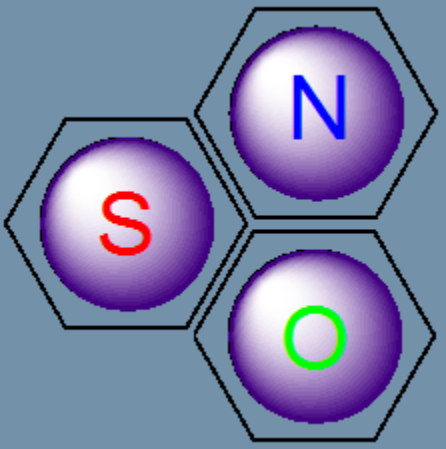

Heterocyclic Organic Chemistry CHEM 341

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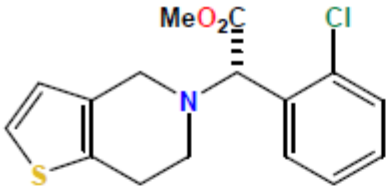
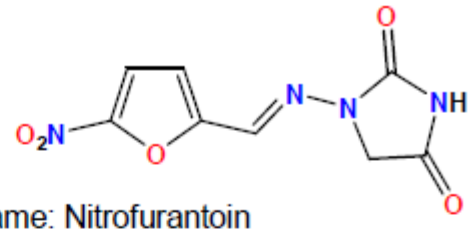
Furan/Thiophene/Pyrrole

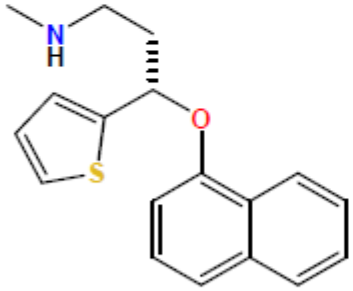
Drugs Containing a Furan/Thiophene/Pyrrole



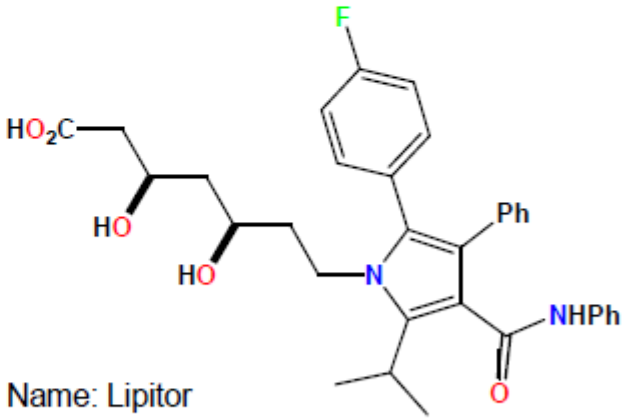
Name: Plavix
2008 Sales: $3.80 billion
2008 Ranking: 3 branded
Company: Bristol-Myers Squibb
Disease: Stroke and heart attack risk



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



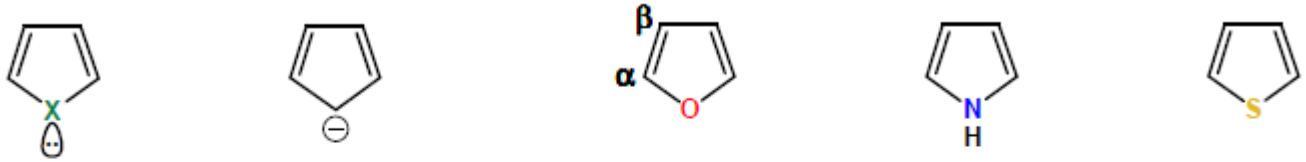
Name: Cymbalta
2008 Sales: $2.17 billion
2008 Ranking: 14 branded
Company: Eli Lilly
Disease: Depression



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

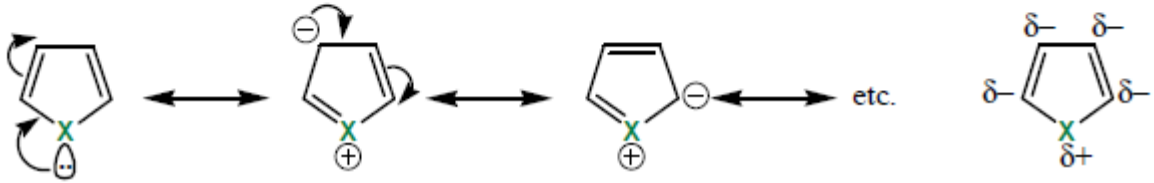
Furans, Pyrroles and Thiophenes – Structure

Structure

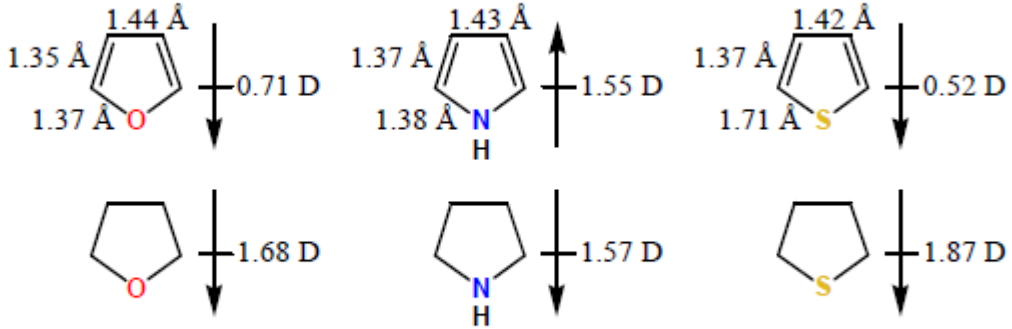


- 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures



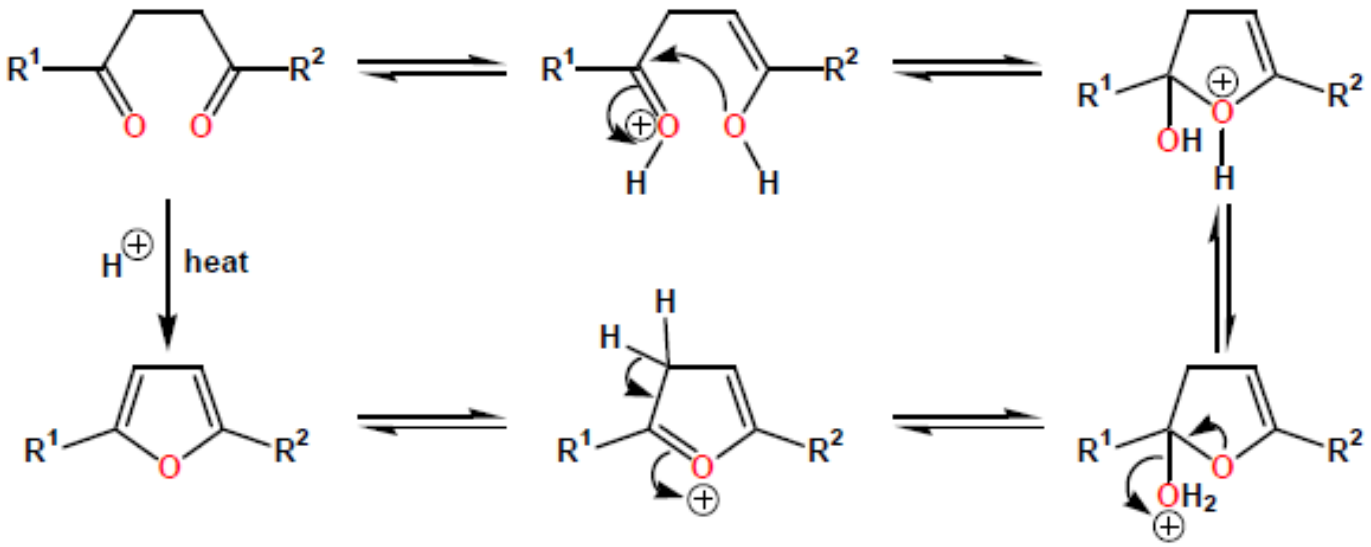
- Electron donation into the ring by resonance but inductive electron withdrawal



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

Furans – Synthesis

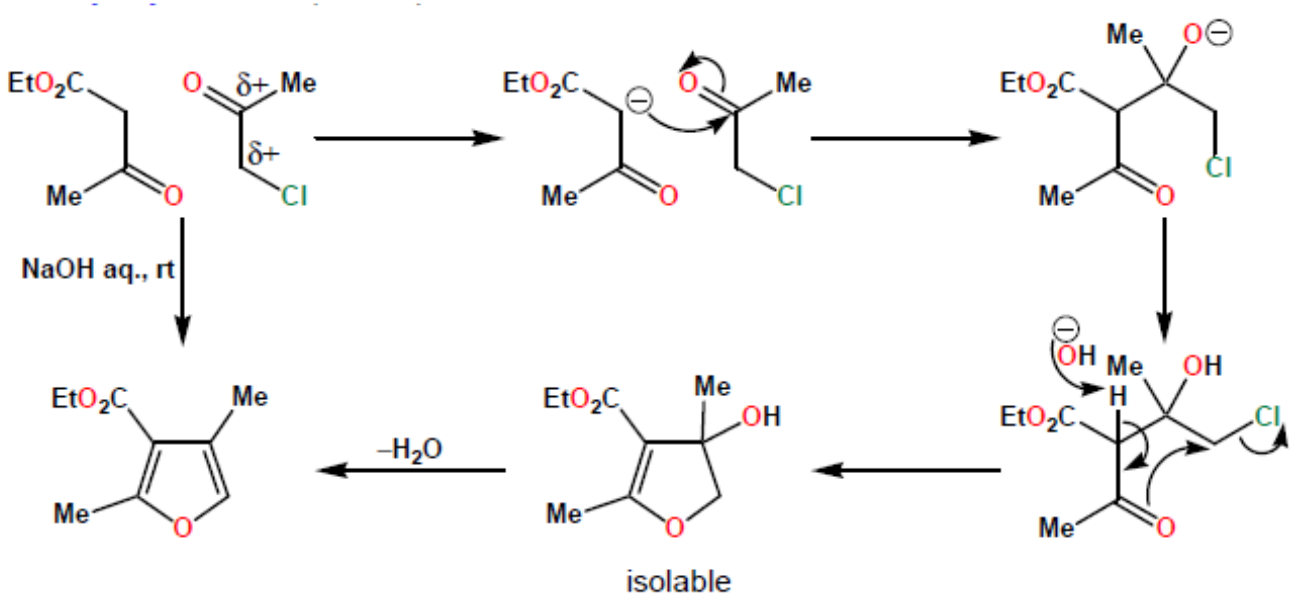
Paal Knorr Synthesis



- 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*-$MeC_6H_4SO_3H$)

Furans – Synthesis

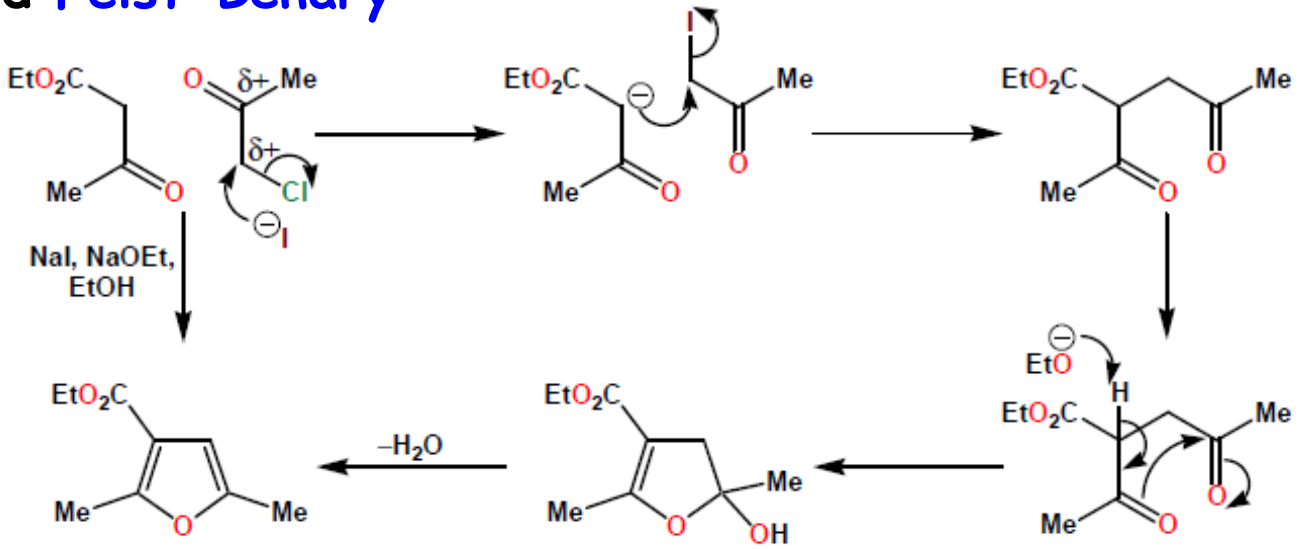
Feist-Benary Synthesis ("3+2")



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

Furans – Synthesis

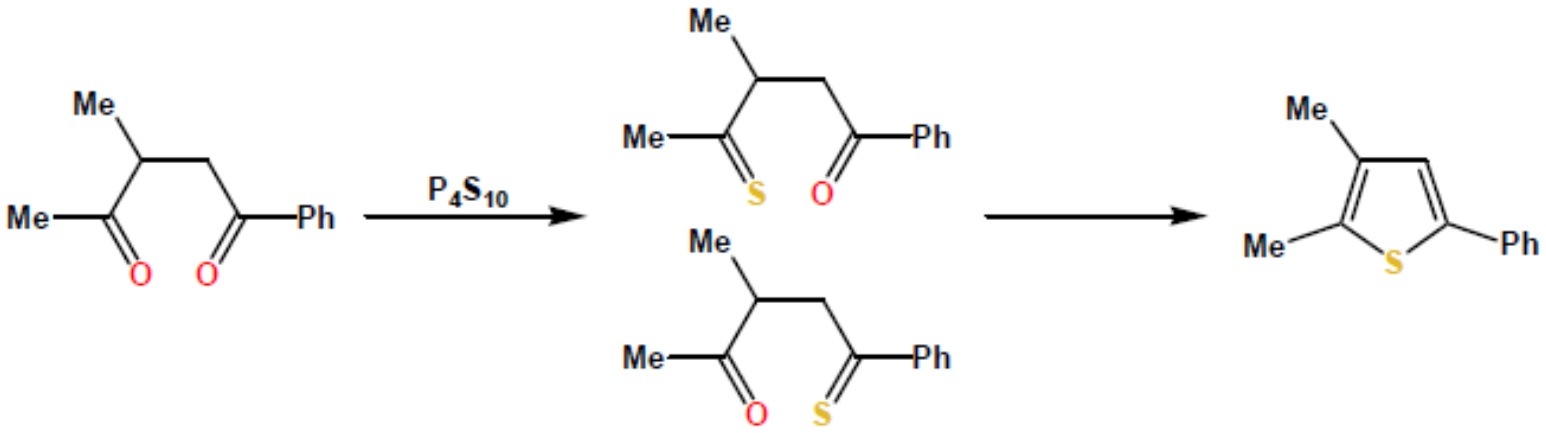
Modified Feist-Benary



- 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

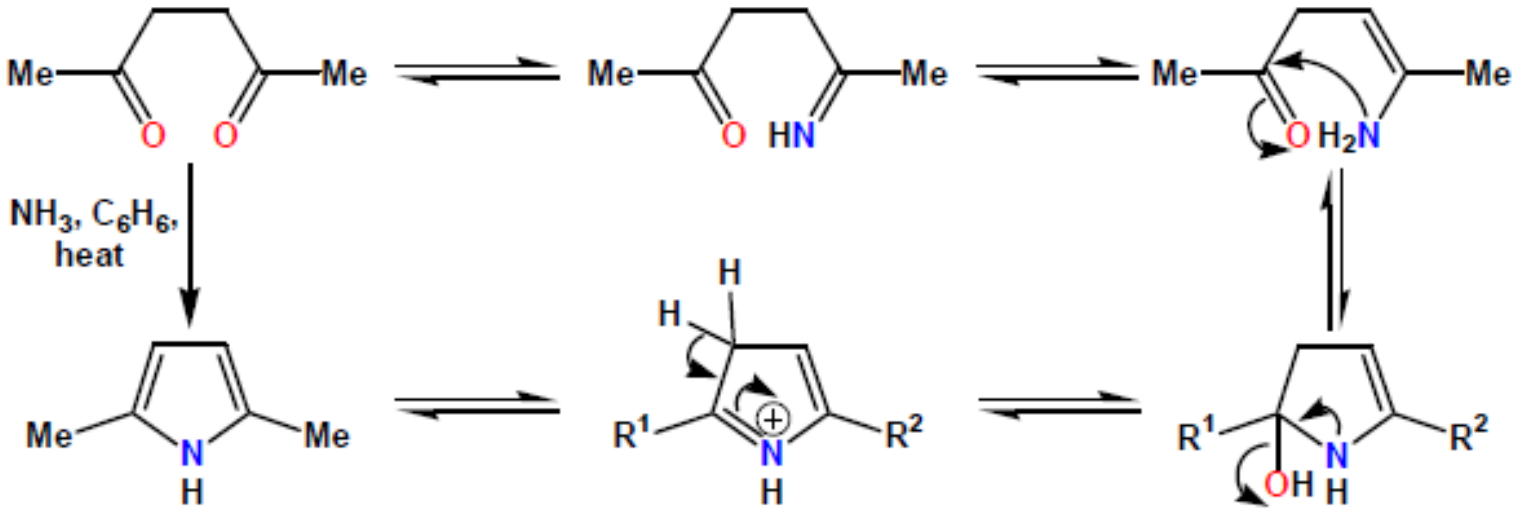
Synthesis of Thiophenes by Paal Knorr type reaction ("4+1")



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

pyrroles – Synthesis

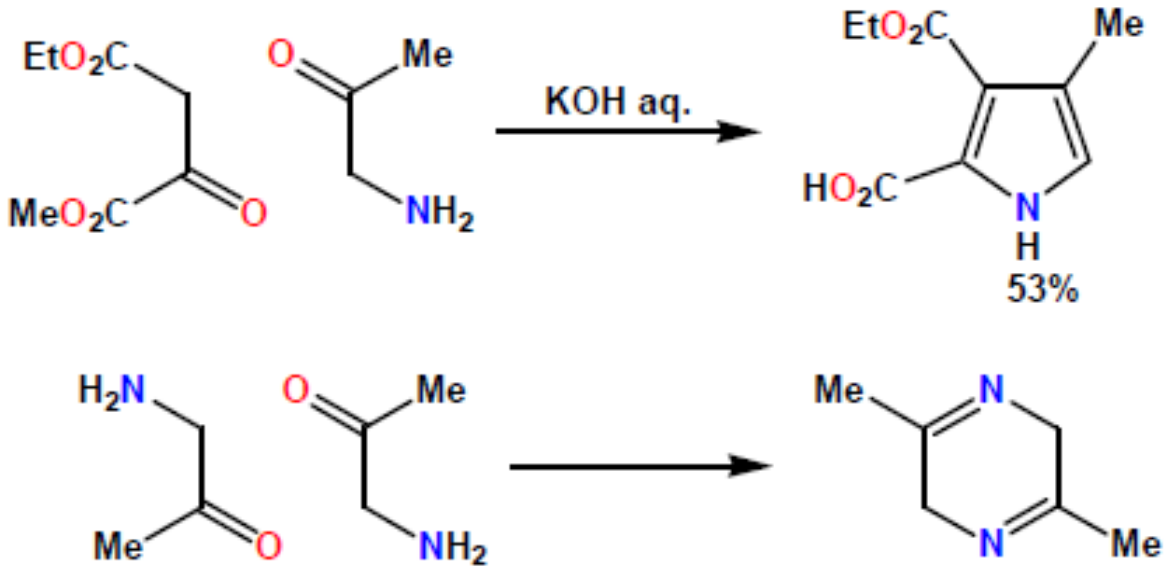
Paal Knorr Synthesis ("4+1")



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

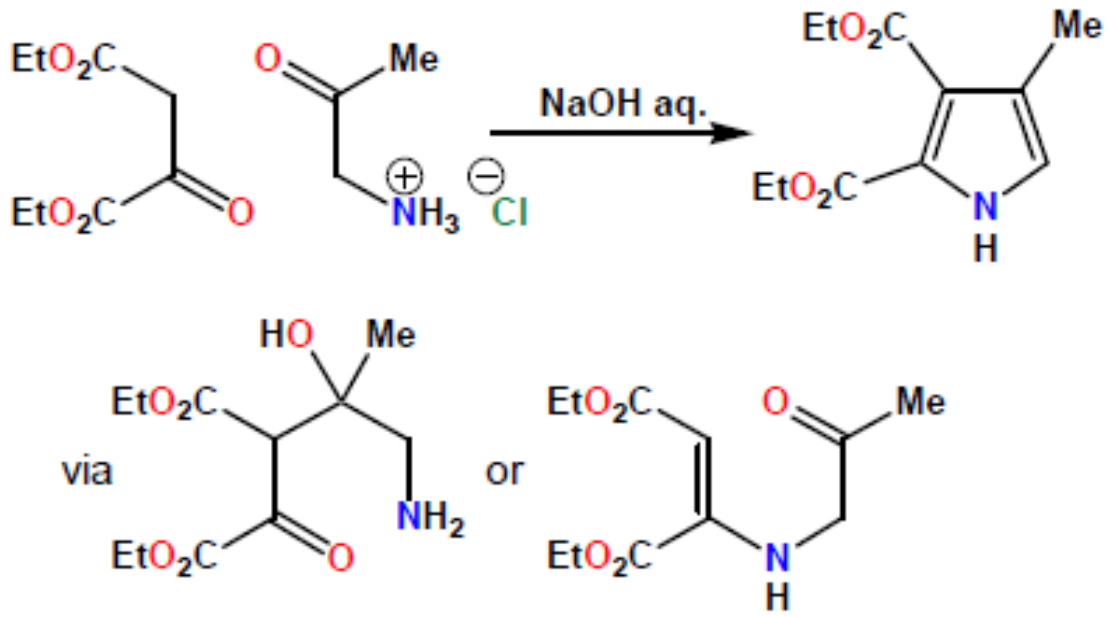
Pyrroles – Synthesis

Knorr Pyrrole Synthesis ("3+2")



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

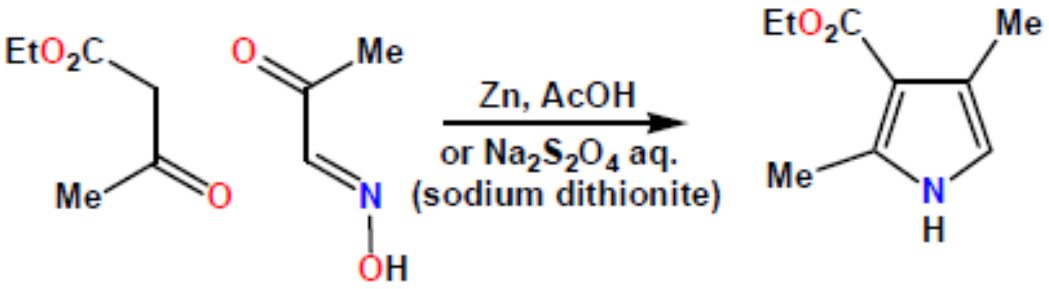
Pyrroles – Synthesis



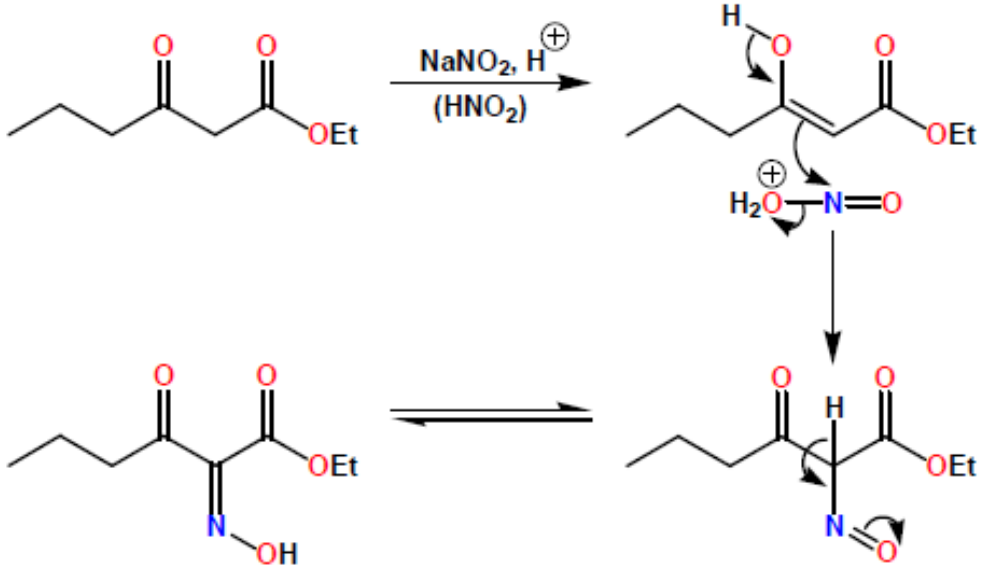
- Problem can be overcome by storing amino carbonyl compound in a protected form.
- Reactive methylene partner required so that pyrrole formation occurs more rapidly than dimer formation.

Pyrroles – Synthesis

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

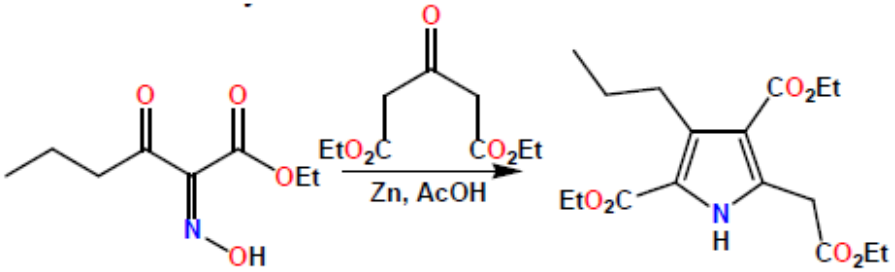


Preparation of α-Keto Oximes from β-Dicarbonyl Compounds

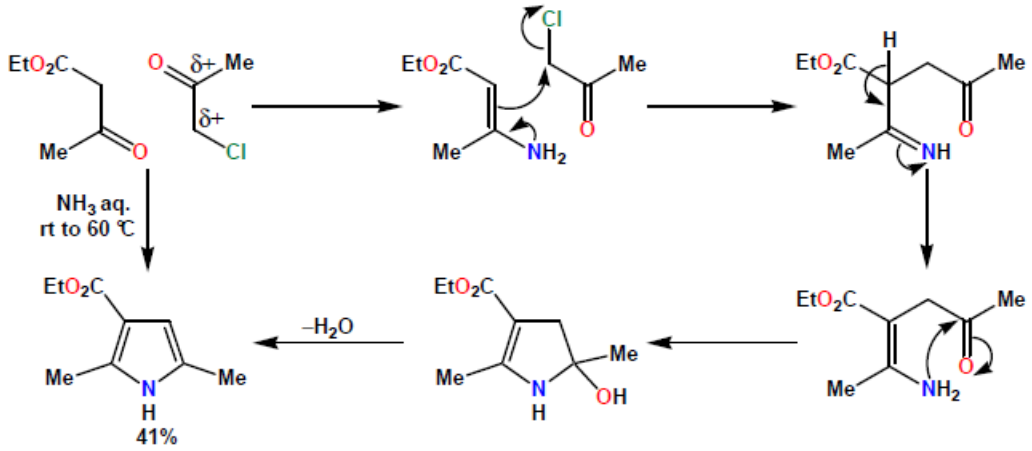


Pyrroles – Synthesis

One-Pot Oxime Reduction and Pyrrole Formation

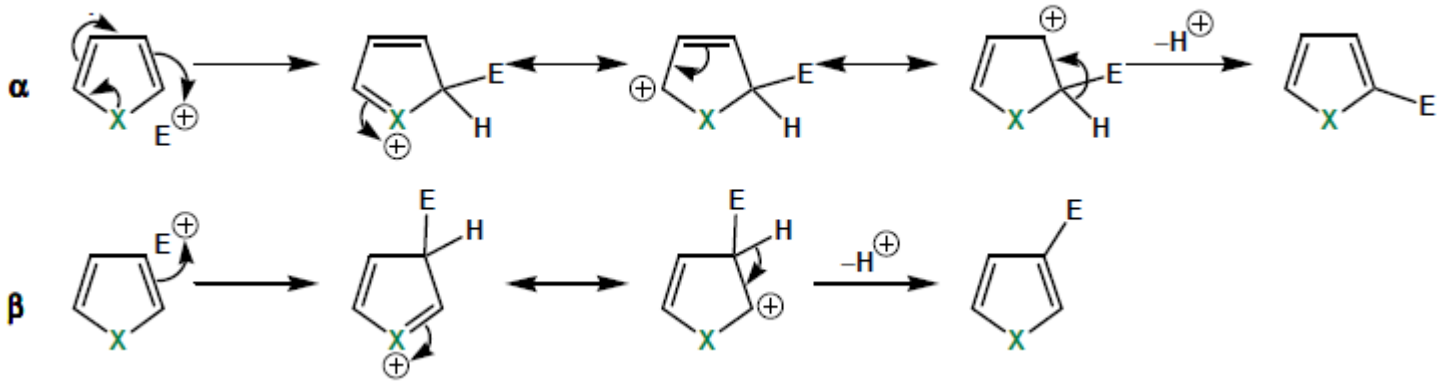


Hantzsch Synthesis of Pyrroles ("3+2")

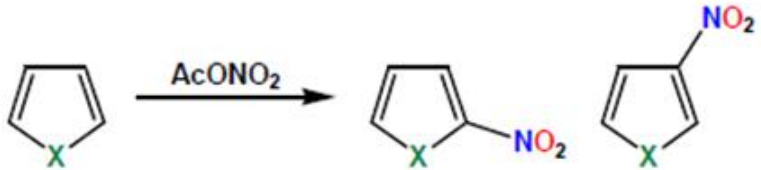


• A modified version of the Feist-Benary synthesis and using the same starting materials: an α-halo carbonyl compound and α,β-keto ester.

Electrophilic Substitution – Regioselectivity

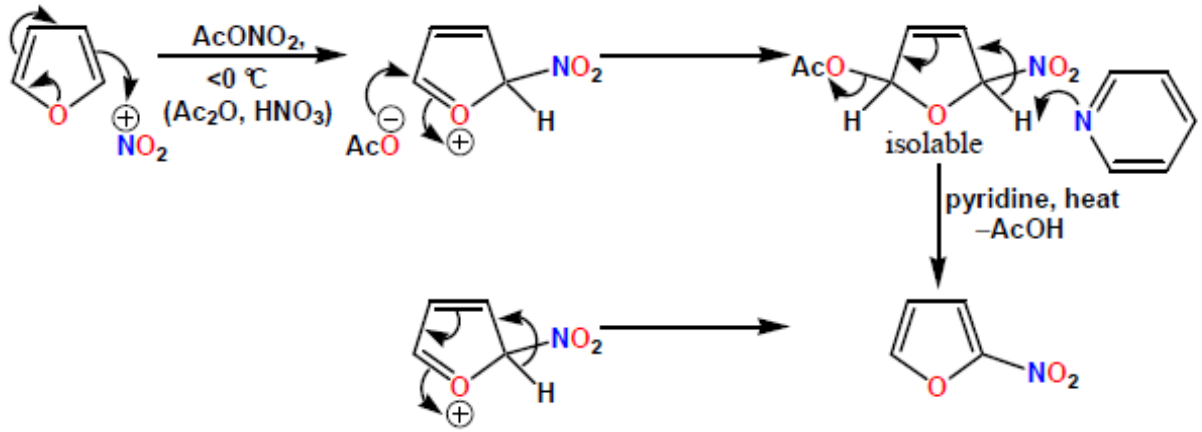


- Pyrrole > furan > thiophene > benzene
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions
- a-Substitution favoured over b-substitution more resonance forms for intermediate and so the charge is less localised (also applies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



Furans – Electrophilic Substitution

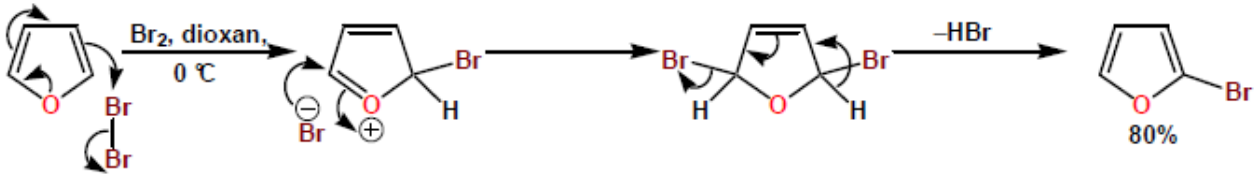
Nitration of Furans



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

Furans – Electrophilic Substitution

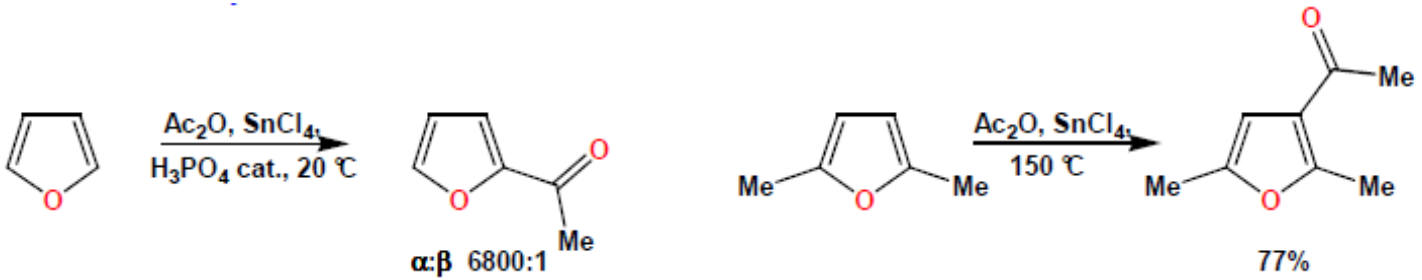
Bromination of Furans



- 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

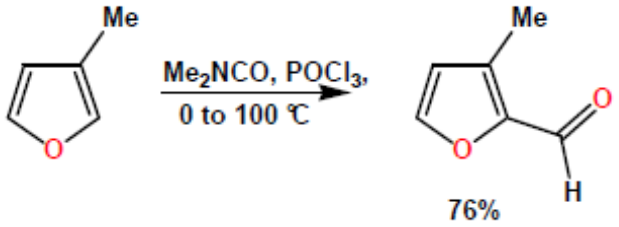
Friedel-Crafts Acylation of Furan



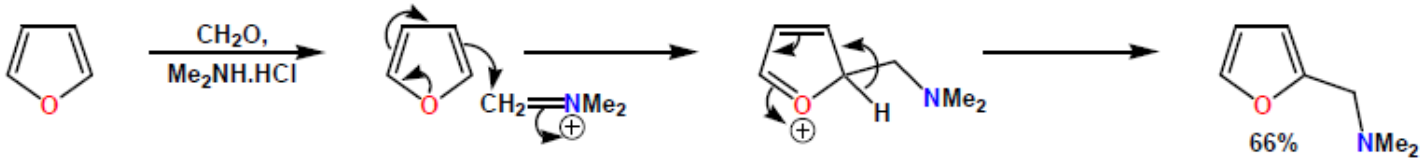
- Blocking groups at the a positions and high temperatures required to give b acylation.

Furans – Electrophilic Substitution

Vilsmeier Formylation of Furan

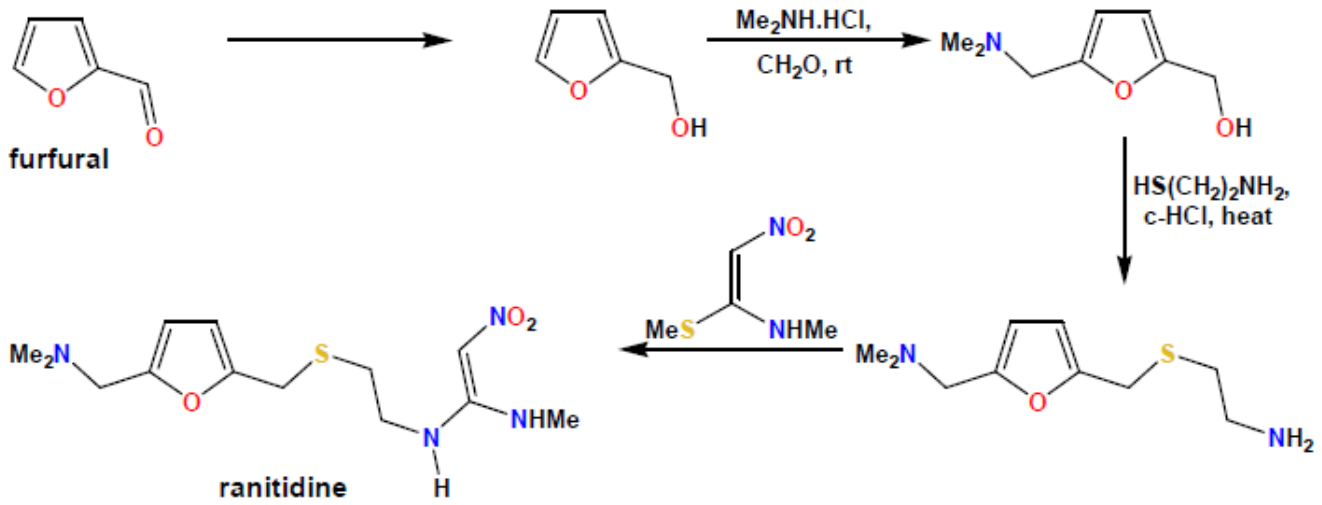


Mannich Reaction of Furans



Furans – Synthesis of a Drug

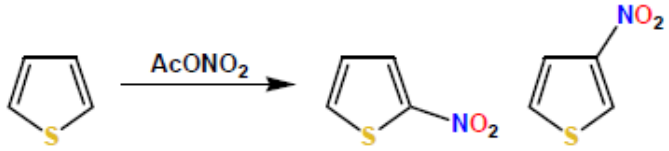
Preparation of Ranitidine (Zantac®) Using a Mannich Reaction



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

Thiophenes – Electrophilic Substitution

Nitration of Thiophenes



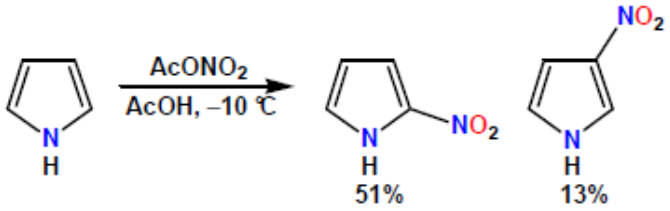
- Reagent $AcONO_2$ generated *in situ* from c-HNO_3 and Ac_2O

Halogenation of Thiophenes

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

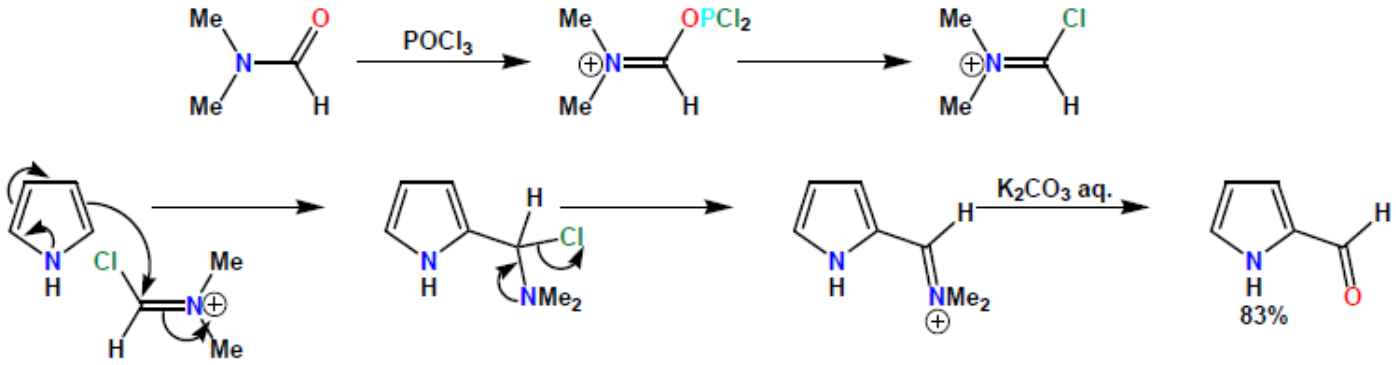
Pyrroles – Electrophilic Substitution

Nitration of Pyrroles

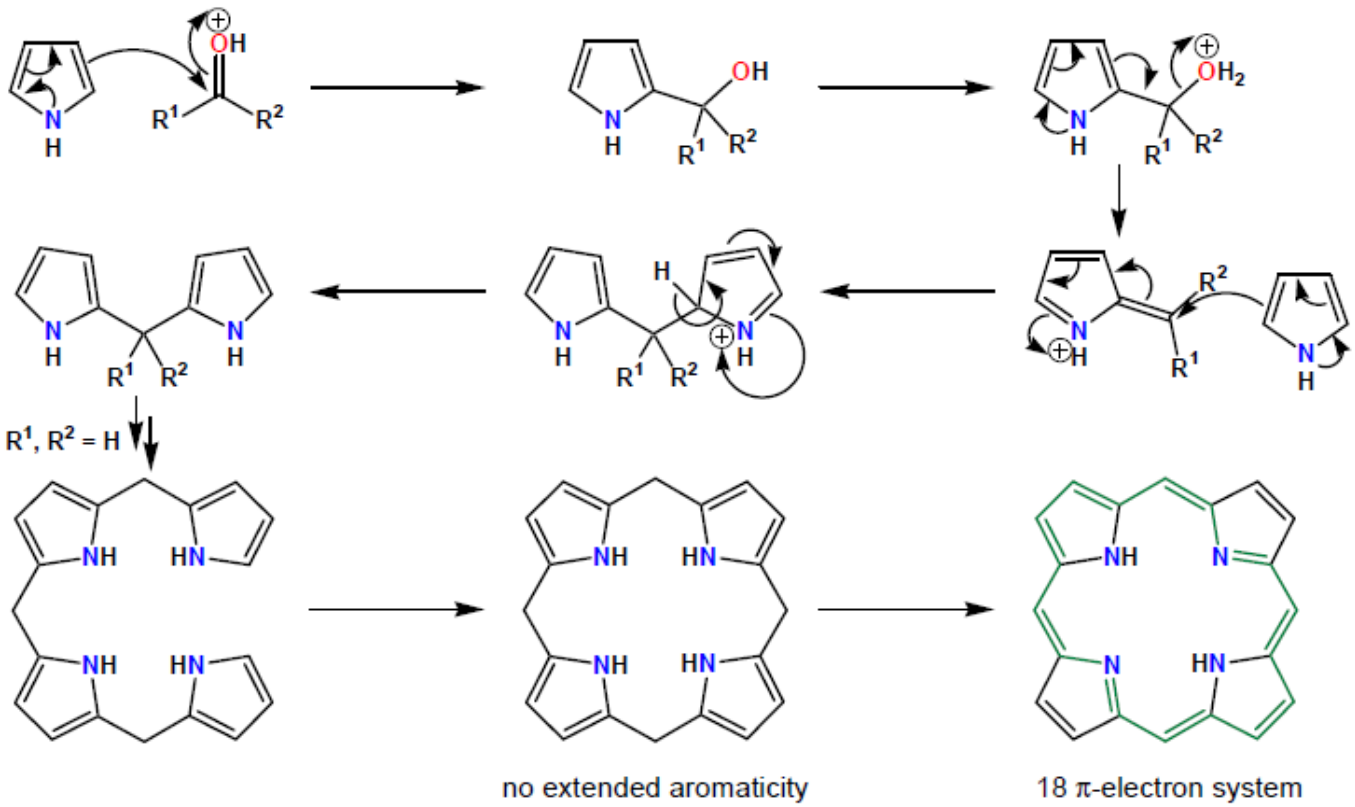


- Mild conditions are required (c-HNO_3 and c-H_2SO_4 gives decomposition).

Vilsmeier Formylation of Pyrroles

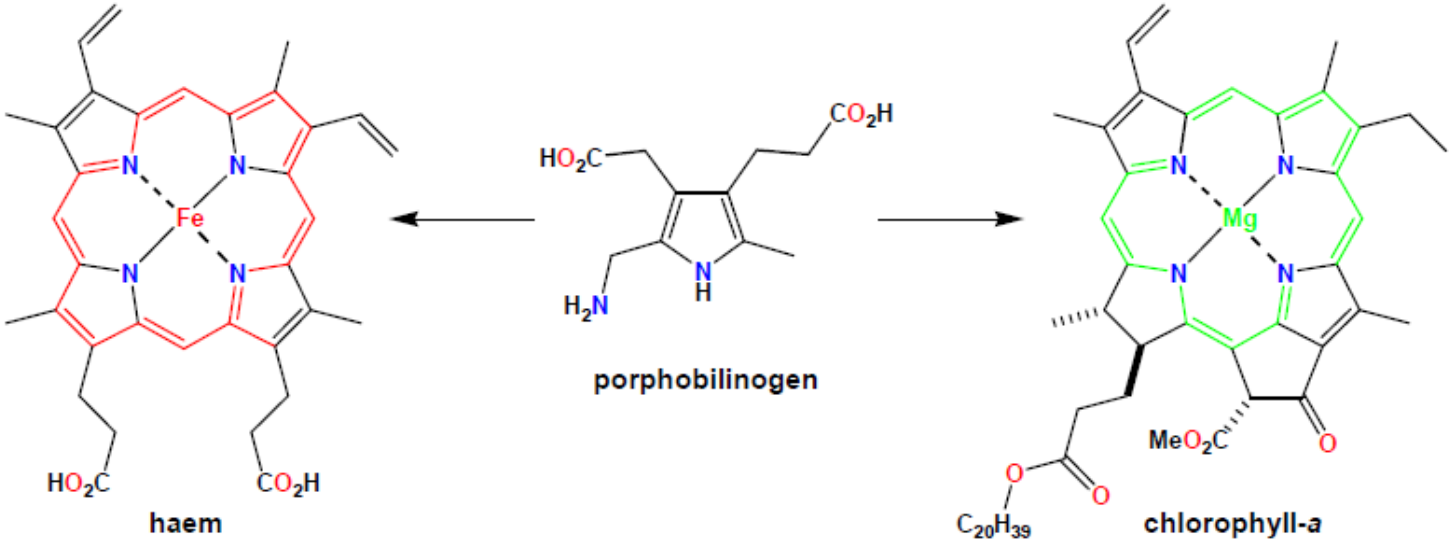


Pyrroles – Porphyrin Formation



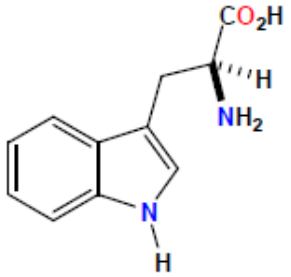
- The extended aromatic 18 p-electron system is more stable than that having four isolated aromatic pyrroles.

Porphyrin Natural Products

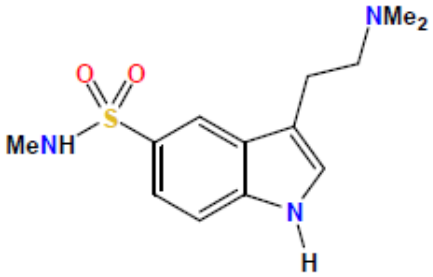


- Chlorophyll-*a* is responsible for photosynthesis in plants.
- The pigment haem is found in the oxygen carrier haemoglobin.
- Both haem and chlorophyll-*a* are synthesised in cells from porphobilinogen.

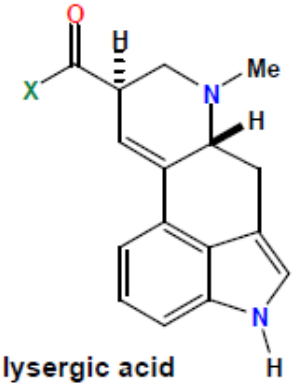
Indoles – Bioactive Indoles



tryptophan



sumatriptan



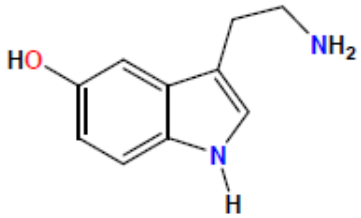
X = OH lysergic acid

X = NEt_2 *l*ysergic acid *d*iethyamide (LSD)

• Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS.

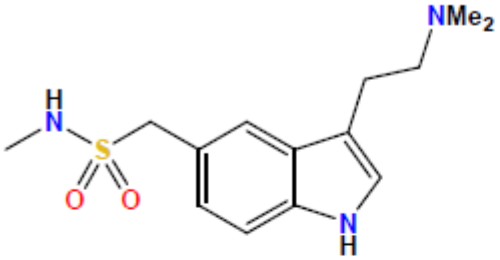
• Tryptophan is one of the essential amino acids and a constituent of most proteins.

• LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural product of the ergot fungus.

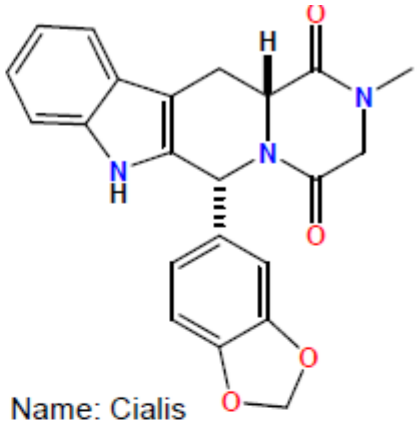


5-hydroxytryptamine (serotonin)

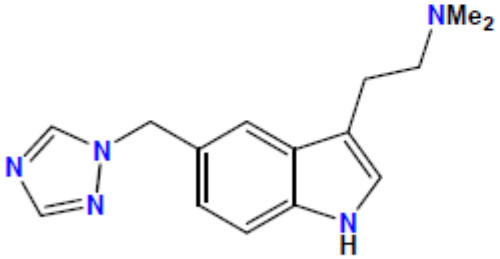
Drugs Containing an Indole



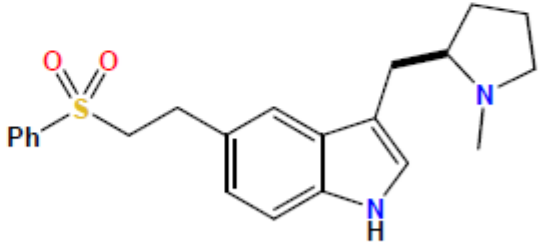
Name: Imitrex
2008 Sales: $0.97 billion
2008 Ranking: 35 branded
Company: GlaxoSmithKline
Disease: Migraine



Name: Cialis
2008 Sales: $0.56 billion
2008 Ranking: 66 branded
Company: Eli Lilly
Disease: Erectile disfunction



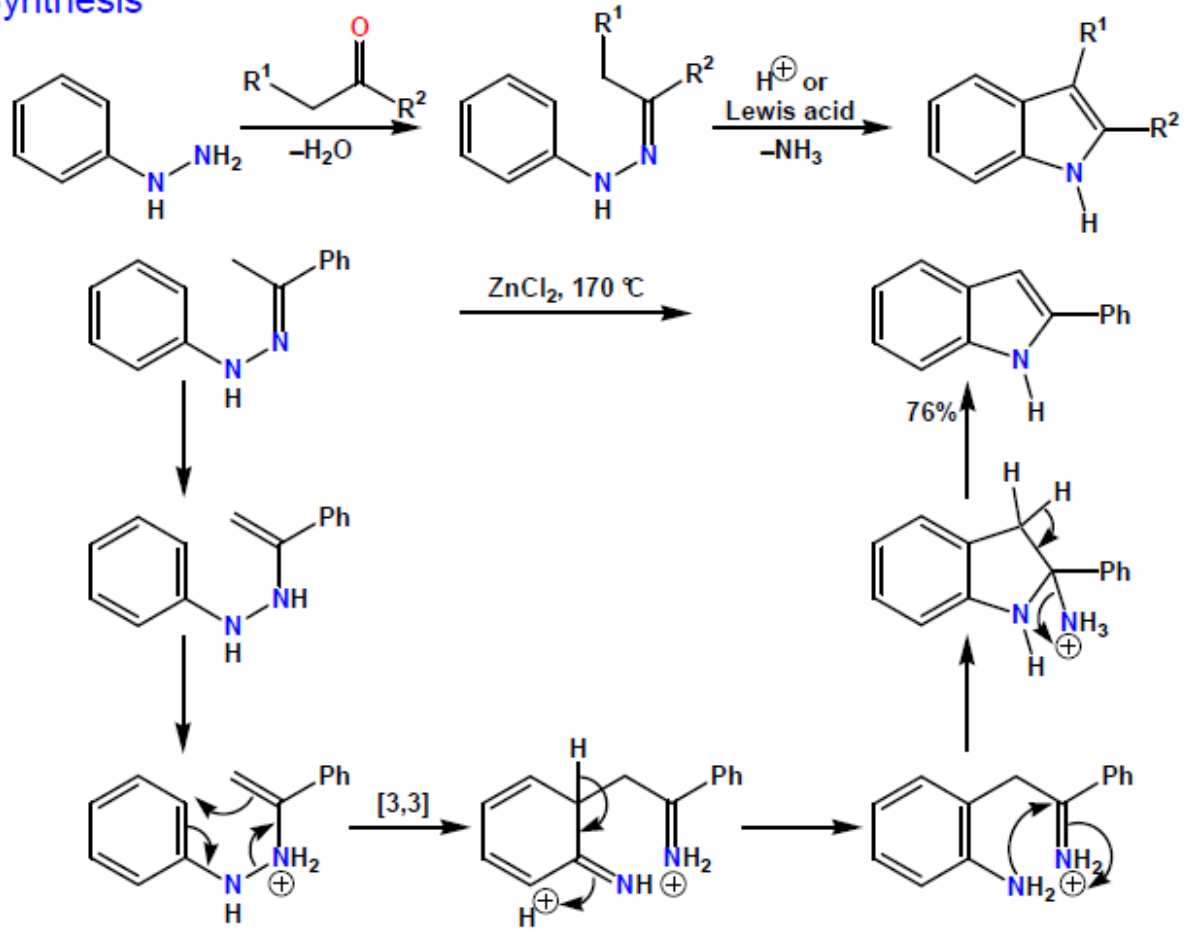
Name: Maxalt
2008 Sales: $0.22 billion
2008 Ranking: 148 branded
Company: Merck
Disease: Migraine



Name: Relpax
2008 Sales: $0.21 billion
2008 Ranking: 151 branded
Company: Pfizer
Disease: Migraine

Indoles - Synthesis

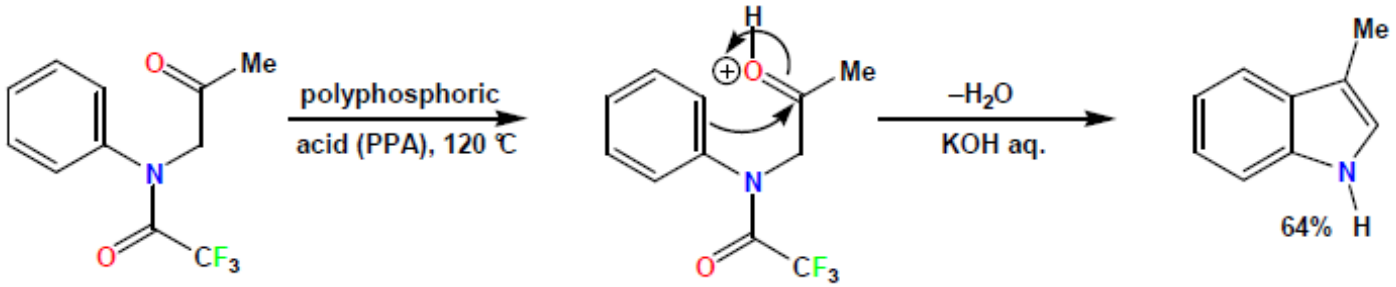
Fischer Synthesis



- A protic acid or a Lewis acid can be used to promote the reaction

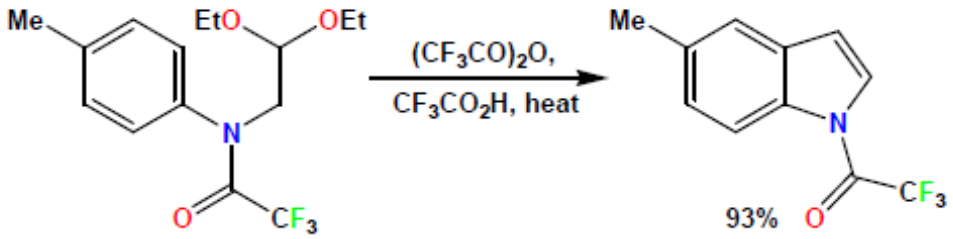
Indoles - Synthesis

Bischler Synthesis



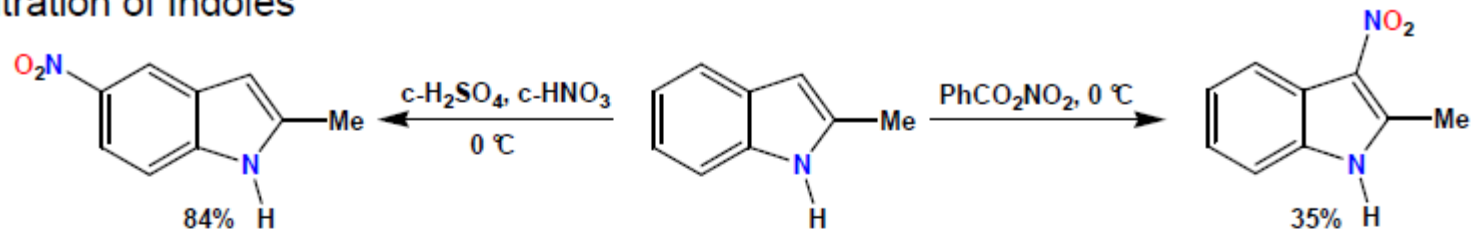
- An α-arylaminoketone is cyclised under acidic conditions

- The reaction also works with acetals of aldehydes



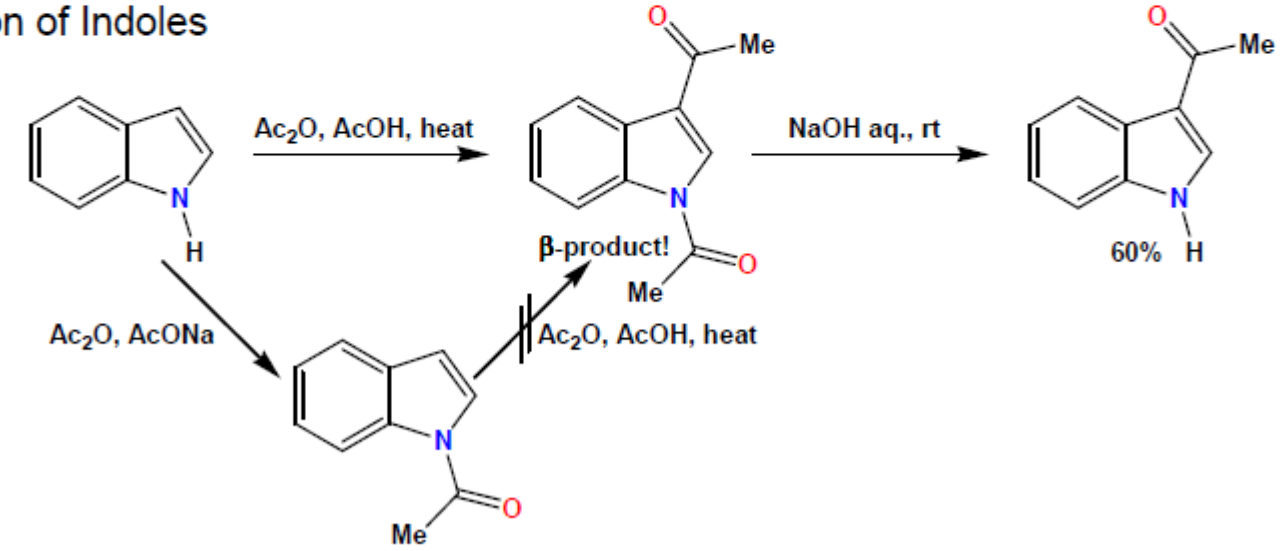
Indoles – Electrophilic Substitution

Nitration of Indoles



- Polymerisation occurs when there is no substituent at the 2-position
- Halogenation is possible, but the products tend to be unstable

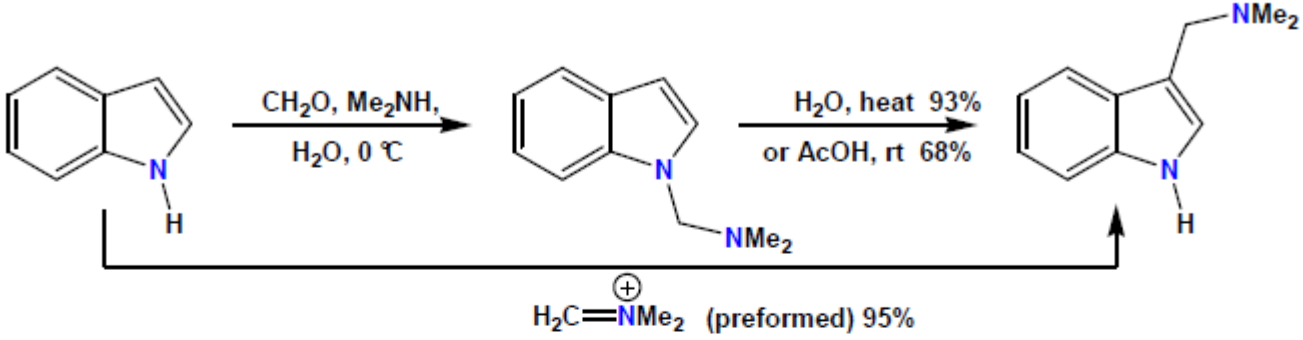
Acylation of Indoles



- Acylation occurs at *C* before *N* because the *N*-acylated product does not react

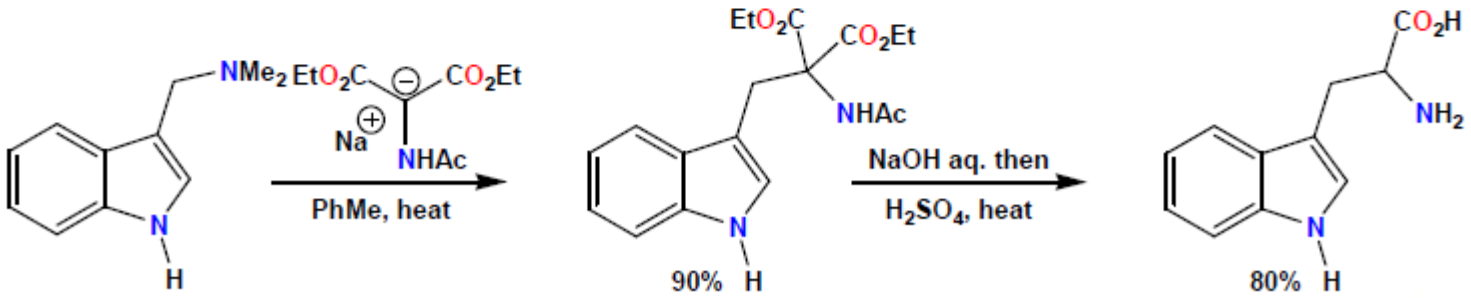
Indoles - Electrophilic Substitution

Mannich Reaction



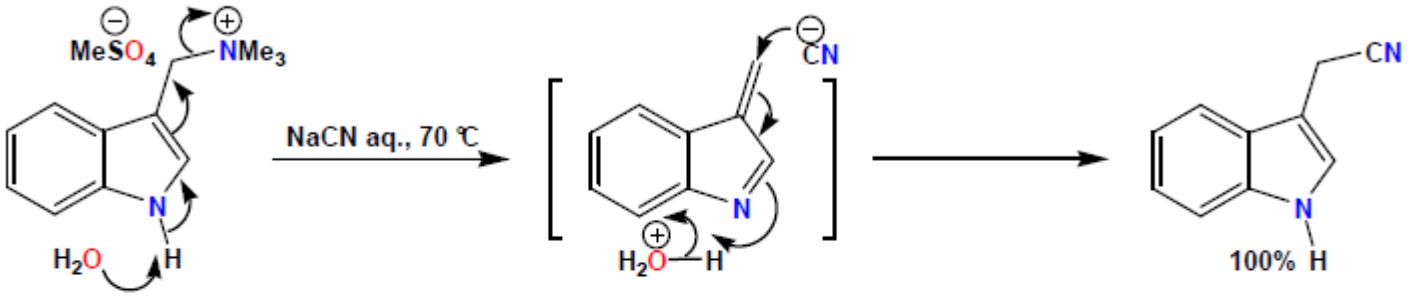
- A very useful reaction for the synthesis of 3-substituted indoles
- The product (gramine) can be used to access a variety of other 3-substituted indoles

Synthesis of Tryptophan from Gramine

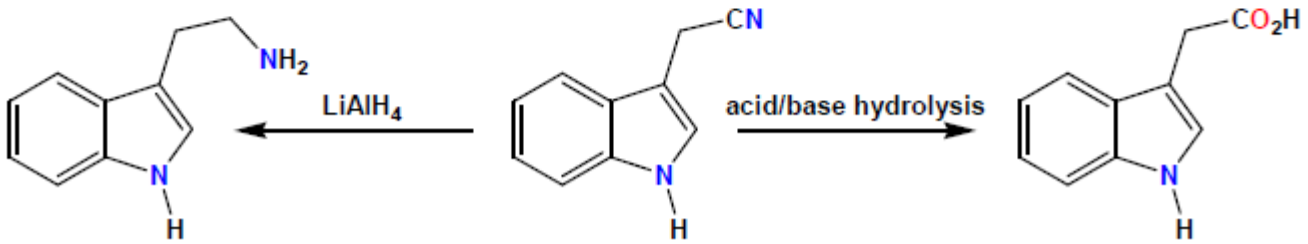


Indoles - Electrophilic Substitution

Synthesis of Other 3-Substituted Indoles from Gramine

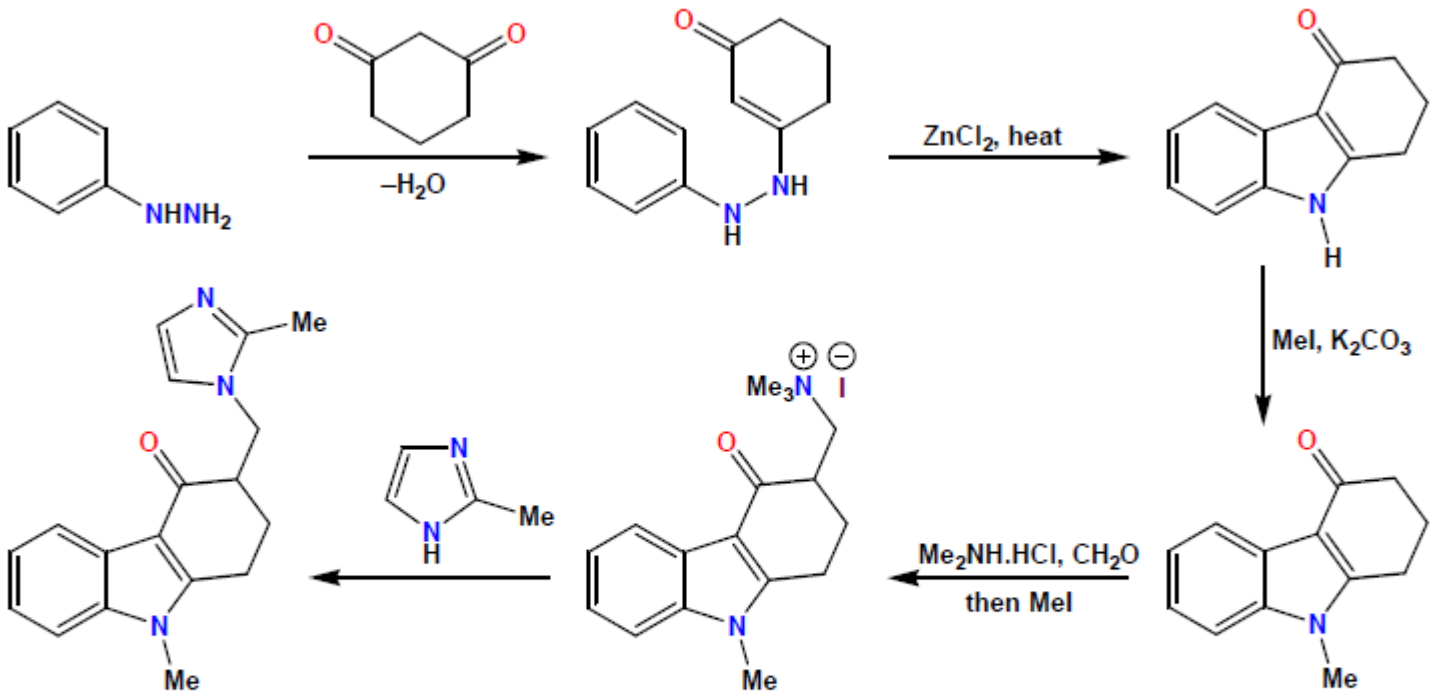


- The nitrile group can be modified to give other useful functionality



Indoles – Synthesis of a Drug

Synthesis of Ondansetron (Zofran®, GSK) using the Fischer Indole Synthesis



- Ondansetron is a selective 5-HT antagonist used as an antiemetic in cancer chemotherapy and radiotherapy
- Introduction of the imidazole occurs *via* the α,β-unsaturated ketone resulting from elimination of the ammonium salt