Reactions of Furan Thiophene Pyrrole Part 1
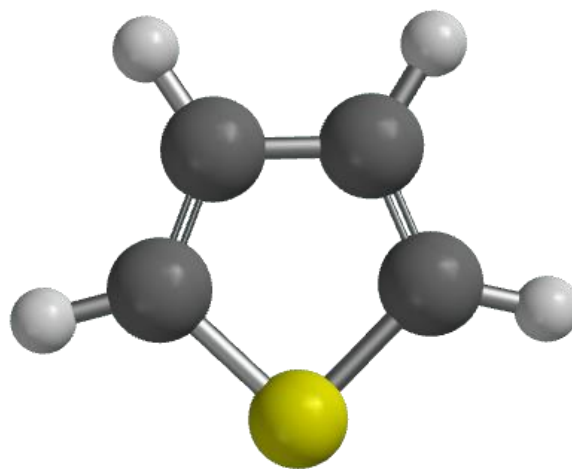
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1) Reactions with Electrophiles

The chemistry of pyrrole and thiophene is dominated by a readiness to undergo electrophilic substitution

(the stark contrast between the five- and six-membered heterocycles: the five-membered systems considered in this chapter react much more readily with electrophiles than does benzene, but the azines react much less readily)

- The substitution occurs preferentially at an *α*-position

- If the *α*-position is blocked, the reaction can also occur at the *β*-position with only slightly slower rate

CH_2O, Et_2NH, AcOH, rt

$[CH_2=NEt_2]^+$

62%
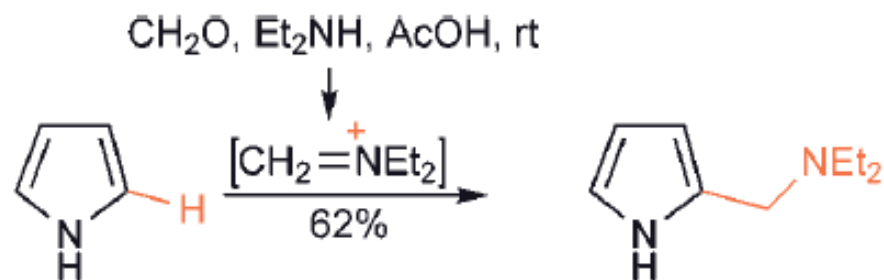
An example of easy α-electrophilic substitution of pyrrole with a weak electrophile
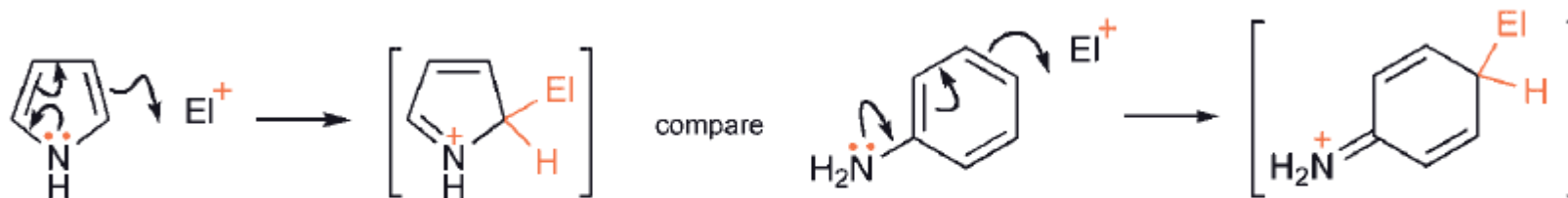
1) Reactions with Electrophiles

The positional selectivity and their high reactivity to electrophilic attack are well explained by a consideration of the **Wheland intermediates**
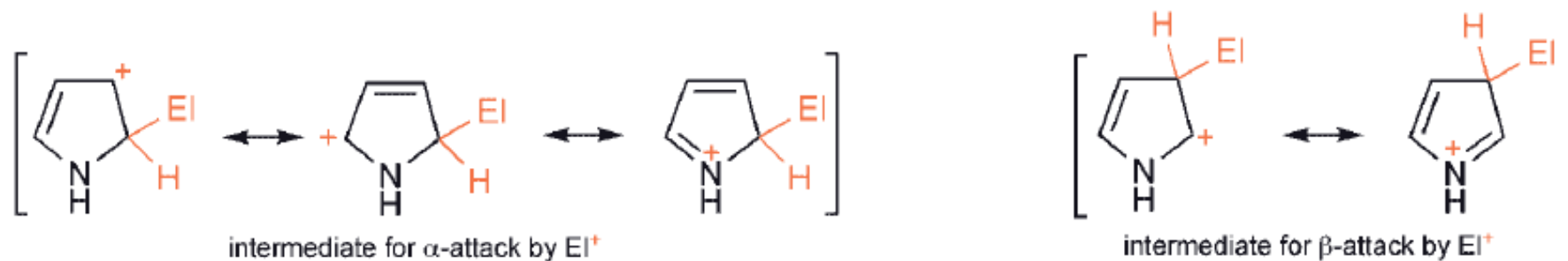
**Intermediates for electrophilic substitution of pyrrole**

- The **delocalisation**, involving donation of electron density from the heteroatom, is **greater** in the intermediate from α-attack

- Note that the **C–C double bond** in the intermediate for β-attack cannot become involved in delocalisation of the charge

- The reactivity towards electrophile of pyrrole is in the same range as aniline

Electrophilic attack on electron-rich pyrrole compared with attack on electron-rich aniline

1) Reactions with Electrophiles – at Heteroatom

The five-membered heterocycles do not react with electrophiles at the heteroatom


whereas

pyrrolidine
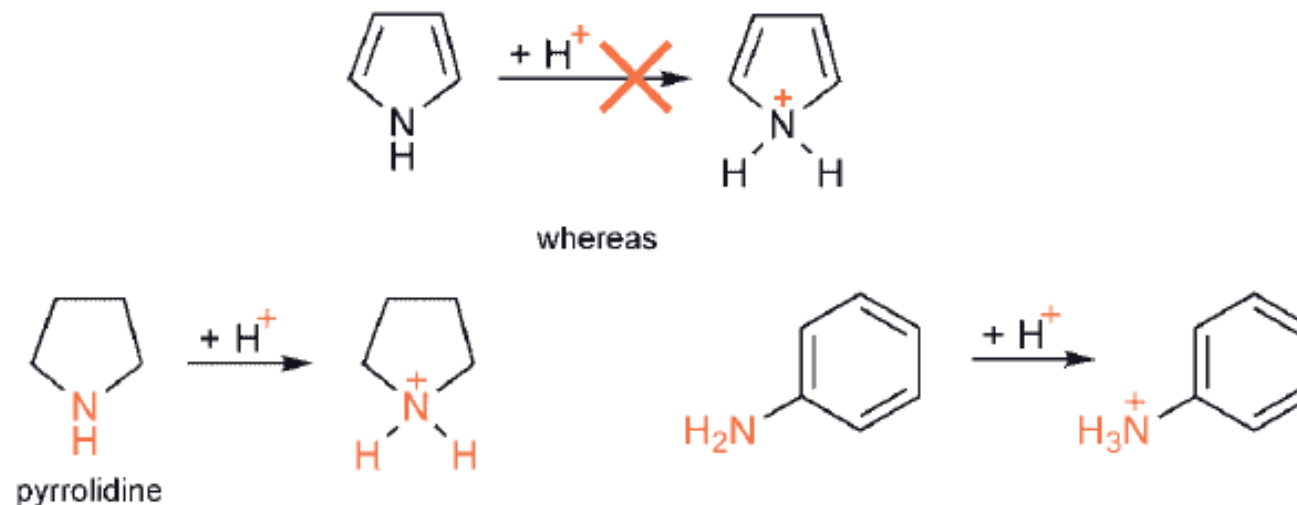
- Electrophilic addition at the nitrogen of pyrrole would lead to a **loss of aromaticity**

- Anilines do react easily with simple electrophiles (e.g. protons) at nitrogen; the majority of the stabilisation energy, associated with the six-electron benzenoid π-system, is retained

1) Reactions with Electrophiles – at Heteroatom

- Any very **strong base** will effect complete conversion of an *N*–unsubstituted pyrrole into the corresponding **pyrryl anion** (perhaps the most convenient being commercial *n*-**butyllithium solution**)

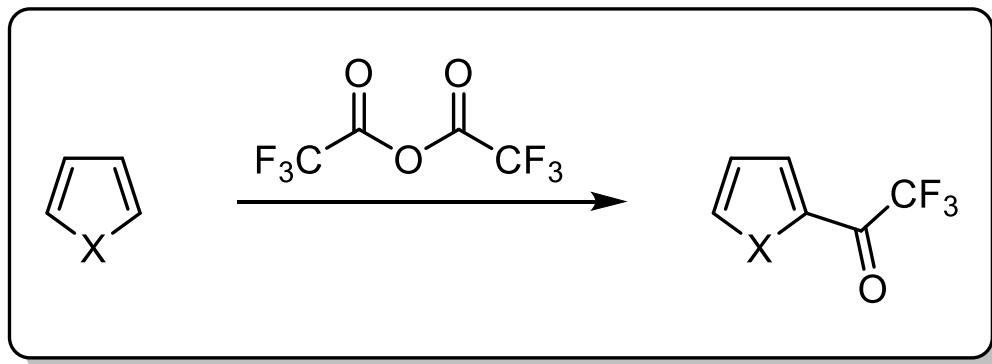- The pyrryl anion is nucleophilic at nitrogen

- However, with weaker base, reactions at nitrogen can proceed via smaller, equilibrium concentrations of pyrryl anion (the preparation of 1-*t*-butoxycarbonylpyrrole)
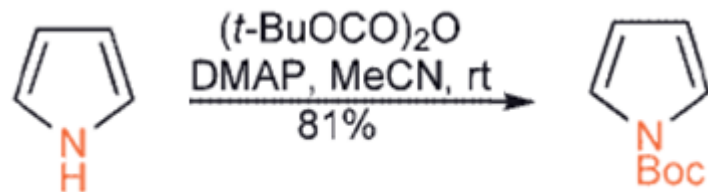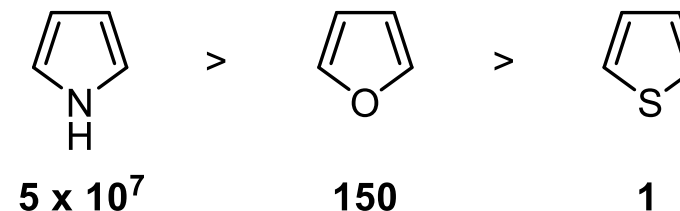
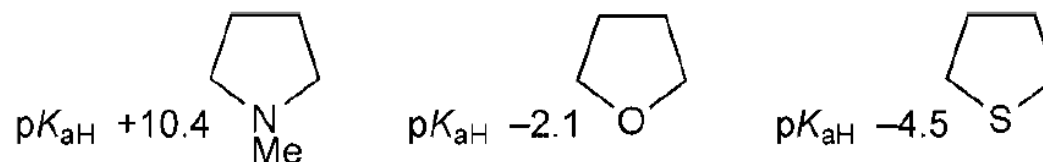# 1) Reactions with Electrophiles – Substitution at Carbon

- **Pyrrole is by far the most susceptible to electrophilic attack** *(2 effects: greater electron-releasing ability of neutral trivalent nitrogen, and the concomitant greater stability of a positive charge on tetravalent nitrogen)*

- Reactivity order = **Pyrrole > Furan > Thiophene**

Relative Rate:

Pyrrole: 5×10^7 > Furan: 150 > Thiophene: 1

- Comparing the relative basicities of saturated amines, ethers and sulphides

pK_{aH} +10.4 (N–Me pyrrolidine) pK_{aH} −2.1 (O, tetrahydrofuran) pK_{aH} −4.5 (S, tetrahydrothiophene)

1) Reactions with Electrophiles – Substitution at Carbon

- **Substituents** ranged on five-membered rings have **directing effects** comparable to those that they exert on a benzene (or pyridine) ring; for example, alkyl groups direct *ortho* and *para*, and nitro groups direct meta

- However, the very strong tendency for *α*-**electrophilic substitution** is the dominating influence in most instances
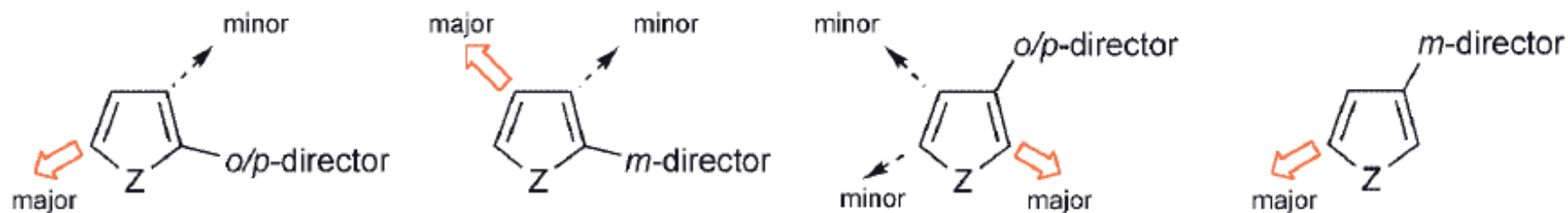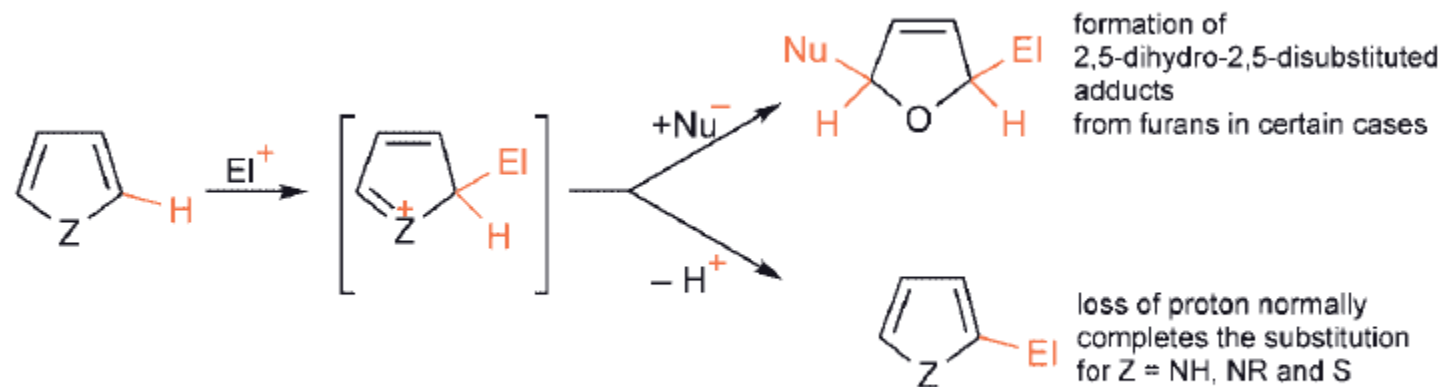

Effect of substitutents on regioselectivity of electrophilic substitution in five-membered heterocycles

- The influence of substituents is felt least in furans

1) Reactions with Electrophiles – Substitution at Carbon

- A significant aspect of the chemistry of **furans** is the occurrence of **2,5-additions** initiated by electrophilic attack *(a Wheland intermediate is formed normally, but then adds a nucleophile, instead of then losing a proton)*

formation of 2,5-dihydro-2,5-disubstituted adducts from furans in certain cases

loss of proton normally completes the substitution for Z = NH, NR and S

Formation of adducts from furans

- The occurrence of such processes in the case of furan is generally considered to be associated with its **lower aromatic resonance stabilisation energy** *(there is less to regain by loss of a proton and the consequent return to an aromatic furan)*