

**B.Sc. Semester-IV
Core Course-IX (CC-IX)
Organic Chemistry-III**



III. Heterocyclic Compounds

22. Furan, Pyrrole and Thiophene : Electrophilic Substitution Reaction



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Heterocyclic Compounds

22 Lectures

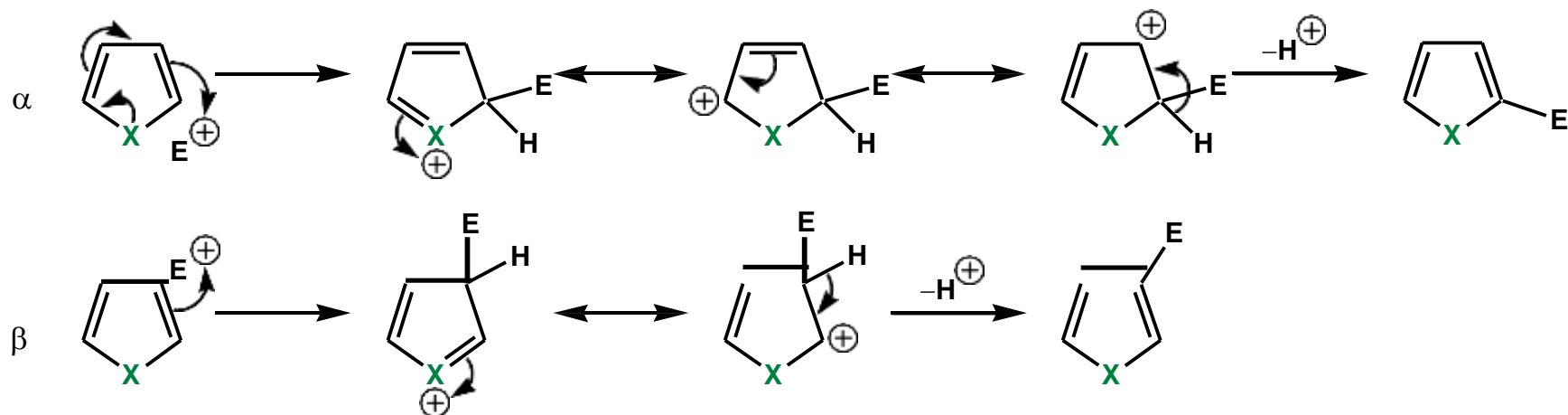
Classification and nomenclature, Structure, aromaticity in 5-numbered and 6-membered rings containing one heteroatom; Synthesis, reactions and mechanism of substitution reactions of: Furan, Pyrrole (Paal-Knorr synthesis, Knorr pyrrole synthesis, Hantzsch synthesis), Thiophene, Pyridine (Hantzsch synthesis), Pyrimidine, Structure elucidation of indole, Fischer indole synthesis and Madelung synthesis), Structure elucidation of quinoline and isoquinoline, Skraup synthesis, Friedlander's synthesis, Knorr quinoline synthesis, Doebner- Miller synthesis, Bischler-Napieralski reaction, Pictet-Spengler reaction, Pomeranz-Fritsch reaction
Derivatives of furan: Furfural and furoic acid.

Coverage:

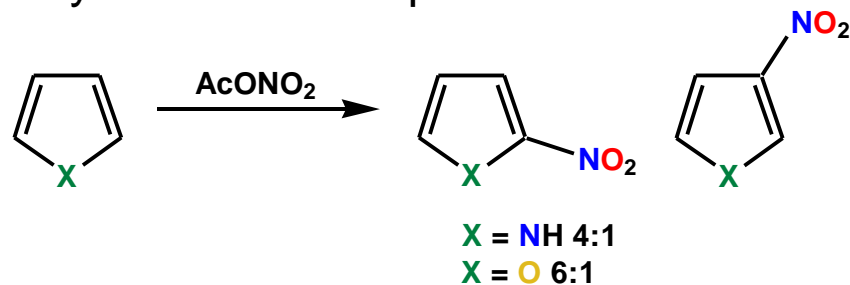
1. Furan, Pyrrole and Thiophene : Electrophilic Substitution Reactions
2. Metallation Reaction / Deprotonation Reaction

Furans, Pyrroles and Thiophenes – Electrophilic Substitution

Electrophilic Substitution – Regioselectivity

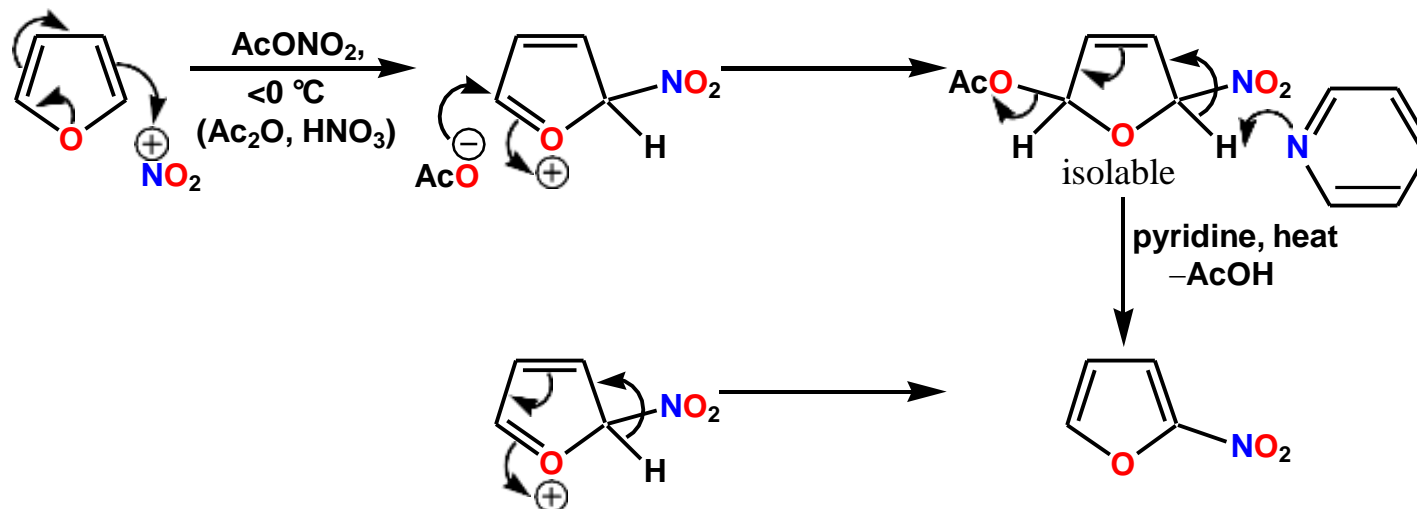


- Pyrrole > furan > thiophene > benzene
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions
- α -Substitution favoured over β -substitution more resonance forms for intermediate and so the charge is less localised (also applies to the transition state)
- Some β -substitution usually observed – depends on X and substituents



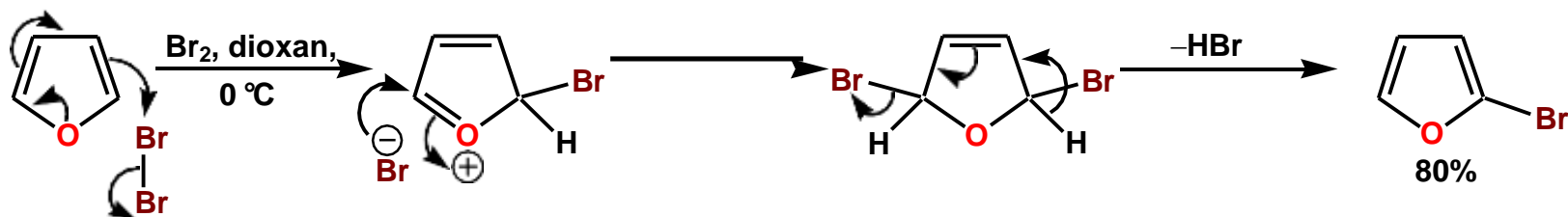
Furans – Electrophilic Substitution

Nitration of Furans



- Nitration can occur by an addition-elimination process
- When NO_2BF_4 is used as a nitrating agent, the reaction follows usual mechanism

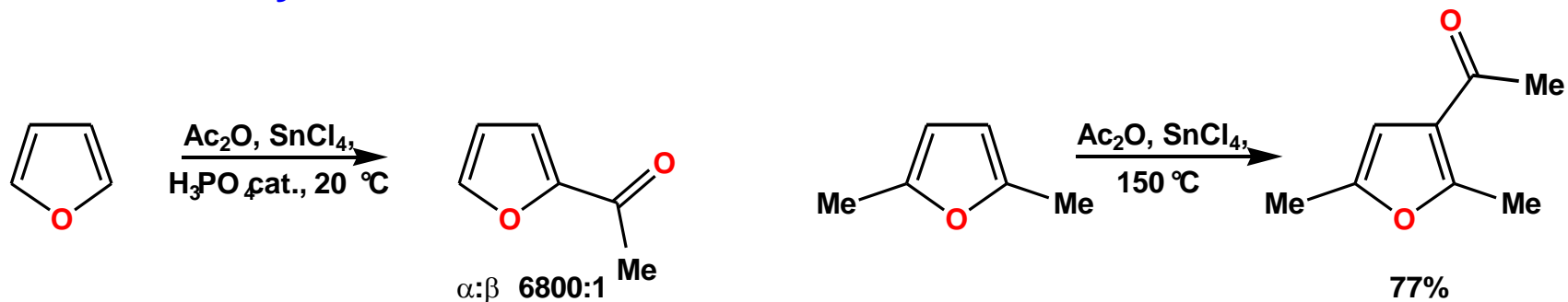
Bromination of Furans



- Furan reacts vigorously with Br_2 or Cl_2 at room temp. to give polyhalogenated products
- It is possible to obtain 2-bromofuran by careful control of temperature

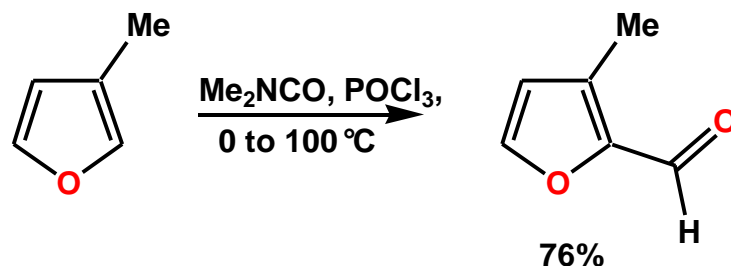
Furans – Electrophilic Substitution

Friedel-Crafts Acylation of Furan

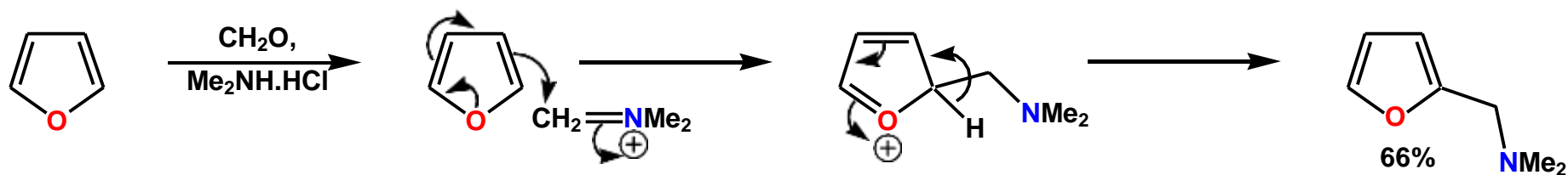


- Blocking groups at the α positions and high temperatures required to give β acylation

Vilsmeier Formylation of Furan

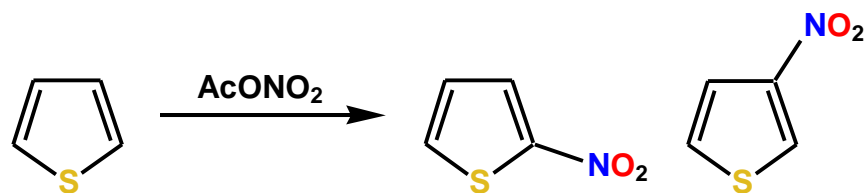


Mannich Reaction of Furans



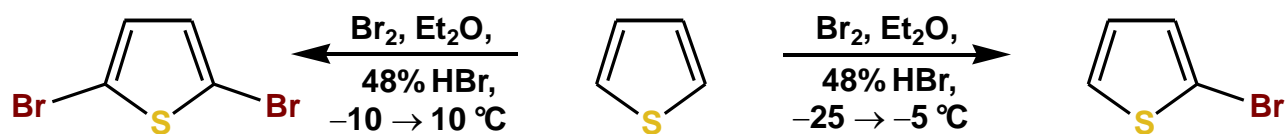
Thiophenes – Electrophilic Substitution

Nitration of Thiophenes



- Reagent AcONO₂ generated *in situ* from c-HNO₃ and Ac₂O

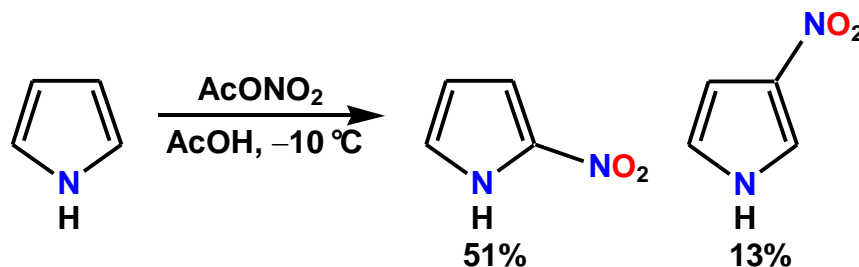
Halogenation of Thiophenes



- Occurs readily at room temperature and even at -30 °C
- Careful control of reaction conditions is required to ensure mono-bromination

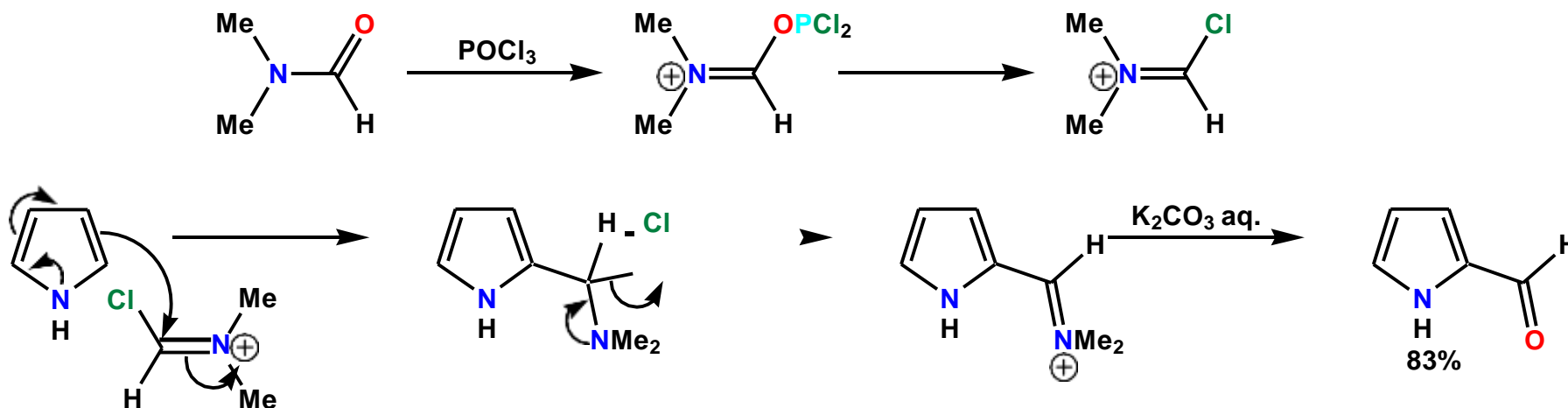
Pyrroles – Electrophilic Substitution

Nitration of Pyrroles

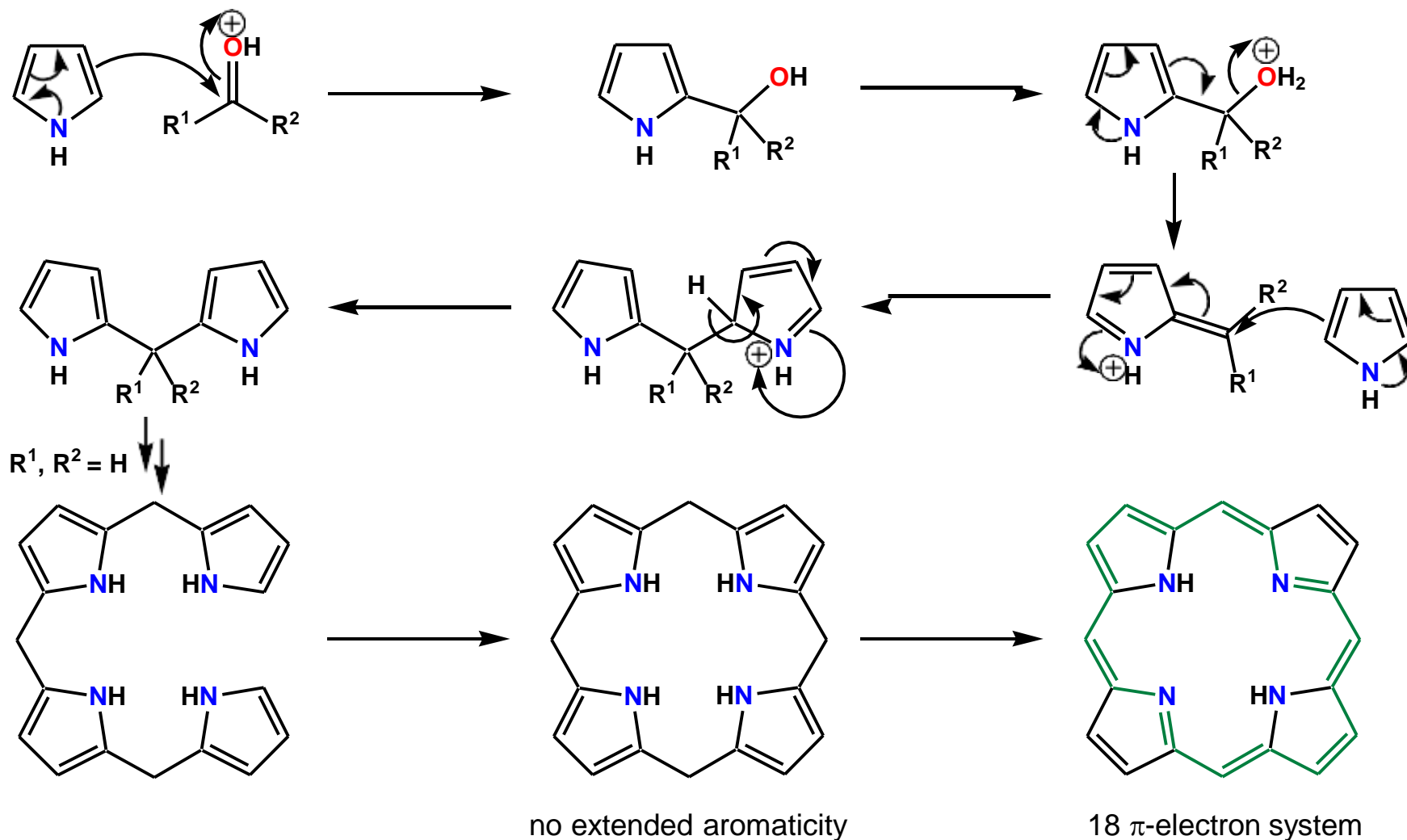


- Mild conditions are required (c-HNO₃ and c-H₂SO₄ gives decomposition)

Vilsmeier Formylation of Pyrroles



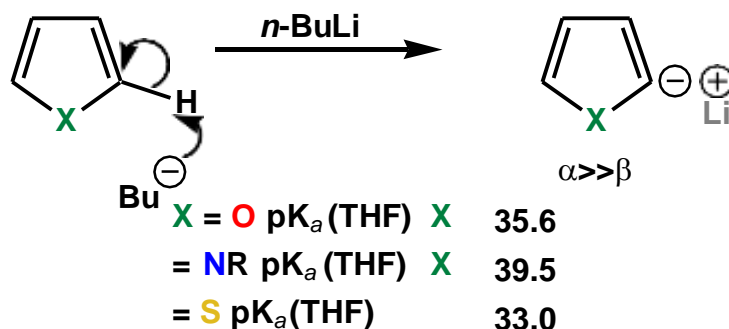
Pyrroles – Porphyrin Formation



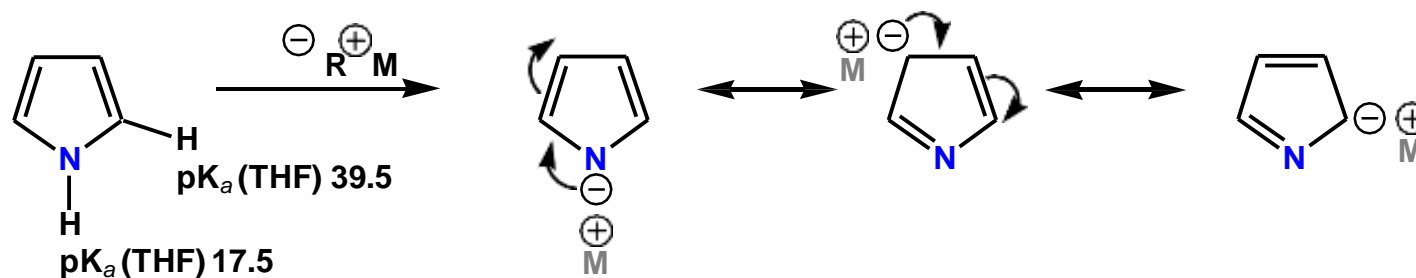
- The extended aromatic 18 π -electron system is more stable than that having four isolated aromatic pyrroles

Furans, Pyrroles Thiophenes – Deprotonation

Metallation



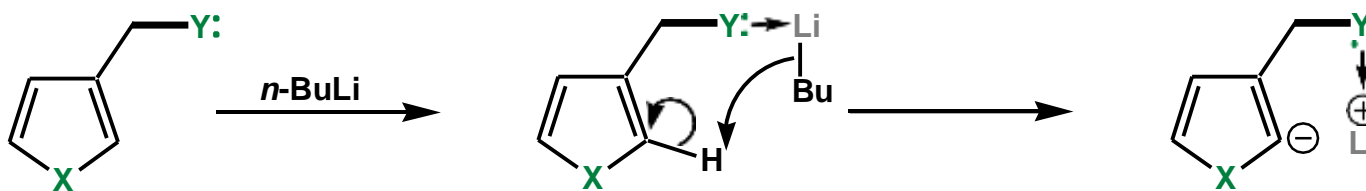
Deprotonation of Pyrroles



- Free pyrroles can undergo *N* or *C* deprotonation
- Large cations and polar solvents favour *N* substitution
- A temporary blocking group on *N* can be used to obtain the *C*-substituted compound

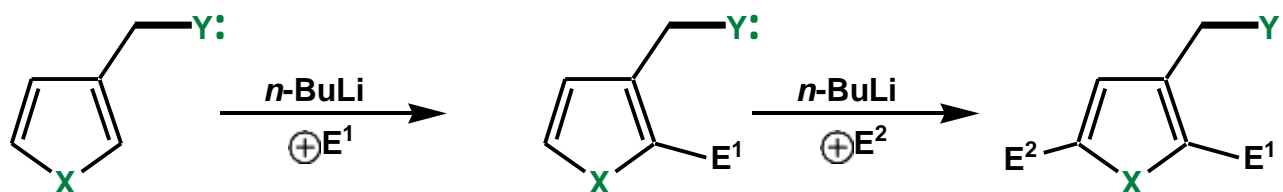
Furans, Pyrroles Thiophenes – Directed Metallation

Control of Regioselectivity in Deprotonation

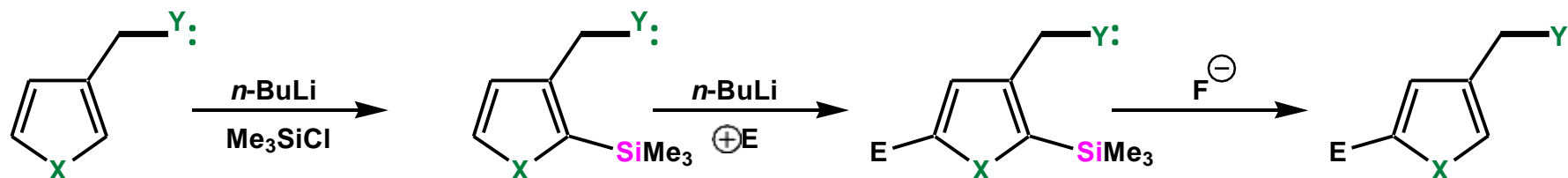


Common directing groups: $\text{CO}_2\text{H(Li)}$, CH_2OMe , CONR_2 , CH(OR)_2

Synthesis of α,α' -Disubstituted Systems

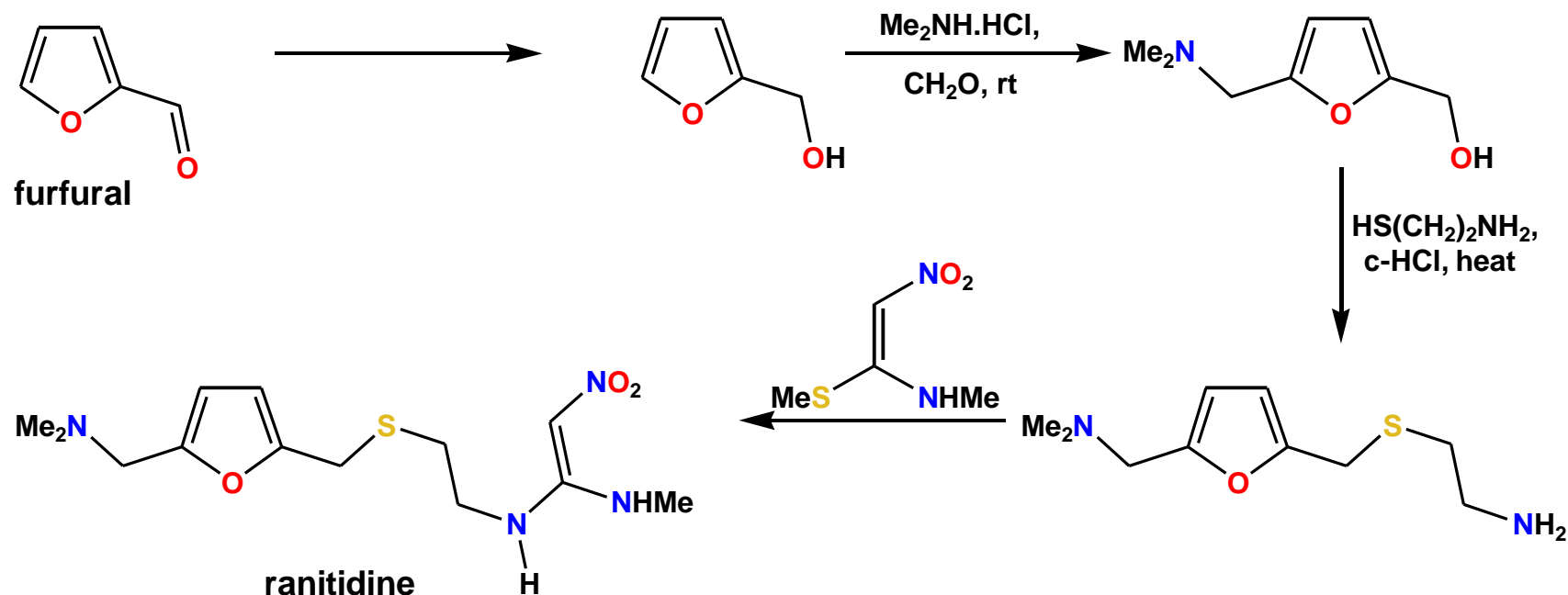


Use of a Trialkylsilyl Blocking Group



Furans – Synthesis of a Drug

Preparation of Ranitidine (Zantac®) Using a Mannich Reaction



- Furfural is produced very cheaply from waste vegetable matter and can be reduced to give the commercially available compound furfuryl alcohol
- The second chain is introduced using a **Mannich reaction** which allows selective substitution at the 5-position
- The final step involves conjugate addition of the amine to the α,β -unsaturated nitro compound and then elimination of methane thiol