Reactivity of Five membered **π**-Excessive Heterocyclic ring by Assist. Prof. Oqba Nafia Ph.D. of Organic Chemistry "Synthesis of Hetero Cyclic" College of Pharmacy-2020

Reactivity of Five membered π-Excessive Heterocyclic ring

Reactivity towards electrophilic substitution

Pyrrole, furan and thiophene are all much more reactive than benzene toward electrophilic substitution.



benzene



thiophene



furan



Thiophene is 100 times more reactive than benzene and pyrrole is the most reactive. Furan is less reactive than pyrrole because oxygen is more electronegative than nitrogen.

There are two position for electrophilic attack, C-2 and C-3.

Each reacts predominately at the <u>2-position</u> (and if that position is already substituted, at the <u>5-position</u>).

If 2- and 5-position are already occupied, electrophilic substitution takes place at 3-position.



Attack at C-2 is preferred because it yields a more stable carbocation (3 resonance structures, while attack at C-3 gives only 2 resonance structures) Although furan is the least aromatic (resonance energy stabilisation 16 Kcal / mol), pyrrole (resonance energy stabilisation 21 Kcal / mol) is most reactive. Thiophene most aromatic with (resonance energy stabilisation 29 Kcal / mol) is least reactive.

This inverted reactivity pattern is because of the excessive participation of nitrogen lone pair is stabilising reactive intermediate for substitution at C-2.



Energy needed to go from the more aromatic pyrrole to its reactive intermediate is less than energy needed for a similar step with furan





It was found that pyrrole reacts readily with some weak electrophiles, while thiophene and furan did not react





$$\int_{0}^{l_2} \int_{0}^{N} \int_$$



Halogenation. Just as is true for aniline, the pyrrole ring is reactive toward bromine or chlorine, giving polysubstituted products



2. Due to the sensitivity to acids nitration is conducted in aprotic media.



Only thiophene (least acid reactive can be nitrated by mixed acid nitration.



4. Because of its low aromaticity reactions of furan in presence of a nucleophile gives in many cases adducts in which intermediate instead of undergoing proton loss reacts with nucleophile, e.g.





5. Acylation of π -excessive molecules can be made either in complete absence of a Lewis acid or in presence of ZnCl₂. Pyrrole is acylated at N and not at C-



Furan and thiophene undergo *Friedel –Craft* reaction while pyrrole did not?



Acidic character of pyrrole

Unlike furan and thiophene, pyrrole is weakly acidic in nature. Thus, on reaction with metallic potassium or potassium hydroxide it forms a potassium salt, which is hydrolyzed back to pyrrole on treatment with water.



The acidic character of pyrrole is due to

Pyrrole is a resonance hybrid of various structures carrying a positive charge on nitrogen.

The greater stability of pyrrole anion compared to pyrrole.

$$\left\langle \sum_{\substack{N \\ H}} \right\rangle = \left\langle \sum_{\substack{N \\ H}} \right\rangle + H^{+}$$

The higher stability of the anion is due to resonance.

The acidic character is also reflected in the formation of pyrrolyl magnesium halide when reacted with alkylmagnesium halide.



The action of acids pyrrole, thiophene and furan



The mechanism of trimerization of pyrrole in acid medium

