

Furan, Pyrrole and Thiophene

(For Semester-V)

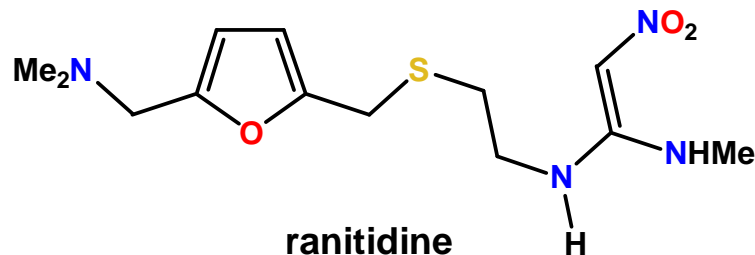
Dr. Biswajit Panda

Assistant Professor

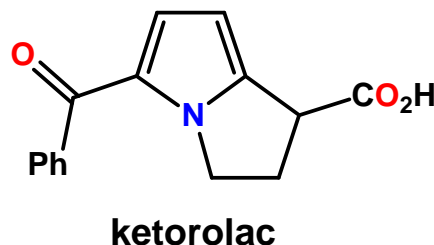
Department of Chemistry

City College, Kolkata-700009

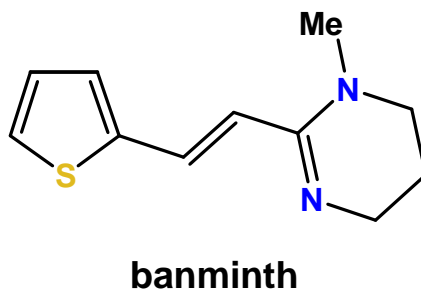
Bioactive Furans, Pyrroles and Thiophenes



- Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H₂-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers

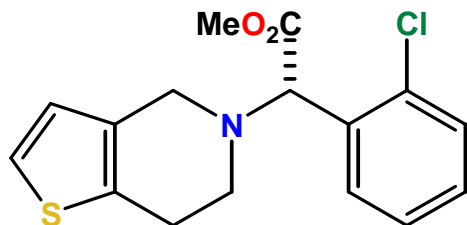


- Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug

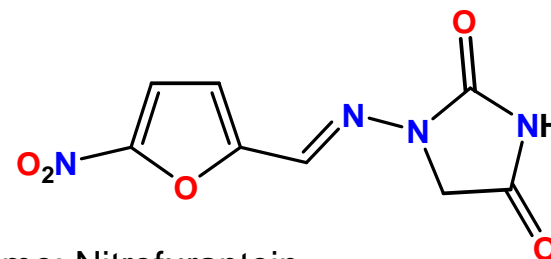


- Pyrantel (Banminth®, Phibro) is an anthelmintic agent and is used to treat worms in livestock

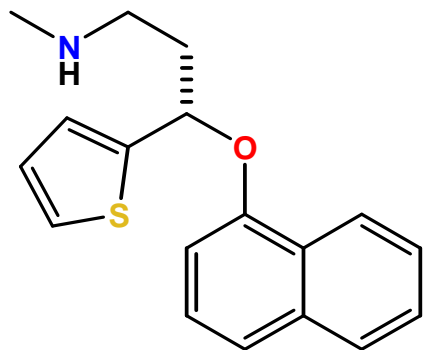
Drugs Containing a Furan/Thiophene/Pyrrole



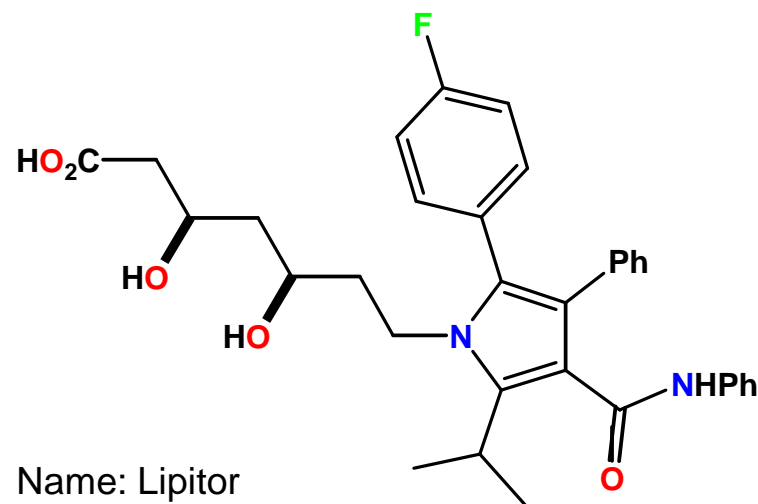
Name: Plavix
2008 Sales: \$3.80 billion
2008 Ranking: 3 branded
Company: Bristol-Myers Squibb
Disease: Stroke and heart attack risk



Name: Nitrofurantoin
2008 Sales: \$92 + 72 million
2008 Ranking: 119 and 149 generic
Company: N/A
Disease: Antibiotic for urinary tract infections



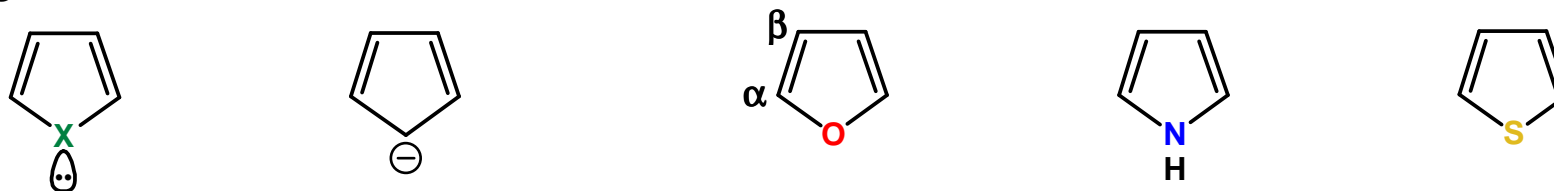
Name: Cymbalta
2008 Sales: \$2.17 billion
2008 Ranking: 14 branded
Company: Eli Lilly
Disease: Depression



Name: Lipitor
2008 Sales: \$5.88 billion
2008 Ranking: 1 branded
Company: Pfizer
Disease: Lowers LDL levels

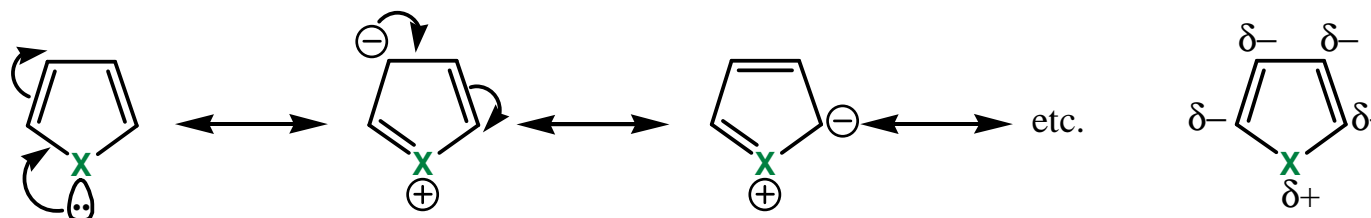
Furans, Pyrroles and Thiophenes – Structure

Structure

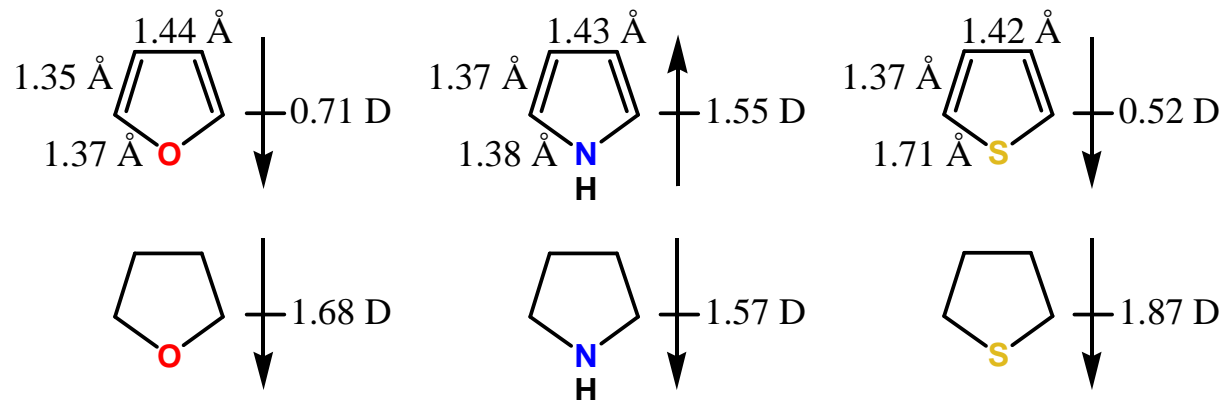


- 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures



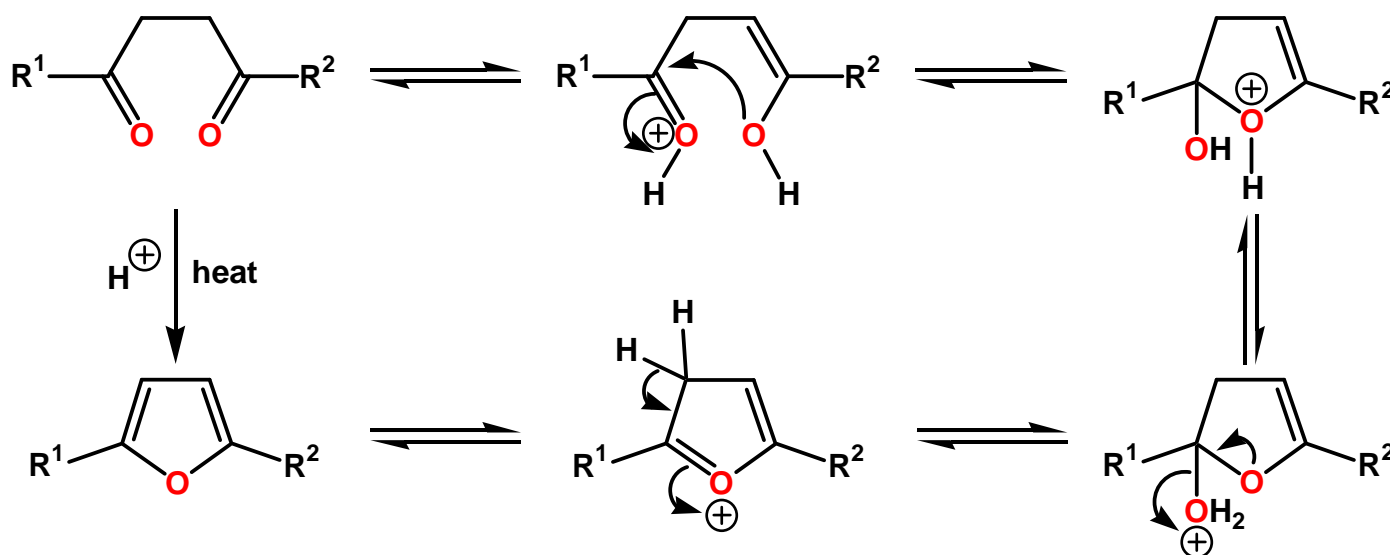
- Electron donation into the ring by resonance but inductive electron withdrawal



- O and S are more electronegative than N and so inductive effects dominate

Furans – Synthesis

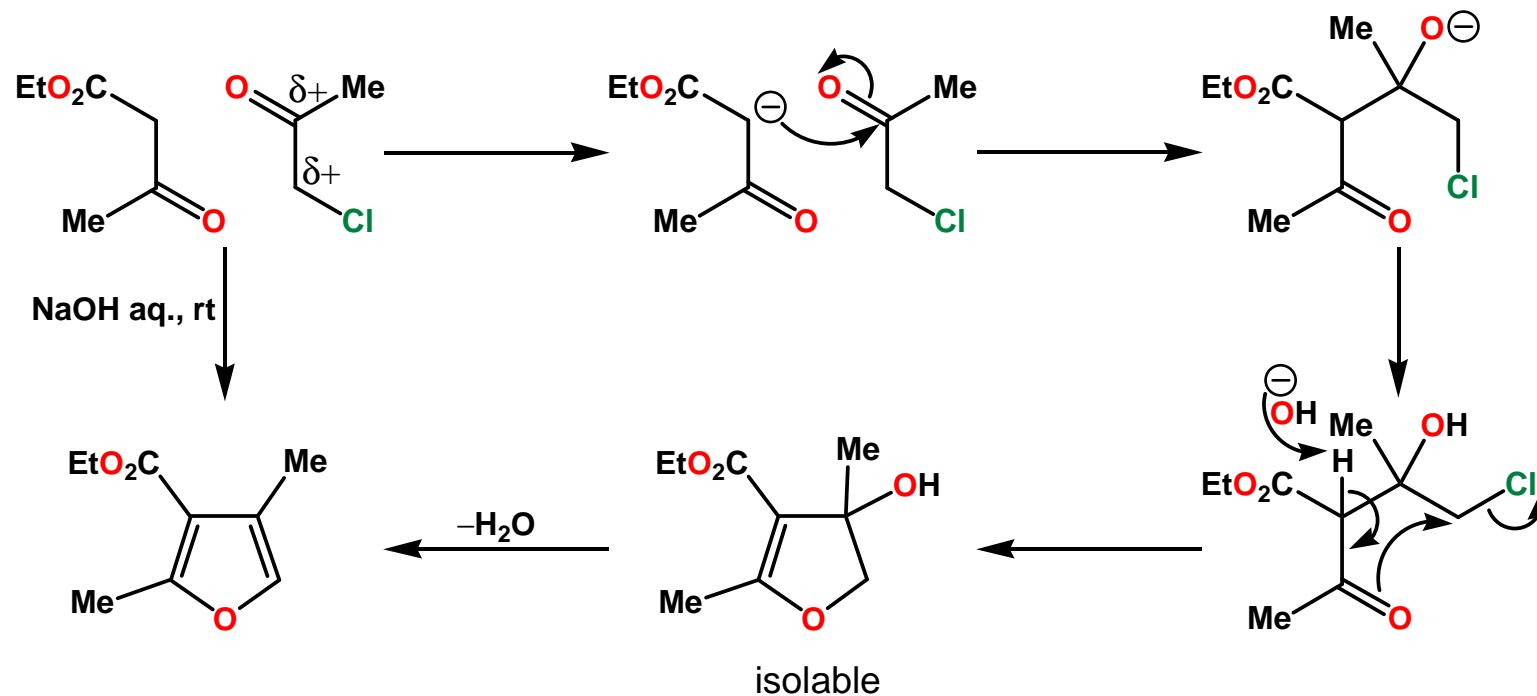
Paal Knorr Synthesis



- The reaction is usually reversible and can be used to convert furans into 1,4-diketones
- A trace of acid is required – usually TsOH (*p*-MeC₆H₄SO₃H)

Furans – Synthesis

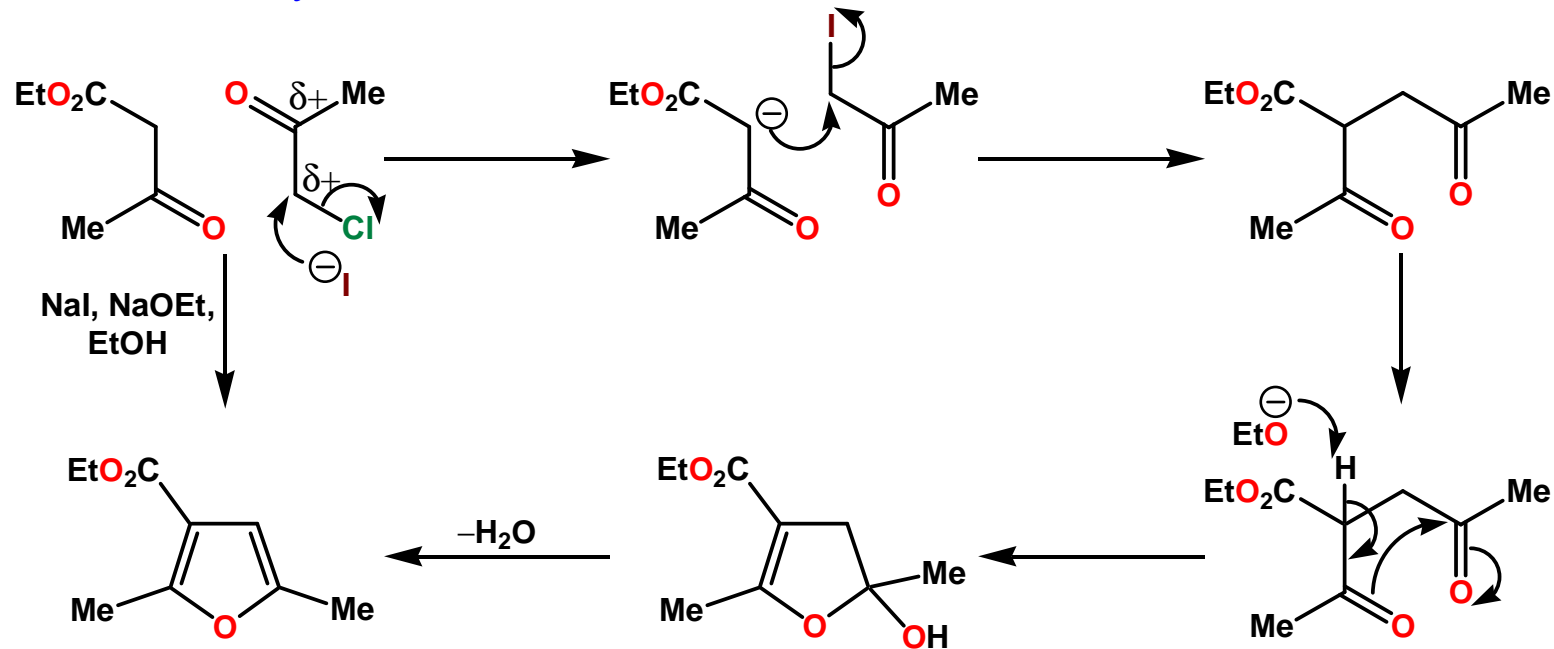
Feist-Benary Synthesis (“3+2”)



- The product prior to dehydration can be isolated under certain circumstances
- Reaction can be tuned by changing the reaction conditions

Furans – Synthesis

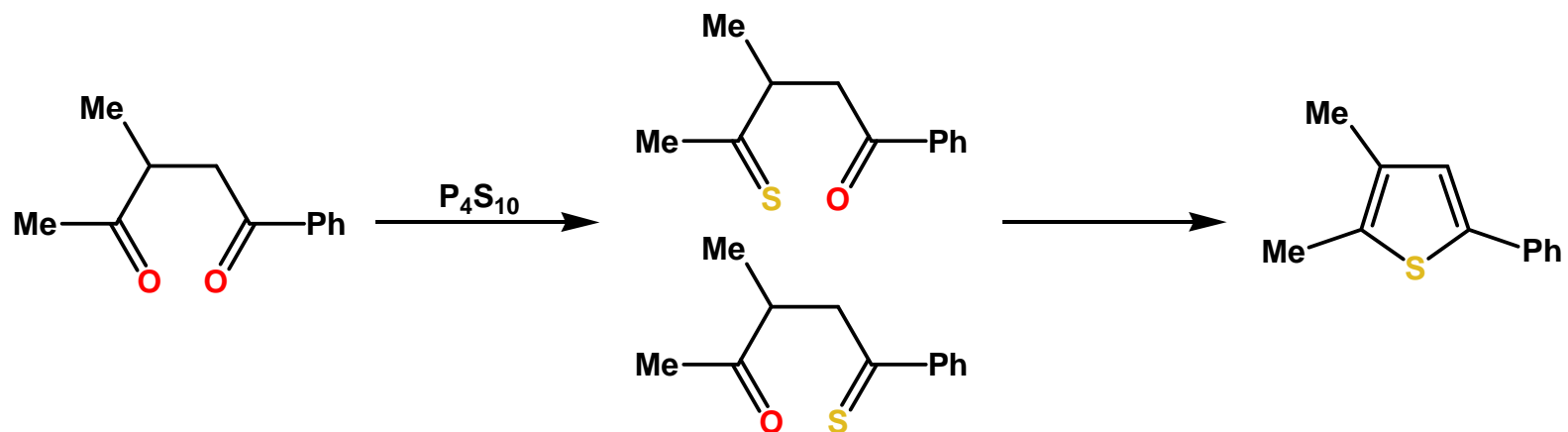
Modified Feist-Benary



- Iodide is a better leaving group than Cl and the carbon becomes more electrophilic
- The [Paal Knorr](#) sequence is followed from the 1,4-diketone onwards
- The regiochemical outcome of the reaction is completely altered by addition of iodide

Thiophenes – Synthesis

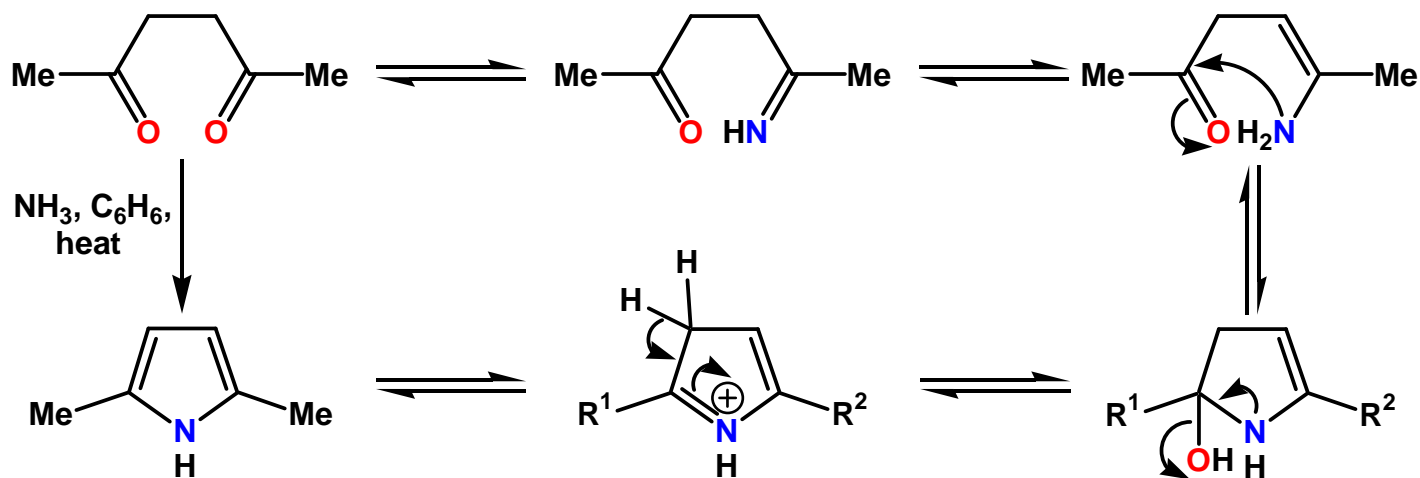
Synthesis of Thiophenes by **Paal Knorr** type reaction (“4+1”)



- Reaction might occur *via* the 1,4-*bis*-thioketone

Pyrroles – Synthesis

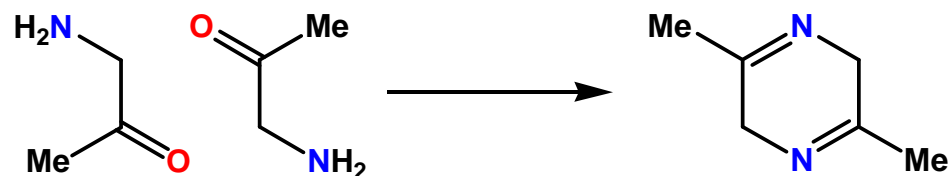
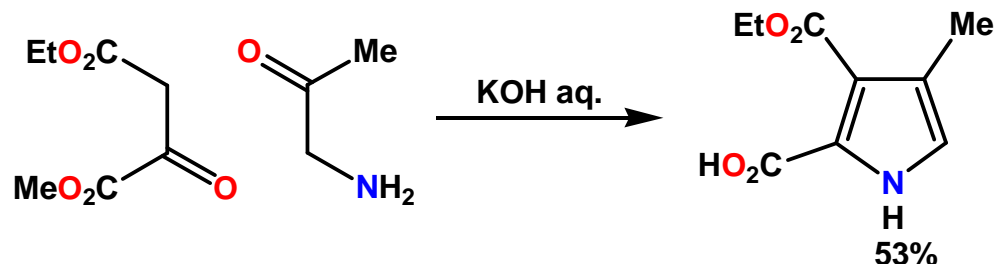
Paal Knorr Synthesis (“4+1”)



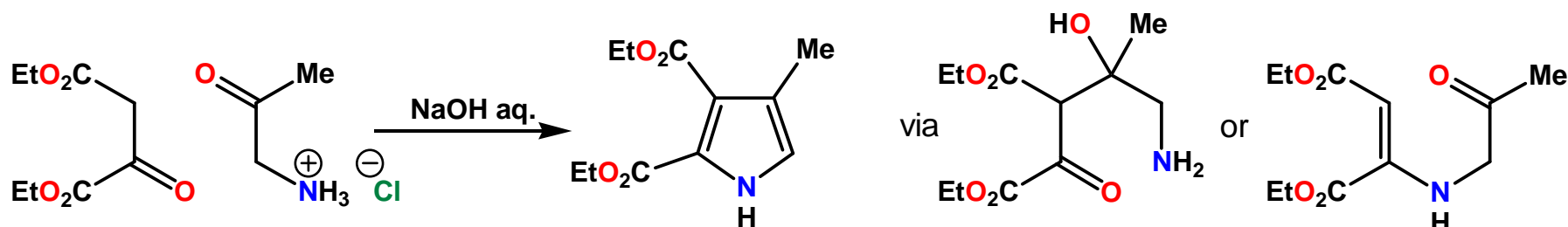
- Ammonia or a primary amine can be used to give the pyrrole or *N*-alkyl pyrrole

Pyrroles – Synthesis

Knorr Pyrrole Synthesis (“3+2”)



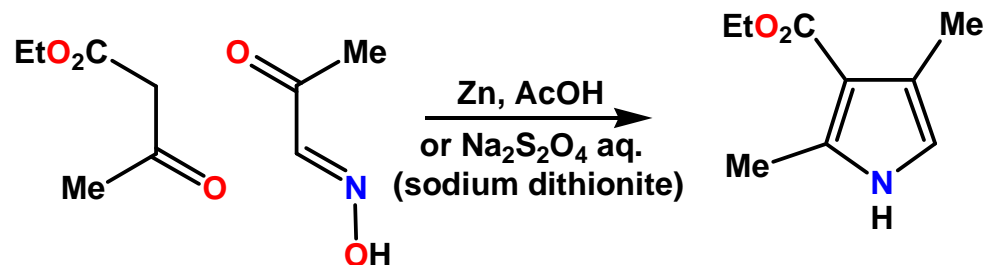
- Use of a free amino ketone is problematic – dimerisation gives a dihydropyrazine



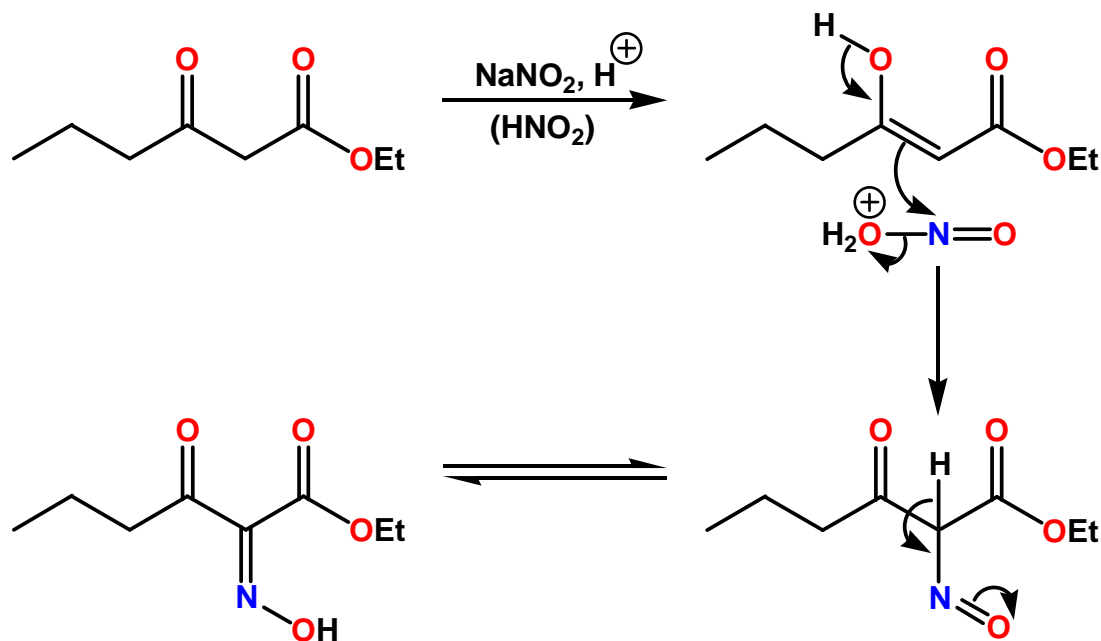
- Problem can be overcome by storing amino carbonyl compound in a protected form
- Reactive methylene partner required so that pyrrole formation occurs more rapidly than dimer formation

Pyrroles – Synthesis

Liberation of an Amino Ketone *in situ* by Oxime Reduction

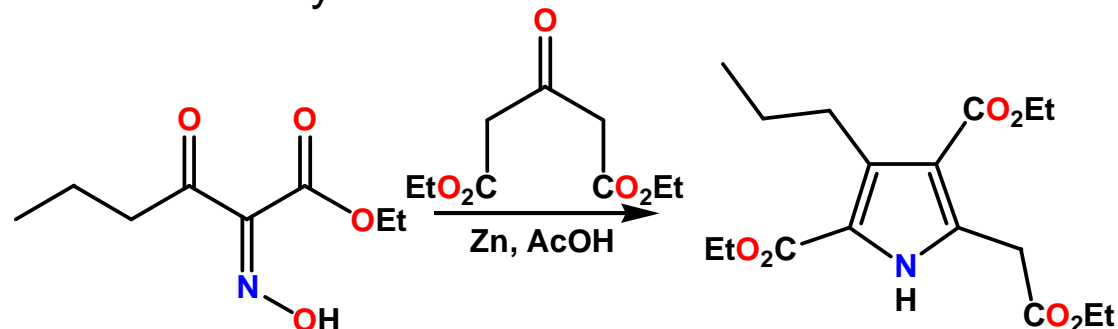


Preparation of α -Keto Oximes from β -Dicarbonyl Compounds

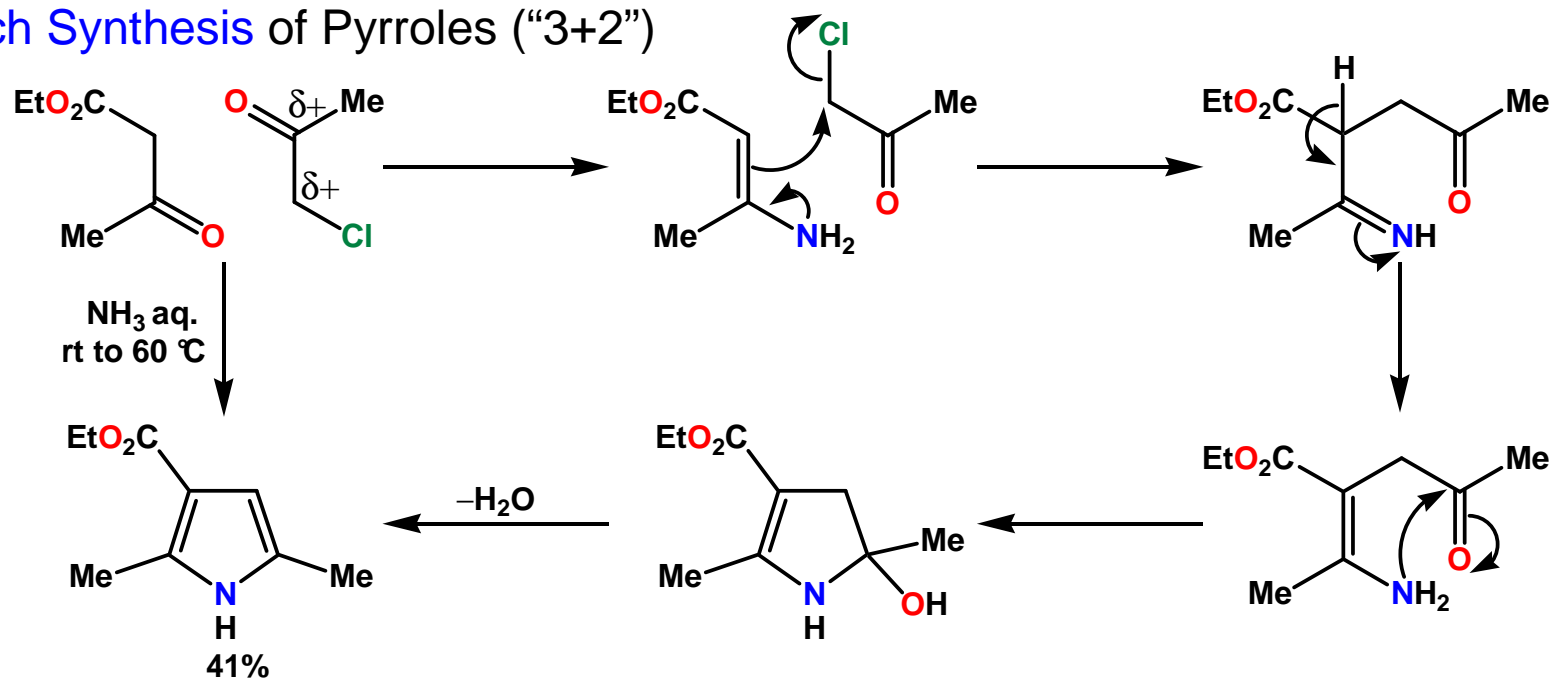


Pyrroles – Synthesis

One-Pot Oxime Reduction and Pyrrole Formation



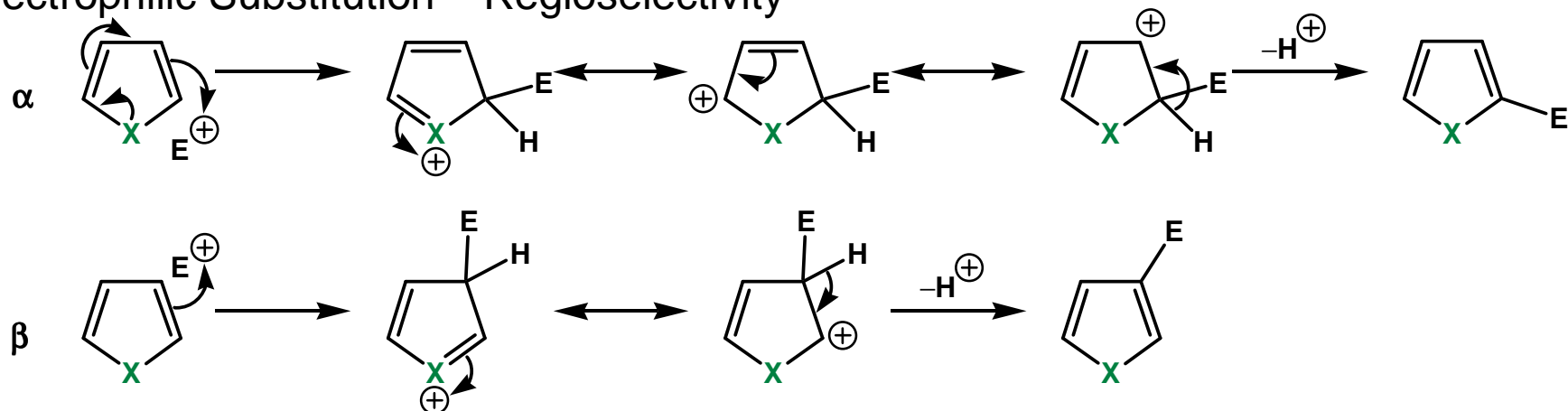
Hantzsch Synthesis of Pyrroles (“3+2”)



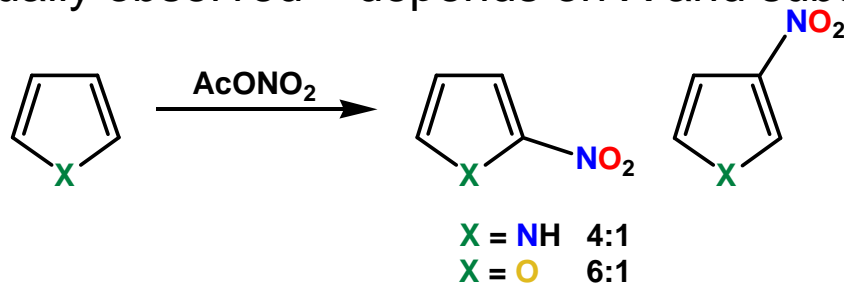
- A modified version of the [Feist-Benary](#) synthesis and using the same starting materials: an α -halo carbonyl compound and a β -keto ester

Furans, Pyrroles Thiophenes – Electrophilic Substitution

Electrophilic Substitution – Regioselectivity

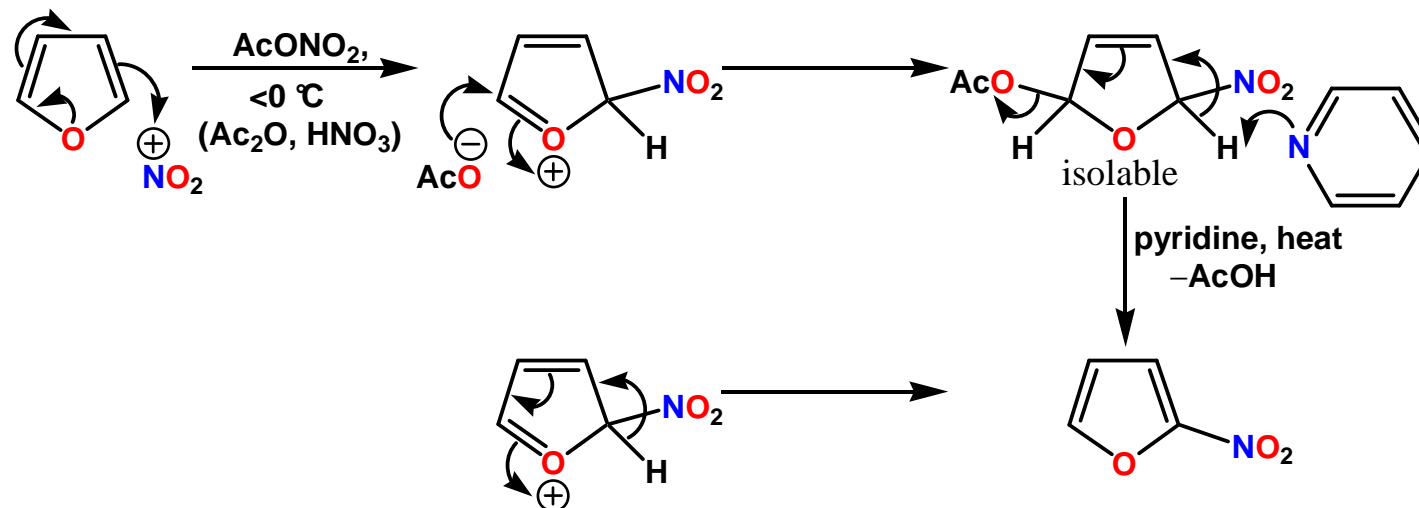


- Pyrrole > furan > thiophene > benzene
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions
- α -Substitution favoured over β -substitution more resonance forms for intermediate and so the charge is less localised (also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



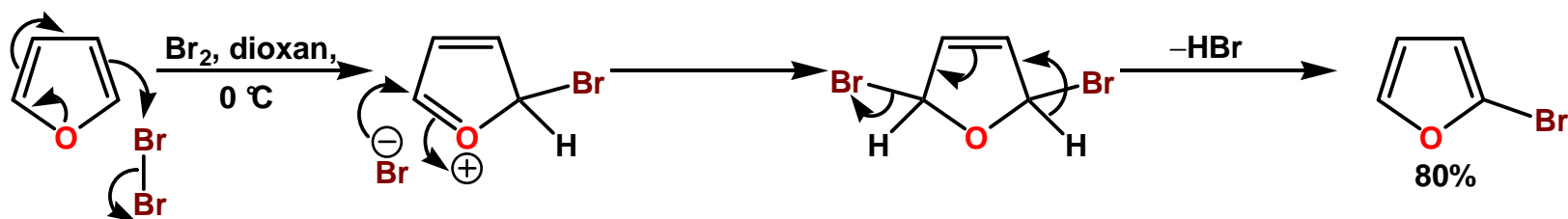
Furans – Electrophilic Substitution

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

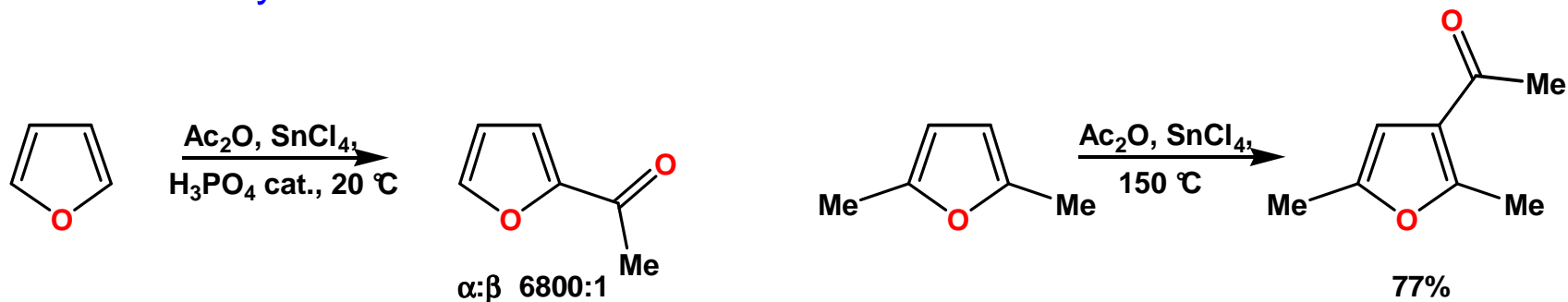
Bromination of Furans



- 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

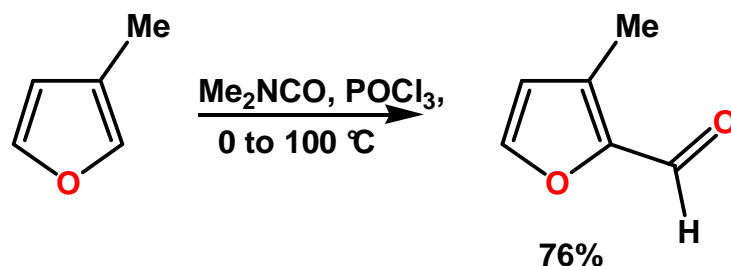
Furans – Electrophilic Substitution

Friedel-Crafts Acylation of Furan

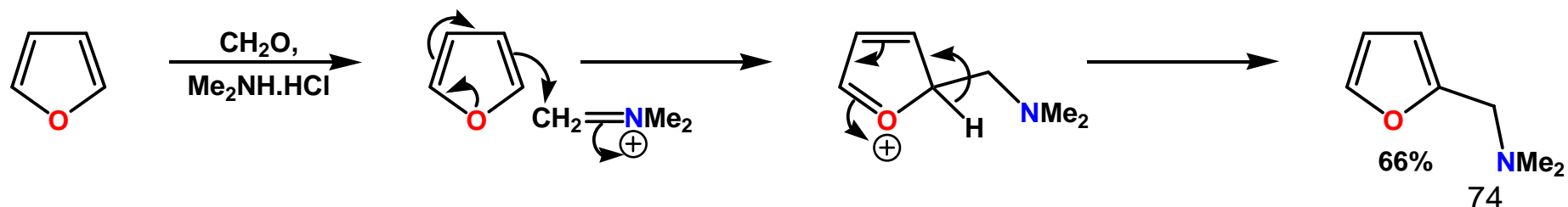


- Blocking groups at the α positions and high temperatures required to give β acylation

Vilsmeier Formylation of Furan

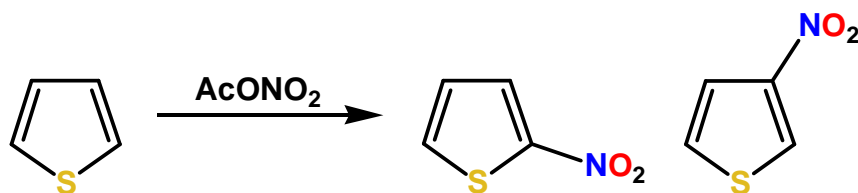


Mannich Reaction of Furans



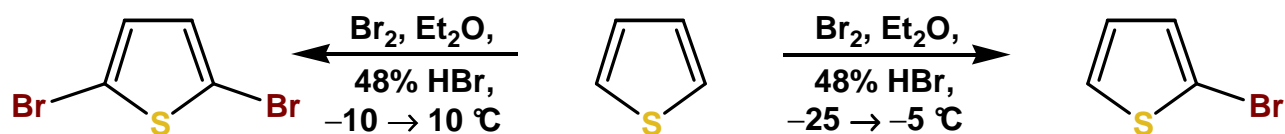
Thiophenes – Electrophilic Substitution

Nitration of Thiophenes



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

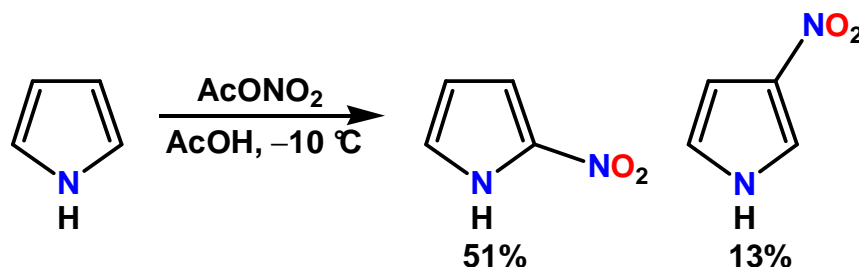
Halogenation of Thiophenes



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

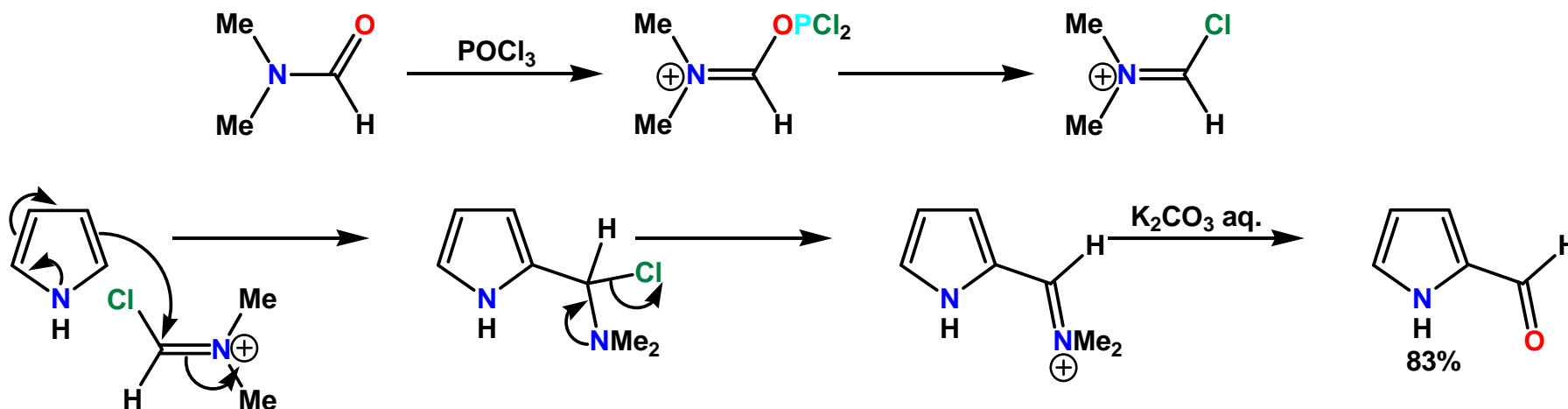
Pyrroles – Electrophilic Substitution

Nitration of Pyrroles

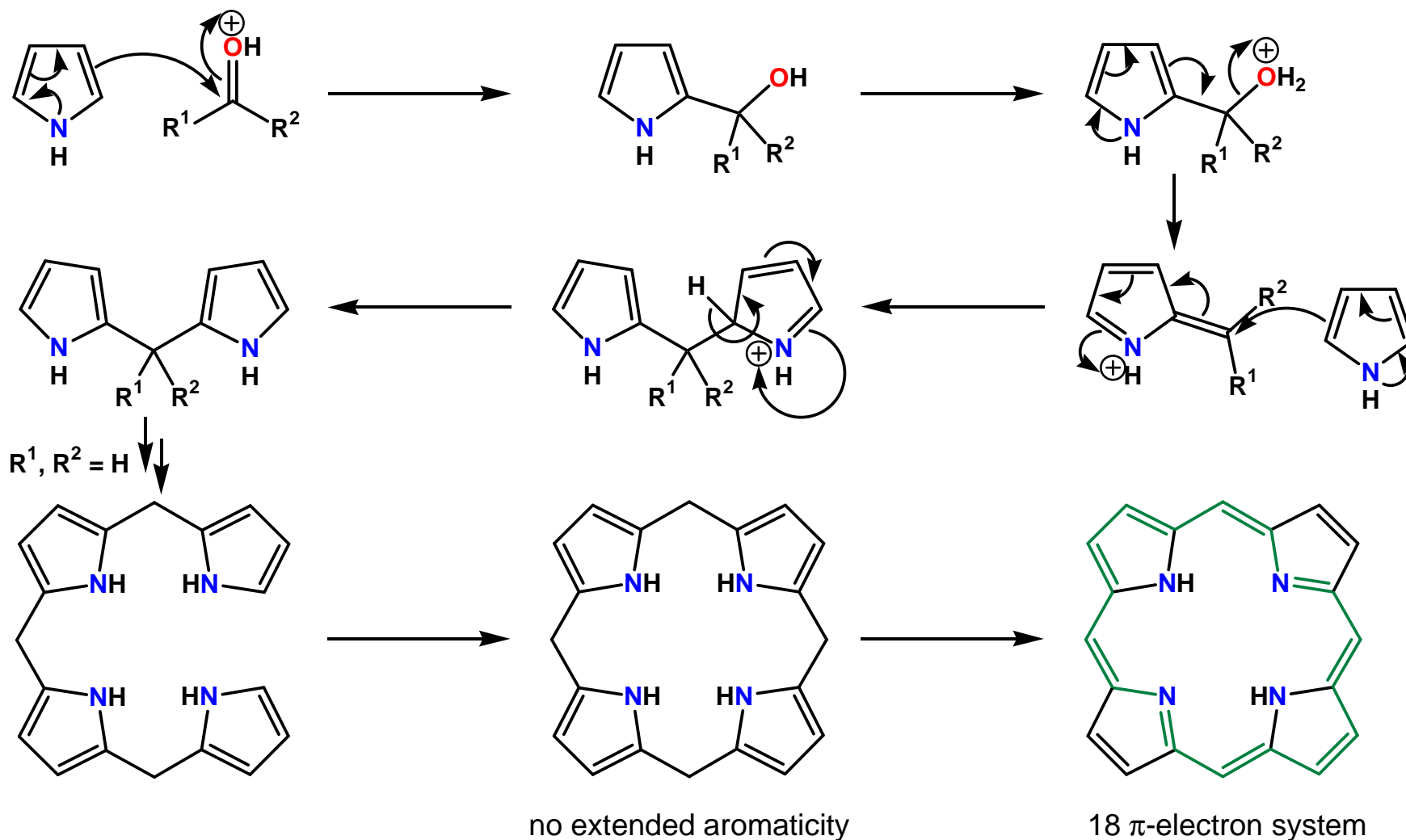


- Mild conditions are required (c-HNO_3 and $\text{c-H}_2\text{SO}_4$ gives decomposition)

Vilsmeier Formylation of Pyrroles

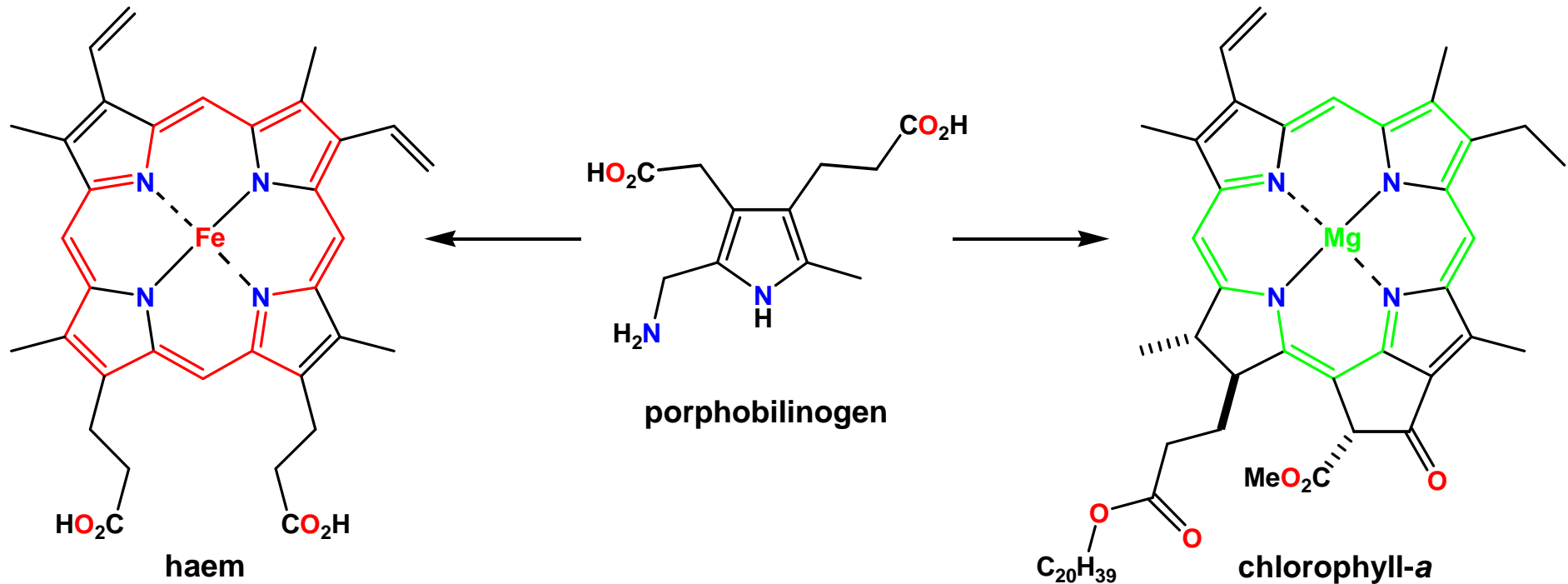


Pyrroles – Porphyrin Formation



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

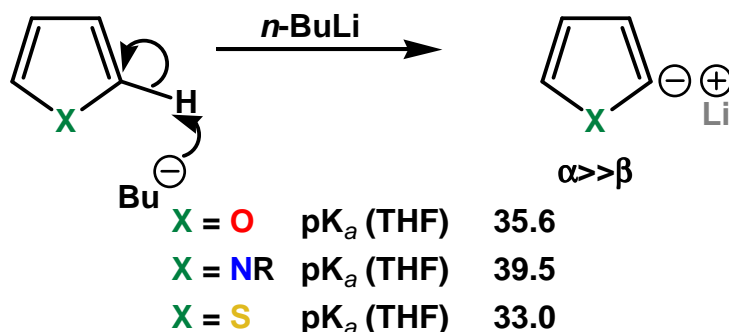
Porphyrin Natural Products



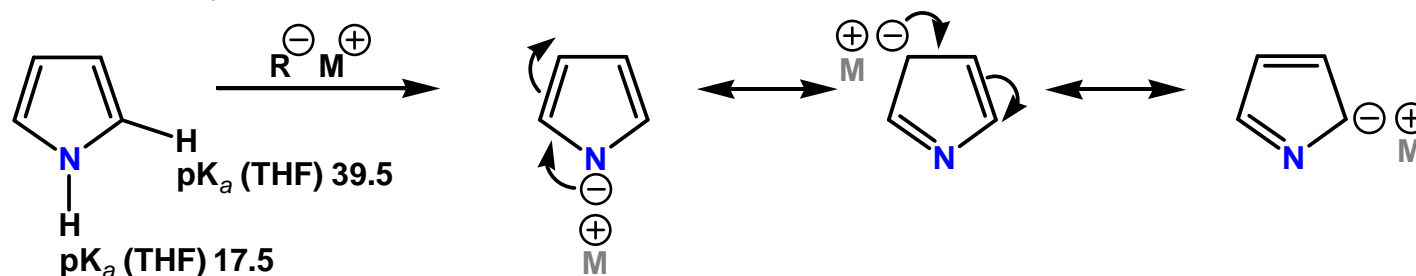
- The pigment haem is found in the oxygen carrier haemoglobin
- Chlorophyll-a is responsible for photosynthesis in plants
- Both haem and chlorophyll-a are synthesised in cells from porphobilinogen

Furans, Pyrroles Thiophenes – Deprotonation

Metallation



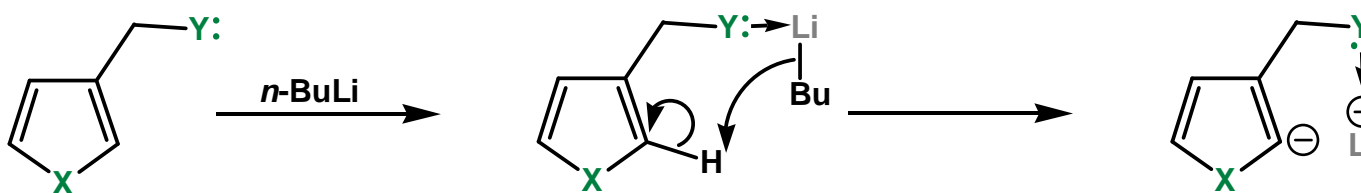
Deprotonation of Pyrroles



- 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

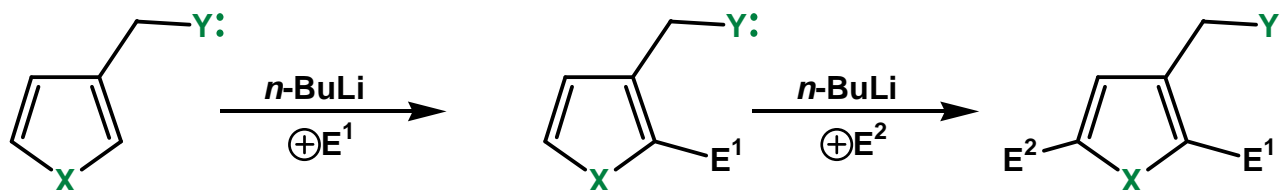
Furans, Pyrroles Thiophenes – Directed Metallation

Control of Regioselectivity in Deprotonation

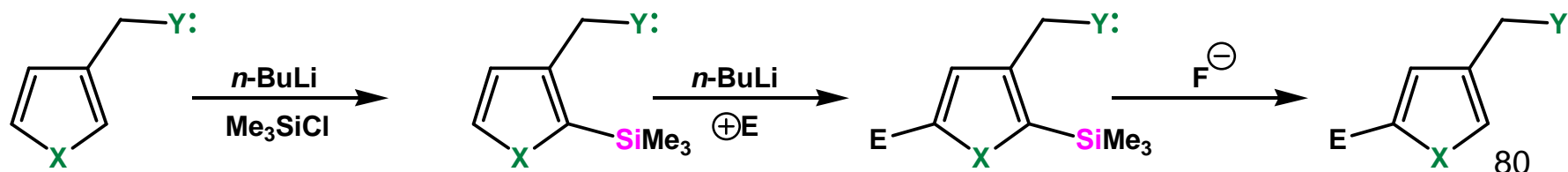


Common directing groups: CO₂H(Li), CH₂OMe, CONR₂, CH(OR)₂

Synthesis of α,α' -Disubstituted Systems

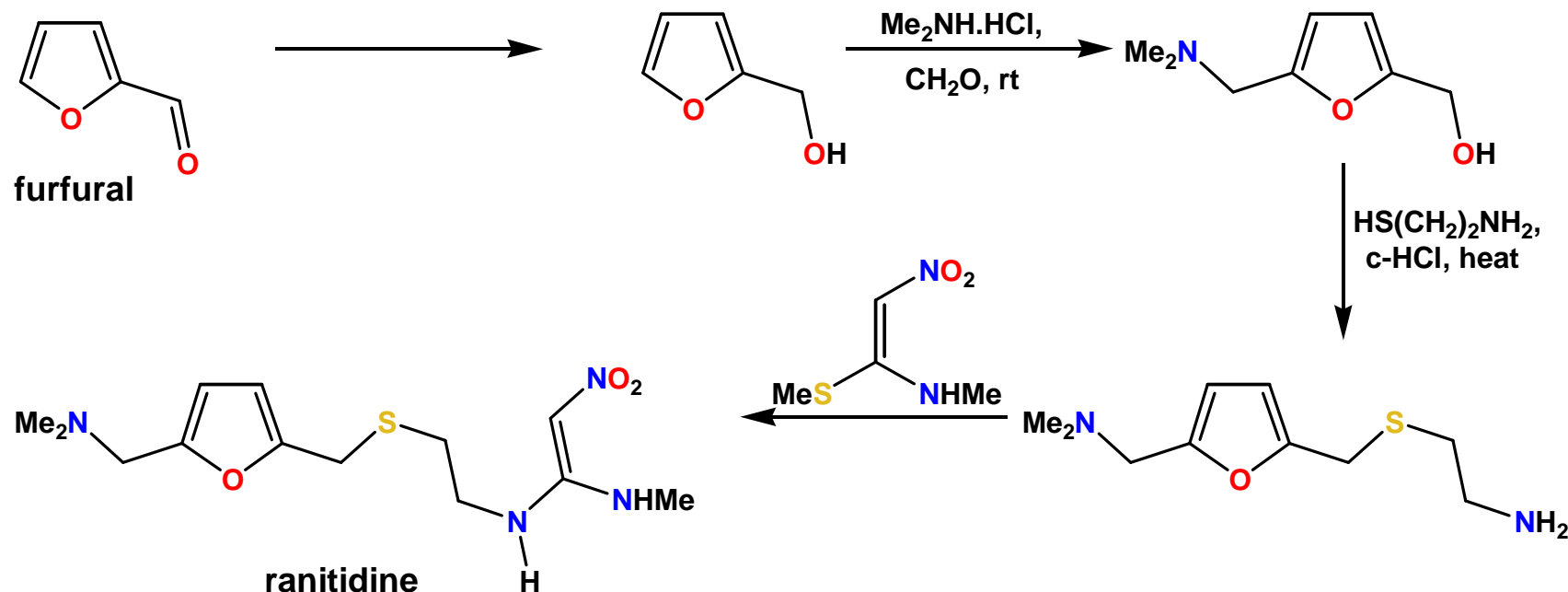


Use of a Trialkylsilyl Blocking Group



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