Anglo-Chinese Junior College
H3 Chemistry
Aromatic Heterocyclic Compounds Lecture Notes

Prepared by: Jun Kiat, Shanghong & Shi Shiun

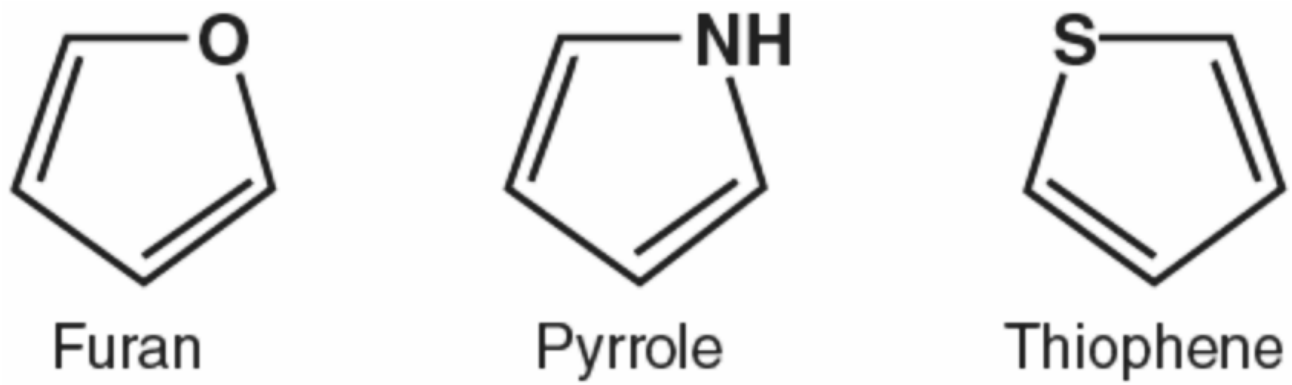
Section Content

References

1. https://chem.libretexts.org/Courses/Brevard_College/CHE_201%3A_Organic_Chemistry_I/04%3A_Aromatic_Compounds_(Arenes)/4.12%3A_Heterocyclic_Aromatic_Compounds
2. https://www.thermofisher.com/sg/en/home/chemicals/organic-chemistry/heterocyclic-compounds.html
3. https://uou.ac.in/lecturenotes/science/MSCCH-17/CHEMISTRY%20LN.%203%20HETEROCYCLIC%20COMPOUNDS-converted%20(1).pdf

Introduction

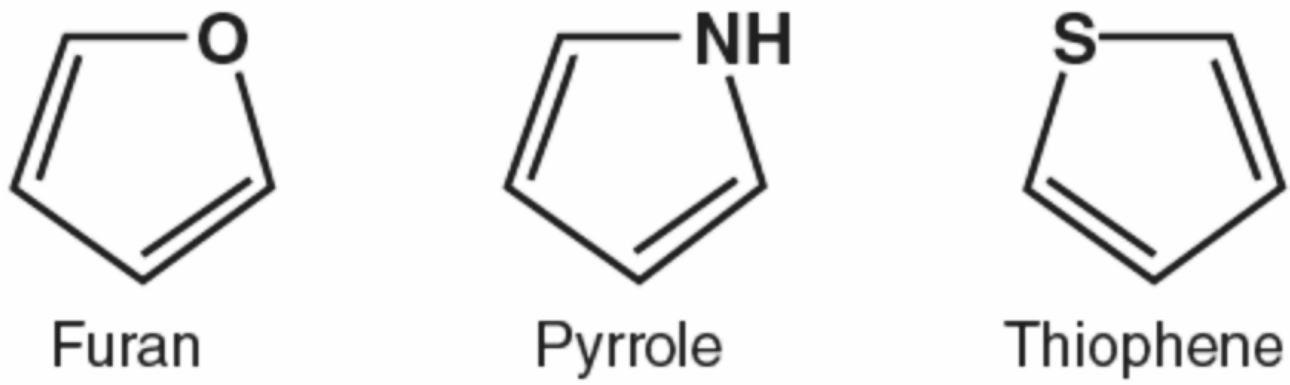
- Heterocyclic compounds, or heterocycles, are **cyclic compounds that have atoms of at least two different elements as members of the ring structure**.
- Organic heterocycles contain one or more carbon atoms and, based on their electronic structure, are classified as **saturated, unsaturated, and aromatic.**
- When the heteroatom (any atom in the molecule that is not a carbon or hydrogen) is a part of an aromatic ring, the compound is called an aromatic heterocycle.
- Aromatic heterocycles can be single-ring heterocycles (e.g., pyrrole, furan, thiophene, pyridine) or ***fused-ring heterocycles*** (e.g., indole, quinoline, and isoquinoline).



Some common examples of heterocycles containing common heteroatoms of O, N, and S

Nomenclature

- The nomenclature is divided into Trivial Method and Systematic Method of nomenclature (additional info)
    - Trivial Method (Does not provide information on structure)



Some common examples of heterocycles under the Trivial Method

    - Systematic Method (Provides information on structure)

S. No.	Heteroatom	Symbol	Prefix
1	Oxygen	O	Oxa
2	Sulphur	S	Thia
3	Selenium	Se	Selena
4	Nitrogen	N	Aza

Some common examples of prefixes of atoms in aromatic heterocyclic compounds

General Structure

Huckel's Rule:
A cyclic, planar, fully conjugated molecule is aromatic if it contains $4n+2$ π-electrons, where n is a non-negative integer (n = 0,1,2,…)

Reactions

Electrophilic Aromatic Substitution

Overall Reaction:

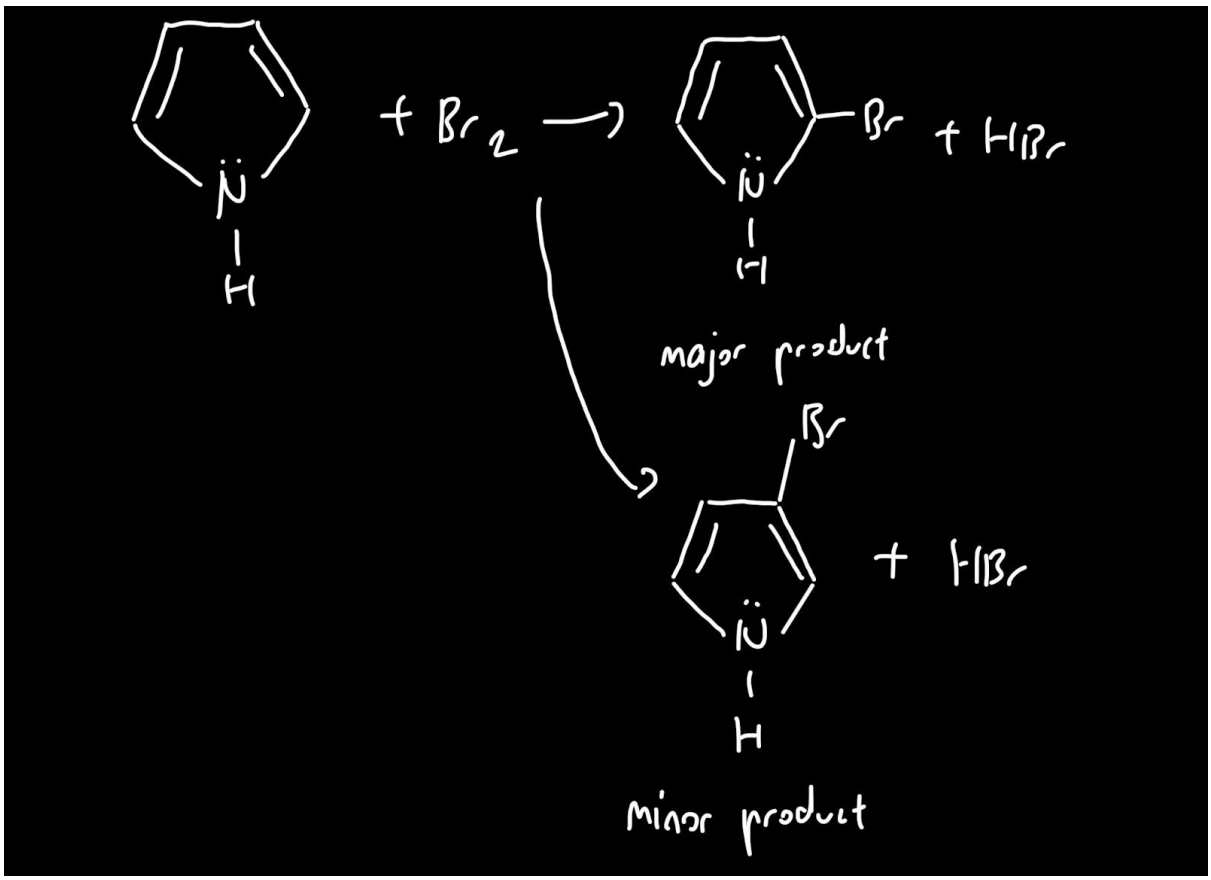


Fig.1

Alike the electrophilic substitution of benzene, a hydrogen atom on the ring is substituted for another substituent on it. The example shows the bromination of pyrrole, with Br+ being generated as the electrophile. As aromatic heterocyclic compounds are far more nucleophilic than benzene, this reaction does not require a Lewis Acid catalyst. Aromatic heterocyclic compounds are, in general, **more nucleophilic than benzene**, as their **carbocation intermediates can stabilise the positive charge to a greater extent than a benzene ring**. The positive charge can be ‘moved’, via resonance, to the electronegative atom (see fig. 4). Carbon atoms bearing positive charges are electron-deficient and will not obey the octet rule, making it unstable.

Relative rates of electrophilic substitution in heterocyclics

In decreasing reactivity of electrophilic aromatic substitution:

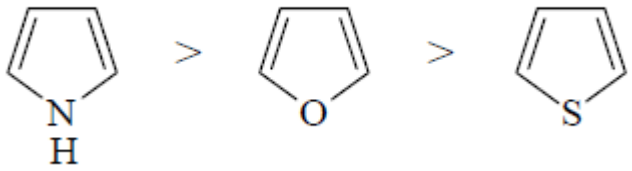


Fig. 3

Pyrrole is more nucleophilic than Furan as nitrogen is less electronegative than oxygen, making the ring more nucleophilic. Electronegative atoms can withdraw electron density from the ring via an inductive effect.

Furan is more nucleophilic than thiophene as the sulfur atom is relatively big compared to a carbon atom (3p in S vs 2p in C). Hence, the extent of effective orbital overlap between the 3p orbitals of sulfur and the 2p orbitals of carbon is low. Hence, thiophene is less nucleophilic than furan. This is despite sulfur being less electronegative than oxygen.

Why is the product at the 2’ position the major product, while the product at the 3’ position is the minor product?

It all ties back to the stability of the carbocation. The carbocation intermediate for the 2’ substituted product can have greater resonance stabilisation than that of the 3’ substituted product due to the presence of more resonance structures. The positive charge for the carbocation intermediate for the 2’ product is able to have its positive charge be dispersed over a greater number of carbon atoms. This stabilises the carbocation intermediate for the 2’ substituted product to a larger extent than that of the 3’ substituted product.

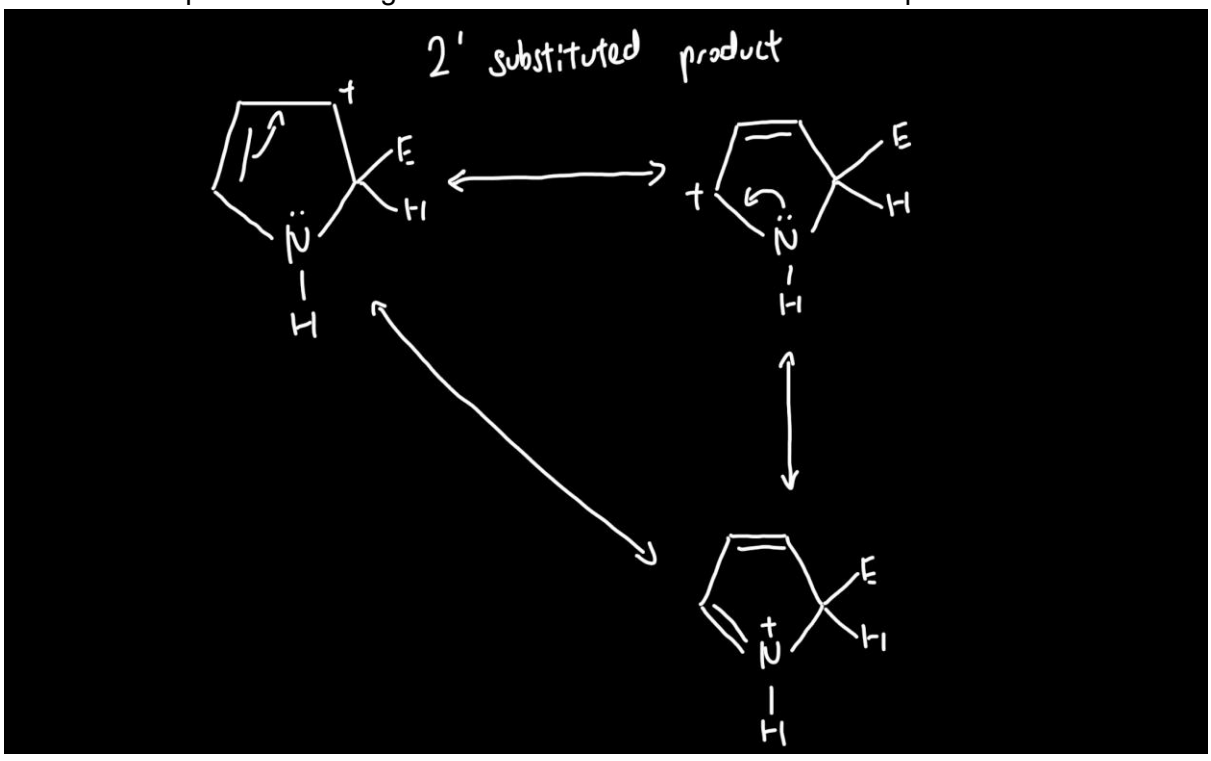


Fig. 4 The resonance structures of the intermediate that gives the 2’ substituted product

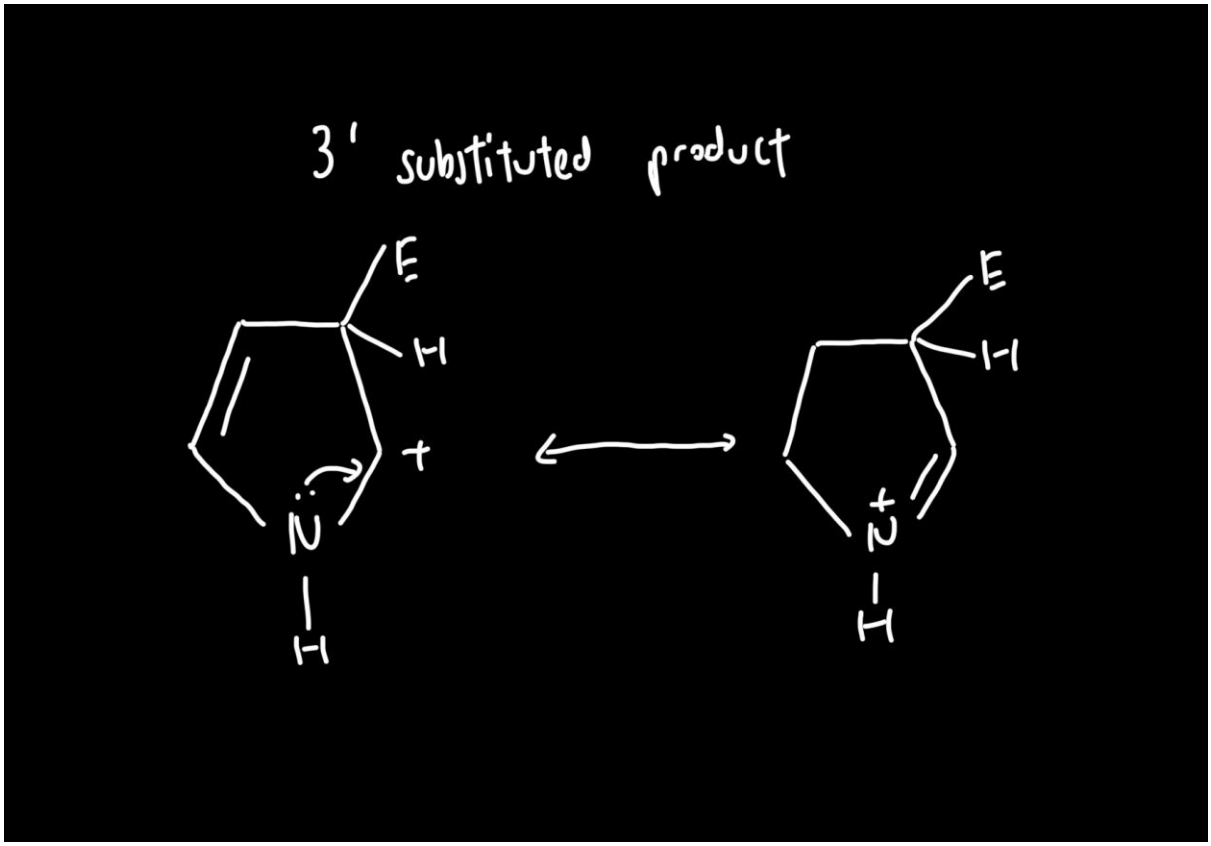


Fig. 5 The resonance structures of the intermediate that gives the 2' substituted product

The mechanism that forms the major product

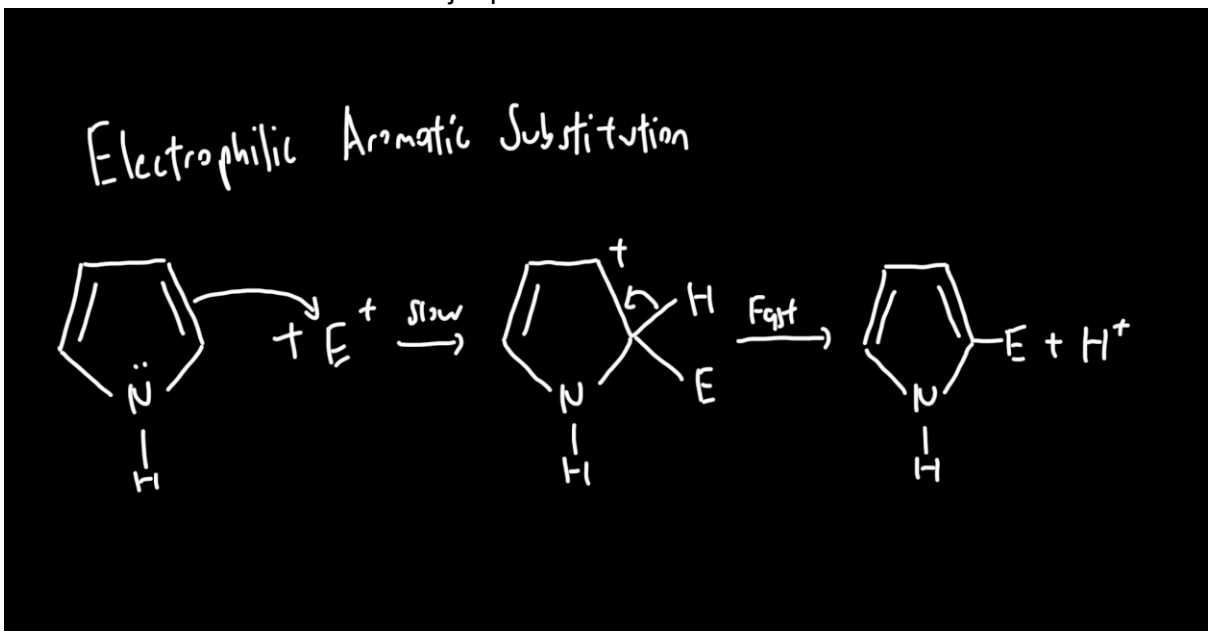


Fig. 6

Aromatic heterocyclic compounds are far more nucleophilic than the benzene ring, so they do not require a Lewis Acid catalyst (AlX3 or FeX3) when they undergo electrophilic substitution. Furthermore, the highly electronegative atom on the ring would coordinate strongly with the Lewis Acid catalyst, which will result in no reaction occurring.

Relative reactivities of some aromatic heterocyclic compounds

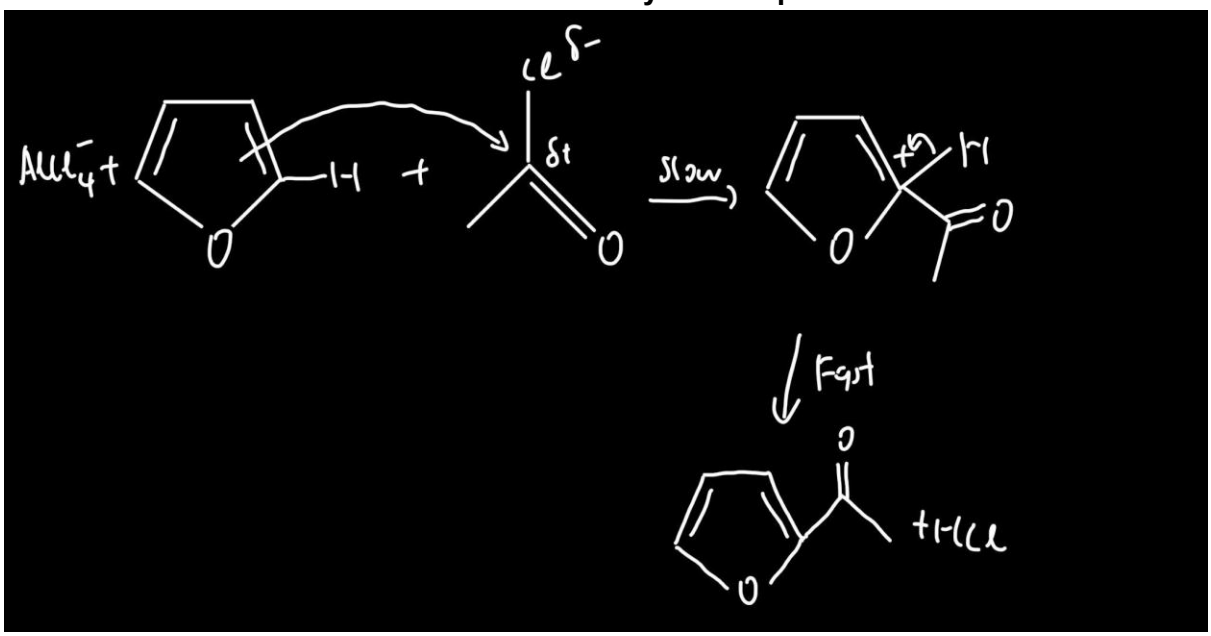


Fig 7

Nucleophilic aromatic substitution, using pyridine as an example

Why does substitution at the 2' or 4' position of pyridine give the major product instead of the 3' position?

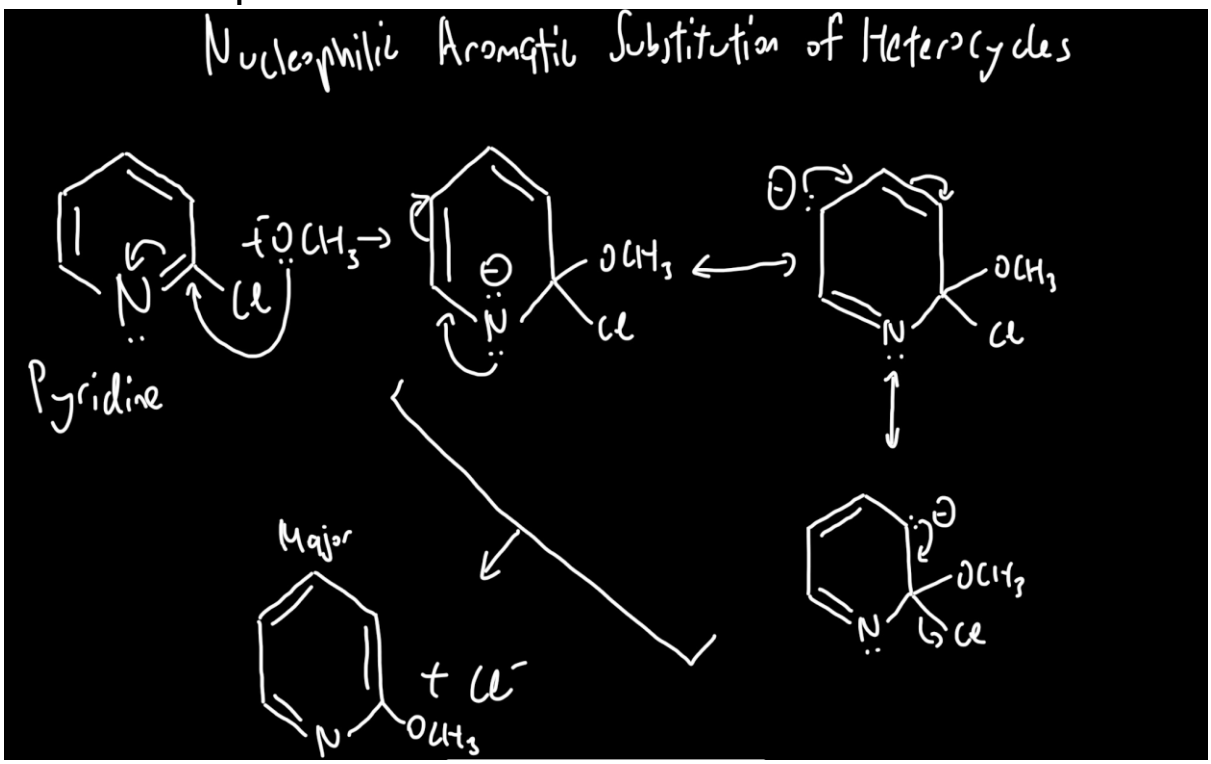


Figure 8: The formation of the major 2' substituted product of pyridine

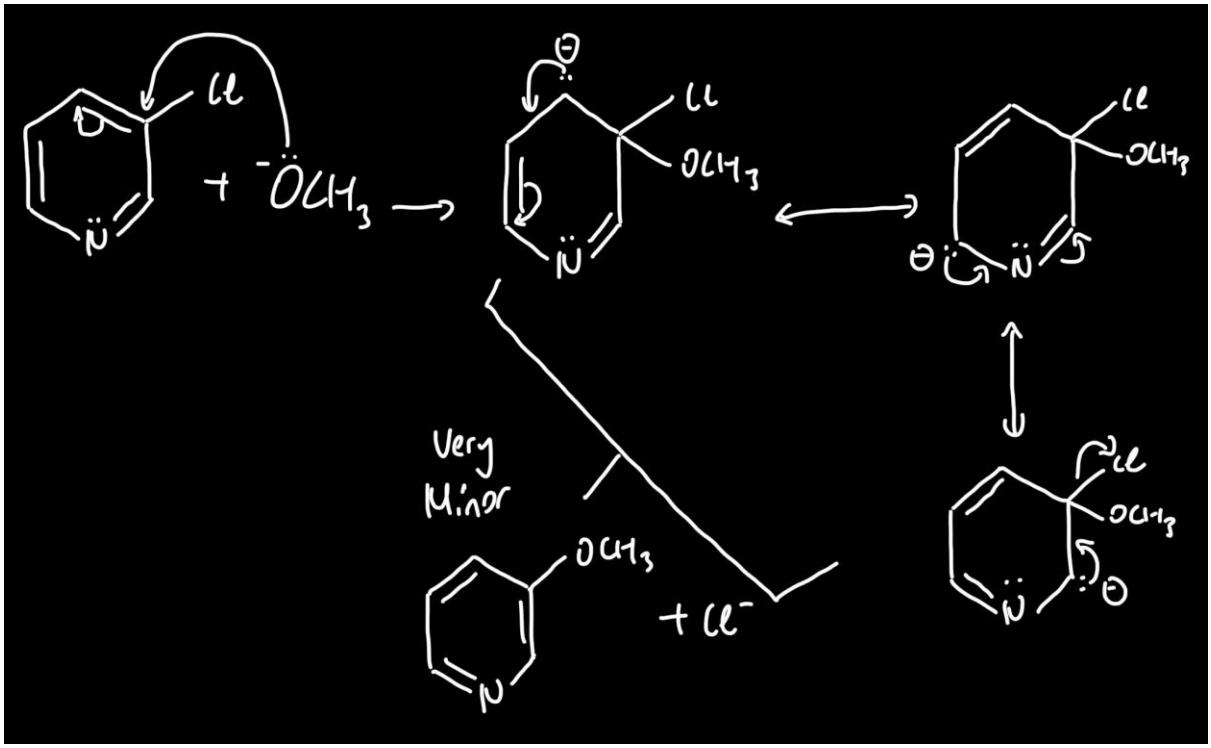


Figure 9: The formation of the very minor 3' substituted product of pyridine

Comparing both figures, the 2’ substituted and also the 4’ substituted product are highly favoured, as one of the resonance structures for the NAS reaction which produces the 2’ substituted product, involves the nitrogen atom bearing a negative charge and following the octet rule. As nitrogen is a highly electronegative atom, this makes the resonance structure highly stable. Conversely, as there is no resonance structure for the production of the 3’ product where nitrogen fulfils the octet rule and has a negative charge, it means that the production of the 2’ substituted product is highly favoured over the 3’ substituted product.

Acid-Base Reaction

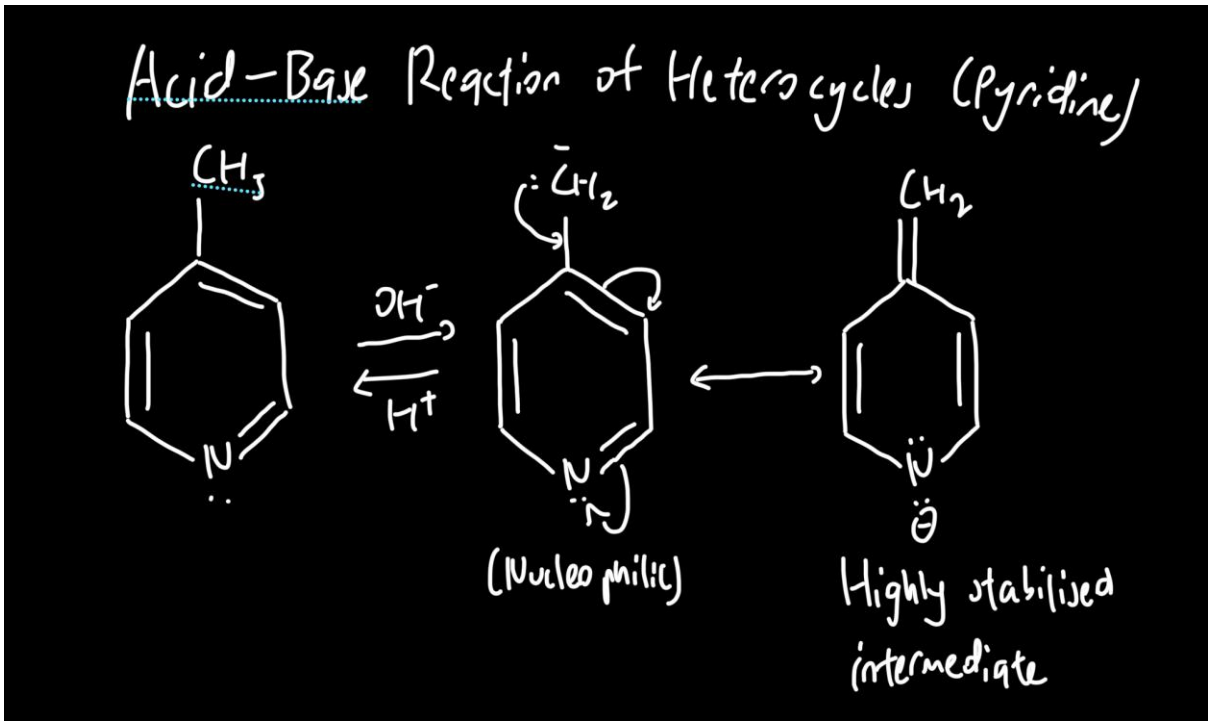


Figure 10: The acid-base reaction of pyridine

The -CH3 side chain of pyridine undergoes an acid-base reaction with OH-, deprotonating it and forming a very stable conjugate base. This generates a nucleophile, which is then used to undergo nucleophilic substitution with alkyl halides. This reaction is seen in figure 11 below.

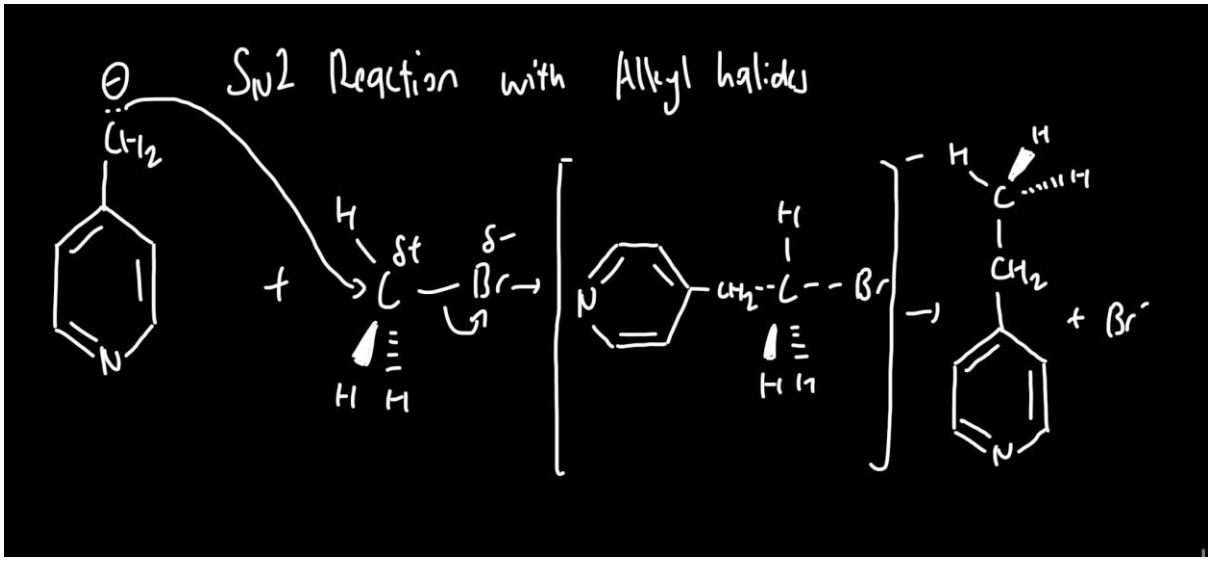


Figure 11: The SN2 Reaction of the conjugate base of pyridine with an alkyl bromide