

Heterocyclic Chemistry

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2011–2012

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

Course Summary

Introduction

- Definition of terms and classification of heterocycles
- Functional group chemistry: imines, enamines, acetals, enols, and sulfur-containing groups

Intermediates used for the construction of aromatic heterocycles

- Synthesis of aromatic heterocycles
- Carbon–heteroatom bond formation and choice of oxidation state
- Examples of commonly used strategies for heterocycle synthesis

Pyridines

- General properties, electronic structure
- Synthesis of pyridines
- Electrophilic substitution of pyridines
- Nucleophilic substitution of pyridines
- Metallation of pyridines

Pyridine derivatives

- Structure and reactivity of oxy-pyridines, alkyl pyridines, pyridinium salts, and pyridine *N*-oxides

Quinolines and isoquinolines

- General properties and reactivity compared to pyridine
- Electrophilic and nucleophilic substitution quinolines and isoquinolines
- General methods used for the synthesis of quinolines and isoquinolines

Course Summary (cont)

Five-membered aromatic heterocycles

- General properties, structure and reactivity of pyrroles, furans and thiophenes
- Methods and strategies for the synthesis of five-membered heteroaromatics
- Electrophilic substitution reactions of pyrroles, furans and thiophenes
- Strategies for accomplishing regiocontrol during electrophilic substitution
- Metallation of five-membered heteroaromatics and use of directing groups

Indoles

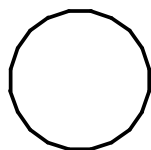
- Comparison of electronic structure and reactivity of indoles to that of pyrroles
- Fisher and Bischler indole syntheses
- Reactions of indoles with electrophiles
- Mannich reaction of indoles to give 3-substituted indoles (gramines)
- Modification of Mannich products to give various 3-substituted indoles

1,2 and 1,3-Azoles

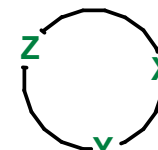
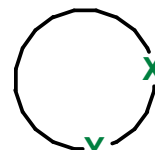
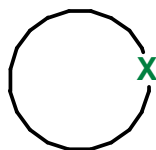
- Structure and reactivity of 1,2- and 1,3-azoles
- Synthesis and reactions of imidazoles, oxazoles and thiazoles
- Synthesis and reactions of pyrazoles, isoxazoles and isothiazoles

Introduction

- Heterocycles contain one or more heteroatoms in a ring



carbocycle

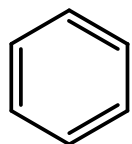


heterocycles – X, Y, Z are usually O, N or S

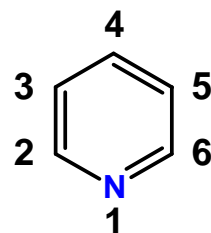
- Aromatic, or partially or fully saturated – this course will focus on aromatic systems
- Heterocycles are important and a large proportion of natural products contain them
- Many pharmaceuticals and agrochemicals contain at least one heterocyclic unit
- Heterocyclic systems are important building-blocks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

Classification – Aromatic Six-Membered

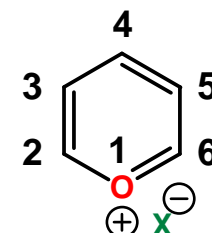
Isoelectronic carbocycle



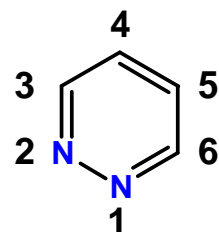
Heterocycles



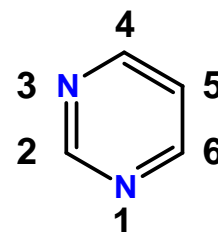
pyridine



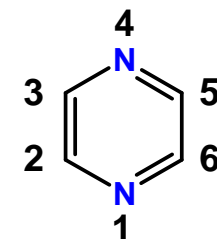
pyrylium



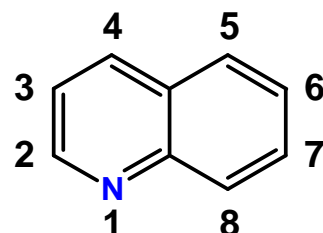
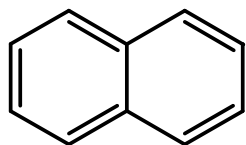
pyridazine



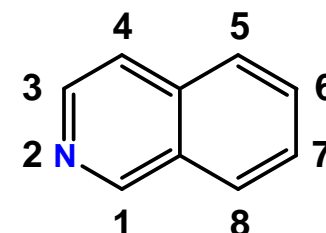
pyrimidine



pyrazine



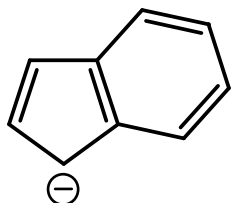
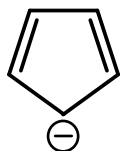
quinoline



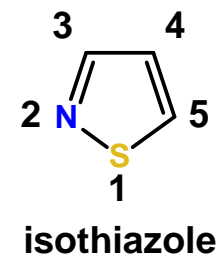
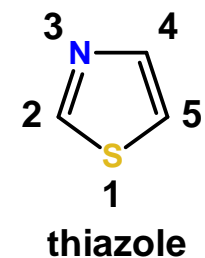
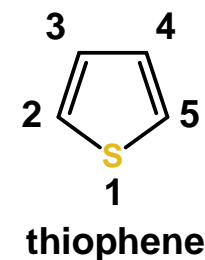
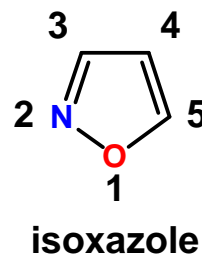
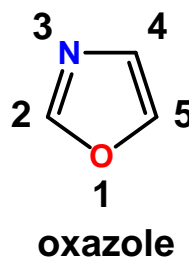
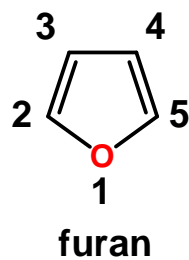
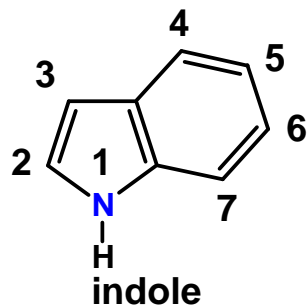
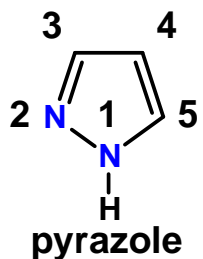
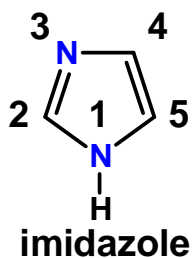
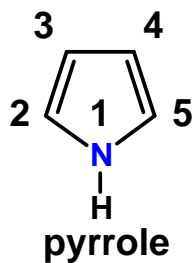
isoquinoline

Classification – Aromatic Five-Membered

Isoelectronic carbocycle

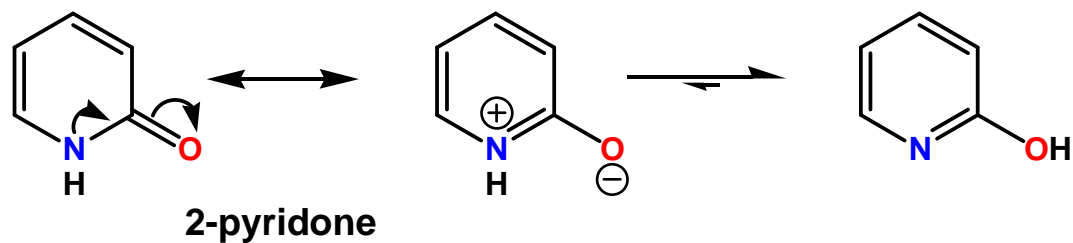
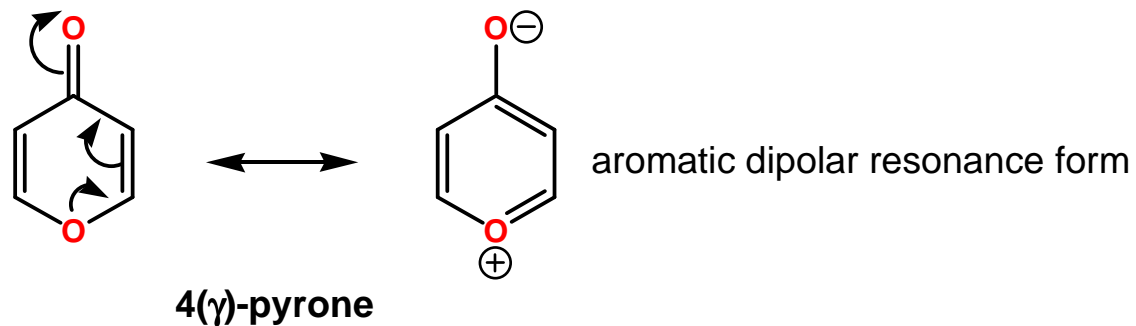


Heterocycles

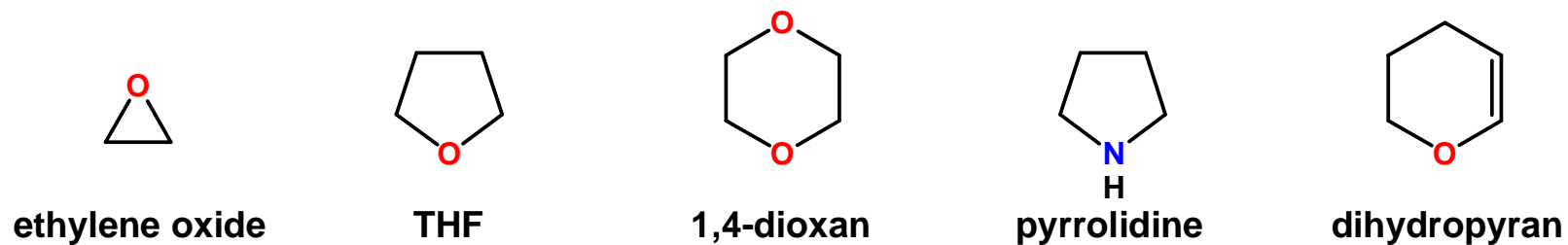


Classification – Unsaturated / Saturated

Unsaturated

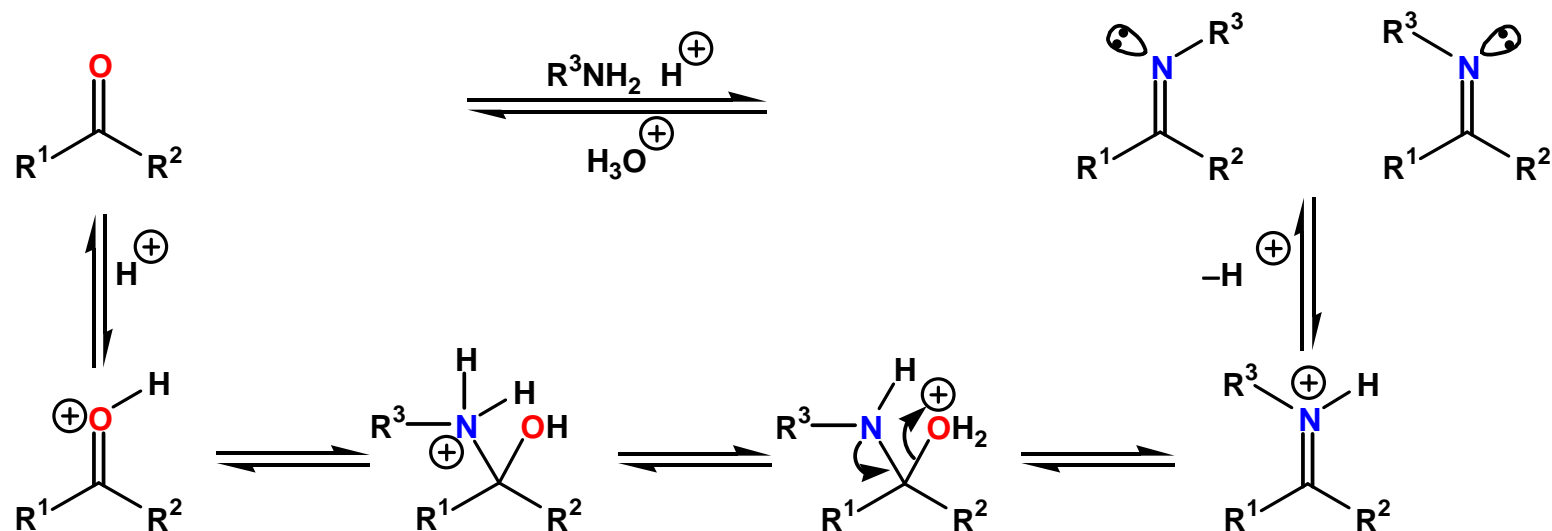


Saturated



Functional Group Chemistry

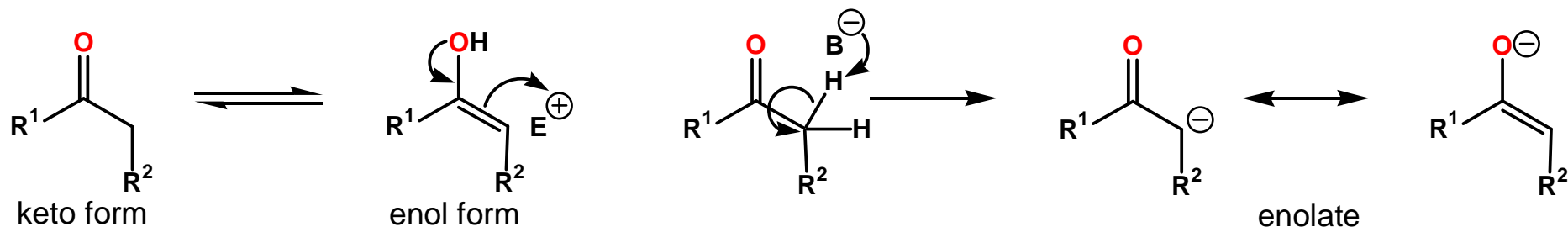
Imine Formation



- 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

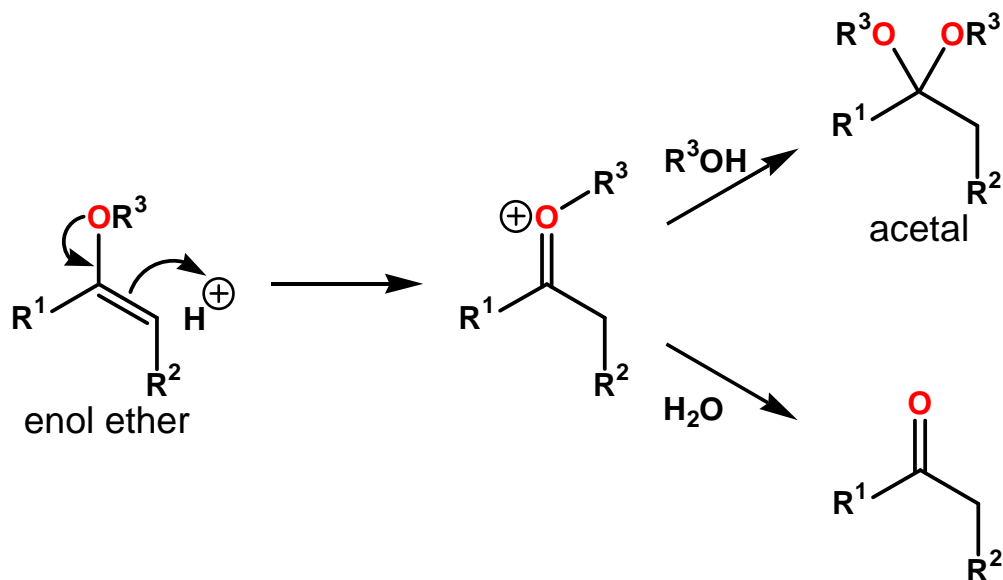
Functional Group Chemistry

Enols and Enolates



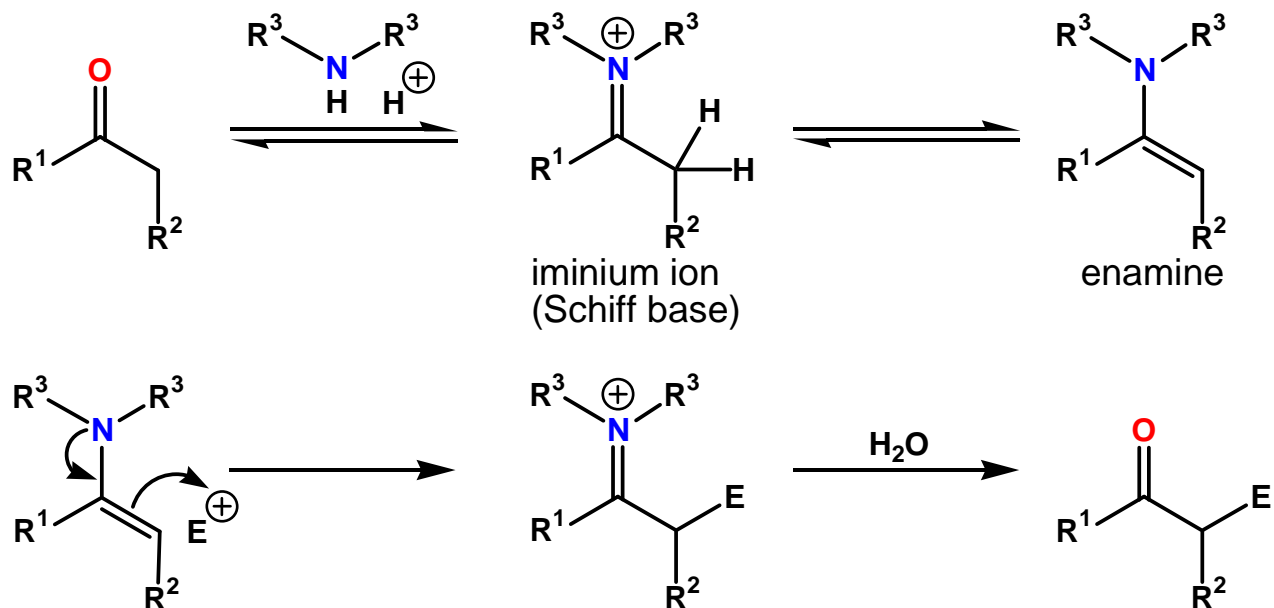
- The enol form is favoured by a conjugating group R^2 e.g. CO_2R , COR , CN , NO_2 etc.
- Avoid confusing enols (generated under neutral/acidic conditions) with enolates (generated under basic conditions)
- Enolates are nucleophilic through C or O but react with C electrophiles through C

Enol Ethers



Functional Group Chemistry

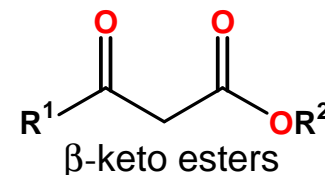
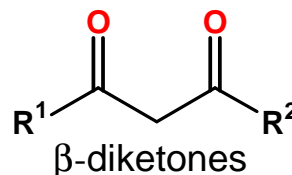
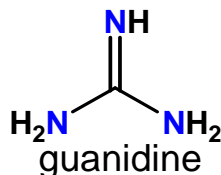
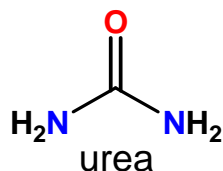
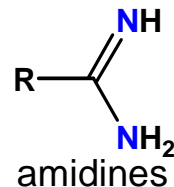
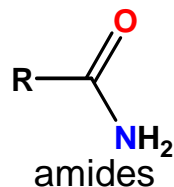
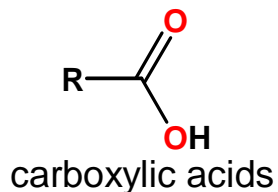
Enamines



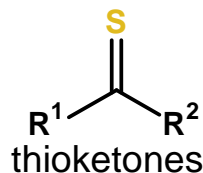
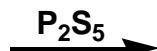
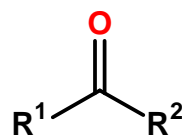
- Analogues of enols but are more nucleophilic and can function as enolate equivalents
- Removal of water (e.g. by distillation or trapping) drives reaction to completion
- Enamines react readily with carbon nucleophiles at carbon
- Reaction at *N* is possible but usually reverses

Functional Group Chemistry

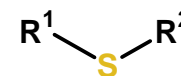
Common Building-Blocks



Building-Blocks for Sulfur-Containing Heterocycles



thiols



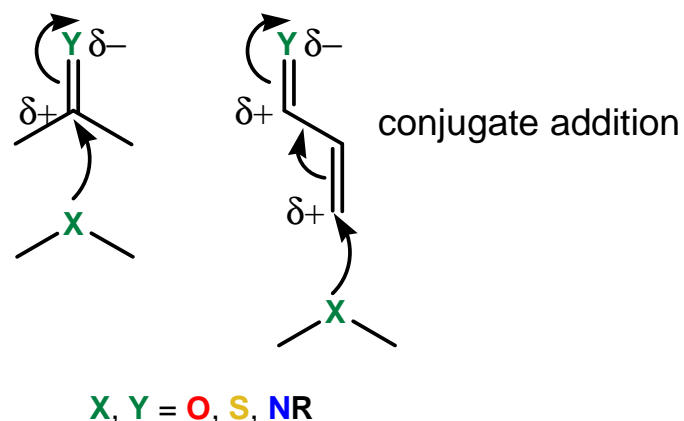
thioethers

- 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)

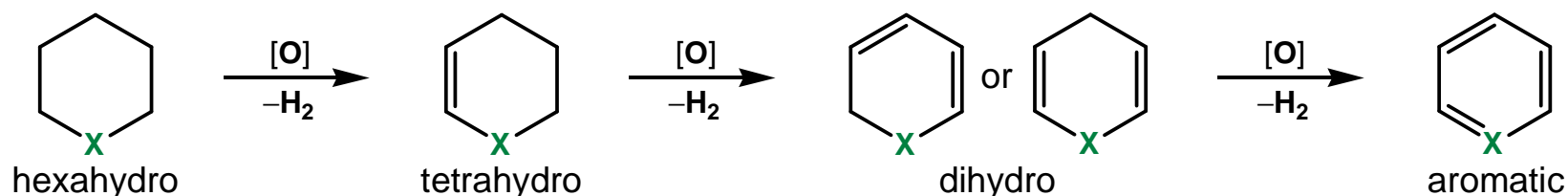
General Strategies for Heterocycle Synthesis

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



Manipulation of Oxidation State

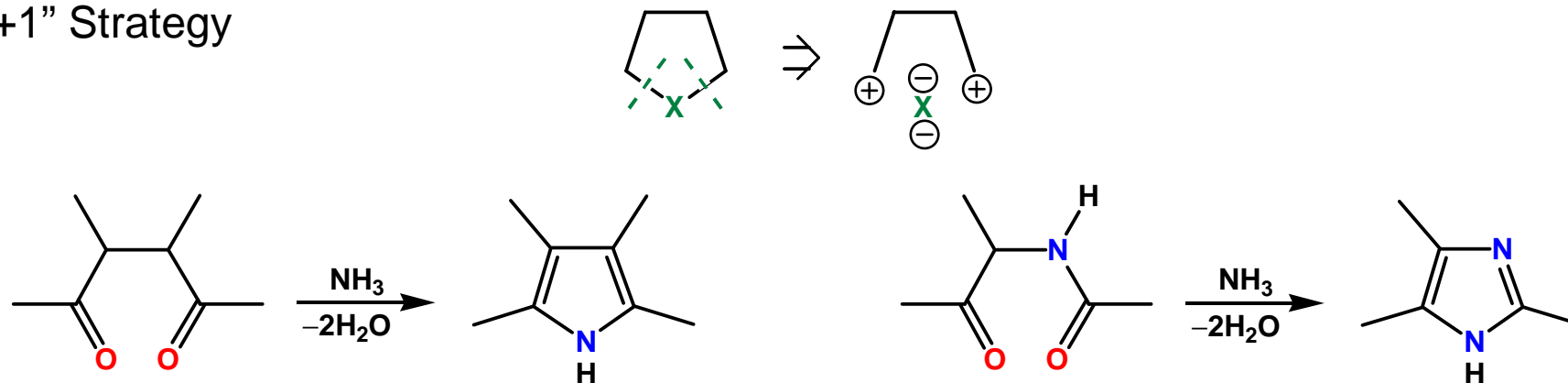


- Unsaturation is often introduced by elimination e.g. dehydration, dehydrohalogenation

General Strategies for Heterocycle Synthesis

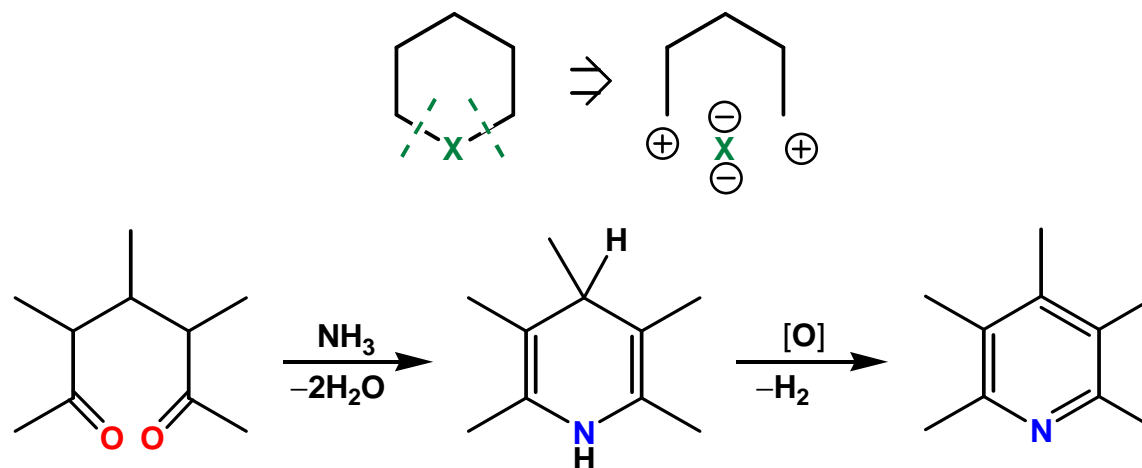
Common Strategies

“4+1” Strategy



- Strategy can be adapted to incorporate more than one heteroatom

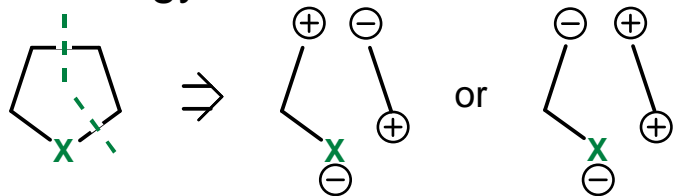
“5+1” Strategy



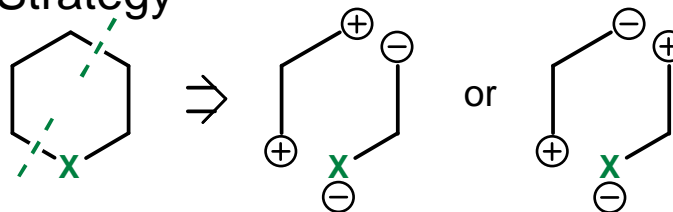
- 1,5-Dicarbonyl compounds can be prepared by [Michael addition](#) of enones

General Strategies for Heterocycle Synthesis

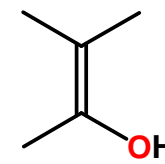
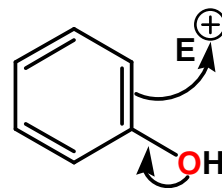
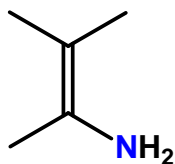
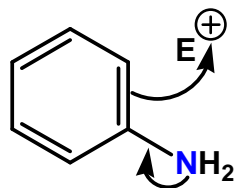
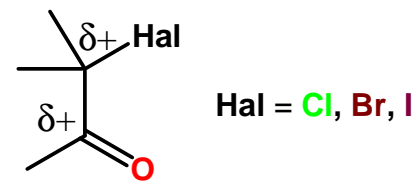
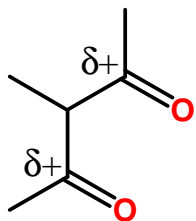
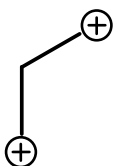
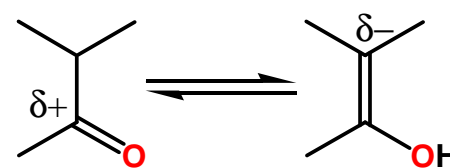
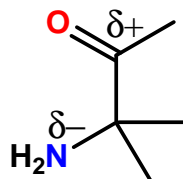
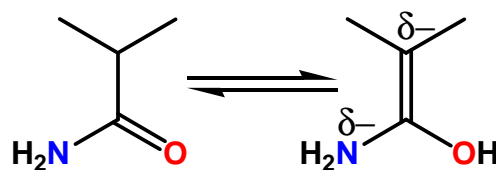
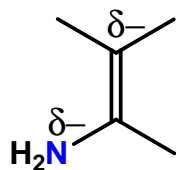
“3+2” Strategy



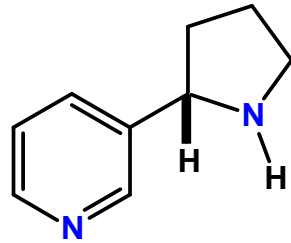
“3+3” Strategy



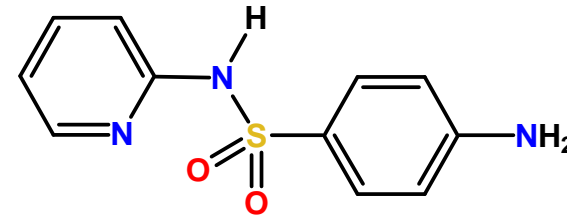
Examples



Bioactive Pyridines

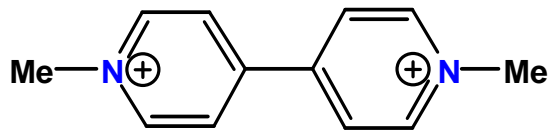


nicotine

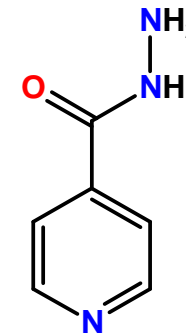


sulphapyridine

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



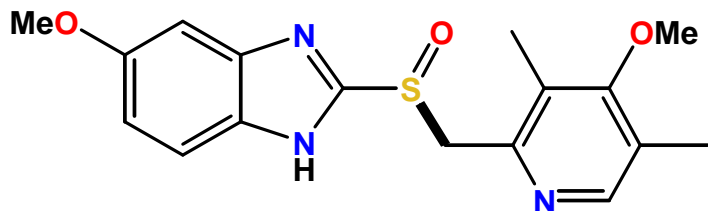
paraquat



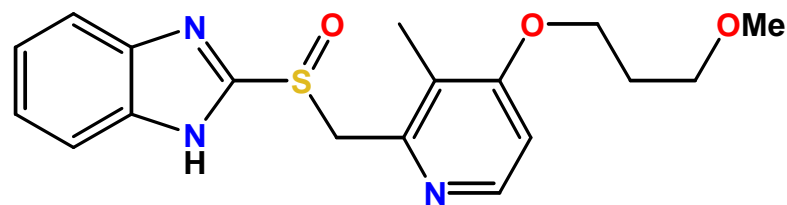
isoniazide

- 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

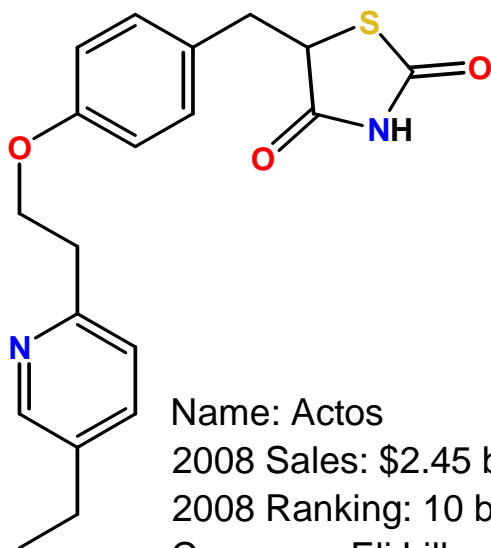
Drugs Containing a Pyridine



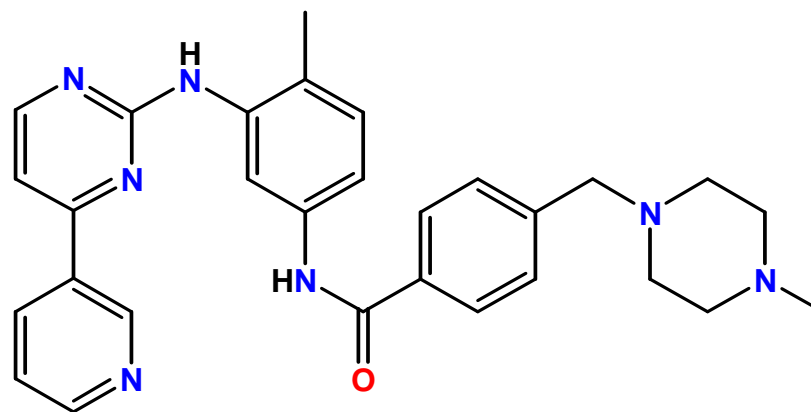
Name: Nexium
2008 Sales: \$4.79 billion
2008 Ranking: 2 branded
Company: AstraZeneca
Disease: Acid reflux



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

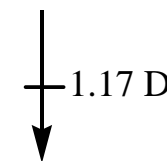
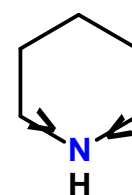
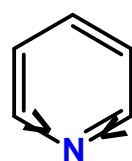
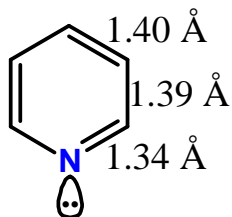


Name: Actos
2008 Sales: \$2.45 billion
2008 Ranking: 10 branded
Company: Eli Lilly
Disease: Type 2 diabetes

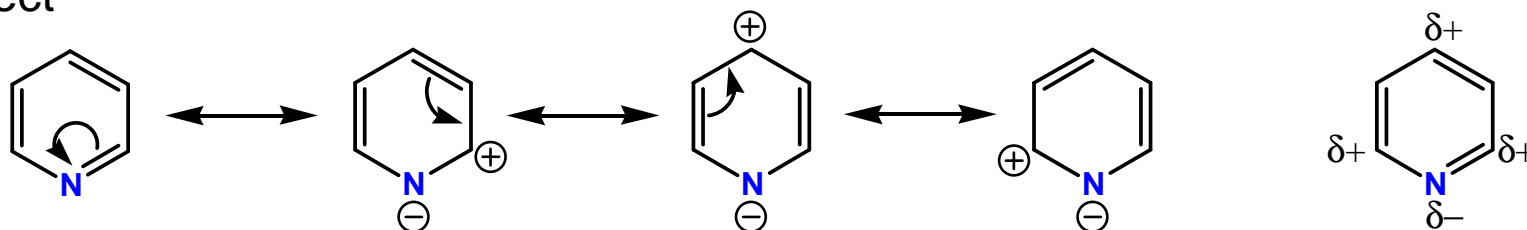


Name: Gleevec
2008 Sales: \$0.45 billion
2008 Ranking: 87 branded
Company: Novartis
Disease: Chronic myeloid leukemia

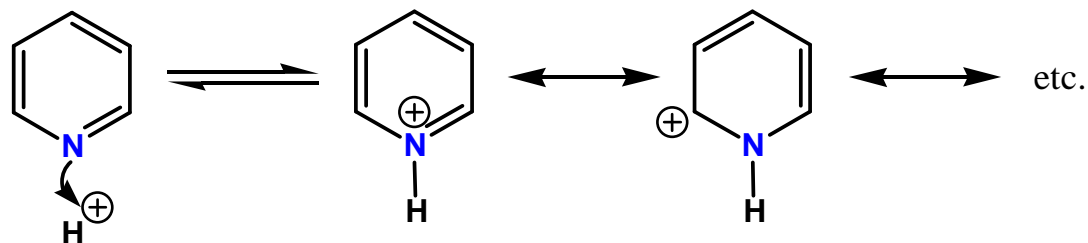
Pyridines – Structure



- Isoelectronic with and analogous to benzene
- Stable, not easily oxidised at C, undergoes substitution rather than addition
- -I Effect (inductive electron withdrawal)
- -M Effect

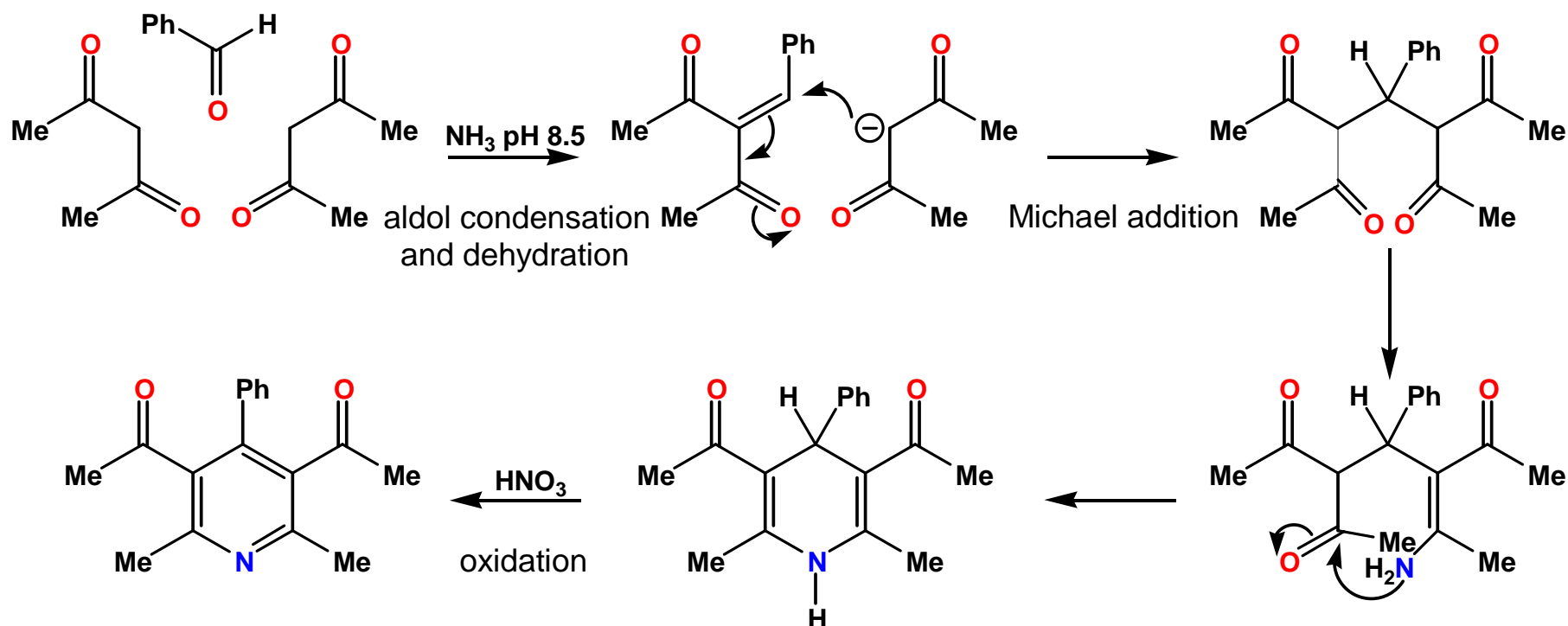


- Weakly basic – $pK_a \sim 5.2$ in H_2O (lone pair is **not** in aromatic sextet)
- Pyridinium salts are also aromatic – ring carbons are more δ^+ than in parent pyridine



Pyridines – Synthesis

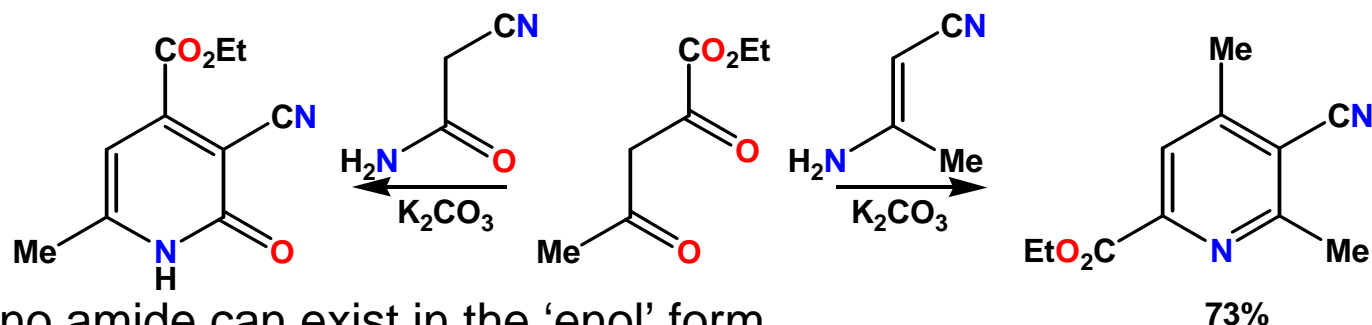
The Hantzsch synthesis (“5+1”)



- 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

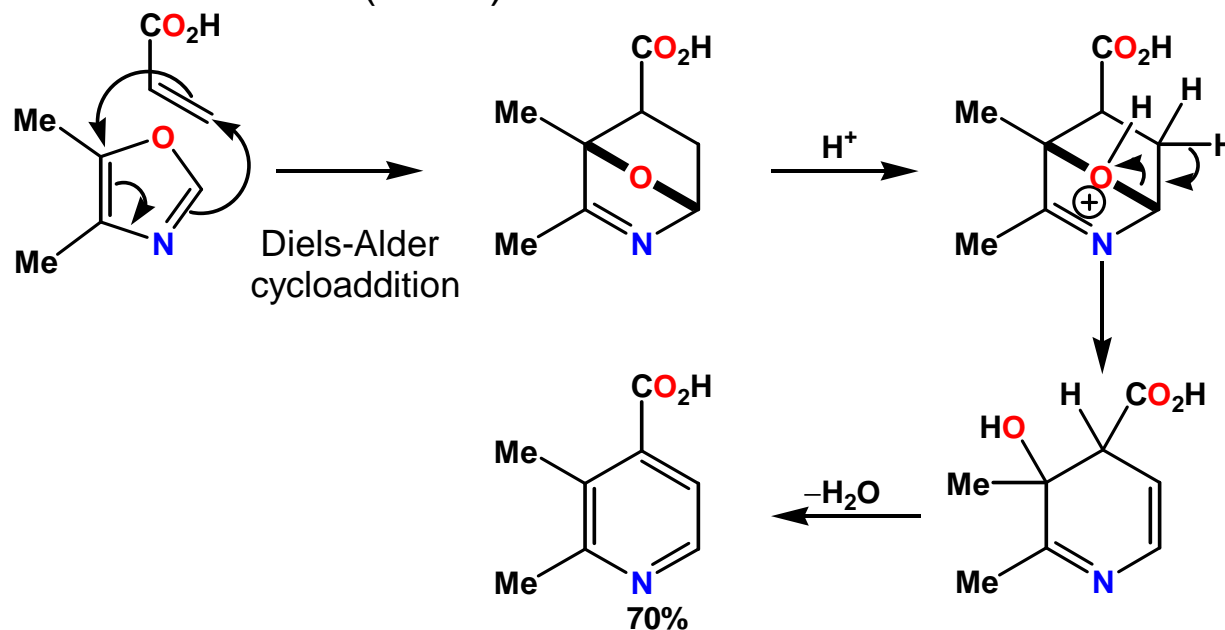
Pyridines – Synthesis

From Enamines or Enamine Equivalents – the **Guareschi synthesis** (“3+3”)



- The β -cyano amide can exist in the ‘enol’ form

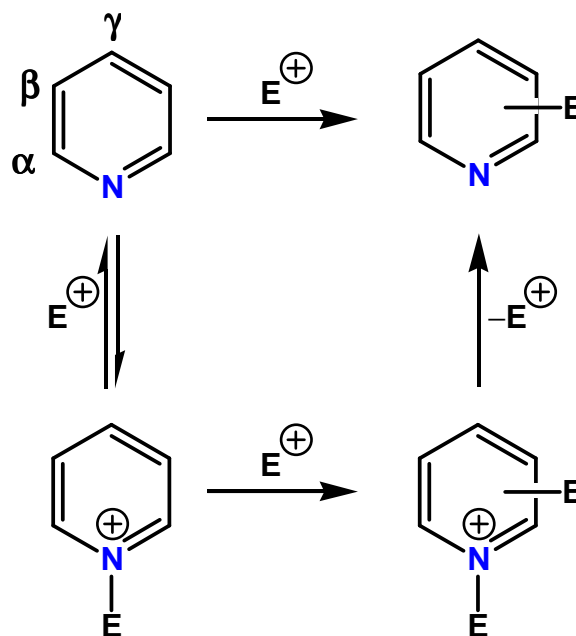
Using Cycloaddition Reactions (“4+2”)



- Oxazoles are sufficiently low in aromatic character to react in the **Diels-Alder reaction**

Pyridines – Electrophilic Reactions

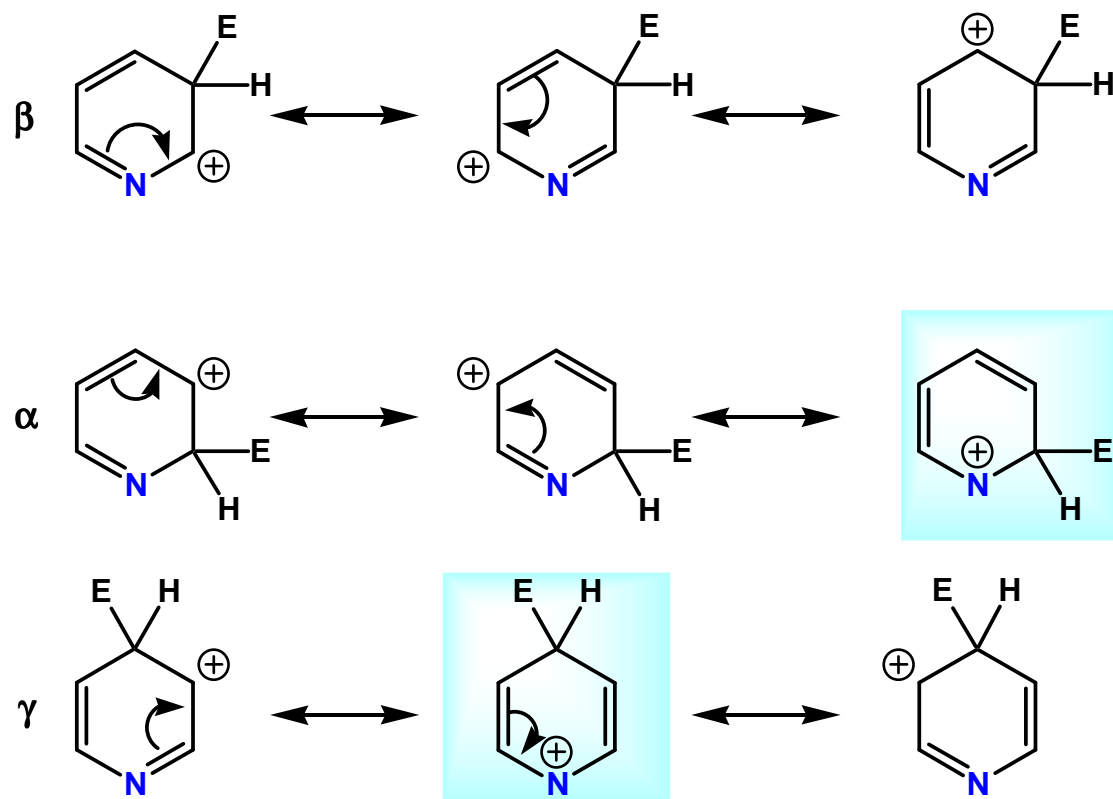
Pathways for the Electrophilic Aromatic Substitution of Pyridines



- The position of the equilibrium between the pyridine and pyridinium salt depends on the substitution pattern and nature of the substituents, but usually favours the salt

Pyridines – Electrophilic Reactions

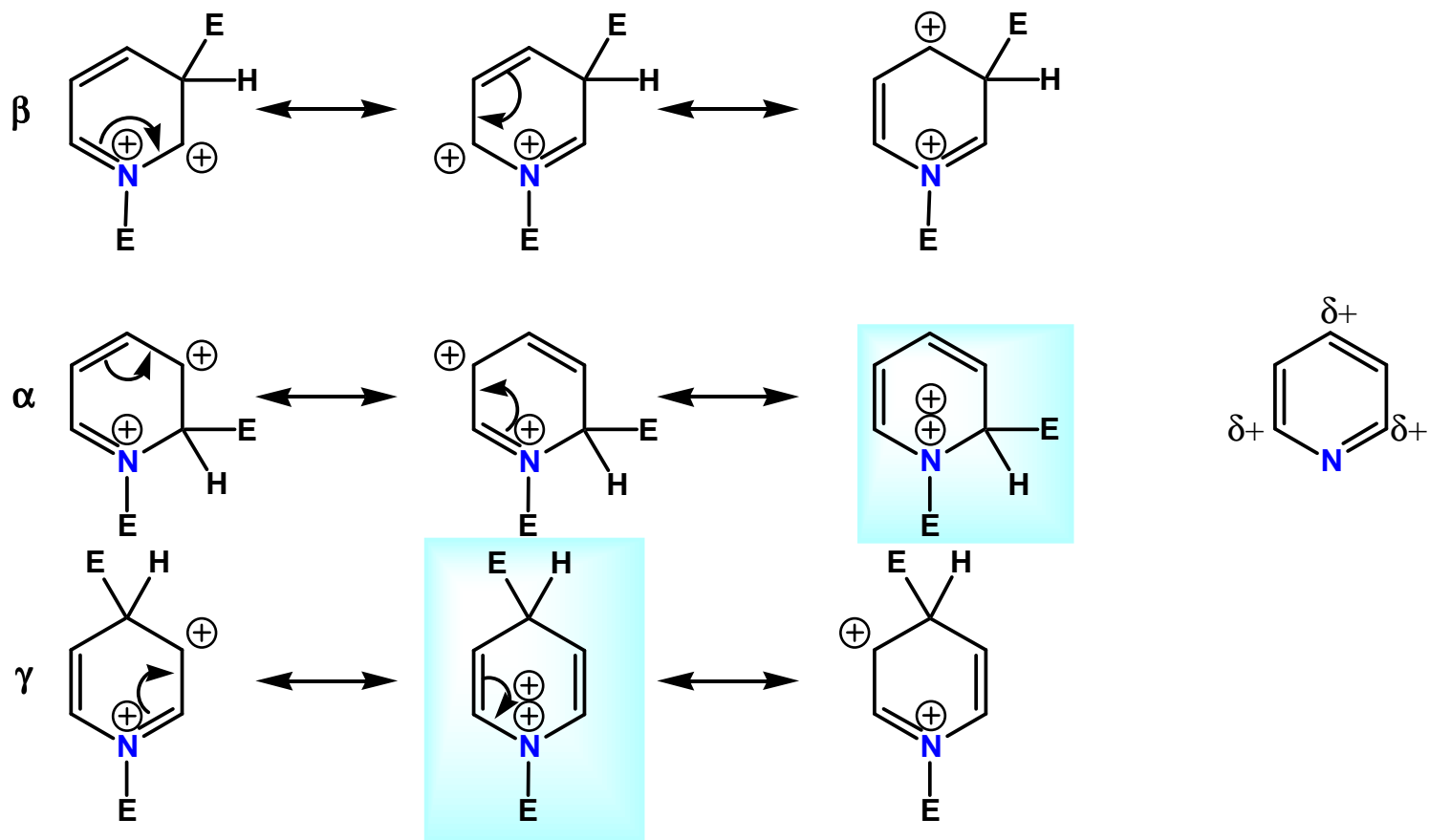
Regiochemical Outcome of Electrophilic Substitution of Pyridines



- Resonance forms with a positive charge on *N* (i.e. 6 electrons) are very unfavourable
- The β -substituted intermediate, and the transition state leading to this product, have more stable resonance forms than the intermediates/transition states leading to the α/γ products

Pyridines – Electrophilic Reactions

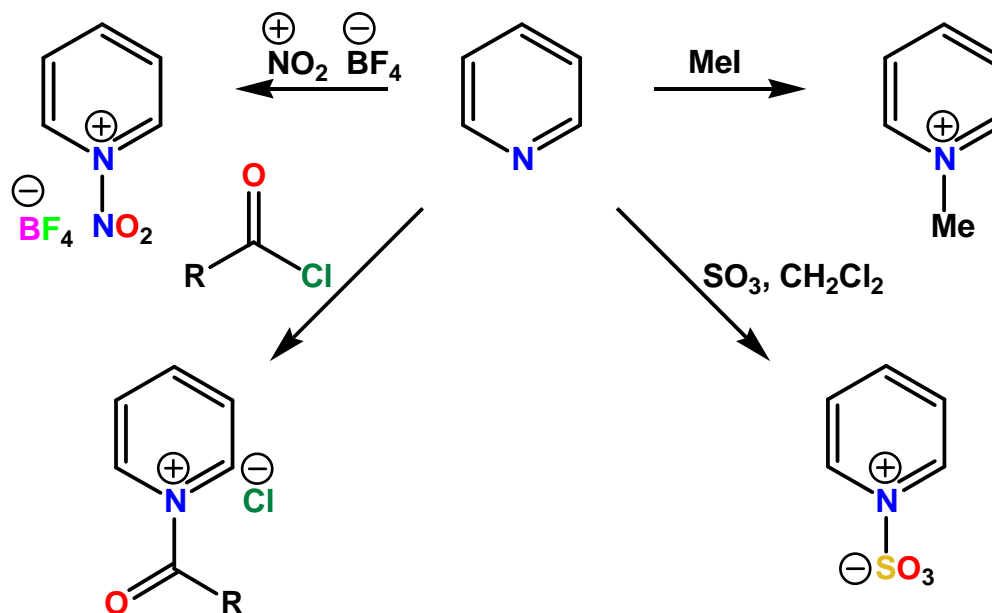
Regiochemical Outcome of Electrophilic Substitution of Pyridinium Ions



- Regiochemical control is even more pronounced in the case of pyridinium ions
- In both pyridine and pyridinium systems, β substitution is favoured but the reaction is slower than that of benzene
- Reaction will usually proceed through the small amount of the free pyridine available

Pyridines – Electrophilic Reactions

N Substitution

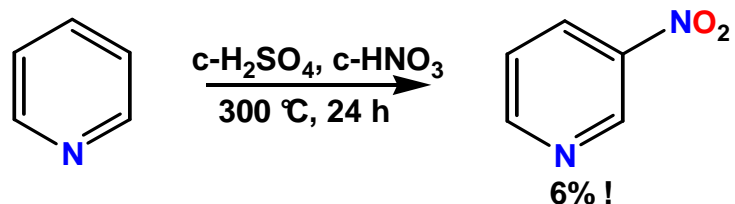


C Substitution

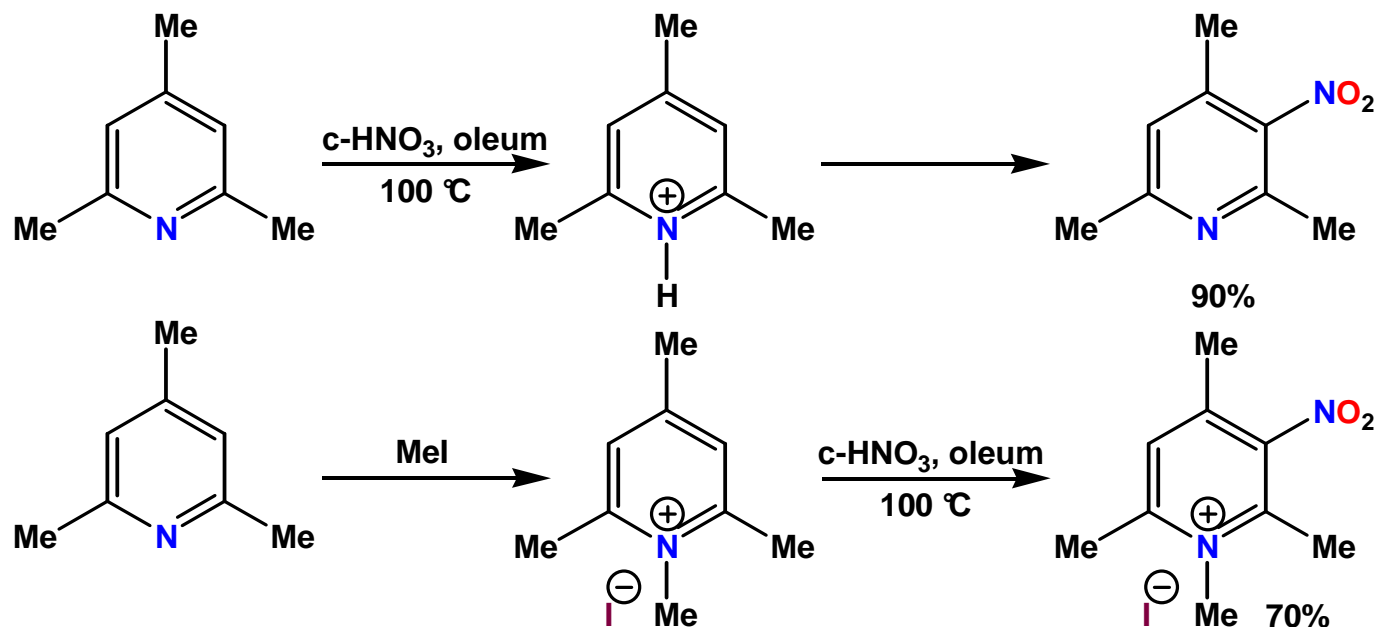
- Reaction at C is usually difficult and slow, requiring forcing conditions
- **Friedel-Crafts reactions** are not usually possible on free pyridines

Pyridines – Electrophilic Reactions

Nitration of Pyridine



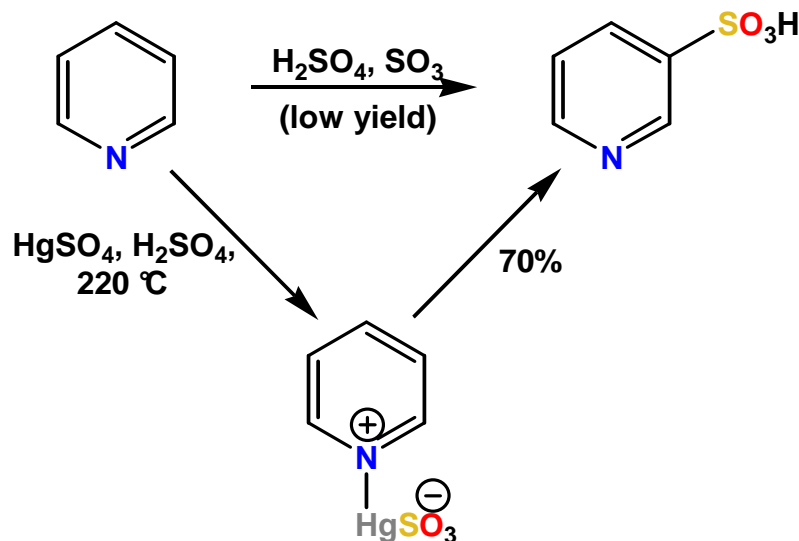
Use of Activating Groups



- 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

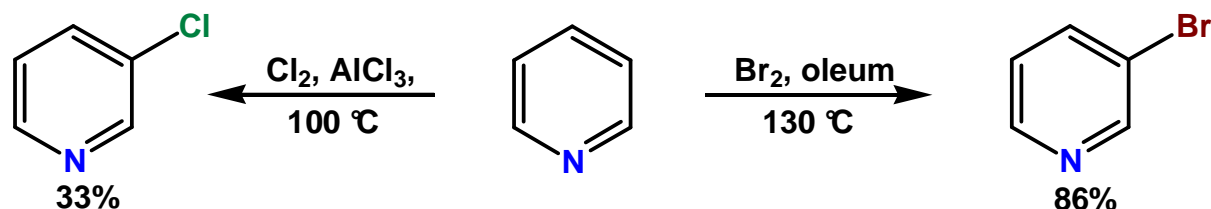
Pyridines – Electrophilic Reactions

Sulfonation of Pyridine



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

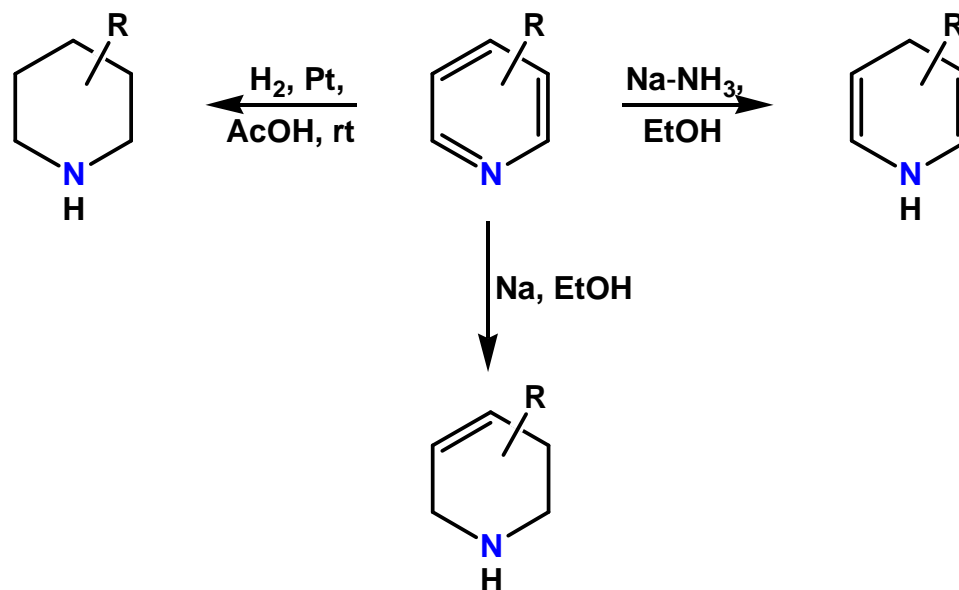
Halogenation of Pyridine



- Forcing reaction conditions are required for direct halogenation

Pyridines – Reduction

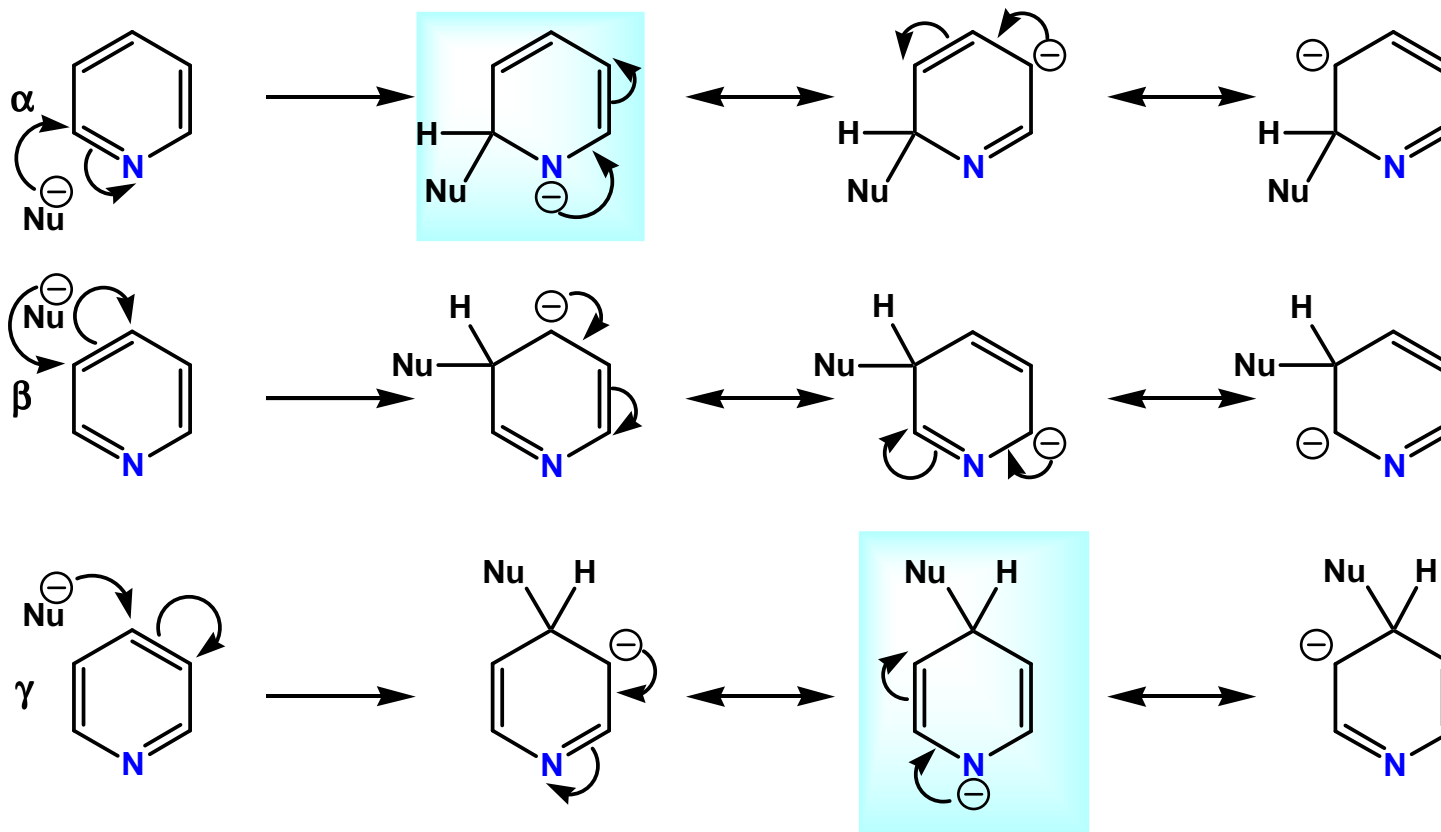
Full or Partial Reduction of Pyridines



- 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

Pyridines – Nucleophilic Reactions

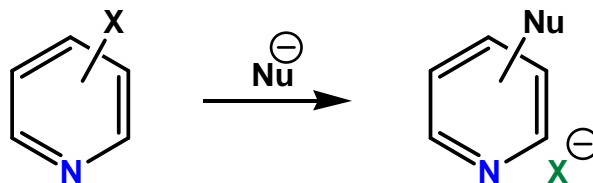
Regiochemical Outcome of Nucleophilic Addition to Pyridines



- Nitrogen acts as an electron sink
- β Substitution is less favoured because there are no stable resonance forms with the negative charge on *N*
- Aromaticity will be regained by loss of hydride or a leaving group, or by oxidation 28

Pyridines – Nucleophilic Reactions

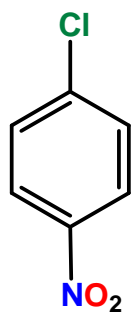
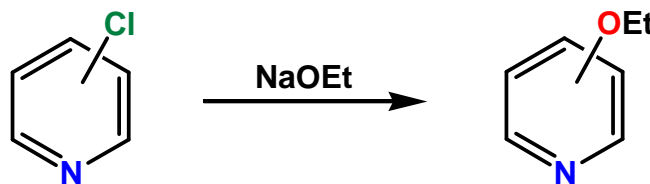
Nucleophilic Substitution



X = Cl, Br, I, (NO₂)

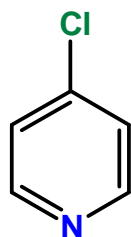
Nu = MeO[⊖], NH₃, PhSH etc.

- Favoured by electron-withdrawing substituents that are also good leaving groups
- The position of the leaving group influences reaction rate ($\gamma > \alpha \gg \beta$)

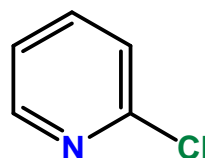


Relative rate

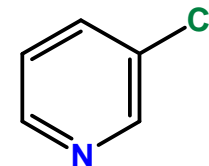
80



40



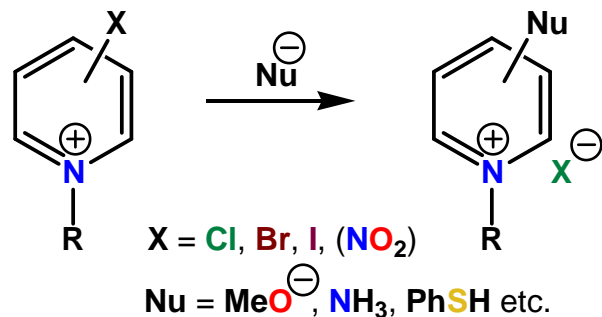
1



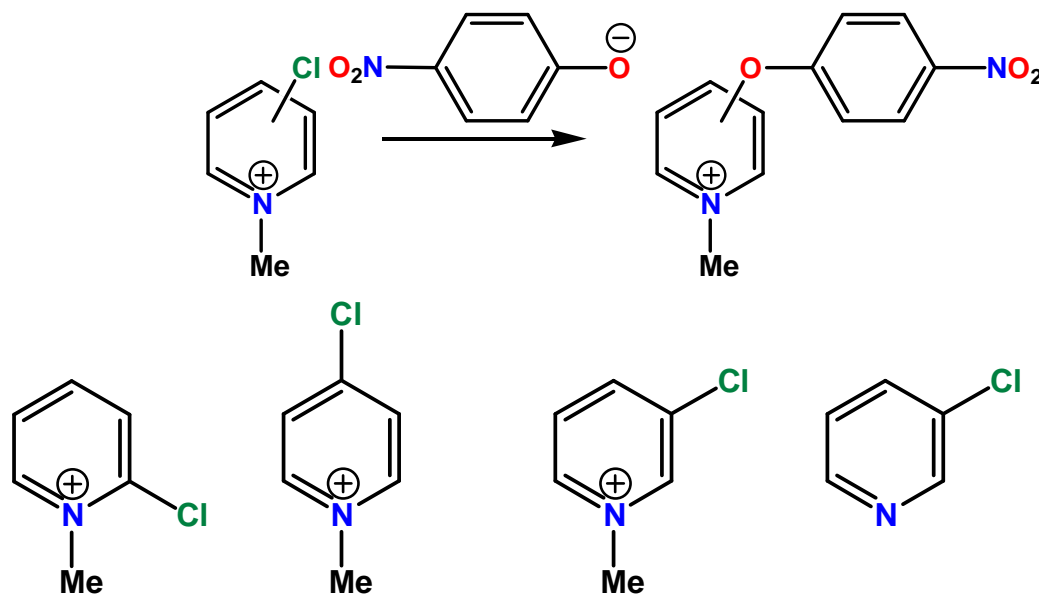
3×10^{-4}

Pyridinium Ions – Nucleophilic Reactions

Nucleophilic Substitution



- Conversion of a pyridine into the pyridinium salt greatly accelerates substitution
- Substituent effects remain the same ($\alpha, \gamma \gg \beta$) but now $\alpha > \gamma$



Relative rate

5×10^7

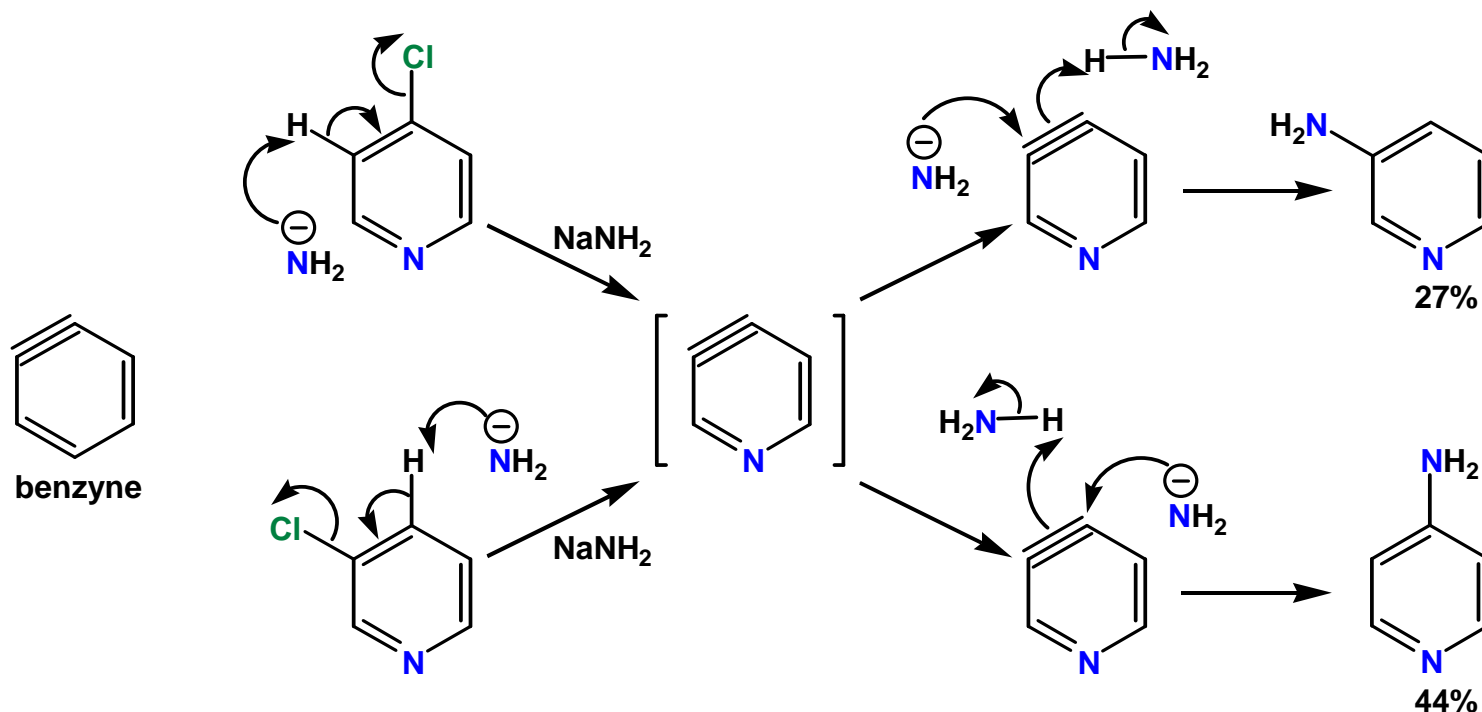
1.5×10^4

1

10^{-4}

Pyridines – Pyridyne Formation

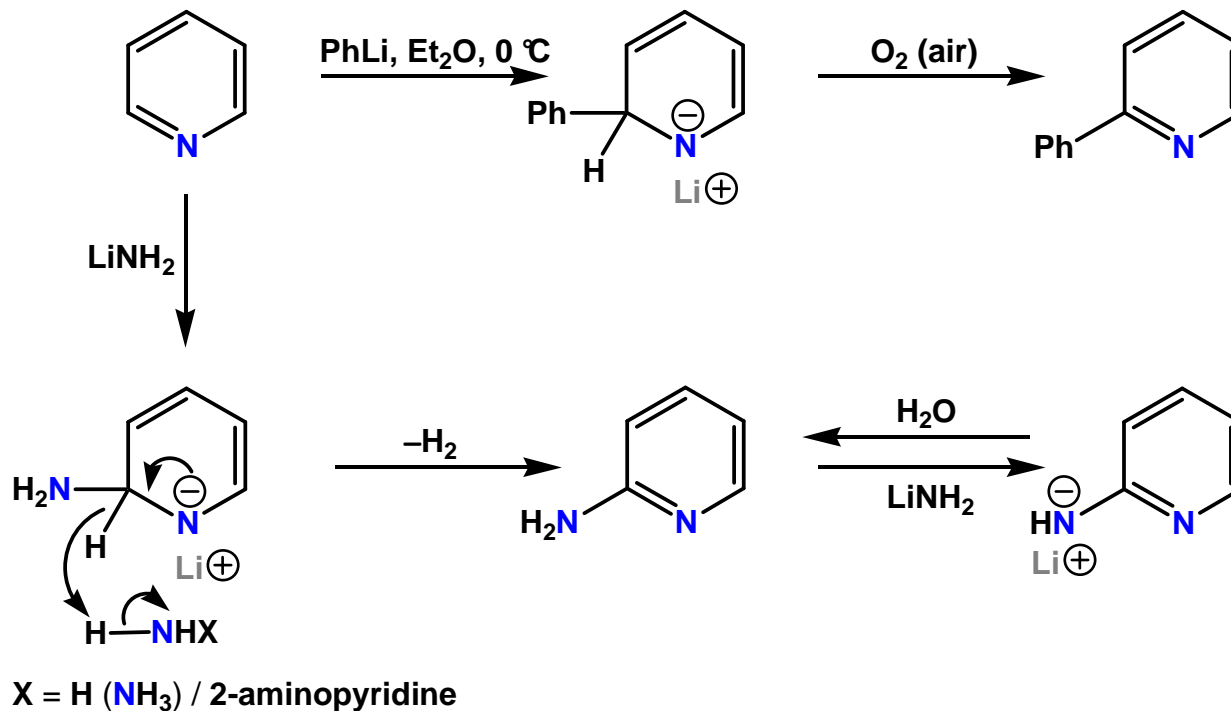
Substitution via an Intermediate Pyridyne



- When very basic nucleophiles are used, a pyridyne intermediate intervenes
- Pyridynes are similar to benzyne and are very reactive (not isolable)

Pyridines – Nucleophilic Reactions

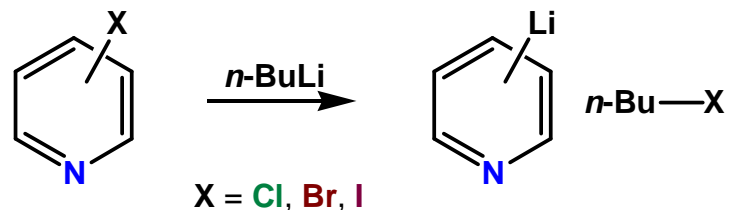
Nucleophilic Attack with Transfer of Hydride



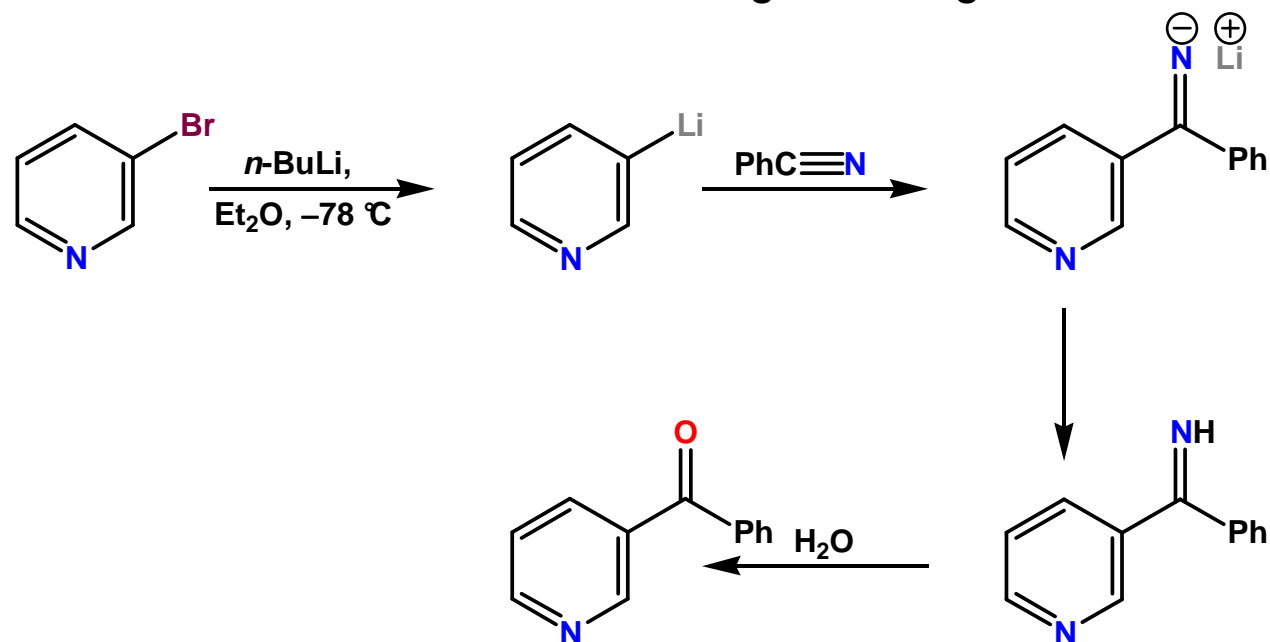
- A hydride acceptor or oxidising agent is required to regenerate aromaticity
- The reaction with LiNH_2 is referred to as the [Chichibabin reaction](#)

Pyridines – Metal-Halogen Exchange

Direct Exchange of Metal and a Halogen

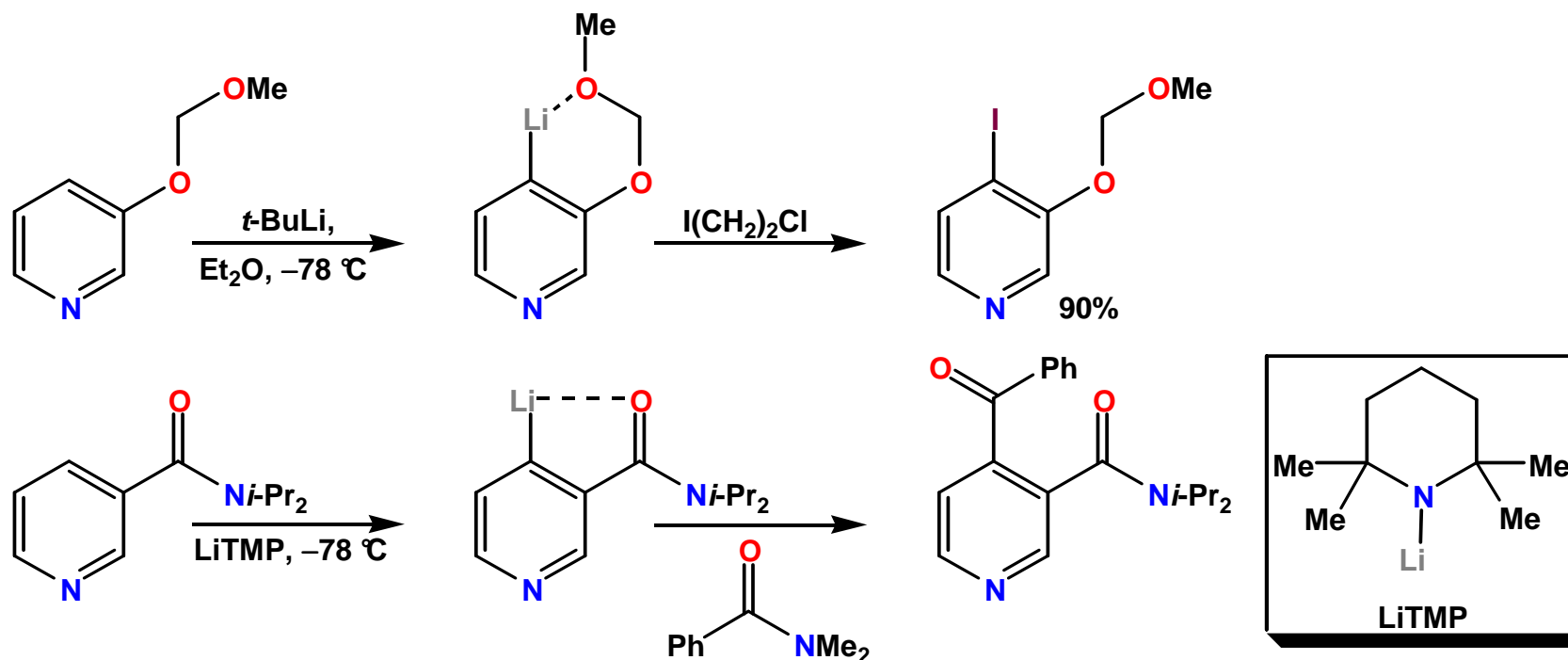


- Halogenated pyridines do not tend to undergo nucleophilic displacement with alkyl lithium or alkyl magnesium reagents
- Metallated pyridines behave like conventional Grignard reagents



Pyridines – Directed Metallation

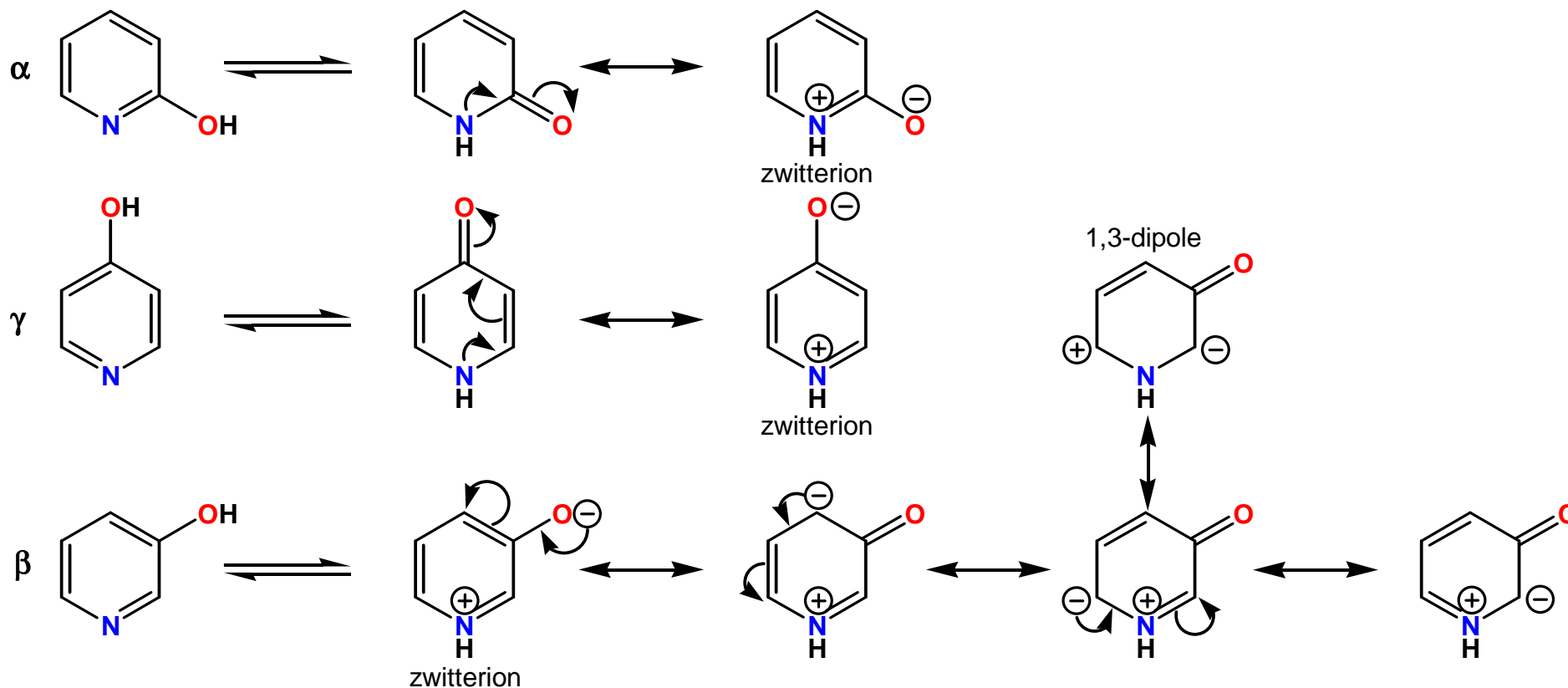
Use of Directing Groups



- Directing groups allow direct lithiation at an adjacent position
- A Lewis basic group is required to complex the Lewis acidic metal of the base

Oxy-Pyridines – Structure

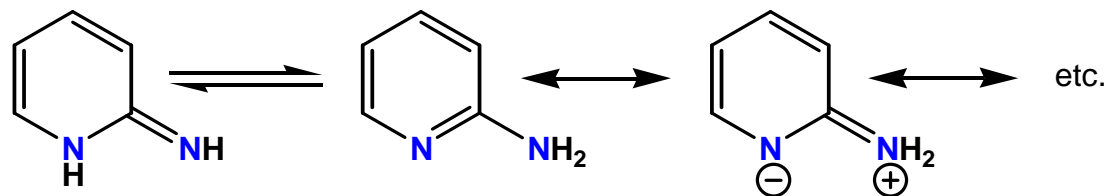
Oxy-Pyridines/Pyridones



- Subject to tautomerism
- The α , γ systems differ from the β systems in terms of reactivity and structure
- In the α case, the equilibrium is highly solvent dependent, but the keto form is favoured in polar solvents

Amino Pyridines – Structure

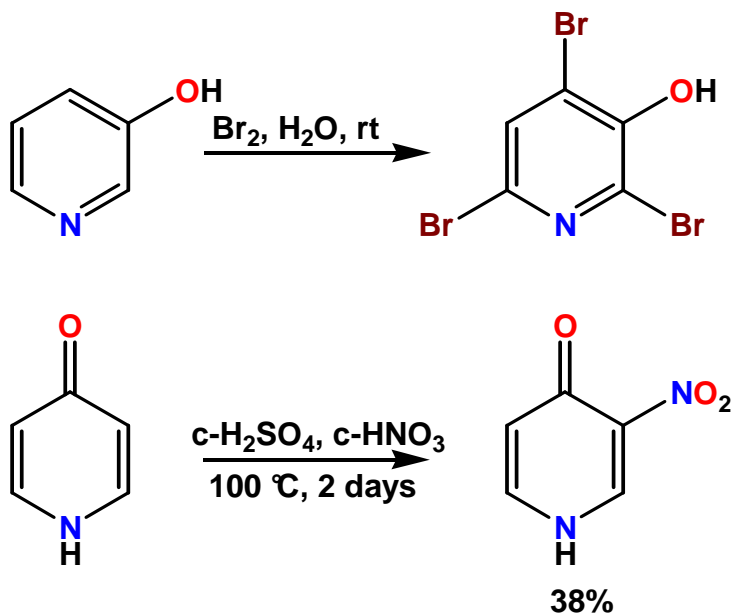
Amino Pyridine Systems



- Contrast with oxy-pyridines
- Amino pyridines are polarised in the opposite direction to oxy-pyridines

Oxy-Pyridines – Reactions

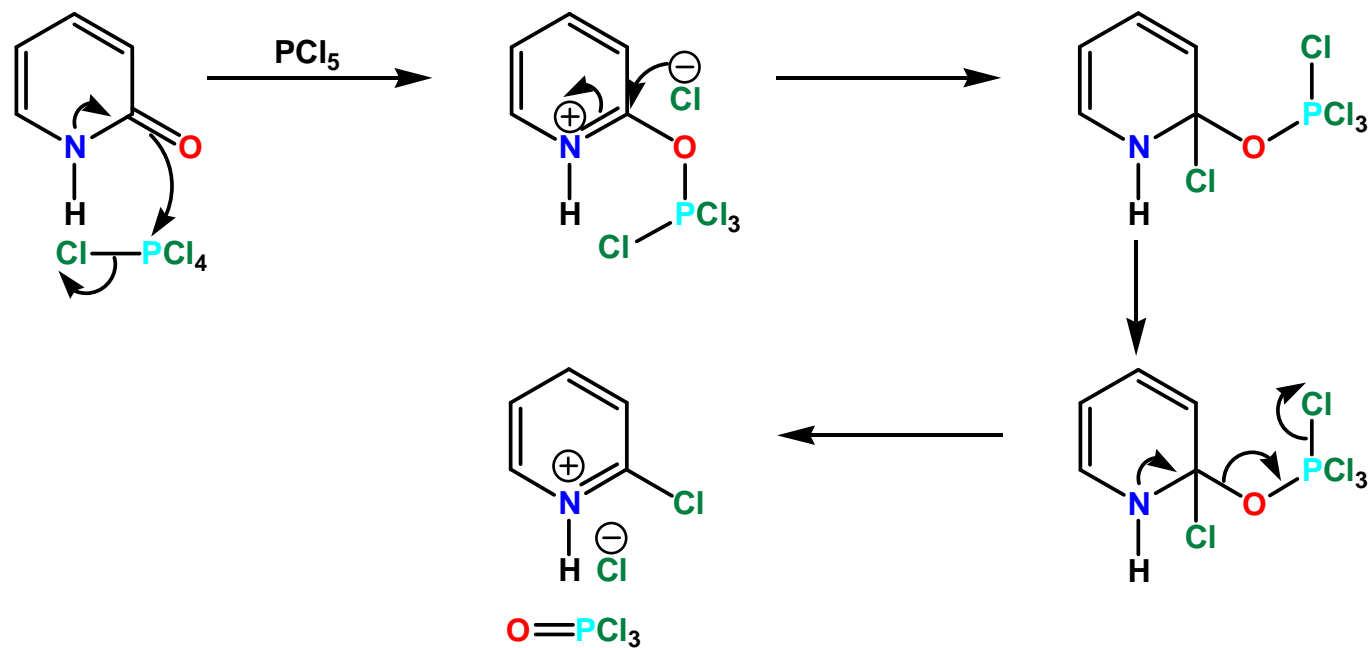
Electrophilic Substitution



- Reactions such as halogenation, nitration, sulfonation etc. are possible
- *N* is much less basic than that in a simple pyridine
- Substitution occurs ortho or para to the oxygen substituent (cf. phenols)

Oxy-Pyridines – Reactions

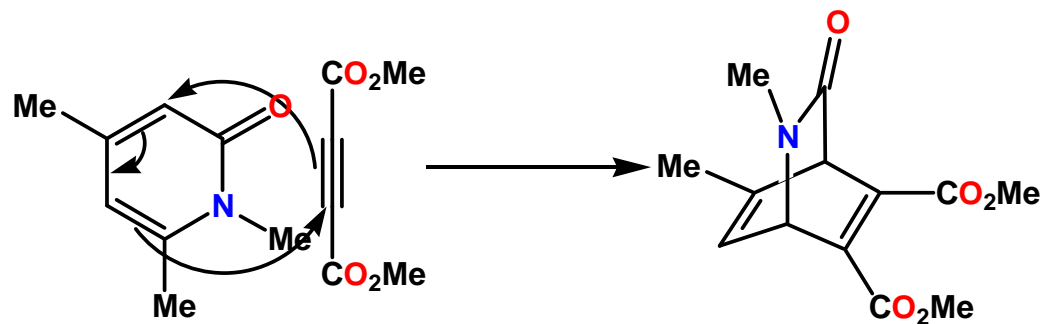
Nucleophilic Substitution



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

Oxy-Pyridines – Reactions

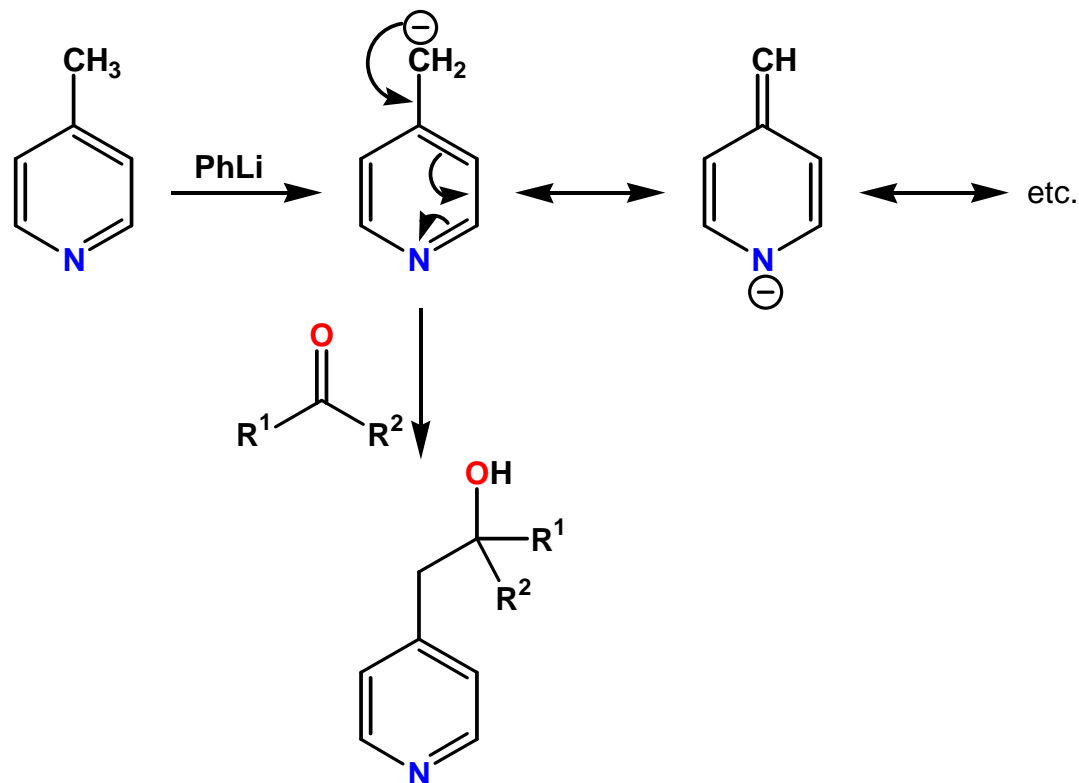
Cycloaddition



- Oxy-pyridines have sufficiently low aromatic character that they are able to participate as dienes in [Diels-Alder reactions](#) with highly reactive dienophiles

Alkyl Pyridines – Deprotonation

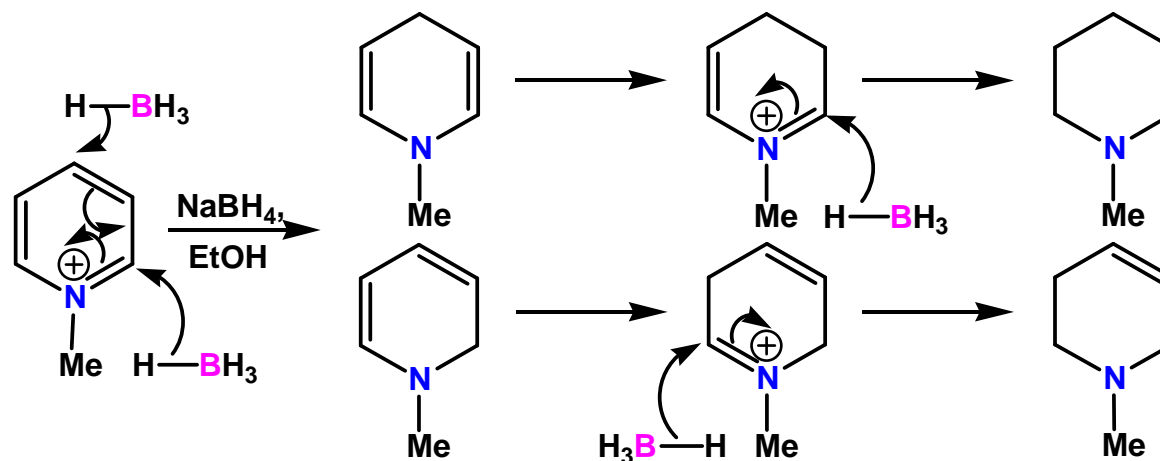
Deprotonation with a Strong Base



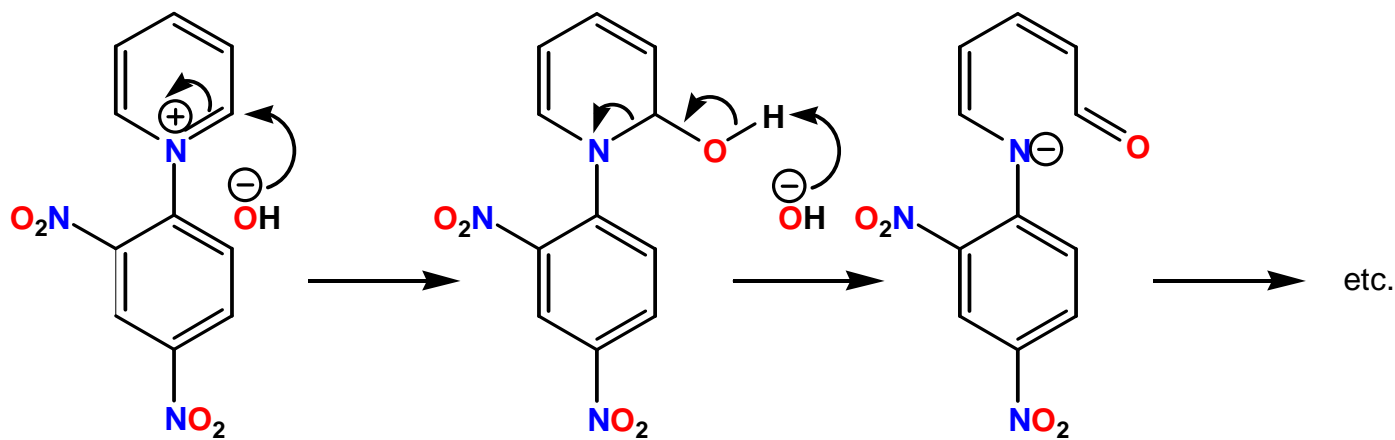
- Deprotonation of α and γ alkyl groups proceeds at a similar rate, but β alkyl groups are much more difficult to deprotonate
- Bases are also potential nucleophiles for attack of the ring

Pyridinium Salts – Reactions

Nucleophilic Attack with Reducing Agents

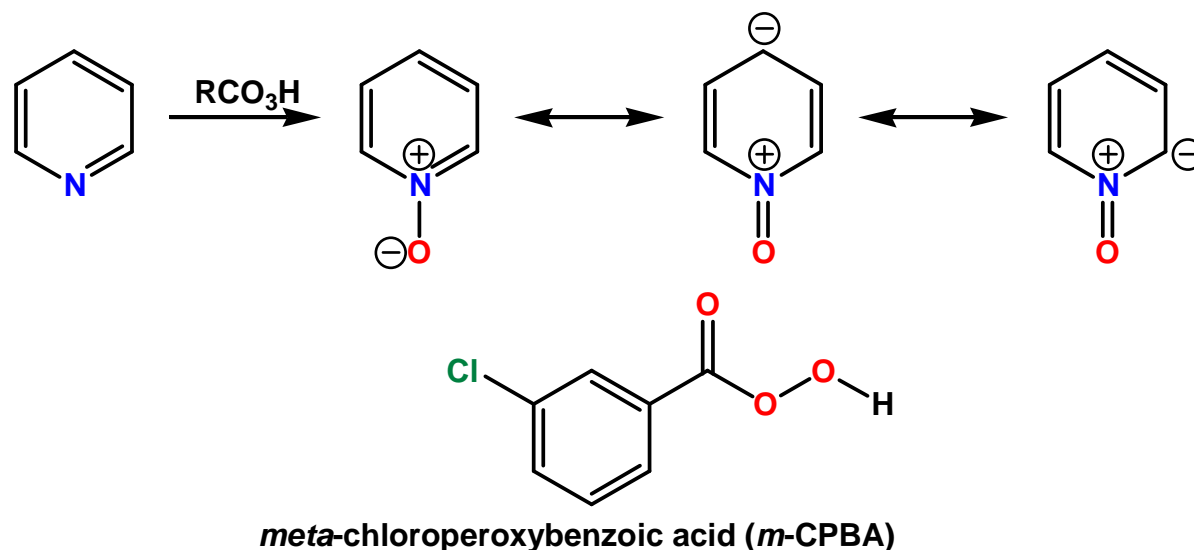


- Nucleophilic attack is much easier (already seen this)
- Deprotonation of alkyl substituents is easier (weak bases are suitable)
- Ring opening is possible by attack of hydroxide



Pyridine *N*-Oxides

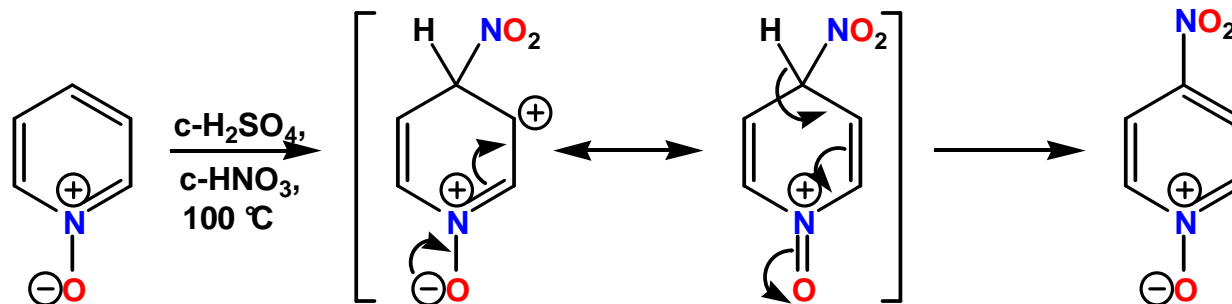
N-Oxide Formation



- 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

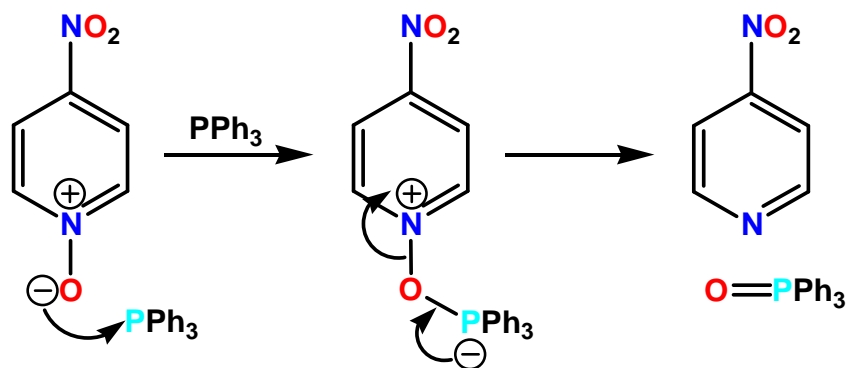
Pyridine *N*-Oxides

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.

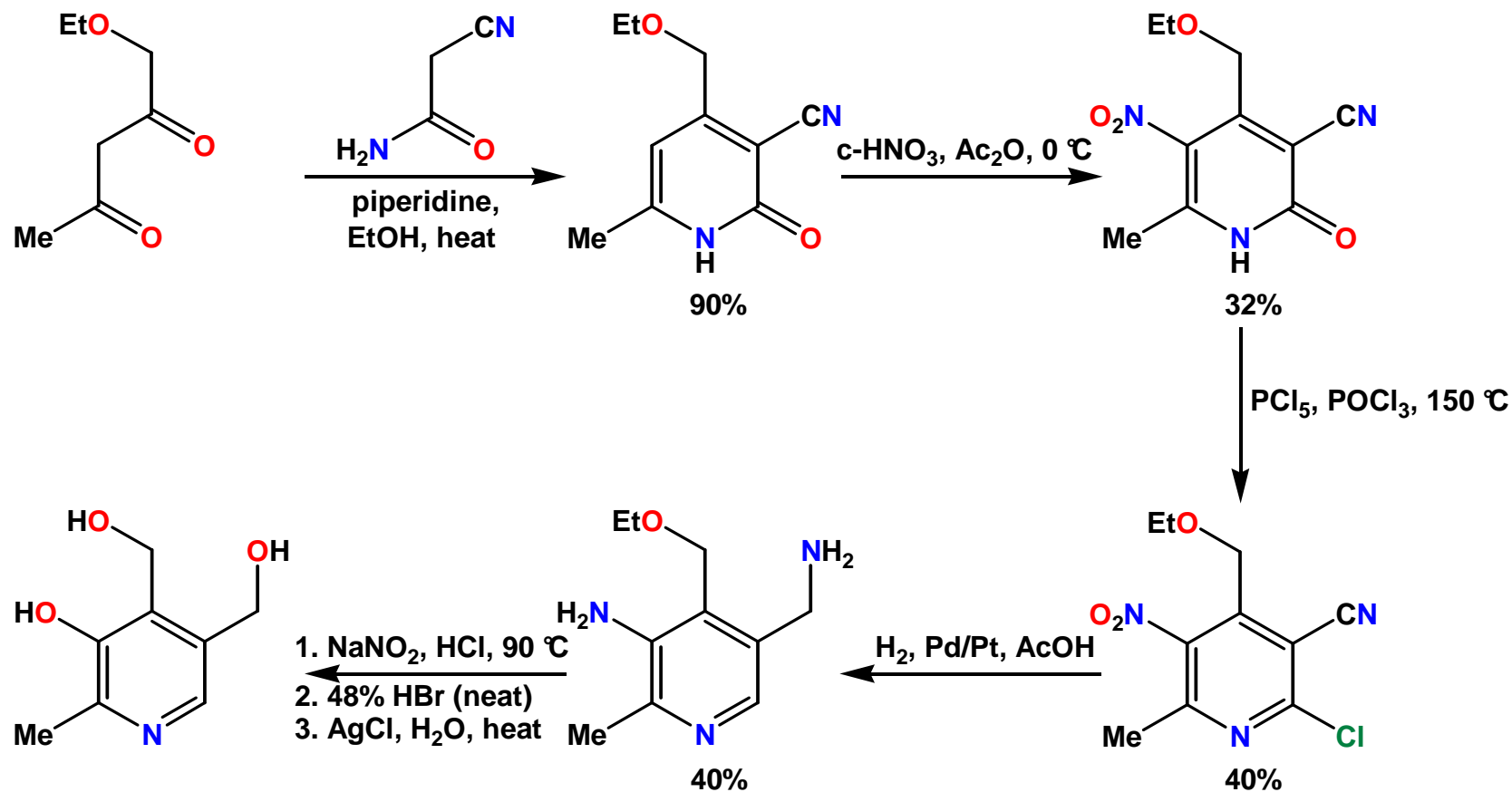
Removal of O



- Deoxygenation is driven by the formation of the very strong $\text{P}=\text{O}$ bond

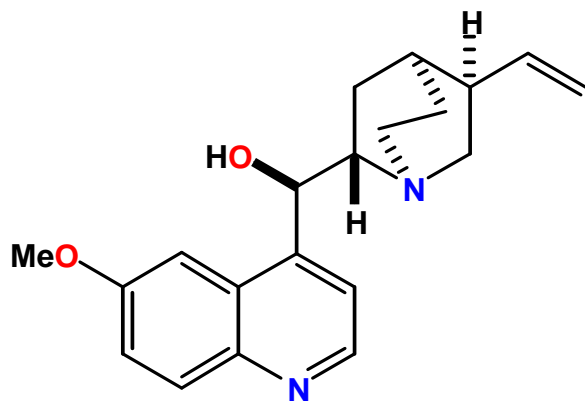
Pyridines – Synthesis of a Natural Product

Synthesis of Pyridoxine (Vitamin B₆) Using the Guareschi Synthesis

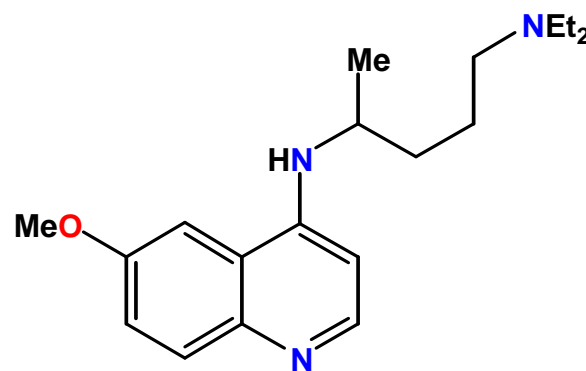


- The final sequence of steps involves formation of a *bis*-diazonium salt from a diamine
- Pyridoxine performs a key role as the coenzyme in transaminases

Bioactive Quinolines/Isoquinolines

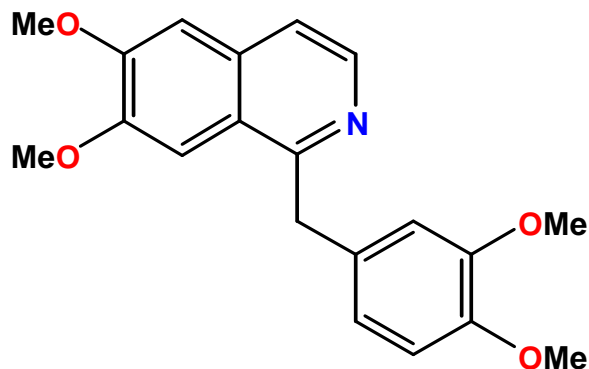


quinine



chloroquine

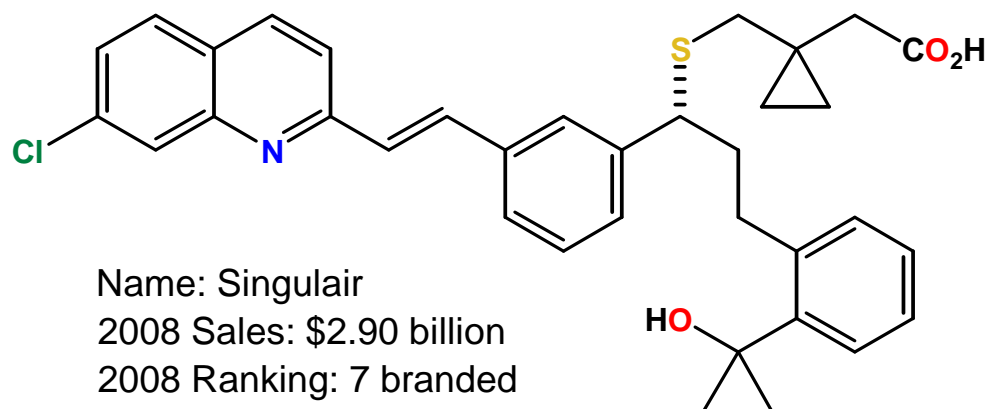
- Quinine is an anti-malarial natural product isolated from the bark of the *Cinchona* tree
- Chloroquine is a completely synthetic anti-malarial drug that has the quinoline system found in quinine – parasite resistance is now a problem



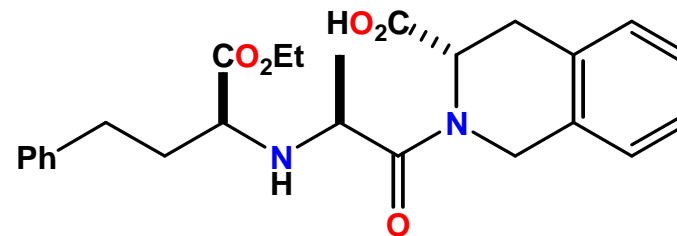
papaverine

- Papaverine is an alkaloid isolated from the opium poppy and is a smooth muscle⁴⁵ relaxant and a coronary vasodilator

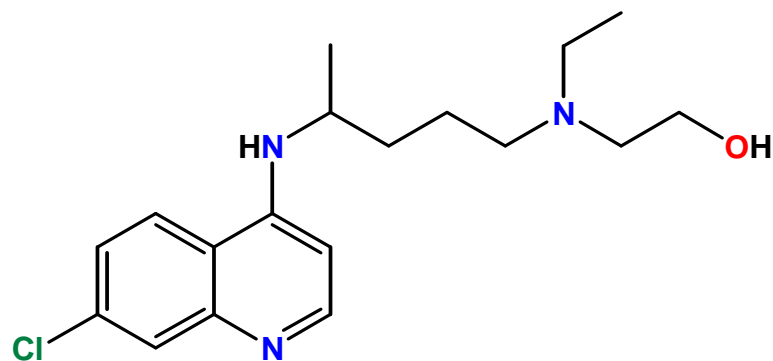
Drugs Containing a Quinoline/Isoquinoline



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



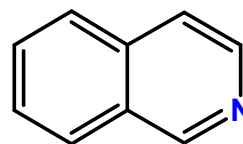
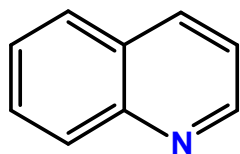
Anopheles mosquito



Plasmodium monocyte

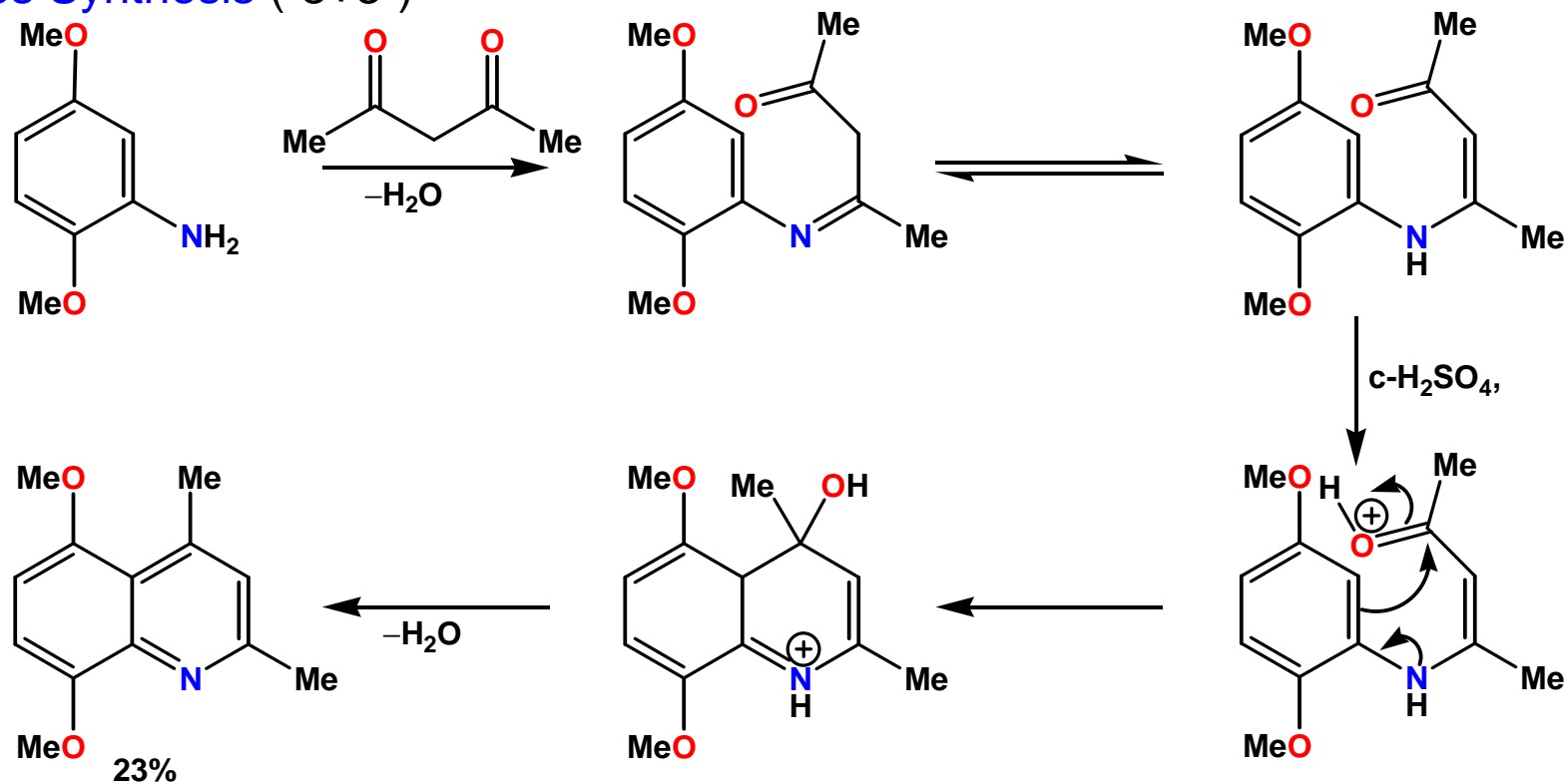
Quinolines – Synthesis

Structure



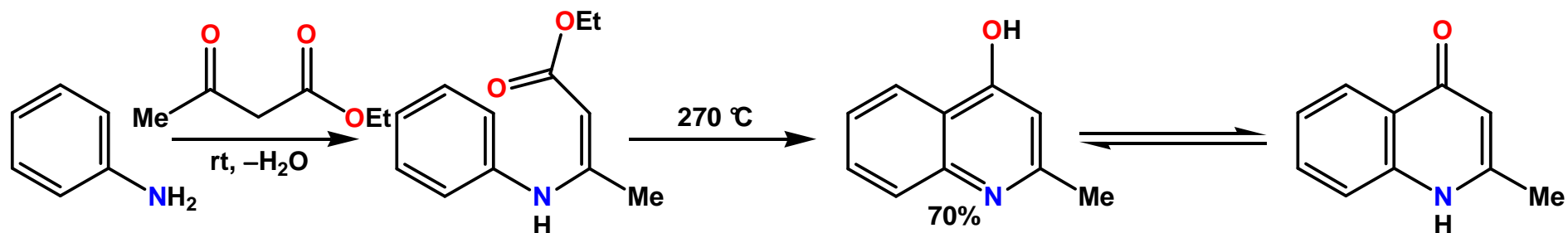
- pK_a values (4.9 and 5.4) are similar to that of pyridine
- Possess aspects of pyridine and naphthalene reactivity e.g. form *N*-oxides and ammonium salts

Combes Synthesis (“3+3”)

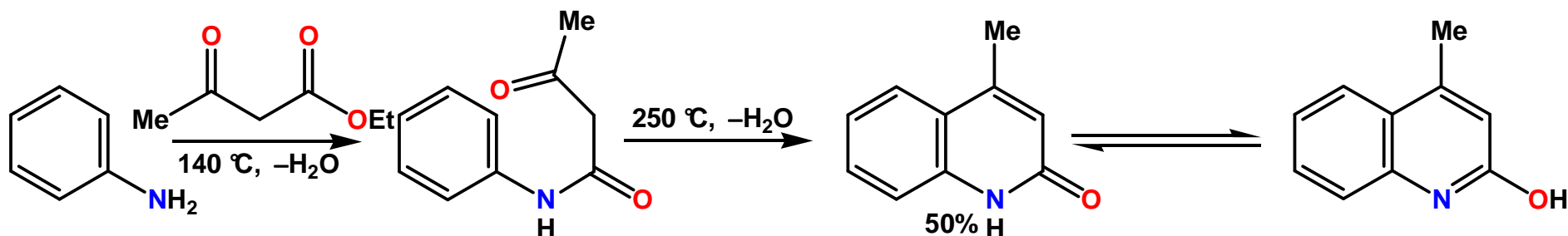


Quinolines – Synthesis

Conrad-Limpach-Knorr Synthesis (“3+3”)

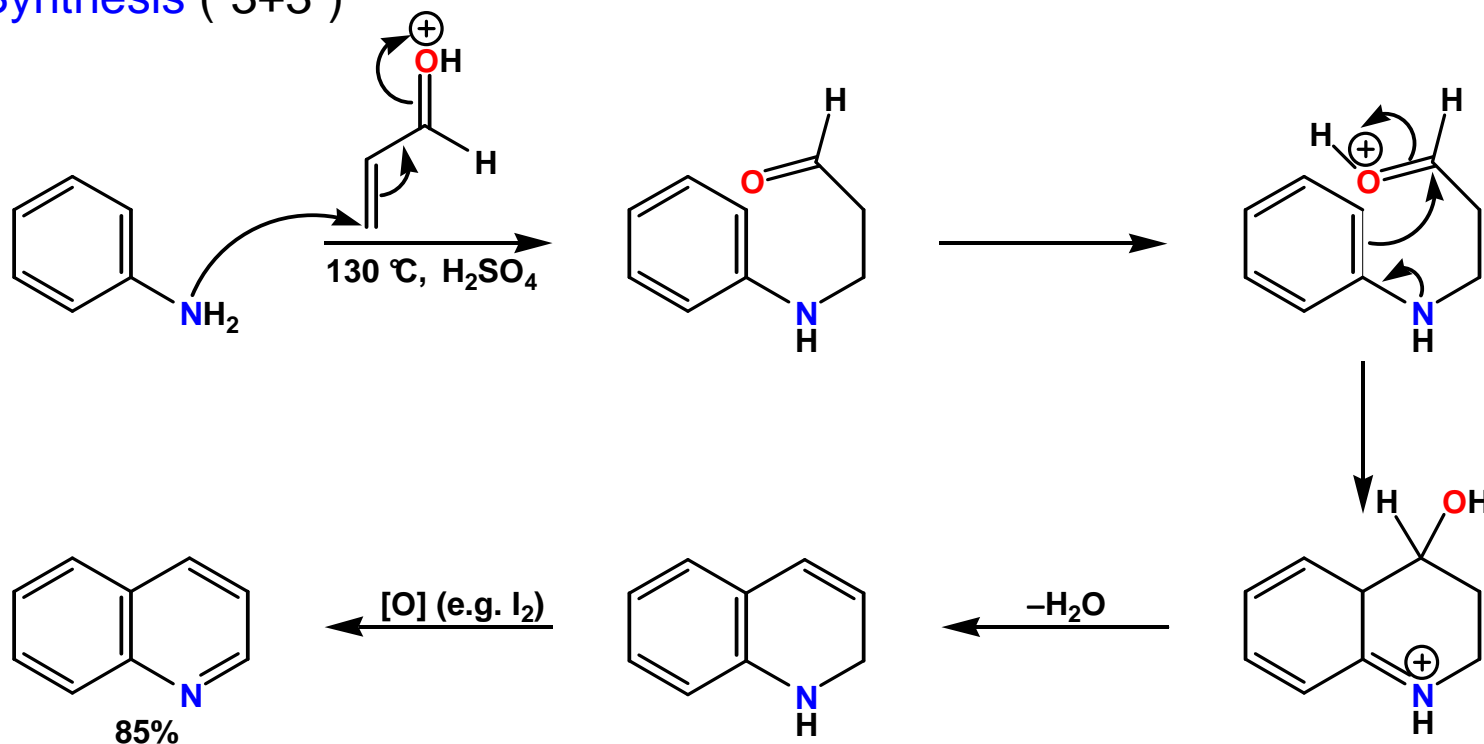


- Very similar to the [Combes synthesis](#) by a β -keto ester is used instead of a β -diketone
- Altering the reaction conditions can completely alter the regiochemical outcome

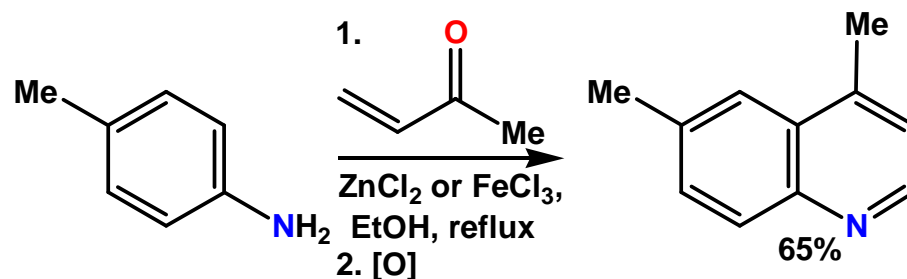


Quinolines – Synthesis

Skraup Synthesis (“3+3”)

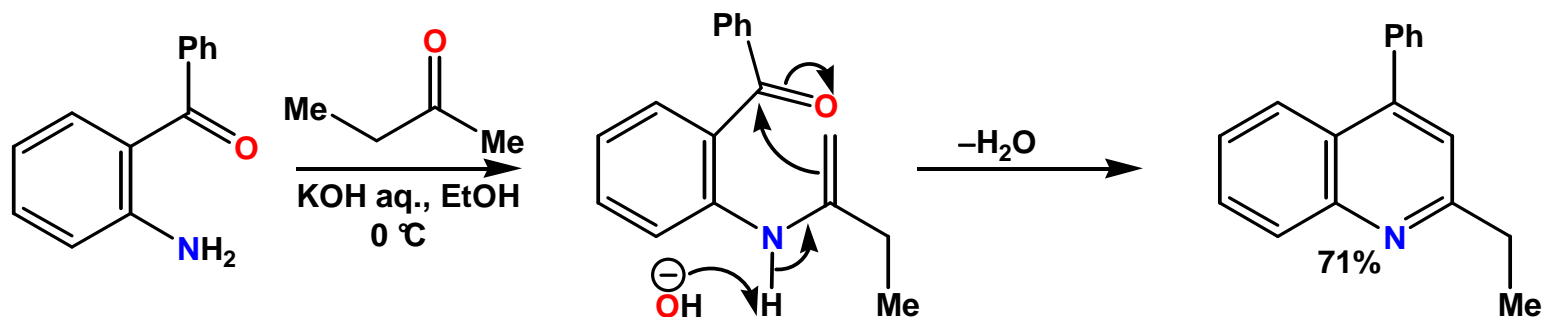
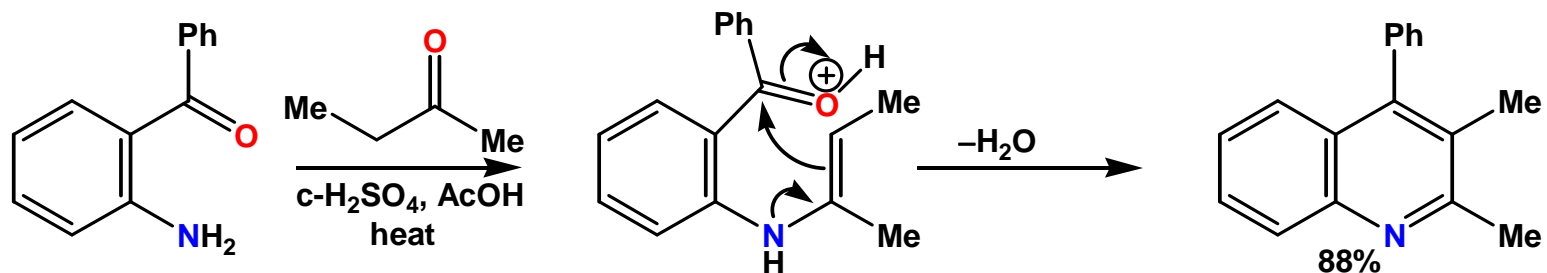


- Acrolein can be generated *in situ* by treatment of glycerol with conc. sulfuric acid
- A mild oxidant is required to form the fully aromatic system from the dihydroquinoline



Quinolines – Synthesis

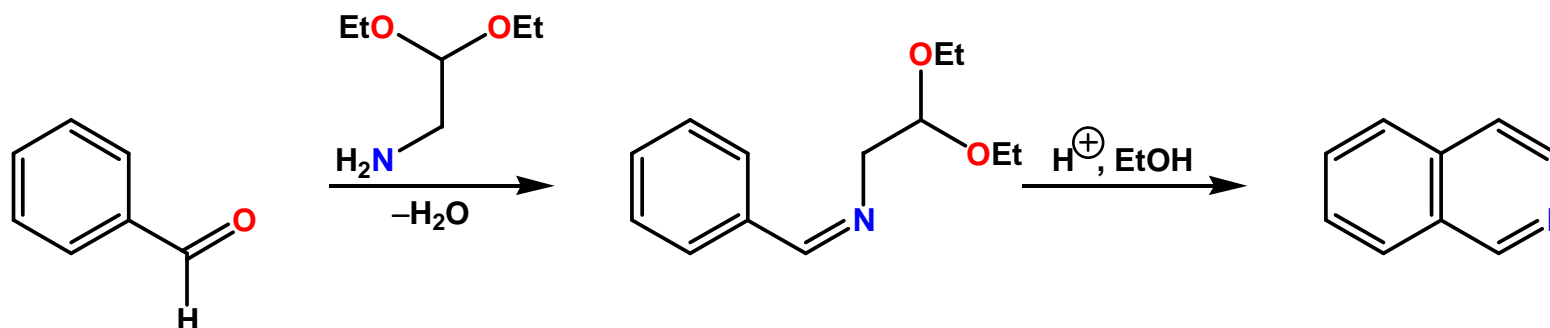
Friedlander Synthesis (“4+2”)



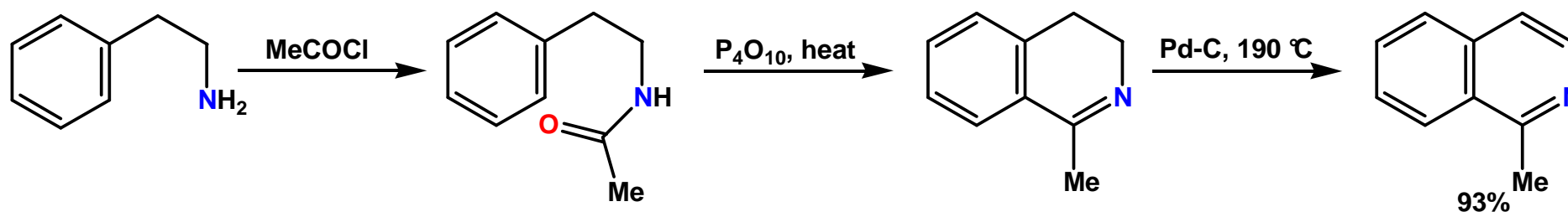
- The starting acyl aniline can be difficult to prepare
- Acidic and basic conditions deliver regioisomeric products in good yields

Isoquinolines – Synthesis

Pomeranz-Fritsch Synthesis (“3+3”)



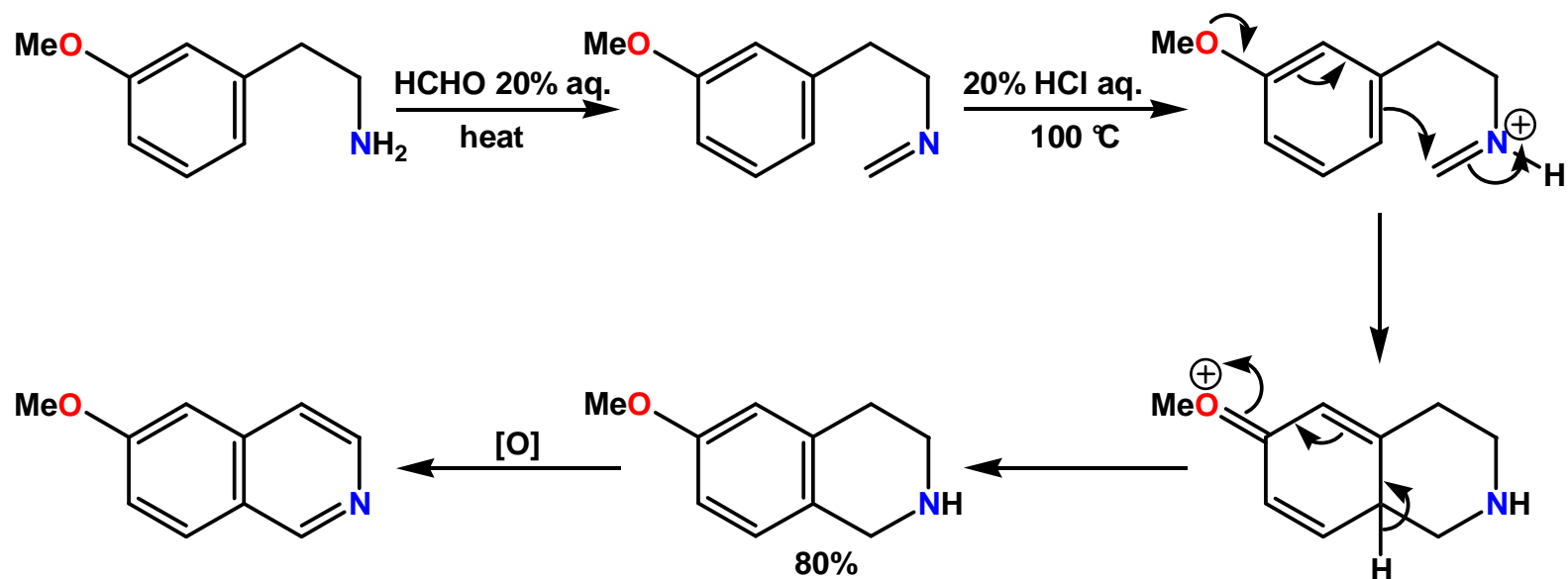
Bischler-Napieralski Synthesis (“5+1”)



- Cyclisation can be accomplished using POCl₃ or PCl₅
- Oxidation of the dihydroisoquinoline can be performed using a mild oxidant

Isoquinolines – Synthesis

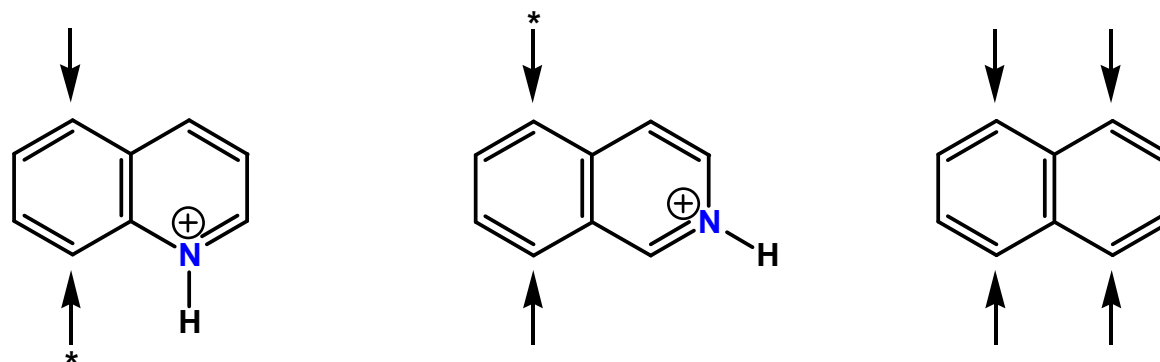
Pictet Spengler Synthesis (“5+1”)



- 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

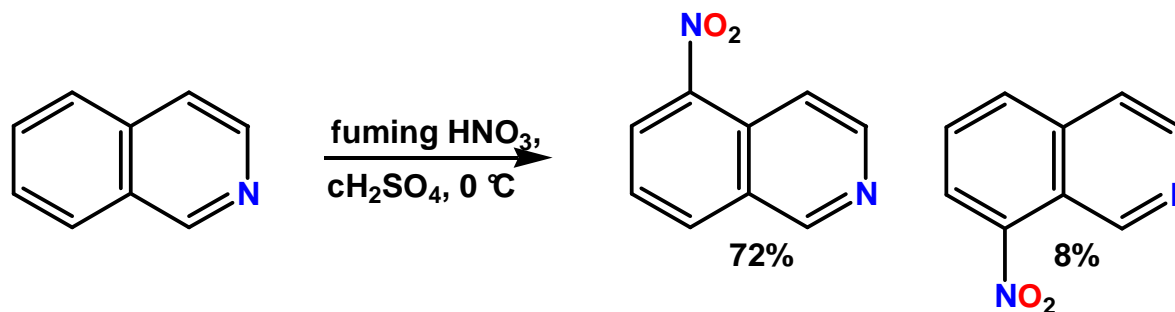
Quinolines/Isoquinolines – Electrophilic Reactions

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

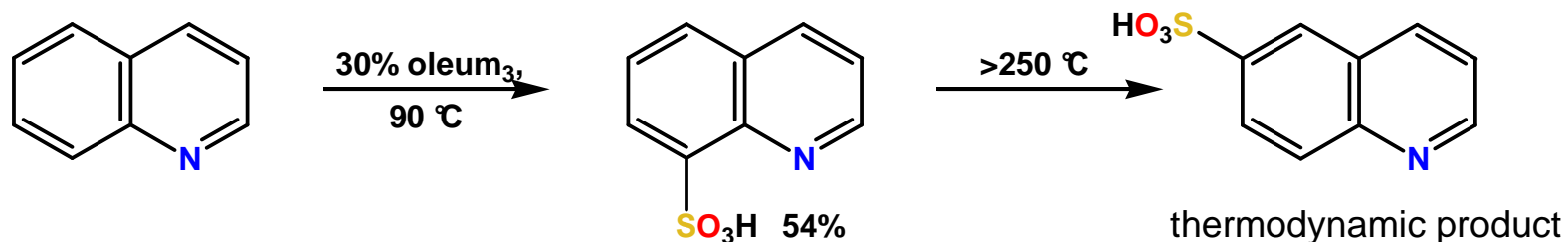
Nitration



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

Quinolines/Isoquinolines – Electrophilic Reactions

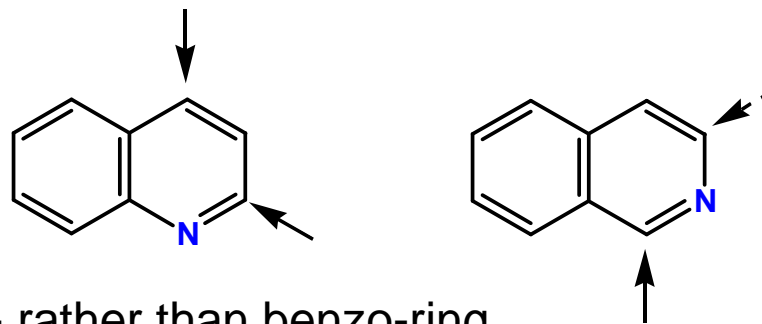
Sulfonation



- 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

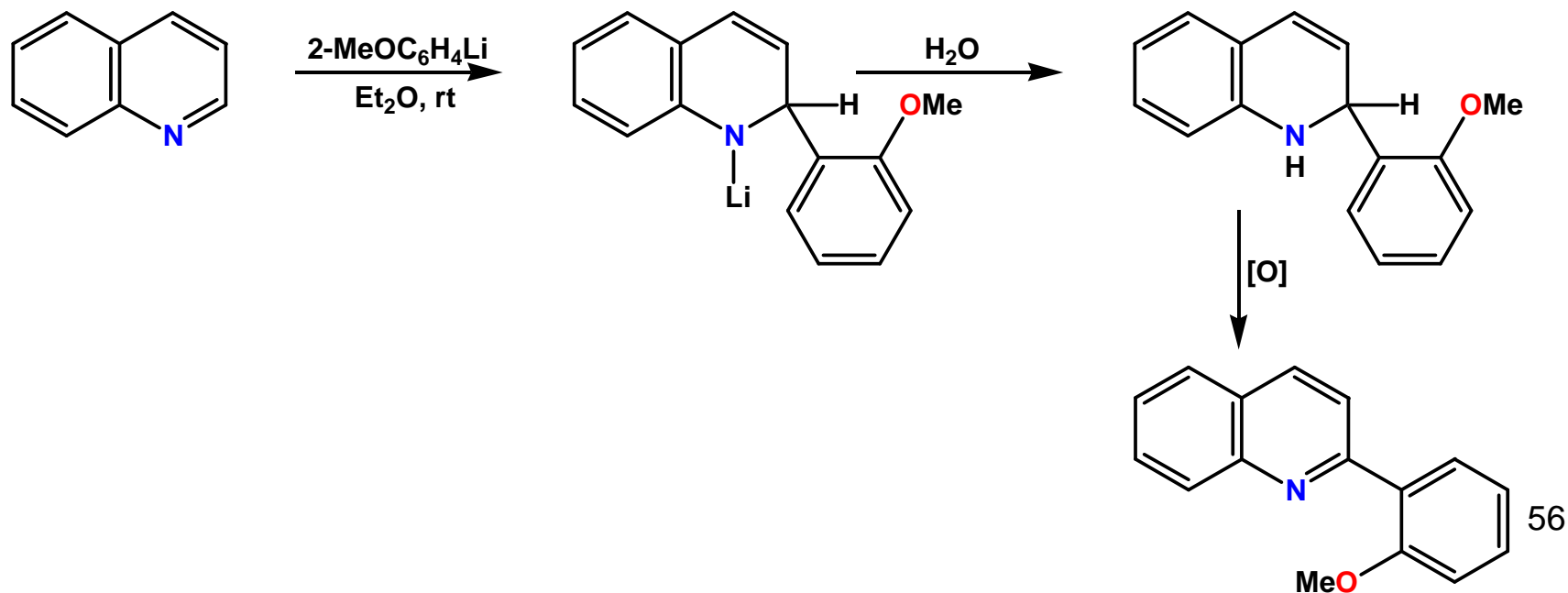
Quinolines/Isoquinolines – Nucleophilic Reactions

Regiochemistry

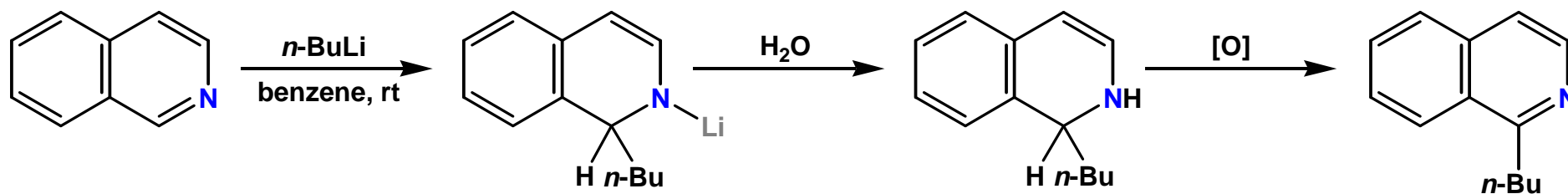


- Attack occurs at hetero- rather than benzo-ring
- They are generally more reactive than pyridines to nucleophilic attack

Carbon Nucleophiles

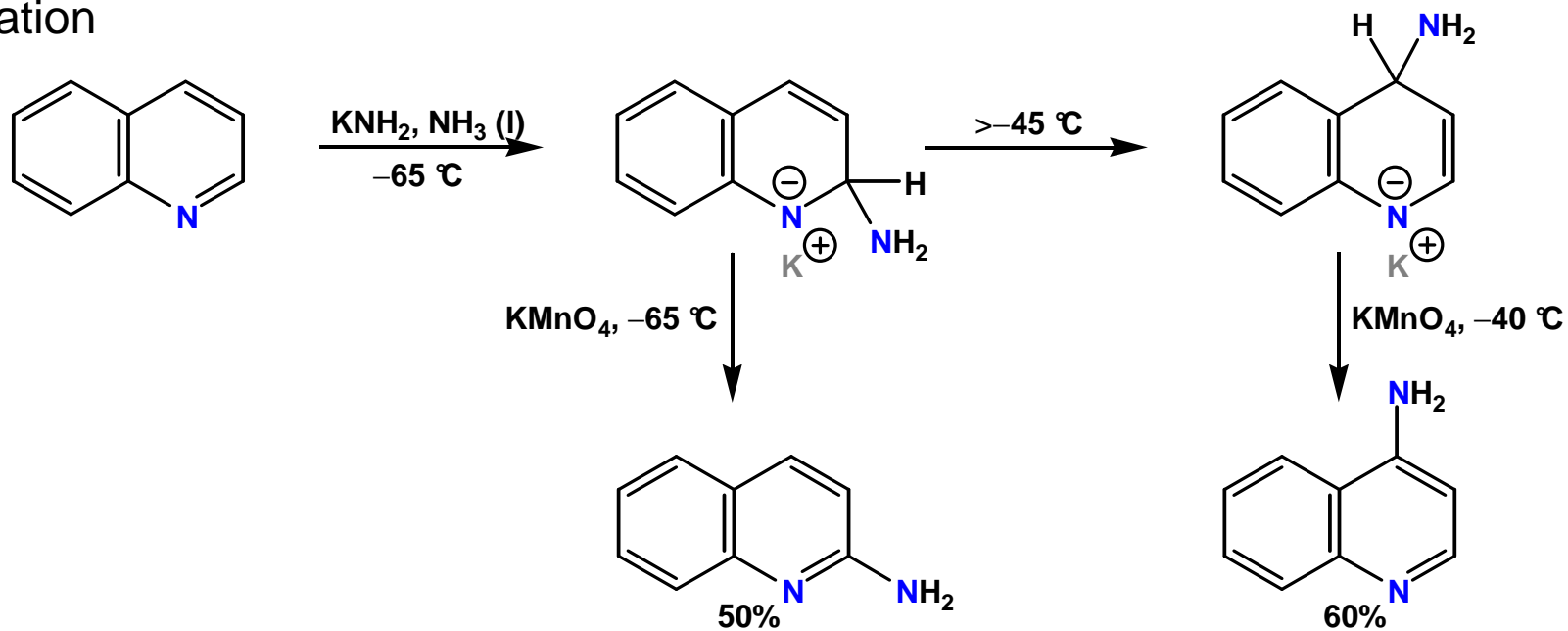


Quinolines/Isoquinolines – Nucleophilic Reactions



- Oxidation is required to regenerate aromaticity

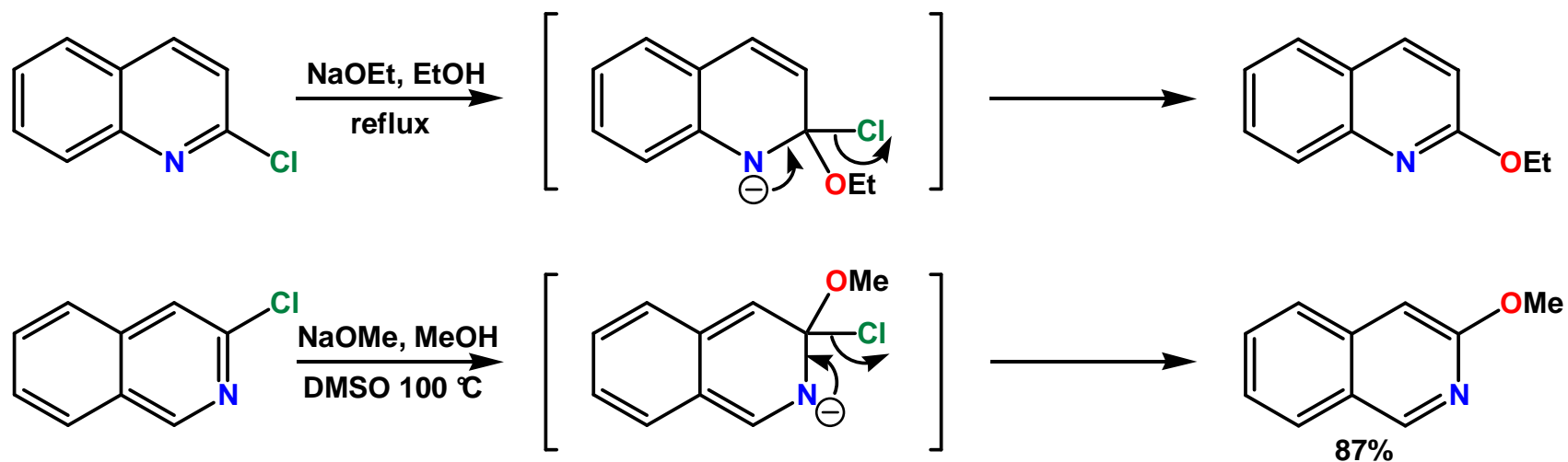
Amination



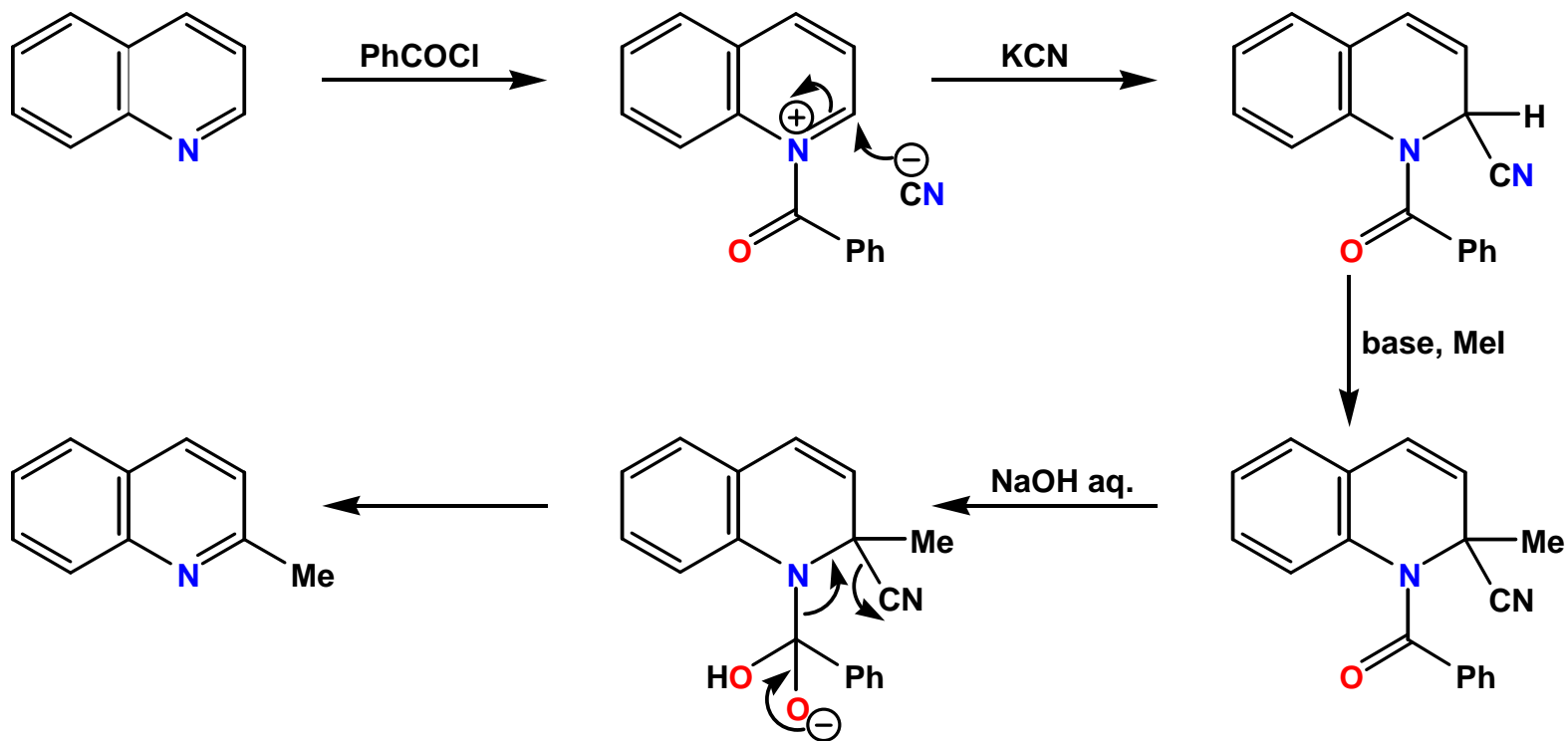
thermodynamic product 57

Quinolines/Isoquinolines – Nucleophilic Substitution

Displacement of Halogen



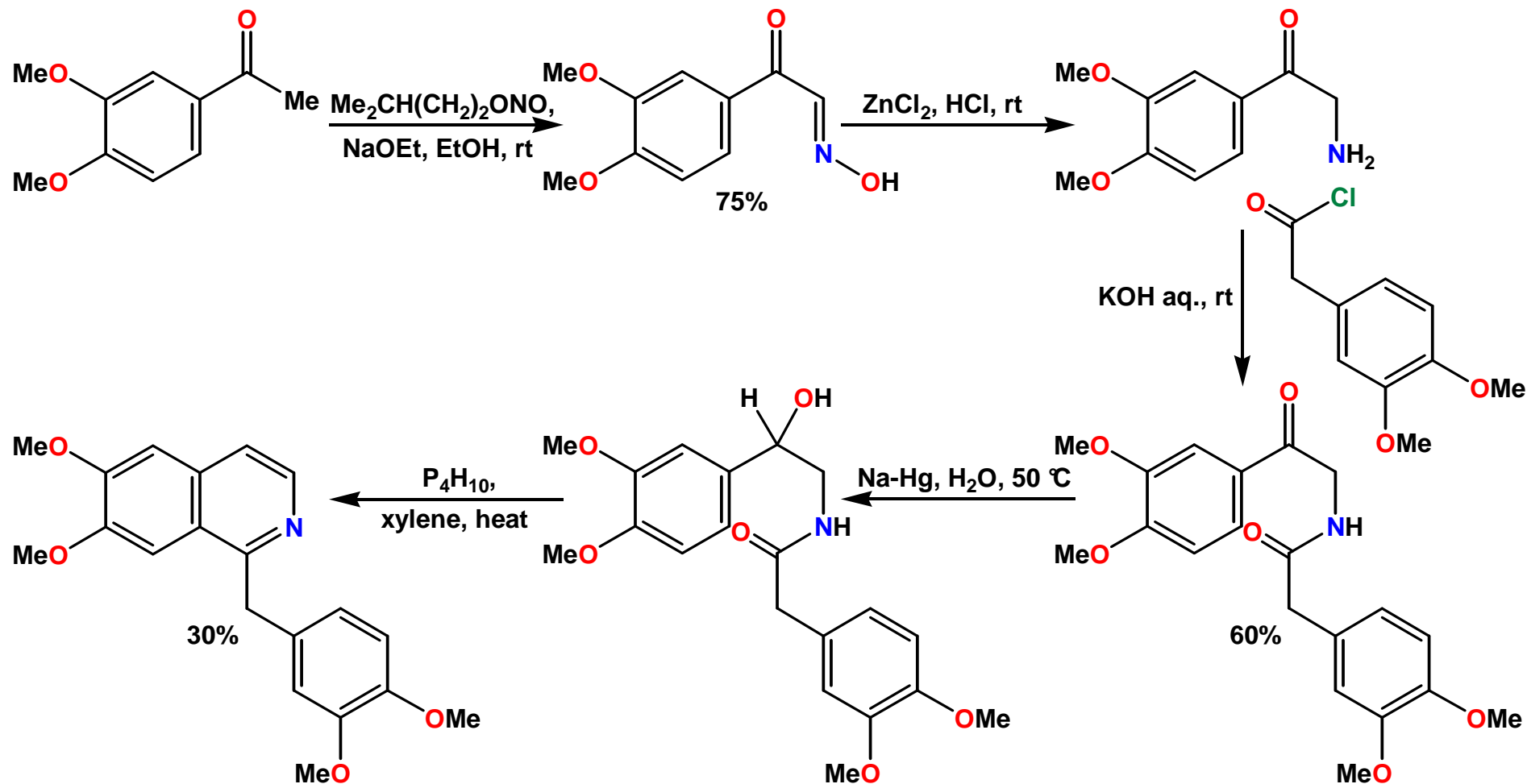
Quinolines/Isoquinolines – The Reissert Reaction



- The proton adjacent to the cyano group is extremely acidic
- The reaction works best with highly reactive alkyl halides

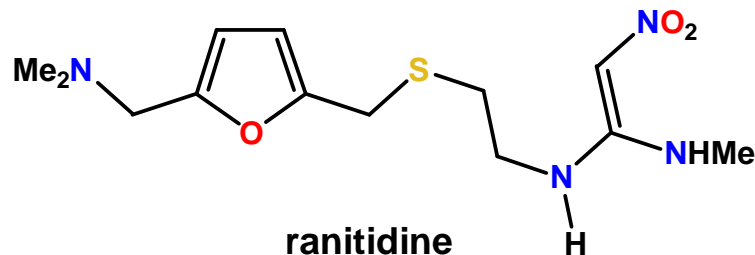
Isoquinolines – Synthesis of a Natural Product

Synthesis of Papaverine

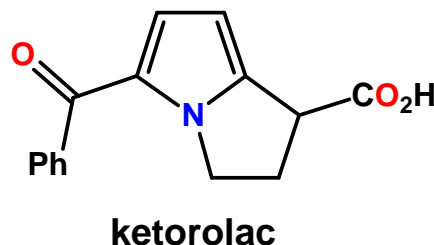


- Cyclisation is achieved by the [Pictet-Grans reaction](#) cf. the [Bischler-Napieralski reaction](#)

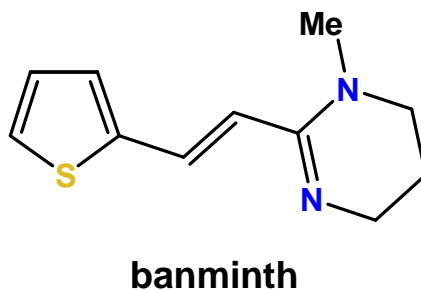
Bioactive Furans, Pyrroles and Thiophenes



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

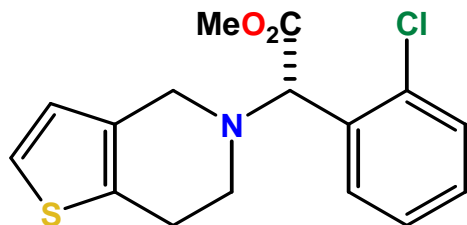


- Ketorolac (Toradol®, Roche) is an analgesic and anti-inflammatory drug

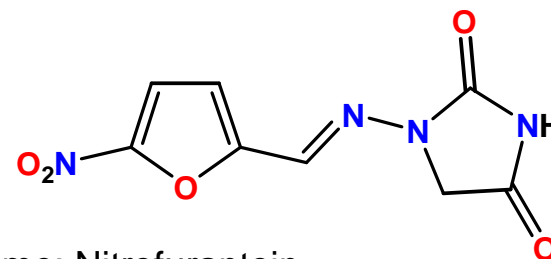


- Pyrantel (Banminth®, Phibro) is an anthelmintic agent and is used to treat worms in livestock

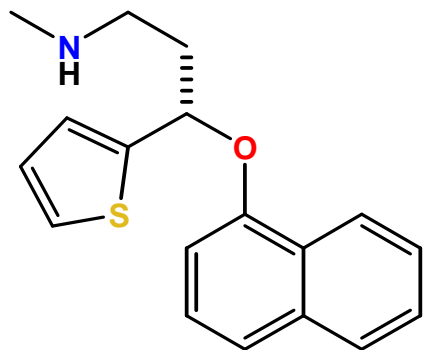
Drugs Containing a Furan/Thiophene/Pyrrole



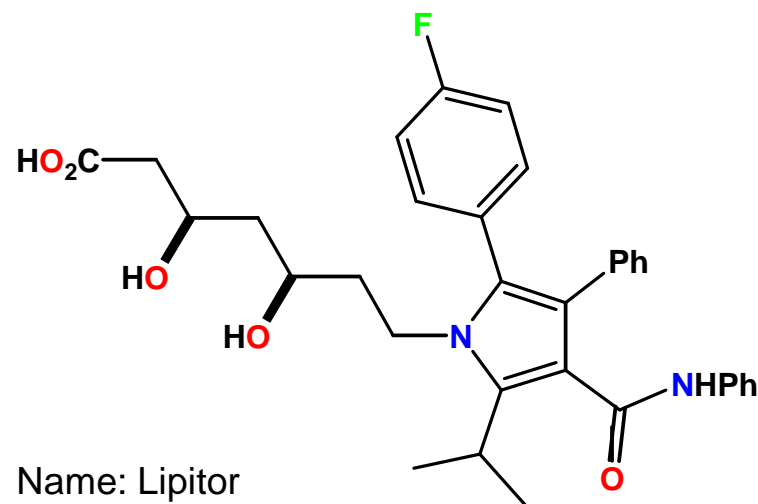
Name: Plavix
2008 Sales: \$3.80 billion
2008 Ranking: 3 branded
Company: Bristol-Myers Squibb
Disease: Stroke and heart attack risk



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



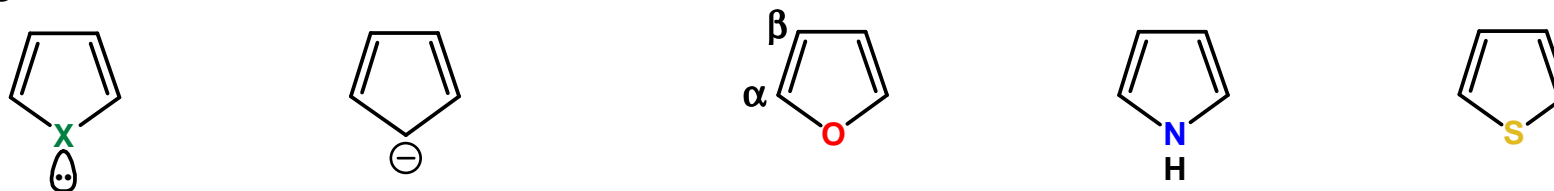
Name: Cymbalta
2008 Sales: \$2.17 billion
2008 Ranking: 14 branded
Company: Eli Lilly
Disease: Depression



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

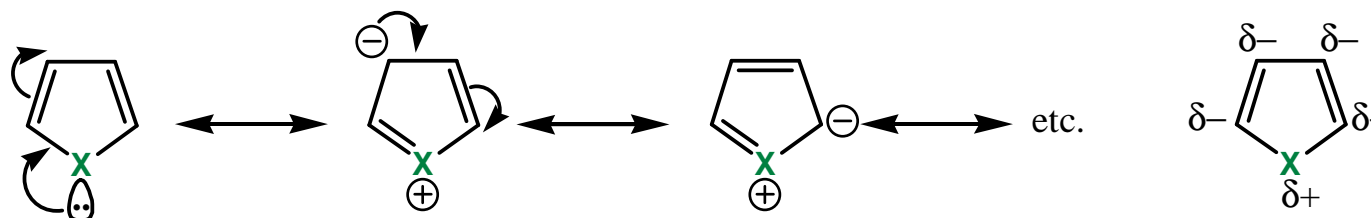
Furans, Pyrroles and Thiophenes – Structure

Structure

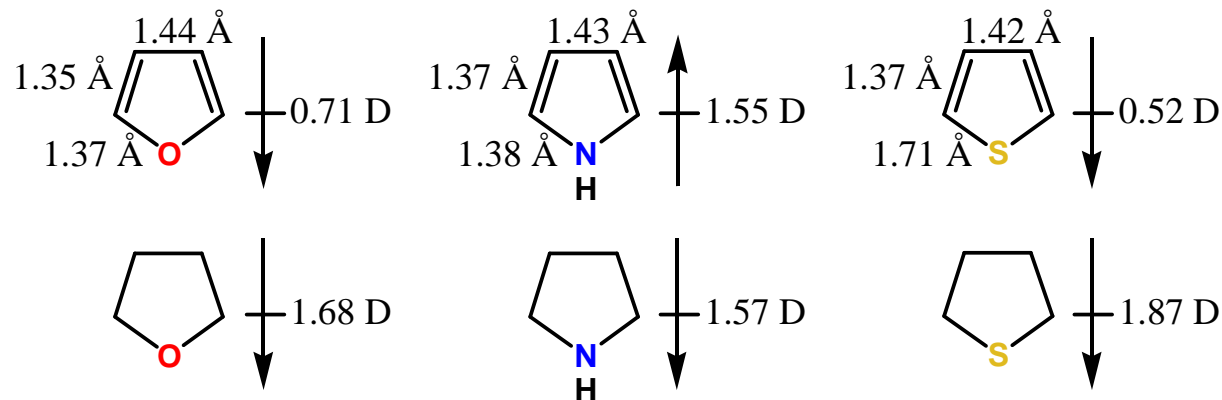


- 6 π electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures



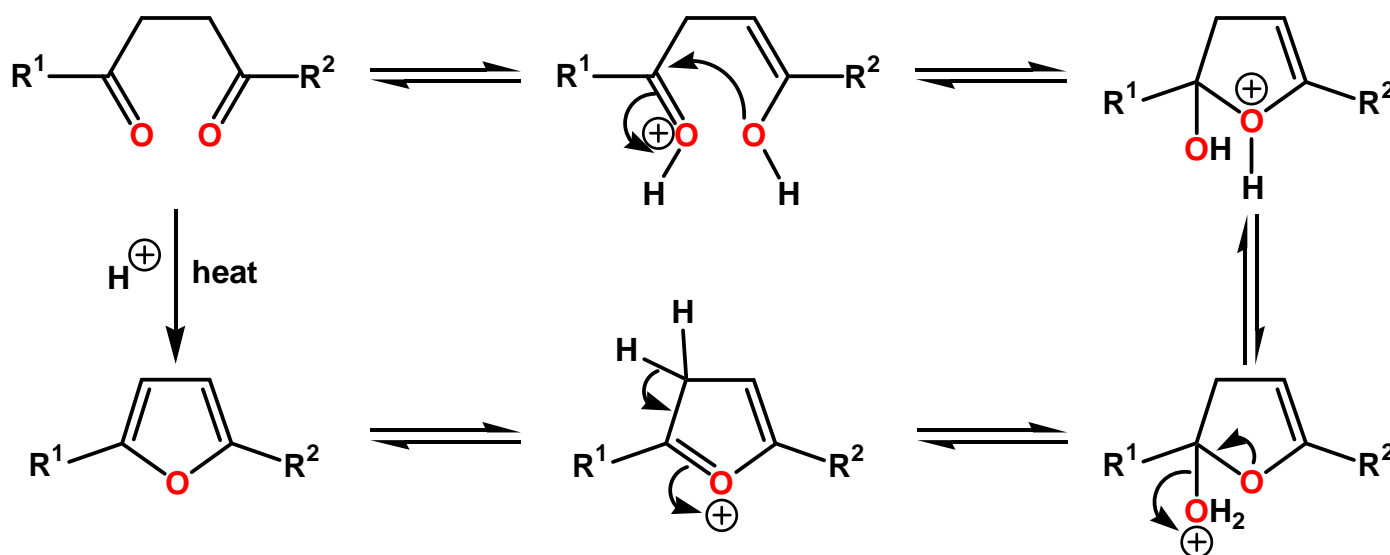
- Electron donation into the ring by resonance but inductive electron withdrawal



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

Furans – Synthesis

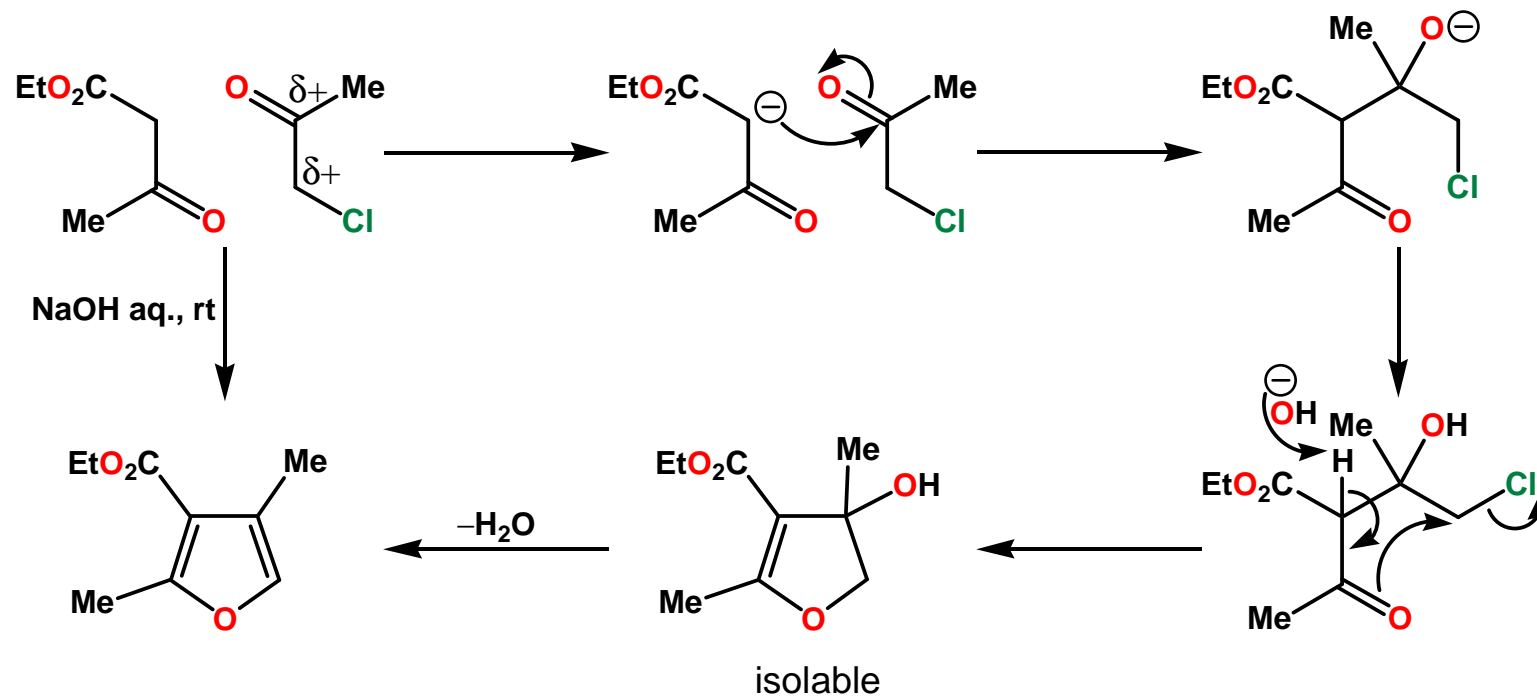
Paal Knorr Synthesis



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

Furans – Synthesis

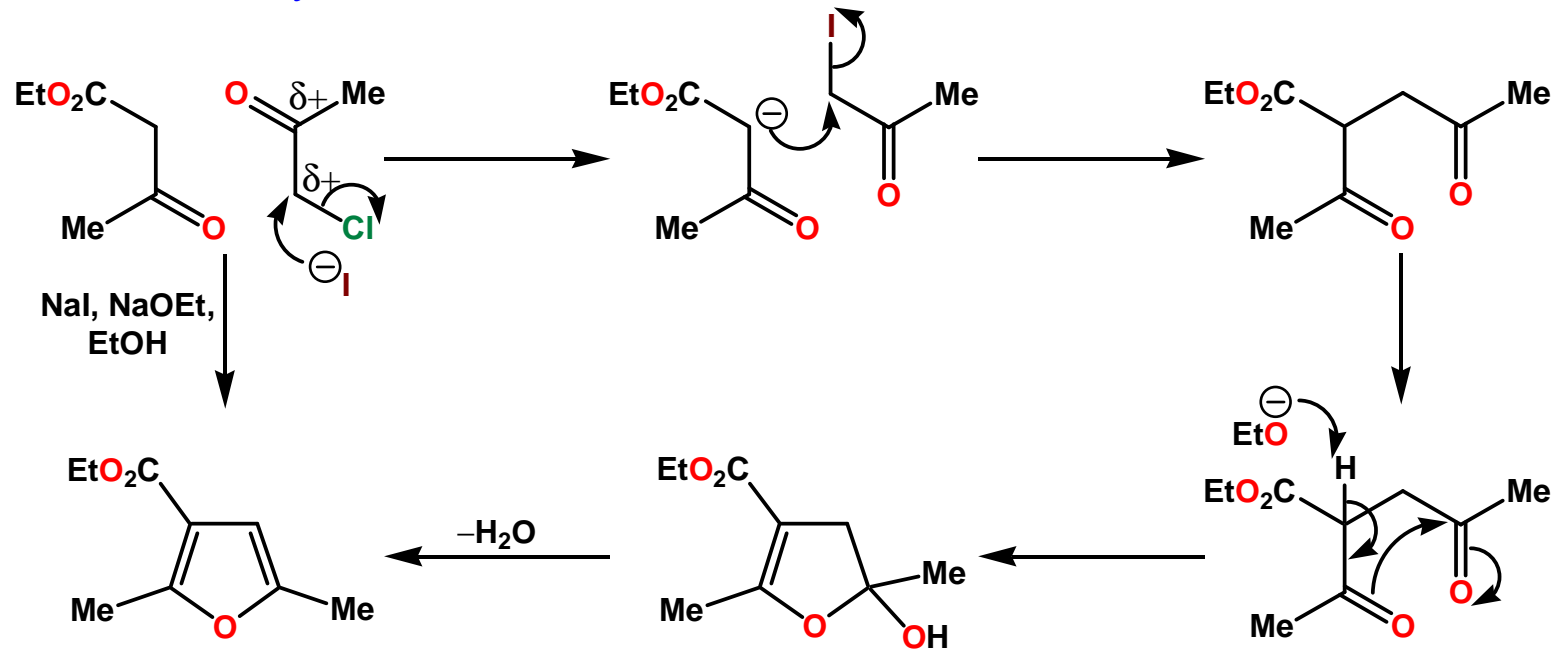
Feist-Benary Synthesis (“3+2”)



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

Furans – Synthesis

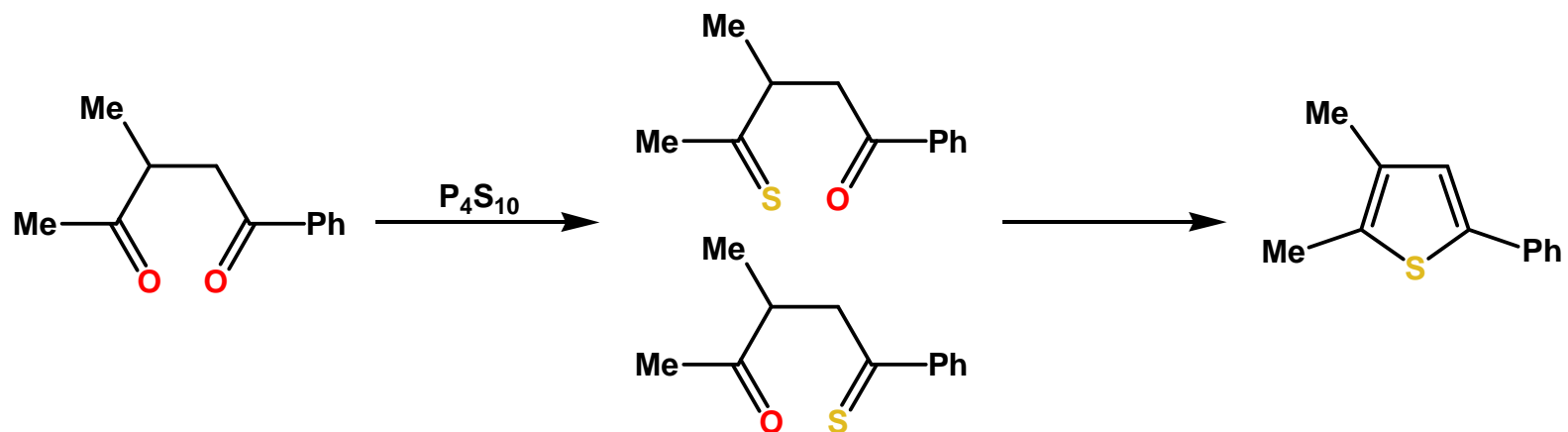
Modified Feist-Benary



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

Thiophenes – Synthesis

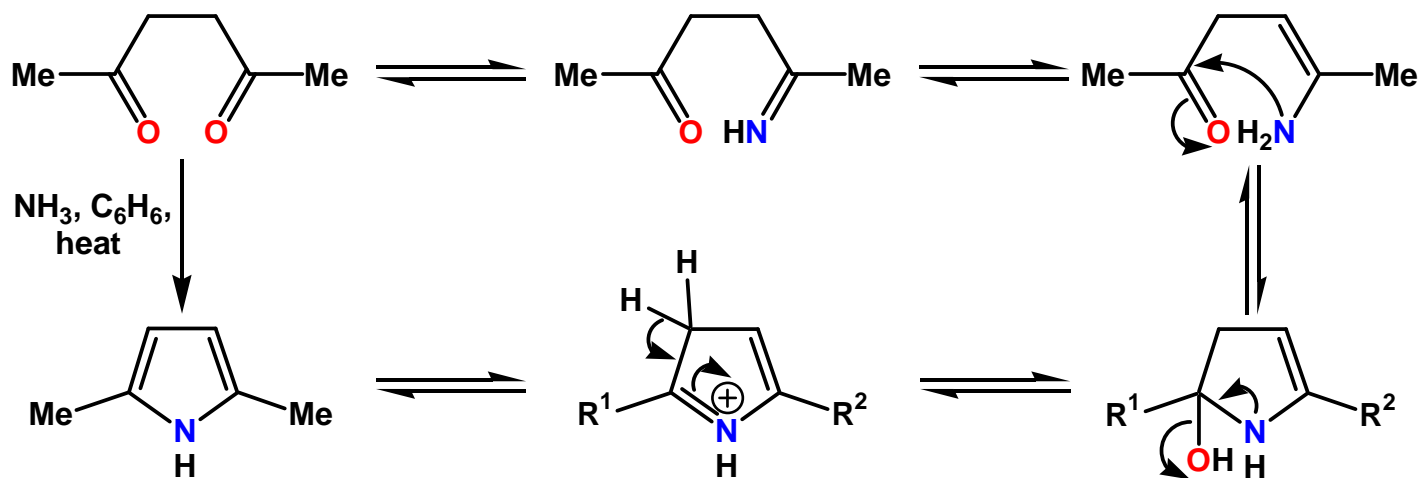
Synthesis of Thiophenes by **Paal Knorr** type reaction (“4+1”)



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

Pyrroles – Synthesis

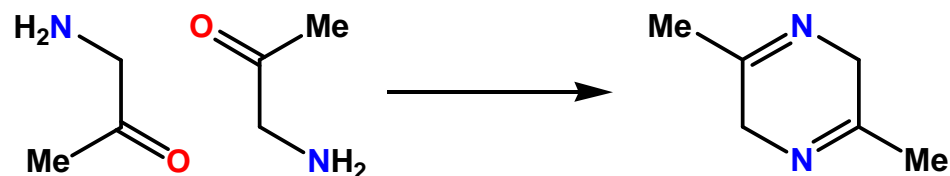
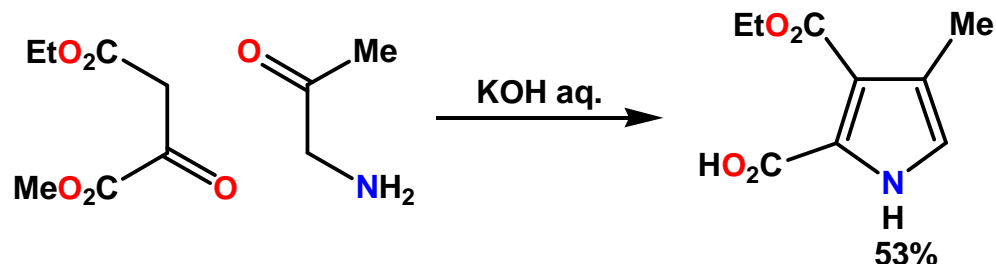
Paal Knorr Synthesis (“4+1”)



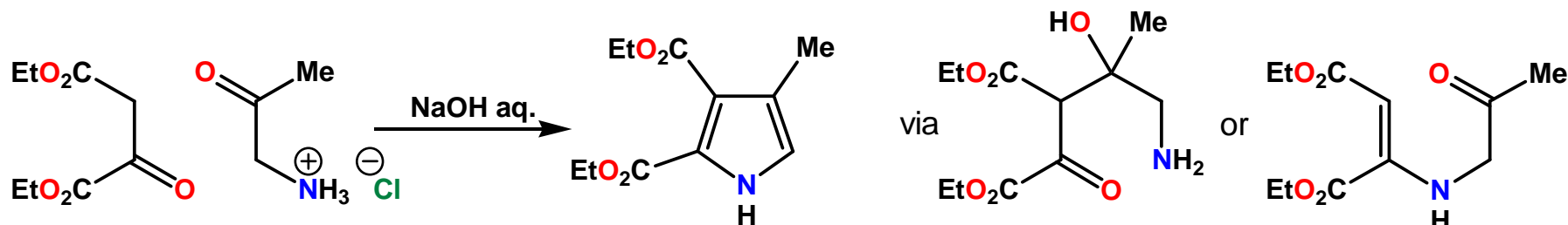
- Ammonia or a primary amine can be used to give the pyrrole or *N*-alkyl pyrrole

Pyrroles – Synthesis

Knorr Pyrrole Synthesis (“3+2”)



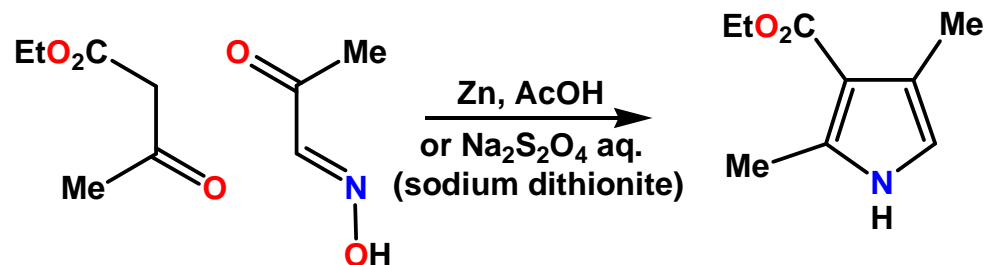
- Use of a free amino ketone is problematic – dimerisation gives a dihydropyridine



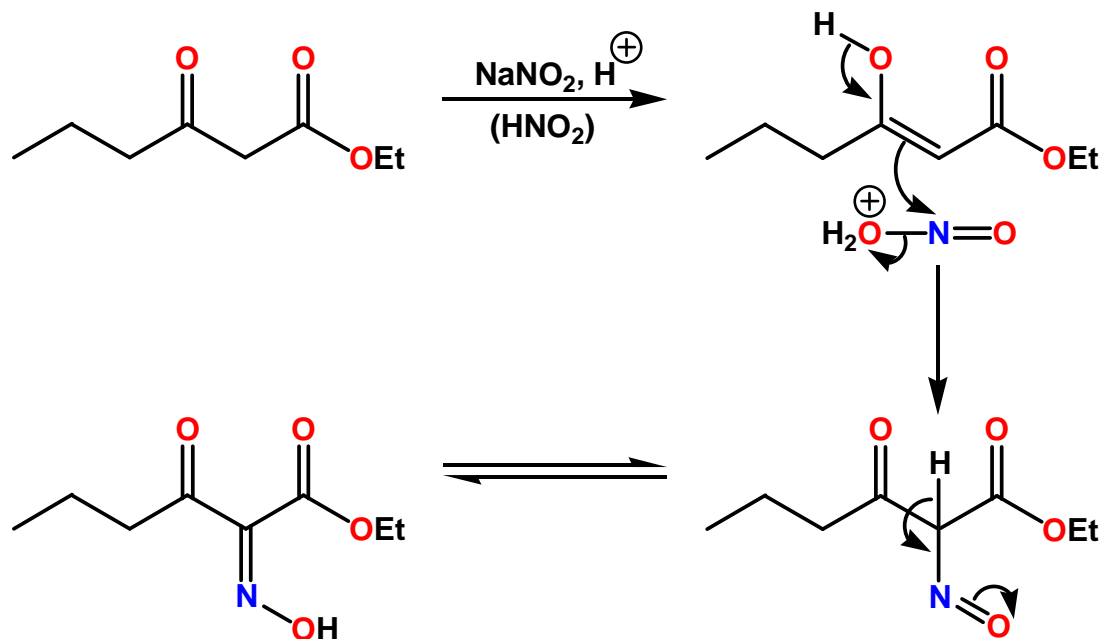
- Problem can be overcome by storing amino carbonyl compound in a protected form
- Reactive methylene partner required so that pyrrole formation occurs more rapidly than dimer formation

Pyrroles – Synthesis

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

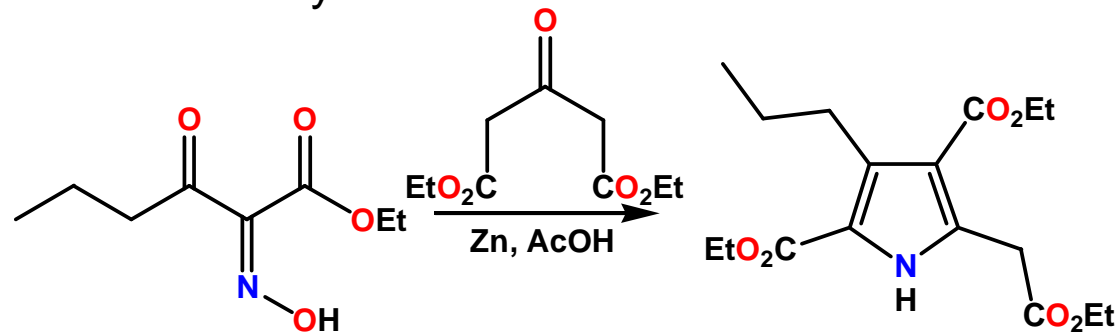


Preparation of α -Keto Oximes from β -Dicarbonyl Compounds

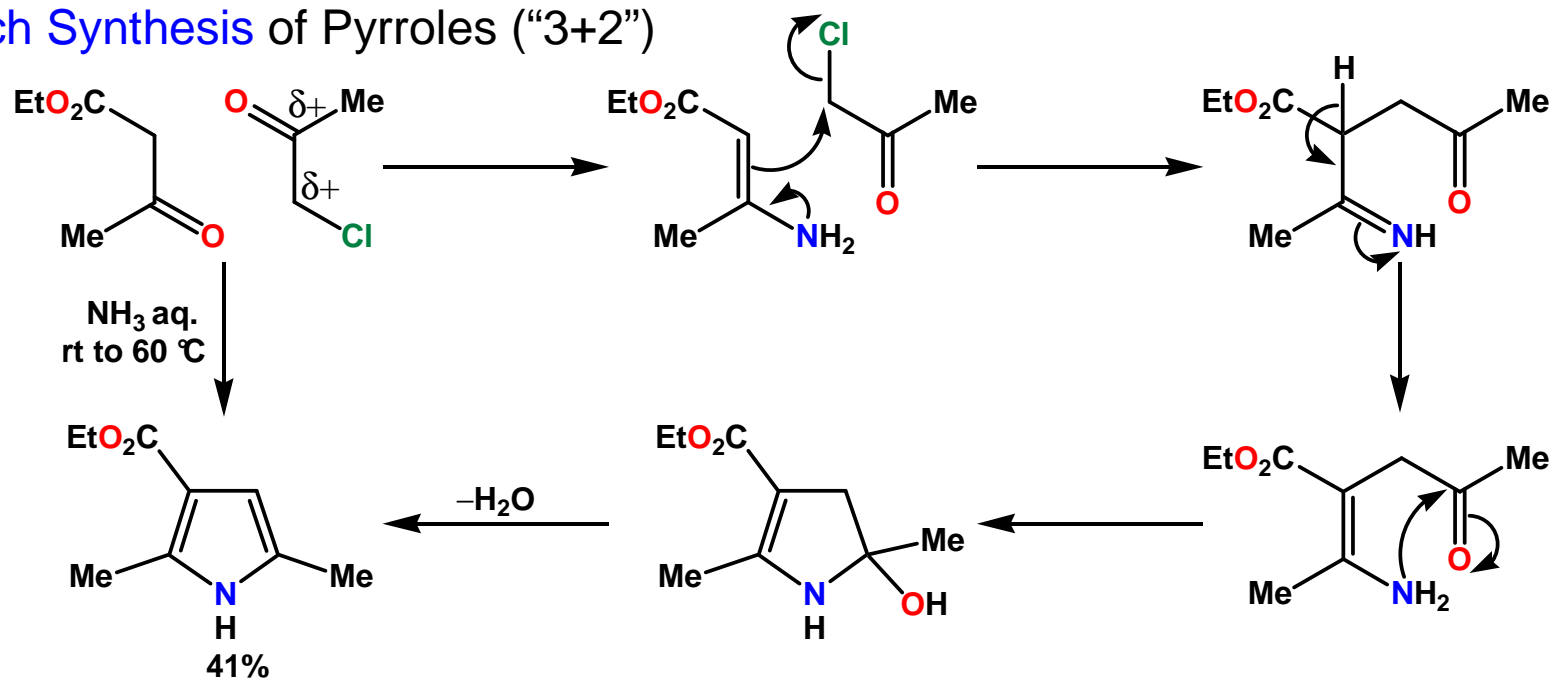


Pyrroles – Synthesis

One-Pot Oxime Reduction and Pyrrole Formation



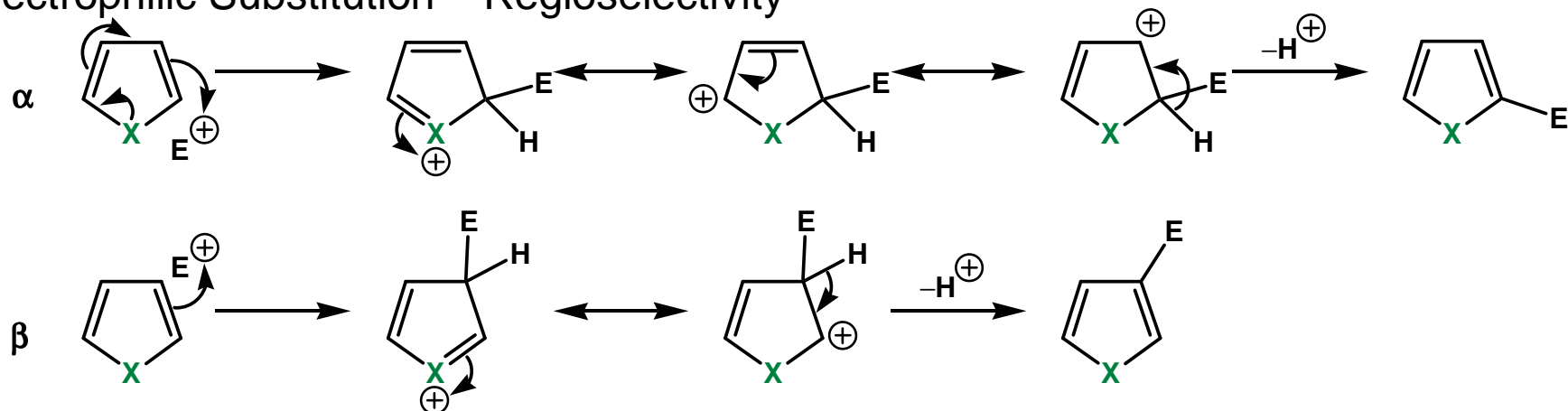
Hantzsch Synthesis of Pyrroles (“3+2”)



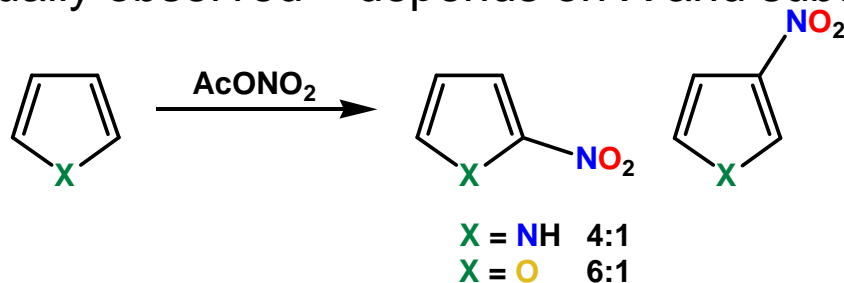
- A modified version of the [Feist-Benary](#) synthesis and using the same starting materials: an α -halo carbonyl compound and a β -keto ester

Furans, Pyrroles Thiophenes – Electrophilic Substitution

Electrophilic Substitution – Regioselectivity

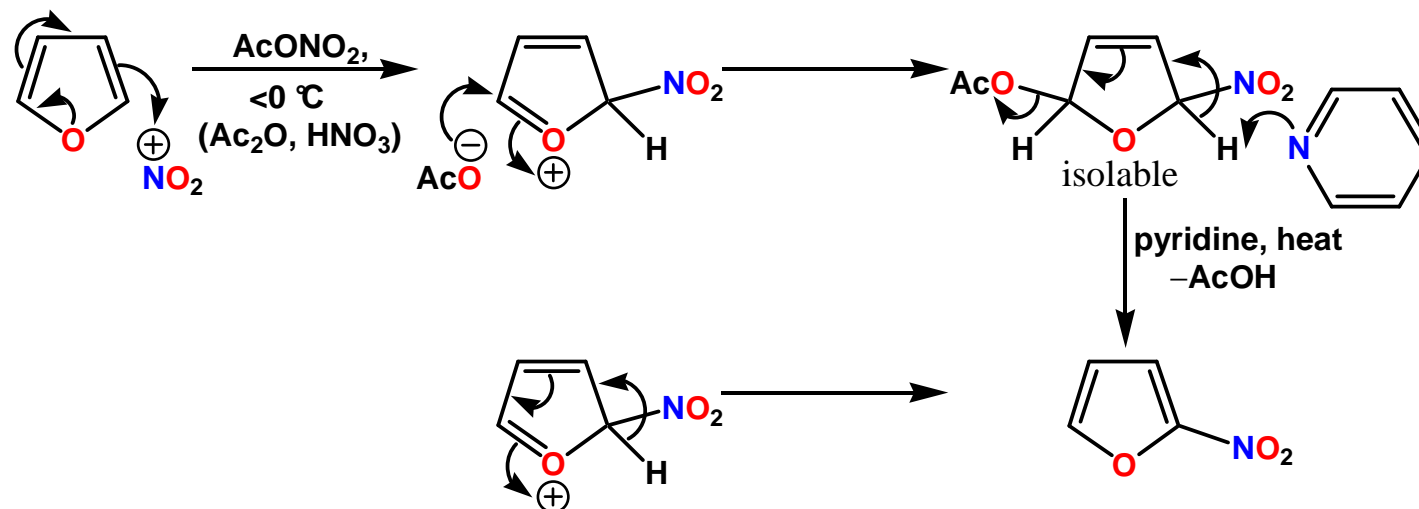


- Pyrrole > furan > thiophene > benzene
- Thiophene is the most aromatic in character and undergoes the slowest reaction
- Pyrrole and furan react under very mild conditions
- α -Substitution favoured over β -substitution more resonance forms for intermediate and so the charge is less localised (also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



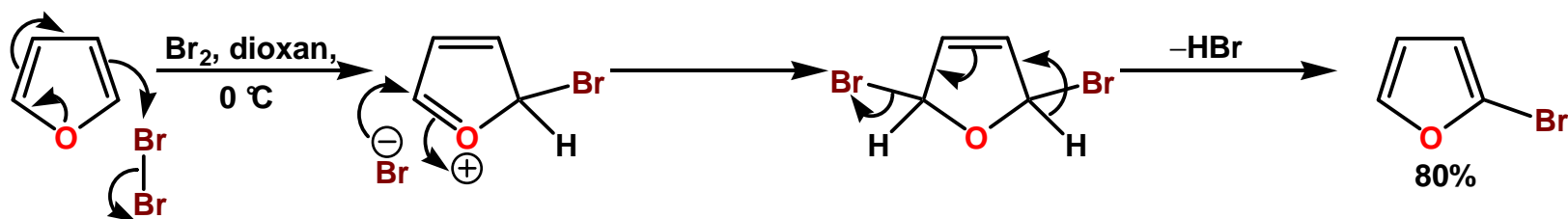
Furans – Electrophilic Substitution

Nitration of Furans



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

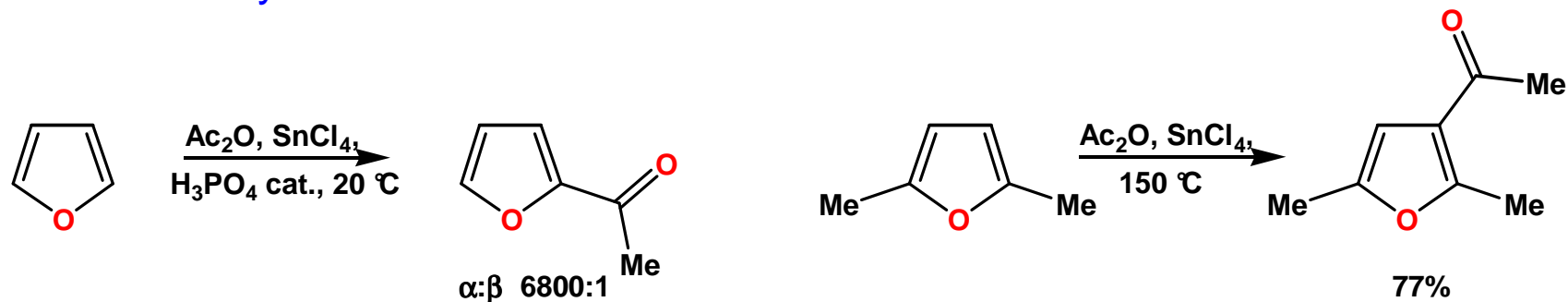
Bromination of Furans



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

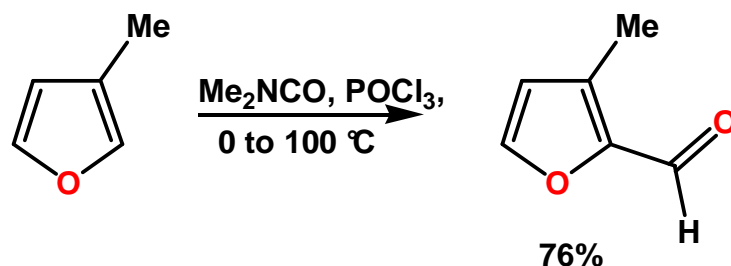
Furans – Electrophilic Substitution

Friedel-Crafts Acylation of Furan

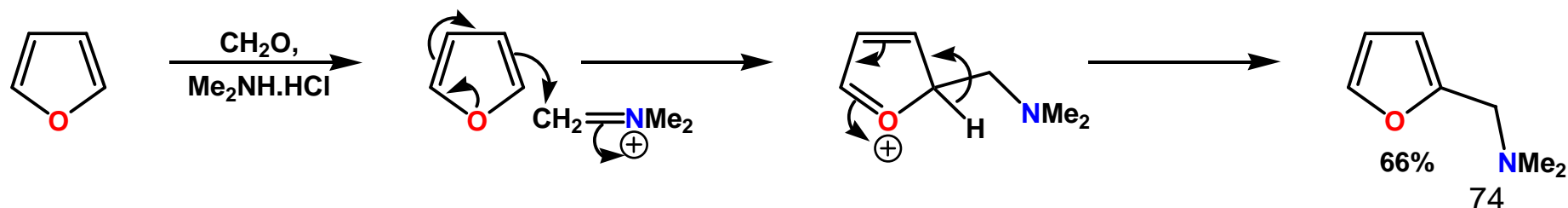


- Blocking groups at the α positions and high temperatures required to give β acylation

Vilsmeier Formylation of Furan

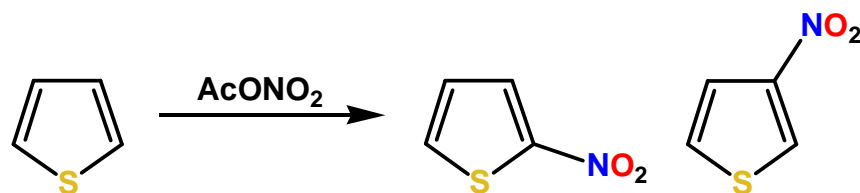


Mannich Reaction of Furans



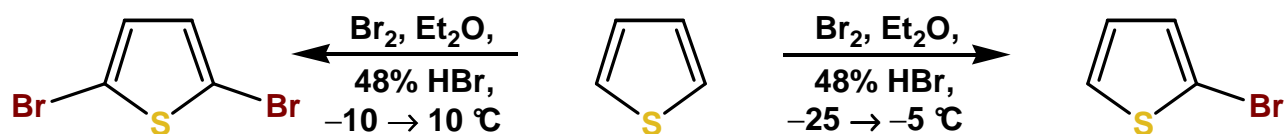
Thiophenes – Electrophilic Substitution

Nitration of Thiophenes



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

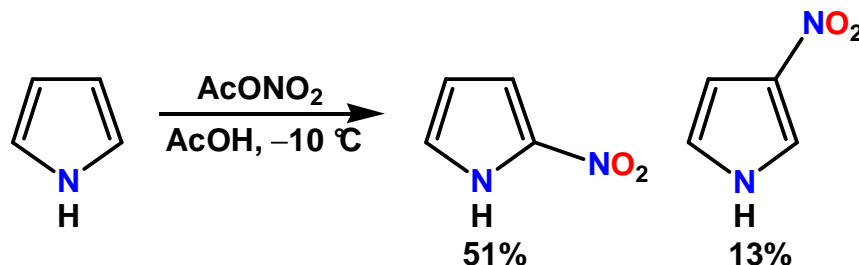
Halogenation of Thiophenes



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

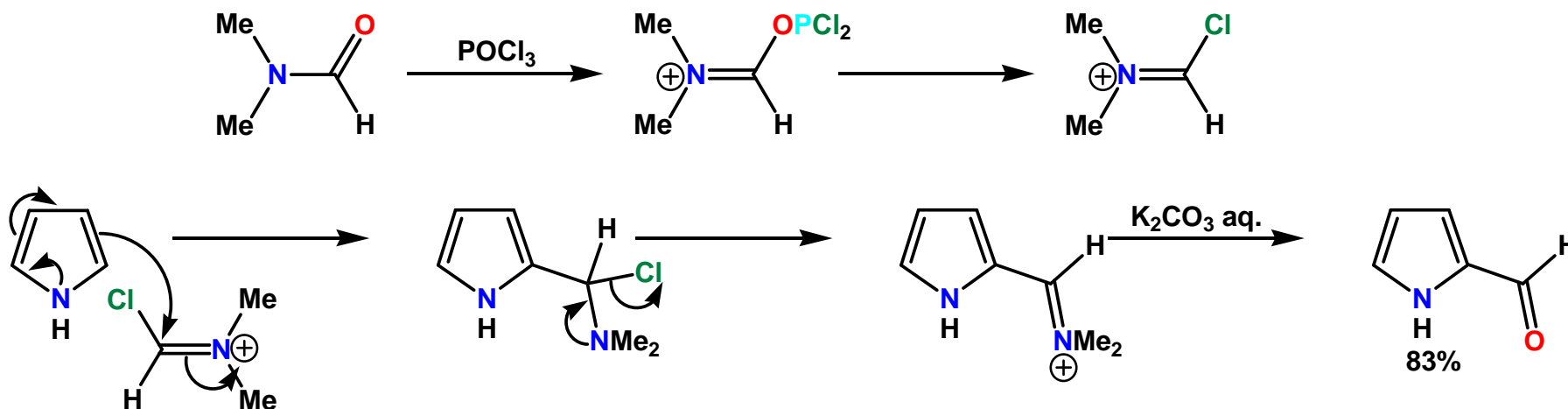
Pyrroles – Electrophilic Substitution

Nitration of Pyrroles

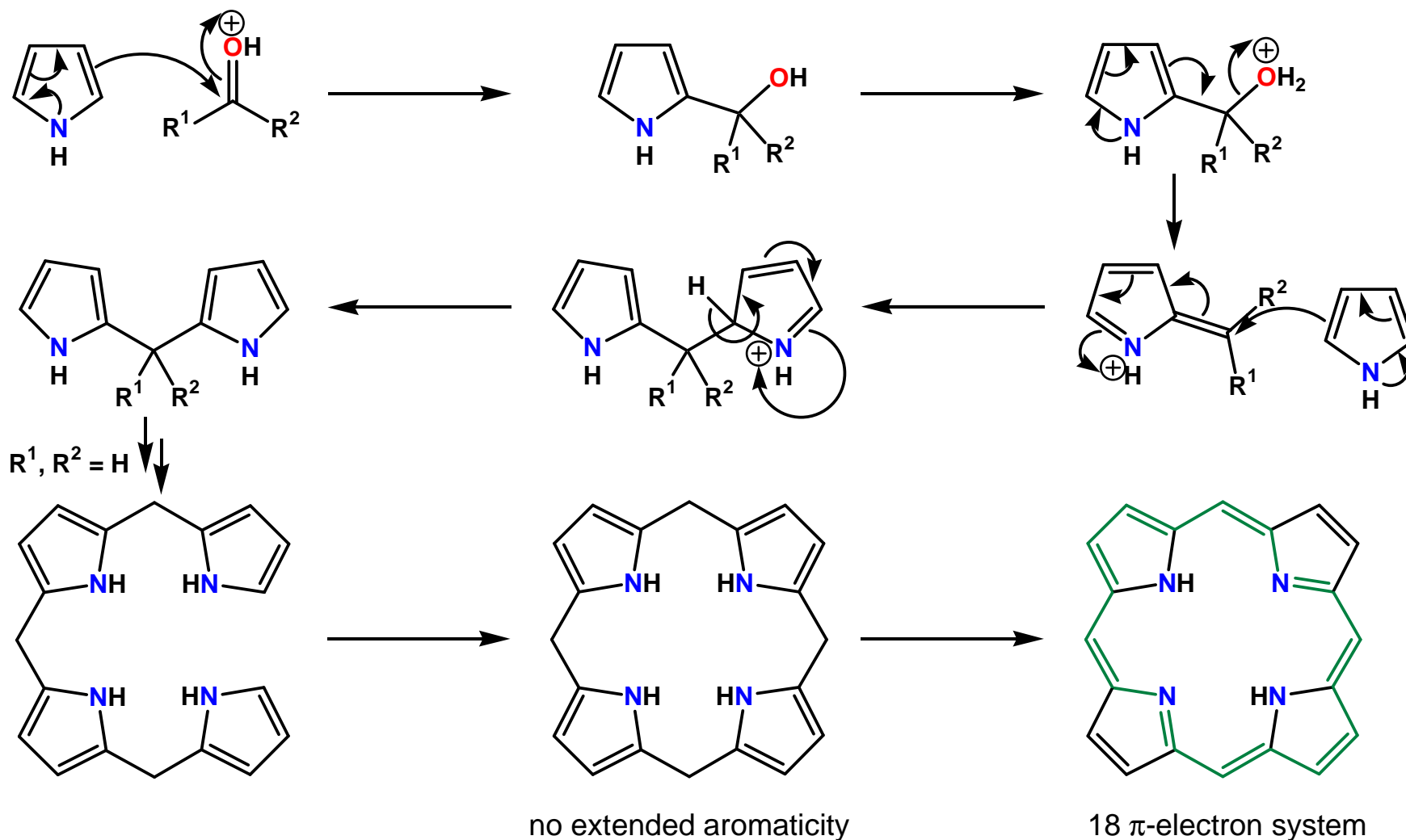


- Mild conditions are required (c-HNO_3 and $\text{c-H}_2\text{SO}_4$ gives decomposition)

Vilsmeier Formylation of Pyrroles

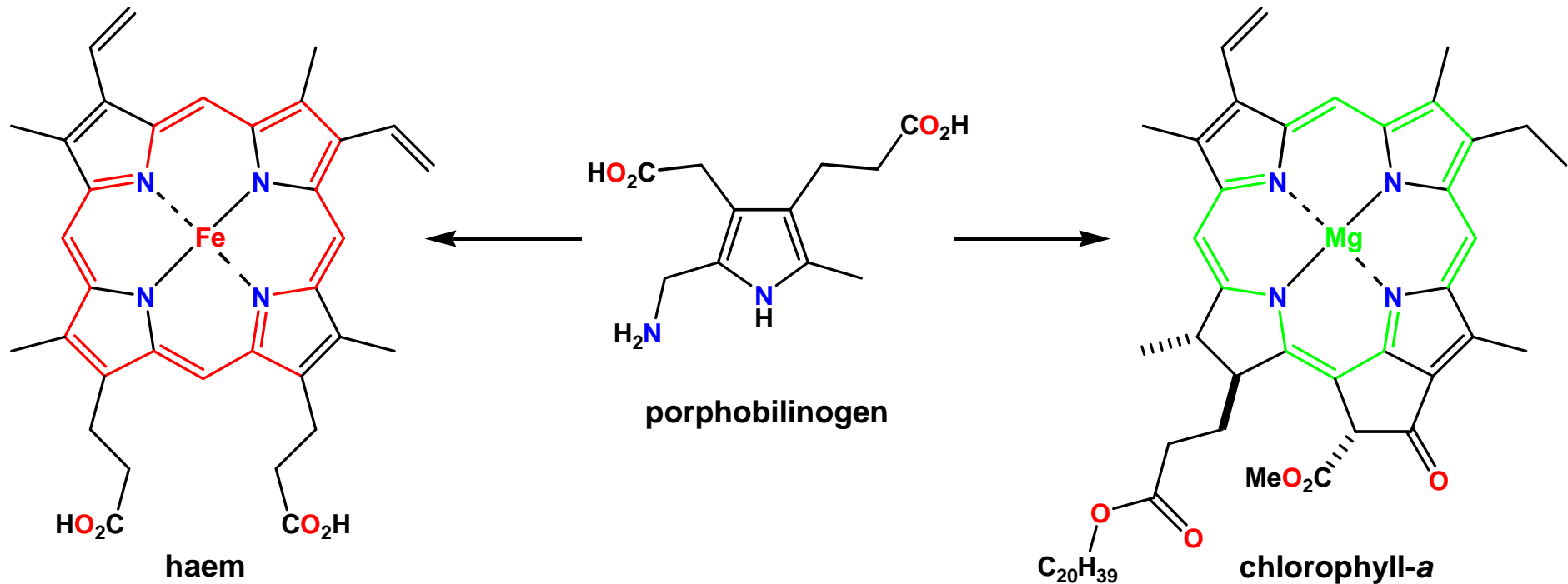


Pyrroles – Porphyrin Formation



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

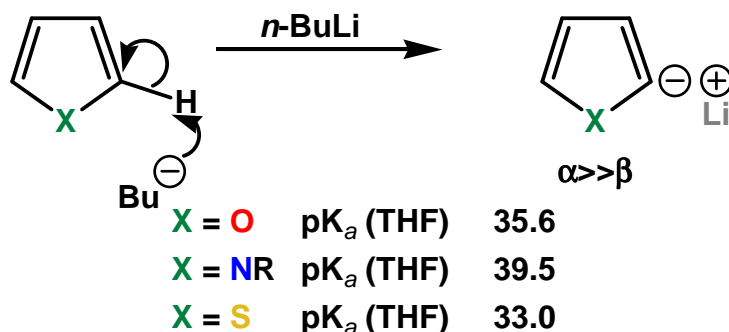
Porphyrin Natural Products



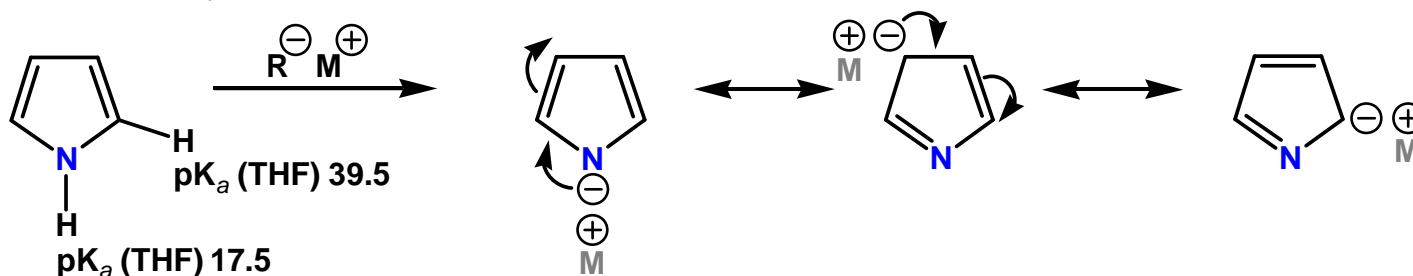
- The pigment haem is found in the oxygen carrier haemoglobin
- Chlorophyll-a is responsible for photosynthesis in plants
- Both haem and chlorophyll-a are synthesised in cells from porphobilinogen

Furans, Pyrroles Thiophenes – Deprotonation

Metallation



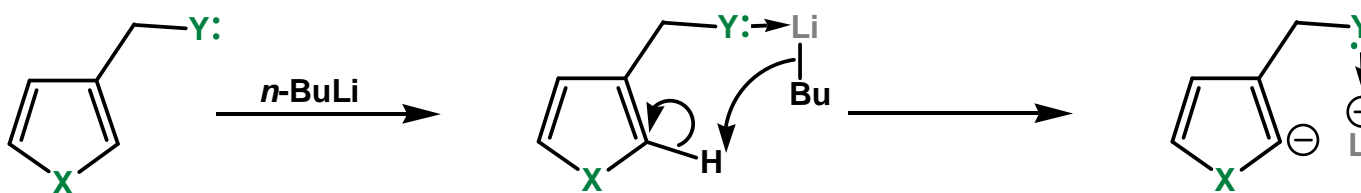
Deprotonation of Pyrroles



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

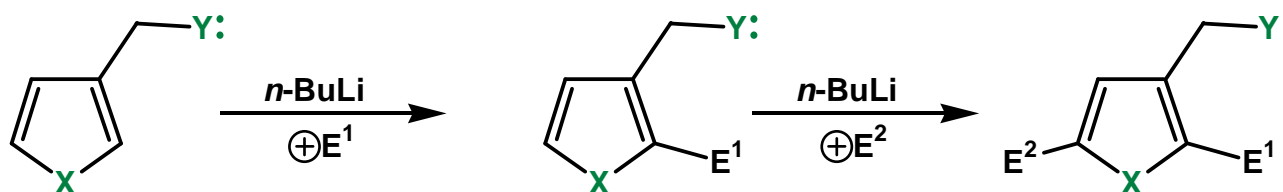
Furans, Pyrroles Thiophenes – Directed Metallation

Control of Regioselectivity in Deprotonation

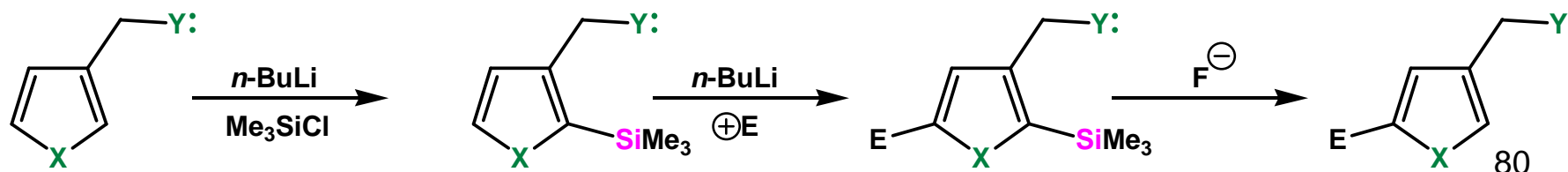


Common directing groups: $\text{CO}_2\text{H}(\text{Li})$, CH_2OMe , CONR_2 , $\text{CH}(\text{OR})_2$

Synthesis of α,α' -Disubstituted Systems

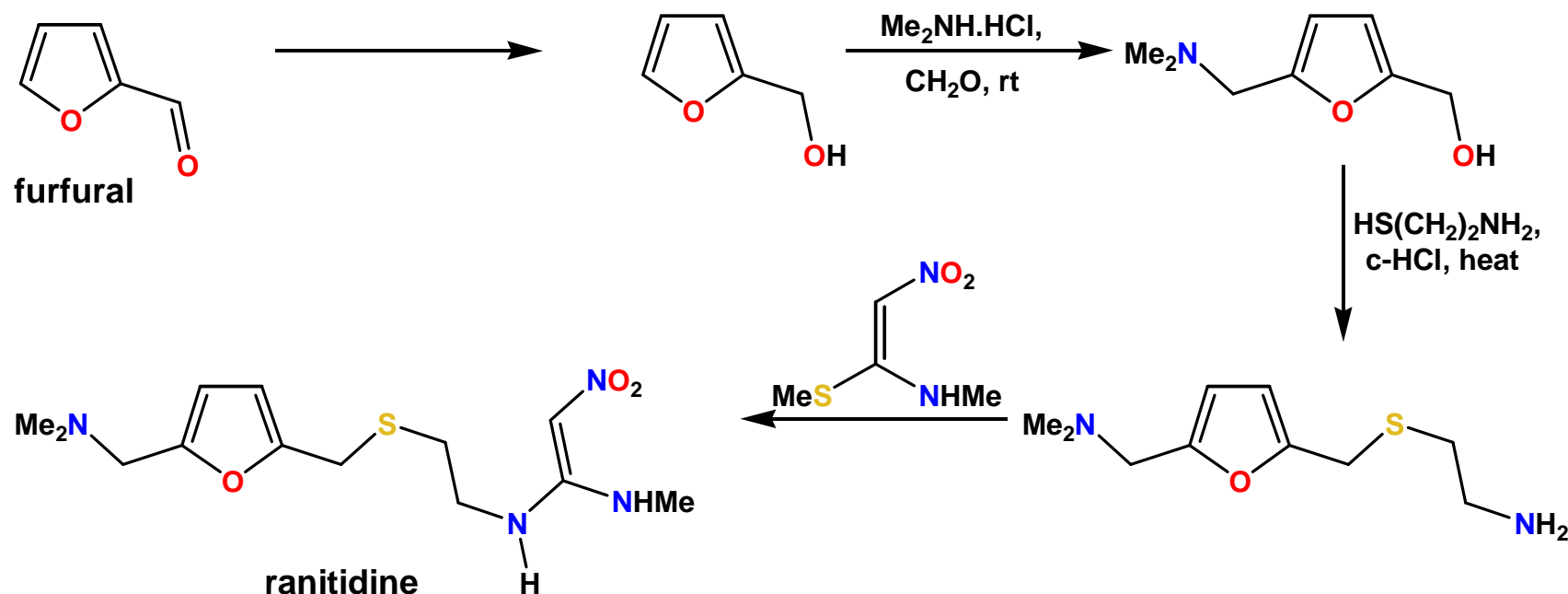


Use of a Trialkylsilyl Blocking Group



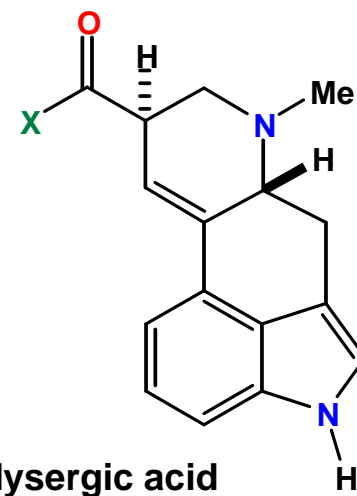
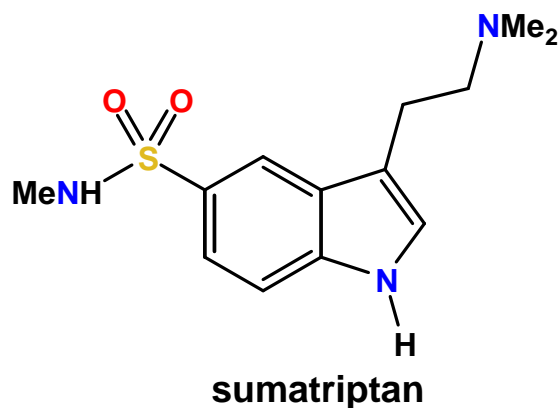
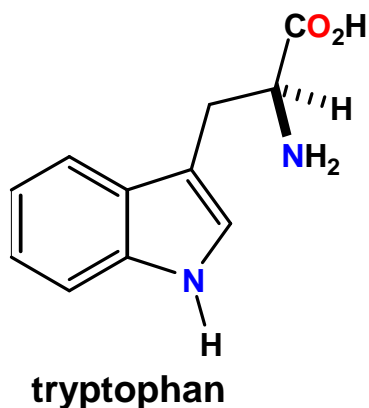
Furans – Synthesis of a Drug

Preparation of Ranitidine (Zantac®) Using a Mannich Reaction



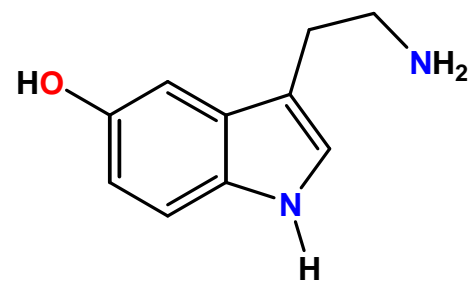
- Furfural is produced very cheaply from waste vegetable matter and can be reduced to give the commercially available compound furfuryl alcohol
- The second chain is introduced using a Mannich reaction which allows selective substitution at the 5-position
- The final step involves conjugate addition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

Indoles – Bioactive Indoles



X = OH lysergic acid
X = NEt₂ lysergic acid diethylamide (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

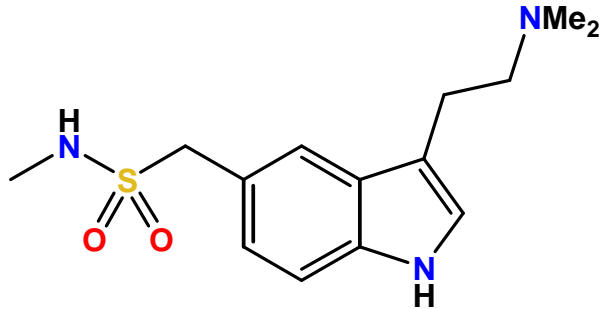


“The Beggars” (“The Cripples”) by Pieter Breugel the Elder (1568)

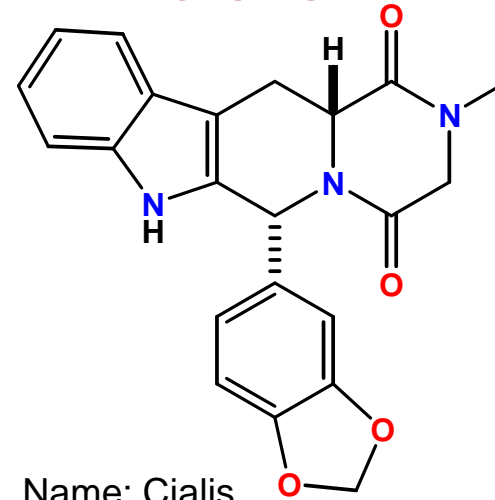
Louvre Museum, Paris



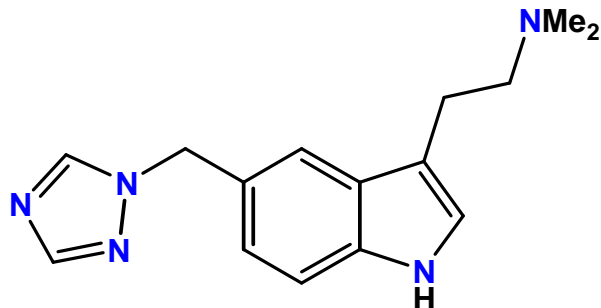
Drugs Containing an Indole



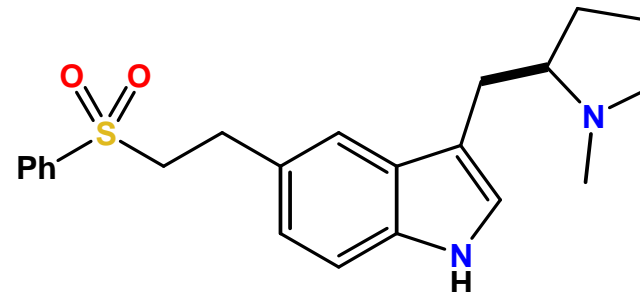
Name: Immitrex
2008 Sales: \$0.97 billion
2008 Ranking: 35 branded
Company: GlaxoSmithKline
Disease: Migraine



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



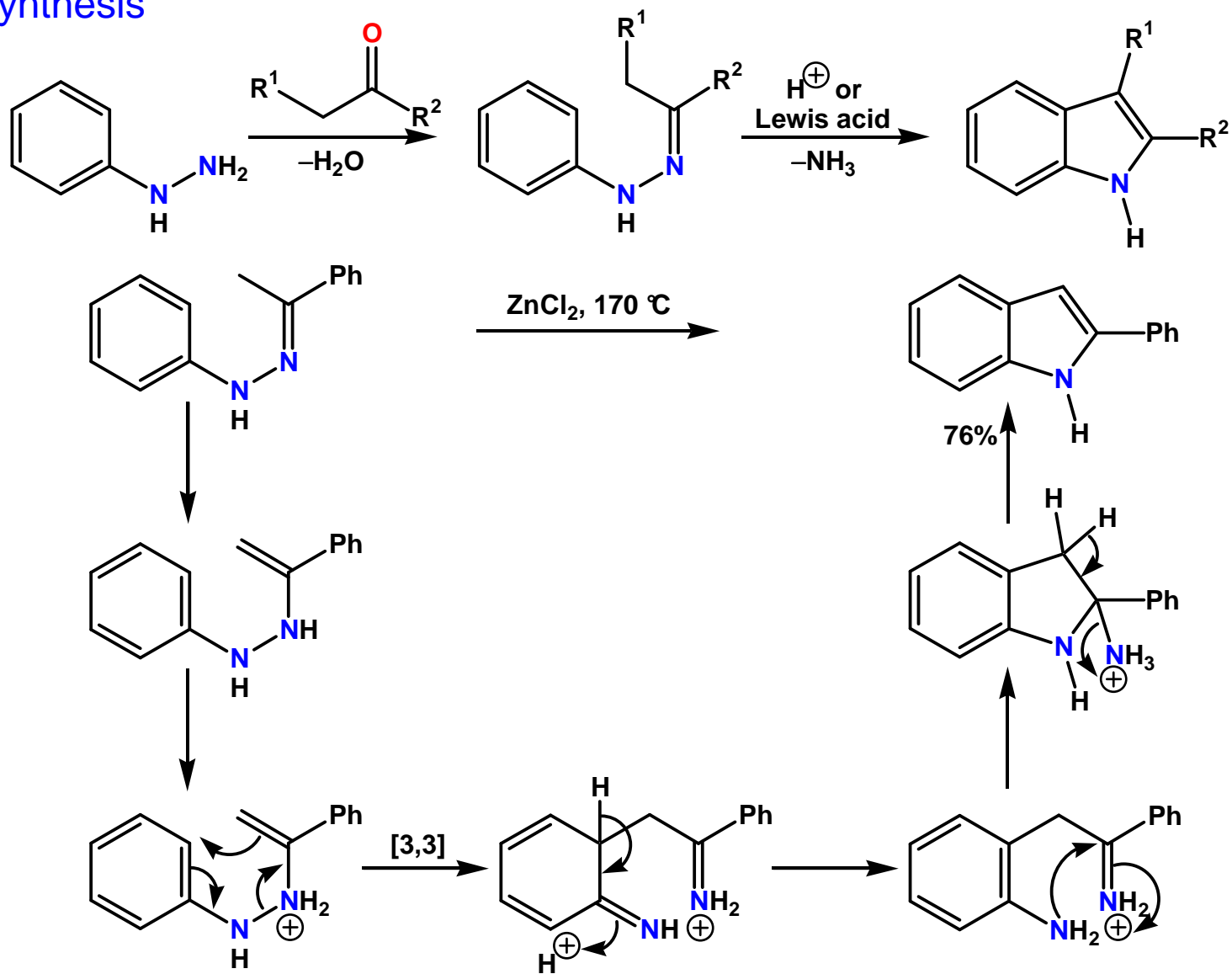
Name: Maxalt
2008 Sales: \$0.22 billion
2008 Ranking: 148 branded
Company: Merck
Disease: Migraine



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

Indoles – Synthesis

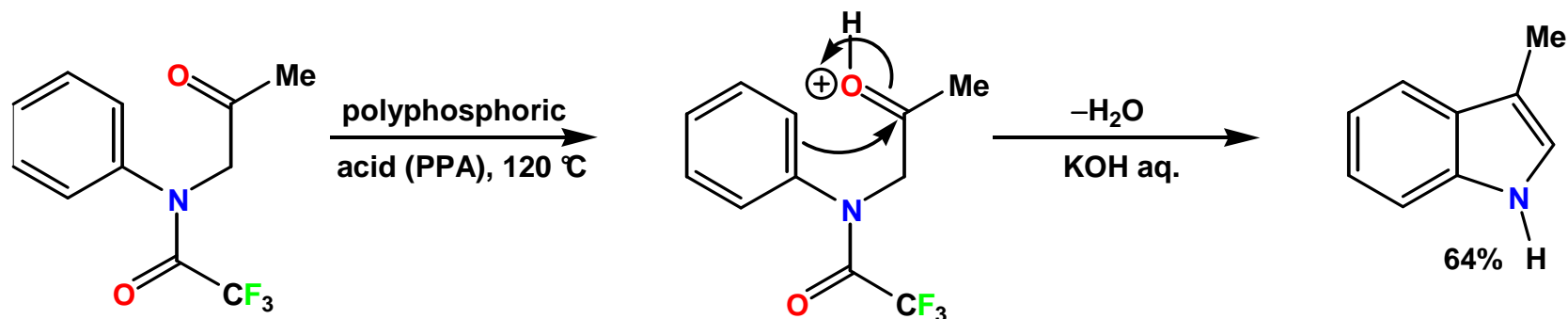
Fischer Synthesis



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

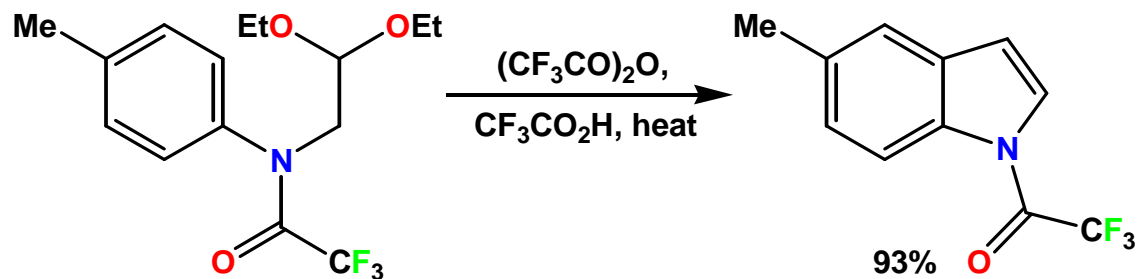
Indoles – Synthesis

Bischler Synthesis



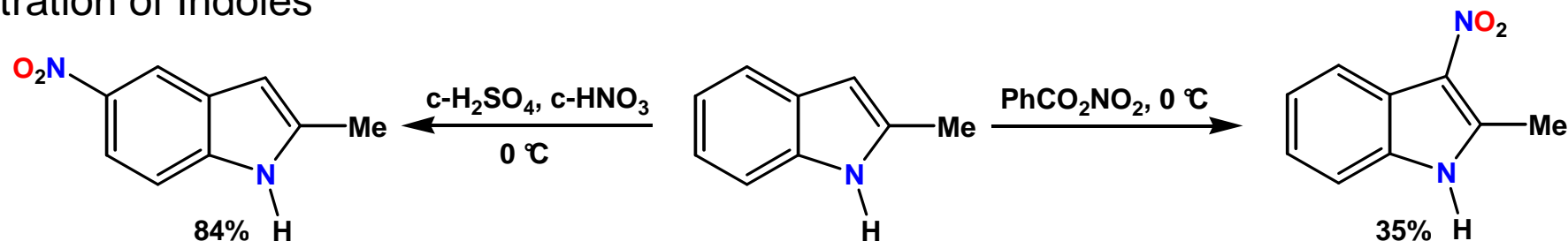
- An α -arylamino ketone is cyclised under acidic conditions

- The reaction also works with acetals of aldehydes



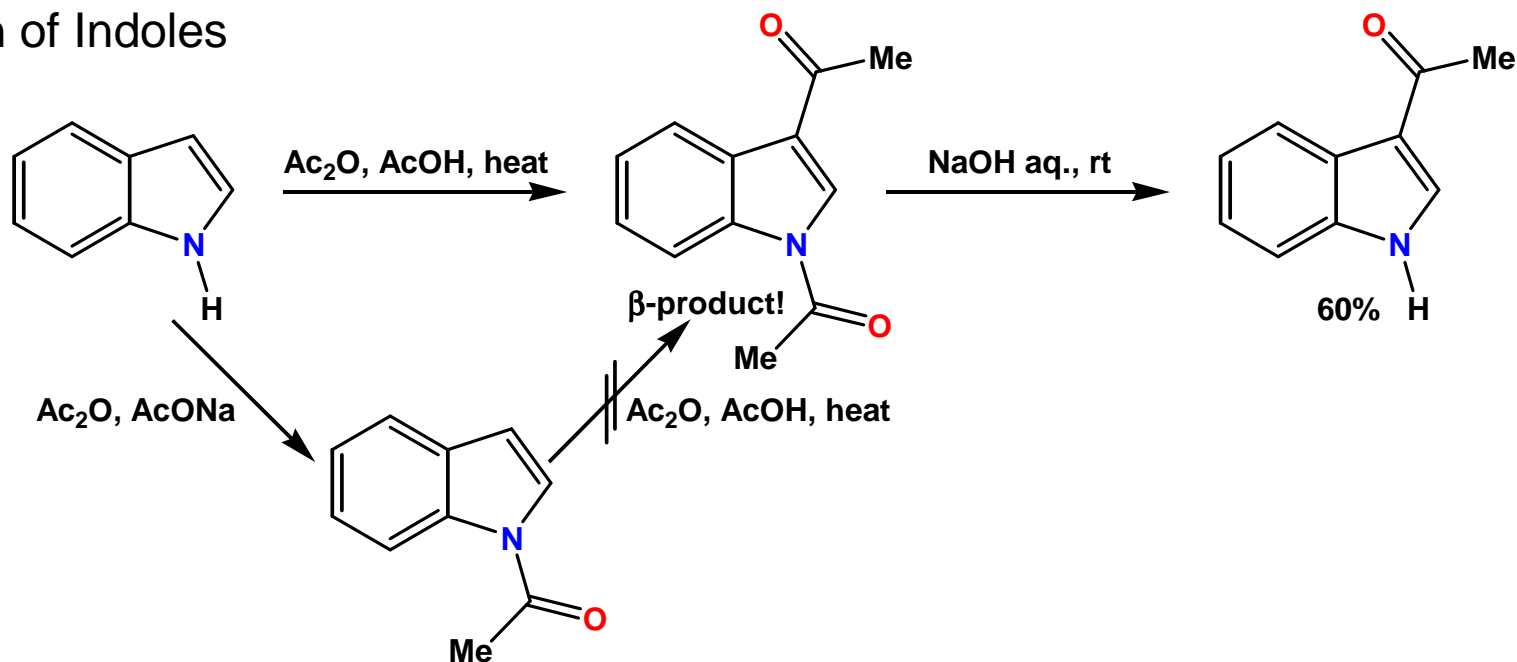
Indoles – Electrophilic Substitution

Nitration of Indoles



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

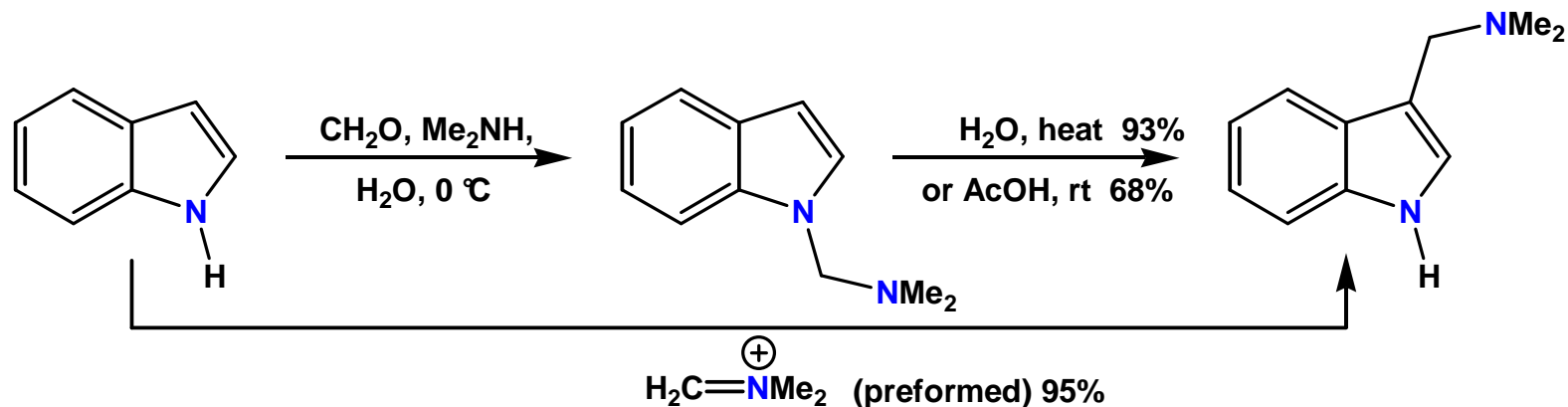
Acylation of Indoles



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

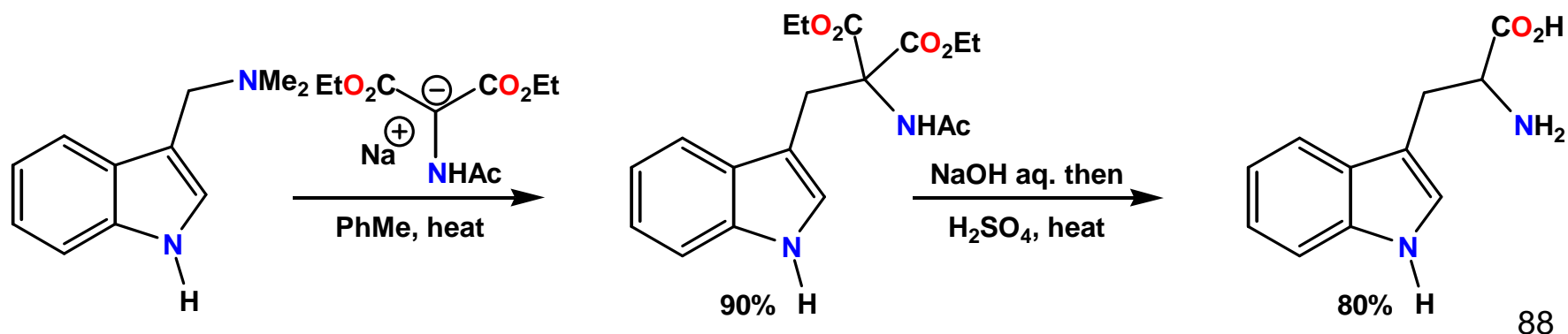
Indoles – Electrophilic Substitution

Mannich Reaction



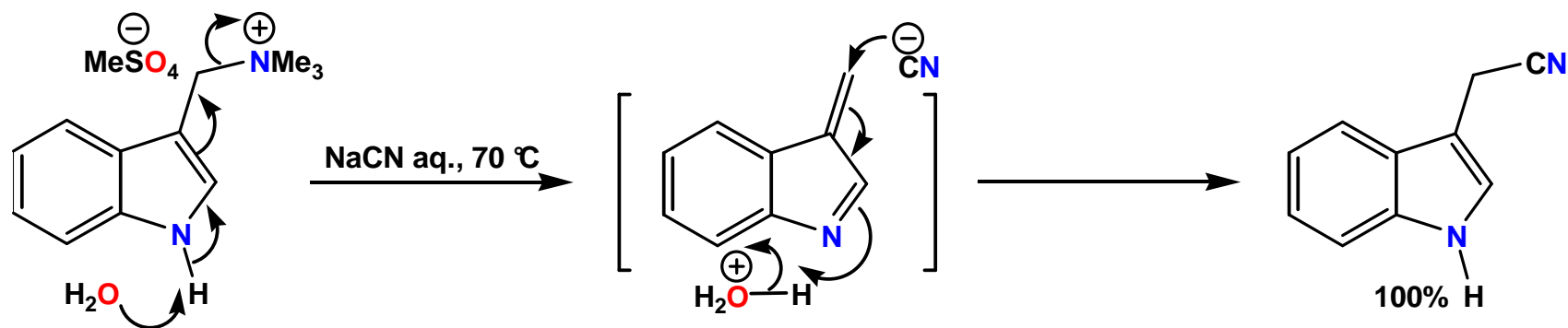
- A very useful reaction for the synthesis of 3-substituted indoles
- The product (gramine) can be used to access a variety of other 3-substituted indoles

Synthesis of Tryptophan from Gramine

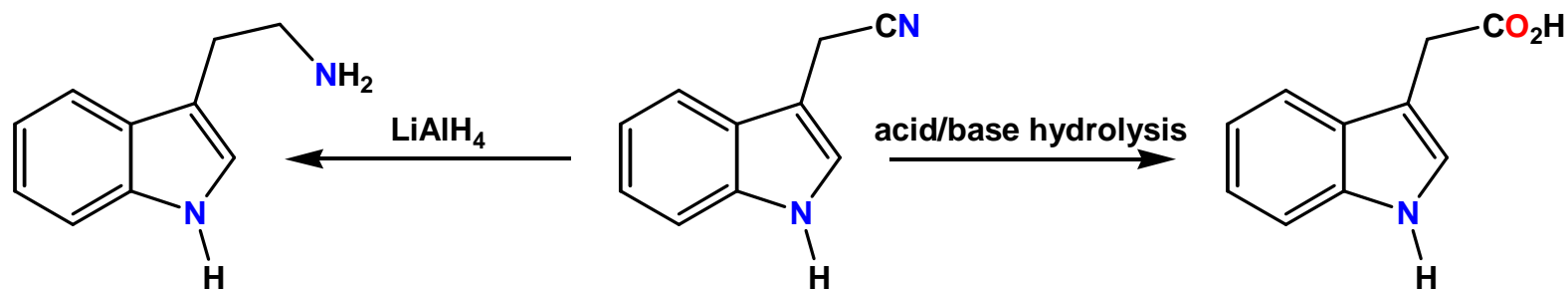


Indoles – Electrophilic Substitution

Synthesis of Other 3-Substituted Indoles from Gramine

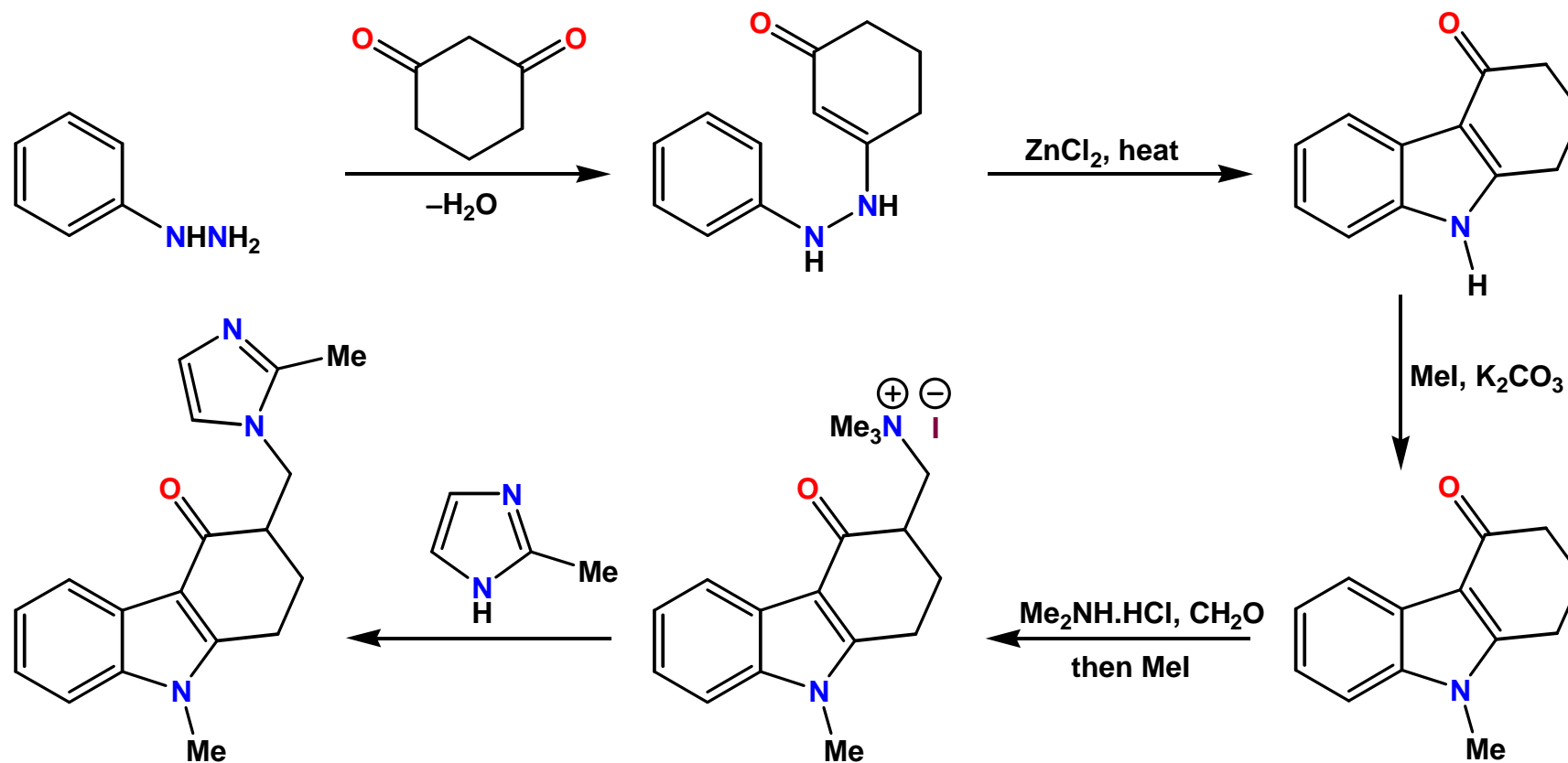


- The nitrile group can be modified to give other useful functionality



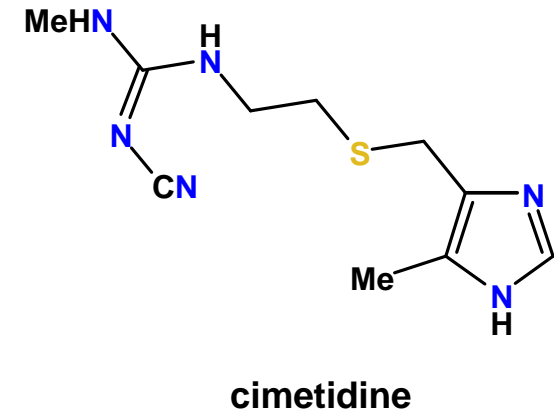
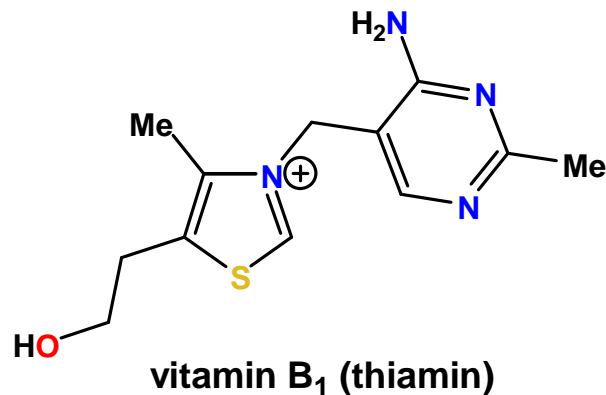
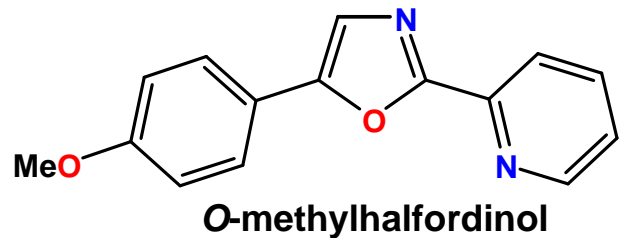
Indoles – Synthesis of a Drug

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



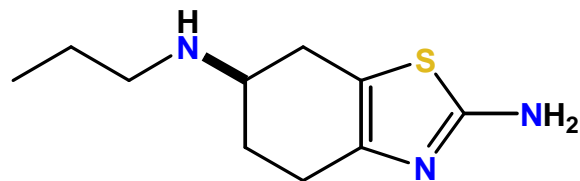
- Ondansetron is a selective 5-HT antagonist used as an antiemetic in cancer chemotherapy and radiotherapy
- Introduction of the imidazole occurs *via* the α,β -unsaturated ketone resulting from elimination of the ammonium salt

1,3-Azoles – Bioactive 1,3-Azoles

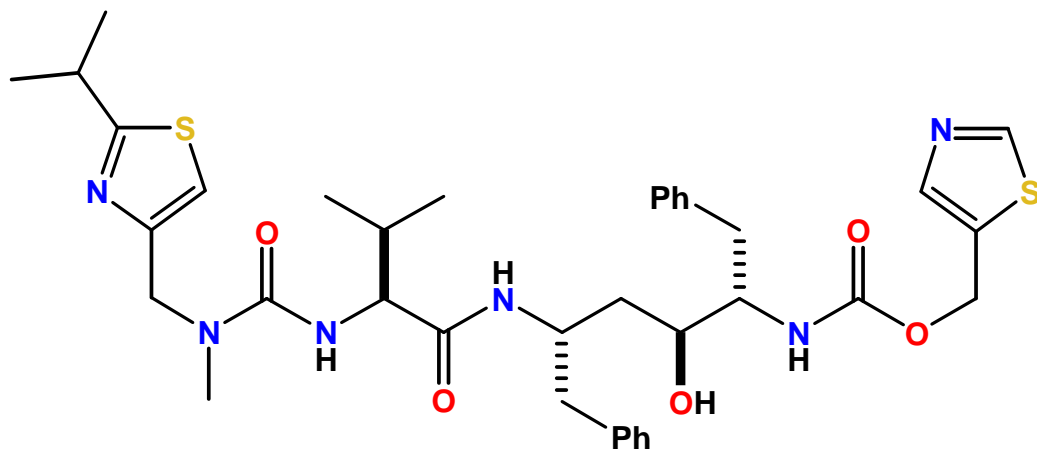


- O-Methylhalfordinol is a plant-derived alkaloid
- Vitamin B₁ (thiamin) is essential for carbohydrate metabolism. Deficiency leads to beriberi, a disease which is characterised by nerve, heart and brain abnormalities
- Cimetidine (Tagamet®, GSK) is an H₂-receptor antagonist which reduces acid secretion in the stomach and is used to treat peptic ulcers and heartburn

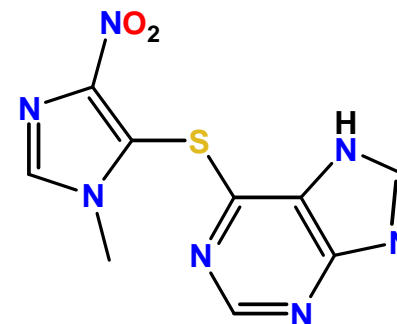
Drugs Containing a 1,3-Azole



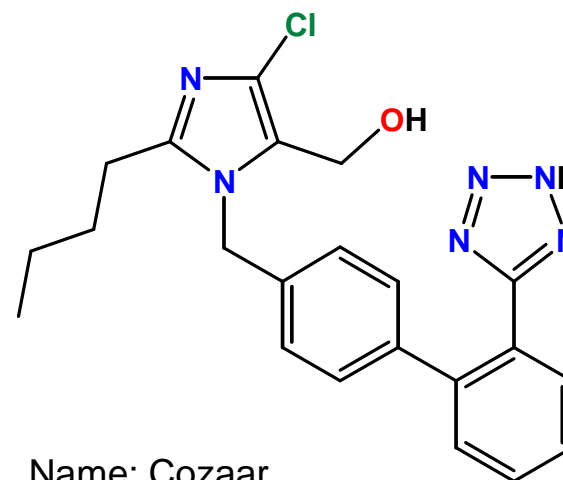
Name: Mirapex
2008 Sales: \$0.34 billion
2008 Ranking: 108 branded
Company: Boehringer Ingelheim
Disease: Parkinson's disease



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



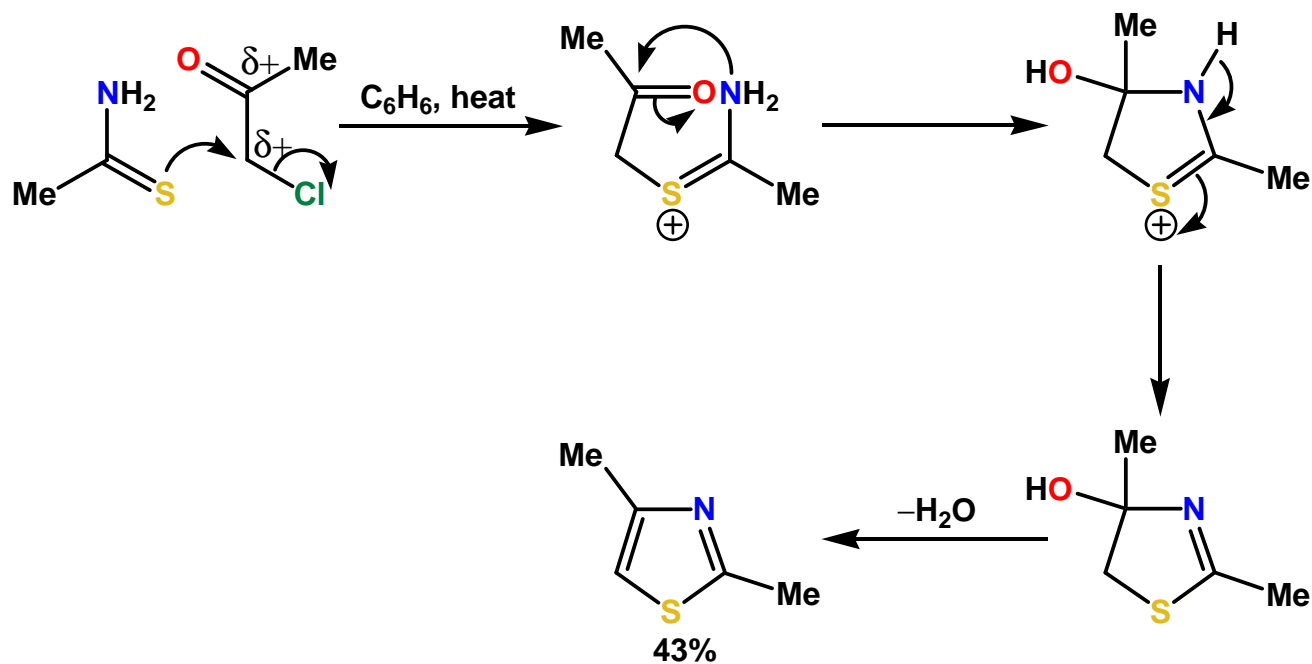
Name: Azathioprine
2008 Sales: \$53 million
2008 Ranking: 178 generic
Company: N/A
Disease: Kidney transplant rejection



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

1,3-Azoles – Synthesis

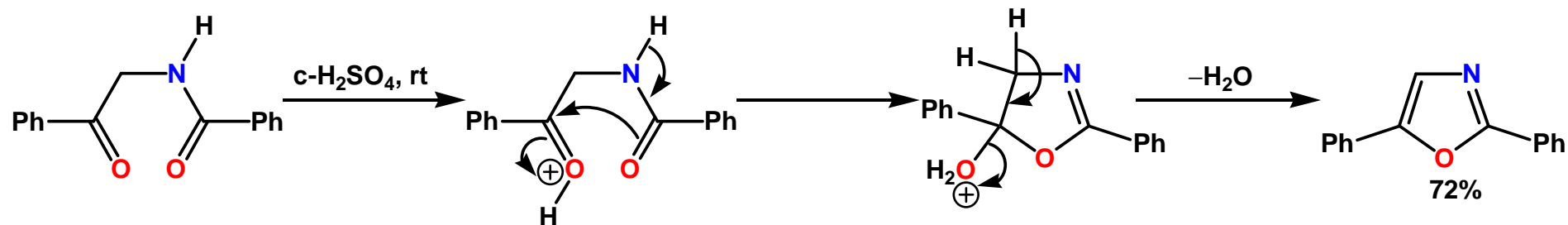
The Hantzsch Synthesis (“3+2”)



- 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

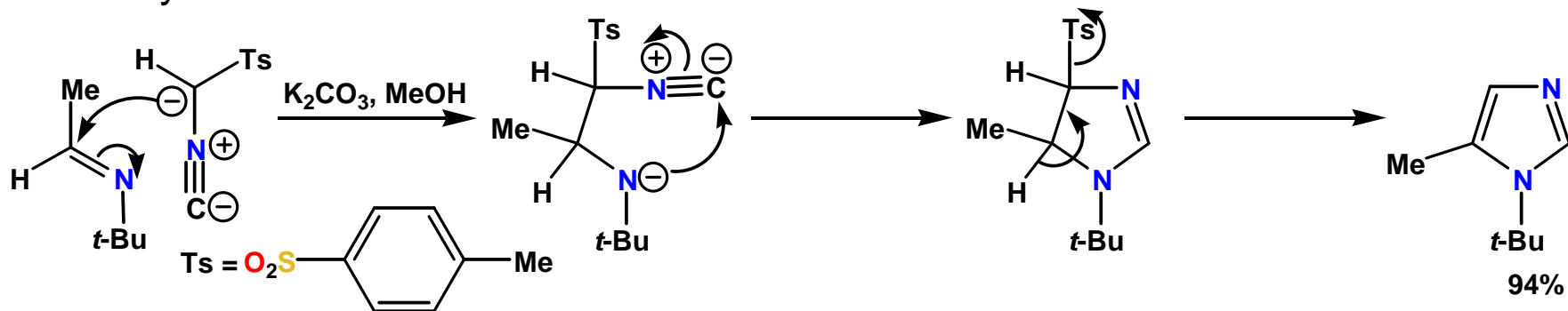
1,3-Azoles – Synthesis

Cyclodehydration of α -acylaminocarbonyl compounds



- A particularly important strategy for the synthesis of oxazoles which is known as the **Robinson-Gabriel Synthesis**
- The starting α -acylaminocarbonyl compounds are easily prepared

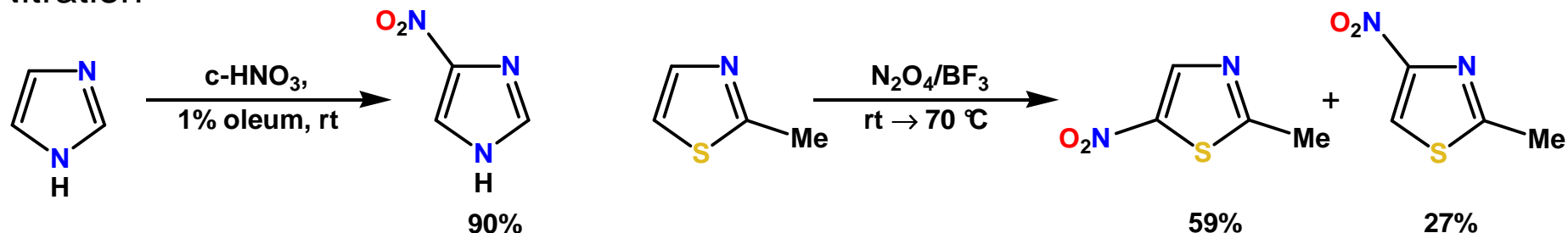
From Isocyanides



- *Tosylmethylisocyanide* (TOSMIC) is a readily available isocyanide
- Route can be adapted to give oxazoles and thiazoles using an acid chloride or a thiocarbonyl compound

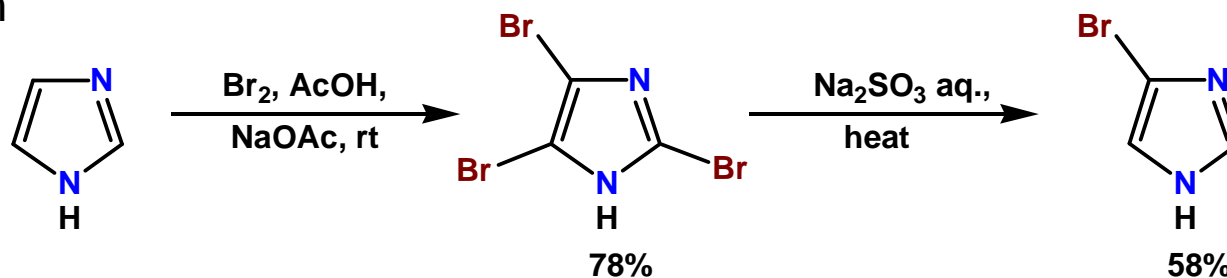
1,3-Azoles – Electrophilic Substitution

Nitration



- Imidazoles are much more reactive to nitration than thiazoles (activation helps)
- Imidazoles usually nitrate at the 4-position and thiazoles tend to react at the 5-position
- Oxazoles do not generally undergo nitration

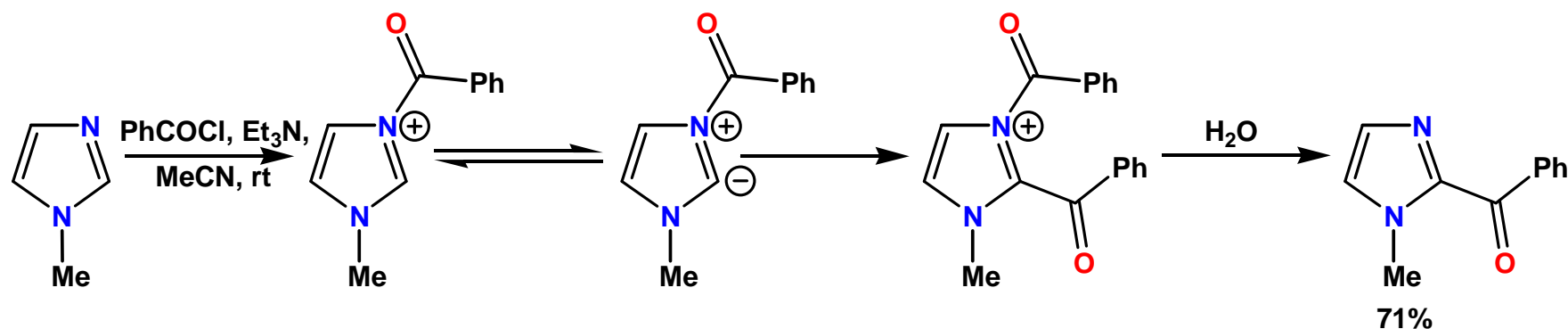
Halogenation



- Imidazoles are brominated easily and bromination at multiple positions can occur
- Thiazole does not brominate easily but 2-alkylthiazoles brominate at the 5-position

1,3-Azoles – Electrophilic Substitution

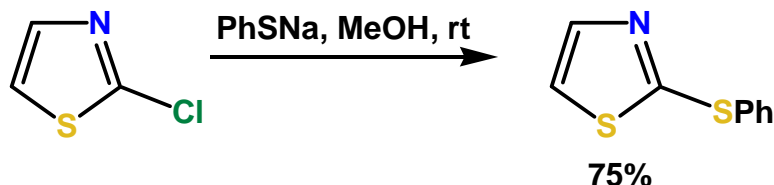
Acylation



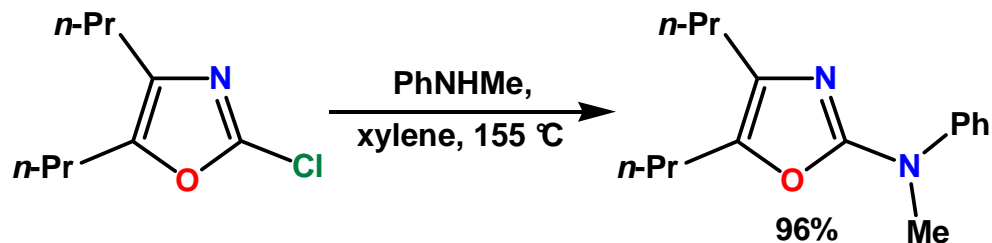
- 1,3-Azoles do not undergo **Friedel-Crafts acylation** because complexation between the Lewis acidic catalyst and *N* deactivates the ring
- Acylation can be accomplished under mild conditions *via* the *N*-acylimidazolium ylide

1,3-Azoles – Nucleophilic Substitution

Displacement of Halogen



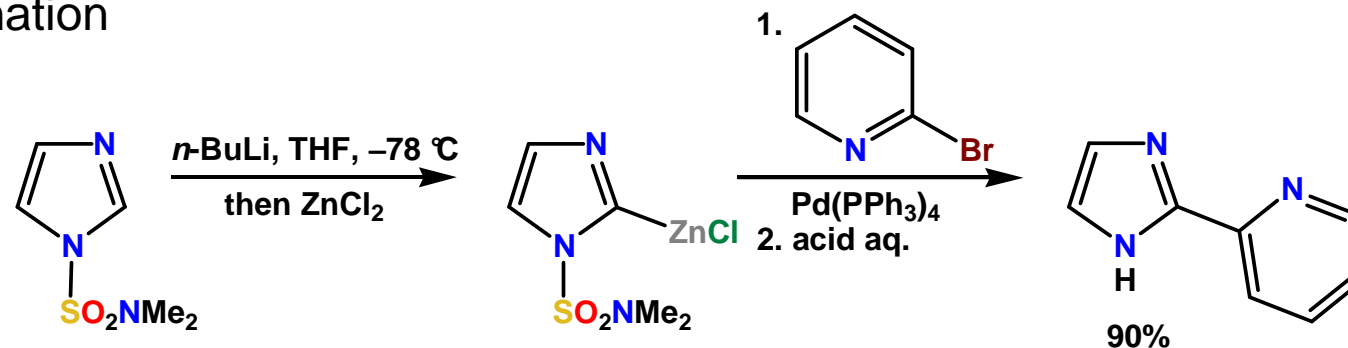
- There are many examples of displacement of halogen at the 2-position
- 2-Halothiazoles react rapidly with sulfur nucleophiles, and are even more reactive than 2-halopyridines



- 2-Halo-1-alkylimidazoles and 2-halooxazoles will react with nitrogen nucleophiles

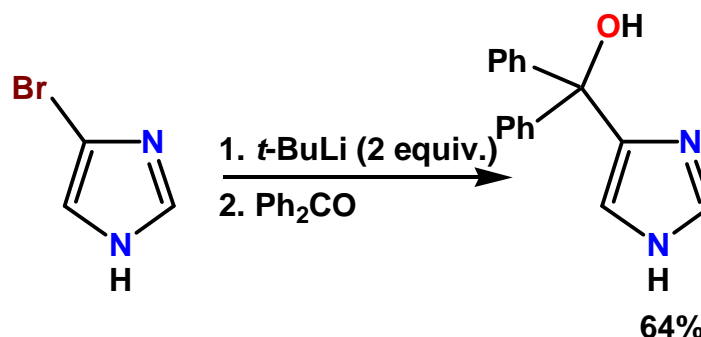
1,3-Azoles – Metallation

Direct Deprotonation



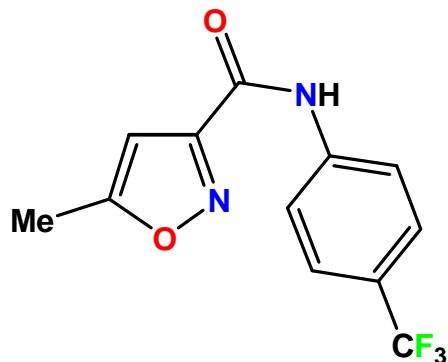
- Direct deprotonation oxazoles, thiazoles and *N*-alkylimidazoles occurs preferentially at either the 2- or 5-position
- Transmetallation of the lithiated intermediate is possible

Metal-Halogen Exchange

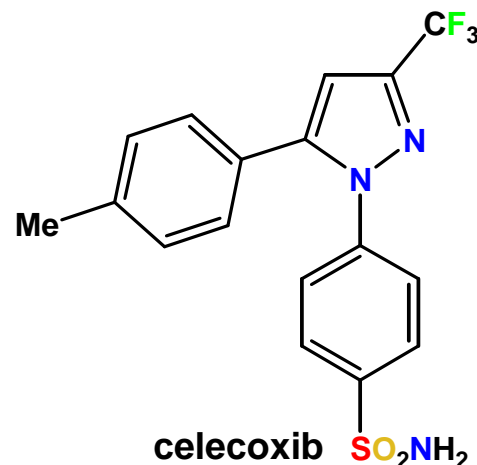


- Metallation at the 4-position can be accomplished by metal-halogen exchange
- In the case of imidazoles without substitution at the 1-position, two equivalents of base are required

1,2-Azoles – Bioactive 1,2-Azoles



leflunomide

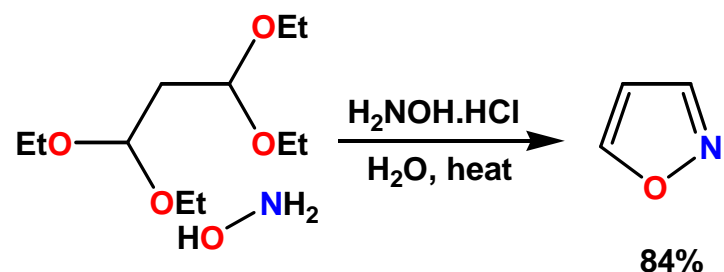
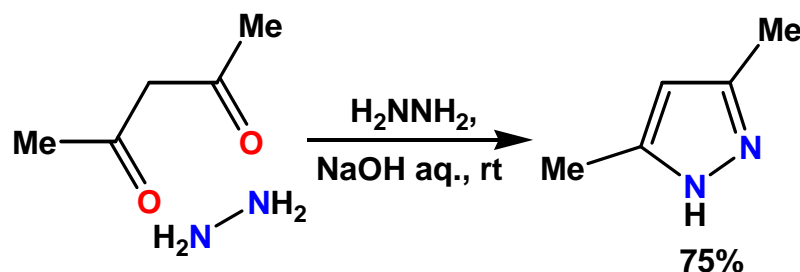


celecoxib SO₂NH₂

- 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-inflammatory (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

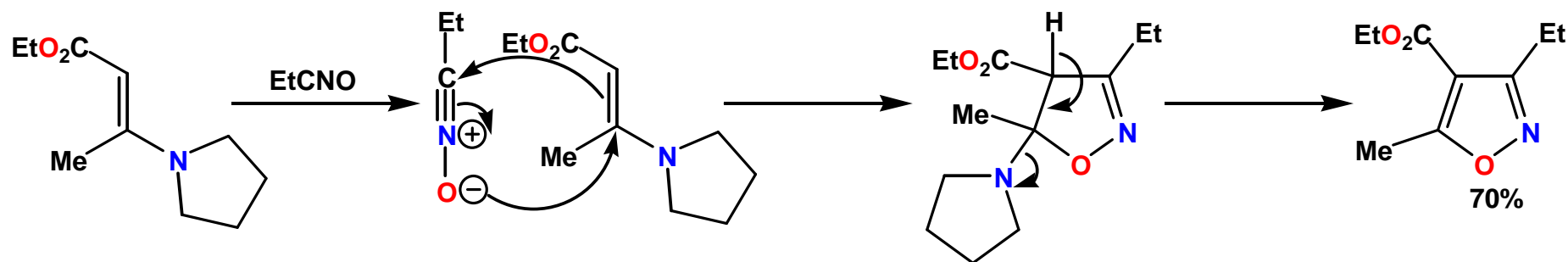
Synthesis of Pyrazoles/Isoxazoles from 1,3-Dicarbonyl Compounds and Hydrazines or Hydroxylamines (“3+2”)



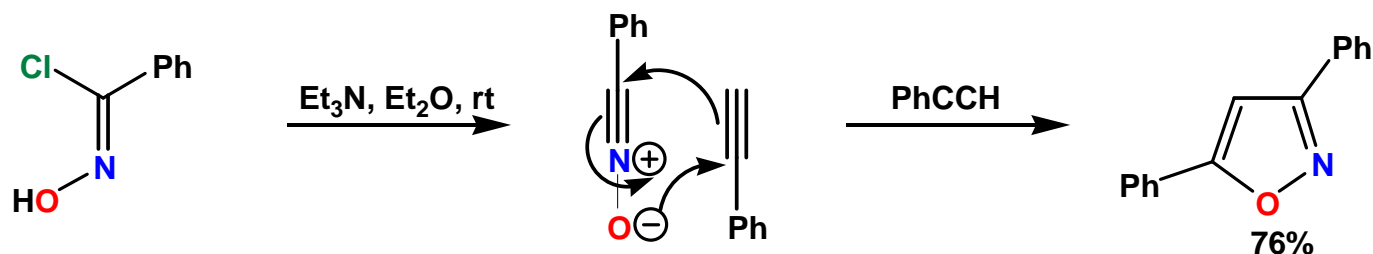
- This is the most widely used route to pyrazoles and isoxazoles
- The dicarbonyl component can be a β -keto ester or a β -keto aldehyde (masked)
- When a β -keto ester is used a pyrazolone/isoxazalone is formed

1,2-Azoles – Synthesis

Synthesis of Isoxazoles by Cycloaddition of Nitrile Oxides to Alkynes or Enamines (“3+2”)



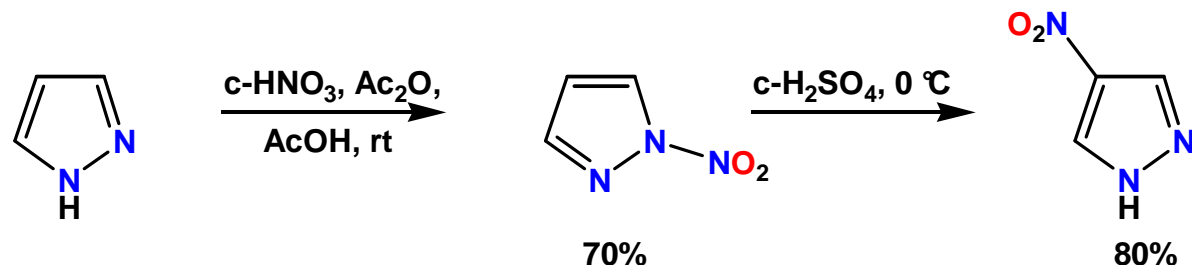
- Nitrile oxides react readily with alkenes and alkynes
- Addition to an alkene generates an isoxazoline unless a leaving group is present



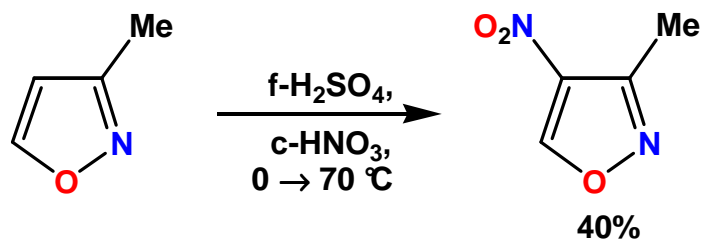
- Mono-alkyl/-aryl alkynes react to give 3,5-disubstituted isoxazoles but when the alkyne possesses two substituents mixtures of 3,4- and 3,5-disubstituted isoxazoles are usually produced

1,2-Azoles – Electrophilic Substitution

Nitration of Isoxazoles, Pyrazoles and Isothiazoles



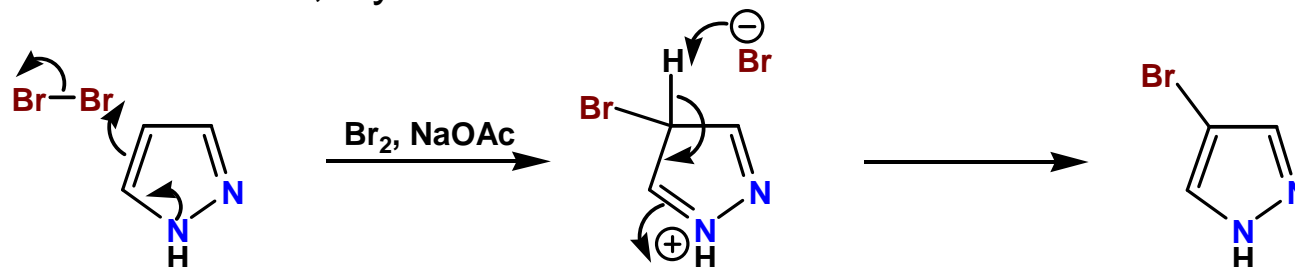
- Pyrazoles and isothiazoles undergo straightforward nitration
- 1-Nitropyrazole is formed in good yield by treatment of pyrazole with the mild nitrating reagent, acetyl nitrate
- 1-Nitropyrazole can be rearranged to give 4-nitropyrazole by treatment with acid at low temperature



- Isoxazole nitrates in very low yield, but 3-methylisoxazole is sufficiently reactive to undergo nitration at the 4-position

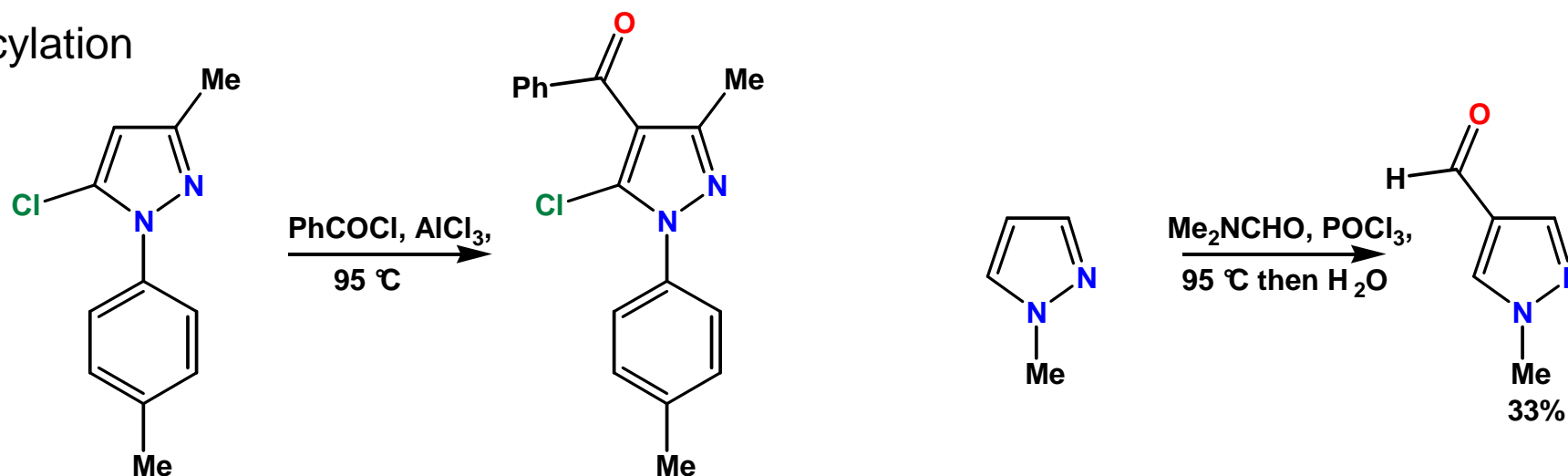
1,2-Azoles – Electrophilic Substitution

Halogenation of Isoxazoles, Pyrazoles and Isothiazoles



- Halogenation (iodination, bromination) of pyrazole leads to the 4-halopyrazole
- Poor yields are obtained when attempting to halogenate isoxazole or isothiazole, but bromination can be accomplished when an activating group is present as a substituent

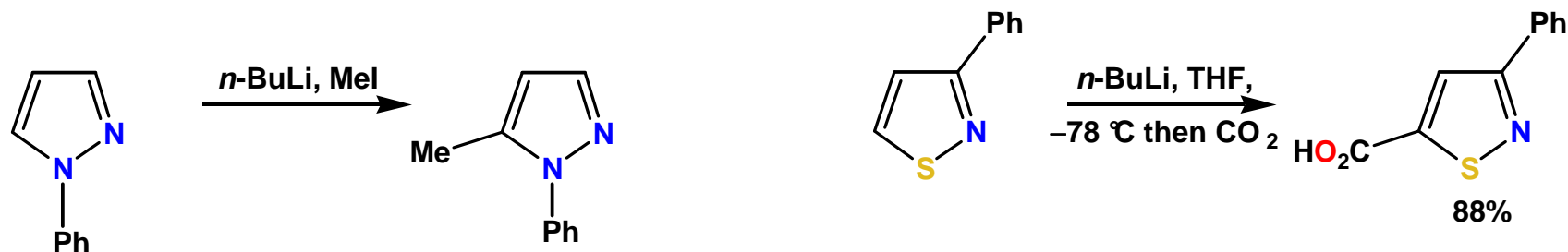
Acylation



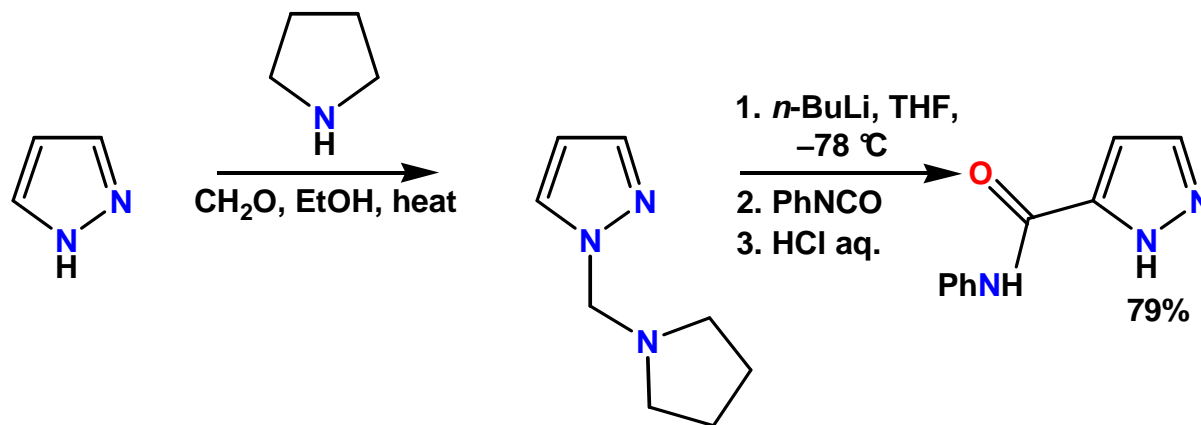
- Only *N*-substituted pyrazoles can be C-acylated directly
- [Vilsmeier formylation](#) produces the 4-formylpyrazole in modest yield

1,2-Azoles – Metallation

Direct Metallation of Isoxazoles, Pyrazoles and Isothiazoles



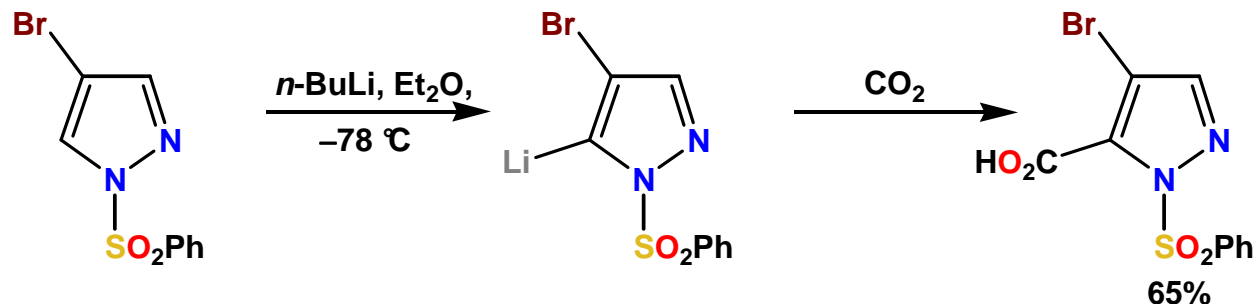
- 1-Substituted pyrazoles and isothiazoles can be lithiated and alkylated at the 5-position



- It is possible to temporarily protect the 1-position of pyrazole and then perform sequential deprotonation and alkylation/acylation at the 5-position

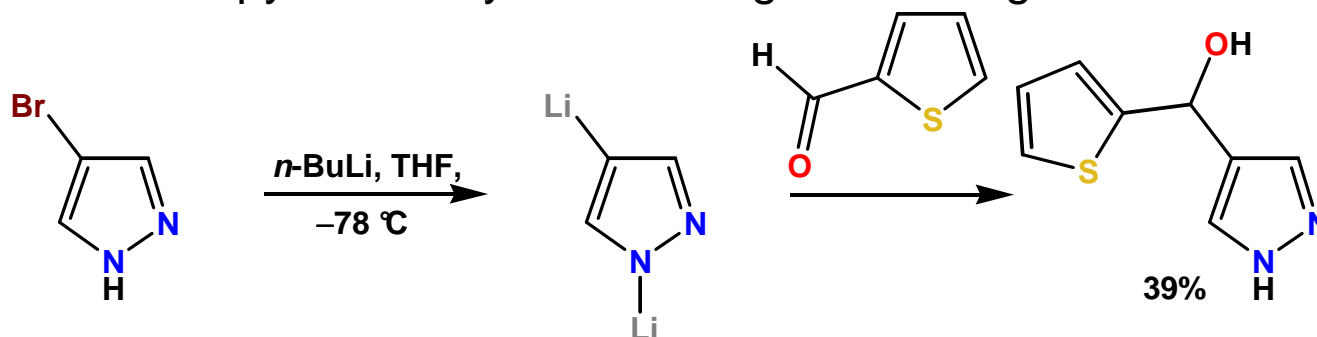
1,2-Azoles – Metallation

Direct Metallation of 4-Bromopyrazoles



- At low temperature, *N*-sulfonyl 4-bromopyrazoles can be lithiated at 5-position without undergoing metal-halogen exchange

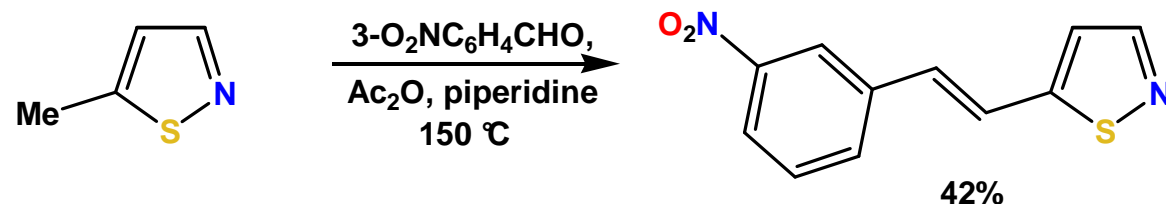
Metallation of 4-Bromopyrazoles by Metal-Halogen Exchange



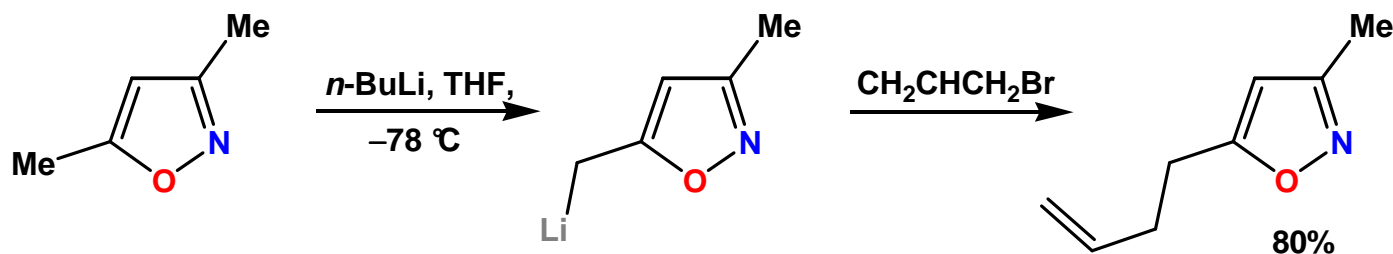
- Treatment of 4-bromopyrazole with two equivalents of *n*-butyllithium results in *N*-deprotonation and exchange of lithium for bromine
- 2,5-Dilithiopyrazole reacts with carbon electrophiles to give the 4-substituted product

1,2-Azoles – Side Chain Deprotonation

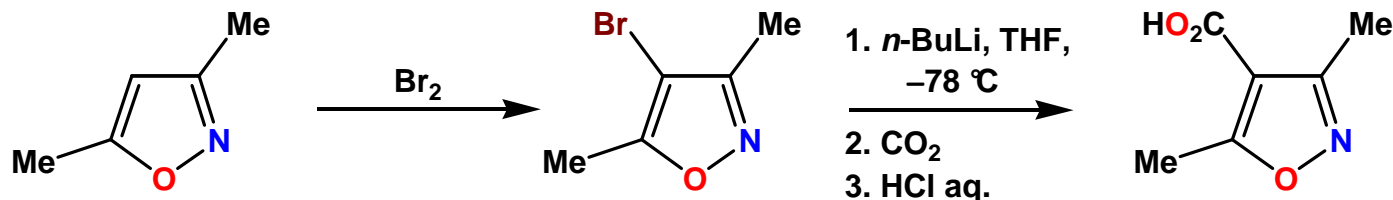
Deprotonation of 5-methylisothiazole and 5-methylisoxazole



- A weak base can be used to deprotonate 5-methylisothiazole and 5-methylisoxazole
- In this case above, dehydration of the initial product occurs in situ
- Surprisingly, 3-methylisothiazole does not deprotonate as easily as 5-methylisothiazole and the same effect is found in isoxazoles

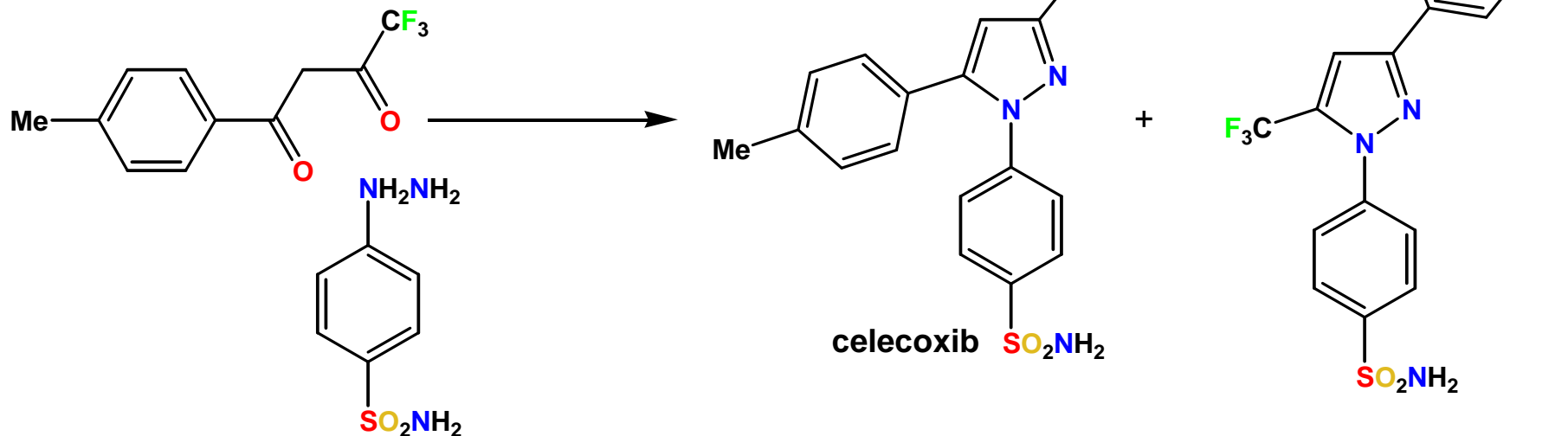


- Metal-halogen exchange can be used to avoid deprotonation of alkyl groups

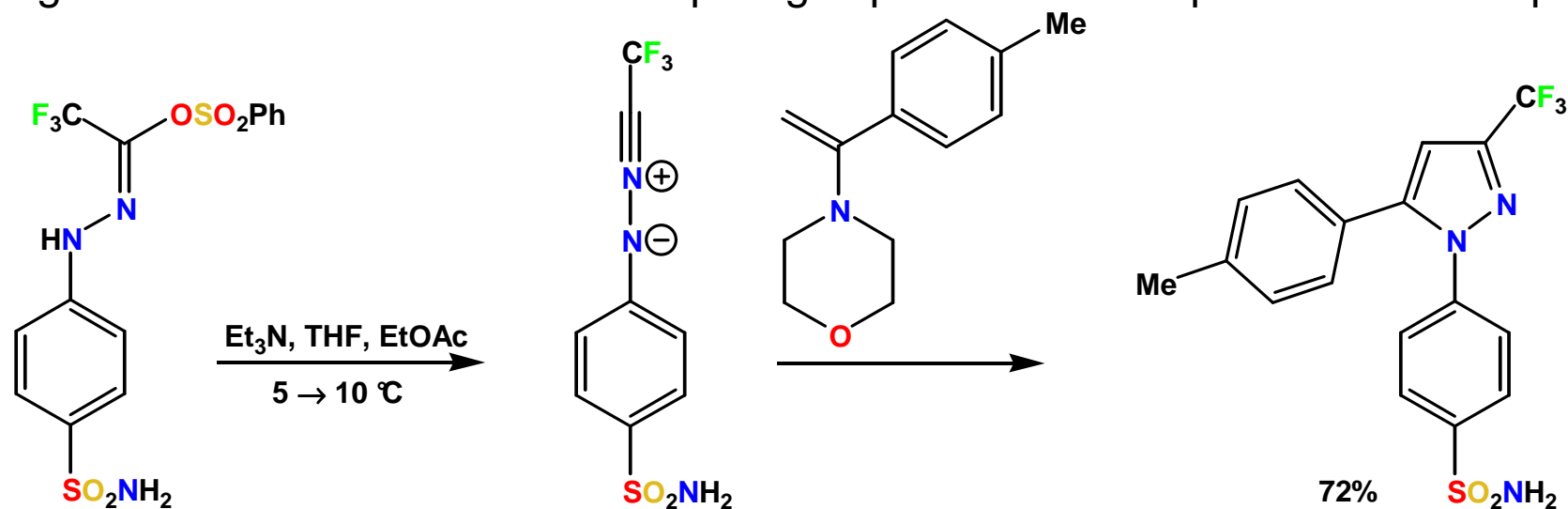


1,2-Azoles – Synthesis of a Drug

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