Chemistry II (Organic)

Heteroaromatic Chemistry
LECTURE 8

Diazoles & diazines: properties, syntheses & reactivity

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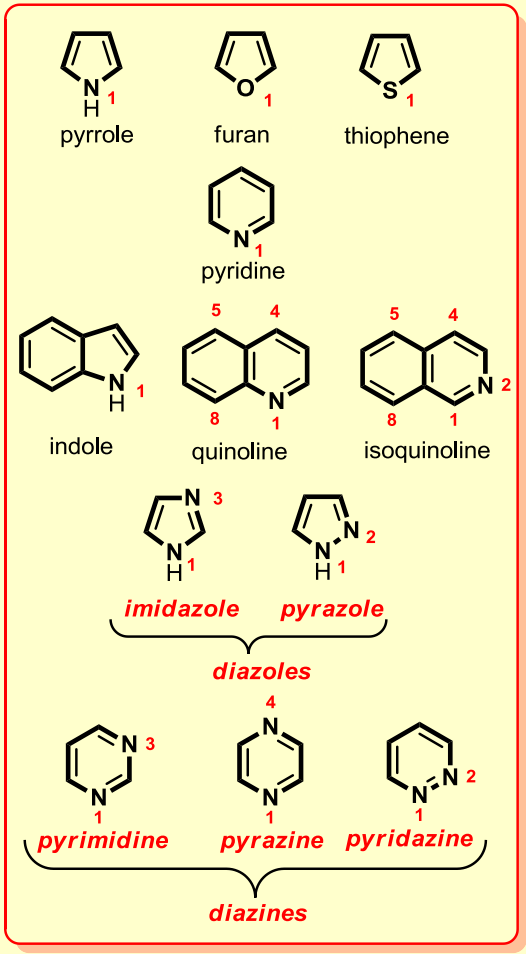
Format & scope of lecture 8

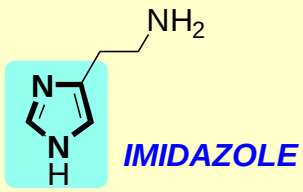
- ***Diazoles:***
  - Imidazole & pyrazole
  - Structure & properties
  - Synthesis
  - Reactivity

- ***Diazines:***
  - pyrimidines, pyrazines & pyridazines:
  - structure & properties
  - syntheses
  - reactivity

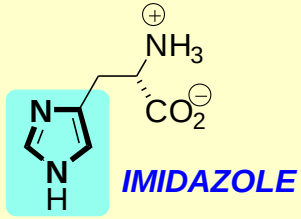


Diazoles: Imidazoles & Pyrazoles – *Importance*

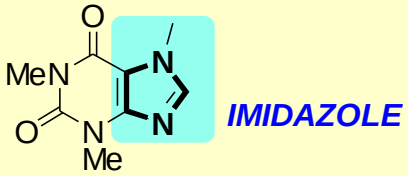
- ***Natural products*:**



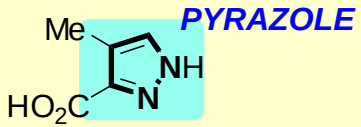
histamine
(inflammatory)



histidine
(protein constituent)

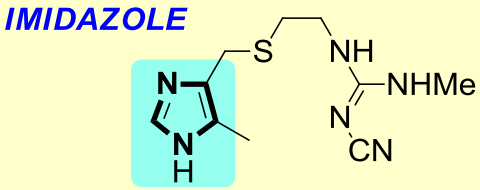


caffeine
(tea/coffee stimulant)

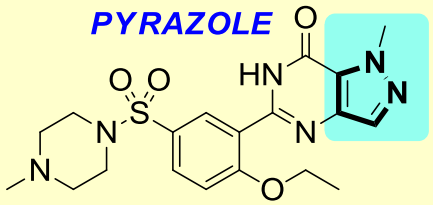


4-methylpyrazol-3(5)-carboxylic acid
('fire sponge' marine natural product)

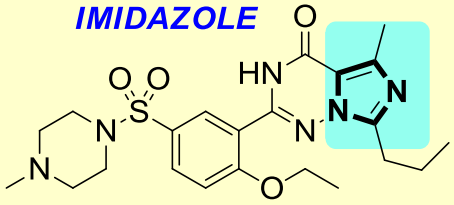
- ***Pharmaceuticals:***



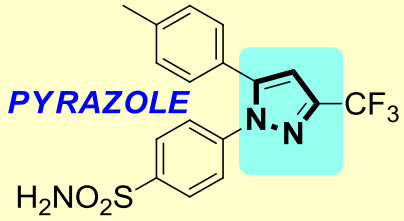
cimetidine
(Tagamet™, anti-ulcer)



sildenafil citrate
(Viagra™, erectile dysfunction)

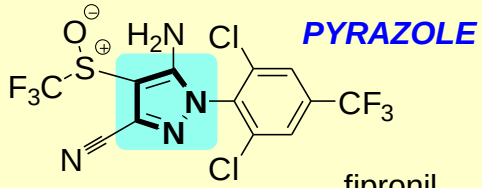


vardenafil citrate
(Levitra™, erectile dysfunction)

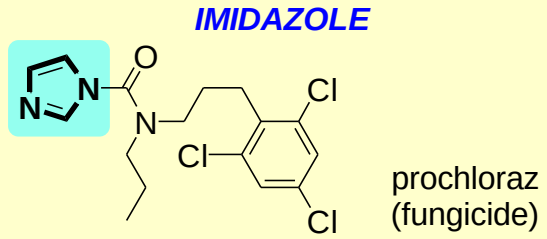


celecoxib
(Celebrex™, COX-2 inhibitor)

- ***Agrochemicals:***



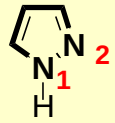
fipronil
(insecticide)

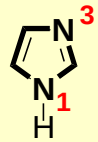


prochloraz
(fungicide)

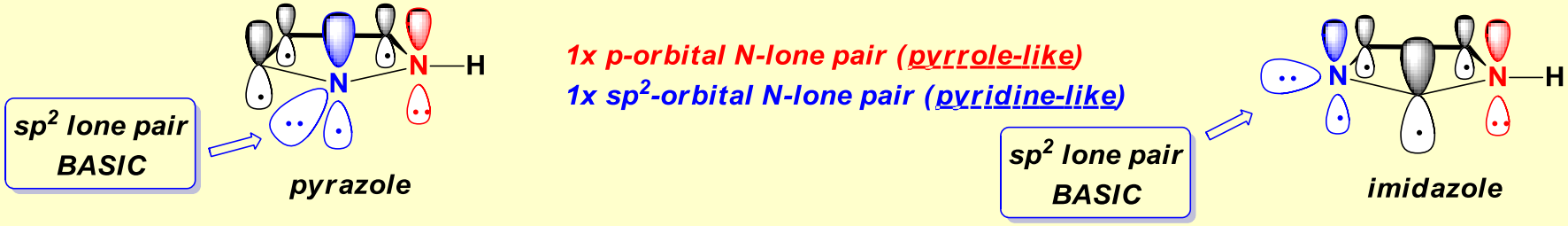
Diazoles *– Bonding & acid/base properties of pyrazole and imidazole*

- ***Diazoles*** can be considered as related to ***pyrrole*** but containing ***an additional N*** in place of one ***CH*** group***:***

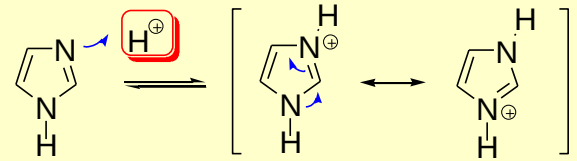
pyrazole 

imidazole 

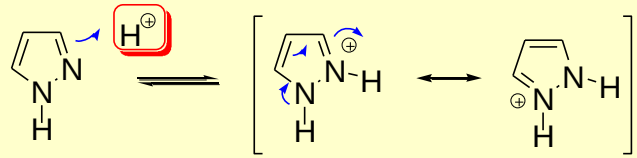
  - in both cases the 'new' ***N*** is ***pyridine-like***, *i.e.* this ***N*** contributes just 1 electron to the aromatic π-system and has a ***basic lone pair*** in the sp^2 orbital in the plane of the ring:



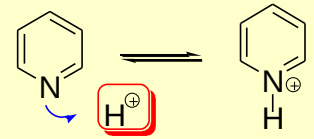
  - For a recent theoretical discussion of pyridine- *vs*. pyrrole-like Ns in imidazole see: Richaud *Org. Lett*. **2011**, 972 [DOI]
  - ***Imidazole*** and ***pyrazole*** are both ***NH-acidic*** (pK_as 14.5 & 14.2 respectively; *cf.* ***pyrrole*** 17.5). The ***basicity*** of the ***pyridine-like N*** varies significantly:
    - ***imidazole*** is a stronger base than pyridine whereas ***pyrazole*** is a weaker base than pyridine:



imidazole (pK_a 7.0)



pyrazole (pK_a 2.5)



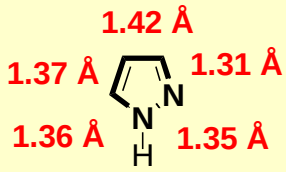
pyridine (pK_a 5.2)

Imidazole and pyrazole – *Structure and Properties*

- ***Imidazole:*** colourless prisms, mp 88 °C; ***pyrazole:*** colourless needles, mp 70 °C
- ***Bond lengths*** and ***^{1}H NMR chemical shifts*** as expected for aromatic systems:

bond lengths:

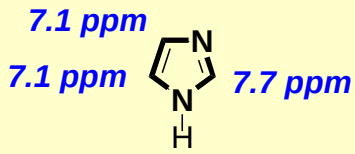
imidazole



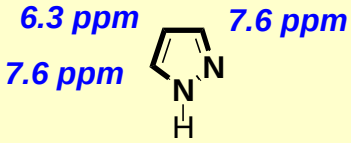
pyrazole

cf. **ave C-C 1.48 Å**
ave C=C 1.34 Å
ave C-N 1.45 Å

^{1}H NMR:



imidazole

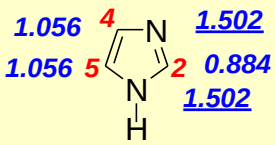


pyrazole

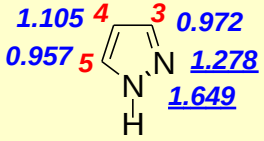
- ***Resonance energies:*** both systems have lower resonance energies than pyrrole (*i.e.* <90 kJmol^{-1})

- ***Electron density:*** relative to pyrrole, the additional (electronegative) ***N*** atom ***decreases the overall electron density*** on the remaining carbons. The precise distribution is rather uneven:
  - for ***imidazole***: ***C4*** & ***C5*** are ***electron rich***, ***C2*** is ***electron deficient***
  - for ***pyrazole: C4*** is ***electron rich***, ***C3*** & ***C5*** are ***electron deficient***

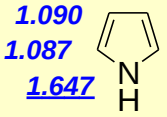
π-electron densities:



imidazole



pyrazole

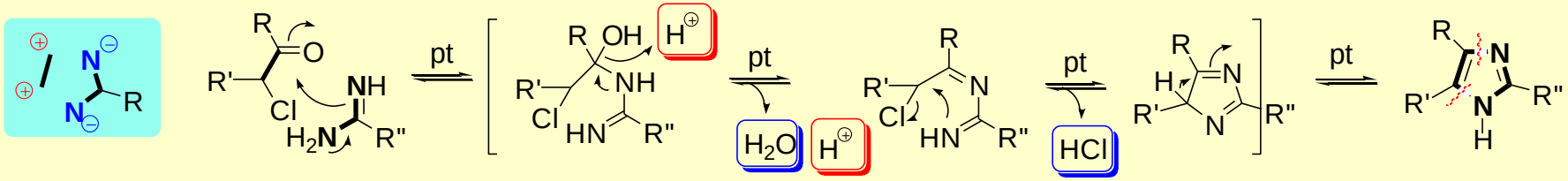


pyrrole

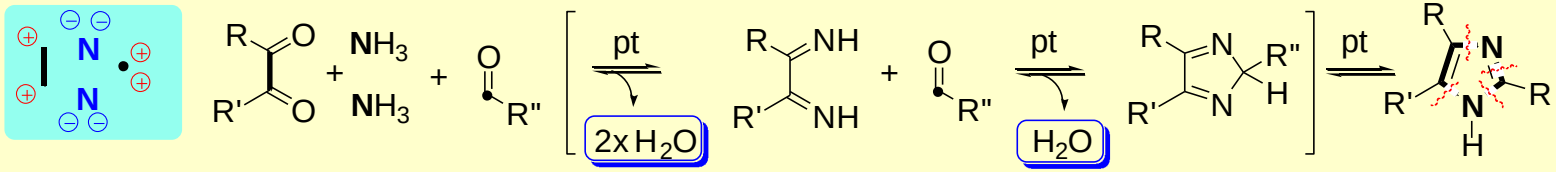
  - → both ***pyrazole*** and ***imidazole*** are:
    - significantly ***less reactive*** towards electrophilic aromatic substitution (S_EAr) than pyrrole (<u>but</u> >benzene)
    - ***reactive*** towards nucleophilic aromatic substitution (S_NAr) at certain ***C***s (*cf.* pyrrole which does <u>not</u> react with nucleophilies)

Imidazoles and pyrazoles – *Syntheses*

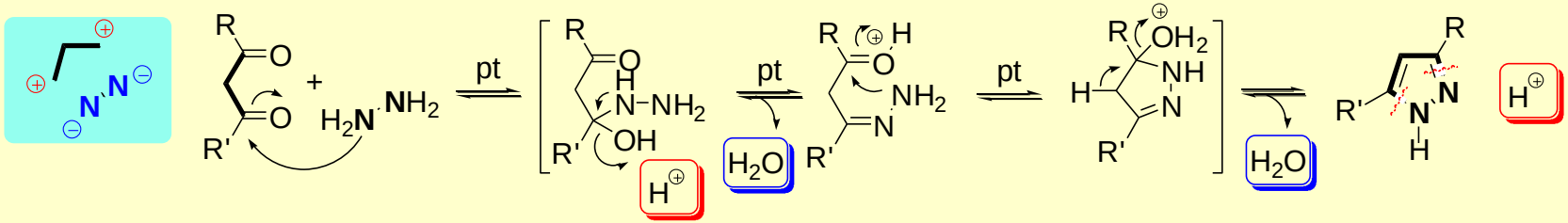
- ***Imidazoles:***
  - α-haloketone with amidine:



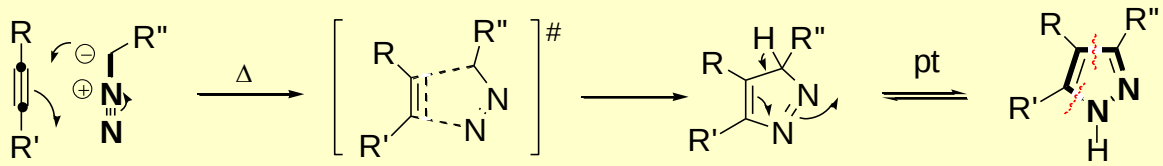
  - 1,2-dicarbonyl & an aldehyde with NH_3:



- ***Pyrazoles:***
  - hydrazine with 1,3-dicarbonyl:



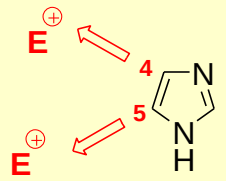
  - ***1,3-dipolar cycloaddition*** of diazoalkane with alkyne:



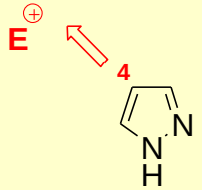
Imidazoles and pyrazoles – *Reactivity*

- ***Electrophilic substitution:*** *via* addition-elimination (S_EAr):
  - **reactivity:** reactive towards many electrophiles (**E^+**); >benzene but <pyrrole, furan & thiophene
  - **regioselectivity:** substitution at electron rich carbons predominate (*cf.* electronic distribution):
    - ***imidazole: C4*** > ***C5*** (for NR systems; if NH then ***C4*** and ***C5*** are identical)
    - ***pyrazole: C4*** – less reactive than imidazole

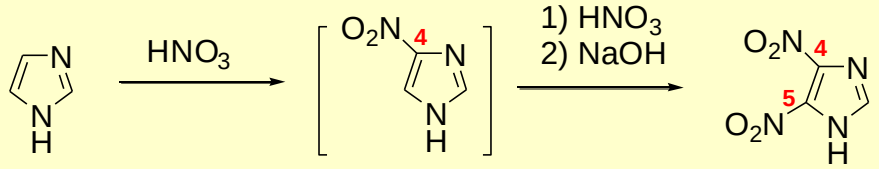
imidazole



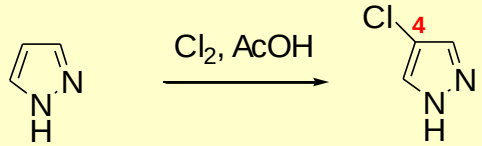
pyrazole



- ***e.g.*** **nitration:** (**E^+** = NO_2^+)
  - ***imidazole:***



- ***e.g.*** **chlorination:** (**E^+** = Cl^+)
  - ***pyrazole:***

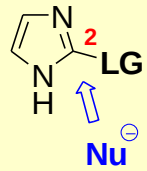


- ***NB.*** **electron donating substituents enhance reactivity towards electrophiles**

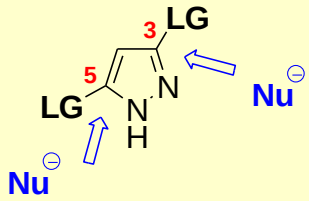
Imidazoles and pyrazoles *– Reactivity cont.*

- ***Nucleophilic substitution:*** *via* addition-elimination (S_NAr)
  - **reactivity:** reactive towards good nucleophilies (**Nu**$^-$) provided leaving group is situated at appropriate carbon
  - **regioselectivity:** substitution of leaving groups (*e.g.* Cl, Br, NO_2) at electron deficient centres possible (*cf.* electronic distribution):
    - ***imidazole: C2*** – relatively reactive centre
    - ***pyrazole: C5*** ~ ***C3*** – neither centre very reactive

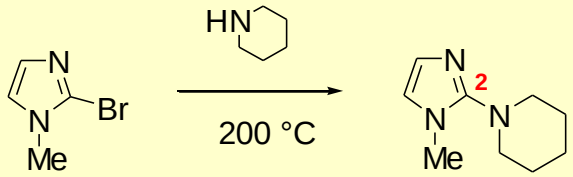
imidazole



pyrazole
(difficult)



- ***e.g.*** **displacement of Br by amine:** (**Nu**$^-$ = R_2N^-, LG = Br)
  - ***imidazole:***

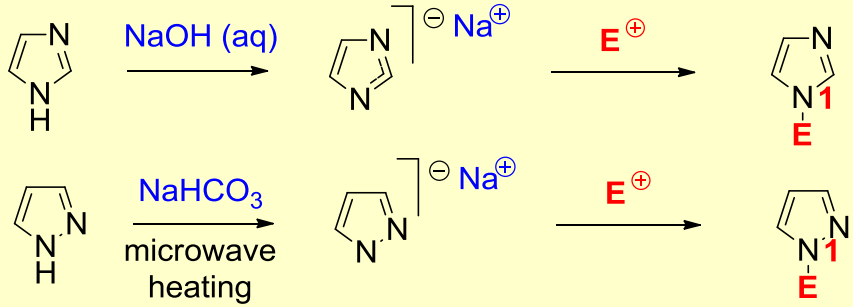


- ***NB.*** **electron withrawing substituents enhance reactivity towards nucleophiles**

Imidazoles and pyrazoles – *Reactivity cont.*

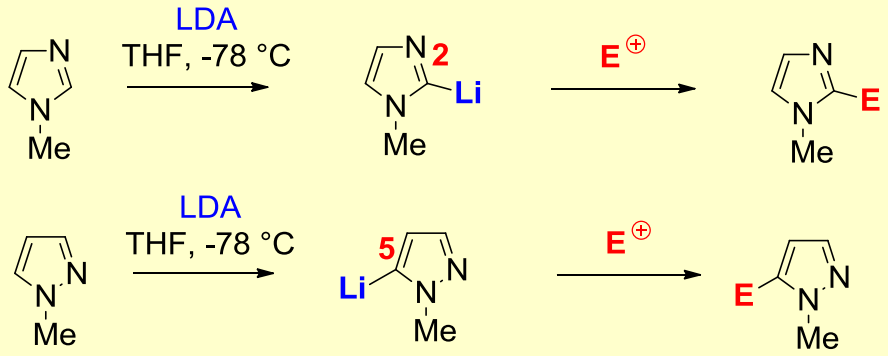
- ***Metallation:*** (***imidazole*** NH pK_a = 14.5; ***pyrazole*** NH pK_a = 14.2)
  - deprotonation by strong bases more facile than for pyrrole (pK_a = 17.5) or indole (pK_a = 16.2):

NH-imidazoles/pyrazoles:
(N-metallation)



$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

NR-imidazoles/pyrazoles:
(C-metallation)

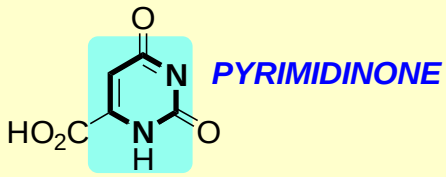


$E^{\oplus}X^{\ominus}$ = MeI, RCOCl *etc.*

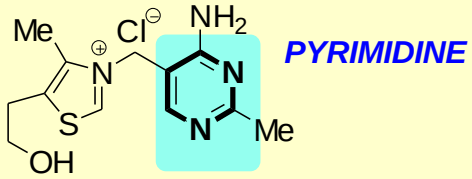
NB. thermodynamic deprotonation ortho to 'pyrrole-like' rather than 'pyridine-like' nitrogen (see Lecture 7)

Diazines: Pyrimidines, Pyridazines & Pyrazines – *Importance*

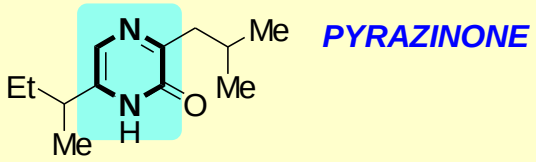
- ***Natural products*:**



orotic acid
(biosynthetic intermediate
for natural pyrimidines)

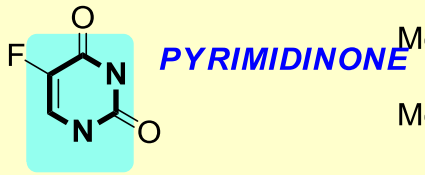


thiamine - vitamin B1
(essential vitamin)

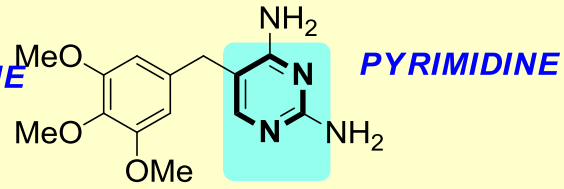


aspergillic acid
(fungal antibiotic)

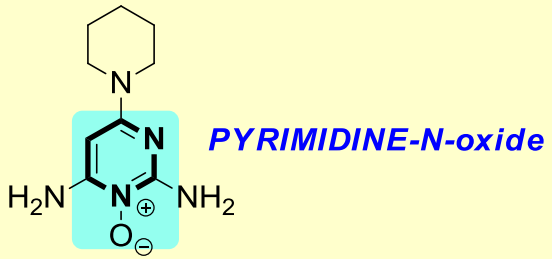
- ***Pharmaceuticals:***



zidovudine
(AZT™, anti-AIDS)

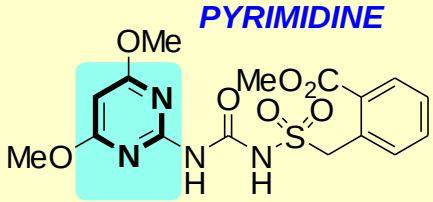


trimethoprim
(Triprim™, antibacterial)

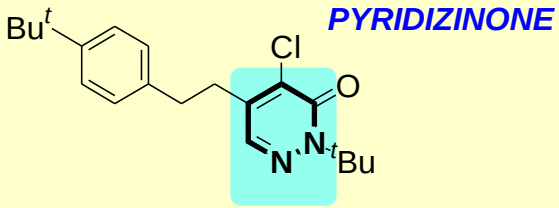


minoxidil
(Vanarex™, anihypertensive)

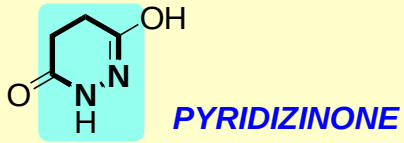
- ***Agrochemicals:***



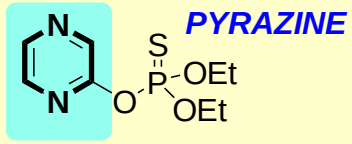
bensulfuronmethyl
(herbicide)



pyridaben
(herbicide)



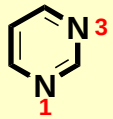
maleic hydrazide
(plant growth inhibitor)

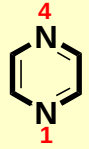


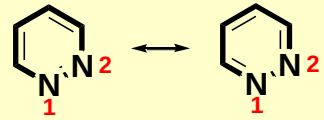
thionazin
(soil insecticide)

Diazines – *Bonding, Structure & Properties*

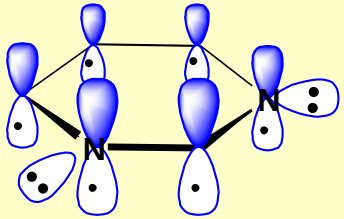
- ***Diazines*** can be considered as related to ***pyridine*** but containing ***an additional N*** in place of one ***CH*** group***:***

pyrimidine 

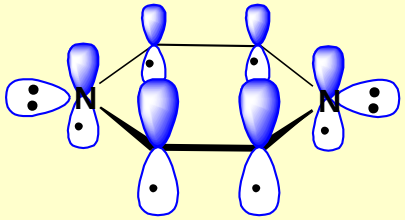
pyrazine 

pyridazine 

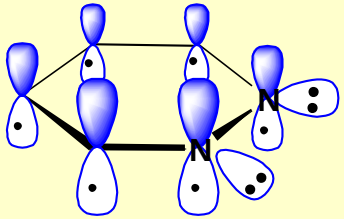
  - in all cases the 'new' ***N*** is ***pyridine-like***, *i.e.* this ***N*** contributes just 1 electron to the aromatic π-system and has a ***basic lone pair*** in the sp^2 orbital in the plane of the ring:



pyrimidine

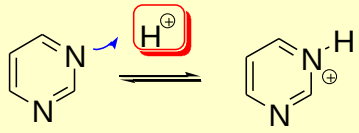


pyrazine

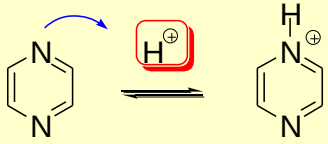


pyridazine

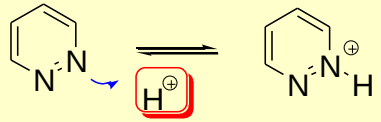
  - All three diazines are significantly ***less basic*** than ***pyridine:***



pyrimidine (pK_a 1.3)



pyrazine (pK_a 0.4)



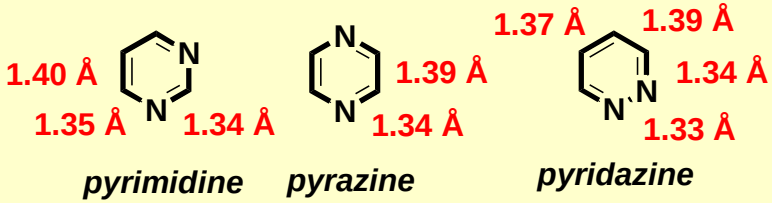
pyridazine (pK_a 2.3)

Diazines *– Structure and Properties*

- ***Pyrimidine:*** colourless prisms, mp 22 °C
- ***Pyridazine:*** colourless liquid, bp 208 °C
- ***Pyrazine:*** colourless prisms, mp 57 °C

- ***Bond lengths*** and ***^{1}H NMR chemical shifts*** as expected for aromatic systems:

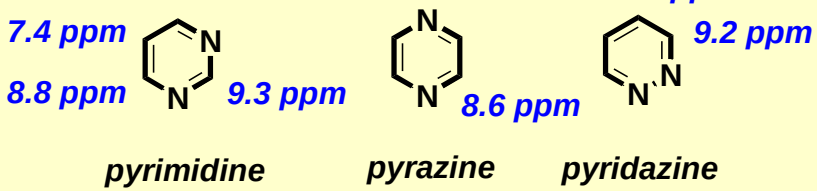
bond lengths:



pyrimidine ***pyrazine*** ***pyridazine***

cf. **ave C-C 1.48 Å**
ave C=C 1.34 Å
ave C-N 1.45 Å

^{1}H NMR:



pyrimidine ***pyrazine*** ***pyridazine***

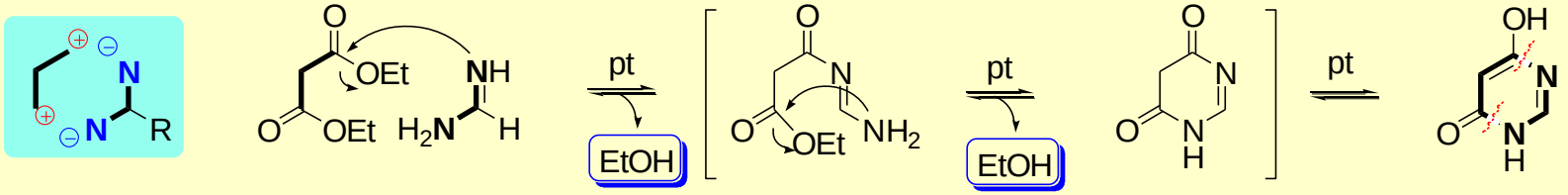
- ***Resonance energies:*** all three systems have ***lower*** resonance energies than ***pyridine*** (117 kJmol^{-1})
  - → susceptible to nucleophilic <u>addition</u> reactions

- ***Electron density:*** all three systems are ***highly electron deficient*** (*cf.* ~pyridine)

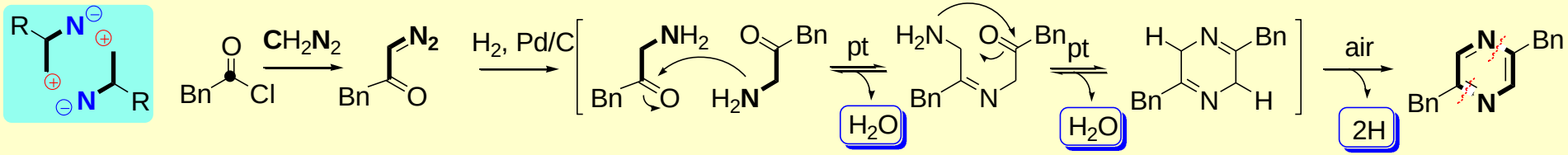
  - → ***unreactive*** towards ***electrophiic substitution*** (S_EAr)
  - → ***reactive*** towards ***nucleophilic substitution*** (S_NAr)

Diazines – *Syntheses*

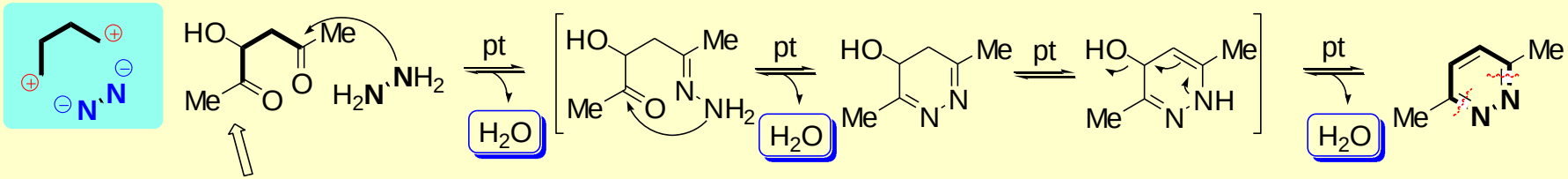
- ***Pyrimidines:***
  - ***Pinner:*** 1,3-dicarbonyl with amidine



- ***Pyrazines:***
  - ***dimerisation*** of α-aminoketone/aldehyde then aerial oxidation:



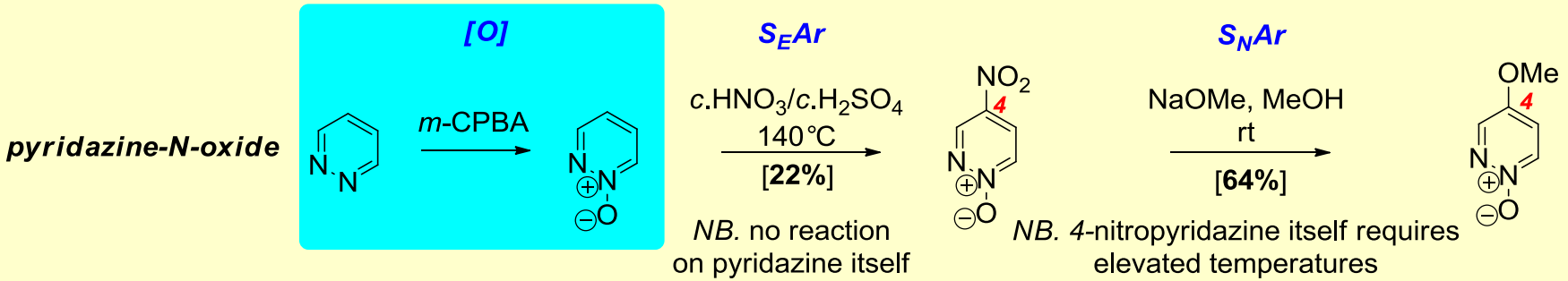
- ***Pyridazines:***
  - ***'Paal-Knorr':*** 1,4-dicarbonyl with hydrazine



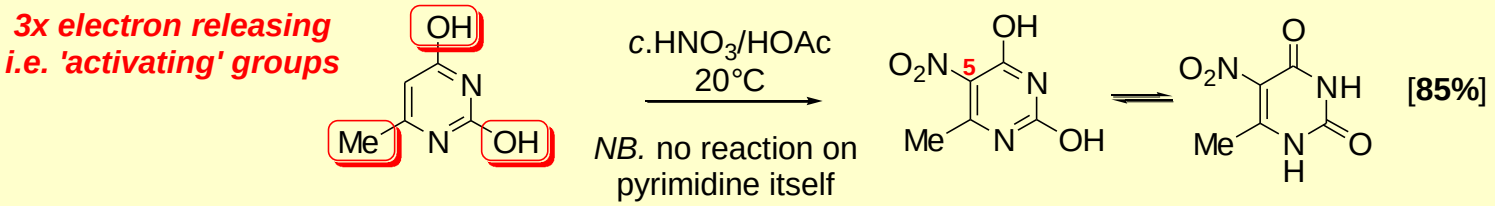
NB. hydroxyl 'leaving group' in 1,4-dicarbonyl obviates oxidation

Diazines – *Reactivity*

- ***Electrophilic <u>addition</u>*** at ***N:***
  - formation of ***N-oxides*** as for pyridine; these derivatives are more susceptible to S_NAr (and S_EAr) than the parent diazines:



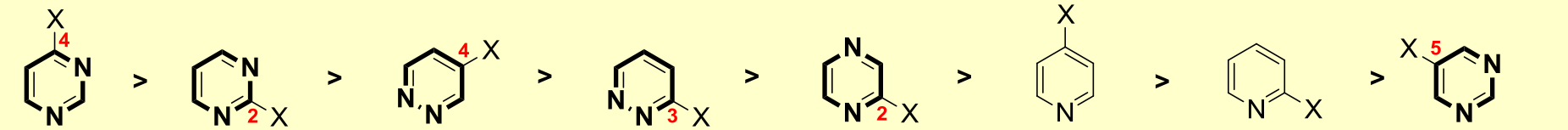
- ***Electrophilic <u>substitution</u>:*** *via* addition-elimination (S_EAr)
  - all diazines are ***highly electron deficient*** → very <u>unreactive</u> towards S_EAr
    - electron donating substituents and/or *N*-oxides (see above) <u>required</u> to allow reaction even at ***C5*** of pyrimidine:



    - ***<u>regioselectivity</u>:*** *via* most stable Wheland intermediate

Diazines – *Reactivity*

- ***Nucleophilic <u>substitution</u>:*** *via* addition-elimination (S_NAr)
  - all diazines are ***highly electron deficient*** → very <u>reactive</u> towards S_NAr (>pyridines)
  - all halodiazines <u>except 5-halopyrimidines</u> react readily with nucleophilies:



C4 & C2 pyrimidines ***C4 & C3 pyridazines*** ***C2 pyrazines*** ***C5 pyrimidine***

- ***Metallation:***
  - all diazines can be metalated *ortho* to ***N*** by LiTMP (pyrimidine at ***C4*** not ***C2***):