Heterocyclic Chemistry

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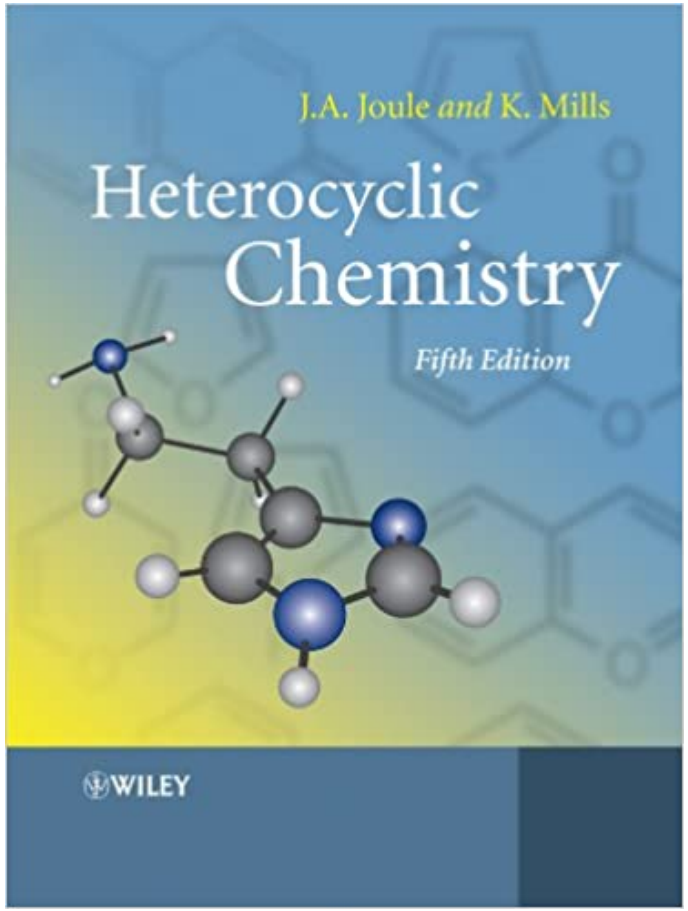
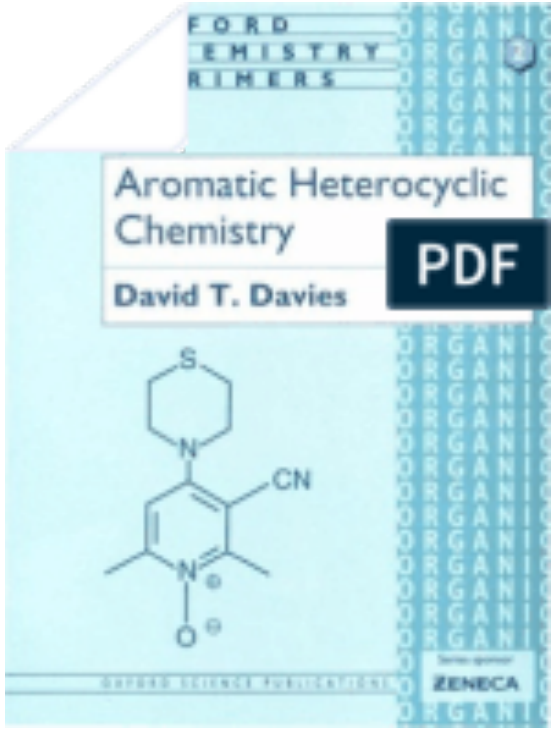
2019–2020

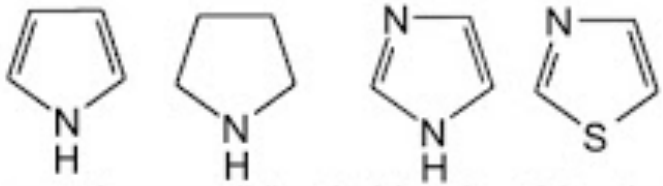
Recommended Reading

- *Heterocyclic Chemistry* – J. A. Joule, K. Mills and G. F. Smith
- *Heterocyclic Chemistry* (Oxford Primer Series) – T. Gilchrist
- *Aromatic Heterocyclic Chemistry* – D. T. Davies



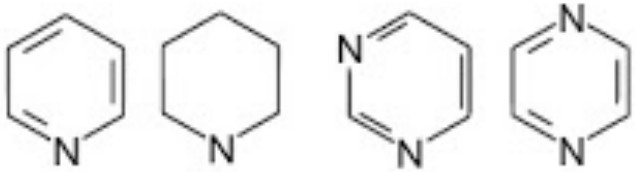


Survey of the most important heterocycles

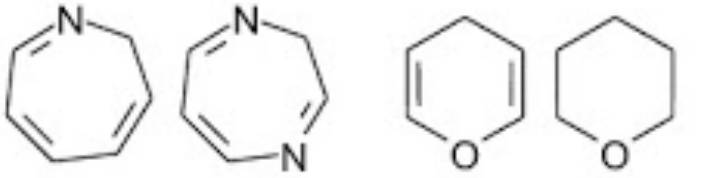


pyrrole pyrrolidine **imidazole** **thiazole**

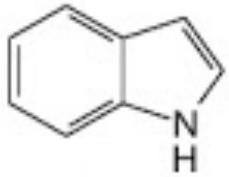
thiofene thiolane furan tetrahydro-furan



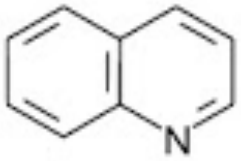
pyridine piperidine **pyrimidine** **pyrazine**



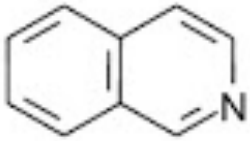
azepine 1,4-diazepine *4H*-pyran tetrahydro-pyran



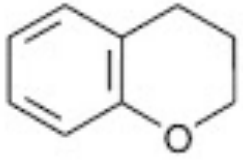
indole



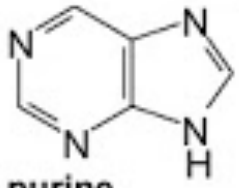
quinoline



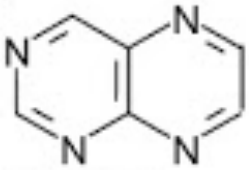
isoquinoline



chroman



purine



pteridine

Introduction

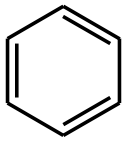
- Heterocycles contain one or more heteroatoms in a ring

carbocycle **heterocycles – X, Y, Z are usually O, N or S**

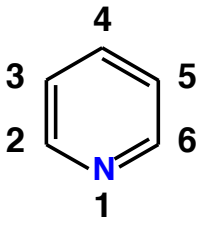
- Aromatic, or partially or fully saturated – this course will focus on aromatic systems
- Heterocycles are important and a large proportion of natural products contain them
- Many pharmaceuticals and agrochemicals contain at least one heterocyclic unit
- Heterocyclic systems are important building-blocks for new materials possessing interesting electronic, mechanical or biological properties

Classification – Aromatic Six-Membered

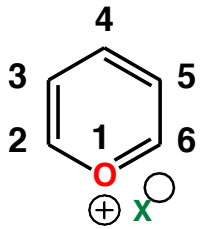
Isoelectronic carbocycle



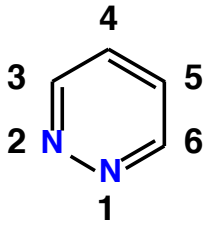
Heterocycles



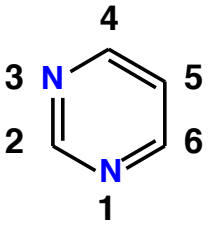
pyridine



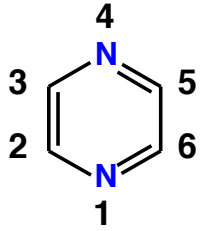
pyrylium



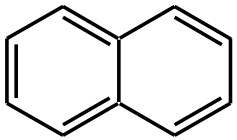
pyridazine

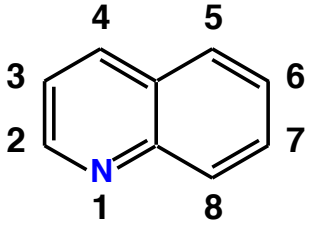


pyrimidine

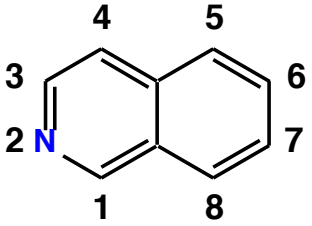


pyrazine





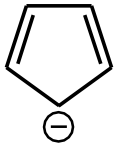
quinoline



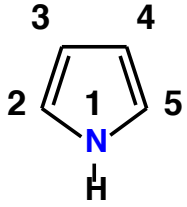
isoquinoline

Classification – Aromatic Five-Membered

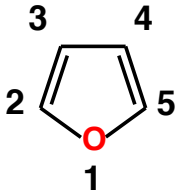
Isoelectronic carbocycle



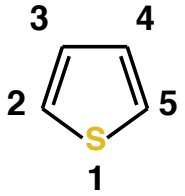
Heterocycles



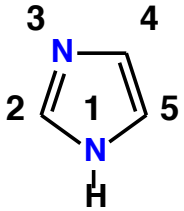
pyrrole



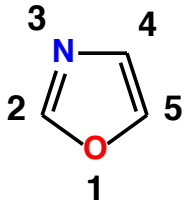
furan



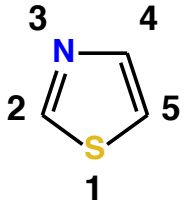
thiophene



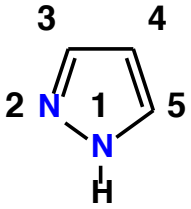
imidazole



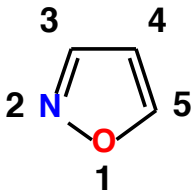
oxazole



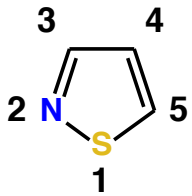
thiazole



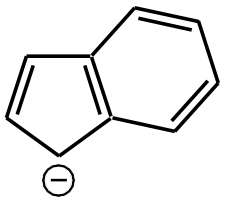
pyrazole

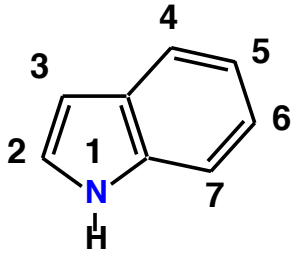


isoxazole

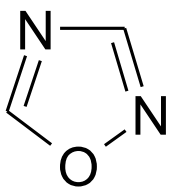


isothiazole

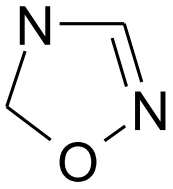




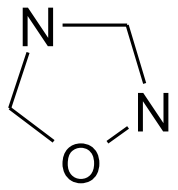
indole



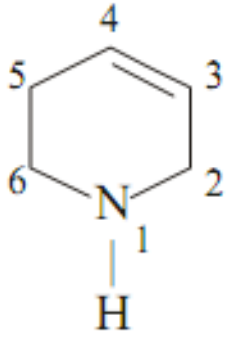
1,2,4-oxadiazole



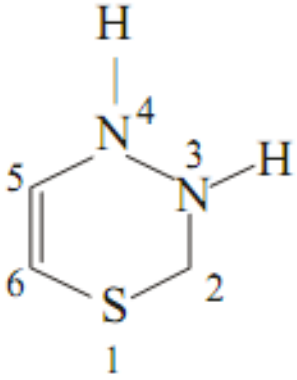
1,2,4-oxadiazoline



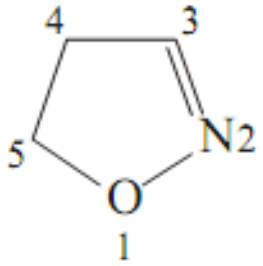
1,2,4-oxadiazolidine



Δ^3-Tetrahydropyridine



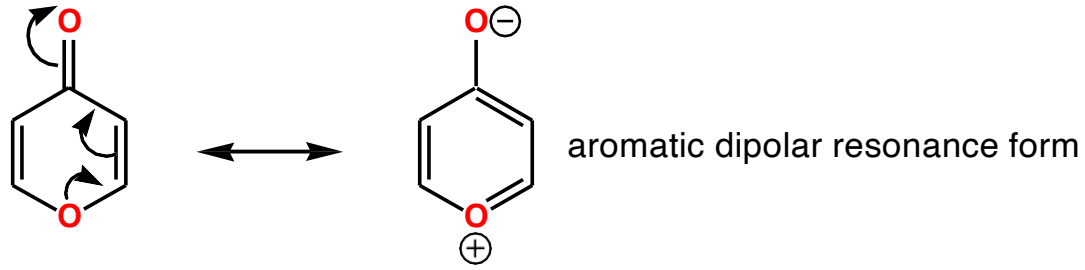
Δ^5-Dihydro-1,3,4-thiadiazine



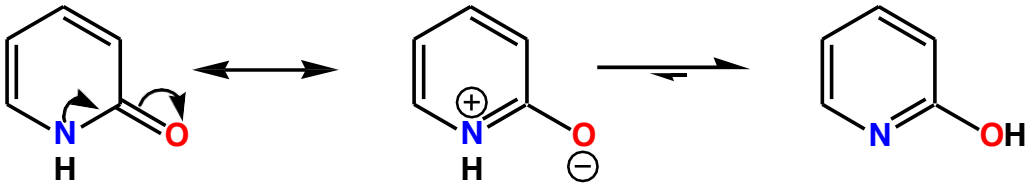
Δ^2-Oxazoline

Classification – Unsaturated / Saturated

Unsaturated

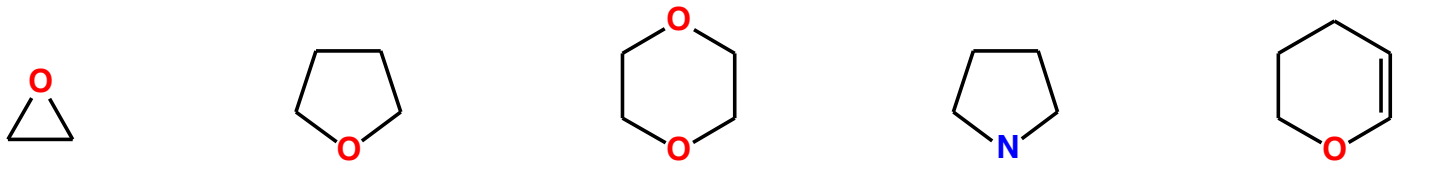


4(γ)-pyrone



2-pyridone

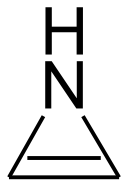
Saturated



ethylene oxide **THF** **1,4-dioxan** **pyrrolidine** **dihydropyran**

Table 1.2 Common Name Endings for Heterocyclic Compounds

Ring size	*Suffixes for fully unsaturated compounds*		*Suffixes for fully saturated compounds*	
	With N	*Without N*	*With N*	*Without N*
3	-irine	-irene	-iridine	-irane
4	-ete	-ete	-etidine	-etane
5	-ole	-ole	-olidine	-olane
6	-ine	-in		-ane
7	-epine	-epin		-epane
8	-ocine		-ocin	-ocane

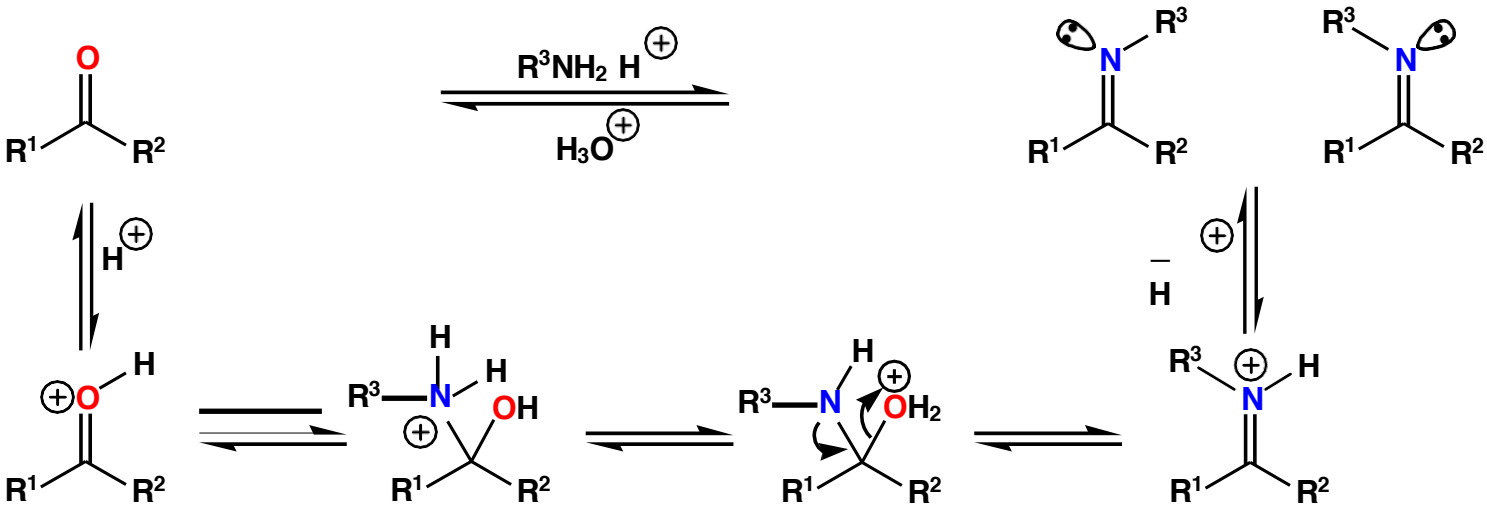


Azirine

Oxepin

Functional Group Chemistry

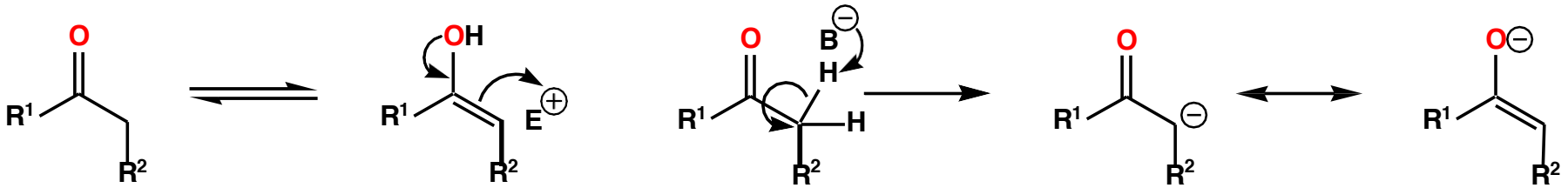
Imine Formation



- Removal of water is usually required to drive the reaction to completion
- If a dialkylamine is used, the iminium ion that is formed can't lose a proton and an enamine is formed

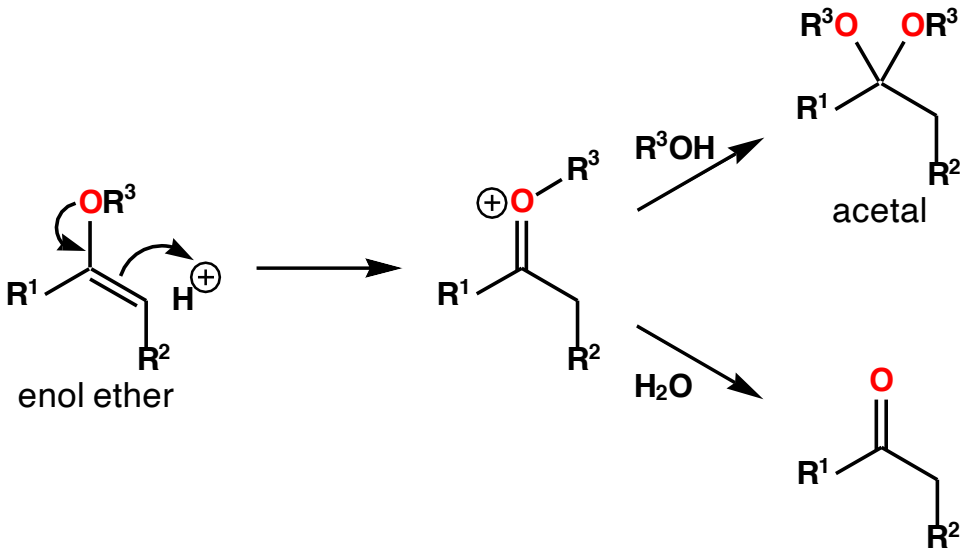
Functional Group Chemistry

Enols and Enolates



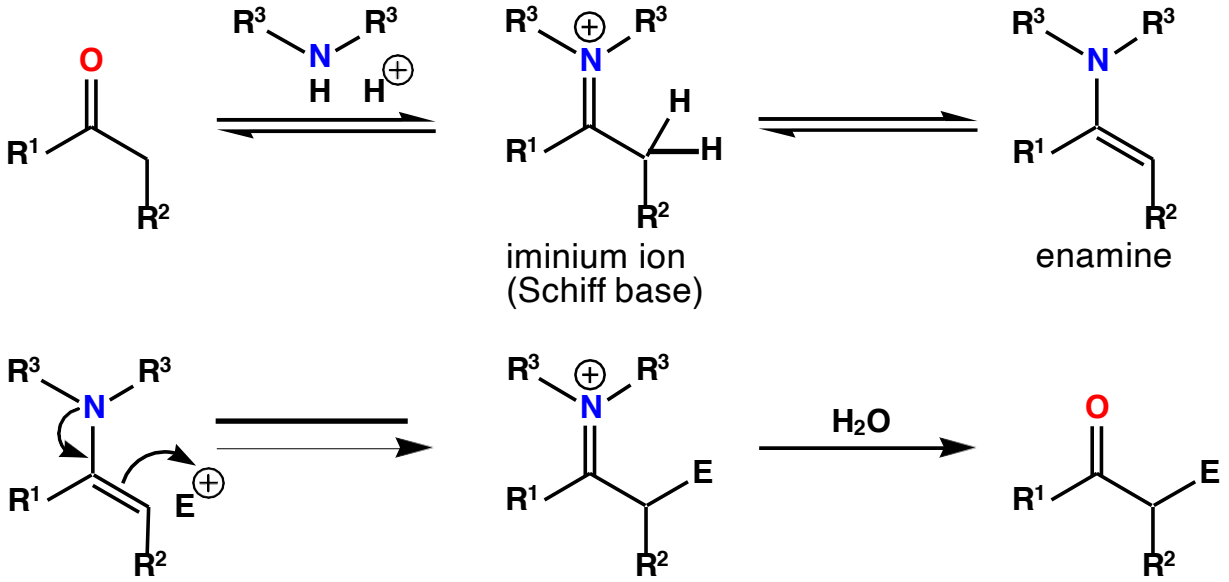
- The enol form is favoured by a conjugating group R^2 e.g. CO_2R, COR, CN, NO_2 etc.
- Avoid confusing enols (generated under neutral/acidic conditions) with enolates (generated under basic conditions)
- Enolates are nucleophilic through *C* or *O* but react with *C* electrophiles through *C*

Enol Ethers



Functional Group Chemistry

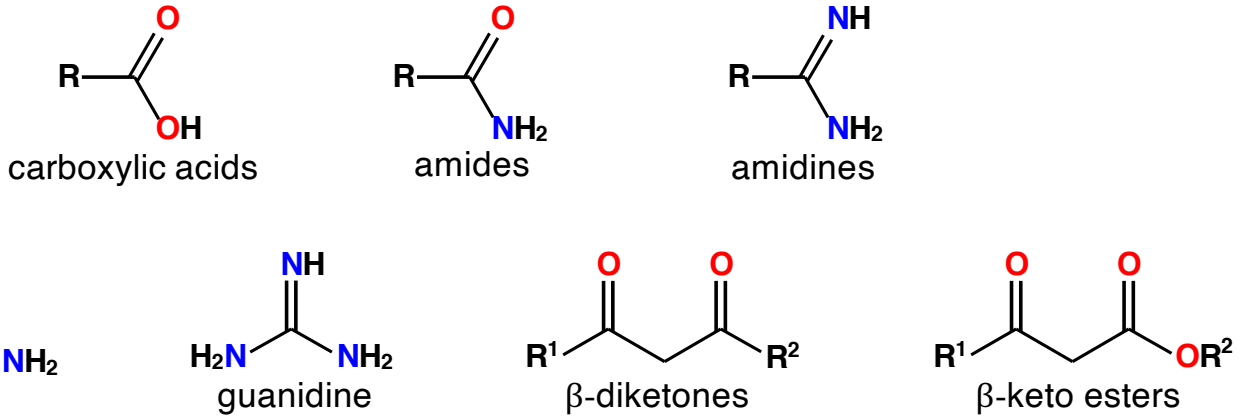
Enamines



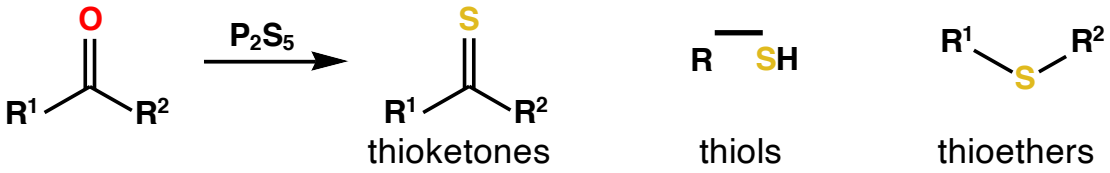
- Analogues of enols but are more nucleophilic and can function as enolate equivalents
- Removal of water (e.g. by distillation or trapping) drives reaction to completion
- Enamines react readily with carbon nucleophiles at carbon
- Reaction at *N* is possible but usually reverses

Functional Group Chemistry

Common Building-Blocks



Building-Blocks for Sulfur-Containing Heterocycles

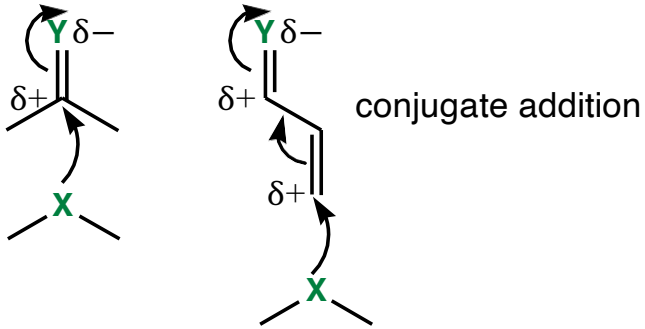


- Heterocycle synthesis requires:
  C–O or C–N bond formation using imines, enamines, acetals, enols, enol ethers C–C bond formation using enols, enolates, enamines
- During heterocycle synthesis, equilibrium is driven to the product side because of removal of water, crystallisation of product and product stability (aromaticity)

General Strategies for Heterocycle Synthesis

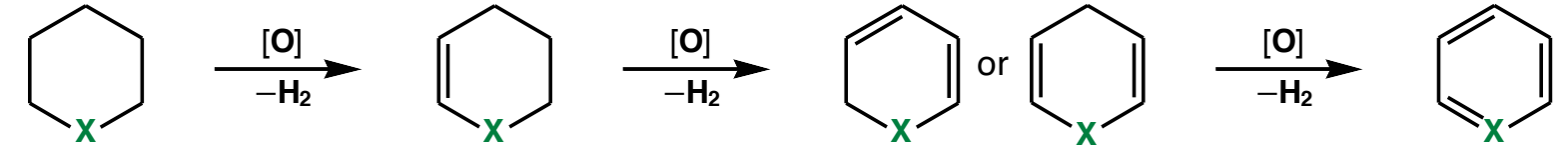
Ring Construction

- Cyclisation – 5- and 6-membered rings are the easiest to form
- C–X bond formation requires a heteroatom nucleophile to react with a *C* electrophile



X, Y = O, S, NR

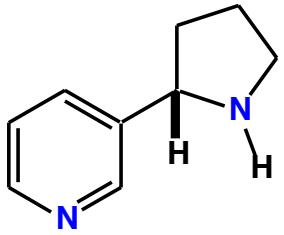
Manipulation of Oxidation State



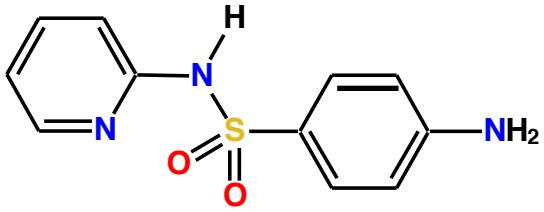
hexahydro tetrahydro dihydro aromatic

- Unsaturation is often introduced by elimination e.g. dehydration, dehydrohalogenation

Bioactive Pyridines

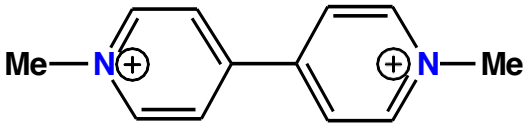


nicotine

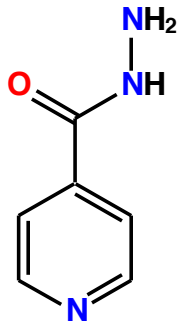


sulphapyridine

- Nicotine is pharmacologically active constituent of tobacco – toxic and addictive
- Sulphapyridine is a sulfonamide anti-bacterial agent – one of the oldest antibiotics



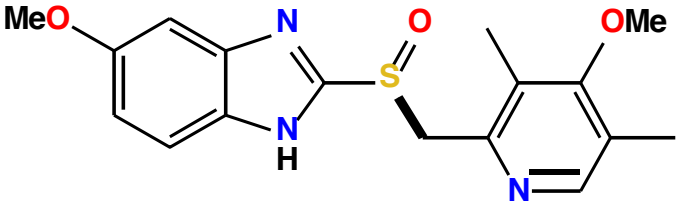
paraquat



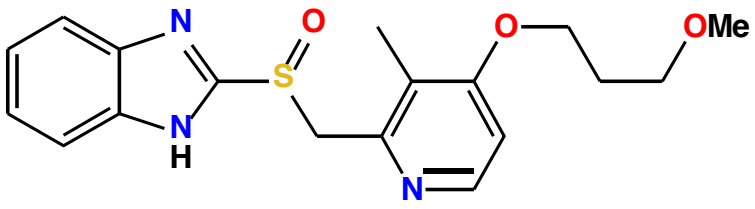
isoniazide

- Paraquat is one of the oldest herbicides – toxic and non-selective
- Isoniazide has been an important agent to treat tuberculosis – still used, but resistance is a significant and growing problem

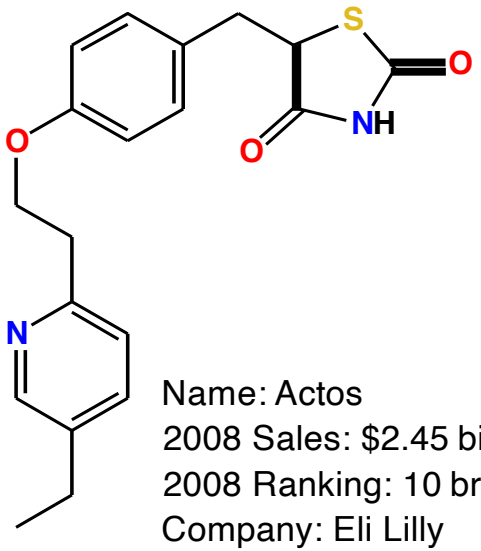
Drugs Containing a Pyridine



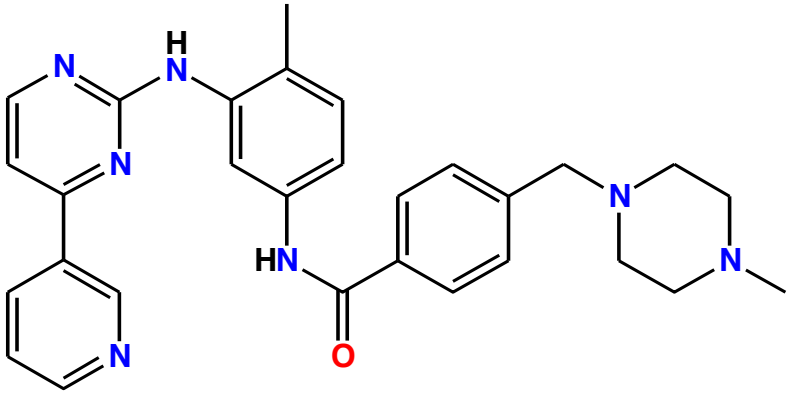
Name: Nexium
2008 Sales: $4.79 billion
2008 Ranking: 2 branded
Company: AstraZeneca
Disease: Acid reflux



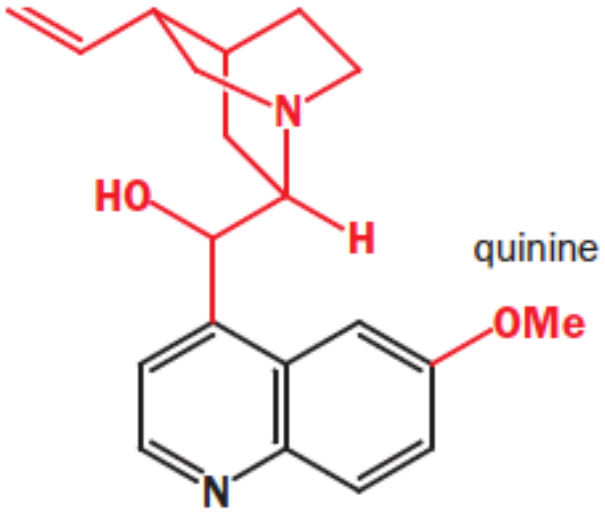
Name: Aciphex
2008 Sales: $1.05 billion
2008 Ranking: 34 branded
Company: Eisai
Disease: Duodenal ulcers and acid reflux



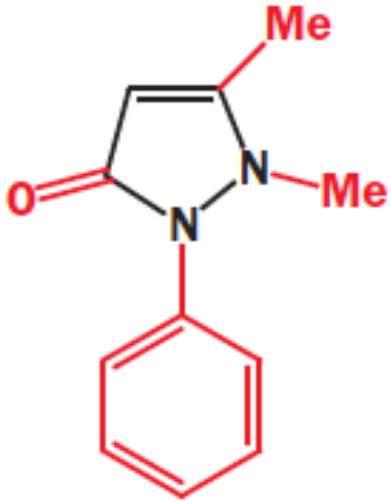
Name: Actos
2008 Sales: $2.45 billion
2008 Ranking: 10 branded
Company: Eli Lilly
Disease: Type 2 diabetes



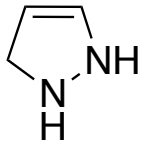
Name: Gleevec
2008 Sales: $0.45 billion
2008 Ranking: 87 branded
Company: Novartis
Disease: Chronic myeloid leukemia



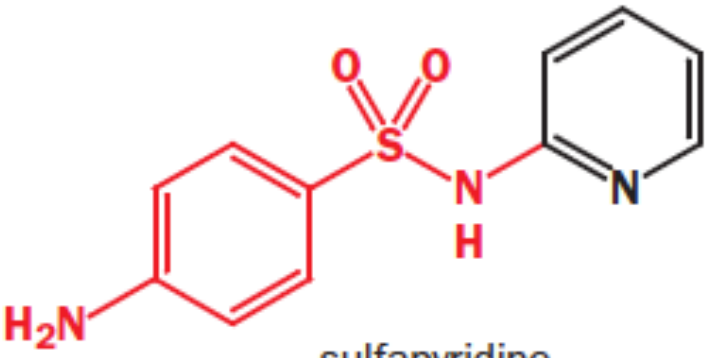
quinine



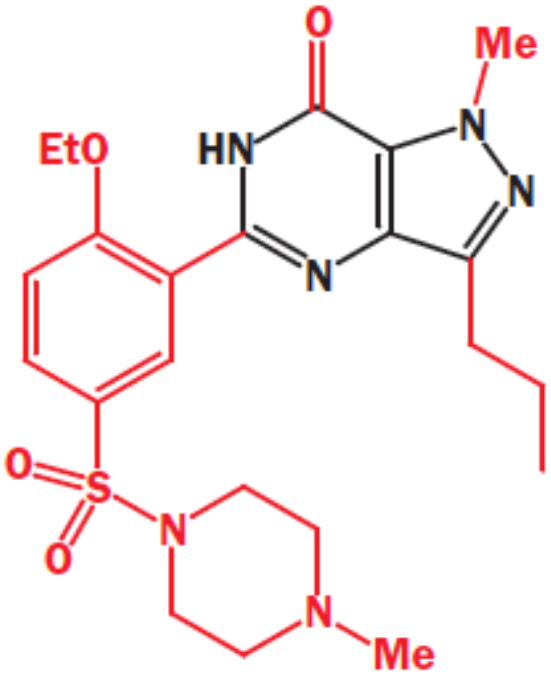
antipyrine



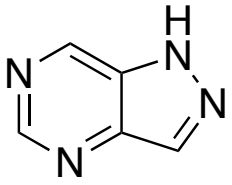
2,3-dihydro-1*H*-pyrazole



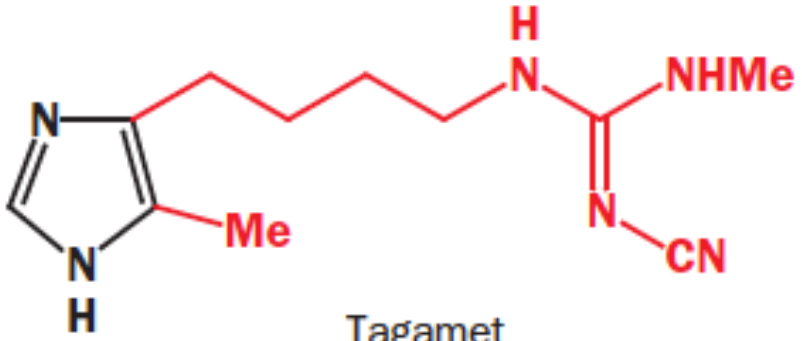
sulfapyridine



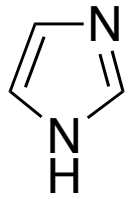
Viagra



1*H*-pyrazolo[4,3-*d*]pyrimidine

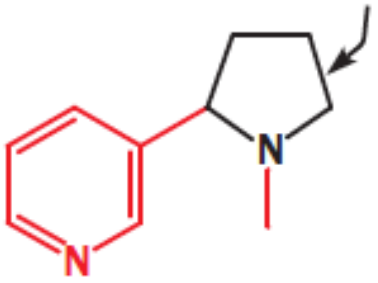


Tagamet



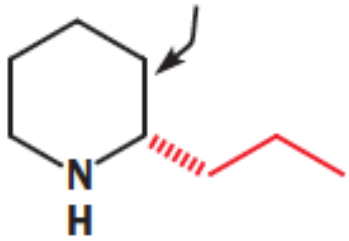
1*H*-imidazole

pyrrolidine ring



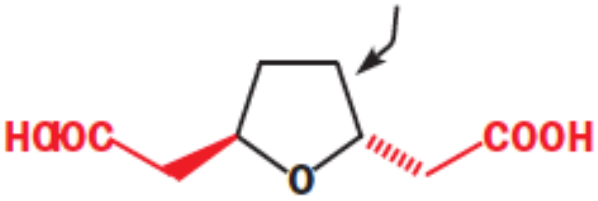
nicotine

piperidine ring



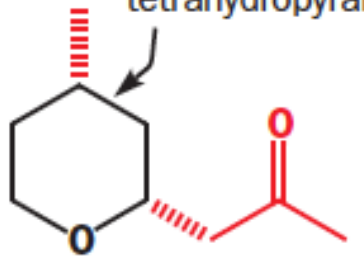
coniine – the poison in hemlock that killed Socrates

tetrahydrofuran ring

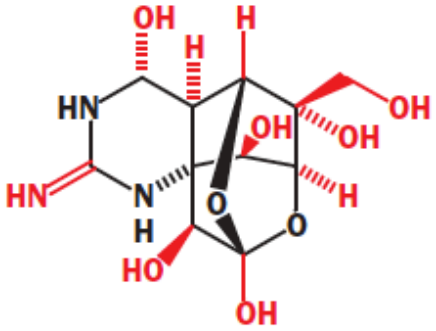


human waste product: 3–5 mg per day excreted in urine

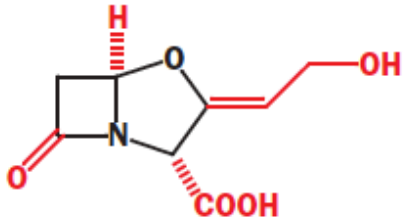
tetrahydropyran ring



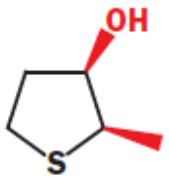
"rose oxide ketone" – isolated from geranium oil and used in the perfume industry



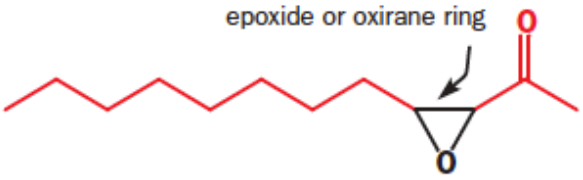
tetrodotoxin – lethal poison in wrongly prepared and cooked Japanese puffer fish



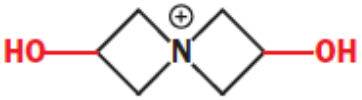
clavulanic acid – an antibiotic



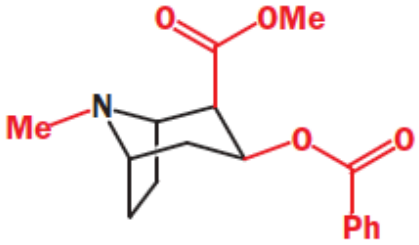
musty taste of "corked" wine



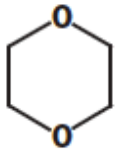
sex pheromone of the Grey Duiker antelope



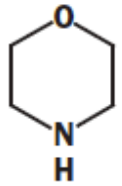
isolated from the green alga *Chara globularis*



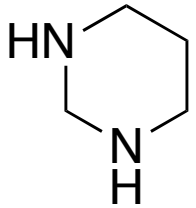
cocaine



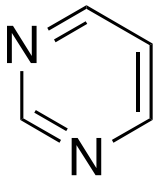
dioxane: a common solvent



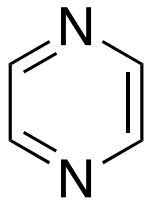
morpholine: an important base



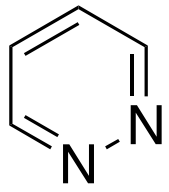
hexahydropyrimidine



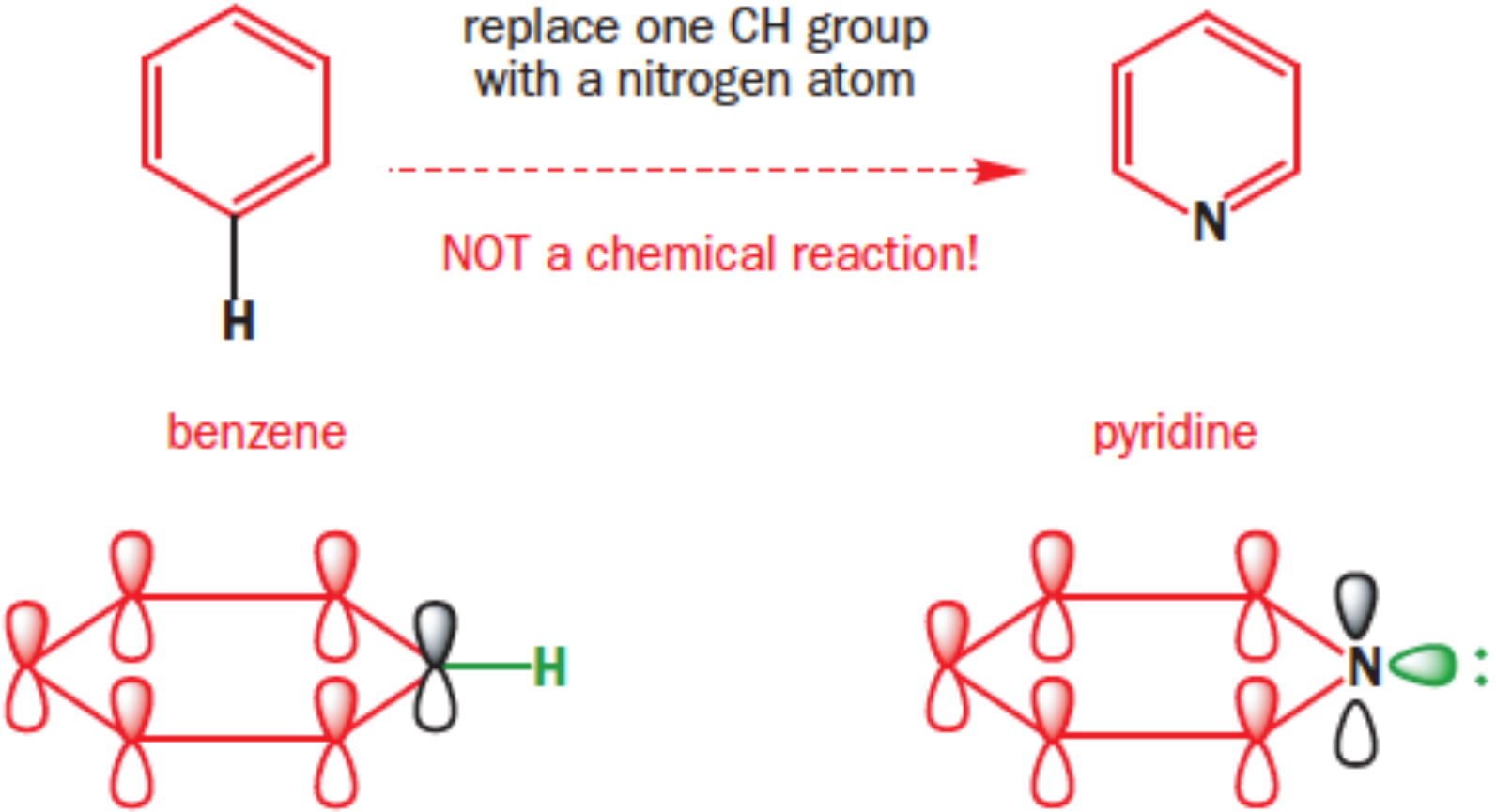
pyrimidine

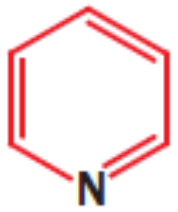


pyrazine



pyridazine

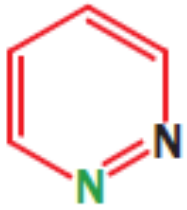

replace one CH group
with a nitrogen atom
NOT a chemical reaction!
H
N
benzene
pyridine
H
N
:



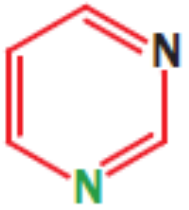
pyridine

replace one CH group
with a nitrogen atom

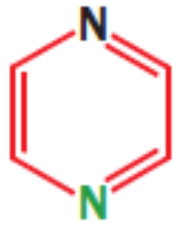
NOT a chemical reaction!



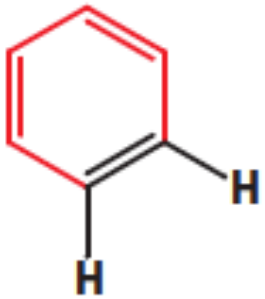
pyridazine



pyrimidine



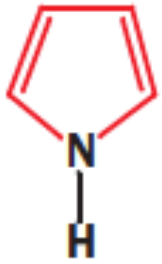
pyrazine



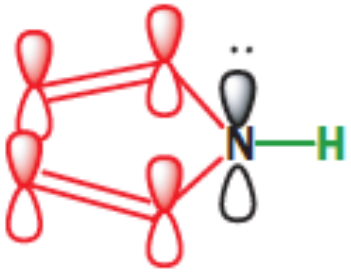
benzene

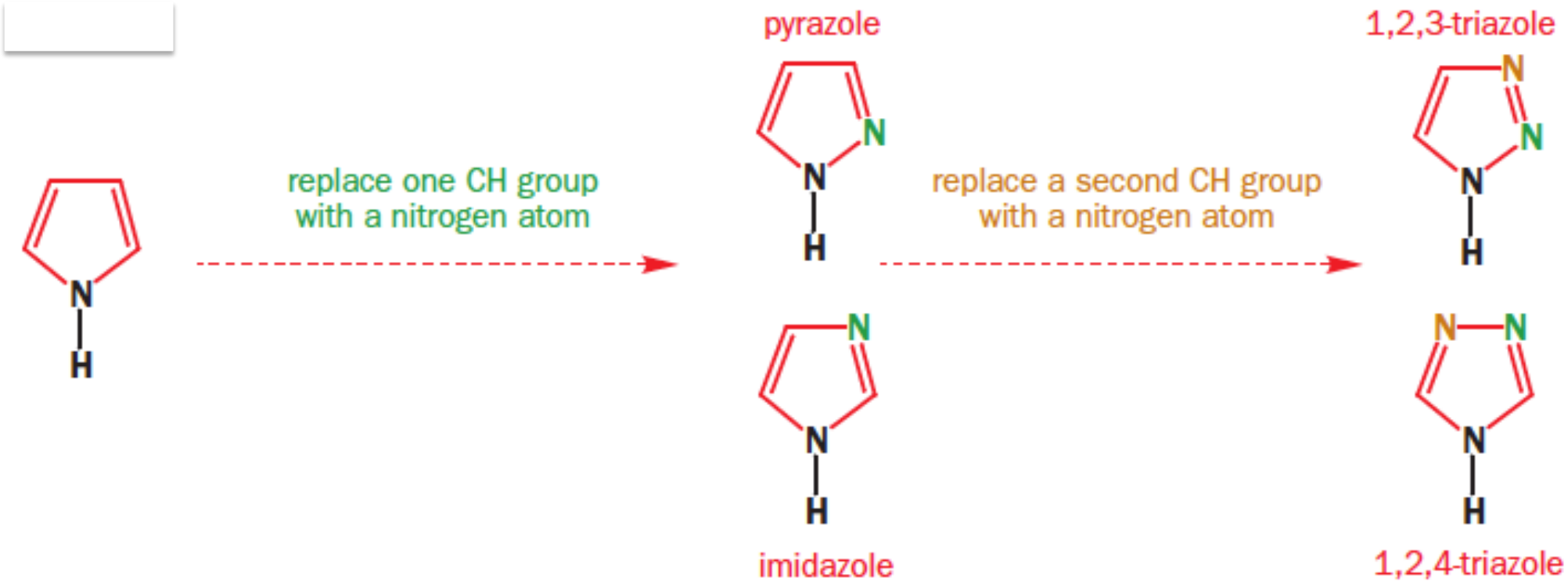
replace a CH=CH unit
with a nitrogen atom

NOT a chemical reaction!



pyrrole

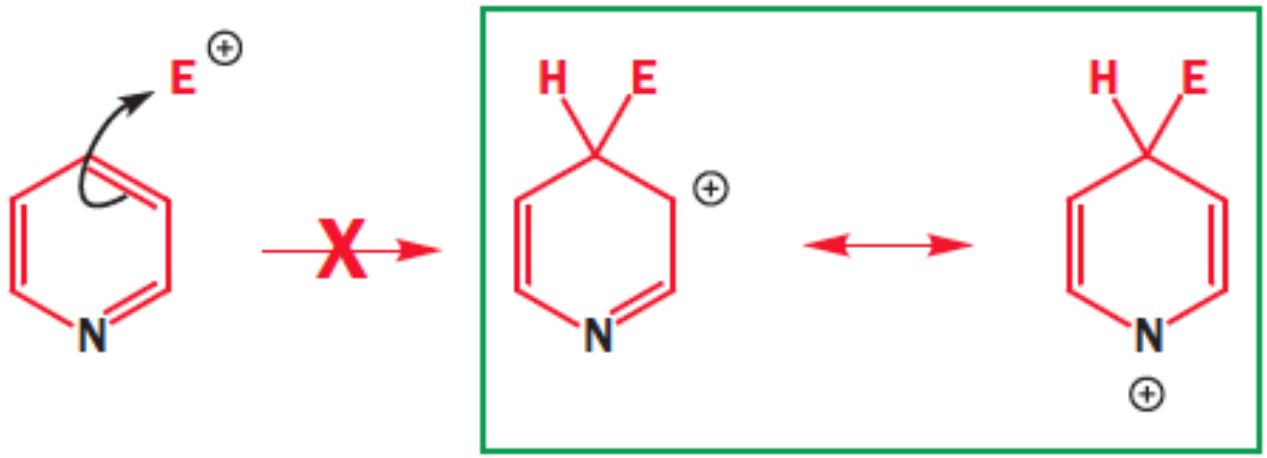



replace one CH group
with a nitrogen atom
pyrazole
imidazole
replace a second CH group
with a nitrogen atom
1,2,3-triazole
1,2,4-triazole

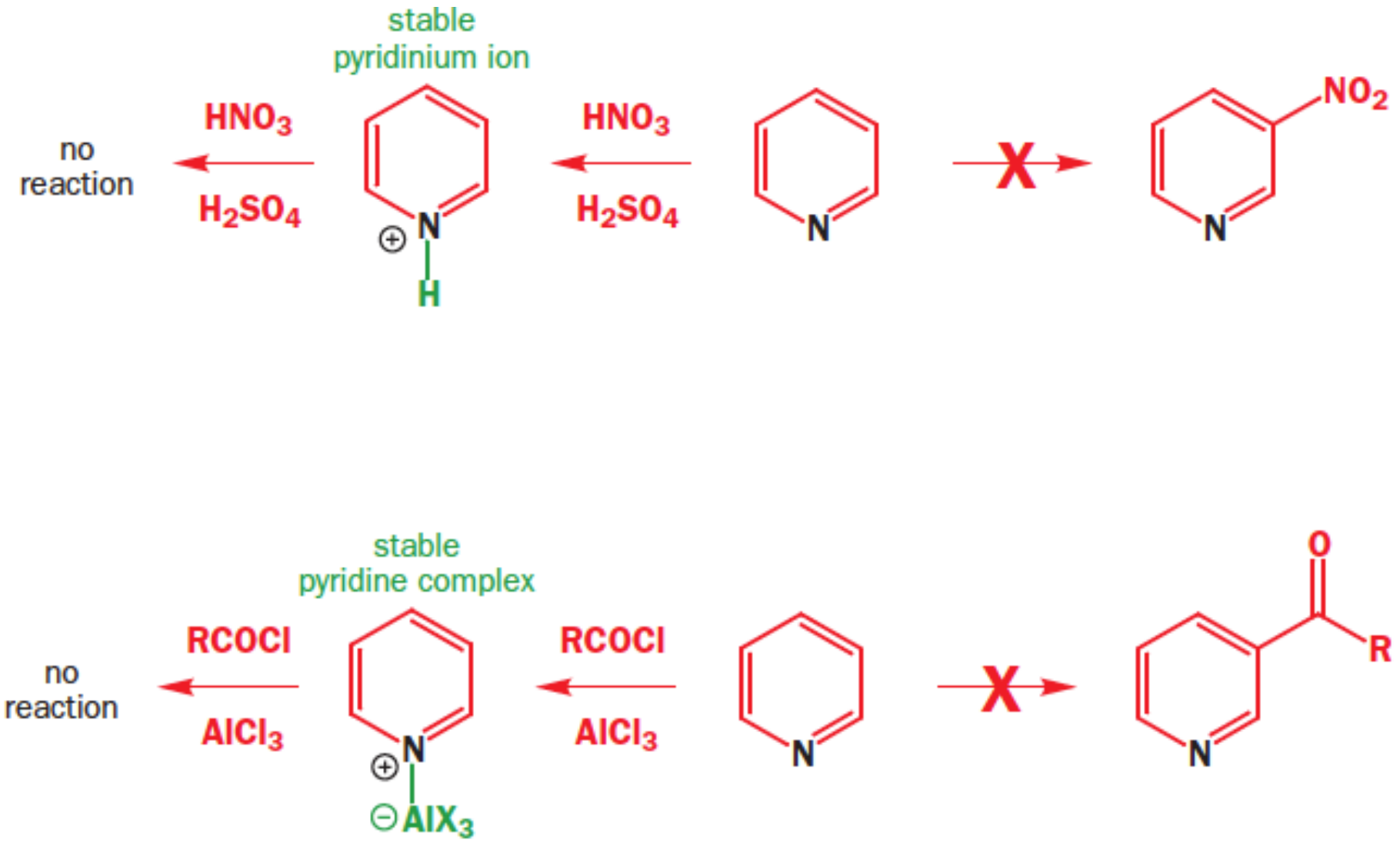
Pyridine is bad at Electrophilic Aromatic Substitution

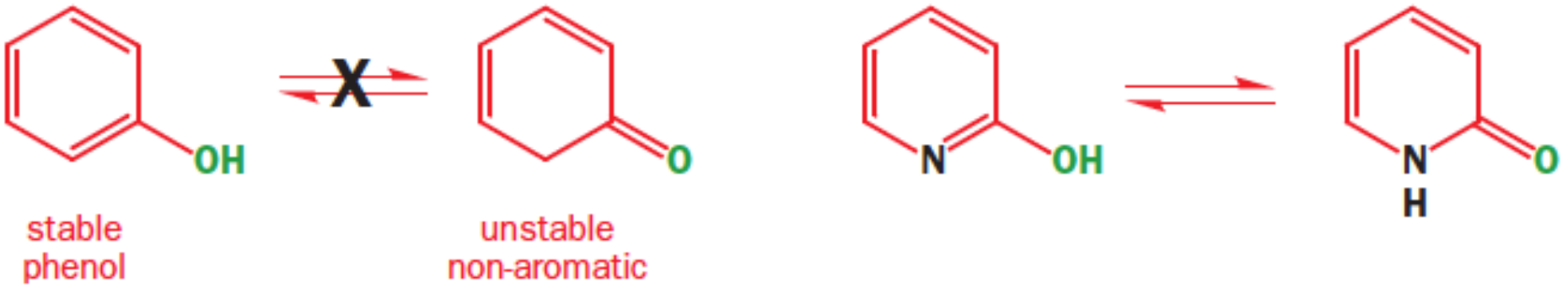
The important orbitals—the p orbitals of the aromatic system—are superficially the same as in benzene, but the more electronegative nitrogen atom will lower the energy of all the orbitals. Lower-energy filled orbitals mean a *less* reactive nucleophile but a lower-energy LUMO means a *more* reactive electrophile.

This is a good guide to the chemistry of pyridine. It is less reactive than benzene in electrophilic aromatic substitution reactions but nucleophilic substitution, which is difficult for benzene, comes easily to pyridine.



unstable electron-deficient cation

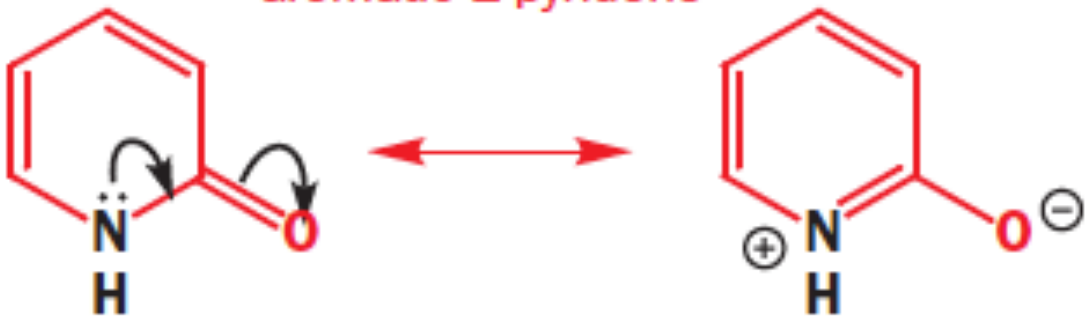

stable
pyridinium ion
HNO3
H2SO4
no
reaction
HNO3
H2SO4
N
H
N
X
NO2
N
stable
pyridine complex
RCOCl
AlCl3
no
reaction
RCOCl
AlCl3
N
AlX3
N
X
O
R
N

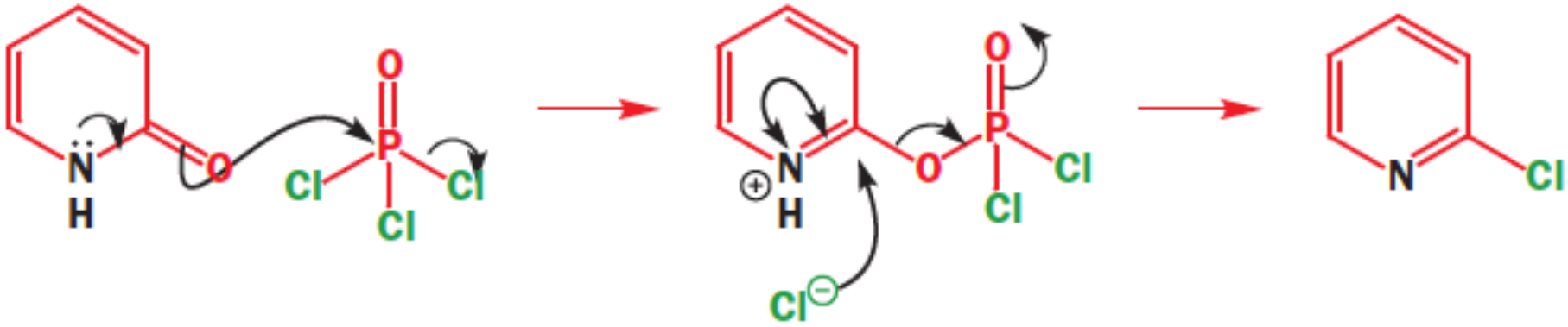


stable phenol

unstable non-aromatic

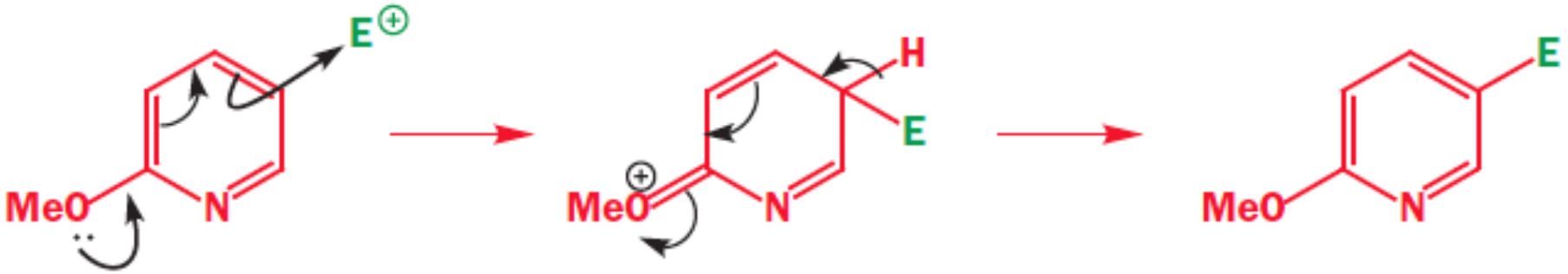
aromatic 2-pyridone

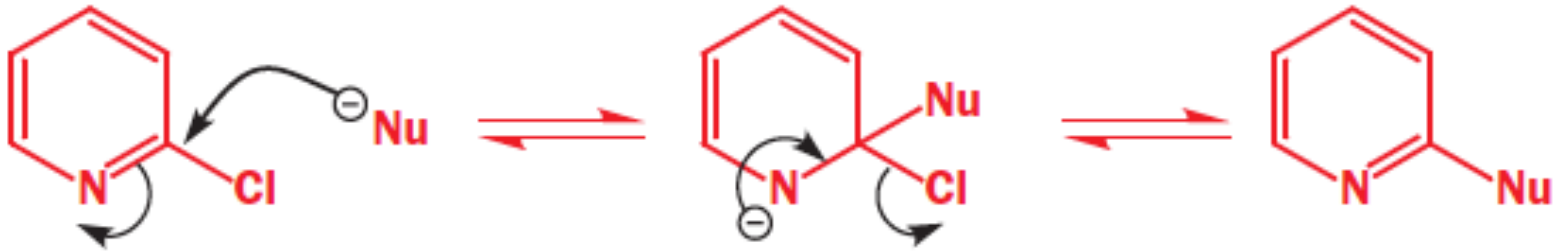



N
H
O
P
O
Cl
Cl
Cl
N
H
O
P
O
Cl
Cl
Cl
N
Cl

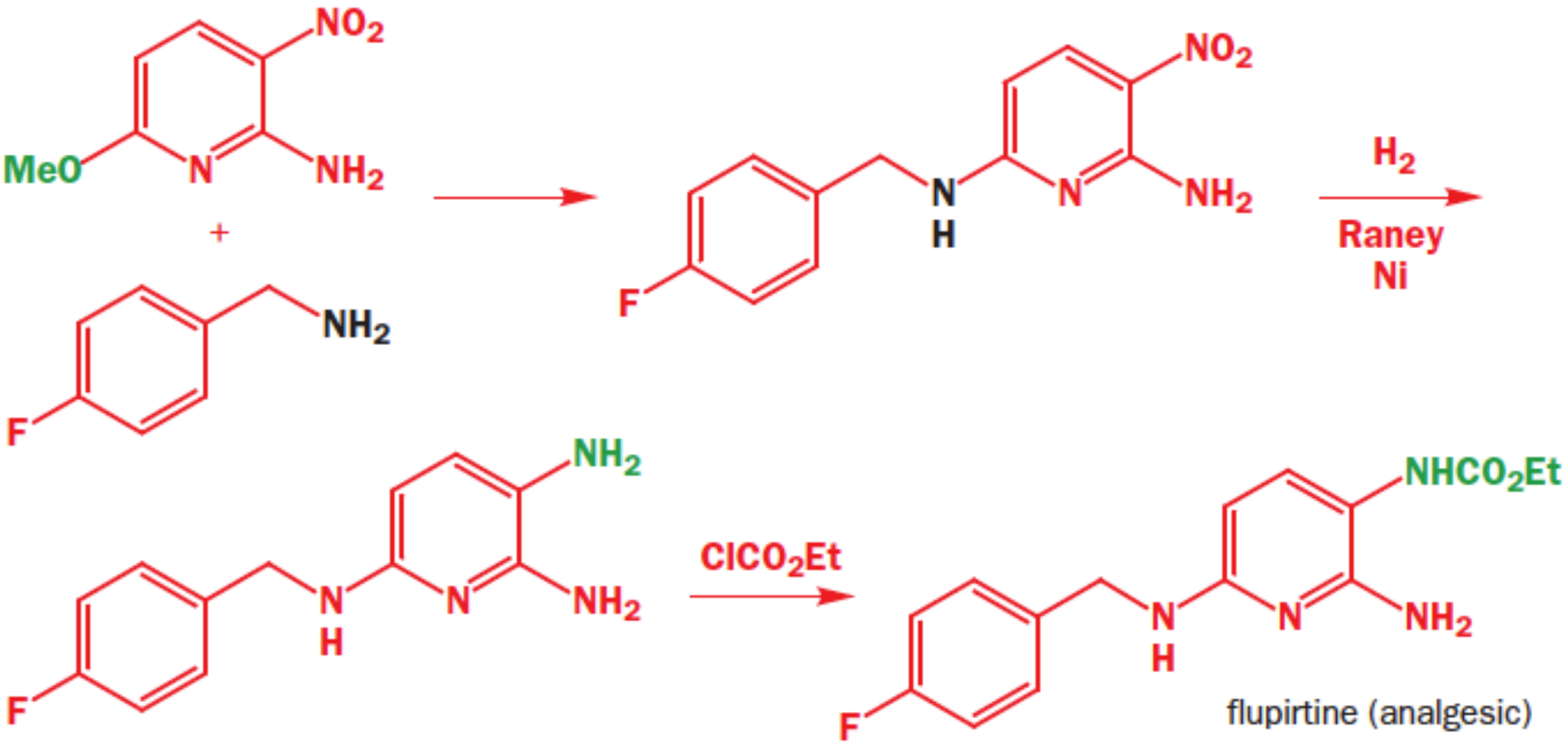
Pyridines undergo nucleophilic substitution

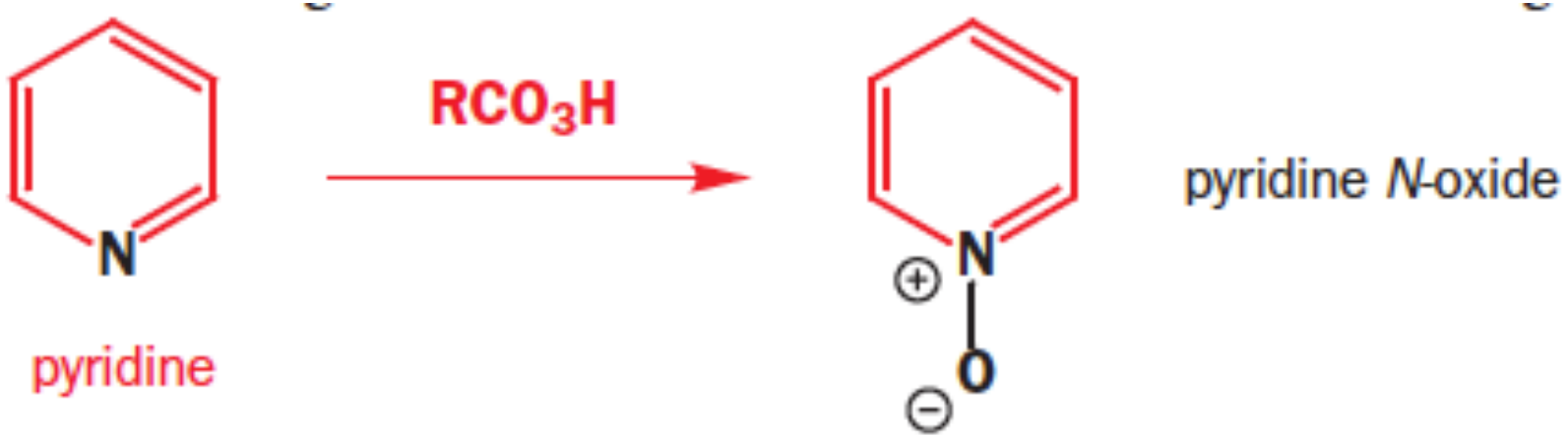
Pyridines can undergo *electrophilic* substitution only if they are activated by electron-donating substituents (see next section) but they readily undergo *nucleophilic* substitution without any activation other than the ring nitrogen atom.



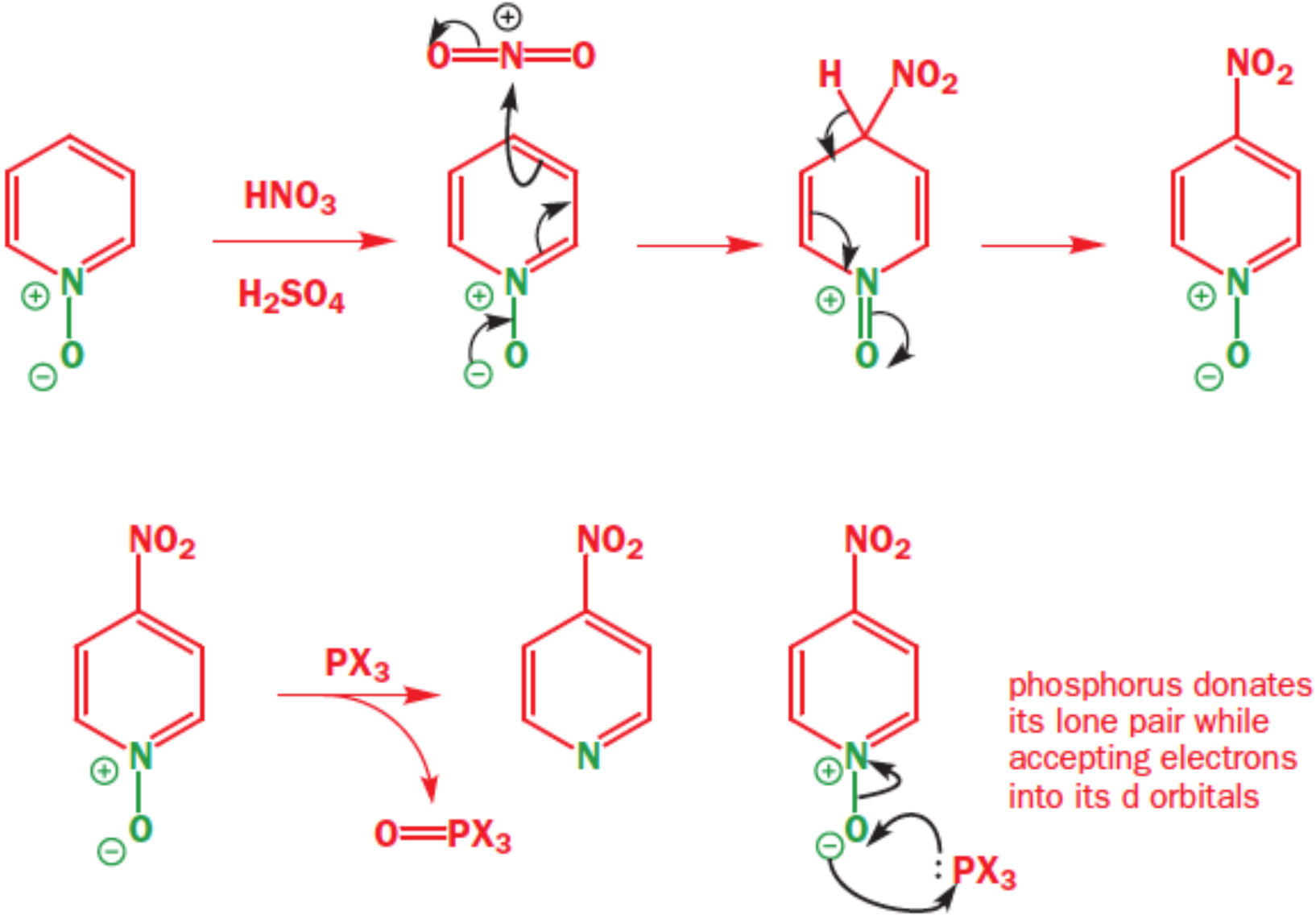


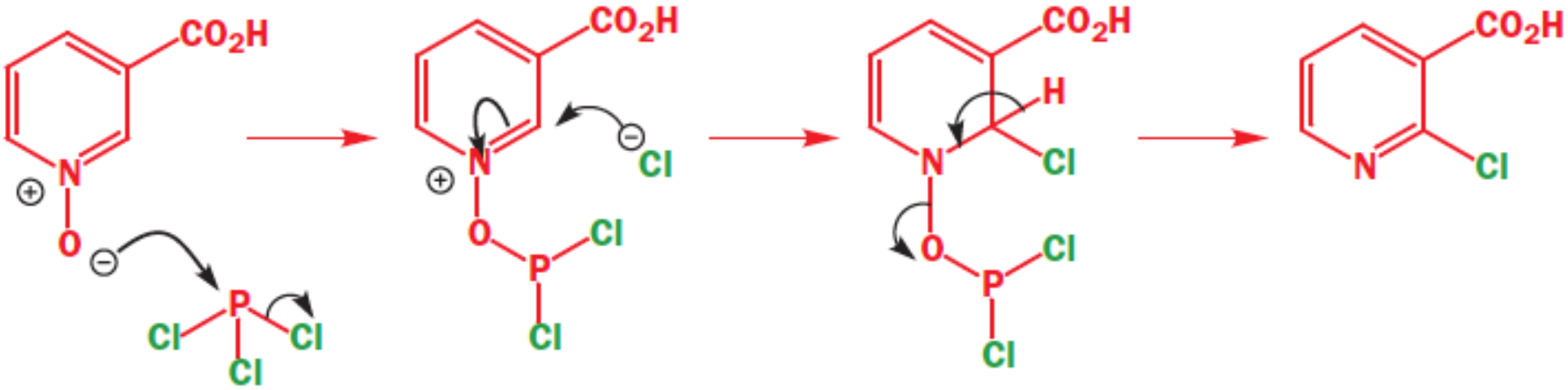
The synthesis of Flupirtine a common analgesic by pyridine electophilic substitution

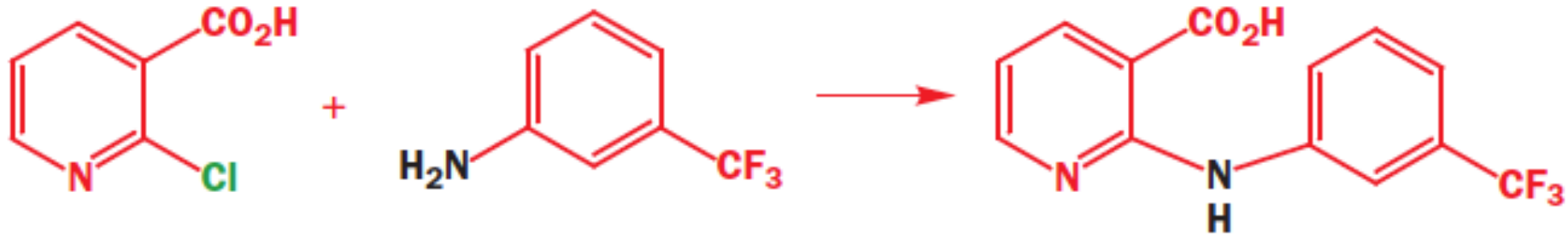




Because the nitrogen atom is nucleophilic, pyridine can be oxidized to pyridine *N* oxide with reagents such as *m*-CPBA or just H_2O_2 in acetic acid. These *N*-oxides are stable dipolar species with the electrons on oxygen delocalized round the pyridine ring, raising the HOMO of the molecule. Reaction with electrophiles occurs at the 2- ('*ortho*') and 4- ('*para*') positions, chiefly at the 4-position to keep away from positively charged nitrogen.


HNO3
H2SO4
PX3
O=PX3
phosphorus donates its lone pair while accepting electrons into its d orbitals

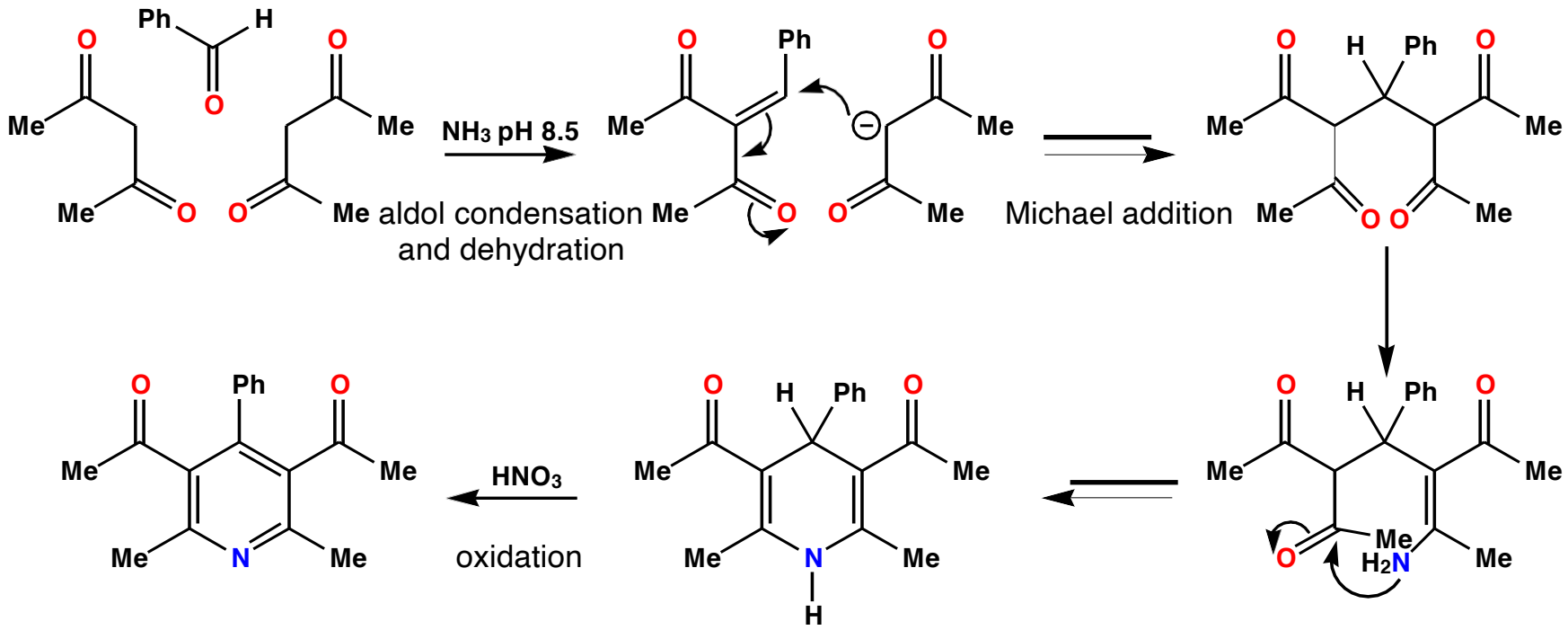




nifluminic acid - analgesic

Pyridines – Synthesis

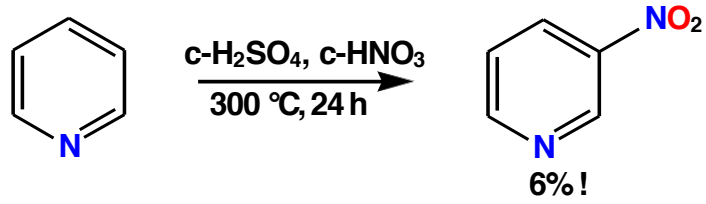
The Hantzsch synthesis ("5+1")



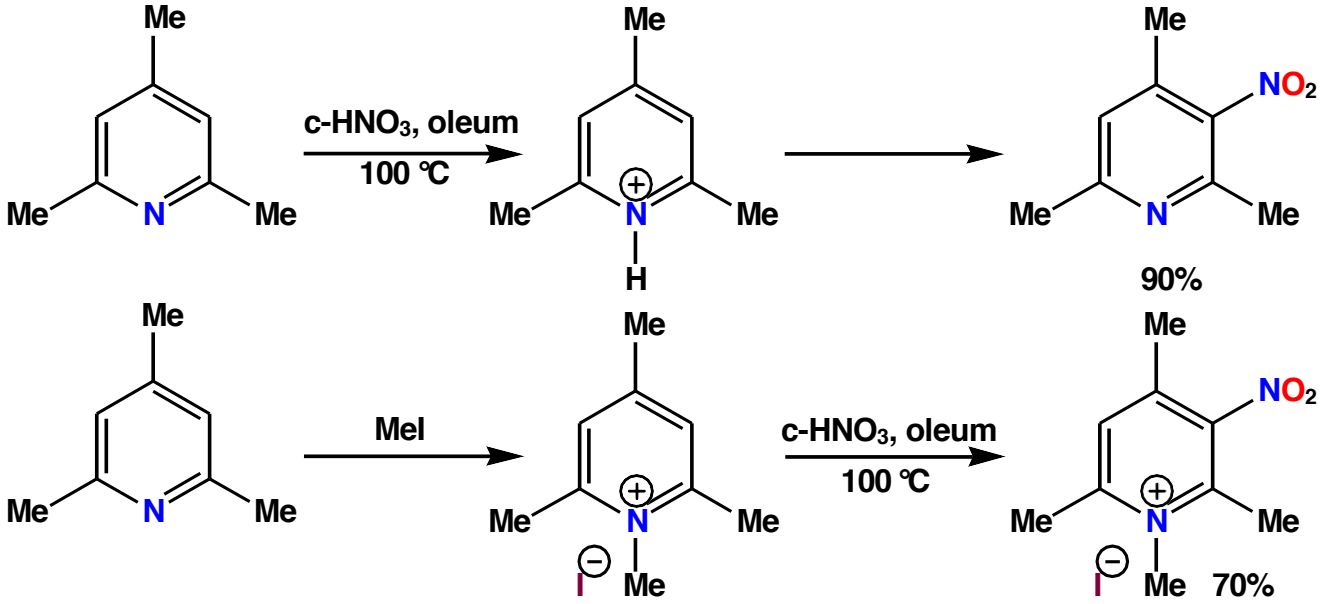
- The reaction is useful for the synthesis of symmetrical pyridines
- The 1,5-diketone intermediate can be isolated in certain circumstances
- A separate oxidation reaction is required to aromatise the dihydropyridine

Pyridines – Electrophilic Reactions

Nitration of Pyridine



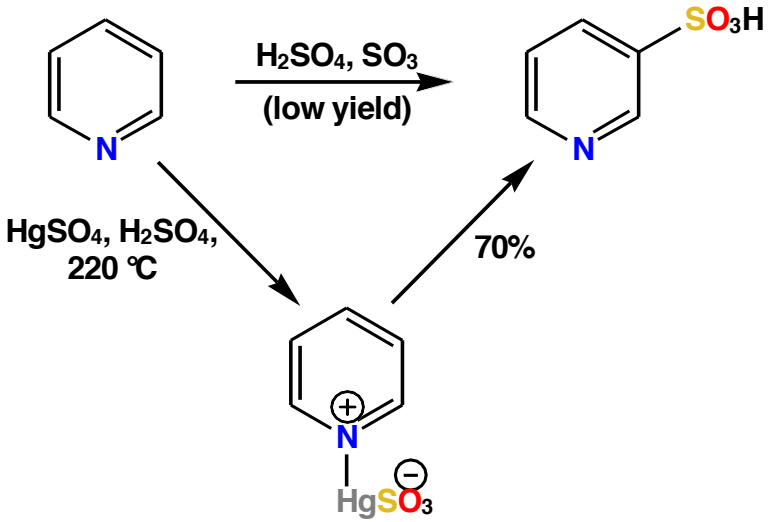
Use of Activating Groups



- Multiple electron-donating groups accelerate the reaction
- Both reactions proceed at similar rates which indicates that the protonation at *N* occurs prior to nitration in the first case

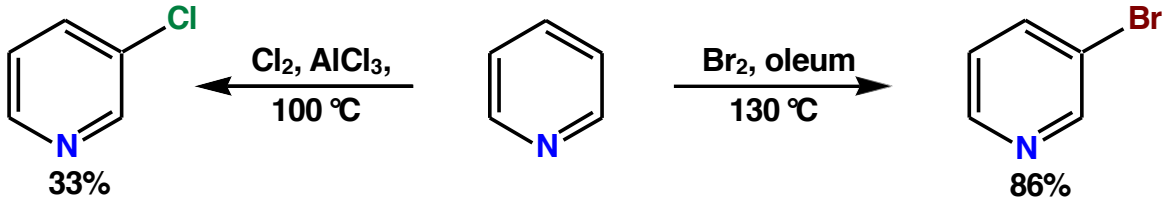
Pyridines – Electrophilic Reactions

Sulfonation of Pyridine



• Low yield from direct nitration but good yield via a mercury intermediate

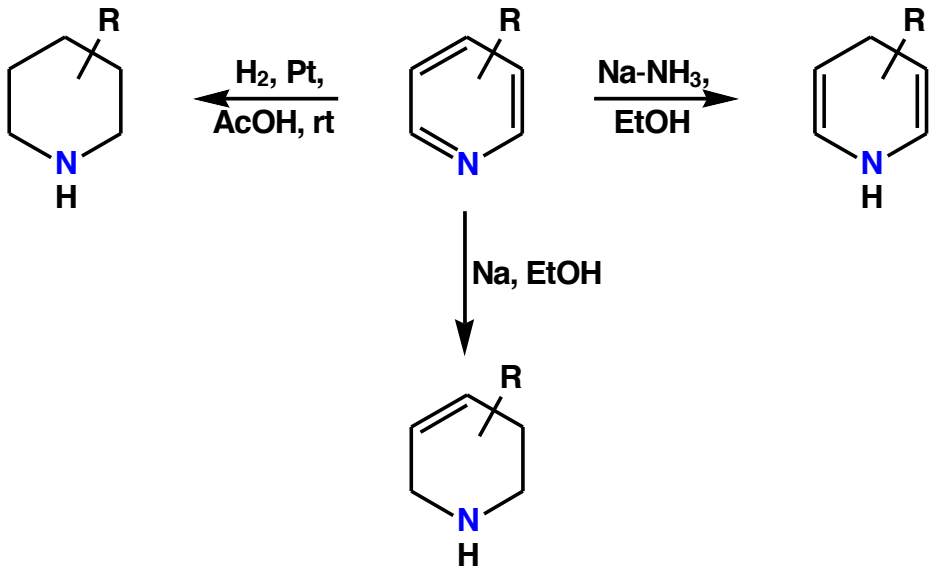
Halogenation of Pyridine



• Forcing reaction conditions are required for direct halogenation

Pyridines – Reduction

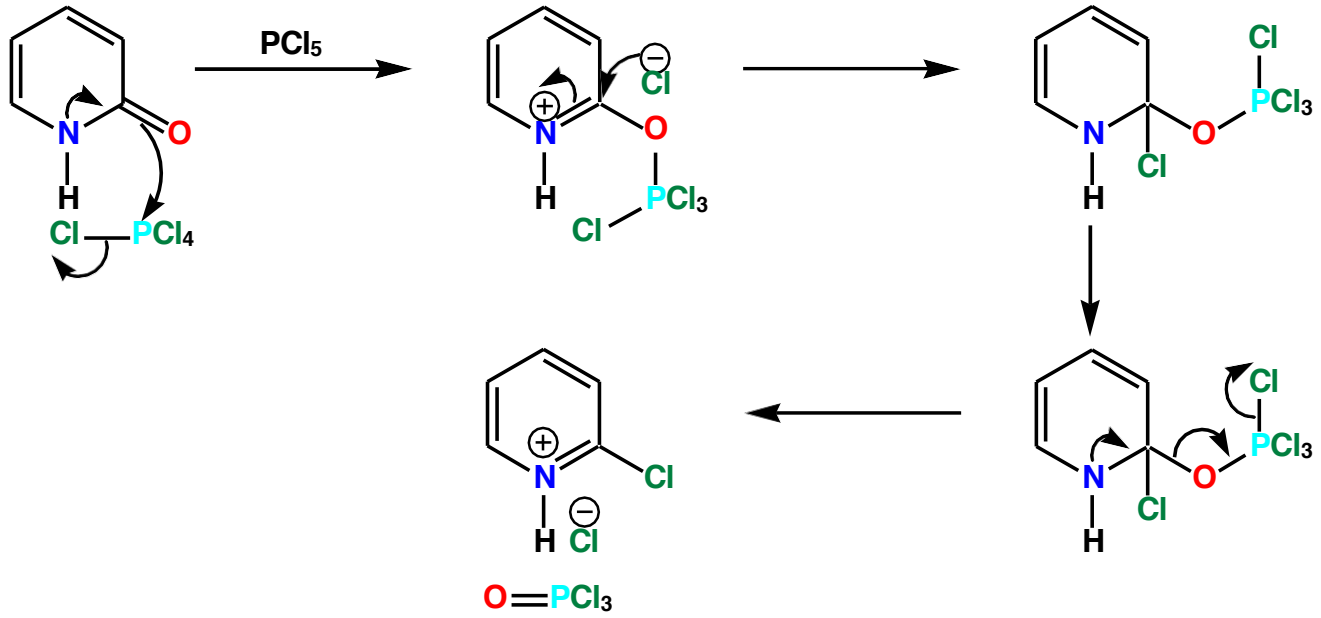
Full or Partial Reduction of Pyridines



- Pyridines generally resist oxidation at ring carbon atoms and will often undergo side-chain oxidation in preference to oxidation of the ring
- Full or partial reduction of the ring is usually easier than in the case of benzene

Oxy-Pyridines – Reactions

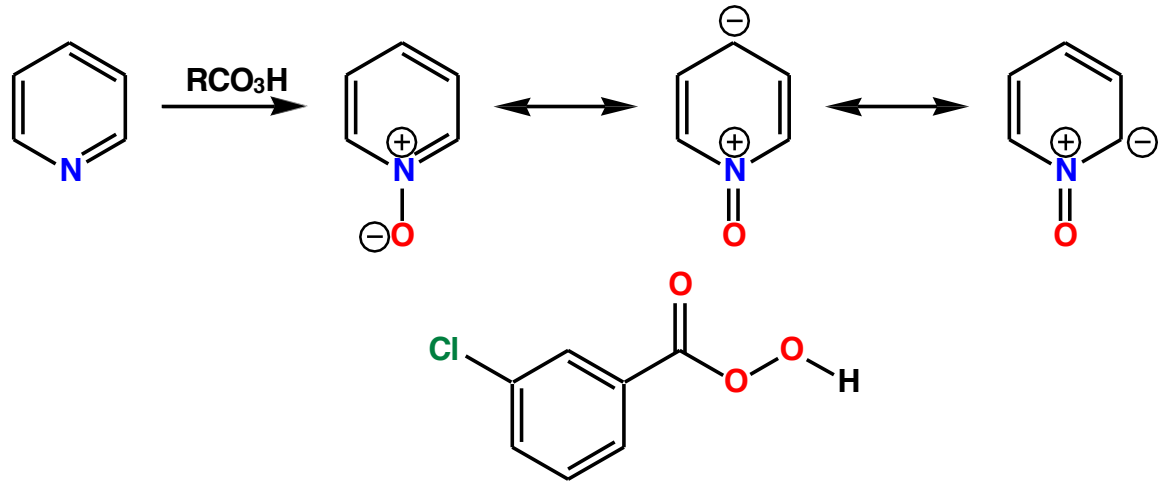
Nucleophilic Substitution



- Replacement of the oxygen substituent is possible
- In this case, the reaction is driven by the formation of the very strong P=O bond

Pyridine *N*-Oxides

N-Oxide Formation

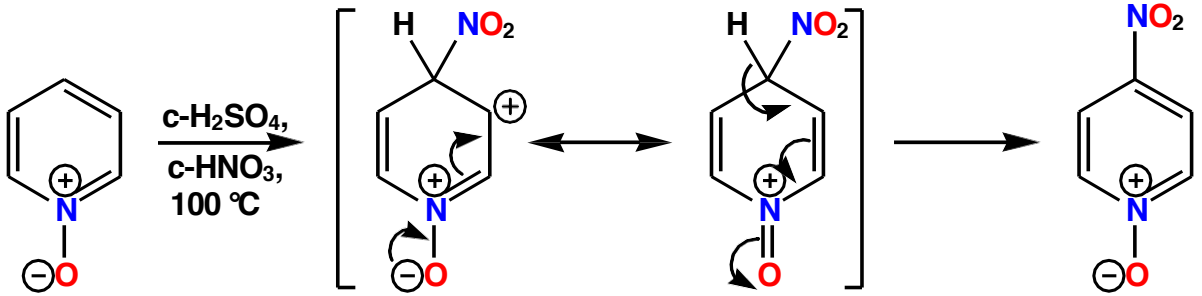


***meta*-chloroperoxybenzoic acid (*m*-CPBA)**

- The reactivity *N*-oxides differs considerably from that of pyridines or pyridinium salts
- A variety of peracids can be used to oxidise *N* but *m*-CPBA is used most commonly
- *N*-Oxide formation can be used to temporarily activate the pyridine ring to both nucleophilic and electrophilic attack

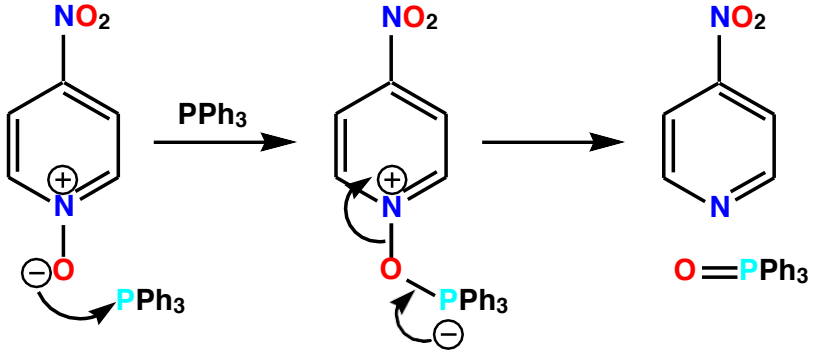
Pyridine *N*-Oxides

Electrophilic Substitution



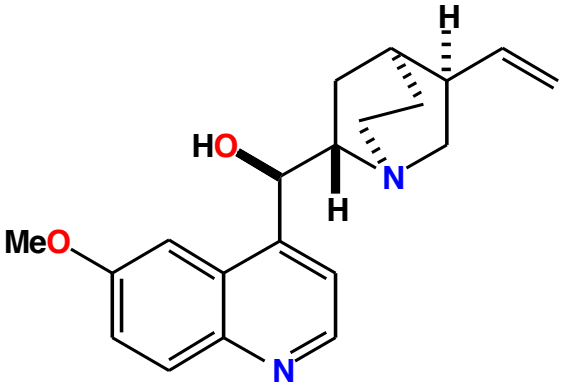
- The *N*-oxide is activated to attack by electrophiles at both the α and γ positions
- Nitration of an *N*-oxide is easier than nitration of the parent pyridine
- Reactivity is similar to that of a pyridinium salt in many cases e.g. nucleophilic attack, deprotonation of alkyl groups etc.

Removal of *O*

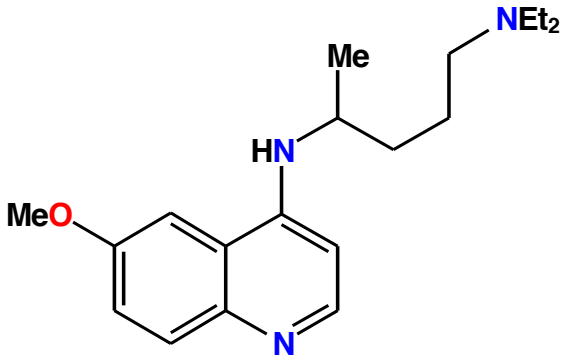


- Deoxgenation is driven by the formation of the very strong P=O bond

Bioactive Quinolines/Isoquinolines

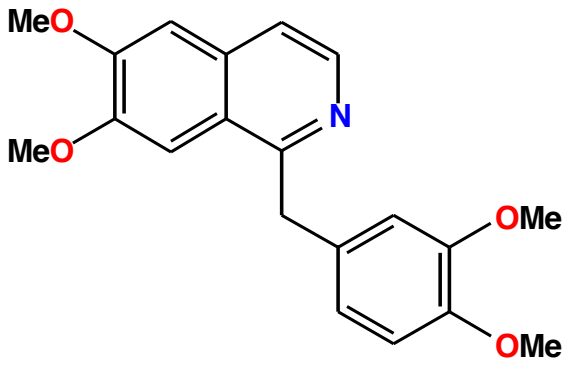


quinine



chloroquine

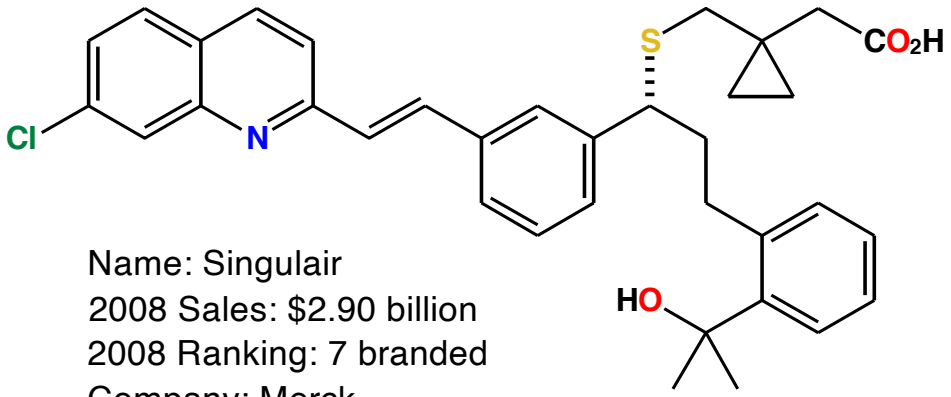
- Quinine is an anti-malarial natural product isolated from the bark of the *Cinchona* tree
- Chloroquine is a completely synthetic anti-malarial drug that has the quinoline system found in quinine – parasite resistance is now a problem



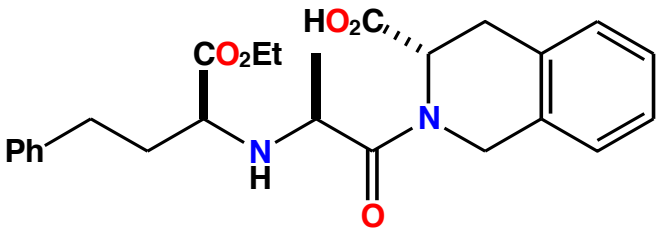
papaverine

- Papaverine is an alkaloid isolated from the opium poppy and is a smooth muscle relaxant and a coronary vasodilator

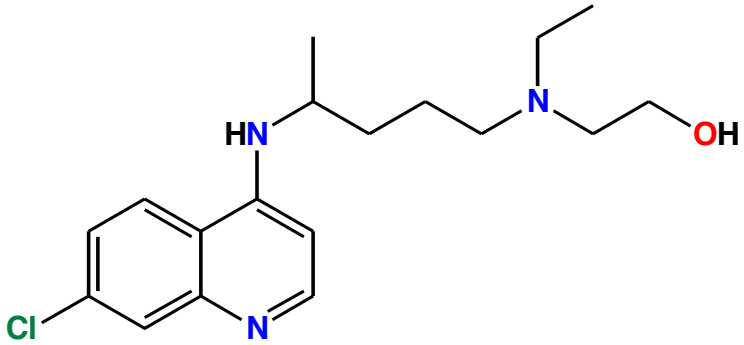
Drugs Containing a Quinoline/Isoquinoline



Name: Singulair
2008 Sales: $2.90 billion
2008 Ranking: 7 branded
Company: Merck
Disease: Asthma and allergies



Name: Quinapril
2008 Sales: $133 million
2008 Ranking: 84 generic
Company: N/A
Disease: Hypertension and heart failure

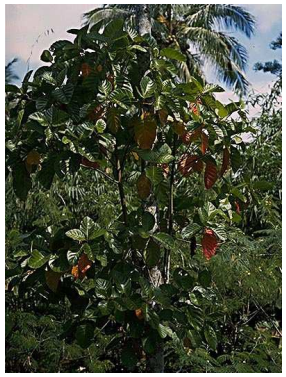


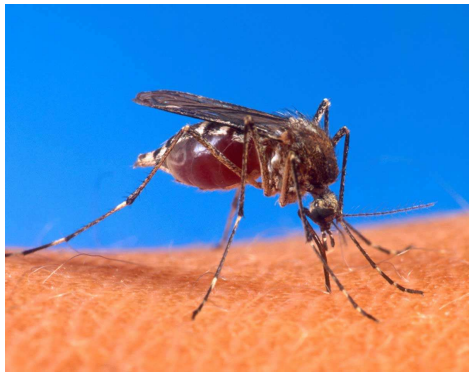
Name: Hydroxychloroquine
2008 Sales: $74 million
2008 Ranking: 146 generic
Company: N/A
Disease: Malaria, lupus erythematosus, rheumatoid arthritis

Malaria

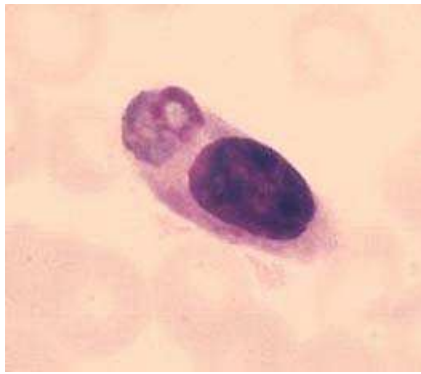
- Approximately 500 million cases of malaria each year and 1–3 million deaths
- Disease is caused by protazoan parasites of the genus *Plasmodium* (*falciparum*, *vivax, ovale and malariae*)
- Disease spread by the *Anopheles* mosquito (female)

Cinchona pubescens





Anopheles mosquito



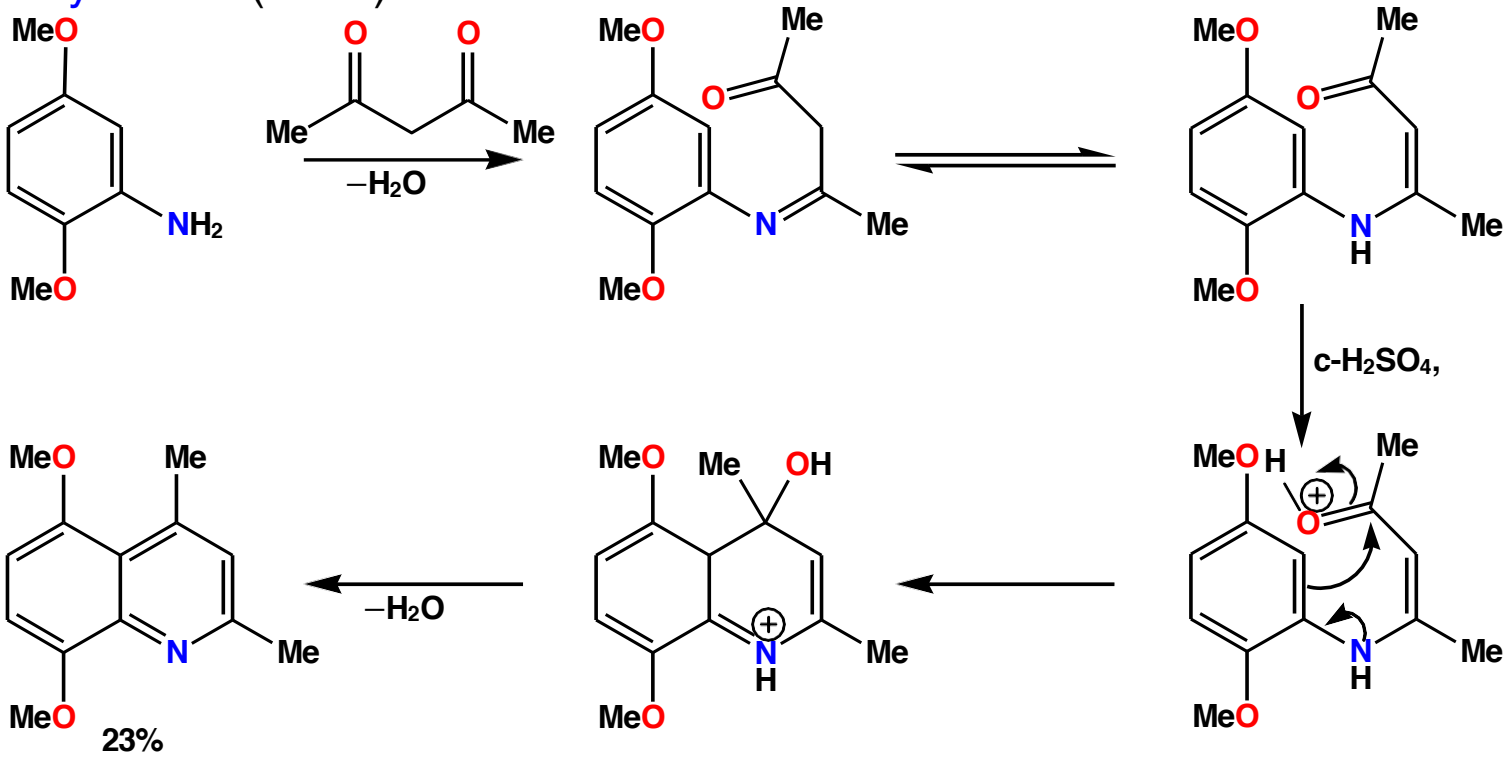
Plasmodium monocyte

Quinolines – Synthesis

Structure

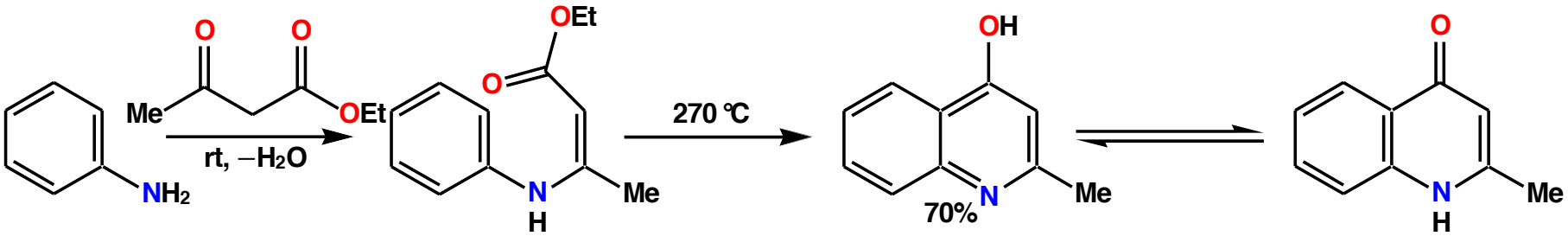
- pK_a values (4.9 and 5.4) are similar to that of pyridine
- Possess aspects of pyridine and naphthalene reactivity e.g. form *N*-oxides and ammonium salts

Combes Synthesis ("3+3")

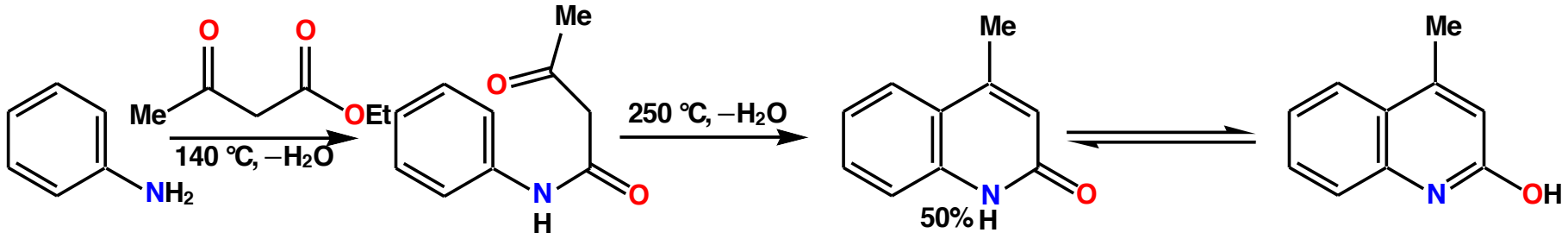


Quinolines – Synthesis

Conrad-Limpach-Knorr Synthesis ("3+3")

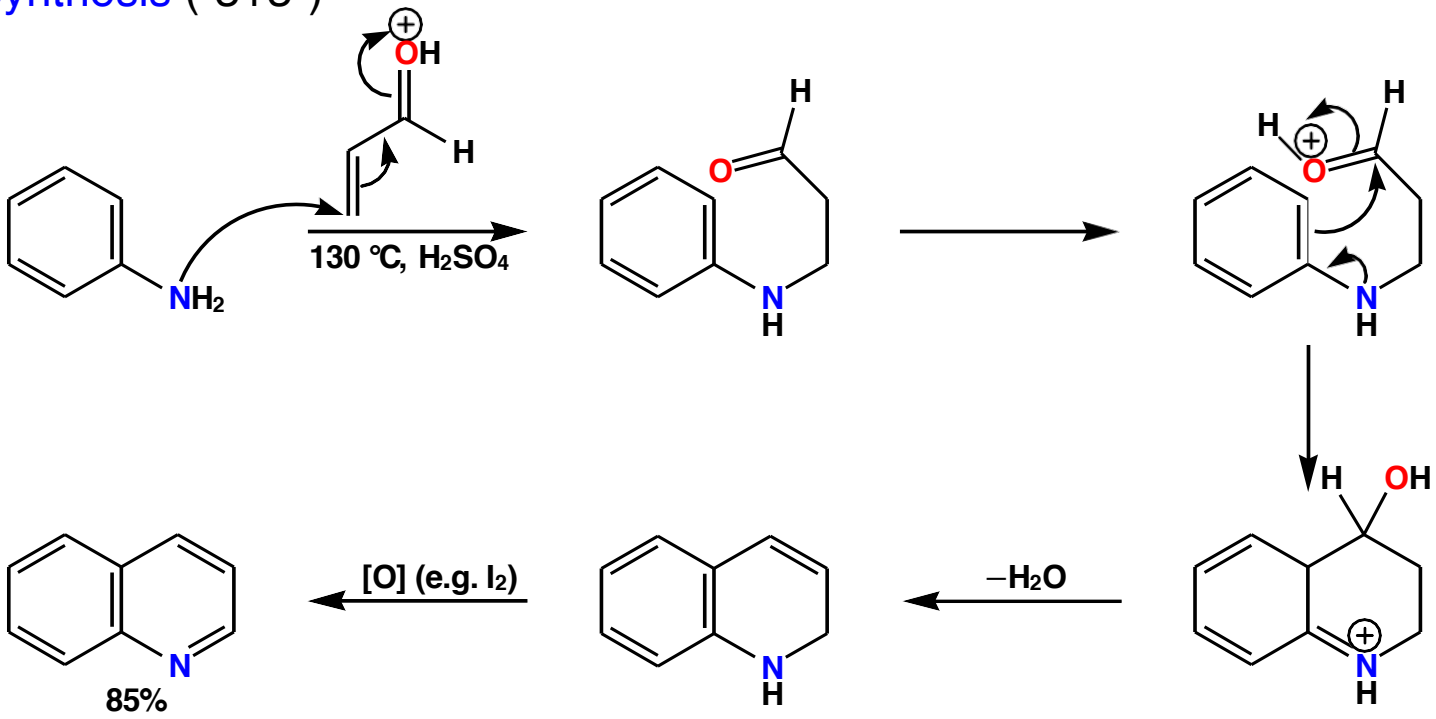


- Very similar to the Combes synthesis by a β-keto ester is used instead of a β-diketone
- Altering the reaction conditions can completely alter the regiochemical outcome

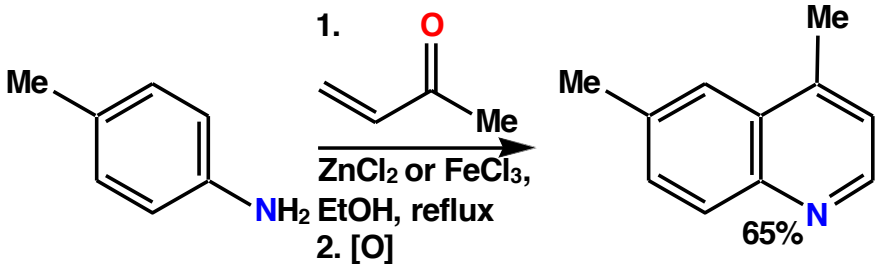


Quinolines – Synthesis

Skraup Synthesis ("3+3")

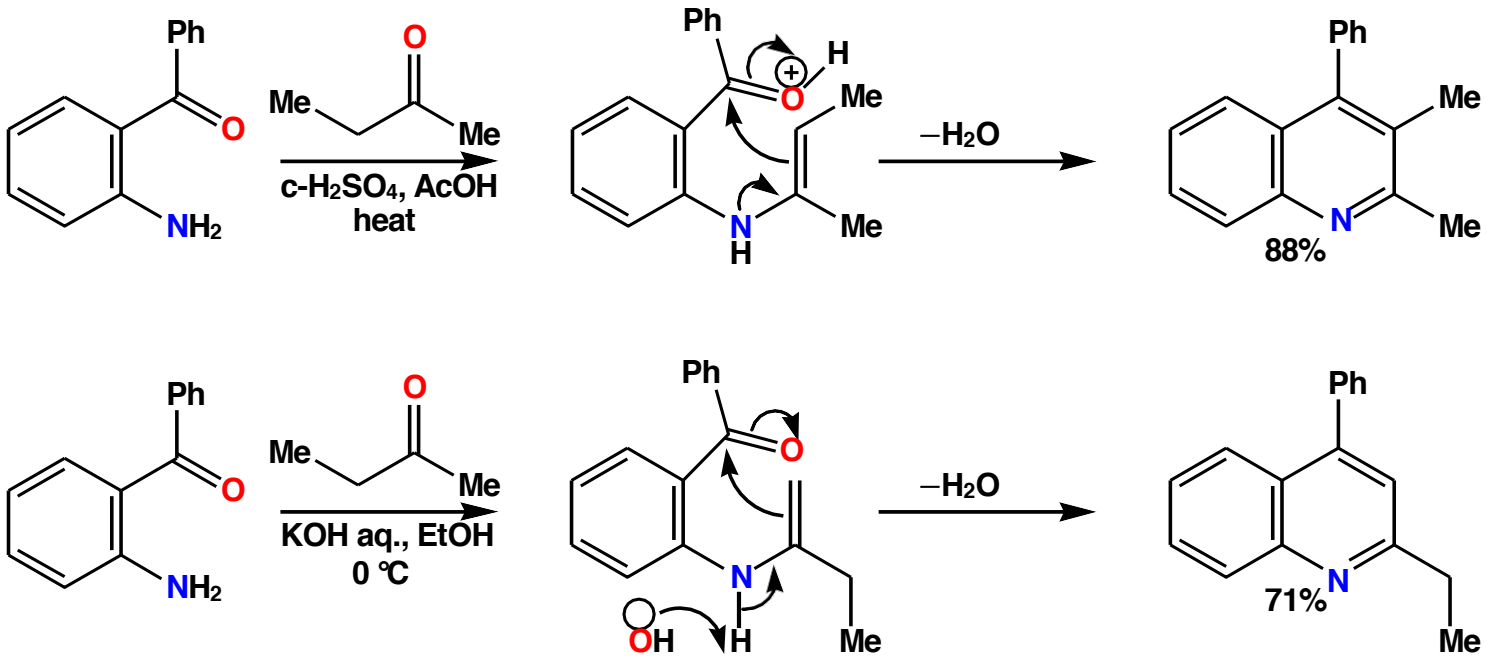


- Acrolein can be generated *in situ* by treatment of glycerol with conc. sulfuric acid
- A mild oxidant is required to form the fully aromatic system from the dihydroquinoline



Quinolines – Synthesis

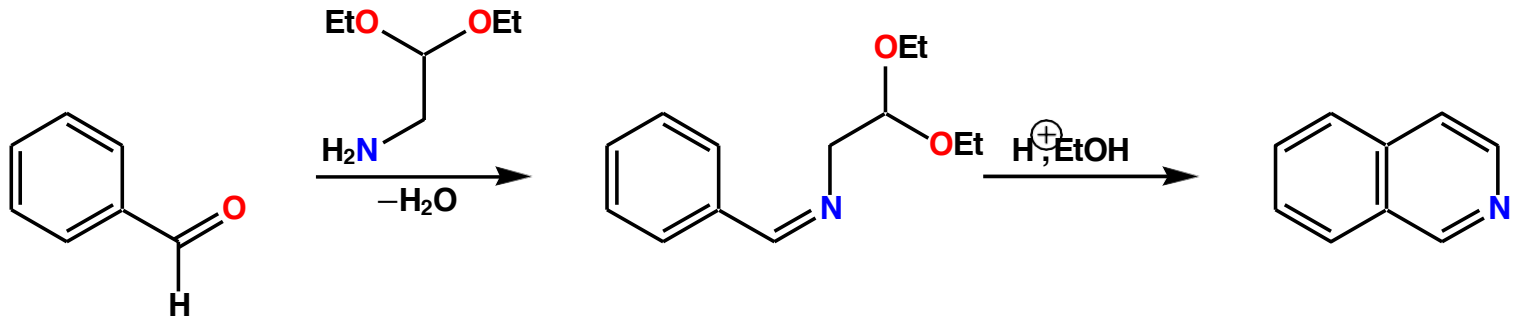
Friedlander Synthesis ("4+2")



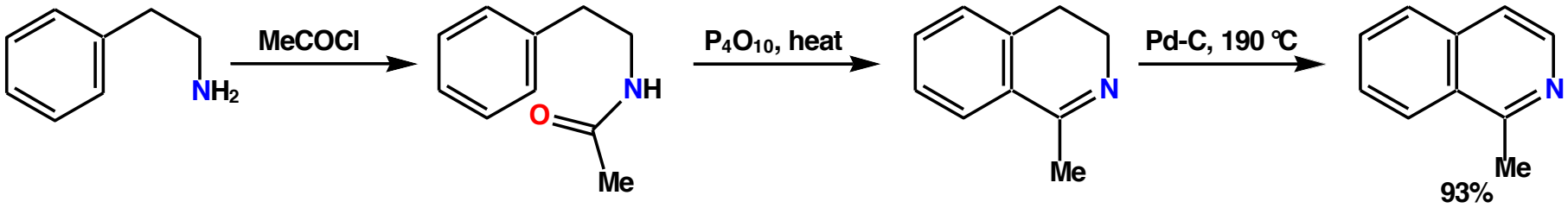
- The starting acyl aniline can be difficult to prepare
- Acidic and basic conditions deliver regioisomeric products in good yields

Isoquinolines – Synthesis

Pomeranz-Fritsch Synthesis ("3+3")



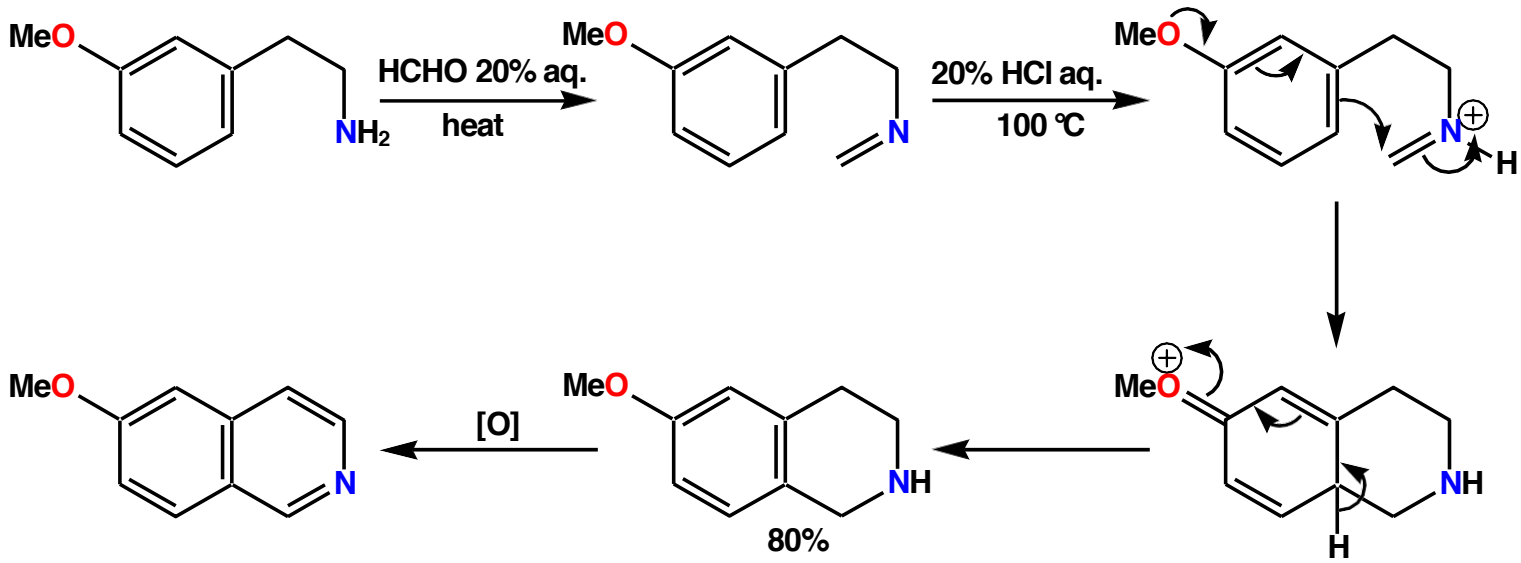
Bischler-Napieralski Synthesis ("5+1")



- Cyclisation can be accomplished using $POCl_3$ or PCl_5
- Oxidation of the dihydroisoquinoline can be performed using a mild oxidant

Isoquinolines – Synthesis

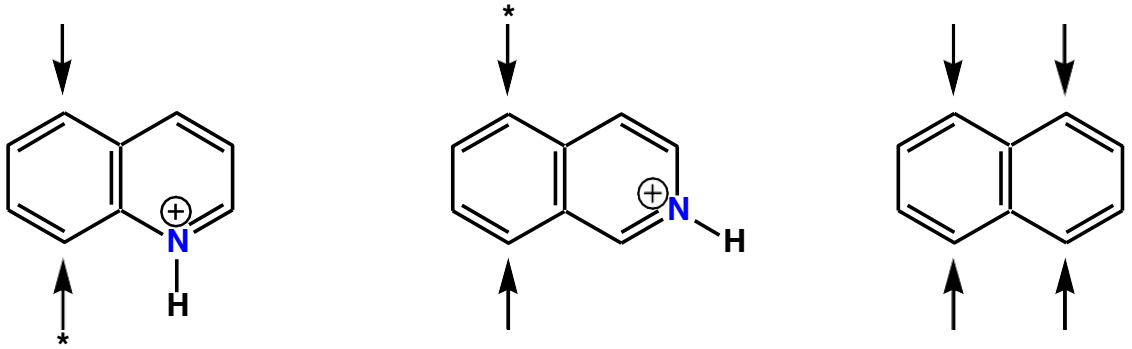
Pictet Spengler Synthesis ("5+1")



- An electron-donating substituent on the carboaromatic ring is required
- A tetrahydroisoquinoline is produced and subsequent oxidation is required to give the fully aromatic isoquinoline

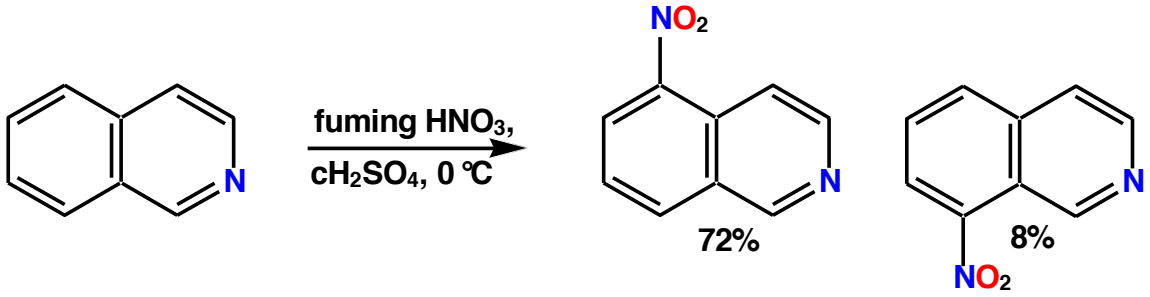
Quinolines/Isoquinolines – Electrophilic Reactions

Regiochemistry



- Under strongly acidic conditions, reaction occurs *via* the ammonium salt
- Attack occurs at the benzo- rather than hetero-ring
- Reactions are faster than those of pyridine but slower than those of naphthalene

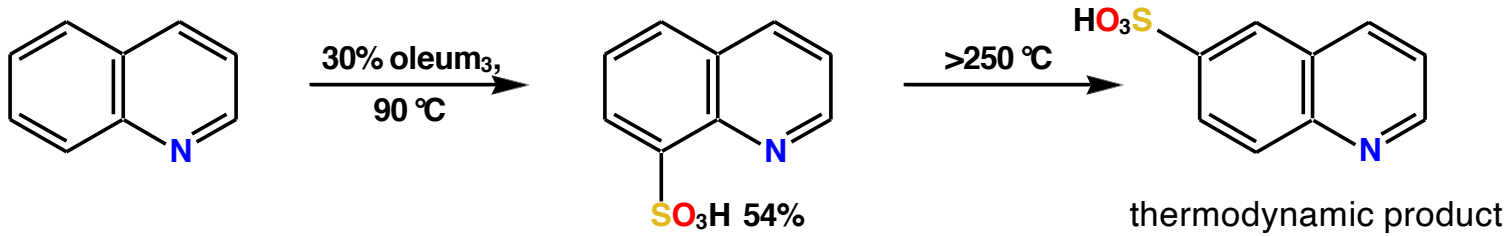
Nitration



- In the case of quinoline, equal amounts of the 5- and 8-isomer are produced

Quinolines/Isoquinolines – Electrophilic Reactions

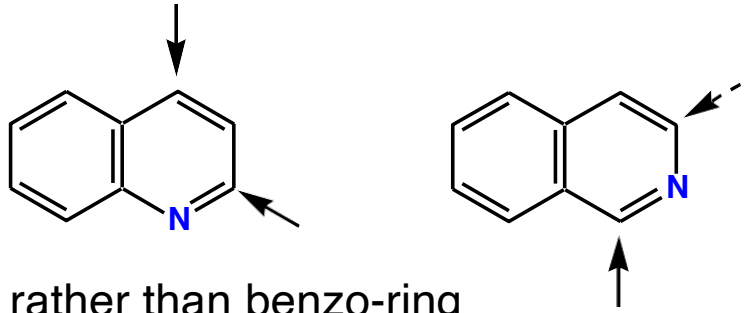
Sulfonation



- Halogenation is also possible but product distribution is highly dependent on conditions
- It is possible to introduce halogens into the hetero-ring under the correct conditions
- Friedel-Crafts alkylation/acylation is not usually possible

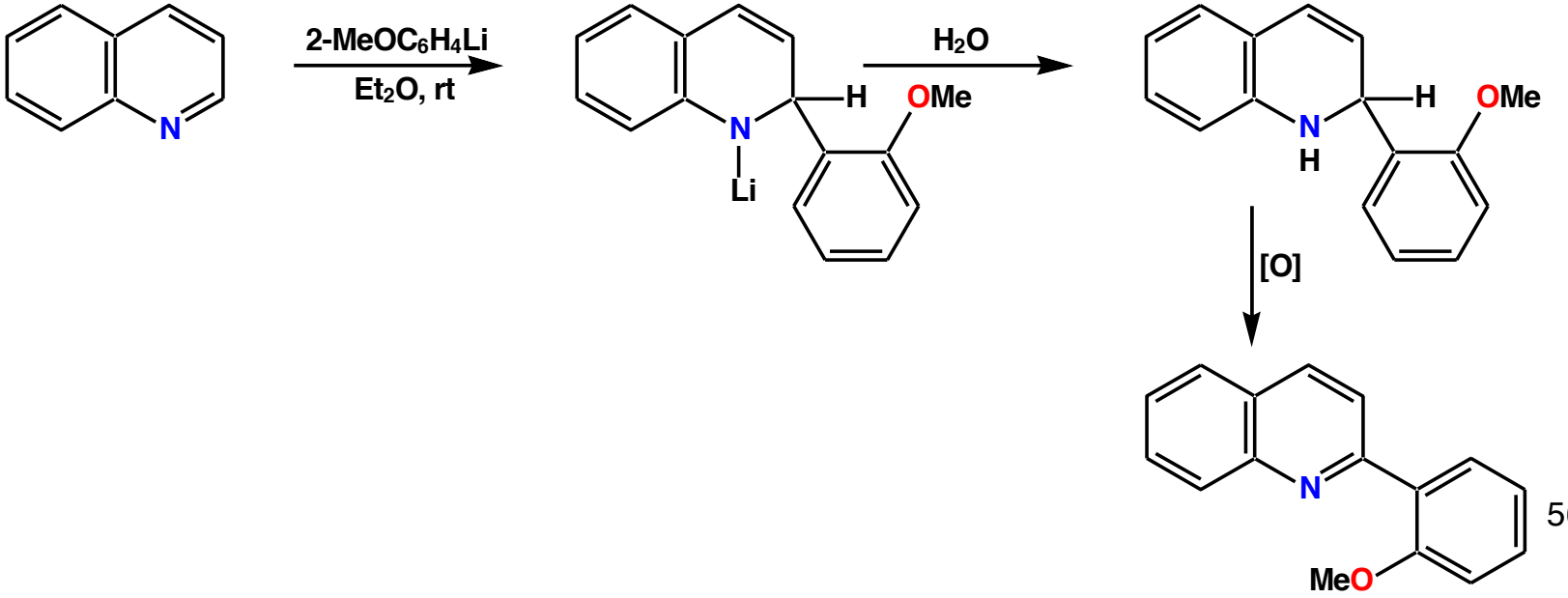
Quinolines/Isoquinolines – Nucleophilic Reactions

Regiochemistry

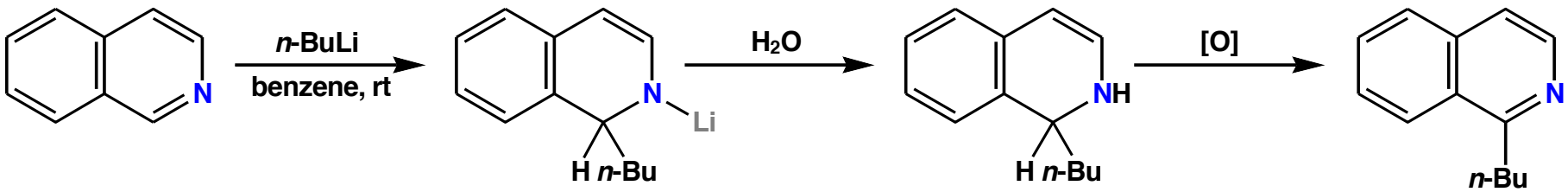


- Attack occurs at hetero- rather than benzo-ring
- They are enerally more reactive than pyridines to nucleophilic attack

Carbon Nucleophiles

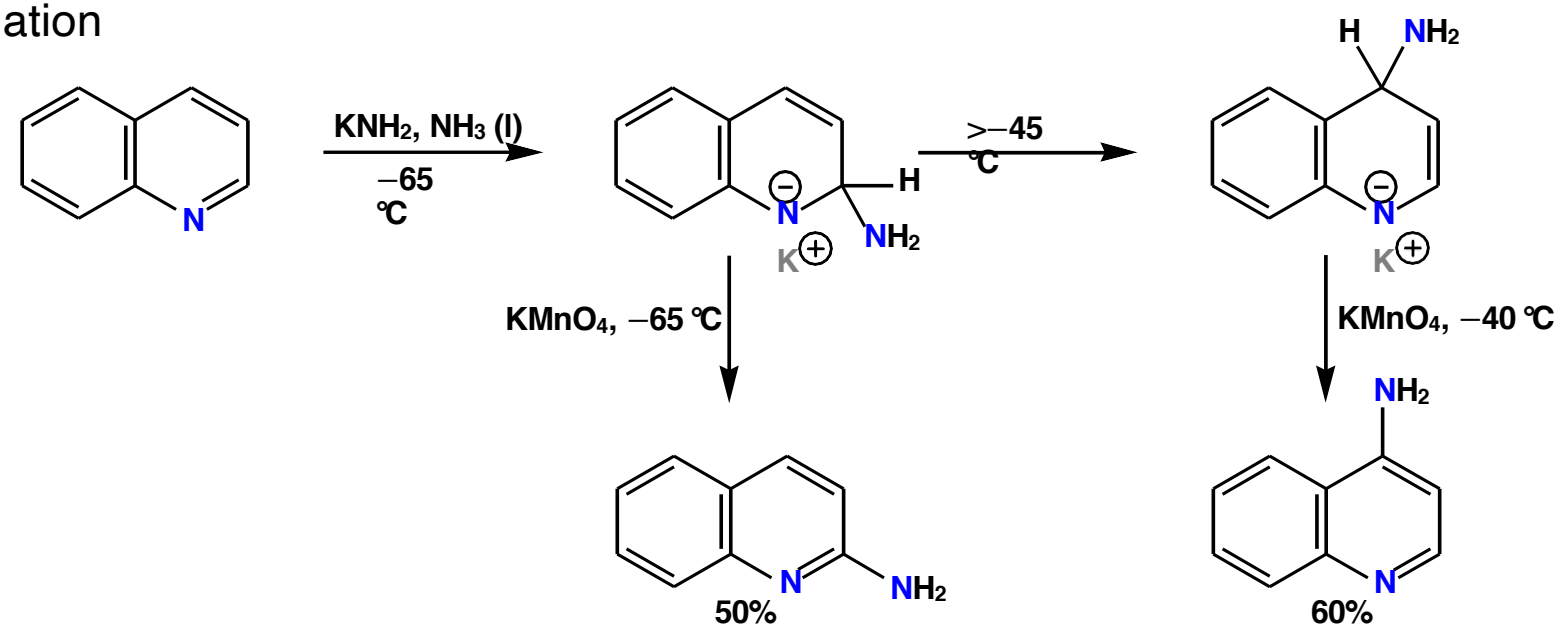


Quinolines/Isoquinolines – Nucleophilic Reactions



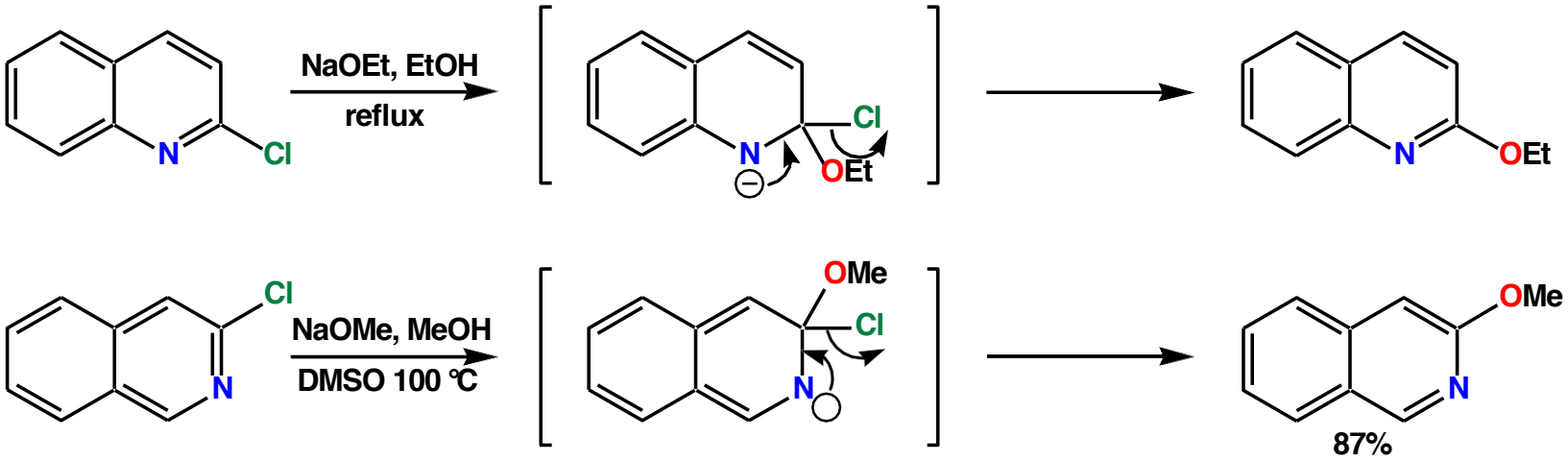
• Oxidation is required to regenerate aromaticity

Amination



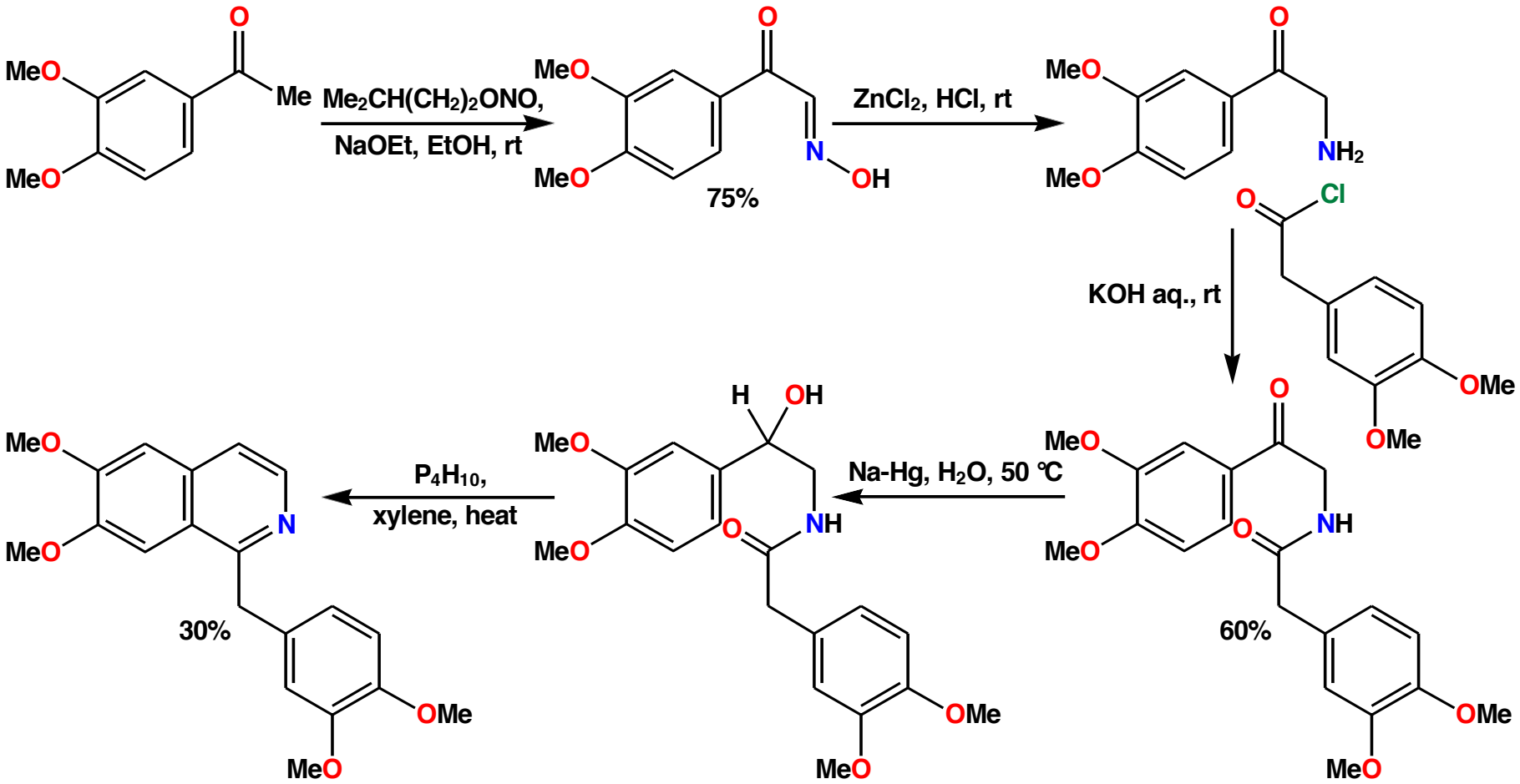
Quinolines/Isoquinolines – Nucleophilic Substitution

Displacement of Halogen



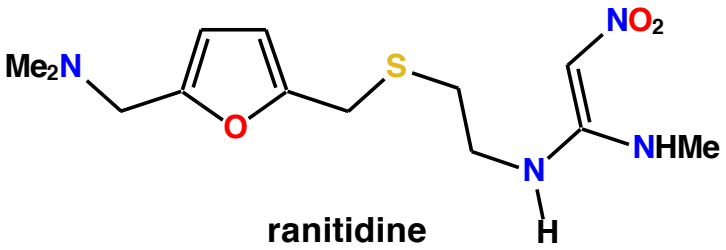
Isoquinolines – Synthesis of a Natural Product

Synthesis of Papaverine



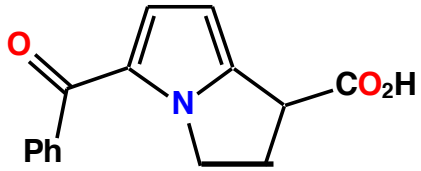
•Cyclisation is achieved by the Pictet-Grams reaction cf. the Bischler-Napieralski reaction

Bioactive Furans, Pyrroles and Thiophenes



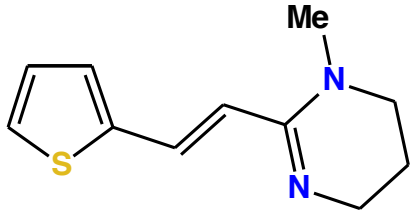
ranitidine

- Ranitidine (Zantac®, GSK) is one of the biggest selling drugs in history. It is an H_2-receptor antagonist and lowers stomach acid levels – used to treat stomach ulcers



ketorolac

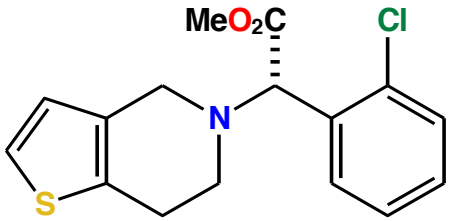
- Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug



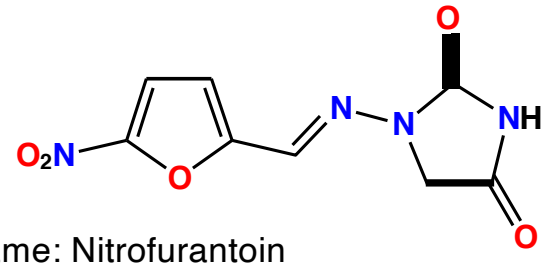
banminth

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

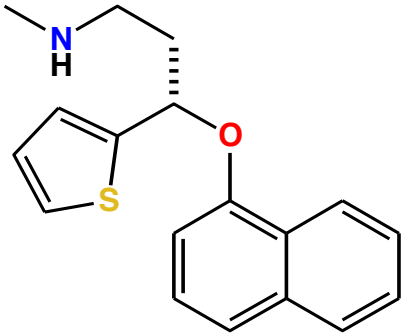
Drugs Containing a Furan/Thiophene/Pyrrole



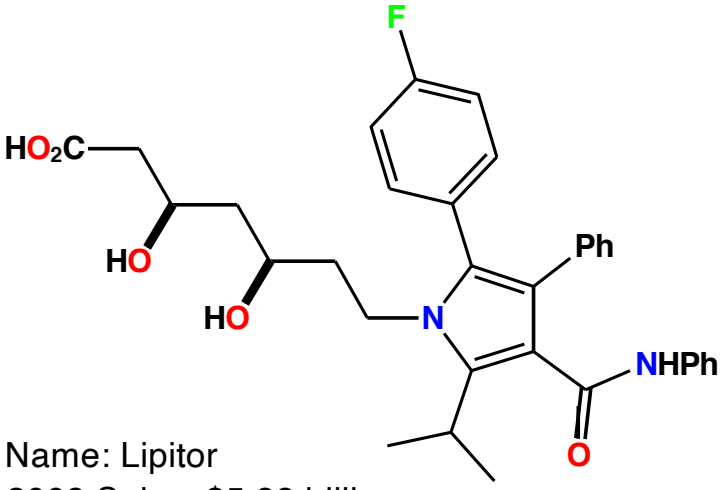
Name: Plavix
2008 Sales: $3.80 billion
2008 Ranking: 3 branded
Company: Bristol-Myers Squibb
Disease: Stroke and heart attack risk



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



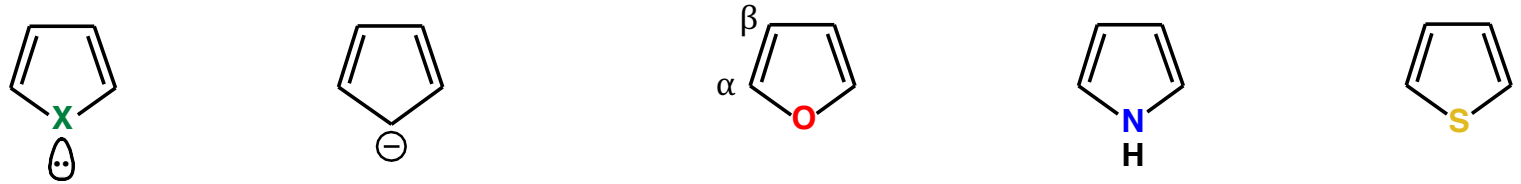
Name: Cymbalta
2008 Sales: $2.17 billion
2008 Ranking: 14 branded
Company: Eli Lilly
Disease: Depression



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

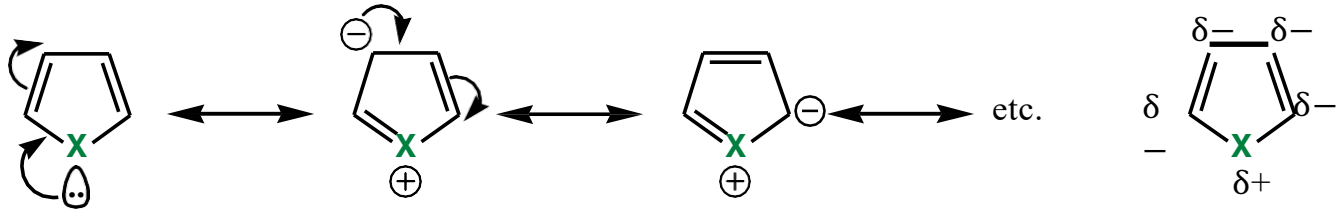
Furans, Pyrroles and Thiophenes – Structure

Structure

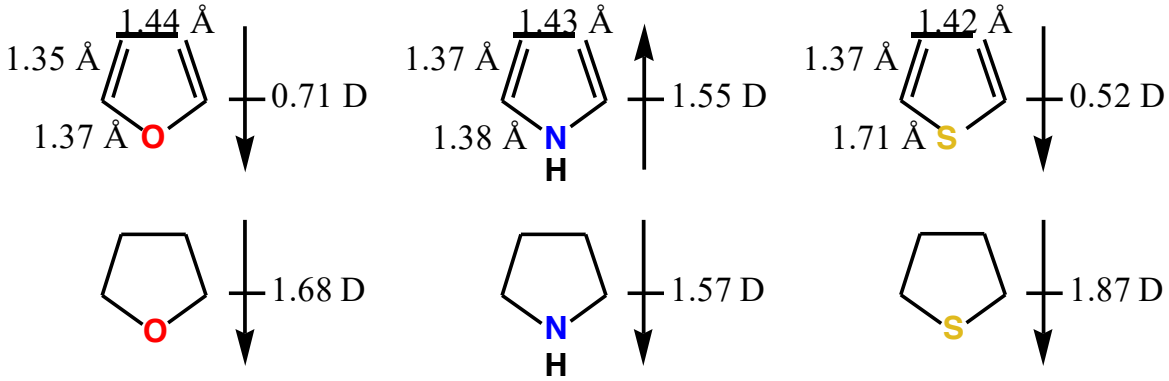


• 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures



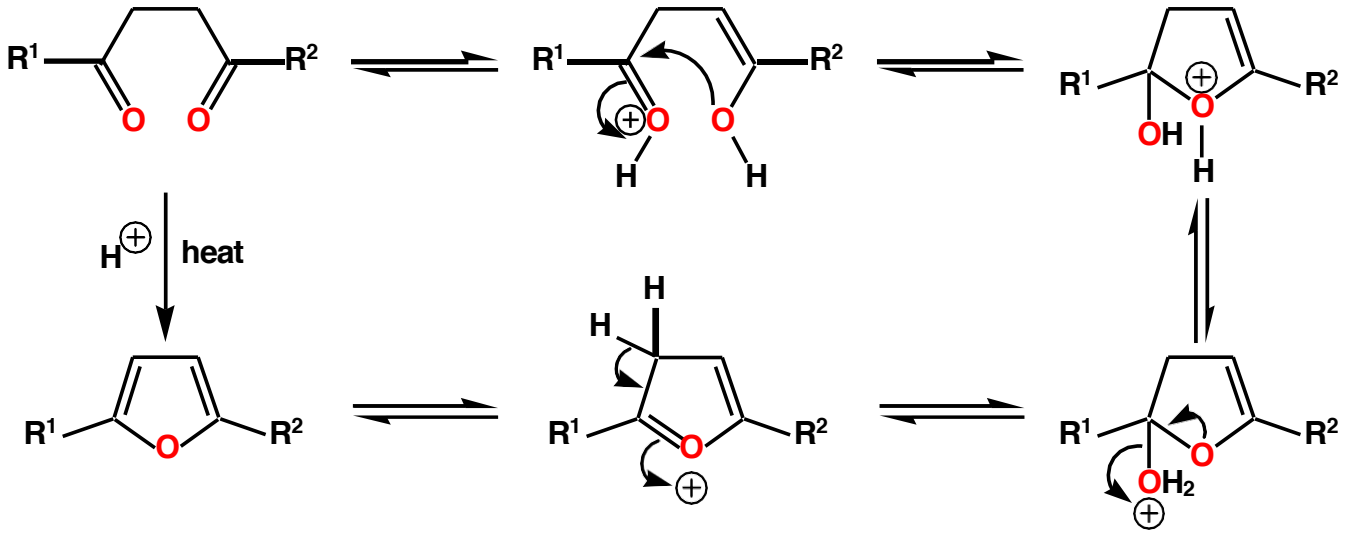
• Electron donation into the ring by resonance but inductive electron withdrawal



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

Furans – Synthesis

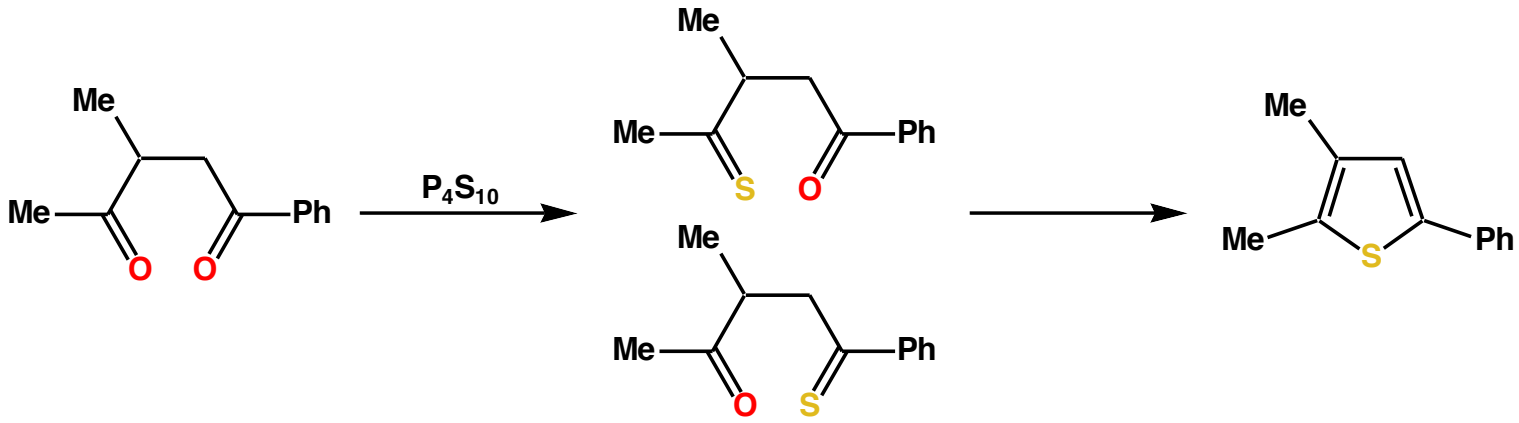
Paal Knorr Synthesis



- 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*-$MeC_6H_4SO_3H$)

Thiophenes – Synthesis

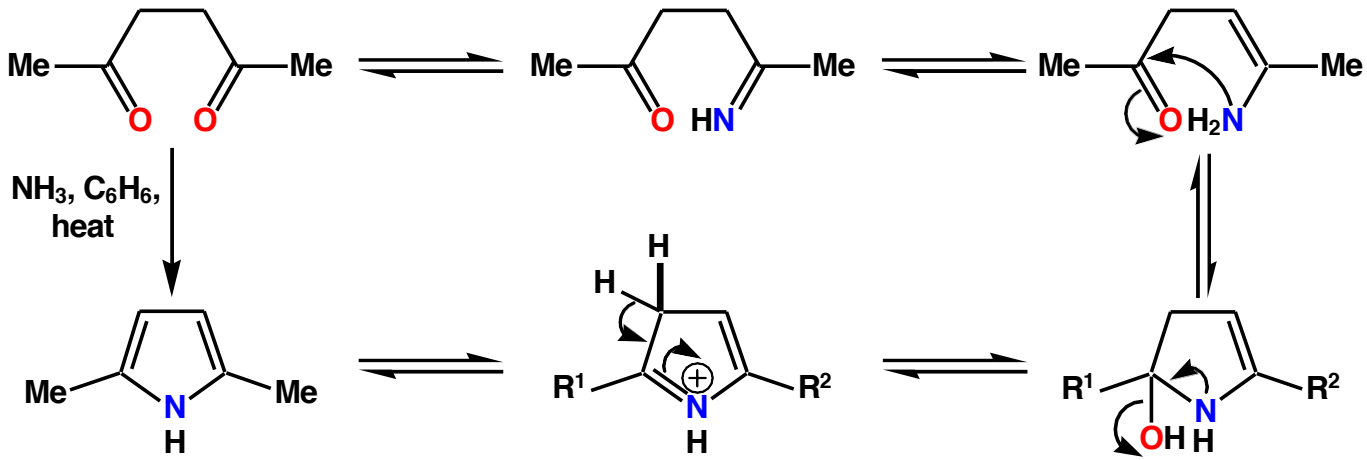
Synthesis of Thiophenes by Paal Knorr type reaction (“4+1”)



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

Pyrroles – Synthesis

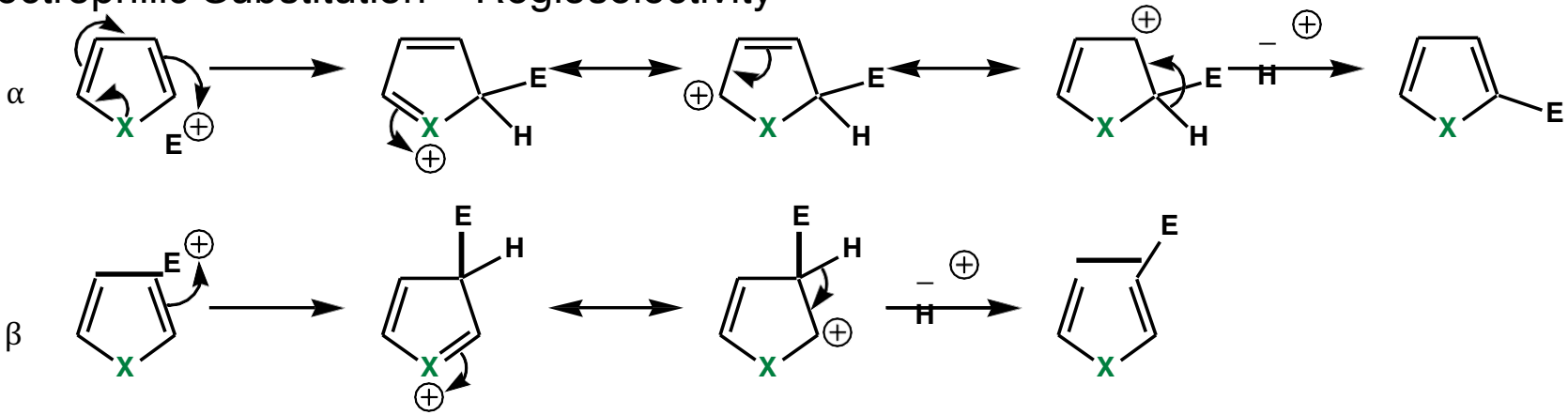
Paal Knorr Synthesis ("4+1")



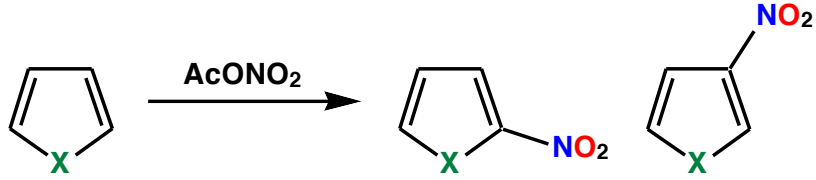
- Ammonia or a primary amine can be used to give the pyrrole or *N*-alkyl pyrrole

Furans, Pyrroles Thiophenes – Electrophilic Substitution

Electrophilic Substitution – Regioselectivity



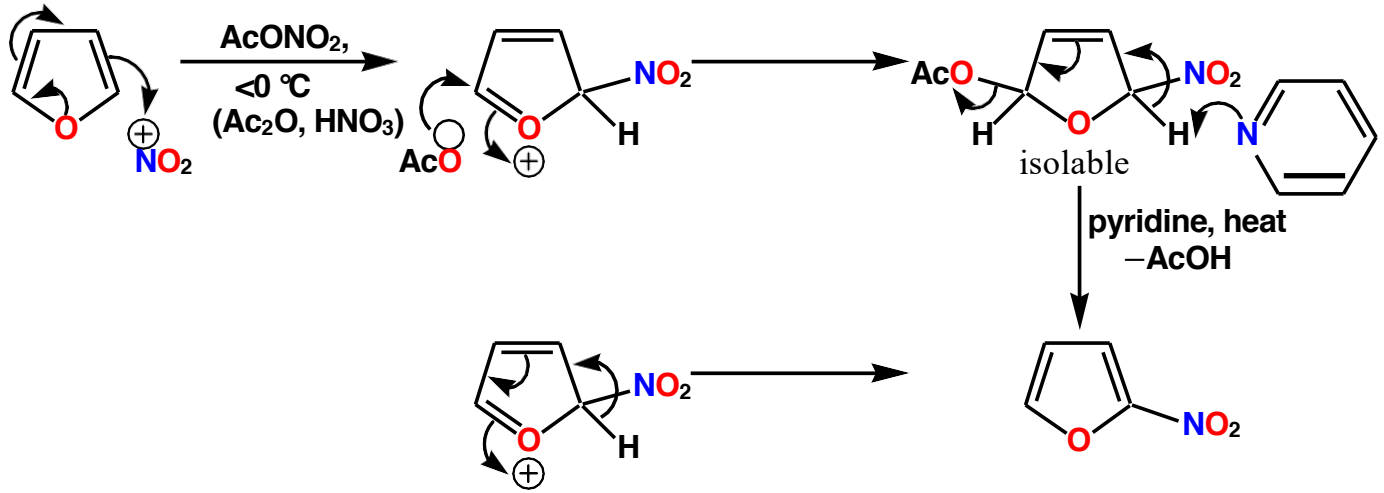
- Pyrrole > furan > thiophene > benzene
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions
- α-Substitution favoured over β-substitution more resonance forms for intermediate and so the charge is less localised (also applies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



X = NH 4:1
X = O 6:1

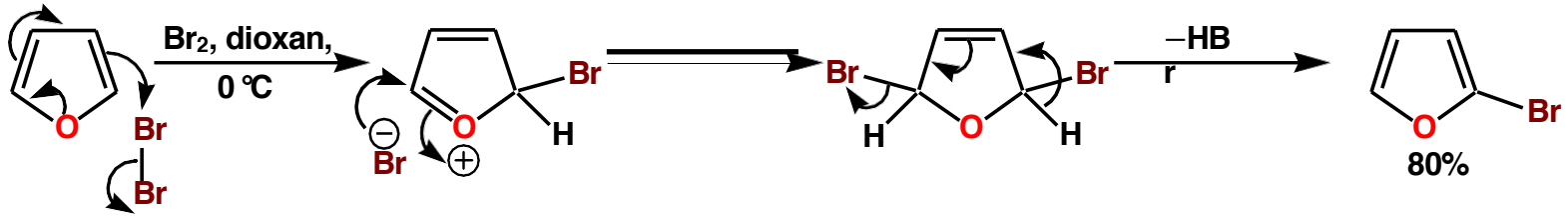
Furans – Electrophilic Substitution

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

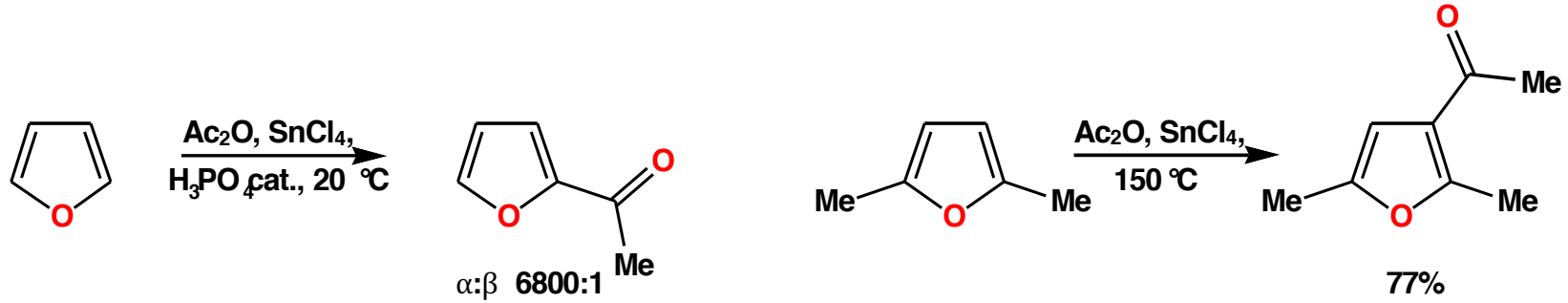
Bromination of Furans



- 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

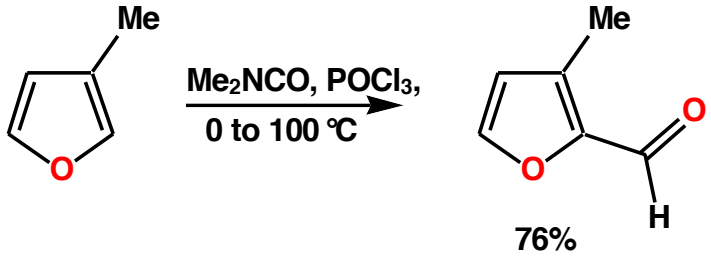
Furans – Electrophilic Substitution

Friedel-Crafts Acylation of Furan

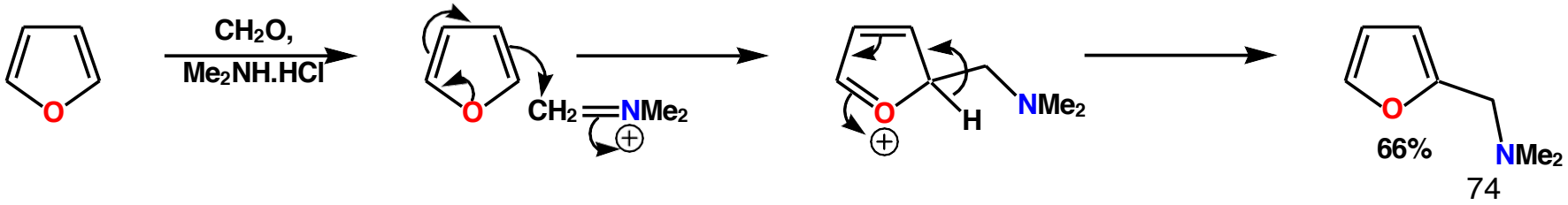


- Blocking groups at the α positions and high temperatures required to give β acylation

Vilsmeier Formylation of Furan

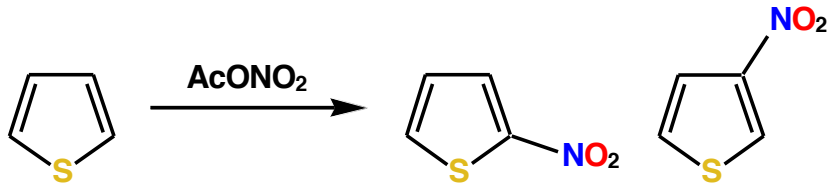


Mannich Reaction of Furans



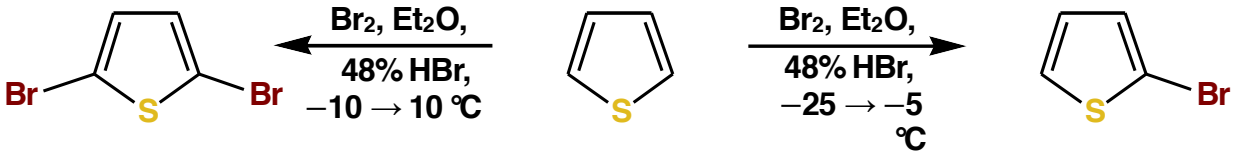
Thiophenes – Electrophilic Substitution

Nitration of Thiophenes



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

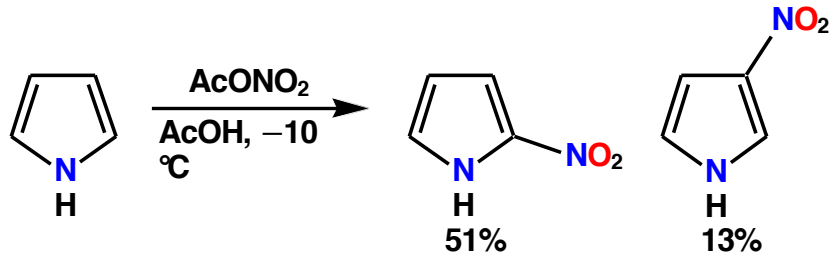
Halogenation of Thiophenes



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

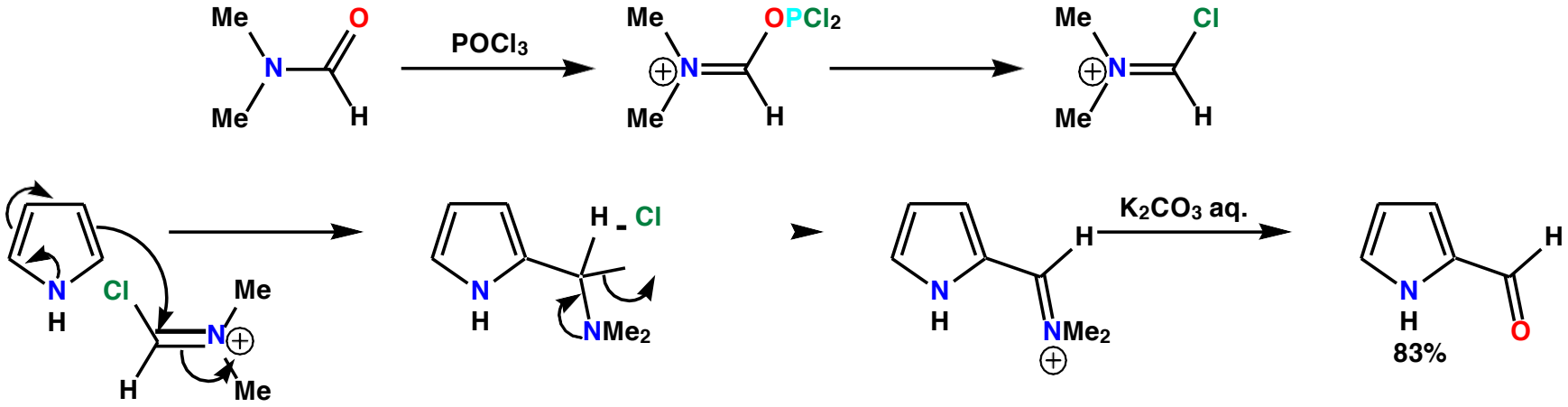
Pyrroles – Electrophilic Substitution

Nitration of Pyrroles

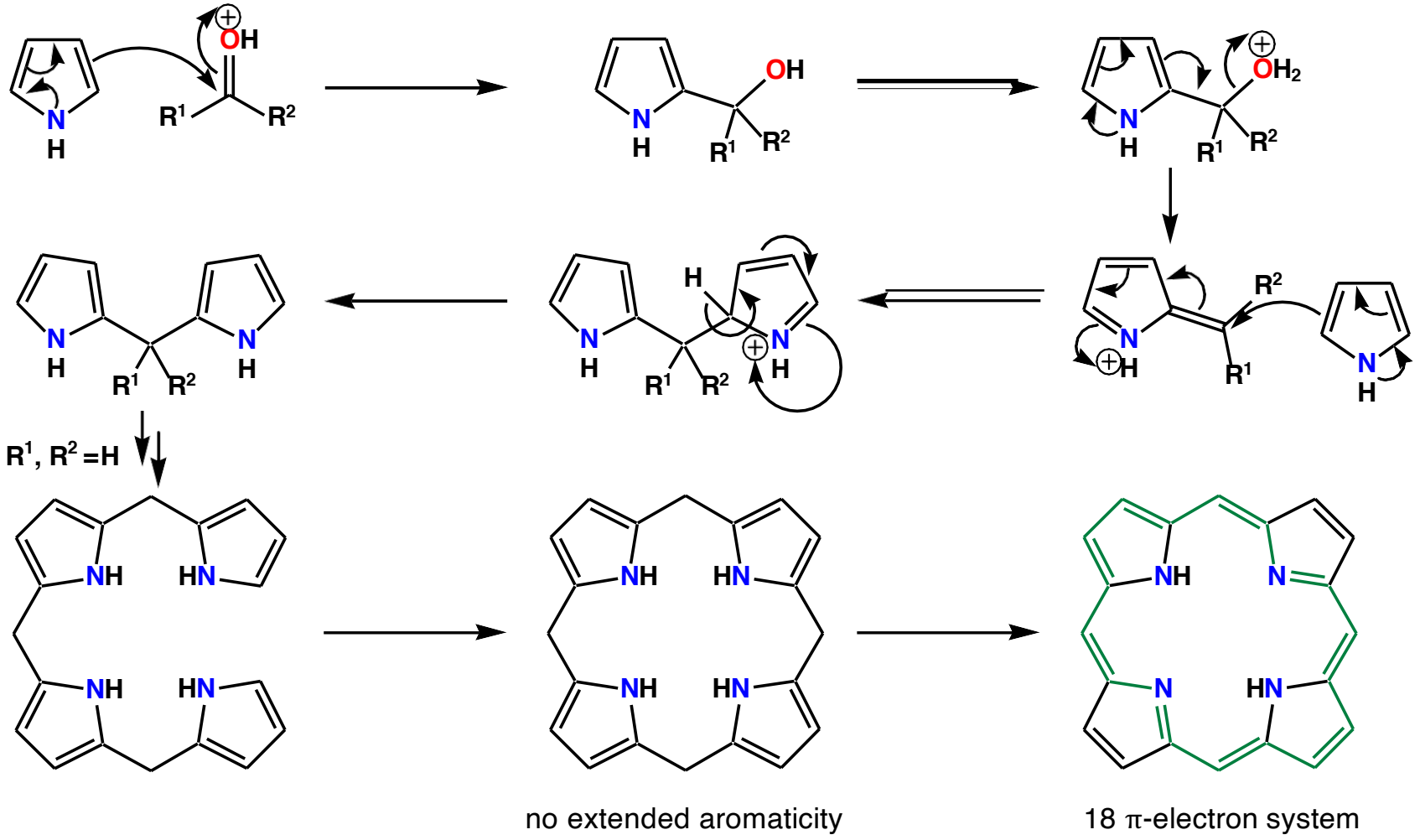


- Mild conditions are required (c-HNO_3 and c-H_2SO_4 gives decomposition)

Vilsmeier Formylation of Pyrroles

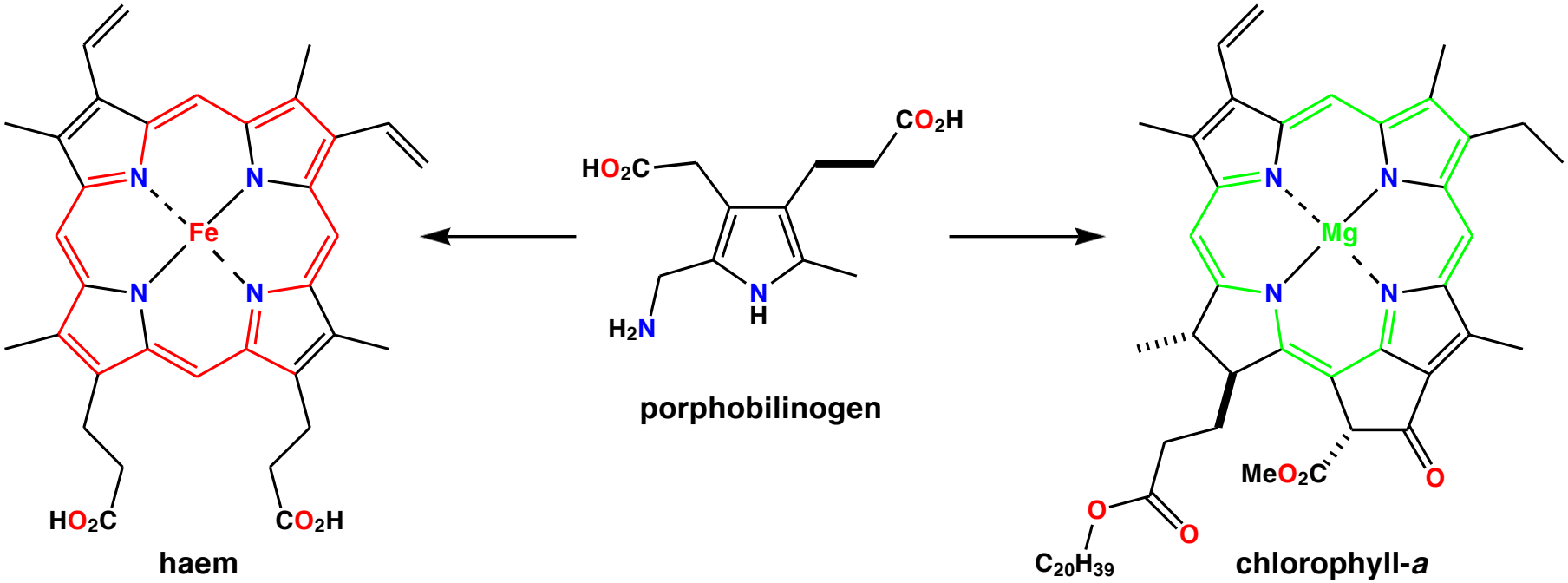


Pyrroles – Porphyrin Formation



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

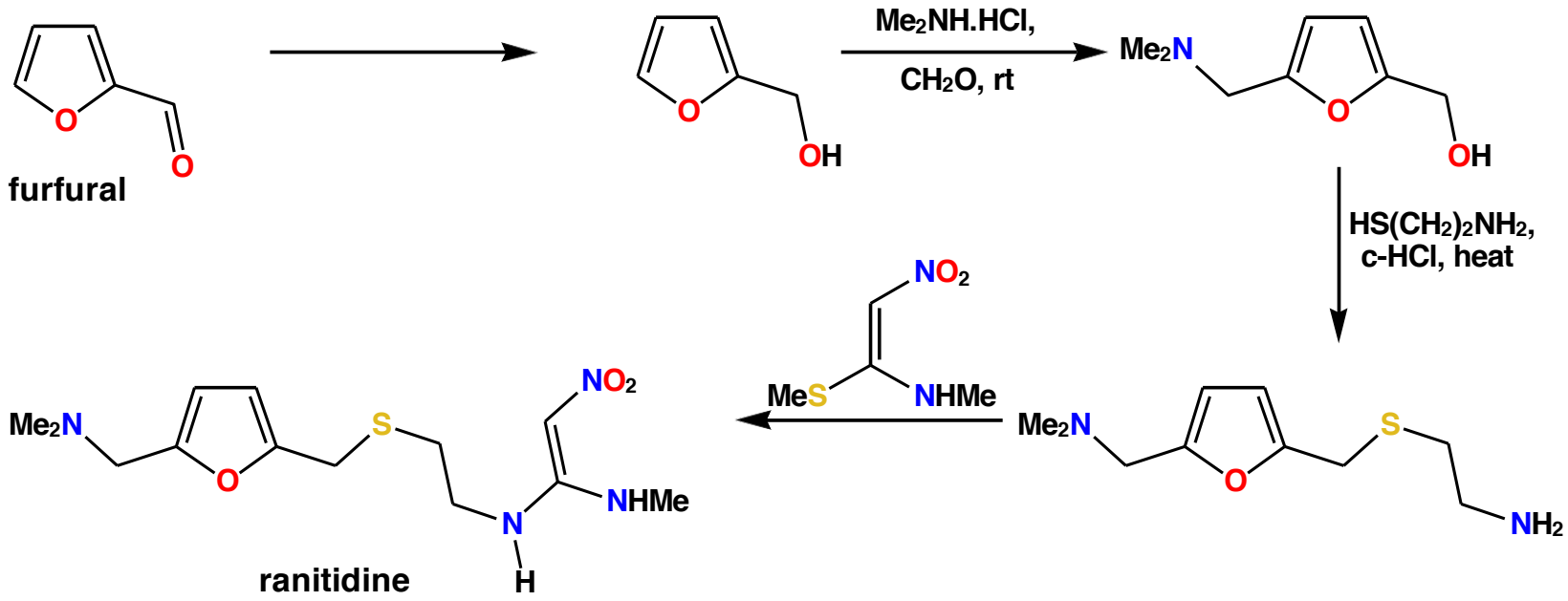
Porphyrin Natural Products



- 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

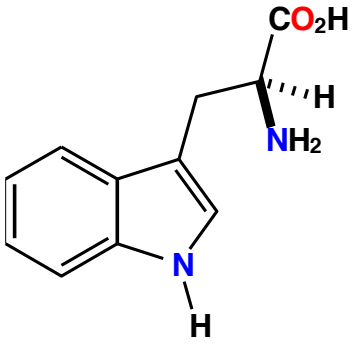
Furans – Synthesis of a Drug

Preparation of Ranitidine (Zantac®) Using a Mannich Reaction

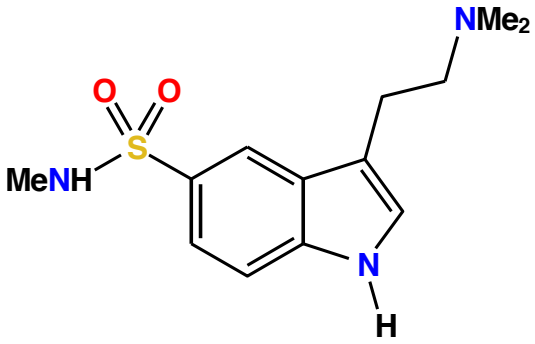


- Furfural is produced very cheaply from waste vegetable matter and can be reduced to give the commercially available compound furfuryl alcohol
- The second chain is introduced using a Mannich reaction which allows selective substitution at the 5-position
- The final step involves conjugate addition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

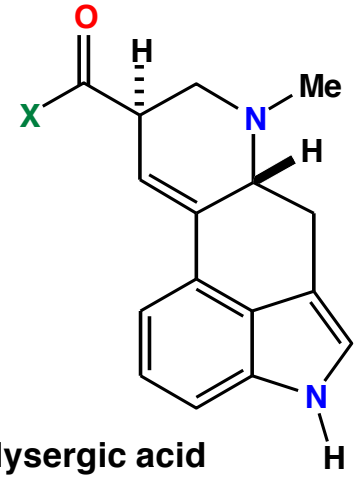
Indoles – Bioactive Indoles



tryptophan



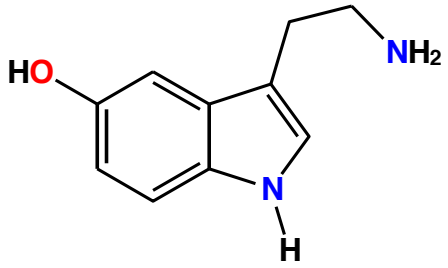
sumatriptan



X = OH lysergic acid

X = NEt_2 *lysergic acid diethyamide* (LSD)

- Tryptophan is one of the essential amino acids and a constituent of most proteins
- Sumatriptan (Imigran®, GSK) is a drug used to treat migraine and works as an agonist for 5-HT receptors for in the CNS
- LSD is a potent psychoactive compound which is prepared from lysergic acid, an alkaloid natural product of the ergot fungus



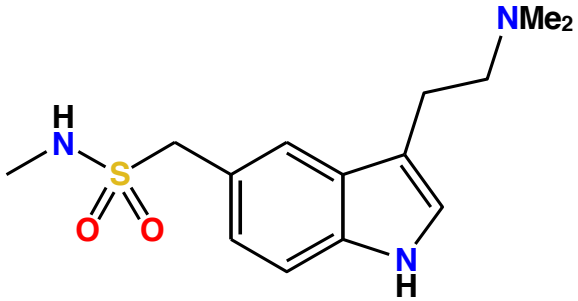
5-hydroxytryptamine (serotonin)

Indoles – Lysergic Acid

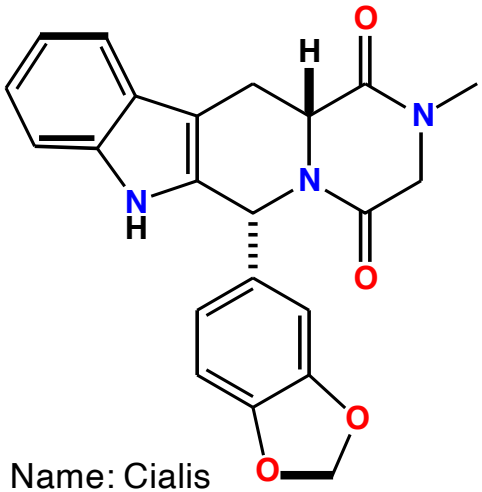
“The Beggars” (“The Cripples”) by Pieter Breugel the Elder (1568)

Louvre Museum, Paris

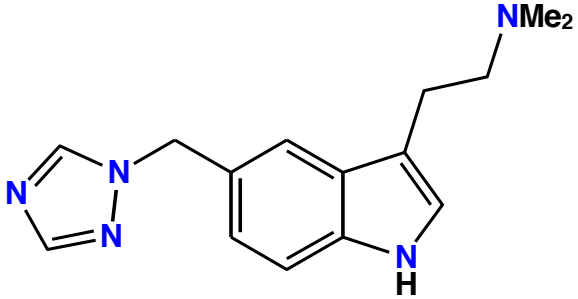
Drugs Containing an Indole



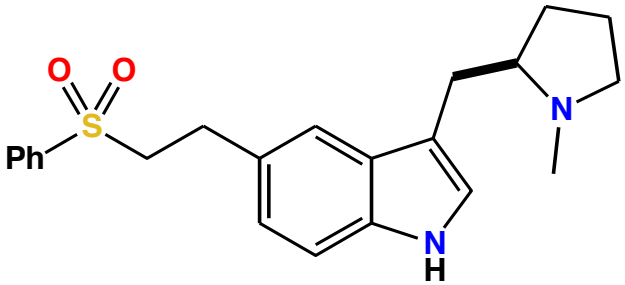
Name: Imitrex
2008 Sales: $0.97 billion
2008 Ranking: 35 branded
Company: GlaxoSmithKline
Disease: Migraine



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



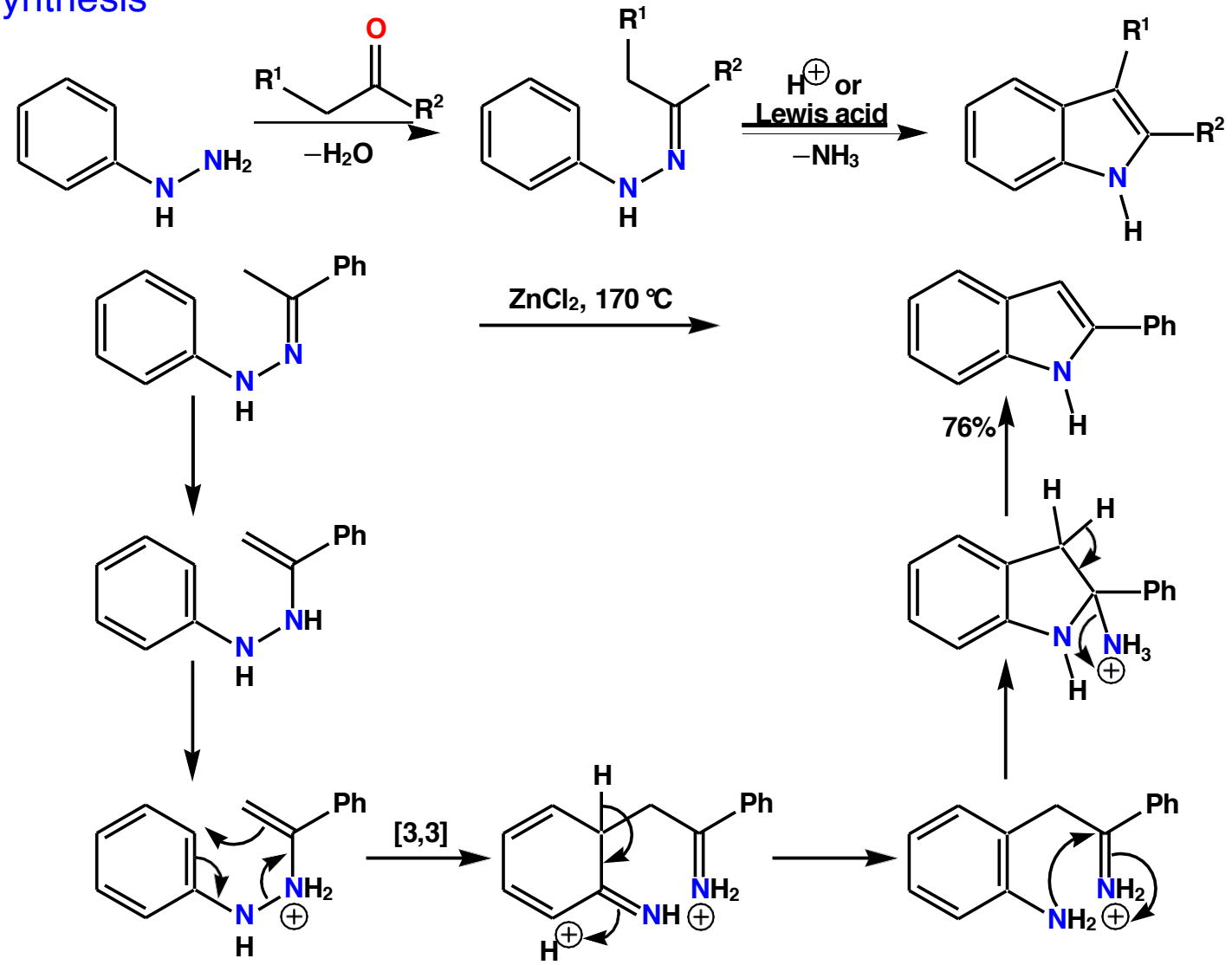
Name: Maxalt
2008 Sales: $0.22 billion
2008 Ranking: 148 branded
Company: Merck
Disease: Migraine



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

Indoles – Synthesis

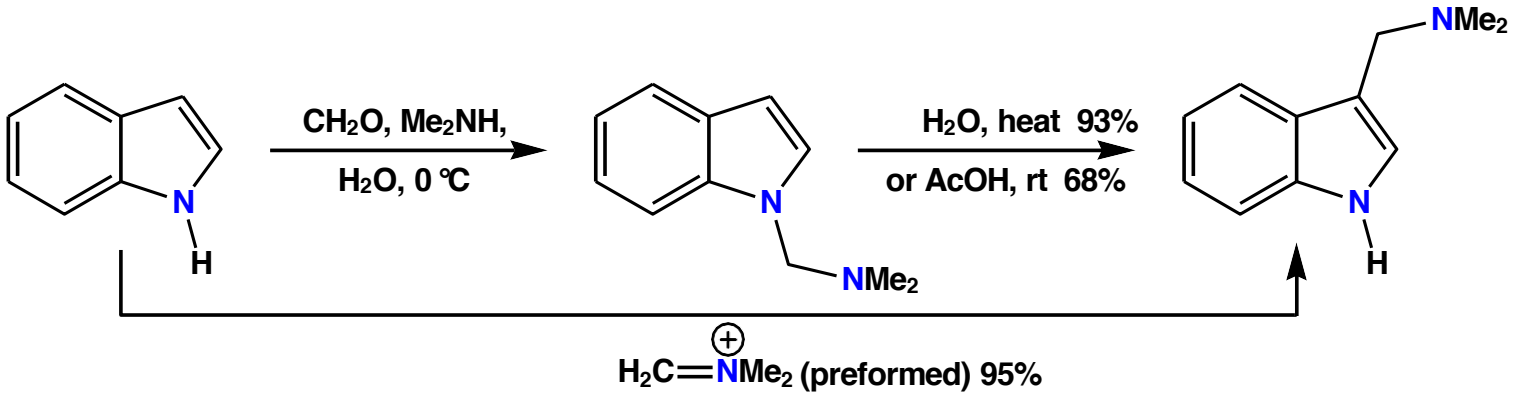
Fischer Synthesis



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

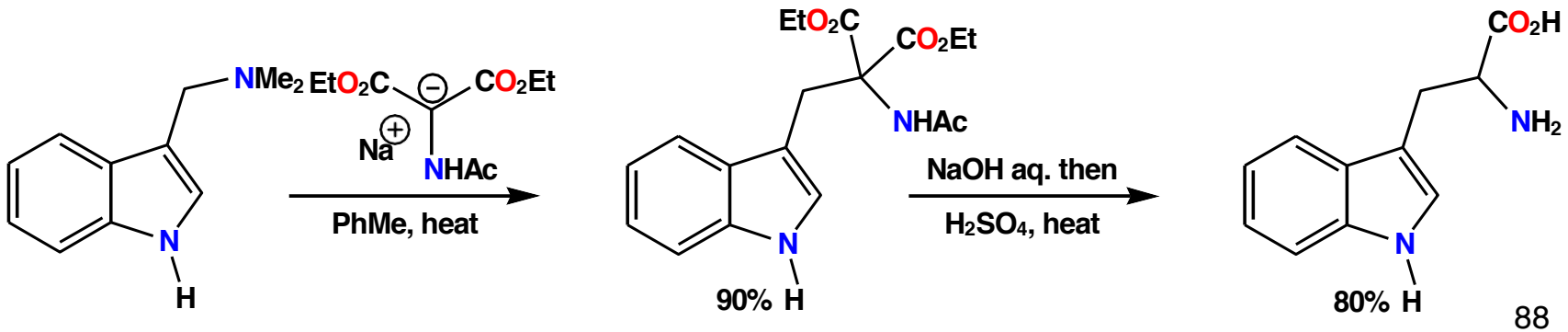
Indoles – Electrophilic Substitution

Mannich Reaction



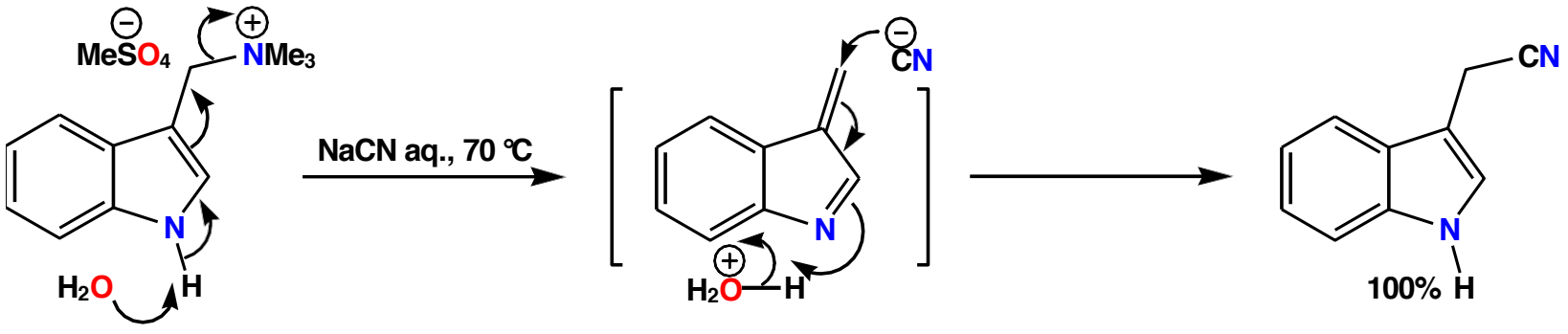
- A very useful reaction for the synthesis of 3-substituted indoles
- The product (gramine) can be used to access a variety of other 3-substituted indoles

Synthesis of Tryptophan from Gramine

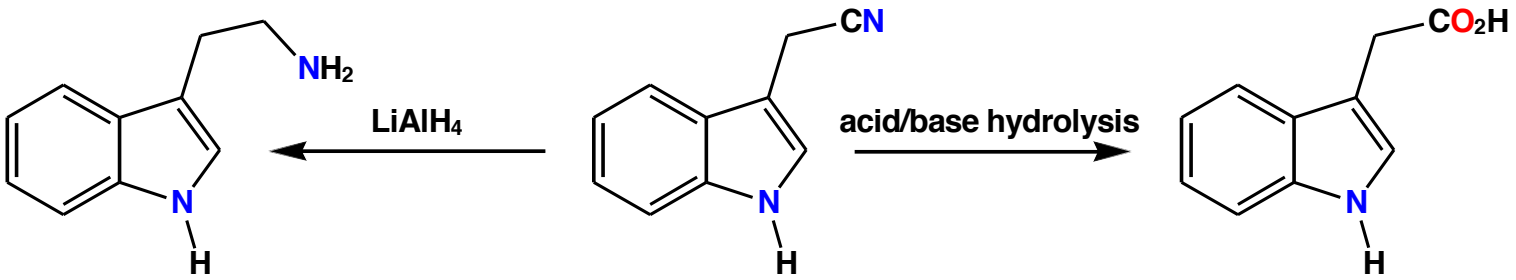


Indoles – Electrophilic Substitution

Synthesis of Other 3-Substituted Indoles from Gramine

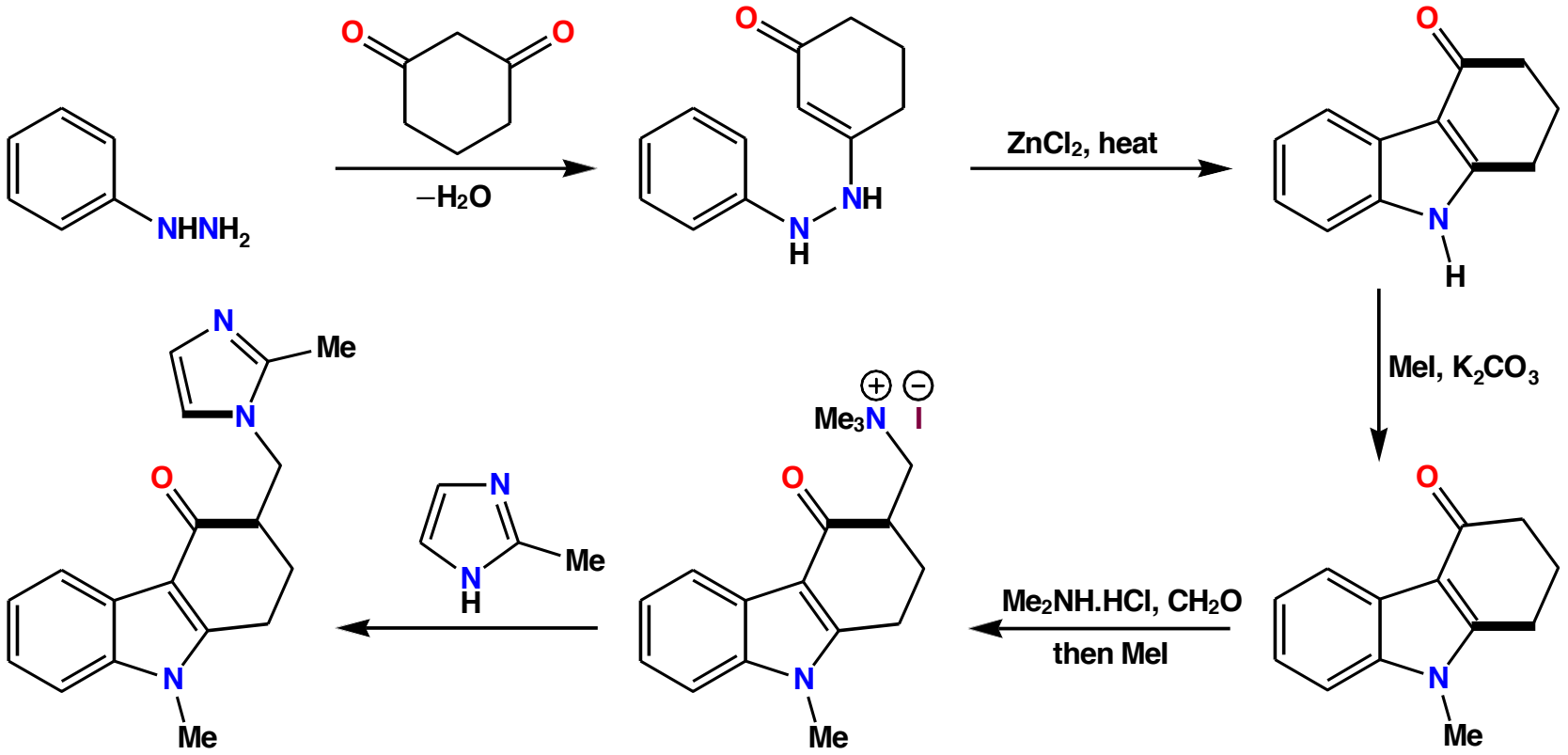


- The nitrile group can be modified to give other useful functionality



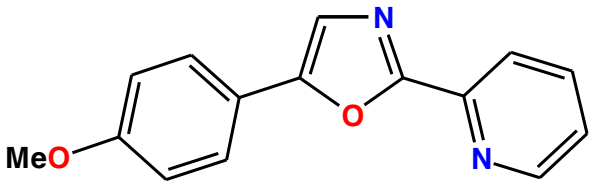
Indoles – Synthesis of a Drug

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

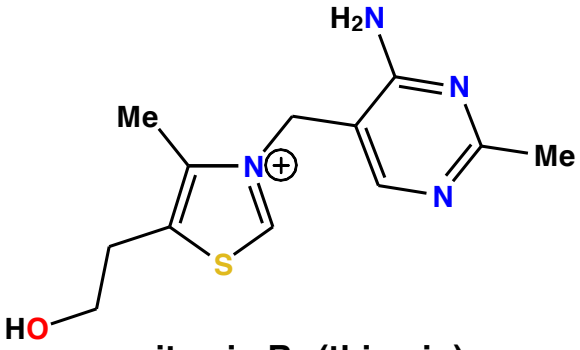


- Ondansetron is a selective 5-HT antagonist used as an antiemetic in cancer chemotherapy and radiotherapy
- Introduction of the imidazole occurs *via* the α,β-unsaturated ketone resulting from elimination of the ammonium salt

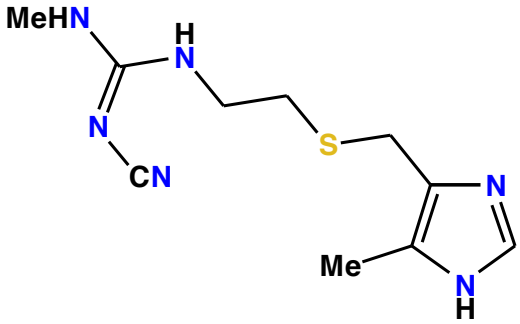
1,3-Azoles – Bioactive 1,3-Azoles



***O*-methylhalfordinol**



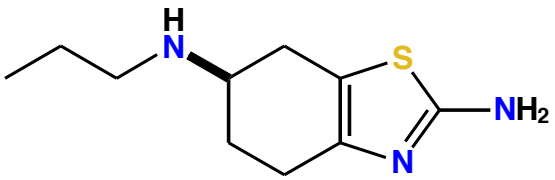
vitamin B_1 (thiamin)



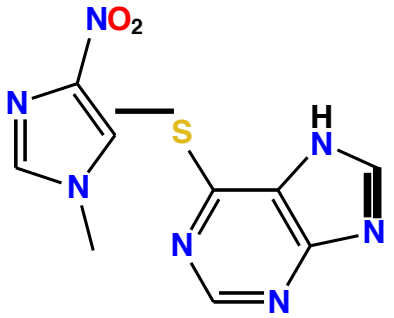
cimetidine

- *O*-Methylhalfordinol is a plant-derived alkaloid
- Vitamin B1 (thiamin) is essential for carbohydrate metabolism. Deficiency leads to beriberi, a disease which is characterised by nerve, heart and brain abnormalities
- Cimetidine (Tagamet®, GSK) is an H_2-receptor antagonist which reduces acid secretion in the stomach and is used to treat peptic ulcers and heartburn

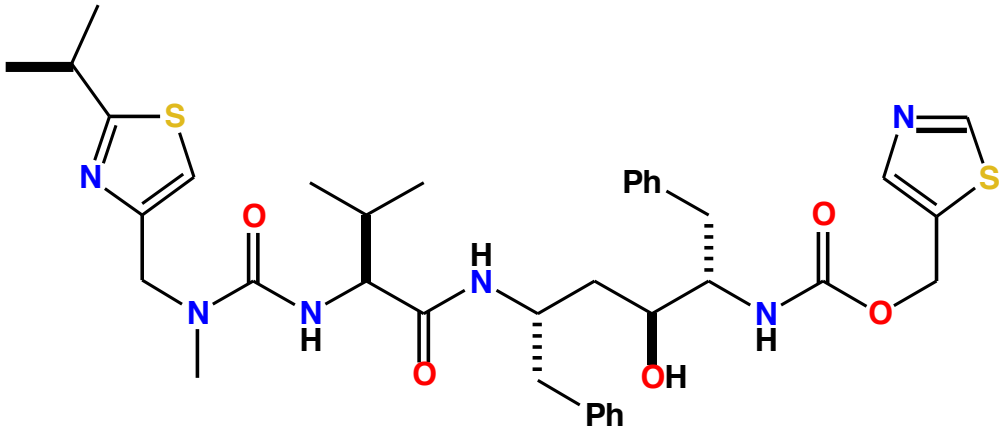
Drugs Containing a 1,3-Azole



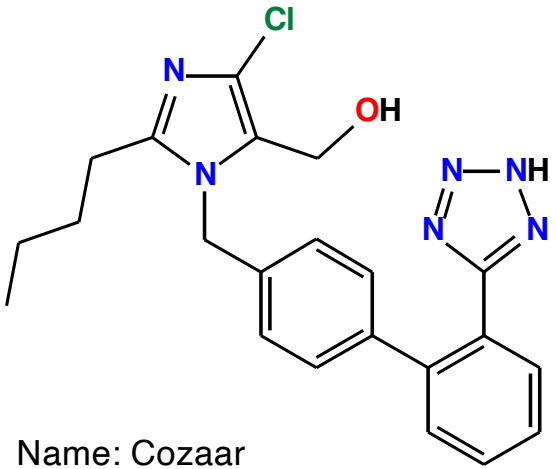
Name: Mirapex
2008 Sales: $0.34 billion
2008 Ranking: 108 branded
Company: Boehringer Ingelheim
Disease: Parkinson's disease



Name: Azathioprine
2008 Sales: $53 million
2008 Ranking: 178 generic
Company: N/A
Disease: Kidney transplant rejection



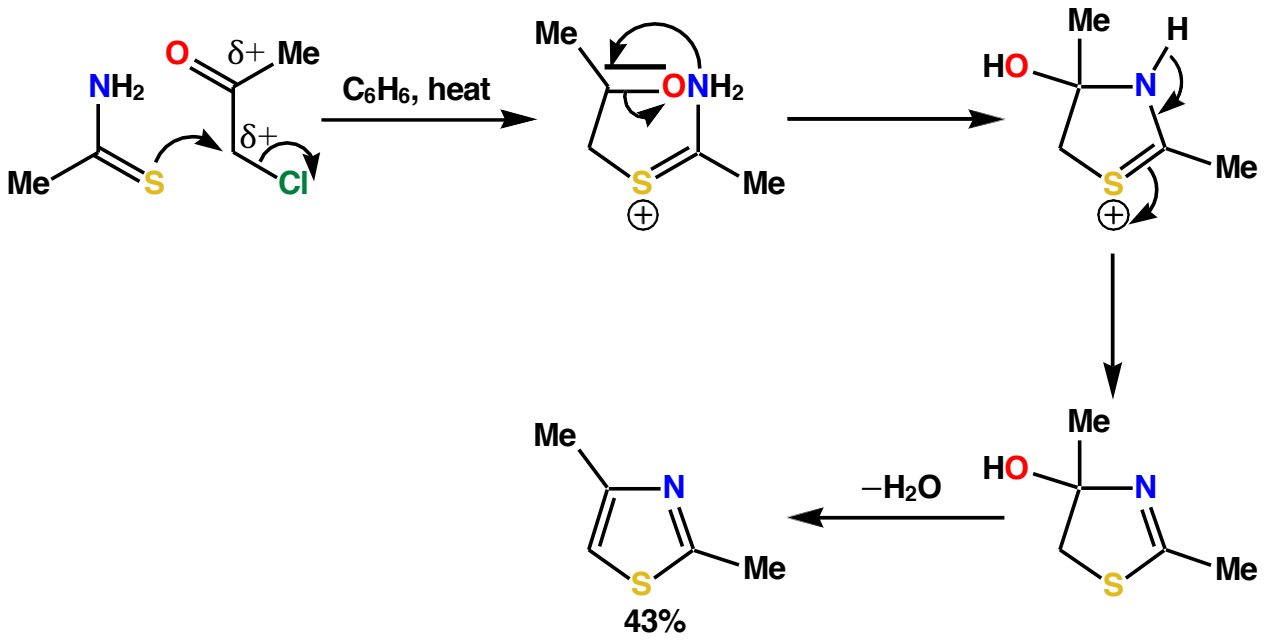
Name: Norvir
2008 Sales: $0.31billion
2008 Ranking: 112 branded
Company: Abbott
Disease: HIV/AIDS



Name: Cozaar
2008 Sales: $0.69 billion
2008 Ranking: 54 branded
Company: Merck
Disease: Hypertension

1,3-Azoles – Synthesis

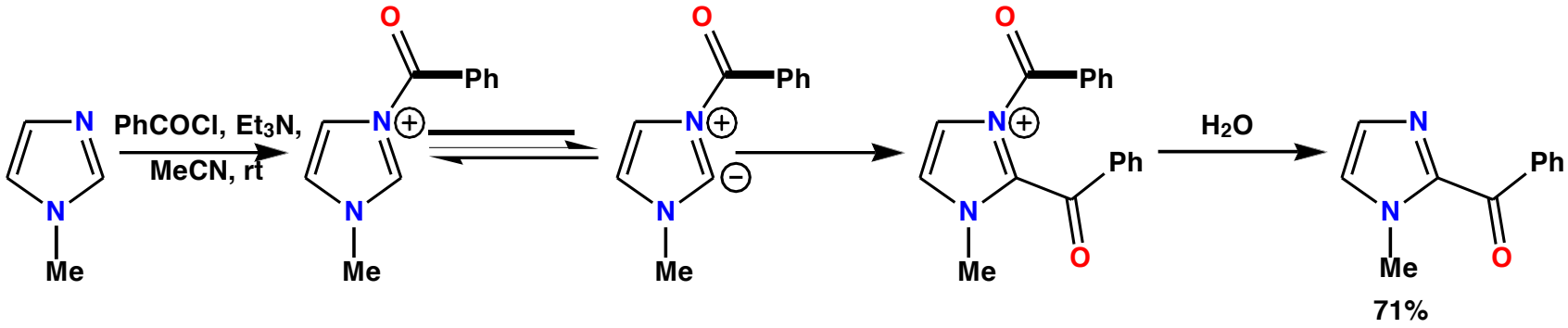
The Hantzsch Synthesis ("3+2")



- The reaction is particularly important for the synthesis of thiazoles
- A thiourea can be used in place of a thioamide leading to a 2-aminothiazole

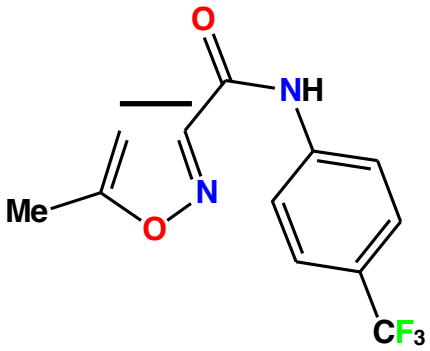
1,3-Azoles – Electrophilic Substitution

Acylation

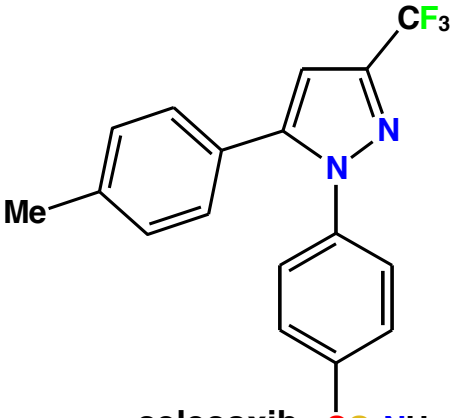


- 1,3-Azoles do not undergo Friedel-Crafts acylation because complexation between the Lewis acidic catalyst and *N* deactivates the ring
- Acylation can be accomplished under mild conditions *via* the *N*-acylimidazolium ylide

1,2-Azoles – Bioactive 1,2-Azoles



leflunomide

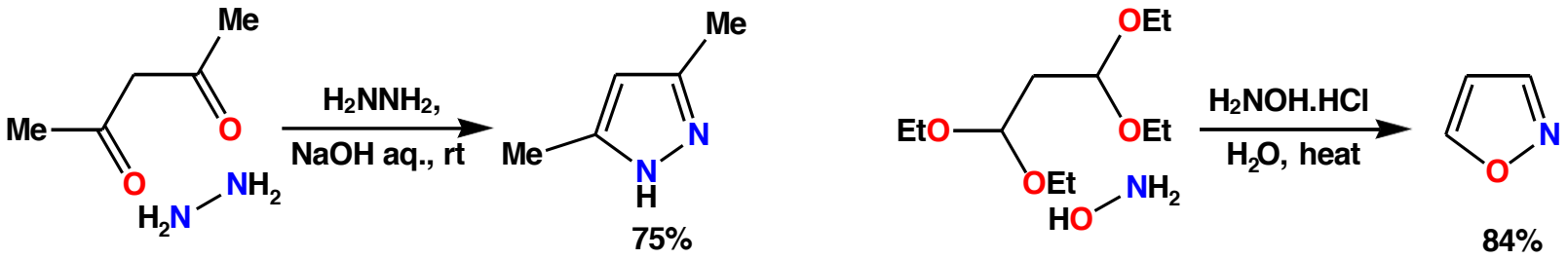


celecoxib

- Leflunomide (Arava®, Sanofi-Aventis) inhibits pyrimidine synthesis in the body and is used for the treatment of rheumatoid arthritis and psoriatic arthritis
- Celecoxib (Celebrex®, Pfizer) is a non-steroidal anti-inflamatory (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms
- Celecoxib is a COX-2 inhibitor, blocking the cyclooxygenase-2 enzyme responsible for the production of prostaglandins. It is supposed to avoid gastrointestinal problems associated with other NSAIDs, but side effects (heart attack, stroke) have emerged

1,2-Azoles – Synthesis

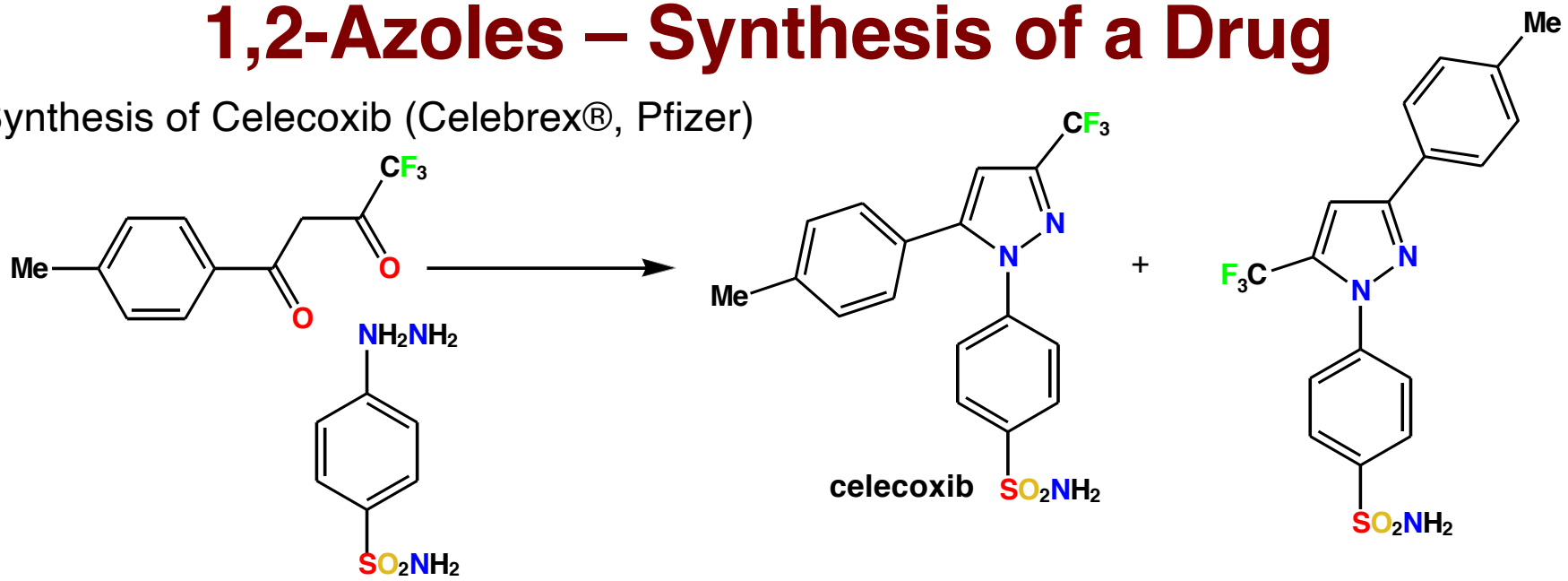
Synthesis of Pyrazoles/Isoxazoles from 1,3-Dicarbonyl Compounds and Hydrazines or Hydroxylamines (“3+2”)



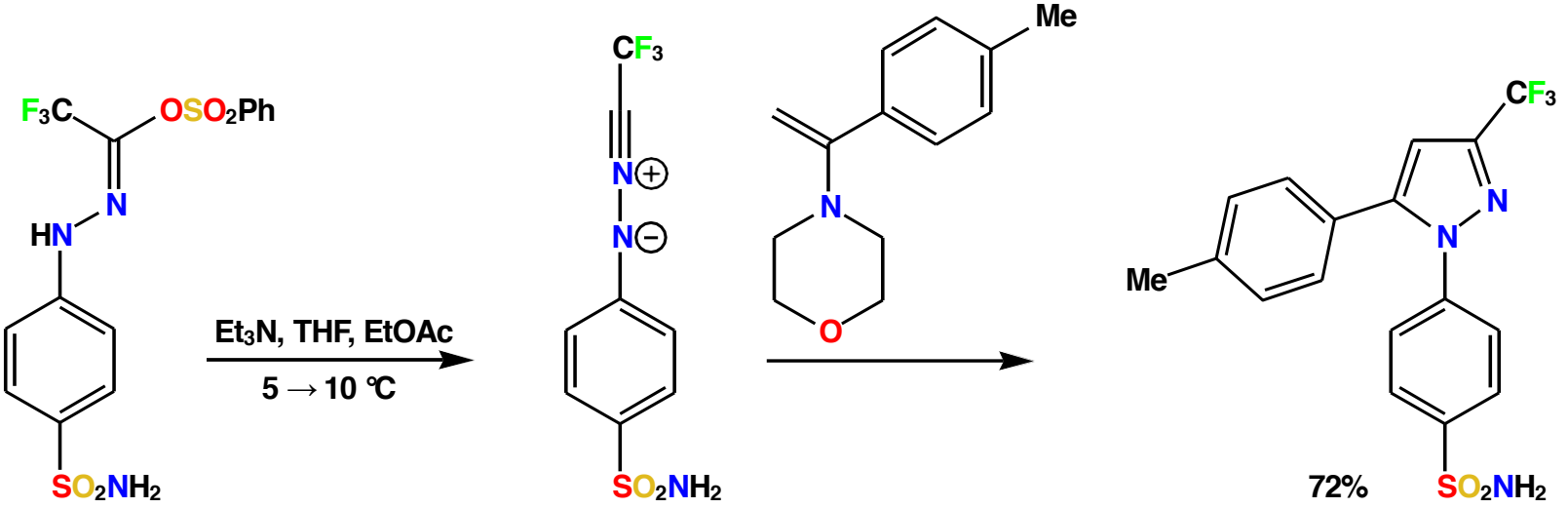
- This is the most widely used route to pyrazoles and isoxazoles
- The dicarbonyl component can be a β-keto ester or a β-keto aldehyde (masked)
- When a β-keto ester is used a pyrazolone/isoxazalone is formed

1,2-Azoles – Synthesis of a Drug

Synthesis of Celecoxib (Celebrex®, Pfizer)



- A regioisomeric mixture is formed requiring separation and disposal of the side product



- 1,3-Dipolar cycloaddition of a nitrile imine offers a regioselective alternative route