

S CHEM 341

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Aromatic Six-Membered Pyridine

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Bioactive Pyridines



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

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Bioactive Pyridines





- 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

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

- · 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



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General Strategies for Heterocycle Synthesis

Common Strategies



· 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

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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

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Pyridines - Synthesis

From Enamines or Enamine Equivalents - the Guareschi synthesis (*3+3")



• The b-cyano amide can exist in the 'enol' form

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Pyridines - Synthesis

Using Cycloaddition Reactions ("4+2")



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

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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.

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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 a / δ products.

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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, b 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.

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N Substitution



C Substitution

 \cdot 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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- 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.

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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

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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

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 is regained by loss of hydride or a leaving group, or by oxidation.

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Nucleophilic Substitution

• Favoured by electron-withdrawing substituents that are also good leaving groups.

• The position of the leaving group influences reaction rate ($\gamma > \alpha > \beta$)

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Nucleophilic Substitution

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

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Acylation at nitrogen

Acid chlorides and arylsulfonic acids react rapidly with pyridines generating 1-acyl- and 1- arylsulfonylpyridinium salts in solution.

Alkylation at nitrogen

Alkyl halides and sulfates react readily with pyridines giving quaternary pyridinium salts.

Pyridines - Pyridyne Formation

Substitution via an Intermediate Pyridyne

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

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Nucleophilic Attack with Transfer of Hydride

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

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

papaverine

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

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Drugs Containing a Quinoline/Isoquinoline

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

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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

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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

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- · 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

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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 POCI₃ or PCI₅
- 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

- 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

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

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Quinolines/Isoquinolines -Electrophilic Reactions

Sulfonation

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

Quinolines/Isoquinolines -Nucleophilic Reactions

Regiochemistry

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

Carbon Nucleophiles

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Quinolines/Isoquinolines -Nucleophilic Reactions

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

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Isoquinolines – Synthesis of a Natural Product

Synthesis of Papaverine

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

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