Heterocyclic Chemistry

# 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

**Introduction**

# Course Summary

* 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 3
* 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 the 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

**X Z X**

**X**

**Y Y**

**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

**4 4**

**1**

**O**

**3 5 3 5**

**2 6 2 6**

**N**

**1 ** **X**

**pyridine**

**4**

**3**

**2 N**

**5**

**6**

**N**

**1**

**4**

**3 N 5**

**2 6**

**N**

**1**

**pyrylium**

**4**

**N**

**3 5**

**2 6**

**N**

**1**

**pyridazine pyrimidine pyrazine**

**4 5 4 5**

**N**

**3**

**2 N**

**6**

**7**

**3 6**

**2 7**

**1 8 1 8**

**quinoline**

**isoquinoline** 6

**3 4 3 4 3 4**

**2 5 2 5 2 5**

**1**

**N O S**

**H 1 1**

**pyrrole furan thiophene**

**3 4 3 4 3 4**

**N N N**

**1**

**2 5 2 5 2 5**

**N O S**

**H 1 1**

**imidazole**

**oxazole**

**thiazole**

**3 4 3 4 3 4**

**N H**

**2 N 1**

**5**

**pyrazole**

**4**

**3 5**

**6**

**2 1**

**O**

**1**

**2 N**

**5**

**isoxazole**

**S**

**1**

**2 N**

**5**

**isothiazole**

**N 7** 7

**H**

**indole**

Unsaturated



**O**

**O**

**O**

**O**

aromatic dipolar resonance form



**4(****)-pyrone**

Saturated

**O OH**

**H H**



**N**

**O**

**N**

**N**

**2-pyridone**

**O**

**O**

**O**

**O O N H**

**ethylene oxide**

**THF**

**1,4-dioxan pyrrolidine dihydropyran**

Imine Formation

**O R3NH2 H**



**R3 R3**

**N N**

**R1 R2**

**H3O**

**R1 R2**

**R1 R2**

**H**

**H**

**H**



**O**

**R3 N**



**H**

**OH**

**R3 N**

**H**

**H**



**R3**

**H**



**OH2 N**

**R1 R2**

**R1 R2**

**R1 R2**

**R1 R2**

* 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

Enols and Enolates



**O**

**B**

**H**

**H**

**O O**



**OH**

**E**

**O**

**R1 R1 R1**

**R2 R2 R2**

**R1 R1**

**R2 R2**

keto form enol form enolate

* The enol form is favoured by a conjugating group R2 e.g. CO2R, COR, CN, NO2 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

**R3O**

**OR3**

**R1 R1**

**OR3**

**H**

**R2**

**R3OH**

**R**

**O**

**3**

**R2**

**R1**

**R2**

acetal

**O**

**H2O**

enol ether

**R1** 10

**R2**

Enamines

**R3 R3**

**R3**

**R3**

**O N N**

**H H H**

**R3 R3**

**N**

**R1 R1  H R1**

**R2 R2 R2**

**R3 R3**



**N**

iminium ion (Schiff base)

**R3 R3**

**N**

**H2O**

enamine

**O**

**E E**

**R1 E R1 R1**

**R2 R2 R2**

* 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

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Common Building-Blocks

**O**

**R**

**OH**

**O**

**R**

**NH2**

**NH**

**R**

**NH2**

carboxylic acids

amides

amidines

**O NH O O O O**

**H2N**

**NH2 H2N**

**NH2 R1**

**R2 R1**

**OR2**

urea guanidine -diketones -keto esters

Building-Blocks for Sulfur-Containing Heterocycles

**O P2S5**

**R1 R2**

**S**

**R1 R2**

**R SH**

**R1 R2**

**S**

* Heterocycle synthesis requires:

thioketones thiols thioethers

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) 12

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

**Y** 

+ conjugate addition

**X**

**Y** 

+



+

**X**

**X**, **Y** = **O**, **S**, **NR**

Manipulation of Oxidation State

[**O**]

**H2**

[**O**]

**H2**

or [**O**]

**H2**

**X**

hexahydro

**X**

tetrahydro

**X X**

dihydro

**X**

aromatic

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

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Common Strategies “4+1” Strategy

**X**



**X**

**NH3**

**2H2O**

**O O**

**H**

**N**

**N O O**

**H**

**NH3**

**2H2O N**

**N**

**H**

* Strategy can be adapted to incorporate more than one heteroatom

“5+1” Strategy

**X**



**X**



**NH3**

**2H2O**

**O O**

[**O**]

**H2**

**H**

**N**

**N**

**H**

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* 1,5-Dicarbonyl compounds can be prepared by Michael addition of enones

“3+2” Strategy “3+3” Strategy

**X**



**X**



**X**



**X**

or  or

**X X**

Examples 







**X H2N**

**H2N O**

**H2N OH**

**O** +





**X H2N**



+



**O OH**

+ +



**O** +

+

**O**

**Hal**

**O**

**Hal** = **Cl, Br, I**

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**E**

**NH2**



**E**

**OH**

**NH2 OH**

**H**

**H**

**N**

**H**

**N**

**N S NH2**

**O**

**N O**

**nicotine**

**sulphapyridine**

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

**NH2**

**O NH**

**Me N**



**paraquat**

**N Me**

**N**

**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 16

**MeO**

**N O OMe S**

**N**

**N O O OMe S**

**N**

**H**

**N**

Name: Nexium

**H**

**N**

Name: Aciphex

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

2008 Sales: $1.05 billion 2008 Ranking: 34 branded Company: Eisai

Disease: Duodenal ulcers and acid reflux

**S**

**O**

**O O NH**

**N**

**H**

**N N**

**N**

**N**

**N**

**HN N**

**O**

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 17

1.40 Å

1.39 Å

**N** 1.34 Å **N**

**..**

2.2 D

1.17 D

**N H**

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



**N N N**



+ +

**N N**



* Weakly basic – pK*a* ~5.2 in H2O (lone pair is **not** in aromatic sextet)
* Pyridinium salts are also aromatic – ring carbons are more + than in parent pyridine

**N N N**



**H H H**

etc.

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The Hantzsch synthesis (“5+1”)

**O Ph H**

**Me O**

**O O Ph**

**Me NH3 pH 8.5 Me**



**O**

**Me**

**O H Ph O**

**Me Me**

**Me O O**

**Me** aldol condensation **Me**

and dehydration

**O O Me**

Michael addition **Me**

**O O Me**

**O Ph O**

**Me**

**Me**

**O H Ph O**

**O H Ph O**

**Me N Me**

**HNO3**

oxidation

**Me N Me H**

**Me**

**O**

**Me**

**Me**

**H2N Me**

* The reaction is useful for the synthesis of symmetrical pyridines

**Me**

**Me**



* The 1,5-diketone intermediate can be isolated in certain circumstances
* A separate oxidation reaction is required to aromatise the dihydropyridine

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

**CO2Et**

**CN**

**CN**

**H2N O**

**CO2Et**

**O**

**O**

**CN Me**

**CN**

**H2N Me**

**Me N O H**

**K2CO3**

**Me**

**K2CO3**

**EtO2C**

**N Me**

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

Using Cycloaddition Reactions (“4+2”)

**73%**

**CO2H**



**O**

**N**

**Me**

**Me**

**Me**

Diels-Alder **Me**

cycloaddition

**CO2H**

**N**



**O**

**Me**

**H+ H**



**CO2H**

**H H**

**O**

**Me N**

**CO2H**

**Me**

**H2O M**

**H CO2H**

**Me N Me N 70%**

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

**HO**

**e**

Pathways for the Electrophilic Aromatic Substitution of Pyridines



 **E E**

 **N N**

**E** **E**



**E**



**E**

**N N**

**E E**

* 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

Regiochemical Outcome of Electrophilic Substitution of Pyridines

**E E**



**N**



**N**



**E**

**H H H**



**N**





**E**

**N**

**H**



**N**

**H**



**N**

**H**

**E E**

**E H E H**



**E H**

**N**





**N N**

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

 / products 22

Regiochemical Outcome of Electrophilic Substitution of Pyridinium Ions

**E E**



**N**



**N**



**E**

**H H H**



**N**

**E E E**

+



**E**

**N**

**E**

**H**





**E E**

**N H N H**

**E E**



**E H**

**N E**

**E H E H**



+ +

**N**



**N N**

**E E**

* Regiochemical control is even more pronounced in the case of pyridinium ions
* In both pyridine and pyridinium systems,  substitution is favoured but the reaction is slower than that of benzene

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* Reaction will usually proceed through the small amount of the free pyridine available

*N* Substitution





**NO2 BF4**



**MeI**

**BF4**

**N O N**

**NO2**



**R Cl**

**N**

**Me**

**SO3,**

**CH2Cl2**



**N Cl**

**N SO3**

**O R**

*C* Substitution

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

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Nitration of Pyridine

Use of Activating Groups

**Me**

**N**

**c-H2SO4, c-HNO3 300 °C, 24 h**

**N**

**Me**



**c-HNO3, oleum 100 °C**

**Me**

**N**

**N 6% !**

**NO2**

**Me**

**N**

**NO2**

**Me Me**

**Me**

**Me N Me**

**H**

**Me**

**Me N**

**I Me**

**Me Me**

**c-HNO3, oleum 100 °C**



**MeI**



**Me Me**

**90%**

**Me**

**N**

**I Me**

**Me**

**NO2**

**Me 70%**

* 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 25

Sulfonation of Pyridine

**N HgSO4, H2SO4,**



**220 °C**

**H2SO4, SO3**

**(low yield)**

**N**

**70%**

**SO3H**

**N HgSO3**

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

Halogenation of Pyridine

**Cl**

**N 33%**

**Cl2, AlCl3, 100 °C**

**N**

**Br2, oleum 130 °C**

**Br**

**N 86%**

* Forcing reaction conditions are required for direct halogenation

# Pyridines – Reduction

Full or Partial Reduction of Pyridines

**R**

**H2, Pt,**

**AcOH, rt**

**N H**

**R R**

**Na**-**NH3, EtOH**

**N N**

**H**

**Na, EtOH**

**R**

**N H**

* 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

Regiochemical Outcome of Nucleophilic Addition to Pyridines

**H H**

**Nu Nu**



**H**

**Nu**

**N**





**N**



**N**

**N**

**Nu**

**H H**

**Nu**





**H**



**N**

**Nu Nu Nu**

**N N N**

**Nu H Nu H**



**Nu H**

**N**

**Nu**





**N**

**N N**

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

Nucleophilic Substitution

**X Nu**

**Nu**

**N N X**

**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 ( >  >> )

**Cl**

**NaOEt**

**OEt**

**N N**

**Cl Cl**

**Cl**

**N**

**N**

**NO2**

**Cl N**

Relative rate 80 40 1 3 × 104 29

**X Nu**



**Nu**

**N N X**

**R X** = **Cl**, **Br**, **I**, (**NO2**) **R**

**Nu** = **MeO** , **NH3**, **PhSH** etc.

* Conversion of a pyridine into the pyridinium salt greatly accelerates substitution
* Substituent effects remain the same (,  >> ) but now  > 

**Cl O2N O NO2**



**O**



**N N**

**Me Me**

**Cl**



**Cl Cl**



**N**



**Cl N N N**

**Me Me Me**

30

Relative rate 5 × 107 1.5 × 104 1 104

**H**



**Cl**



**H NH2**

**NH2**

**N**

**H2N**

**NH2 N**

**NaNH2**

**N 27%**

**benzyne**



**Cl**

**H NH2**

**H2N H**

**N**



**NH2**

**NaNH**

**NH2**

**2**

**N N N**

**44%**

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

**N**

**LiNH2**

**PhLi, Et2O, 0 °C**

**Ph**

**N**

**H Li**

**O2 (air)**

**Ph**

**N**

**H2N**

**H**

**H**

**N**

**Li ** **NHX**

**H2**

**H2N N**

**HN N**



**H2O**

**LiNH2**

**Li **

**X** = **H** (**NH3**) / **2-aminopyridine**



* A hydride acceptor or oxidising agent is required to regenerate aromaticity
* The reaction with LiNH2 is referred to as the Chichibabin reaction

**X**

***n*-BuLi**

**N X** = **Cl**, **Br**, **I**

**Li**

***n*-Bu X**

**N**

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

**Br**

**N**

***n*-BuLi,**

**Li**

**PhC N**

1. **Li**

**Ph**

**Et2O,** **78 °C**

**N N**

**O**

**Ph H2O**

**NH**

**Ph**

**N N** 33

**OMe**

**O**

***t*-BuLi,**

**Et2O,** **78 °C**

**N**

**Me**

**O**

**Li**

**O**

**I(CH2)2Cl**

**N**

**I**

**O**

**N 90%**

**OMe**

**O Li O**

**N*i*-Pr2 LiTMP,** **78 °C**

1. **Ph**

**O**

**N*i*-Pr2**

**O**

**Me**

**Me**

**N**

**Li LiTMP**

**Me**

**Me**

**N*i*-Pr2**

**N N N**

**Ph NMe2**

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

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Oxy-Pyridines/Pyridones





**N**

**O**

**N OH**

**H**

**OH**



**O**



**N N**

**H**

**N O**

**H**



zwitterion



**O**

**N H**

zwitterion

1,3-dipole

**O**



**N H**

**OH O O O**



**O**



**N**



**N N N N**

**H H H H**

zwitterion

* Subject to tautomerism
* The ,  systems differ from the  systems in terms of reactivity and structure
* In the  case, the equilibrium is highly solvent dependent, but the keto form is favoured

in polar solvents 35

Amino Pyridine Systems

**N NH**

**H**

**N NH2**

**N NH2**

etc.

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

Electrophilic Substitution

**Br**

**N**

**OH OH**

**Br2, H2O, rt**

**N Br Br**

**O**

**c-H2SO4, c-HNO3**

**100 °C, 2 days**

**N H**

**O**

**N H**

**38%**

**NO2**

* 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)

Nucleophilic Substitution



**N**

**O**

**H**

**Cl PCl4**



**PCl5**



**N**

**Cl**

**O**

**H PCl3**

**Cl**

**Cl PCl3**

**O**

**N**

**Cl**

**H**

**Cl**

**N**

**H Cl**

**O PCl3**

**Cl**

**PCl3**



**N O**

**Cl**

**H**

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

Cycloaddition

**Me O**

**N**

**Me**

**Me**

**CO2Me**

**CO2Me**



**O**

**Me**

**Me**

**N**

**CO2Me**

**CO2Me**

* 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

**CH3 CH**



**CH2**

**PhLi**

**N N**

etc.

**N**

**O**

**R1 R2**

**OH**

**R2**

**R1**

**N**

* Deprotonation of  and  alkyl groups proceeds at a similar rate, but  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

**H BH3**



**N**

**NaBH4, Me EtOH**

**N**

**Me H BH3 Me**



**N**

**N**

**Me H BH3**

**N N**



**N**

**H Me**

**Me H3B Me**

* 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

**O2N**



**N**

**OH**

**O2N**

**N O**

**OH O2N**



**H**

**O**

etc.

**N**

**NO2**

**NO2**

41

**NO2**

*N*-Oxide Formation

**RCO3H**

**N N N N**

**O O O O**

**Cl O**

**O H**

***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

42

Electrophilic Substitution

**H NO2**



**H NO2**



**NO2**

**c-H2SO4, c-HNO3,**

**N 100 °C N N N**

**O**



**O**



**O**

**O**

* The *N*-oxide is activated to attack by electrophiles at both the  and  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*

**NO2**

**NO2**

**N**

**NO2**

**PPh3**

**N**

**PPh3**

**O**

**O**

**PPh3**



**N**

**O PPh3**

* Deoxgenation is driven by the formation of the very strong P=O bond 43

# Pyridines – Synthesis of a Natural Product

Synthesis of Pyridoxine (Vitamin B6) Using the Guareschi Synthesis

**EtO CN EtO EtO**

**O**

**CN O2N CN**

**O H2N O c-HNO3, Ac2O, 0 °C**

**piperidine,**

**Me EtOH, heat Me**

**N O**

**H**

**90%**

**Me N O H**

**32%**

**PCl5, POCl3, 150 °C**

**H2N**

**HO**

**OH**

**HO**

1. **NaNO2, HCl, 90 °C**
2. **48% HBr (neat)**

**EtO**

**NH2**

**O2N**

**H2, Pd/Pt, AcOH**

**EtO**

**CN**

**Me N**

1. **AgCl, H2O, heat Me**

**N 40%**

**Me N Cl 40%**

* 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

44

# Bioactive Quinolines/Isoquinolines

**H**



**HO**

**N**

**H**

**N**

**NEt2**

**Me**

**MeO**

**HN**

**MeO**

**N**

**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

**MeO**

**N**

**MeO**

**OMe**

**papaverine**

**OMe**

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

# Drugs Containing a Quinoline/Isoquinoline

**Cl N**

**S CO2H**

**Ph**



**CO2Et**

**N H**

**HO2C**

**N**

**O**

Name: Singulair

2008 Sales: $2.90 billion **HO** 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

**N**

**HN OH**

**N**

**Cl**

Name: Hydroxychloroquine 2008 Sales: $74 million 2008 Ranking: 146 generic

Company: N/A 46

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

47

*Plasmodium* monocyte

Structure

**N**

**N**

* 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”)

**MeO**

**NH2**

**O O**

**Me Me**

**H2O**

**MeO Me**

**Me**

**O**

**N**

**MeO Me**

**O**

**N Me**

**H**

**MeO**

**MeO Me**

**N**

**MeO**

**MeO Me OH**



**MeO**

**MeO H**



**c-H2SO4,**

**Me**

**O**

**MeO**

**23%**

**H2O**

**Me**

**MeO**

**N Me**

**H**

**MeO**

**N Me**

**H**

48

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

**NH2**

**Me**

**O O**

**rt,** **H2O**

**OEt**

**OEt**

**O**

**N H**

**OH O**

**270 °C**

**70% N**

**Me**

**N**

**Me Me**

**H**

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

**O O Me Me Me**

**N**

**N**

**O**

**O**

**250 °C,** **H2O**

**N**

**O**

**140 °C,** **H2O H2**

**Me**

**N**

**OEt**

**H**

**OH**

**50% H**

49

Skraup Synthesis (“3+3”)



**OH**

**H**

**130 °C, H2SO4**

**H**



**H**

**H**

**O**

**N**

**O**

**N**

**NH2 H H**

**H OH**



1. **(e.g. I2)** **H2O**

**N**

**N**

**N**

**85% H H**

* 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
  1. **O Me**

**65% N**

**Me Me**

**Me**

**NH2**

**ZnCl2 or FeCl3,**

**EtOH, reflux** 50

**2. [O]**

Friedlander Synthesis (“4+2”)

**Ph O**

**NH2**

**Me**

**O Me**

**Ph**

**H**



**O Me**

**Ph**

**Me**

**88%**

**N**

**H2O**

**c-H2SO4, AcOH**

**heat**

**N Me Me**

**H**

**Ph O Ph Me**

**NH2**



**O**

**N**

**OH**

**H**

**Me**

**O Me**

**Ph**

**H2O**

**KOH aq., EtOH 0 °C**

**71%N**

**Me**

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

Pomeranz-Fritsch Synthesis (“3+3”)

**EtO OEt**

**OEt**

**H2N**

**O**

**H2O**

**OEt**

**N**

**H , EtOH**

**H**

**N**

Bischler-Napieralski Synthesis (“5+1”)

**NH**

**O**

**N**

**N**

**MeCOCl**

**NH2**

**P4O10, heat**

**Pd-C, 190 °C**

**Me Me**

* Cyclisation can be accomplished using POCl3 or PCl5

**Me**

**93%**

* Oxidation of the dihydroisoquinoline can be performed using a mild oxidant

Pictet Spengler Synthesis (“5+1”)

**N**



**MeO**

**MeO HCHO 20% aq.**

**20% HCl aq.**

**MeO**

**MeO**

**N**

**NH2**

**heat**

**[O]**

**MeO**

**100 °C N**

**H**

**80% H**

**NH**



**MeO**

**NH**

* 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

Regiochemistry **\***

**N**



**N**

**H**

 **H **  

**\***

* 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

**NO2**

**fuming HNO3, cH2SO4, 0 °C**

**N**

**72%**

**N**

**NO2**

**N**

**8%**

* In the case of quinoline, equal amounts of the 5- and 8-isomer are produced 54

Sulfonation

**N**

**30% oleum3,**

**N**

**90 °C**

**>250 °C**

**HO3S**

**SO3H 54%** thermodynamic product

**N**

* 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

55

Regiochemistry



**N**



**N**

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

**N**

**2-MeOC6H4Li**

**Et2O, rt**

**H OMe**

**H2O**

**H OMe**

**N**

**Li**

**N H**

**[O]**

56

**N**

**MeO**

***n*-BuLi**

**N benzene, rt**

**H *n*-Bu**

**H2O**

**Li**

**N**

**H *n*-Bu**

**[O]**

**NH**

**N**

***n*-Bu**

* Oxidation is required to regenerate aromaticity

Amination

**H NH2**

**N**

**KNH2, NH3 (l)**

**N**



**65 °C**

**N K**

**KMnO4,** **65 °C**

**H NH2**

>**45 °C**

**K**



**KMnO4,** **40 °C NH2**

**NH2**

**50%**

**N**

**N**

**60%**

thermodynamic product 57

Displacement of Halogen

**NaOEt, EtOH**

**N**

**reflux**

**Cl**

**OEt**

**N**

**Cl**

**N**



**N**

**Cl**

**OEt**

**NaOMe, MeOH DMSO 100 °C**

**OMe**

**87%**



**Cl**

**N**

**N**

**OMe**

**PhCOCl**

**N**



**N**

**CN**

**O Ph**

**KCN**

**H CN**

**N**

**O Ph**

**base, MeI**

**NaOH aq.**

**N**

**N**

**M**

**CN**

**HO**

**Ph**

**O**

**e Me**

**Me N**

**CN**

**O Ph**

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

Synthesis of Papaverine

**O**

**MeO**

**O**

**MeO**

**O**

**MeO**

**MeO**

**Me Me2CH(CH2)2ONO,**

**NaOEt, EtOH, rt**

**MeO**

**75%**

**ZnCl2, HCl, rt**

**N**

**OH**

**MeO**

**NH2**

**O Cl**

**KOH aq., rt**

**MeO**

**MeO**

**P4H10,**

1. **xylene, heat**

**MeO**

**MeO**

**H OH**

1. **NH**

**MeO Na-Hg, H2O, 50 °C**

**MeO**

**O**

**O NH**

**OMe**

**OMe**

**30% 60%**

**MeO**

**OMe**

**MeO**

**OMe**

**MeO**

**OMe**

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

**Me2N**

**S**

**O**

**ranitidine**

**NO2**

**NHMe**

**N**

**H**

* 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

**CO2H**

**O**

**N**

**Ph**

**ketorolac**

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

**Me**

**S**

**N**

**N**

**banminth**

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

**MeO2C Cl**

**N**

**S**

**O2N O**

**O**

**N N NH**

Name: Plavix

2008 Sales: $3.80 billion

Name: Nitrofurantoin **O**

2008 Sales: $92 + 72 million

2008 Ranking: 3 branded Company: Bristol-Myers Squibb

Disease: Stroke and heart attack risk

2008 Ranking: 119 and 149 generic Company: N/A

Disease: Antibiotic for urinary tract infections

**F**



**HO2C**

**N H**

**S**

**O**

**HO**

**HO**

**Ph**

**N**

**NHPh**

Name: Cymbalta

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

Name: Lipitor **O**

2008 Sales: $5.88 billion 2008 Ranking: 1 branded

Company: Pfizer 62

Disease: Lowers LDL levels

# Furans, Pyrroles and Thiophenes – Structure

Structure





**X O N S**

**.. H**

* 6  electrons, planar, aromatic, isoelectronic with cyclopentadienyl anion

Resonance Structures

etc.



**X**

**..**



 

 

**X X X**

  +

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

1.44 Å

Å

1.35 Å

0.71 D

1.43 Å

1.37 Å

1.55 D

1.42 Å

1.37 Å

0.52 D

* 1. **O**
  2. Å **N**

**H**

1.71 Å **S**

1.68 D

**O**

1.57 D

**N H**

1.87 D

**S**

63

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

Paal Knorr Synthesis

**R1 R2**

**O O**

**R1 R2**

**O O**

**H H**

**R1 O R2 OH**

**H**



**H heat**



**H**

**H**

**O**

**R1 O R2**

**R1 R2**

**R1 R2**

* The reaction is usually reversible and can be used to convert furans into 1,4-diketones



**O OH2**

* A trace of acid is required – usually TsOH (*p*-MeC6H4SO3H)

Feist-Benary Synthesis (“3+2”)

+

+



**Me O**

**Cl**

**O**

**EtO2C**

**O Me**

**EtO2C**

**O Me**

**EtO2C**

**Me O Cl Me O Cl Me**

**NaOH aq., rt**

**OH Me OH**

**EtO2C Me**

**Me O**

**H2O**

**EtO C Me**

**OH**

**2**

**Me O**

**H**

**EtO2C Cl**

**Me O**

isolable

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

Modified Feist-Benary

**EtO2C O**

+ **Me**

+

**Cl**

**I**

**Me O**

**EtO2C**

**Me**

**I**

**O**

**O**

**Me EtO2C Me**

**Me**

**O**

**O**

**NaI, NaOEt, EtOH**

**EtO2C**

**Me O**

**H2O**

**Me**

**EtO2C**

**Me**

**Me O OH**

**EtO**

**EtO2C Me**



**H**

**O**

**O**

**Me**

* 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

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

**Me**

**Me Ph**

**O O**

**Me**

**Me Ph**

**P4S10 S O**

**Me**

**Me**

**Me S Ph**

**Me Ph**

**O S**

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

Paal Knorr Synthesis (“4+1”)



**O H2N**

**Me Me**

**O O**

**NH3, C6H6,**

**heat**

**Me Me**

**O HN**



**H**

**H**

**Me Me**

**Me N Me H**

**R1 N R2 H**

**R1 R2**

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



**N OH H**

Knorr Pyrrole Synthesis (“3+2”)

**EtO2C**

**O Me**

**KOH aq.**

**EtO2C Me**

**MeO2C**

**O NH2**

**HO2C**

**N H**

**53%**

**H2N**

**O Me**

**Me N**

**Me O NH2**

**N Me**

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

**EtO2C**

**O Me**

**EtO2C**

**HO Me**

**Me**

**EtO2C**

**EtO2C**

**O Me**

**EtO2C O**

**NH3**

**NaOH aq.**

**Cl**

**EtO2C N H**

via

**EtO2C**

or

**NH2**

**O**

**EtO2C N H**

* 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 69

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

**EtO2C**

**O Me**

**Zn, AcOH**

**or Na2S2O4 aq.**

**EtO2C Me**

**Me**

**Me O N OH**

**(sodium dithionite) N H**

Preparation of -Keto Oximes from -Dicarbonyl Compounds

**H**



**O**

**O**

**O O**

**OEt**

**NaNO2, H (HNO2)**

**H2O N O**



**OEt**

**O O O O**



**H**

**N**

**O**

**OEt**

**N**

**OH**

**OEt**

70

One-Pot Oxime Reduction and Pyrrole Formation

**O**

**O O**

**EtO2C CO2Et**

**CO2Et**

**OEt**

**N**

**OH**

**Zn, AcOH**

**EtO2C N H**

**CO2Et**

Hantzsch Synthesis of Pyrroles (“3+2”) **Cl**



**H**

+

+

**EtO2C O Me**



**Me O Cl NH3 aq.**

**EtO2C**

**Me**

**Me**

**O**

**NH2**

**EtO2C Me**

**O**

**Me NH**

**rt to 60 °C EtO2C**

**Me**

**N Me**

**H 41%**

**H2O**

**EtO2C**

**Me**

**Me N OH H**

**EtO2C**

**Me**

**Me**

**O NH2**

* A modified version of the Feist-Benary synthesis and using the same starting materials:

an -halo carbonyl compound and a -keto ester 71

# Electrophilic Substitution

Electrophilic Substitution – Regioselectivity



**X E**



 **E E**



**X**

**H**



**X H**



**E**

**H**

**X**



**E**

**H**

**H**



**E**



**H**

**E**

**X H X E E**

**X X X**

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

**NO2**

**AcONO2**

**X**

**X NO2 X** 72

**X = NH X = O**

**4:1**

**6:1**

Nitration of Furans



**AcONO2,**



**<0 °C**

**NO2**

**AcO**



**NO2**

**O (Ac2O, HNO3) O H**

**H O H N**

**NO2 AcO**

isolable

**pyridine, heat**

**AcOH**

**NO2**



**O**

**H**

* Nitration can occur by an addition-elimination process

**O NO2**

* When NO2BF4 is used as a nitrating agent, the reaction follows usual mechanism

Bromination of Furans



**O**

**Br2, dioxan, 0 °C**

**Br**

**O**

**Br**

**H**



**Br Br**

**H**



**Br**

**HBr**

**Br**

**O H**

**O Br**

**80%**

* Furan reacts vigorously with Br2 or Cl2 at room temp. to give polyhalogenated products

73

* It is possible to obtain 2-bromofuran by careful control of temperature

Friedel-Crafts Acylation of Furan

**Ac2O, SnCl4,**

**O**

**O**

**O**

**Me**

**Ac2O, SnCl4,**

**H PO cat., 20 °C 150 °C**

**3 4**

**O**

**:** **6800:1 Me**

**Me O Me**

**Me O Me**

**77%**

* Blocking groups at the  positions and high temperatures required to give  acylation

Vilsmeier Formylation of Furan

**Me**

**O**

Mannich Reaction of Furans

**Me2NCO, POCl3, 0 to 100 °C**

**Me**

**76% H**



**O**

**H**

**O**

**O**

**CH2O, Me2NH.HCl**

**O**

**O CH2 NMe2**



**NMe2**

**66%**

**O**

**NMe2**

Nitration of Thiophenes

**S**

**AcONO2**

**S NO2**

**NO2**

**S**

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

Halogenation of Thiophenes

**Br2, Et2O, Br2, Et2O,**

**48% HBr, 48% HBr,**

**Br S Br**

**10**  **10 °C**

**S** **25**  **5 °C**

**S Br**

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

Nitration of Pyrroles

**AcONO2 AcOH,** **10 °C**

**N H**

**N NO2 N**

**H H**

**NO2**

**51% 13%**

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

Vilsmeier Formylation of Pyrroles



**Me O**

**N**

**POCl3**

**Me OPCl2 N**

**Me Cl**

**N**



**Me H**

**Me H**

**Me H**

**H H**



**N H**

**Cl**

**Me**

**N**

**Cl**

**N N**

**K2CO3 aq.**

**H**

**N**

**H Me**

**H NMe2**

**H NMe2**

**H O**

**83%**

**R2**



**OH**

**N**

**R1**

**H H R1**

**OH R2**

**N**

**H R1**

**OH2 R2**

**R2**



**N**



**H**

**N H**

**R1**

**R2**

**N H**

**N H**

**R1**

**R2**

**N H**

**N**

**H 1 N H**



**R1, R2 = H**

**NH**

**HN**

**NH**

**HN**

**NH**

**HN**

**NH**

**HN**

**NH**

**N**

**N**

**HN**

**R**

no extended aromaticity 18 -electron system

* The extended aromatic 18 -electron system is more stable than that having four

isolated aromatic pyrroles 77

**HO2C**

**N**

**N**

**Fe**

**N**

**N**

**CO2H**

**N N**

**Mg**

**N N N**

**H2N H**

**HO2C CO2H**

**porphobilinogen**

**MeO2C O**

**O**

**O**

**haem**

**C20H39**

**chlorophyll-*a***

* 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

Metallation

# Deprotonation

***n*-BuLi**



**X**

**H**



**X**

**Li**

**Bu**

**X = O pK***a* **(THF) 35.6**

**>>**

**X = NR**

**pK***a* **(THF)**

**39.5**

**X = S**

**pK***a* **(THF) 33.0**

Deprotonation of Pyrroles

**R M**



**N**



**M**

**N H N N M**

**pK***a* **(THF) 39.5**

**H**

**pK***a* **(THF) 17.5 M**

* 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

# Directed Metallation

Control of Regioselectivity in Deprotonation

**Y**

***n*-BuLi**

**X**

**Y Li**

**Bu**



**Y**

**Li**

**X**

**X H**

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

Synthesis of ,’-Disubstituted Systems

**Y**

***n*-BuLi**



**E1**

**X X**

**Y**

***n*-BuLi**



**E2**

**E1**

**Y**

**E E1**

**2**

**X**

Use of a Trialkylsilyl Blocking Group

**Y**

***n*-BuLi**

**Y Y Y**

***n*-BuLi F**



**E**

**Me3SiCl**

**X**

**X SiMe3**

**E X SiMe3**

**E**

**X** 80

Preparation of Ranitidine (Zantac®) Using a Mannich Reaction

**O**

**O**

**furfural**

**Me2NH.HCl,**

**CH2O, rt**

**O**

**OH**

**Me2N**

**O**

**OH**

**NO2**

**HS(CH2)2NH2,**

**c-HCl, heat**

**Me2N**

**S**

**O**

**ranitidine**

**NO2**

**NHMe**

**N**

**H**

**MeS NHMe**

**Me2N**

**O**

**S**

**NH2**

* 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 ,-unsaturated nitro

compound and then elimination of methane thiol 81

**O**



**H**

**Me**

**N**

**H**

**N**

**CO2H**

**NH2**

**N**

**H**

**X**

**NMe2**

**O O**

**S**

**N**

**MeNH**

**H H X = OH lysergic acid H**

**tryptophan**

**sumatriptan**

**X = NEt2**

***l*y*s*ergic acid *d*iethyamide (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

**HO NH2**

**N**

**H**

**5-hydroxytryptamine (serotonin)** 82

# Indoles – Lysergic Acid

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

Louvre Museum, Paris

83

# Drugs Containing an Indole

**O**

**H**

**N**

**NMe2 N**

**S**

**O O**

**N**

**N H**

**H N**

**O**

**H**

Name: Imitrex

**O**

Name: Cialis **O**

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

2008 Sales: $0.56 billion 2008 Ranking: 66 branded Company: Eli Lilly

Disease: Erectile disfunction

**NMe2**

**N**

**O O**

**S**

**N**

**N**

**N N**

**N**

**H**

Name: Maxalt

2008 Sales: $0.22 billion 2008 Ranking: 148 branded Company: Merck

Disease: Migraine

**Ph**

**H**

Name: Relpax

2008 Sales: $0.21 billion 2008 Ranking: 151 branded

Company: Pfizer 84

Disease: Migraine

Fischer Synthesis

**O**

**R1**

**R1 R1**

**R2 H or**

**N**

**NH2**

**N H**

**R2**

**H2O**

**Ph**



**N**

**76%**

**H**

**H**

**H**

**N**

**H**

**NH**

**Lewis acid**

**N** **NH3**

**N H**

**R2**

**H**

**ZnCl2, 170 °C**

**Ph**

**N**

**N H**

**Ph**

**NH**

**N**

**Ph**

**3**

**H**

**Ph**



**N**

**NH2**

**[3,3]**

**H**

**H**

**Ph**



**NH2**

**NH**

**H**

**Ph**

**NH2 NH2**



85

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

Bischler Synthesis

**H Me**

**N**



**O**

**N**

**O**

**N**

**O CF3**

**Me**

**polyphosphoric acid (PPA), 120 °C**

**Me**

**O CF3**

**H2O**

**KOH aq.**

**64% H**

* An -arylaminoketone is cyclised under acidic conditions
* The reaction also works with acetals of aldehydes

**Me EtO**

**N**

**O**

**CF3**

**OEt**

**Me**

**(CF3CO)2O,**

**CF3CO2H, heat**

**93% O**

**CF3**

86

**N**

Nitration of Indoles

**O2N**

**N**

**Me**

**c-H2SO4, c-HNO3**

**0 °C**

**PhCO2NO2, 0 °C**

**Me**

**N**

**NO2**

**Me**

**N**

**84% H H 35% H**

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

Acylation of Indoles

**O**

**O**

**M**

**Ac2O, AcOH, heat**

**N**

**-product!**

**Me**

**O**

**Ac2O, AcOH, heat**

**N**

**O**

**N**

**e Me**

**NaOH aq., rt**

**N**

**H 60% H**

**Ac2O, AcONa**

**Me** 87

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

Mannich Reaction

**NMe2**



**CH2O, Me2NH,**

**H2O, heat 93%**

**N**

**H**

**H2O, 0 °C**

**N**

**or AcOH, rt 68%**

**NMe2**

**N**

**H**

**H2C NMe2**

**(preformed) 95%**

* 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

**NMe2 EtO2C CO2Et**

**N**



**Na NHAc**

**EtO2C**

**CO2Et NHAc**

**NaOH aq. then**

**CO2H**

**NH2**

**N**

**PhMe, heat**

**H**

**N**

**90% H**

**H2SO4, heat**

**80% H** 88

Synthesis of Other 3-Substituted Indoles from Gramine



**CN CN**

**NaCN aq., 70 °C**

**H2O H**



**MeSO4**

**NMe3**

**N**

**N**

**H2O H**

**100% H**

**N**

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

**NH2**

**N**

**CN**

**LiAlH4 acid/base hydrolysis**

**N**

**N**

**CO2H**

**H H H**

89

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

**O O O O**

**N**

**NHNH2**

**H2O**

**ZnCl2, heat**

**NH**

**N H**

**H**

**N**

**N**

**Me MeI, K CO**

**N Me**

**O**

**N**

**N**

**H**

**Me**



**Me3N I**

**O**

**N**

**Me**

**2 3**

**O**

**N**

**Me2NH.HCl, CH2O**

**then MeI**

**Me**

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

elimination of the ammonium salt 90

**MeO**

**N**

**O**

**N**

***O*-methylhalfordinol**

**H2N**

**HO**

**vitamin B1 (thiamin)**

**MeHN**

**N**



**N**

**Me**

**N**

**N**

**S**

**Me**

**H N**

**S**

**CN N**

**Me N**

**H**

**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 H2-receptor antagonist which reduces acid secretion in the stomach and is used to treat peptic ulcers and heartburn

91

**H N**



Name: Mirapex

**S**

**NH2**

**N**

**NO2**

**N H**

**S N**

**N**

**N N**

**N**

Name: Azathioprine

2008 Sales: $0.34 billion 2008 Ranking: 108 branded

Company: Boehringer Ingelheim Disease: Parkinson's disease

2008 Sales: $53 million 2008 Ranking: 178 generic Company: N/A

Disease: Kidney transplant rejection

**Cl**

**S N**

**N Ph S**

**N H**

**O O**

**H N**

**N N O**

**H**

**O OH**

**Ph**

**N**

**OH**

1. **N NH**

**N N**

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 92

Disease: Hypertension

The Hantzsch Synthesis (“3+2”)

**Me Me H**

**O**

**NH2**

**S**

+ **Me**

**C6H6, heat**

+

**Cl**



**ONH2**



**N**

**S**

**HO**

**Me S Me Me**

**Me**

**N**

**S Me**

**43%**

**H2O**

**Me**

**HO N**

**S Me**

* 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

93

Cyclodehydration of -acylaminocarbonyl compounds

**H H**



**H**

**H N**

**Ph**

**H2O**

**O**



**N**

**O O**

**N c-H2SO4, rt** **H2O**

**Ph**

**N**

**Ph Ph**

1. **O**

**Ph Ph**

**H**

**Ph O Ph 72%**

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

From Isocyanides



**Ts Ts**



**H Ts**



**Me**

**N**

**H N**

**C**

**H**

**K2CO3, MeOH**

**Me**

**H**

**N C**

**N**

**H N Me**

**H N Me**

**N**

**N**

***t*-Bu**

**Ts = O2S**

***t*-Bu**

**Me**

***t*-Bu**

***t*-Bu**

**94%**

* *Tos*yl*m*ethyl*i*so*c*yanide (TOSMIC) is a readily available isocyanide
* Route can be adapted to give oxazoles and thiazoles using an acid chloride or a thiocarbonyl compound 94

Nitration

**N**

**N H**

**c-HNO3,**

**1% oleum, rt**

**O2N**

**N**

**N H**

**90%**

**S Me**

**N2O4/BF3**

**rt**  **70 °C**

**O2N**

**O2N**

+

**N**

**N**

**S Me**

**59%**

**S Me**

**27%**

* Imidazoles are much more reactive to nitration than thiazoles (activation helps)

**N**

* Imidazoles usually nitrate at the 4-position and thiazoles tend to react at the 5-position
* Oxazoles do not generally undergo nitration

Halogenation

**N**

**N H**

**Br2, AcOH,**

**NaOAc, rt**

**Br**

**Br N Br H**

**N**

**78%**

**Na2SO3 aq., heat**

**Br**

**N H**

**N**

**58%**

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

Acylation

**O O O**



**Ph**

**N**



**Ph**

**N**



**Ph**

**N**

**N**

**PhCOCl, Et3N,**

**N**

**MeCN, rt**

**N N**

**Me Me**

**N**

**Me Me**

**H2O**

**Ph**

**O**

**Ph**

**Me O**

**N**

**N**

**71%**

* 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

Displacement of Halogen

**S Cl**

**N**

**PhSNa, MeOH, rt**

**S SPh**

**N**

**75%**

* 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

***n*-Pr**

**N**

**O**

***n*-Pr**

**PhNHMe,**

**xylene, 155 °C**

**Cl**

***n*-Pr**

**Ph**

**N**

***n*-Pr O N**

**96% Me**

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

Direct Deprotonation **1.**

***n*-BuLi, THF,** **78 °C**

**N**

**N**

**then ZnCl2**

**N SO2NMe2**

**N ZnCl SO2NMe2**

**N Br**

**Pd(PPh3)4**

* 1. **acid aq.**

**90%**

**N**

**N**

**N H**

* 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 **OH**

**Ph**

**Br**

**N**

**Ph**

**N**

* + 1. ***t*-BuLi (2 equiv.)**
    2. **Ph2CO**

**N N**

**H H**

**64%**

* 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 98

**O**

**NH**

**CF3**

**N Me**

**Me O**

**leflunomide**

**CF3**

**celecoxib**

**N**

**N**

**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-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

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

**Me Me**

**OEt**

**Me O**

**O NH2**

**H N**

**H2NNH2,**

**NaOH aq., rt Me N N**

**H**

**EtO**

**OEt**

**HO**

**OEt NH2**

**H2NOH.HCl**

**H2O, heat O**

**N**

**2 75%**

**84%**

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

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

**EtO2C**

**Me**

**EtCNO**

**Et**

**EtO C**



**2**

**C**

**N**

**Me**

**O**

**H Et**

**EtO2C Et**

**Me N**

**O**

**70%**

**N**

**N**

* Nitrile oxides react readily with alkenes and alkynes



**EtO2C**

**Me**

**N**

**N**

**O**

* Addition to an alkene generates an isoxazoline unless a leaving group is present

**Cl Ph**

**N**

**HO**

**Ph**

**Et3N, Et2O, rt PhCCH**



**N**

**O**

**Ph**

**Ph**

**O 76%**

**Ph**

**N**

* 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

Nitration of Isoxazoles, Pyrazoles and Isothiazoles

**O2N**

**c-HNO3, Ac2O,**

**N AcOH, rt**

**N H**

**c-H2SO4, 0 °C**

**N NO N**

**2**

**N N**

**H**

**70%**

* Pyrazoles and isothiazoles undergo straightforward nitration

**80%**

* 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

**Me**

**N**

**f-H2SO4, c-HNO3,**

**O 0**  **70 °C**

**O2N**

**Me**

**O 40%**

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

**N**

Halogenation of Isoxazoles, Pyrazoles and Isothiazoles



**H Br**

**N**

**N H**

**Br**

**Br Br**



**N**

**N H**

**Br**

**Br2, NaOAc**

**N**

**N H**

* 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

**Me**

**Cl**

**N**

**N**

**O**

**P Me**

**h**

**Cl**

**N**

**PhCOCl, AlCl3, N**

**O**

**H**

**Me2NCHO, POCl3,**

**95 °C**

**Me Me**

**N 95 °C then H 2O N N N**

**Me Me**

**33%**

• Only *N*-substituted pyrazoles can be *C*-acylated directly

• Vilsmeier formylation produces the 4-formylpyrazole in modest yield

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Direct Metallation of Isoxazoles, Pyrazoles and Isothiazoles

***n*-BuLi, MeI**

**N N**

**N Me N**

**Ph**

***n*-BuLi, THF,**

**N**

**S**

**78 °C then CO 2**

**Ph**

**HO2C**

**N**

**S**

**Ph Ph**

**88%**

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

**N**

**H**

**N CH2O, EtOH, heat**

**1. *n*-BuLi, THF,**

**78 °C**

**O**

**N 2. PhNCO N**

**N N 3. HCl aq.**

**H**

**PhNH**

**N**

**N H**

**79%**

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

Direct Metallation of 4-Bromopyrazoles

**Br Br**

***n*-BuLi, Et2O,**

**Br**

**CO2**

**N** **78 °C N**

**N Li N**

**HO C N**

**N**

**2**

**SO2Ph**

**SO2Ph**

**SO2Ph 65%**

• 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

**S**

**H OH**

**Br Li**

***n*-BuLi, THF, O S**

**N** **78 °C N**

**N N**

**H**

**Li**

**N**

**N**

**39% H**

• Treatment of 4-bromopyrazole with two equivalents on *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

**3-O2NC6H4CHO,**

**Me**

**N**

**Ac2O, piperidine**

**S 150 °C**

**O2N**

**42%**

**N**

**S**

• 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

**Me**

**N**

**Me O**

***n*-BuLi, THF,**

**78 °C**

**Me Me**

**CH2CHCH2Br**

**N**

**O**

**N**

**O**

**Li 80%**

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

**Me**

**Me**

**N**

**Br2**

**O**

**Br Me**

**O**

**Me**

**N**

1. ***n*-BuLi, THF,**

**78 °C**

1. **CO2**
2. **HCl aq.**

**HO2C Me**

**O**

**Me**

**N**

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# 1,2-Azoles – Synthesis of a Drug Me

Synthesis of Celecoxib (Celebrex®, Pfizer)

**N**

**N**

**CF3**

**N**

**CF3**

**Me O**

**Me**

**O NH2NH2**

+ **F3C N**

**SO2NH2**

**celecoxib**

**SO2NH2**

**SO2NH2**

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

**Me**



**N**

**F3C OSO2Ph**

**CF3**

**CF3**

**N**

**N**

**N N**

**N**

**HN**

**Me**

**Et3N, THF, EtOAc O**

**5**  **10 °C**

**SO2NH2**

**SO2NH2**

**72%**

**SO2NH2**

107

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