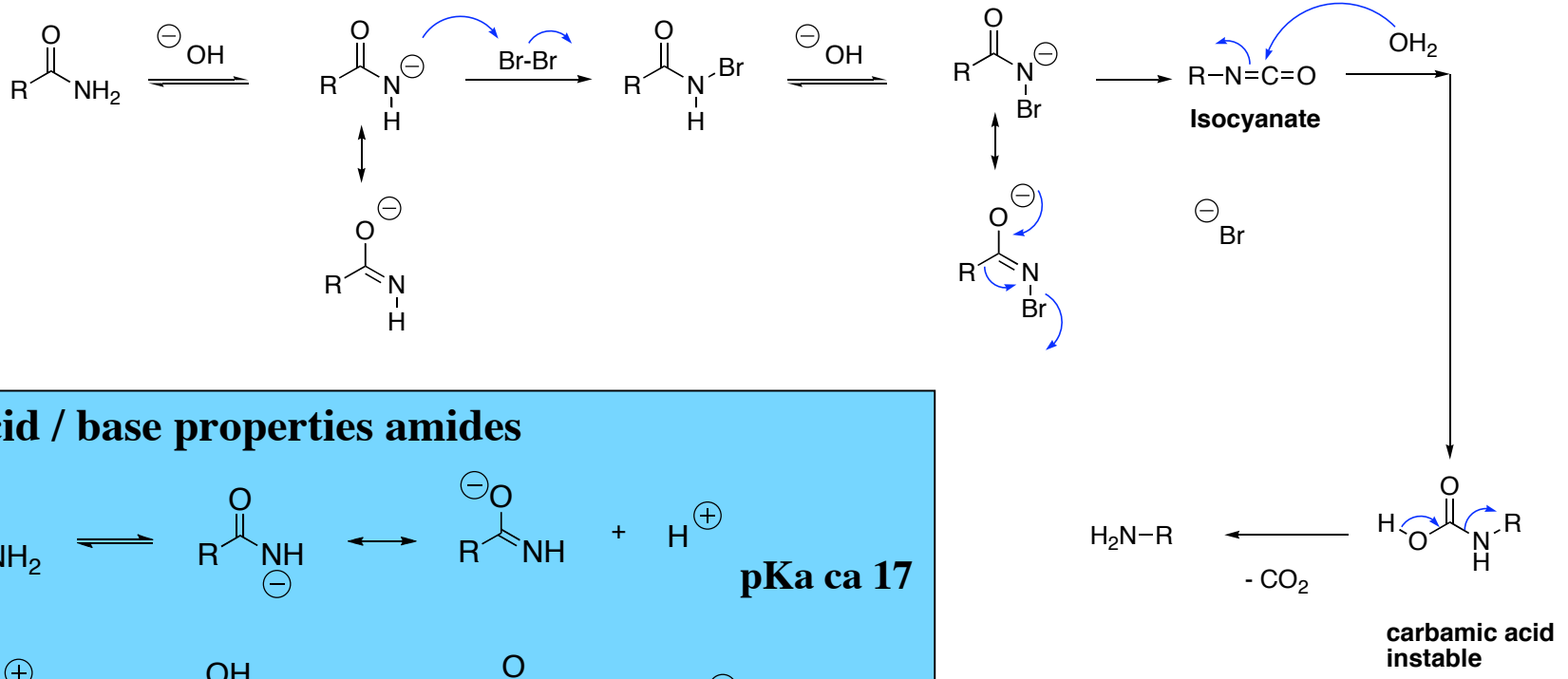
$$Ar\text{-}NO_2 \xrightarrow{[red]} Ar\text{-}NH_2$$

Red: H_2 / cat
$SnCl_2$, H^+

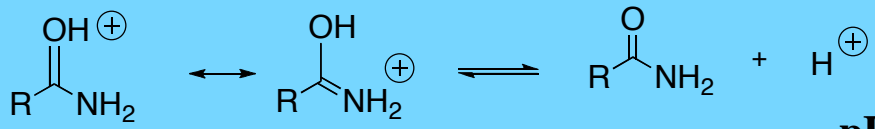
Synthesis: "New" reactions

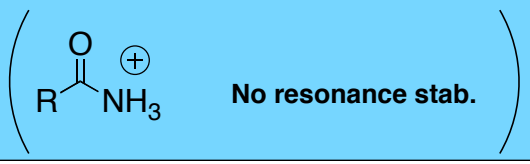
Hofmann rearrangement



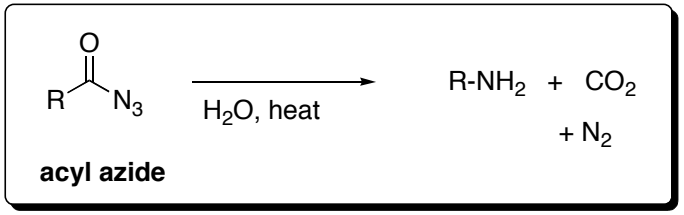


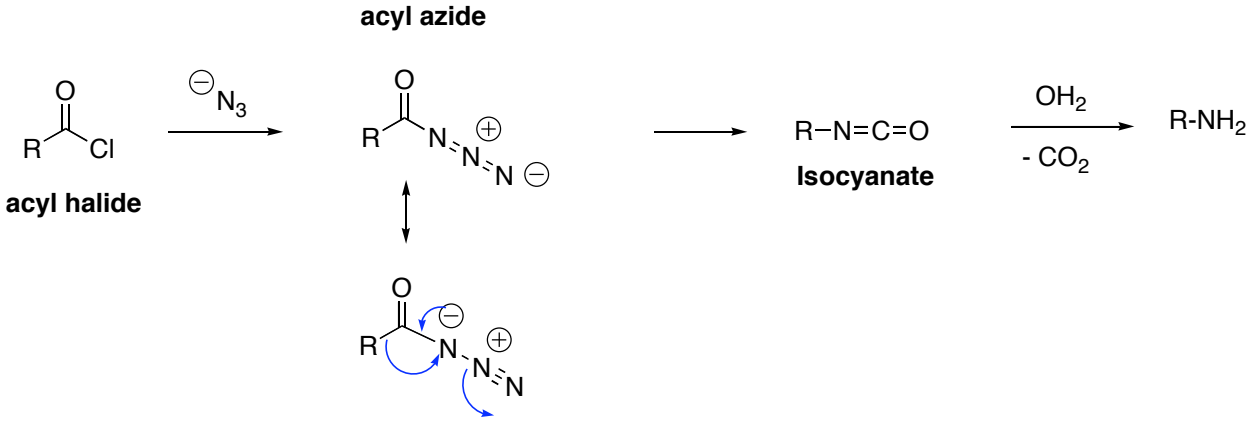
Acid / base properties amides



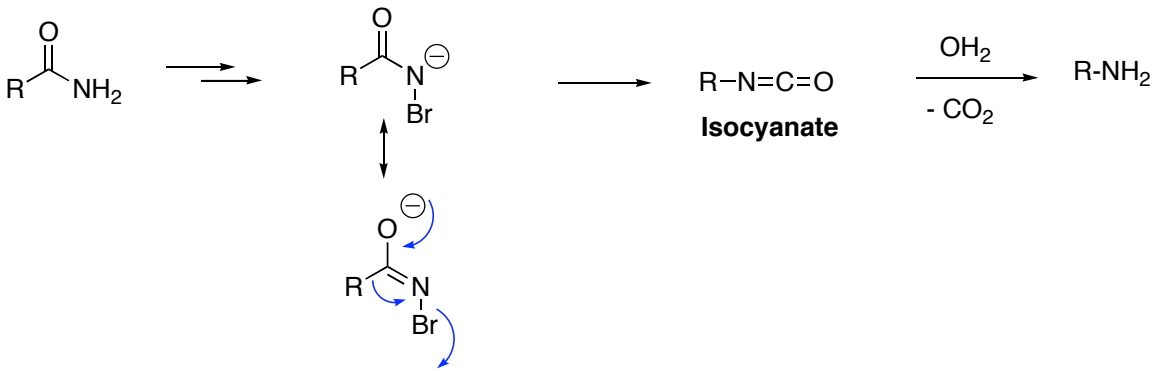


Curtius rearrangement





Mechanistic. related to Hofmann rearrang.



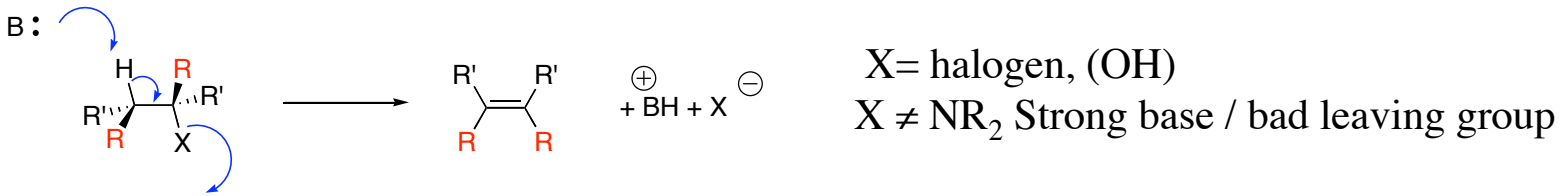
Reactions of amines (Alkylamines)

Alkylamines:

- **Alkylation**
- **Acylation / synth of amide**
- **Hofmann elimination (≠ Hofmann rearrangement)**

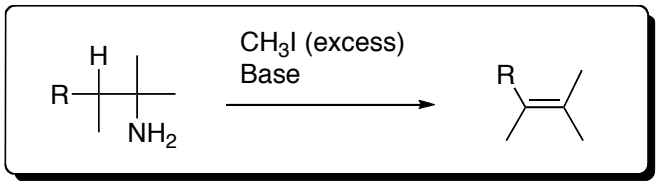
E2 elimination to form alkene

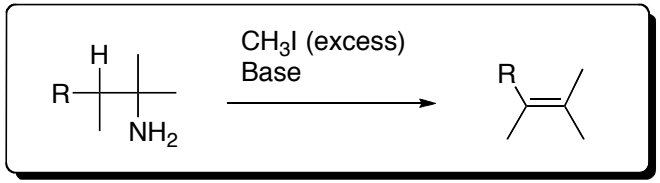
E2: mechanism



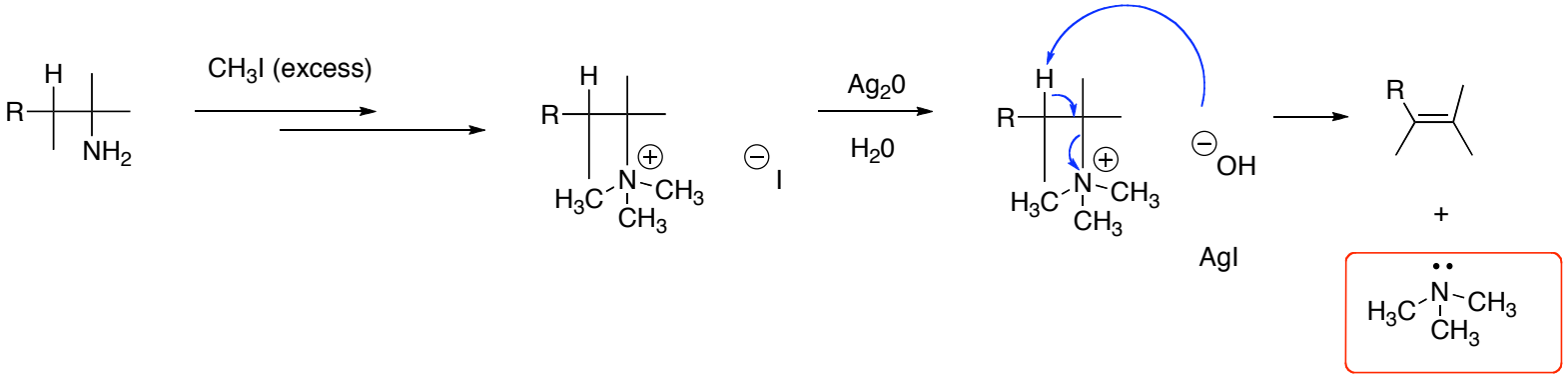
X= halogen, (OH)

X ≠ NR_2 Strong base / bad leaving group



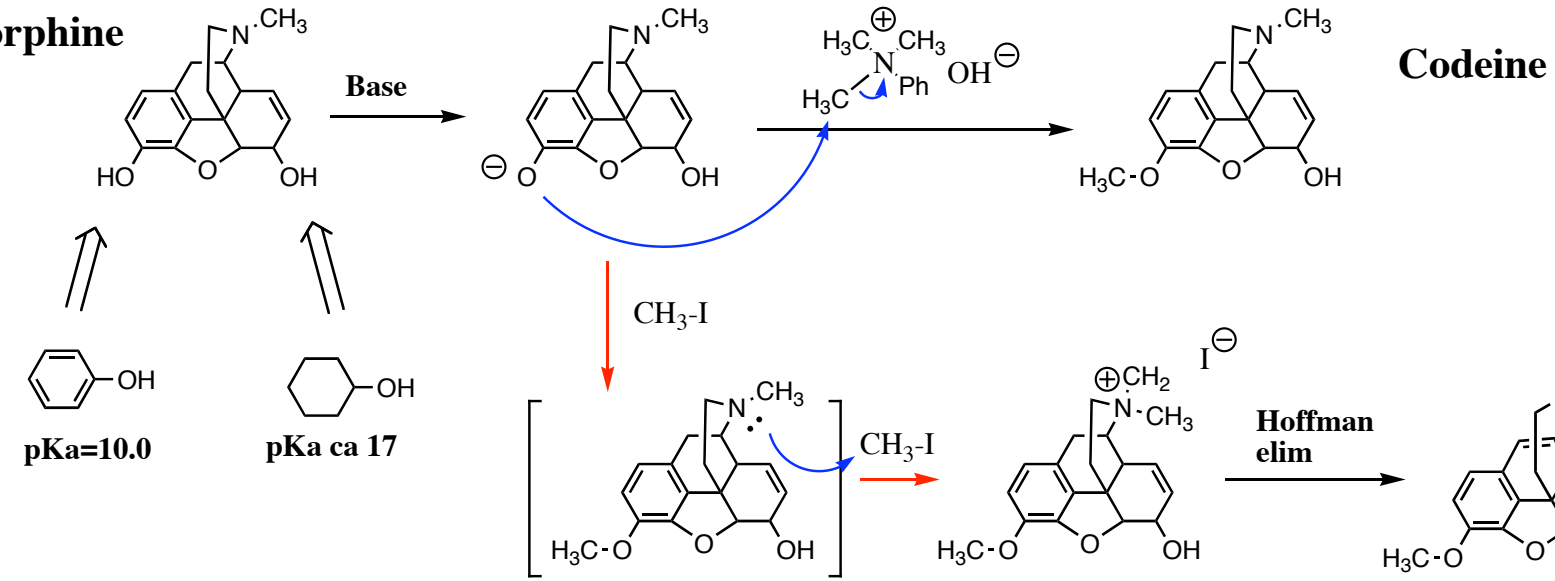


Removal of less sterically hindered H
Not necessarily most stable alkene formed

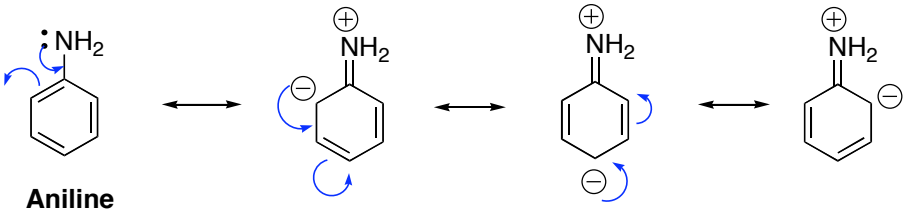


Much better leaving group than $R_2N^{\ominus}$

Morphine

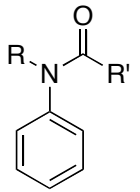


Reactions of Arylamines (aniline derivatives)

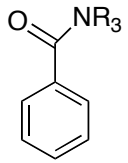


Aniline

- **Weak base (pKa ca 4.6)**
- **Highly Activated for E-fil Ar Subst (o/p)**
- **Protect. as amide: Less activated, still o/p**



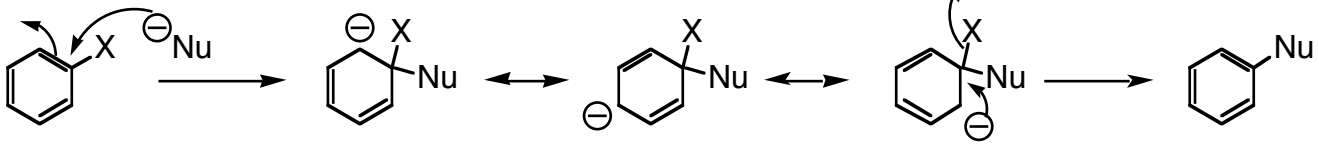
o/p directing



m-directing

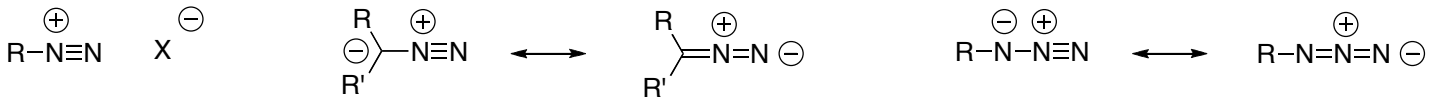
Nucleophilic Aromatic Substitution - Mechanisms

- S_NAr √

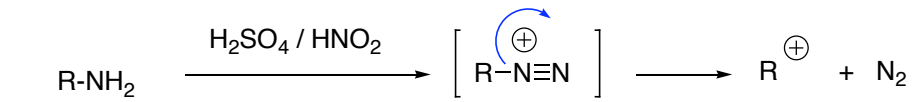


- **S_N1**
- Benzyne √
- **SRN1: Involves radicals**
- (VNS: Vicarious Nucl. Subst.)

Formation of Diazonium Salts and the Sandmeyer Reaction

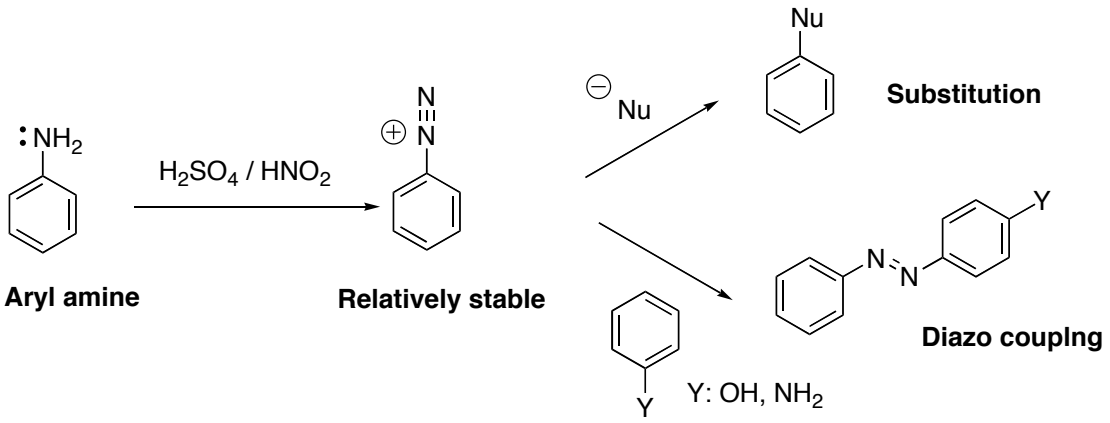


Diazonium salt **Diazo compound** **Azide**



prim alkylamine **very unstable**

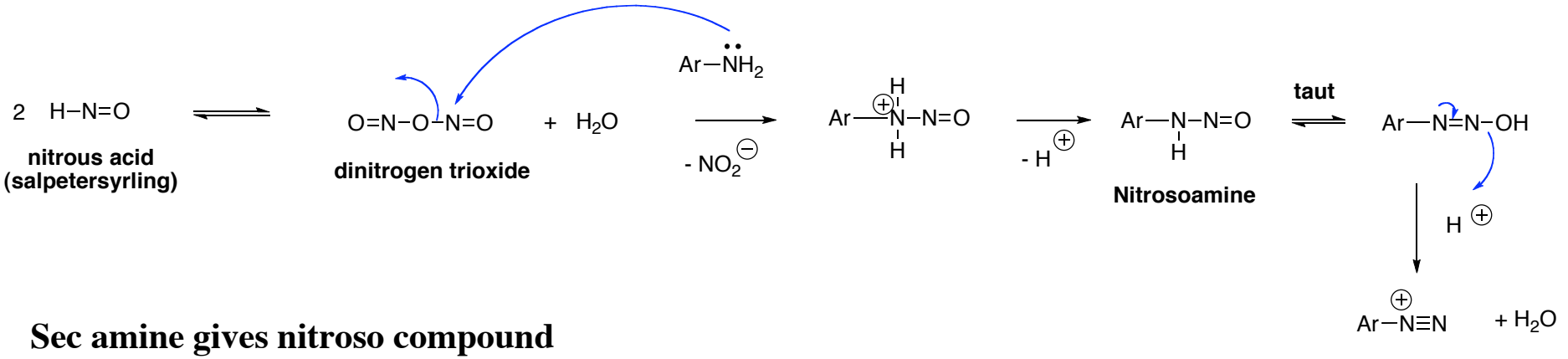
Synthetically seldom useful



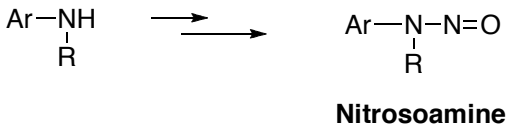
Aryl amine **Relatively stable** **Substitution** **Diazo coupling**

Y: OH, NH_2

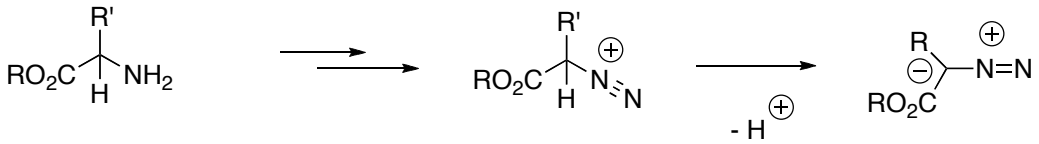
Diazotation of primary amine



Sec amine gives nitroso compound

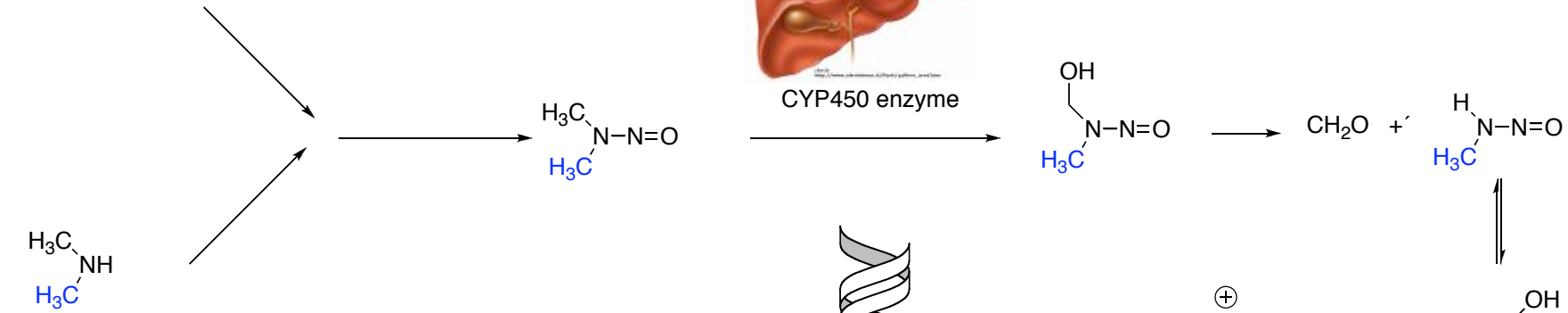


Amines with acidic a-H may give diazo compounds

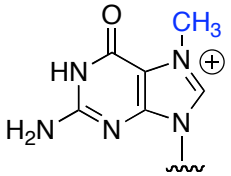


Toxicity nitroso compounds (not in McM) - Alkylation of biomolecules

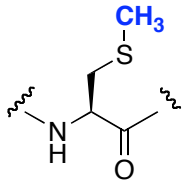
$NO_2^{\ominus}$ / $NO_3^{\ominus}$



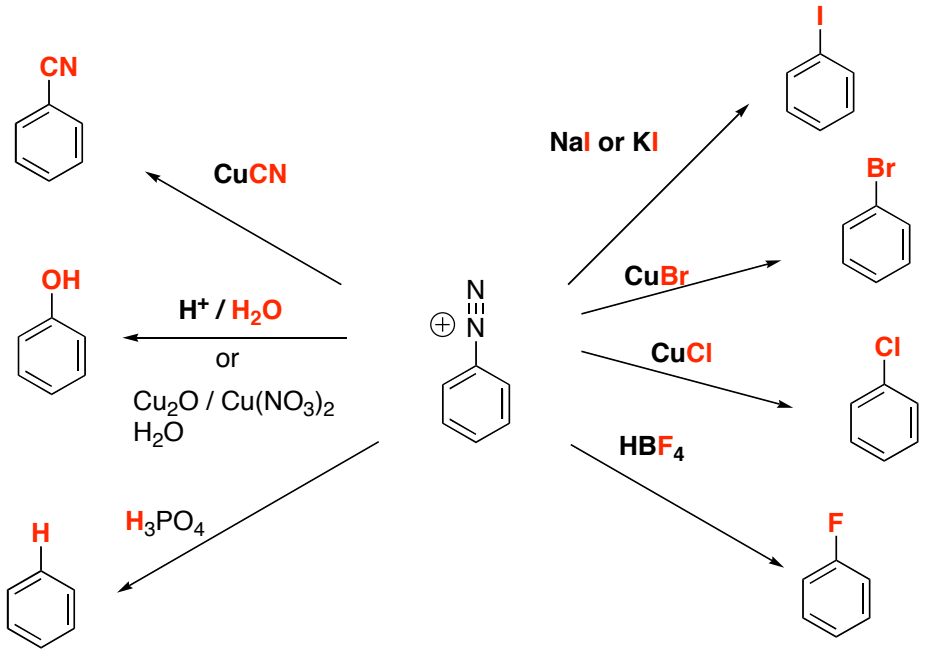
sec alkylamine



N-7 alkylation of guanine in DNA

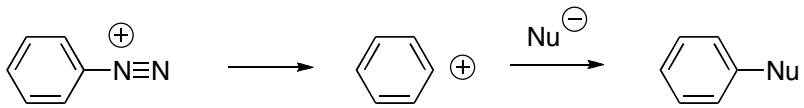


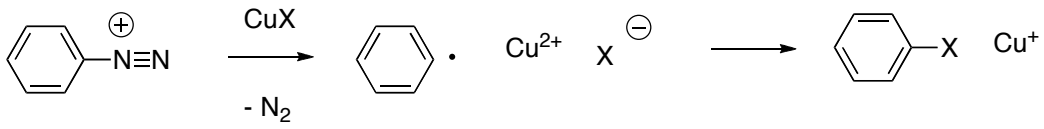
S-methylated cysteine in a peptide/protein



N_2 as leaving group

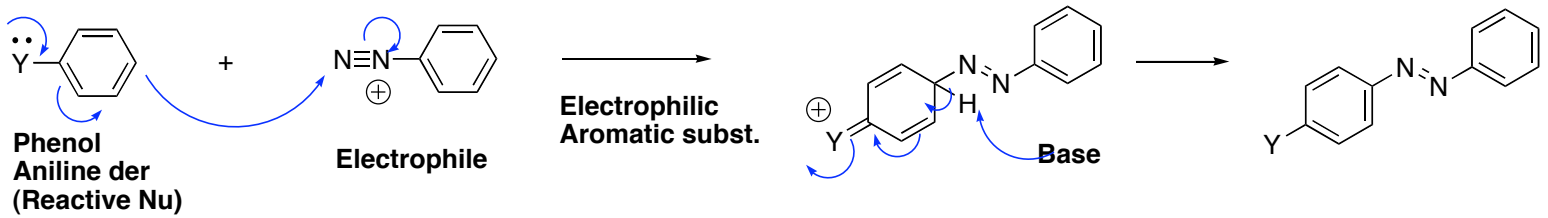
SN1 like mechanism or radical mechanism



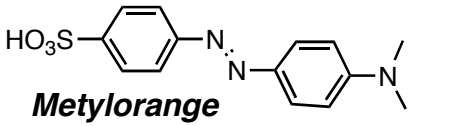


Cu-salt mediated react.
Sandmeyer react.
(radical mech.)

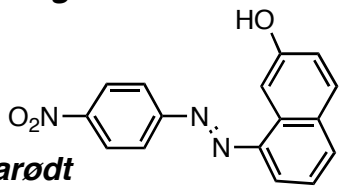
Diazo coupling



Azo dyes
Bayer etc
Late 1800-century, ex.

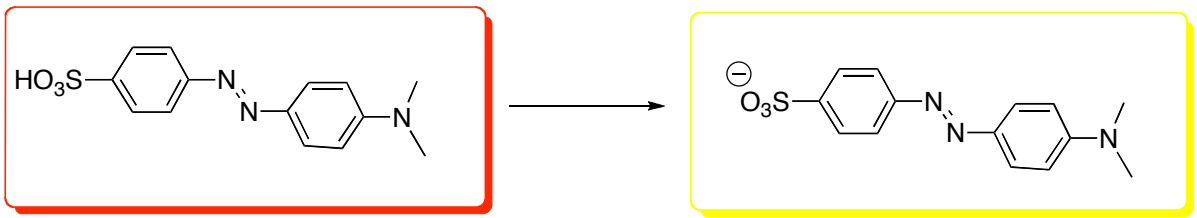


Metylorange



Pararødt

Metylorange

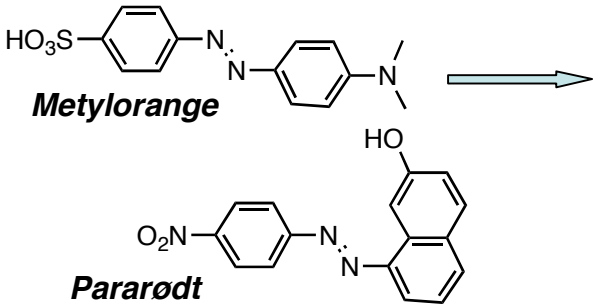


pH < 3.1

pH >4.4

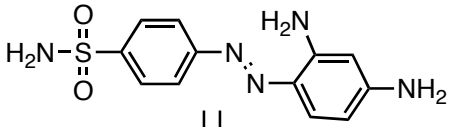
Antibacterial sulfonamides

Azo dyes
Bayer etc
Late 1800-century, ex.

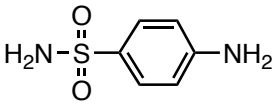


Screening of dyes as antibacterials

1932: ***Prontocil*** active against Streptoccocces infection
no activity on bacterial cultures

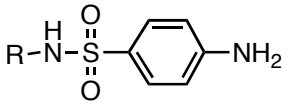


1935: Prontocil metabilized (azoreductase) to ***Sulfanilamid*** *in vivo*



(rel. toxisk)

Modern sulfa drugsr

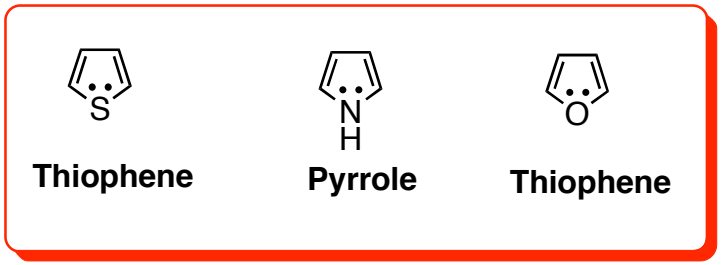


R: Aryl or hetroaryl

Heterocycles (McM chapt 24)

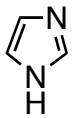
- **Monocyclic or fused rings**
- **Cont. one ore more ring atom ≠ C (normally O; N; S)**
- **Aromatic, partly saturated or saturated ring(s)**

5-Membered rings (Heteroatom N, O, S)



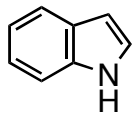
Thiophene **Pyrrole** **Thiophene**

Other examples

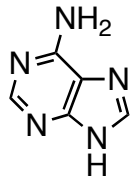


Imidazole

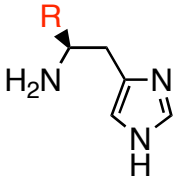
Thiazole



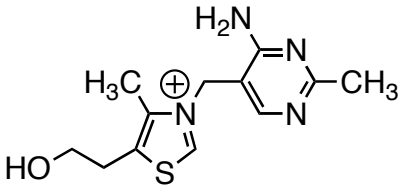
Indole



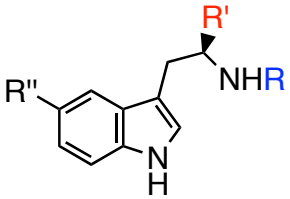
Adenine
(purine der.)



R=CO_2H: **Histidine**
R=H: **Histamine**



Thiamin
(Vit B1)



R=H
R'=CO_2H
R'''=H
} **Tryptophane**

R=H
R'=H
R'''=OH
} **Serotonin**

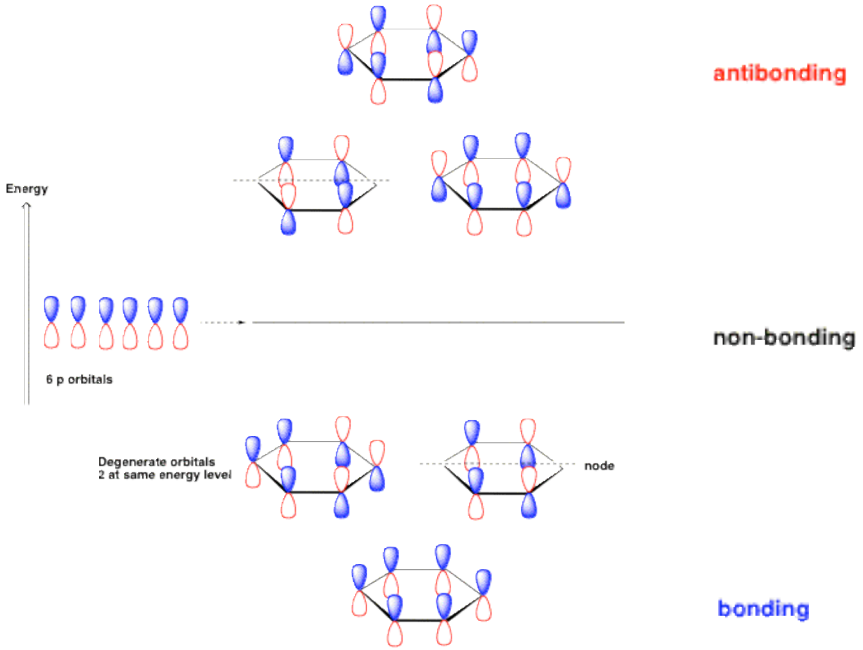
R=Ac
R'=H
R'''=OCH_3
} **Melatonin**

Criteria for Aromaticity (Hückel)

(Monocyclic) ring

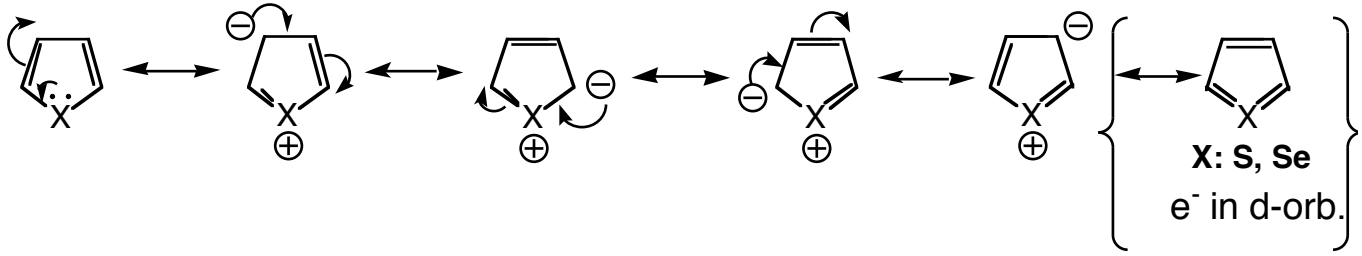
Planar

No of π-electrons in conjugation 4n+2 (n: 0, 1, 2,....)

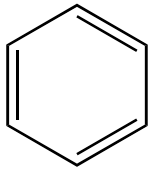


Cyclopentadienyl anion

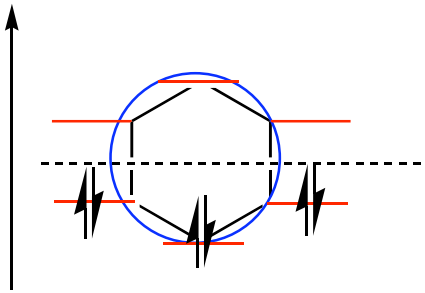
Thiophene



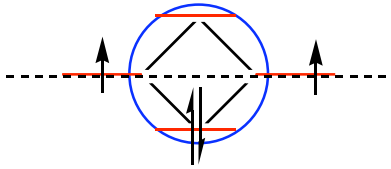
Benzene
6 π electrons



Energy

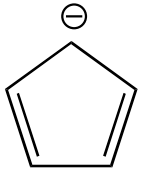


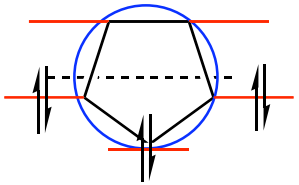
Cyclobutadiene
4 π electrons



Diradical

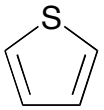
Cyclopentadienyl anion
6 π–electrons



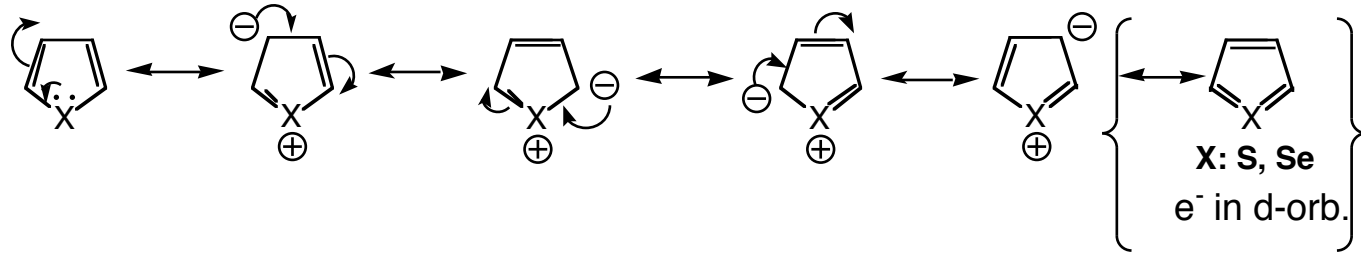


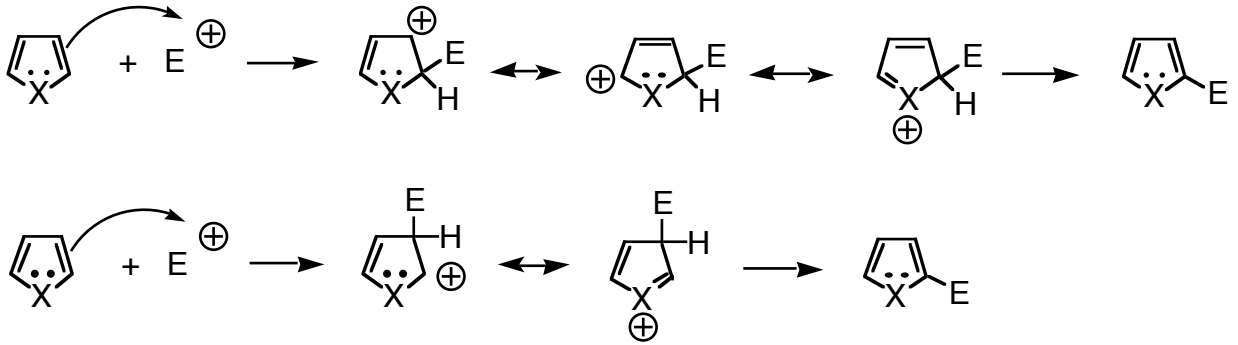
All π electrons in the bonding MO

Thiophene
6 π–electrons



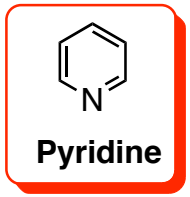
5-membered rings - electron rich on C - reactive i E-fil. Ar subst.



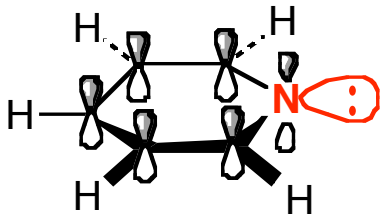


React. in α-position generally preferred
Selectivity not always good
React.: Pyrrole > thiophene > furan

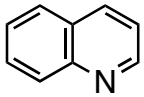
6-Membered rings (Heteroatom N)



Pyridine

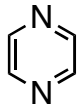


Other examples



Quinoline

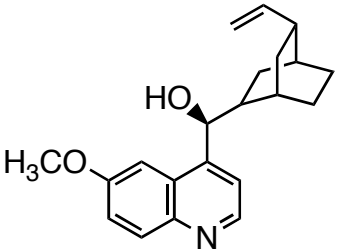
Pyrimidine



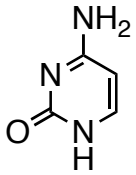
Pyrazine

Pyridazine

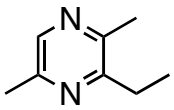
Rare in nature



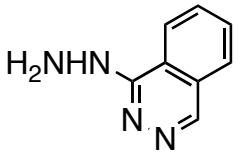
Quinine



Cytosine

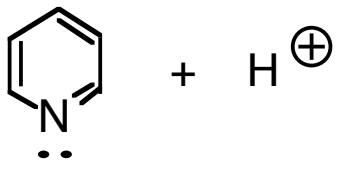


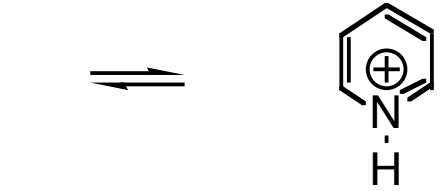
Ant pheremone



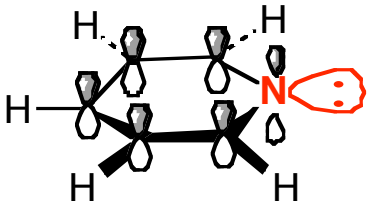
Hydralazine
Antihypertensive drug

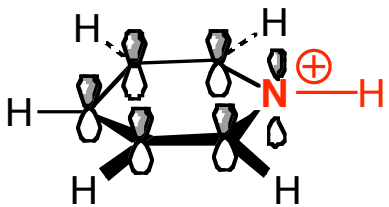
Pyridine as a base



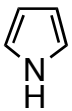


pKa: 5.2

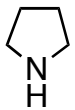




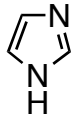
sp_2 N less basic than sp_3



pKa 0.4



pKa 11.3

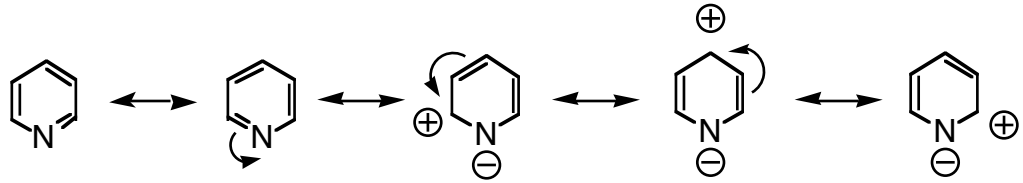


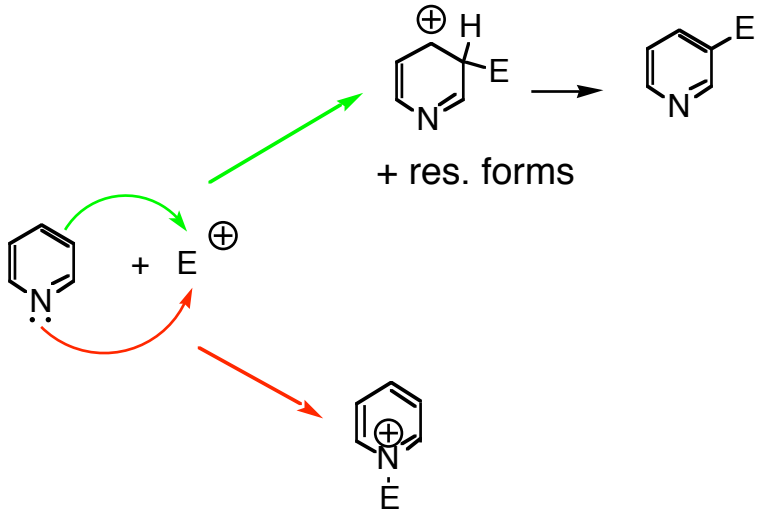
pKa 7.1 (≈amidine)

pKa 2.5

Electrophilic Reaction on Carbon: E-phil. Ar. Subs.

6-membered rings - electron deficient on C - ↓ reactivity

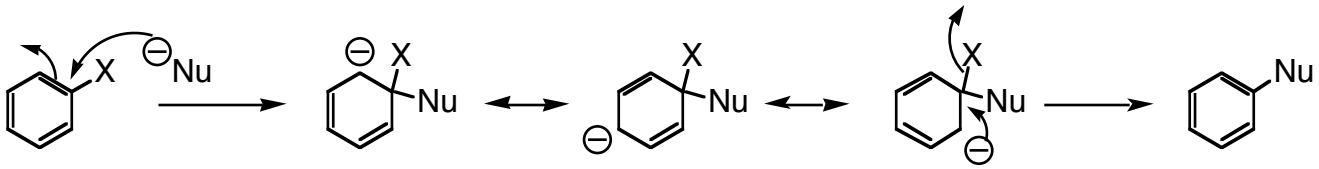




- **Both C and N may react**
- **3/5 pos. most reactive C**
- **Diazines less reactive**
- **Sulfonation, Nitration, halogenatil**
- **Not FC react.**

Nucleophilic Aromatic Substitution

•S_NAr



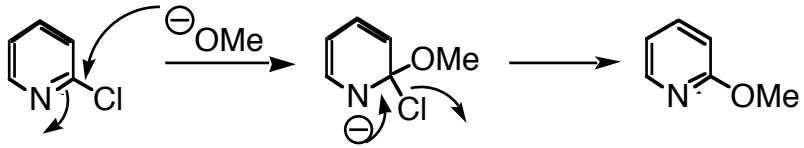
•S_N1: Via arylic cation

•Benzyne

•SRN1: Involves radicals

•VNS: Vicarious nucl. Subst.

6-membered rings - electron deficient - reactive in Nu-fil. Ar subst.



2 / 4 Pos. reactive; electron def. C, neg. charge partly on N in intermed
3 / 5-Pos. much less reactive (benzenoid pos.)