People's Democratic Republic of Algeria
Ministry of Higher Education & Scientific Research
University of Djelfa
Faculty of Exact Sciences and Computer Science
Department of Chemistry — UE: Fondamentale

PEDAGOGICAL DOCUMENT

HETEROCYCLIC CHEMISTRY

Master 1 — Organic Chemistry

Semester 1 | Academic Year 2025–2026

Dr. Nadji Belkheiri

Table des matières

Pedagogical Objectives

Upon successful completion of this course, the student will be able to:

1. Classify heterocyclic compounds based on ring size, number of fused rings, degree of saturation, and the nature and number of heteroatoms present in the ring.
2. Apply the IUPAC Hantzsch-Widman nomenclature system to name monocyclic, bicyclic, and polycyclic heterocycles, and distinguish this from trivial and replacement (a-) nomenclature.
3. Rationalize the aromaticity, electronic structure, and acid-base properties of five- and six-membered heterocyclic systems using resonance, frontier molecular orbital theory, and Hückel's rule.
4. Present and mechanistically justify the main synthetic pathways for the following ring systems: pyrrole, furan, thiophene, indole, oxazole, thiazole, imidazole, pyrazole, pyridine, quinoline, isoquinoline, pyrimidine, and purines.
5. Predict and explain the regioselectivity of electrophilic aromatic substitution (EAS) and nucleophilic aromatic substitution (NAS) reactions on a range of heterocyclic substrates.
6. Identify the biological, pharmaceutical, and industrial relevance of heterocyclic scaffolds in natural products, vitamins, enzyme cofactors, and clinically used drugs.
7. Compare the physicochemical properties of related heterocycles (e.g. pyrrole vs. furan vs. thiophene) in terms of aromaticity, basicity, and reactivity.
8. Solve synthesis, retrosynthesis, mechanism, and naming problems involving mono- and bicyclic heterocycles of moderate complexity.

Prerequisites

Students enrolling in this course are expected to have mastered the following topics from their Bachelor (Licence) studies in organic chemistry:

- **Aromaticity:** Hückel's 4n+2 π-electron rule; aromaticity in benzene, naphthalene, and related carbocyclic systems; anti-aromaticity and non-aromaticity. Resonance and delocalization in aromatic rings.
- **Reaction Mechanisms:** Electrophilic Aromatic Substitution (EAS): arenium ion mechanism, orienting effects of substituents; Nucleophilic Aromatic Substitution (NAS): addition-elimination (SNAr) and elimination-addition (benzyne) mechanisms.

- **Carbonyl Chemistry:** Aldol condensation, Claisen condensation, Knoevenagel condensation, Michael addition, Beckmann rearrangement, and ester/amide reactivity.
- **Pericyclic Reactions:** Diels-Alder [4+2] cycloaddition, 1,3-dipolar cycloaddition, and [3,3]-sigmatropic rearrangements (Cope, Claisen). These are central to several heterocycle syntheses.
- **Functional Group Transformations:** Oxidation/reduction, halogenation, amination, condensation, cyclodehydration, and Grignard reactions.
- **Stereochemistry:** Configuration (R/S), conformation, chirality, and stereoelectronic effects in organic reactions.
- **Spectroscopy:** Interpretation of ^{1}H NMR, ^{13}C NMR, IR, and mass spectra for structural identification of organic compounds.

Chapter 1: Classification and Nomenclature of Heterocyclic Compounds

1.1 What is a Heterocyclic Compound?

A heterocyclic compound — also referred to simply as a 'heterocycle' — is a cyclic organic molecule whose ring contains at least one atom other than carbon. These non-carbon ring atoms are called heteroatoms. The most commonly encountered heteroatoms are oxygen (O), nitrogen (N), and sulfur (S); less common but synthetically important ones include phosphorus (P), silicon (Si), selenium (Se), and boron (B). The ring may contain one or several heteroatoms, which may be identical or different.

The field of heterocyclic chemistry is arguably the largest and most dynamic branch of organic chemistry. Heterocyclic compounds appear in virtually every area of science and industry:

- More than 70% of all known organic compounds contain at least one heterocyclic ring.
- All nucleic acid bases (adenine, guanine, cytosine, thymine, uracil) are heterocycles.
- Most vitamins (B1, B2, B3, B6, B9, B12, D, E, K) contain a heterocyclic moiety.
- The majority of clinically used drugs contain at least one heterocyclic scaffold (penicillins, cephalosporins, fluoroquinolones, antivirals, antihistamines, etc.).
- Many natural pigments and dyes (heme, chlorophyll, indigo, porphyrins) are polyheterocyclic systems.

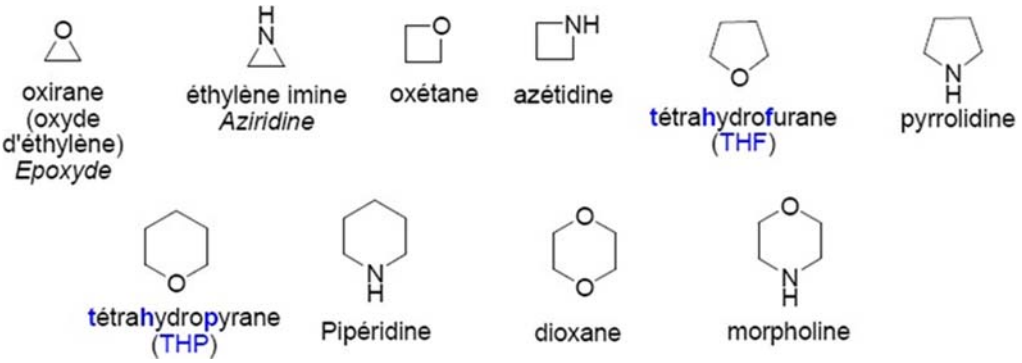


Figure 1.1. Examples of heterocyclic compounds: pyrrole, furan, thiophene, pyridine, imidazole, indole, quinoline, purine.

1.2 Classification of Heterocycles

Heterocycles are systematically classified according to three criteria, which together define the compound uniquely:

1.2.1 Nature and Number of Heteroatoms

The type of heteroatom strongly influences the electronic properties (electron-rich vs. electron-poor), the aromaticity, and the chemical reactivity. For example, replacing benzene CH with N

gives pyridine (electron-poor); inserting O or N with its lone pair into a five-membered unsaturated ring gives furan or pyrrole (electron-rich).

Table 1.1 – Heteroatoms and their electronic effects on ring systems

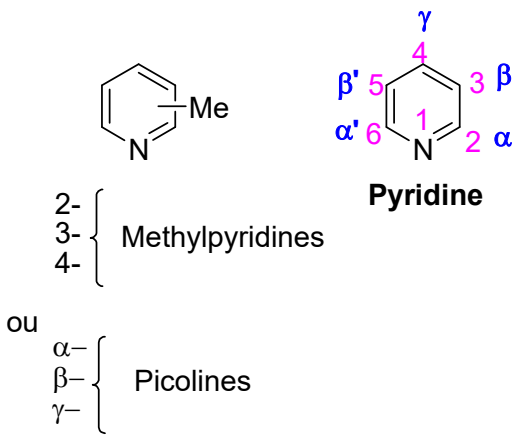
Heteroatom	Effect on Ring Electron Density
Oxygen (O)	Strong electron-withdrawing by induction; lone pair donation to ring
Nitrogen (N)	Moderate electron withdrawal (pyridine-N) or donation (pyrrole-N)
Sulfur (S)	Mild electron withdrawal; 3p lone pair overlaps well with ring π
Phosphorus (P)	Similar to N but more polarizable; rare in natural products

1.2.2 Ring Size and Degree of Fusion

Heterocycles are classified as three-, four-, five-, six-, seven-membered, etc. The most important in organic chemistry are five- and six-membered rings. They can be monocyclic (single ring), bicyclic (two fused rings, e.g., indole = benzene + pyrrole; quinoline = benzene + pyridine), or polycyclic (e.g., purines, porphyrins, acridine).

1.2.3 Degree of Saturation

Heterocycles may be aromatic (fully conjugated, satisfy Hückel's rule), partially saturated (one or more sp3 carbons), or fully saturated. Aromatic heterocycles are thermodynamically stabilized and display characteristic spectroscopic and chemical properties distinct from their non-aromatic counterparts. For example, pyridine is aromatic; piperidine (fully saturated) is not.



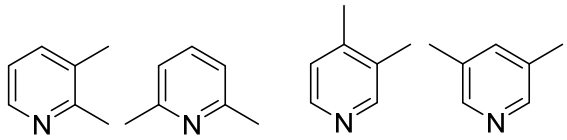


Figure 1.2. Diagram comparing: pyridine (aromatic) vs. 1,2,3,6-tetrahydropyridine (partially saturated) vs. piperidine (fully saturated).

1.3 The Hantzsch-Widman Nomenclature System

The International Union of Pure and Applied Chemistry (IUPAC) has codified the nomenclature of heterocyclic compounds in a system developed jointly by Arthur Rudolf Hantzsch and Oskar Widman. This system is applicable to monocyclic rings containing 3 to 10 atoms. The name of a heterocycle is constructed from three elements:

The three elements of a Hantzsch-Widman name:

1. PREFIX — Encodes the type, number, and positions of heteroatoms (e.g., 'oxa' for O, 'aza' for N, 'thia' for S).
2. ROOT — Indicates the total ring size (implicitly, since the suffix already encodes ring size).
3. SUFFIX (Termination) — Specifies simultaneously the ring size AND the degree of saturation.

Table 1.2 below lists the heteroatom prefixes in their priority order (O > S > Se > Te > N > P > As > Si > Ge > Sn > Pb > B). When a ring contains two or more different heteroatoms, the highest-priority atom receives position 1, and the name is constructed from the highest-priority prefix first. When two heteroatoms are identical, multiplying prefixes (di-, tri-, tetra-) are used.

Table 1.2 — Hantzsch-Widman prefixes for common heteroatoms

Heteroatom	Valence	Hantzsch-Widman Prefix	Example Compound
O (Oxygen)	2	Oxa-	Oxirane (epoxide)
S (Sulfur)	2	Thia-	Thiirane
Se (Selenium)	2	Selena-	Selenophene
Te (Tellurium)	2	Tellura-	Tellurophene

N (Nitrogen)	3	Aza-	Azetidine
P (Phosphorus)	3	Phospha-	Phosphole
As (Arsenic)	3	Arsa-	Arsole
Si (Silicon)	4	Sila-	Silole
Ge (Germanium)	4	Germa-	Germole
Sn (Tin)	4	Stanna-	Stannole
B (Boron)	3	Bora-	Borole

Table 1.3 — Suffixes for ring size and saturation:

Ring Size	Unsaturated (no N)	Unsaturated (with N)	Saturated (no N)	Saturated (with N)
3	-irene	-irine	-irane	-iridine
4	-ete	-ete	-etane	-etidine
5	-ole	-ole	-olane	-olidine
6	-ine (O,S,Se...)	□ine (N,Si...)	□ane	□ane
7	—	-epine	—	-epane
8	—	-ocine	—	-ocane
9	—	-onine	—	-onane
10	—	-ecine	—	-ecane

Worked examples of Hantzsch-Widman naming:

- A five-membered, fully unsaturated ring with one oxygen → 'Oxole' (= furan).
- A six-membered, fully unsaturated ring with one nitrogen → 'Azine' (= pyridine).
- A five-membered unsaturated ring with N at position 1 and O at position 3 (O > N: oxa first, then aza) → '1,3-Oxazole' (the O comes first in name).
- A five-membered saturated ring with one nitrogen (no other N) → 'Azolidine' = pyrrolidine.

- A partially saturated five-membered ring: add prefix 'dihydro', 'tetrahydro', etc., with locants.

In practice, many common heterocycles retain their historical trivial names (pyrrole, furan, thiophene, indole, quinoline, etc.). IUPAC accepts these trivial names for well-established compounds. The Hantzsch-Widman name appears in parentheses as an alternative: furan (= oxole), pyridine (= azine), piperidine (= azinane).

1.4 Naming Monocyclic Heterocycles

1.4.1 Single Heteroatom

Numbering of the ring begins at the heteroatom (position 1) and proceeds around the ring to give the lowest locant set to substituents. For example, in 3-methylthiophene, the sulfur is atom 1, the methyl group is at position 3 (not position 4, which would give a higher locant sum).

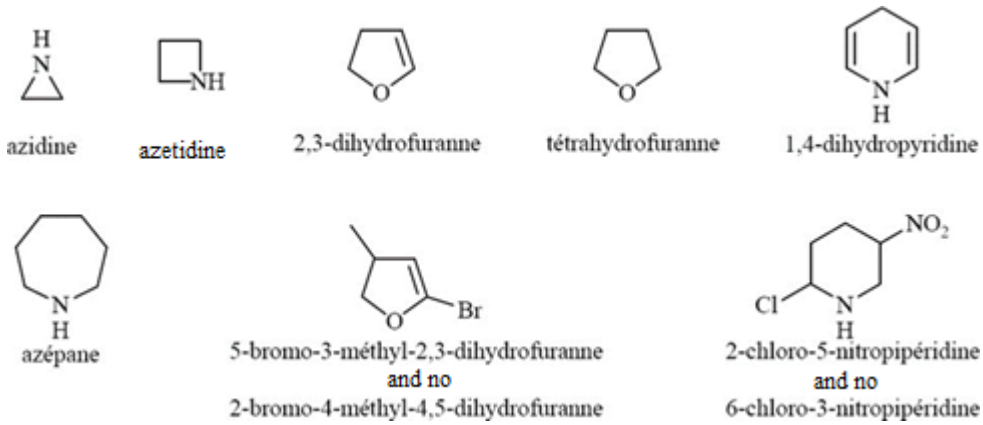
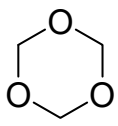


Figure 1.3. Numbering examples for monocycles with one heteroatom.

1.4.2 Multiple Identical Heteroatoms

Use di-, tri-, tetra- multiplying prefixes. Place numbering so that the sum of heteroatom locants is minimized. Example: a five-membered unsaturated ring with two N atoms → 1,2-diazole (pyrazole) or 1,3-diazole (imidazole).



1,3,5-trioxane

Figure 1.4. Monocycles with several identical heteroatoms.

1.4.3 Multiple Different Heteroatoms

Apply priority order: O > S > N > … Position 1 is assigned to the highest-priority heteroatom. The suffix reverts to the lowest-priority heteroatom (the one with the highest name in the list). Example: a five-membered ring with O at 1 and N at 3 is named 1,3-oxazole (oxa for O, suffix azole = 5-membered unsaturated nitrogen-containing).

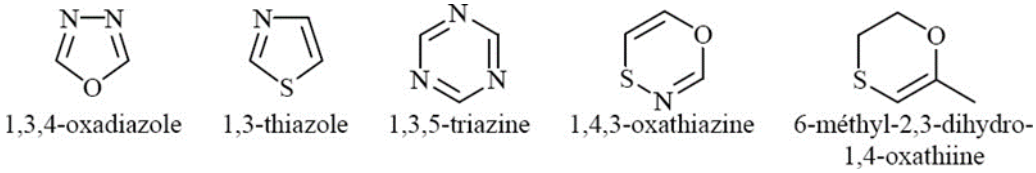


Figure 1.5. Monocycles with different heteroatoms and their IUPAC names.

1.5 Bicyclic Systems: Fusion with Benzene

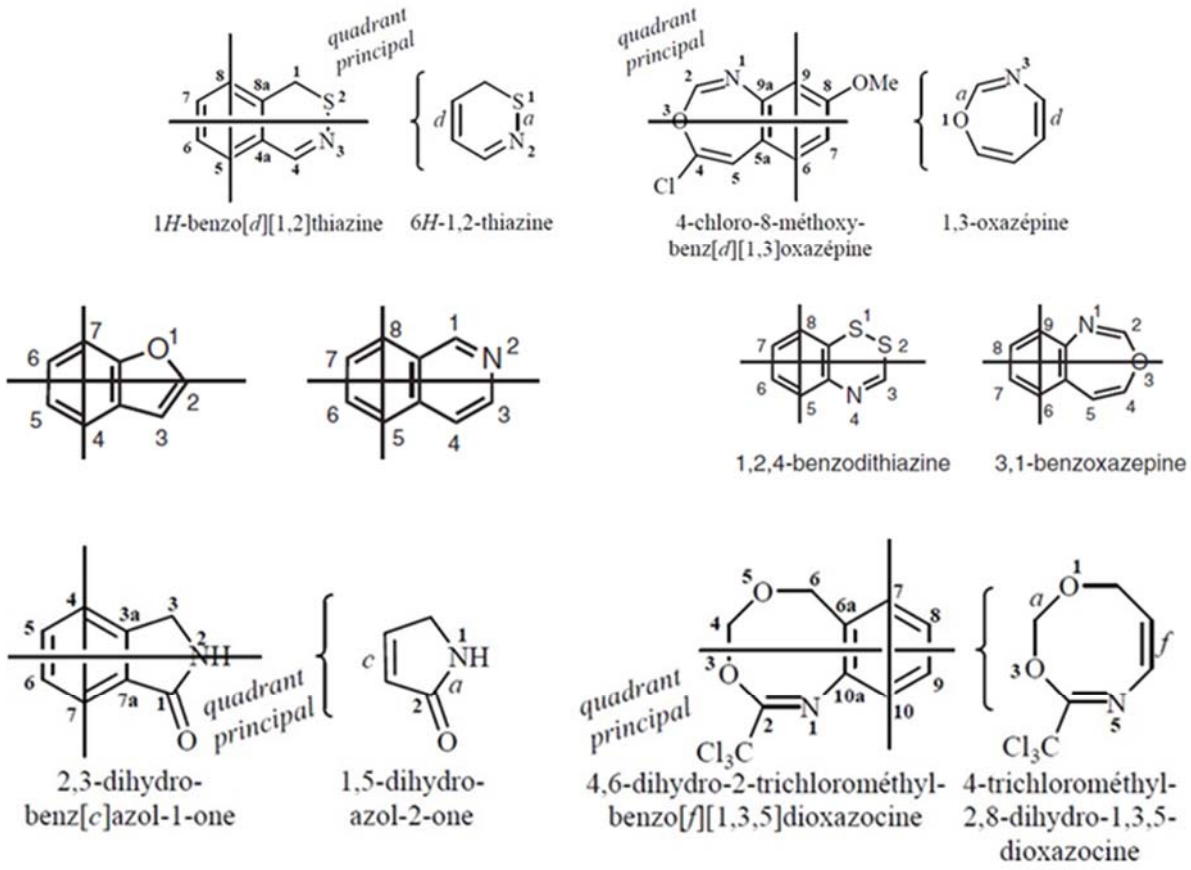
Many of the most important heterocycles are formed by fusing a hetero ring to a benzene ring. In most cases these compounds have well-established trivial names (Table 1.4) accepted by IUPAC. When systematic names are required, the prefix 'benzo-' (with elision of 'o' before a vowel) is added before the heterocycle name, followed in square brackets by a letter denoting the bond of the heterocycle at which fusion occurs. Letters are assigned alphabetically starting with 'a' for the bond between the heteroatom and the adjacent carbon.

Table 1.4 – Common bicyclic heterocycles derived from benzene fusion

Trivial Name	Systematic Name	Ring Composition
Indole	Benzo[b]pyrrole	Benzene + Pyrrole (via b-bond)
Benzofuran	Benzo[b]furan	Benzene + Furan (via b-bond)
Benzothiophene	Benzo[b]thiophene	Benzene + Thiophene (via b-bond)
Quinoline	Benzo[b]pyridine (= 1-azanaphthalene)	Benzene + Pyridine
Isoquinoline	Benzo[c]pyridine (= 2-azanaphthalene)	Benzene + Pyridine
Quinoxaline	Benzo[g]pyrazine	Benzene + Pyrazine
Benzimidazole	Benzo[d]imidazole	Benzene + Imidazole

Benzothiazole	Benzo[d]thiazole	Benzene + Thiazole
Purine	Imidazo[4,5-d]pyrimidine	Imidazole + Pyrimidine

Numbering of bicyclic systems follows a separate rule (independent of the naming numbering): (1) Draw cycles horizontally; (2) place a cross on the benzene ring; (3) identify the quadrant containing the principal heterocycle; (4) assign position 1 to the heteroatom and number continuously, skipping ring-junction carbons which receive the number of the preceding atom plus 'a' (e.g., 4a, 8a).

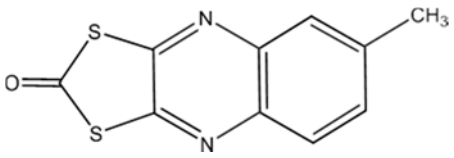


Figures 1.6. Numbering of bicyclic heterocycles.

1.6 Polycyclic Systems: Multiple Fused Heterocycles

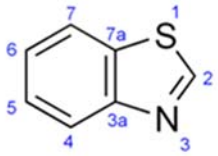
For molecules composed of several fused heterocycles, the base structure (principal component) is chosen by applying rules in decreasing priority:

- Rule 1: The ring with the most condensed cycles that can be named by a single name is the base.

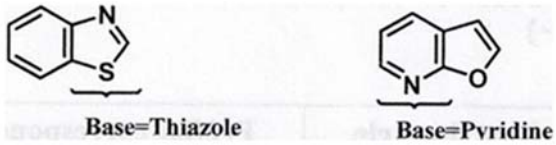


7-methyldithiolo[b]quinoxaline (Basic constituent = Quinoxaline).

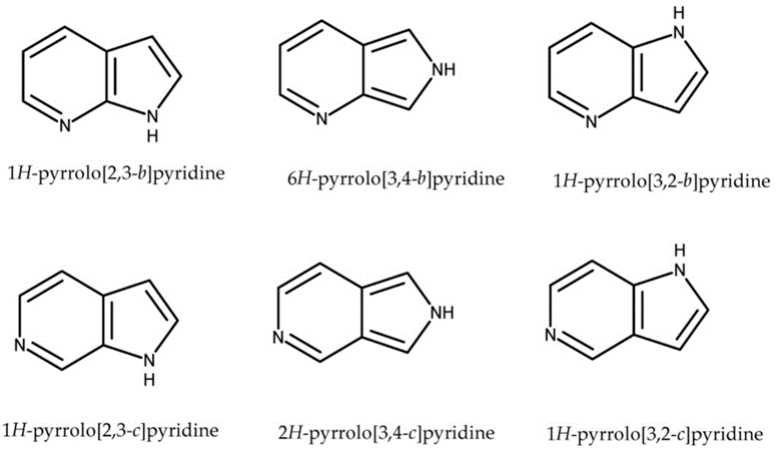
- Rule 2: If one ring contains nitrogen, it is preferred as base.



Hétérocycle de base : le ***Thiazole***

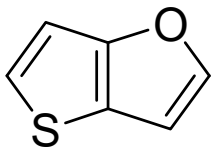


- Rule 3: If both rings contain nitrogen, the larger ring is the base.



Pyrrolopyridine.

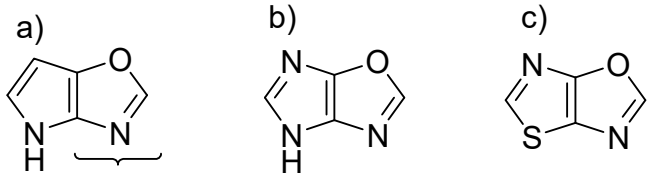
- Rule 4: If neither ring contains nitrogen, the ring with the higher-priority heteroatom (O > S > Se…) is the base.



The base here is furan.

Structure of Thiolofuran.

- Rule 5: For systems with more than 2 heteroatoms, choose the ring with the greatest number of heteroatoms (a), then the greatest variety (b), then the highest-priority atom (c).



base oxazole

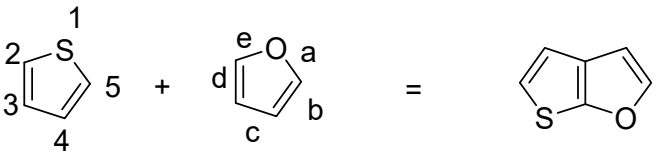
- Rule 6: The name of each secondary ring is added as a prefix. The terminal 'e' of the trivial name is replaced by 'o' (e.g., thiazole → thiazolo-).

Tableau 3. Exceptions

Nom du cycle	Préfixe correspondant
Pyridine	Pyrido-
Quinoline	Quino-
Isoquinoline	Isoquino-
Furane	Furo-
Thiophene	Thieno-
Imidazole	Imidazo-
Benzène	Benzo-

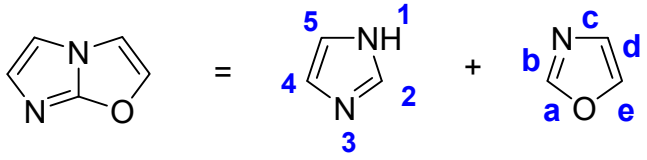
- Rule 7: Bonds of the base ring are labelled a, b, c, ... alphabetically. The bond shared between the two rings is specified in brackets.

Constituant secondaire Constituant de base



Thiophène Furane(base) Thiéno[2,3-*b*]furane

- Rule 8: Shared atoms are indicated by their locants and the letter in brackets immediately after the secondary ring prefix.



Imidazo[2,1-*b*]oxazole Imidazole Oxazole

1.7 Replacement (a-) Nomenclature

In 'a' (replacement) nomenclature, the heterocycle is conceptually derived from a corresponding carbocyclic ring by replacing one or more carbons with heteroatoms. Since all heteroatom prefixes in Table 1.1 end in 'a', this system is called 'a' nomenclature. The carbocycle parent name is written first, preceded by the locanted heteroatom prefix(es) in priority order. Example: replacement of C-1 of cyclohexane by O gives '1-oxacyclohexane' (= tetrahydropyran); replacement of C-1 and C-4 by O gives '1,4-dioxacyclohexane' (= 1,4-dioxane).

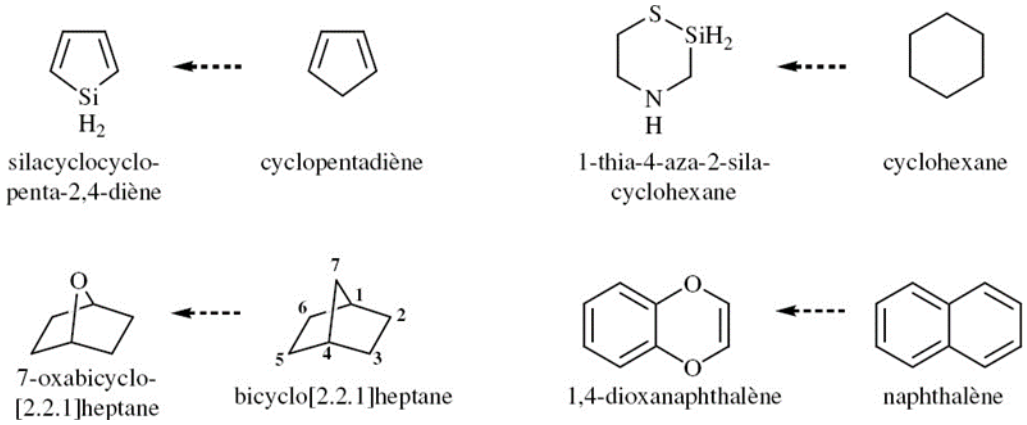


Figure 1.7. Replacement nomenclature examples.

Chapter 2: Five-Membered Aromatic Heterocycles with One Heteroatom

The three canonical five-membered aromatic heterocycles with a single heteroatom are pyrrole (N), furan (O), and thiophene (S). Each contains a heteroatom that contributes two electrons (its lone pair) to the aromatic π system, completing the 6-electron Hückel aromatic sextet (4n+2 with n=1). This lone-pair participation has profound consequences for reactivity, basicity, and physical properties. Table 2.1 provides a comparative overview.

Table 2.1 — Comparative properties of five-membered and six-membered aromatic heterocycles:

Property	Pyrrole	Furan	Thiophene	Pyridine
Heteroatom	N (group 15)	O (group 16)	S (group 16)	N (group 15)
π electrons	6	6	6	6
Lone pair in π?	Yes (N sp^2)	Yes (O sp^2)	Yes (S sp^3-like)	No (N sp^2)
Aromaticity (RE kcal/mol)	~ 24	~ 16	~ 29	~ 43
pKa (NH or OH)	17.5	—	—	—
pKa (BH^+)	−3.8	−5.2	−5.0	5.23
EAS position	C-2 (α)	C-2 (α)	C-2 (α)	C-3 (β)
NAS position	—	—	—	C-2 / C-4
Diels-Alder (diene)	Rare	Yes (reactive)	No	No
Key natural product	Heme, Chl	Ascorbic acid	Biotin	NAD^+, B_6

2.1 Pyrrole

Pyrrole (C_4H_5N, MW = 67.09 g/mol) is a colourless liquid (bp 130 °C) with a characteristic unpleasant odour. It is found in coal tar and as a metabolic breakdown product of chlorophyll. The pyrrole ring is planar and fully conjugated; the nitrogen atom is sp^2-hybridized, and its p-orbital lone pair is part of the aromatic π system.

> **Key electronic facts about pyrrole:**

• N lone pair is in the aromatic π system → NOT available for protonation → very weak base (pKa of N-H conjugate acid ≈ −3.8).

• N-H bond is relatively acidic (pKa ≈ 17.5); the pyrryl anion formed by deprotonation is aromatic and stabilized.

• Electron density: highest at C-2 and C-5 (α-positions) — these are the preferred sites for EAS.

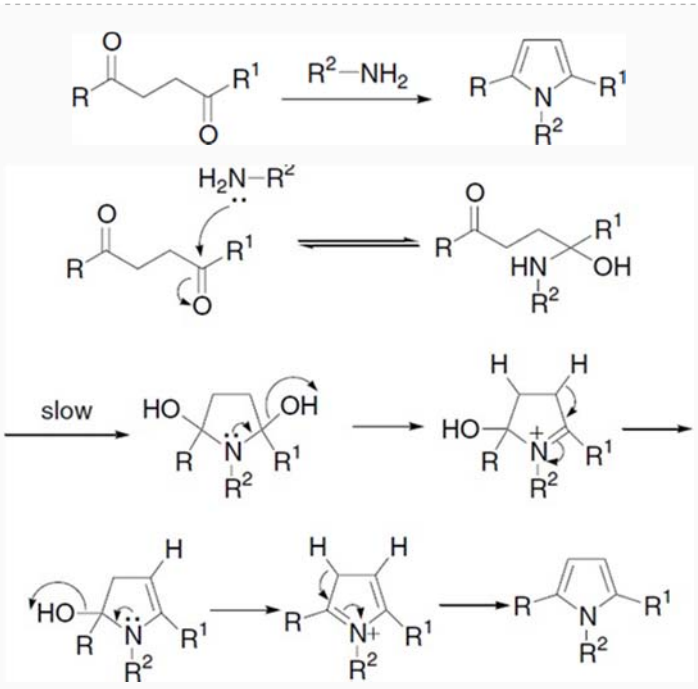
• Strong Brønsted or Lewis acids must be avoided: they protonate C-2, break aromaticity, and cause polymerization.

2.1.1 Synthesis of Pyrrole

A. Paal-Knorr Synthesis (1884)

The Paal-Knorr synthesis is the most widely applied and versatile route to pyrroles. It was independently reported by Carl Paal and Ludwig Knorr in 1884. A 1,4-dicarbonyl compound (1,4-diketone, keto-aldehyde, or dialdehyde) undergoes double condensation with a primary amine or ammonia to give an N-substituted (or unsubstituted) pyrrole.

Mechanism: (1) Nucleophilic addition of the amine to one carbonyl gives a hemiaminal; (2) dehydration gives an imine (Schiff base); (3) intramolecular nucleophilic addition of nitrogen to the second carbonyl, followed by dehydration; (4) tautomerization/aromatization gives the aromatic pyrrole. The reaction is catalyzed by acid.

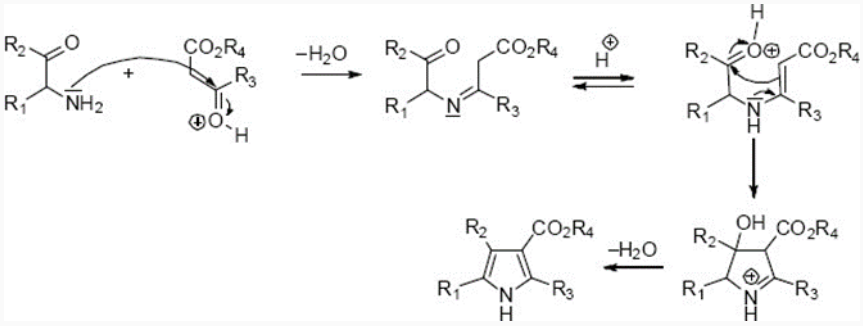


Scheme 2.1. Paal-Knorr Synthesis: general reaction and step-by-step mechanism.

Scope and applications: The Paal-Knorr synthesis tolerates a wide range of primary amines (aliphatic, aromatic, benzylamine, amino acids), giving N-substituted pyrroles. With ammonia, the parent pyrrole is obtained. Recent modifications allow the use of microwave irradiation and solvent-free conditions to improve yield and reduce reaction time.

B. Knorr Synthesis

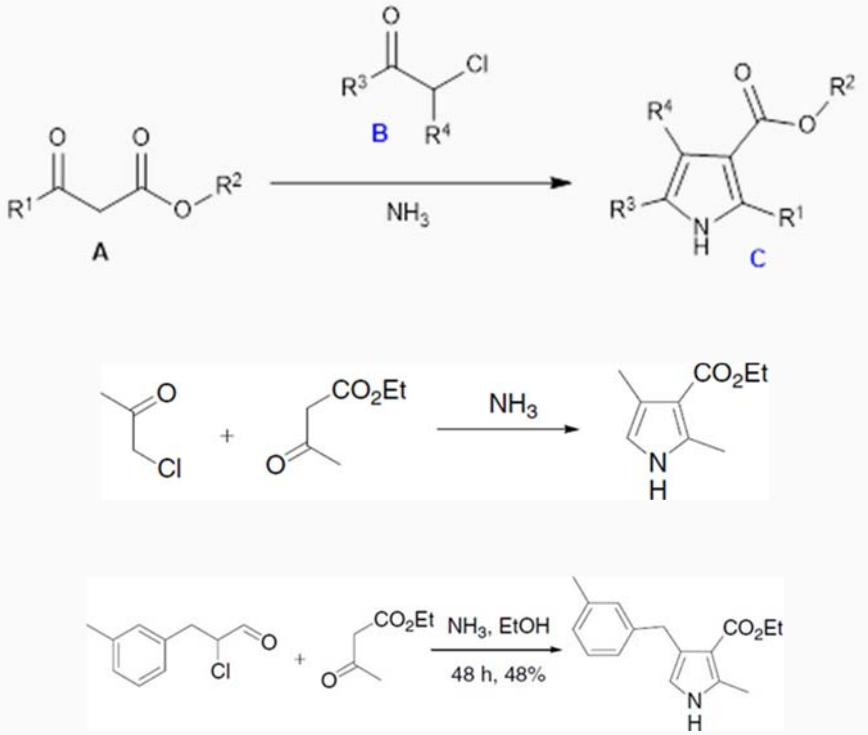
Originally described by Ludwig Knorr in 1884, this method uses an α-aminoketone (which provides the nitrogen and C-2/C-3 atoms) and a β-ketoester with an active methylene group α to the carbonyl. The mechanism involves: (1) Formation of a Schiff base between the amino group of the α-aminoketone and the carbonyl of the β-ketoester; (2) tautomerization to the enol form; (3) intramolecular cyclodehydration to give the dihydropyrrole; (4) oxidation/tautomerization to the aromatic pyrrole. The Knorr synthesis is especially valued for preparing pyrroles bearing ester or carboxylic acid substituents (e.g., in porphyrin chemistry).



Scheme 2.2. Knorr Synthesis mechanism.

C. Hantzsch Pyrrole Synthesis

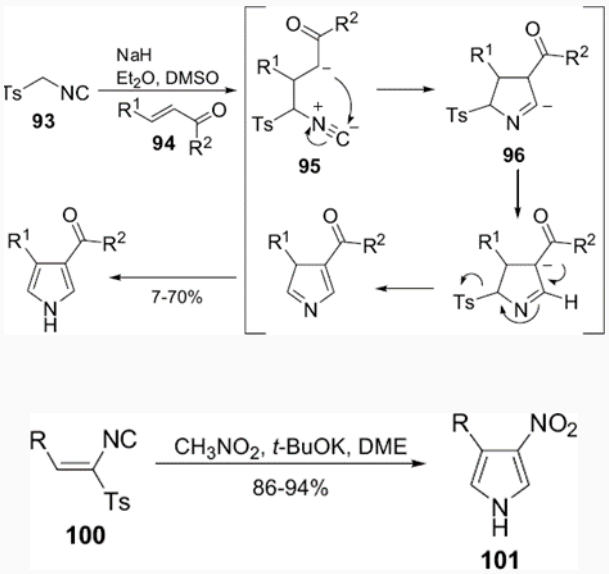
The Hantzsch synthesis (named for Arthur Rudolf Hantzsch) proceeds by condensation of an α-halogenocarbonyl compound (α-haloketone or α-haloester) with a β-ketoester in the presence of ammonia or a primary amine. The reaction involves: (1) S-alkylation or N-alkylation is possible, but with β-ketoesters the nitrogen attacks first; (2) the resulting enamine cyclizes; (3) loss of the halide triggers ring closure; (4) tautomerization gives the pyrrole. This method is useful for preparing 2,4-disubstituted pyrroles.

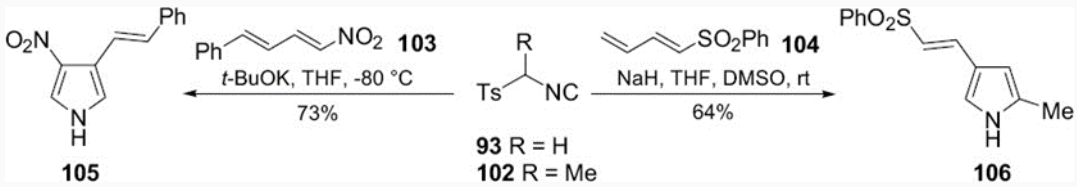


Scheme 2.3. Hantzsch Synthesis of Pyrrole.

D. Van Leusen Synthesis

This modern method uses TosMIC (toluenesulfonylmethyl isocyanide) as a one-carbon building block that reacts with activated carbonyl compounds (aldehydes or activated ketones) in the presence of a base. The reaction is highly versatile and tolerant of diverse functional groups. The mechanism involves 1,3-dipolar cycloaddition of the isocyanide anion with the acceptor, followed by elimination of the tosyl group.

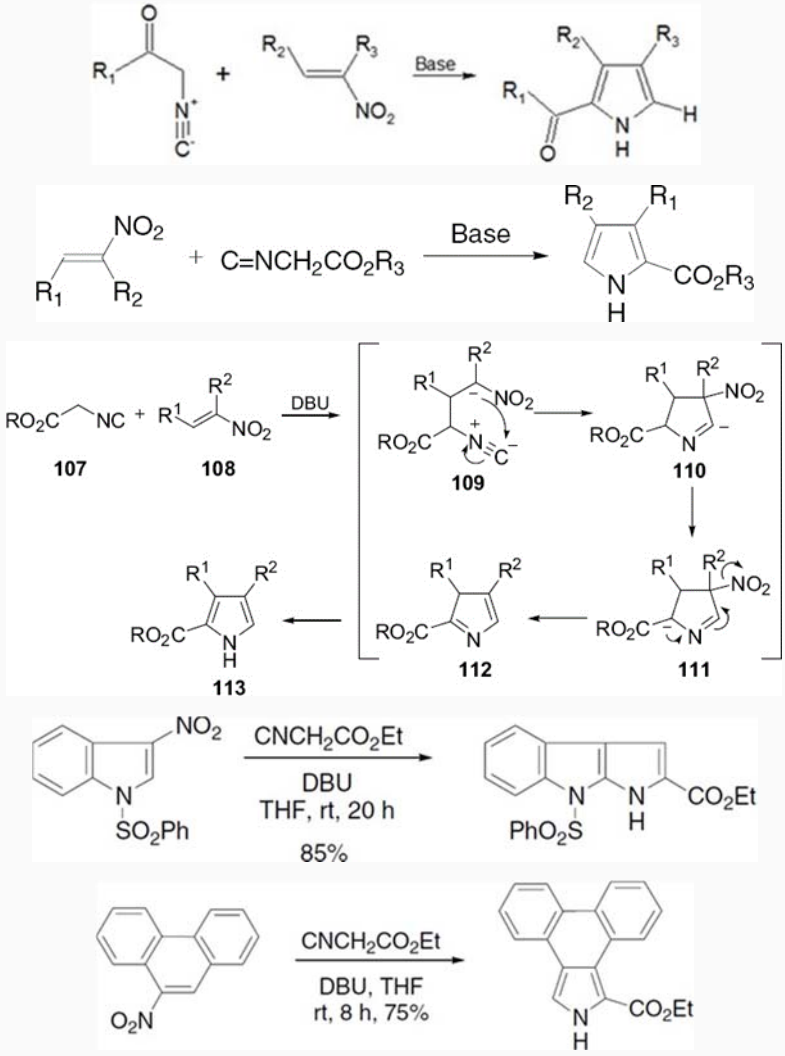




Scheme 2.4. Van Leusen Pyrrole Synthesis (TosMIC method).

E. Barton-Zard Synthesis

The Barton-Zard synthesis employs a nitroalkene as the acceptor and an α-isocyanatoacetate as the donor. In the presence of a hindered base (DBU), the α-isocyanatoacetate enolate performs a Michael addition to the nitroalkene. The nitro group acts as a good leaving group in the subsequent ring closure, generating the pyrrole ring. This method is particularly useful for accessing pyrroles with ester groups at C-3 and C-4 (pyrrole-3,4-dicarboxylates).



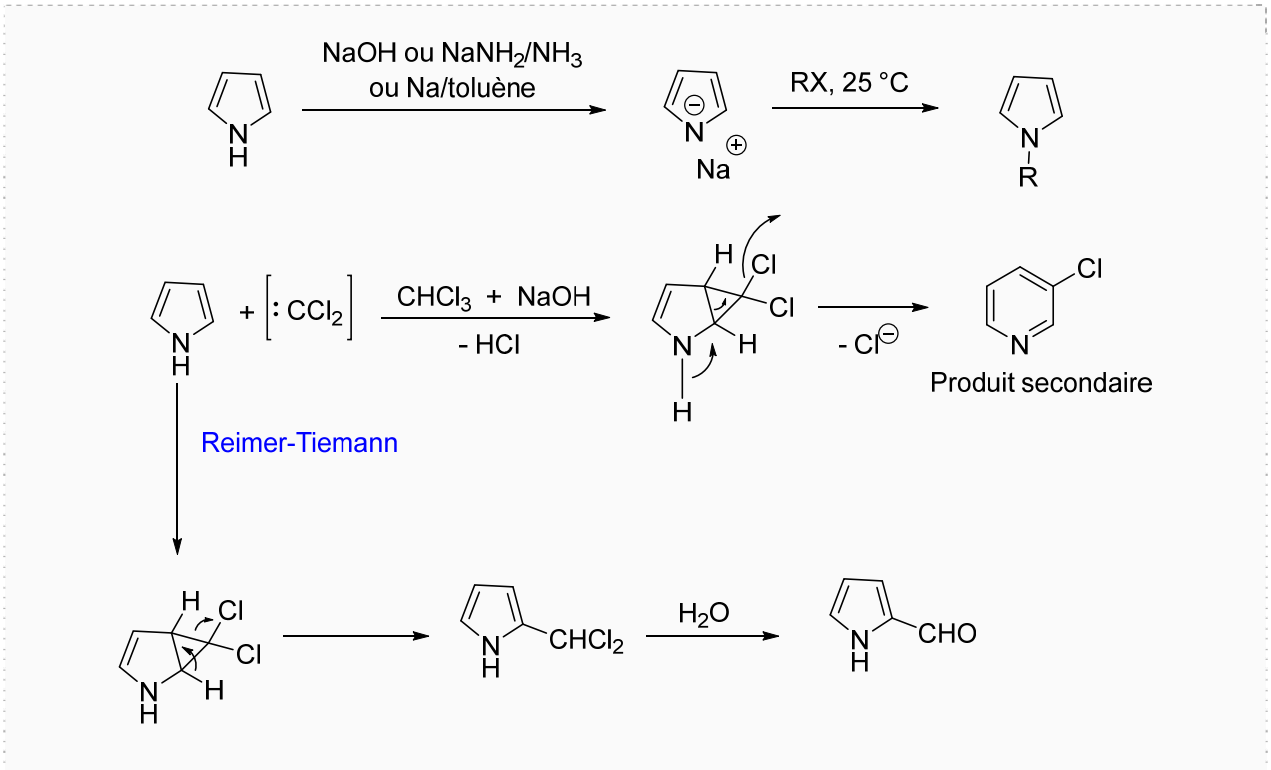
Scheme 2.5. Barton-Zard Synthesis mechanism.

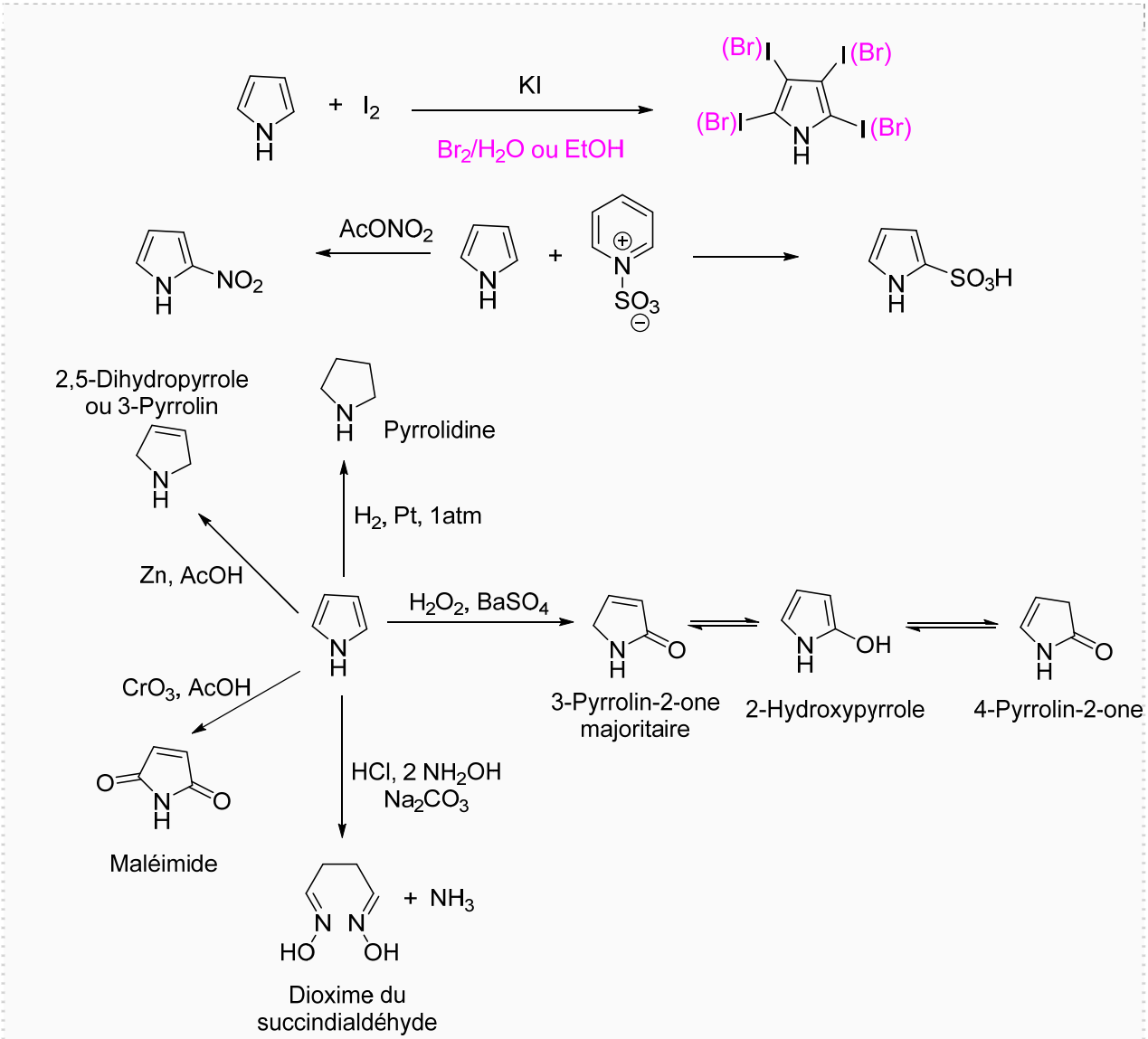
2.1.2 Reactivity of Pyrrole

Pyrrole is an electron-rich aromatic system and undergoes EAS far more readily than benzene. The dominant site of attack is C-2 (α-position), where the highest HOMO coefficient is found. The reaction must be conducted under mild conditions (no strong Brønsted or Lewis acids) to avoid protonation at C-2, which destroys aromaticity.

EAS at the α-position

- Formylation (Vilsmeier-Haack): $POCl_3$/DMF gives 2-formylpyrrole (pyrrole-2-carbaldehyde) as the major product.
- Acylation: Under mild conditions (acid anhydrides, acid chlorides + base), C-2 acylation predominates. Friedel-Crafts conditions with $AlCl_3$ should be avoided.
- Halogenation: Br_2 or NBS in THF/CCl_4 gives 2-bromopyrrole; excess reagent leads to 2,3,4,5-tetrabromopyrrole.
- Nitration: Acetyl nitrate (prepared from AcOH + HNO_3 below 0 °C) gives 2-nitropyrrole selectively. Concentrated HNO_3/H_2SO_4 cannot be used.
- Sulfonation: The complex of SO_3 and pyridine (Py·SO_3) provides pyrrole-2-sulfonic acid without causing polymerization.
- Mannich reaction: Pyrrole, formaldehyde, and a secondary amine react at C-2 to give aminomethylated (Mannich base) products.





Scheme 2.6. Summary of EAS reactions of Pyrrole.

2.1.3 Biological Importance of Pyrrole

The pyrrole ring is one of the most biologically important structural motifs known:

- Porphyrins and Heme: Four pyrrole rings linked by methine bridges form the porphyrin macrocycle. Heme (iron-porphyrin) is the prosthetic group of hemoglobin, myoglobin, cytochromes, and catalase. Chlorophyll (magnesium-porphyrin) is the photosynthetic pigment.
- Vitamin B12 (Cobalamin): Contains a corrin ring (modified porphyrin) with cobalt. Essential for DNA synthesis and nerve function.
- Bile Pigments: Bilirubin and biliverdin are open-chain tetrapyrroles formed by heme catabolism.

- Nicotine: N-methylpyrrolidine ring system; the principal alkaloid of tobacco; nicotinic acetylcholine receptor agonist.
- L-Proline: Cyclic amino acid (pyrrolidine) essential for collagen synthesis and protein folding.
- Prodigiosins: Tripyrrole-based antibacterial and antifungal pigments produced by Serratia marcescens.

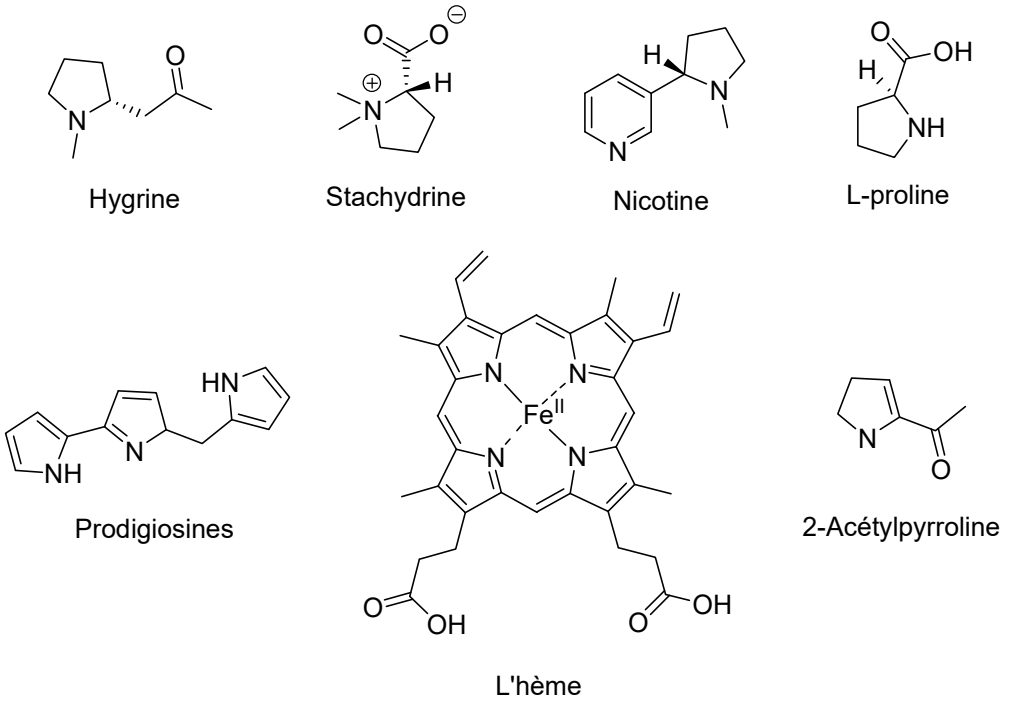


Figure 2.1. Pyrrole-based natural products: heme, proline, nicotine, prodigiosin.

2.2 Furan

Furan (C_4H_4O, bp 31 °C) is a colourless, volatile, flammable liquid with an ether-like smell. It occurs naturally in wood tars and as an industrial chemical obtained by decarbonylation of furfural (2-furaldehyde), which is in turn produced from agricultural byproducts (corn cobs, oat hulls) rich in pentose sugars. The aromaticity of furan is weaker than that of thiophene or benzene (resonance energy ≈ 16 kcal/mol) because oxygen's high electronegativity reduces the availability of its lone pair for ring delocalization.

Key electronic facts about furan:

• O lone pair in aromatic π system → oxygen is slightly less electron-donating than N in pyrrole.

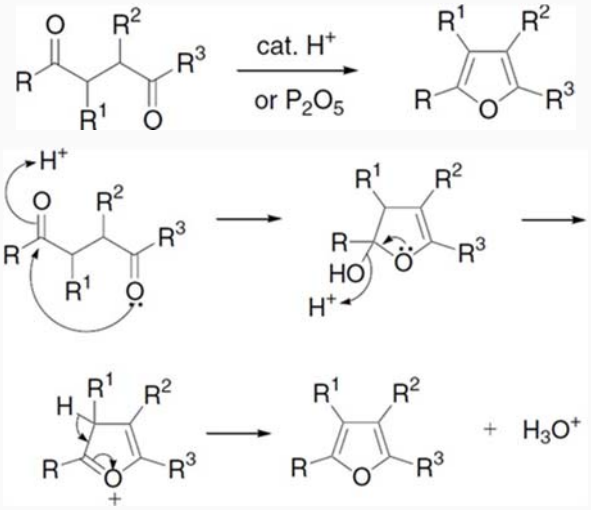
• Ring is electron-rich; EAS occurs preferentially at C-2 (α).

- Under strongly acidic conditions, the ring opens (electrophilic ring-opening) and/or polymerizes.
- Furan behaves as a 1,3-diene in Diels-Alder reactions: reacts with electron-poor dienophiles (maleic anhydride, DEAD).

2.2.1 Synthesis of Furan

A. Paal-Knorr Synthesis (Acid-Catalysed)

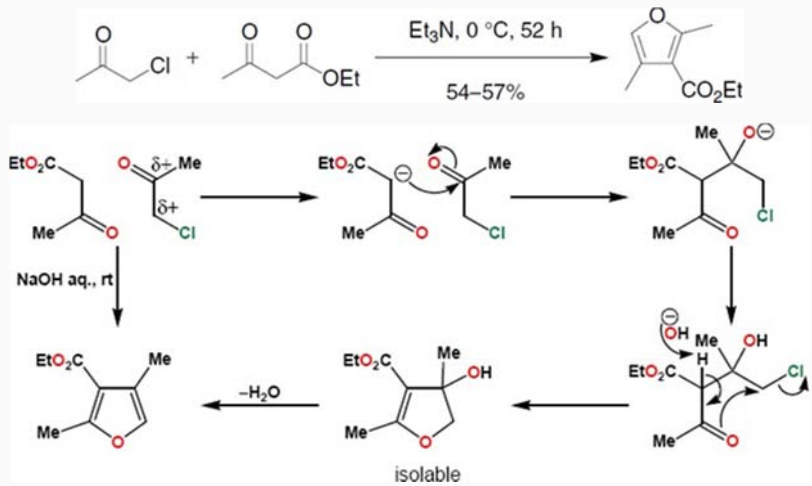
1,4-Dicarbonyl compounds cyclodehydrate in the presence of acid catalysts (H_2SO_4, p-TsOH, $BF_3{\cdot}OEt_2$, $POCl_3$) to give furans. The mechanism: (1) protonation of one carbonyl; (2) intramolecular nucleophilic attack by the enol of the second carbonyl; (3) cyclization and dehydration; (4) a second dehydration and tautomerization gives the furan. This is the principal industrial route to substituted furans.



Scheme 2.7. Paal-Knorr Synthesis of Furan (mechanism).

B. Feist-Benary Synthesis

The Feist-Benary synthesis uses α-halogenated ketones and β-ketoesters (or β-diketones) with a basic or acidic catalyst (an amine such as pyridine or piperidine is typical). The first step is a Knoevenagel-type condensation; the resulting Michael acceptor then undergoes intramolecular O-alkylation (SN2 displacement of halide) to close the furan ring. A second dehydration provides the aromatic furan. This is a versatile method for preparing highly substituted furans.



Scheme 2.8. Feist-Benary Synthesis (reaction and mechanism).

2.2.2 Reactivity of Furan

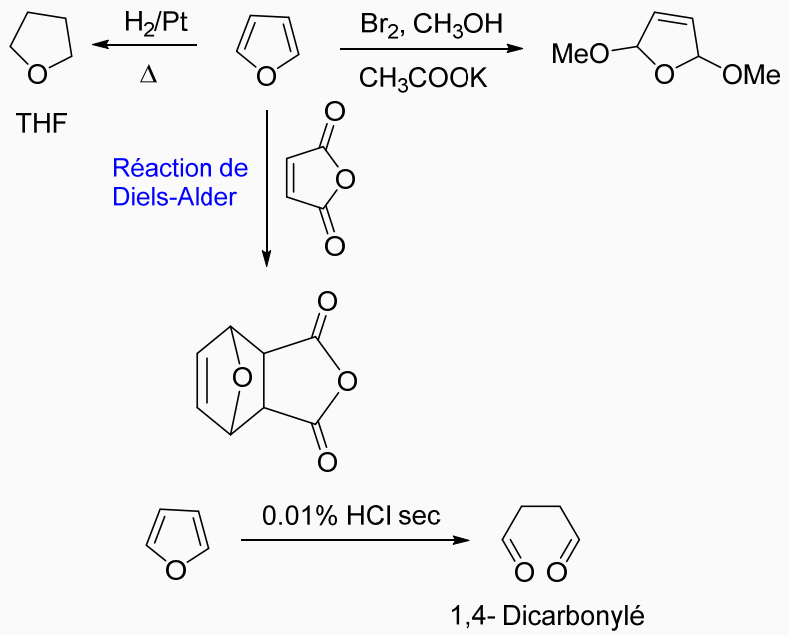
A. Electrophilic Aromatic Substitution

Furan reacts at C-2 (α) preferentially. Because the ring is weaker aromatic and more diene-like, EAS reactions can occasionally be accompanied by ring-opening byproducts when strong electrophiles are used. Main reactions:

- Nitration: Acetyl nitrate gives 2-nitrofuran (α) as the major product.
- Bromination: NBS or Br_2 in acetic acid gives 2-bromofuran; tetrabromide can form in excess.
- Friedel-Crafts Acylation: Possible with acid chloride/BF_3 at low temperature to give 2-acylfuran.
- Vilsmeier Formylation: DMF/$POCl_3$ at 0 °C gives 2-furaldehyde (furfural).
- Mannich Reaction: Reaction of furan with HCHO and secondary amines gives 2-(aminomethyl)furan.

B. Diels-Alder Reactions

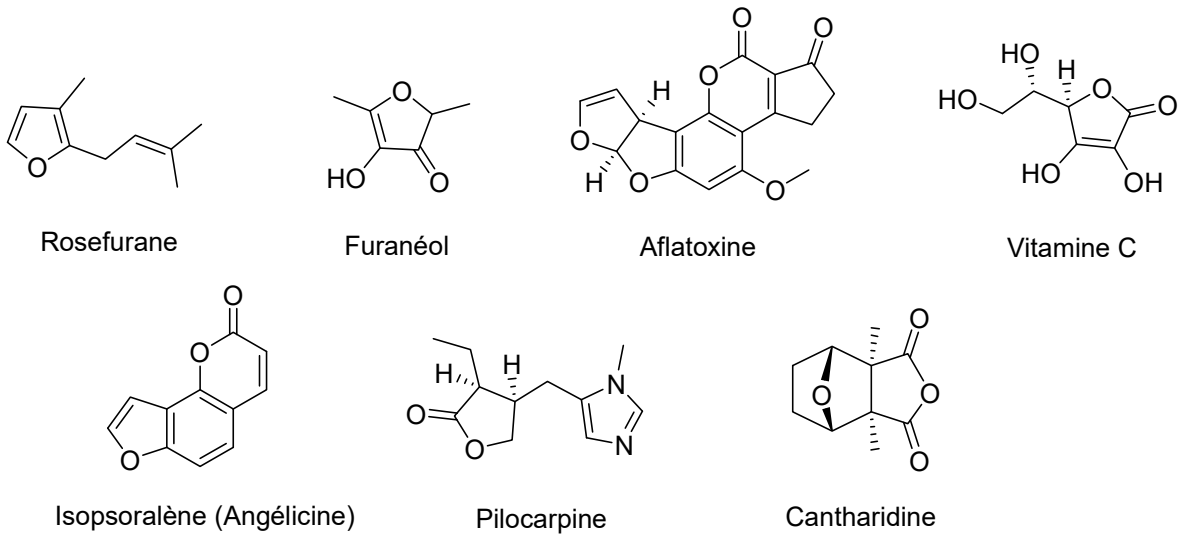
Furan is an excellent 1,3-diene for [4+2] cycloadditions. Its s-cis conformation is locked in the five-membered ring. It reacts with electron-poor dienophiles (maleic anhydride, DMAD, DEAD, quinones) to give bicyclic adducts (7-oxabicyclo[2.2.1]heptenes). The reaction is thermally reversible (retro-Diels-Alder). This chemistry is extensively used in the synthesis of natural products and in polymer chemistry.



Scheme 2.9. Diels-Alder reaction of Furan with maleic anhydride.

2.2.3 Biological Importance of Furan

- Vitamin C (Ascorbic Acid): γ-Lactone (butenolide) ring derived from L-gulonolactone. Essential antioxidant, collagen synthesis cofactor, and iron absorption promoter.
- Aflatoxins: Furanobenzopyranone mycotoxins produced by Aspergillus flavus; among the most potent known carcinogens; contaminate grain and peanuts.
- Pilocarpine: Furanoid alkaloid from Pilocarpus jaborandi; parasympathomimetic agent used ophthalmically to treat glaucoma.
- Furanéol (HDMF): Prominent aroma compound of strawberries, pineapple, and tomato.
- Rosefuran: Constituent of rose essential oil. Important in the fragrance and flavour industries.
- Cantharidine: Anhydride of 2,3-dimethyl-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid; defensive toxin secreted by blister beetles; historical use as a vesicant.



Figures 2.2. Biologically important furan derivatives: vitamin C, pilocarpine, aflatoxin.

2.3 Thiophene

Thiophene (C_4H_4S, bp 84 °C) is a colourless liquid with a smell similar to benzene. It occurs in coal tar and is the major impurity in benzene obtained from coal tar processing. Thiophene has the highest aromaticity among the three five-membered systems (resonance energy ≈ 29 kcal/mol), because sulfur's 3p lone pair overlaps more effectively with the π system than oxygen's 2p lone pair. From a reactivity standpoint, thiophene more closely resembles benzene than do pyrrole or furan.

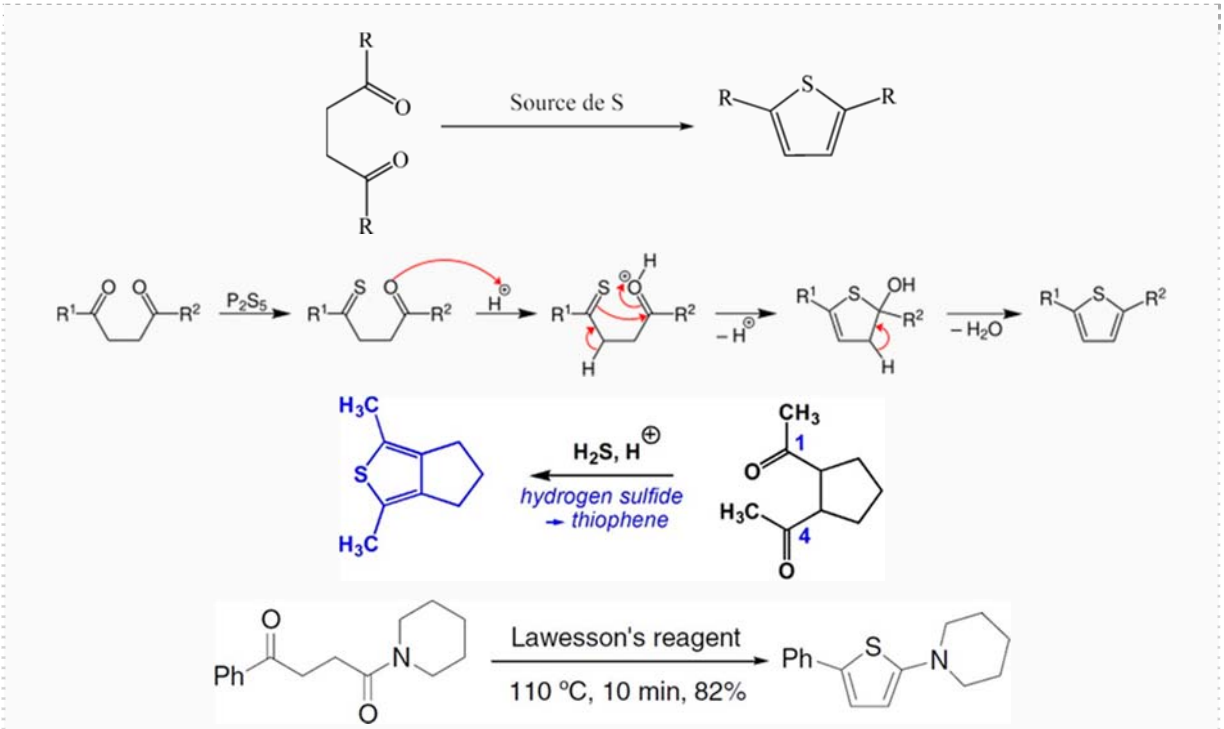
Key electronic facts about thiophene:

- S lone pair in aromatic π system; but S is less electronegative than O → stronger π donation than furan.
- EAS occurs preferentially at C-2 (α), where HOMO density is highest.
- Does NOT undergo Diels-Alder reactions as a diene (unlike furan).
- Hydrogenation over Ni/Raney leads to desulfuration, not ring reduction — a key diagnostic test.
- S-C bonds are longer than C-C; the ring is slightly non-planar but aromatic.

2.3.1 Synthesis of Thiophene

A. Paal-Knorr Synthesis (Thionation)

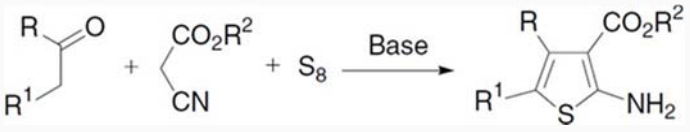
1,4-Dicarbonyl compounds react with phosphorus pentasulfide (P_4S_{10}) or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) to give thiophenes. The thionation replaces both carbonyl oxygens with sulfur, and the sulfide formed closes the ring. Lawesson's reagent is preferred over P_4S_{10} because it is easier to handle and more selective.

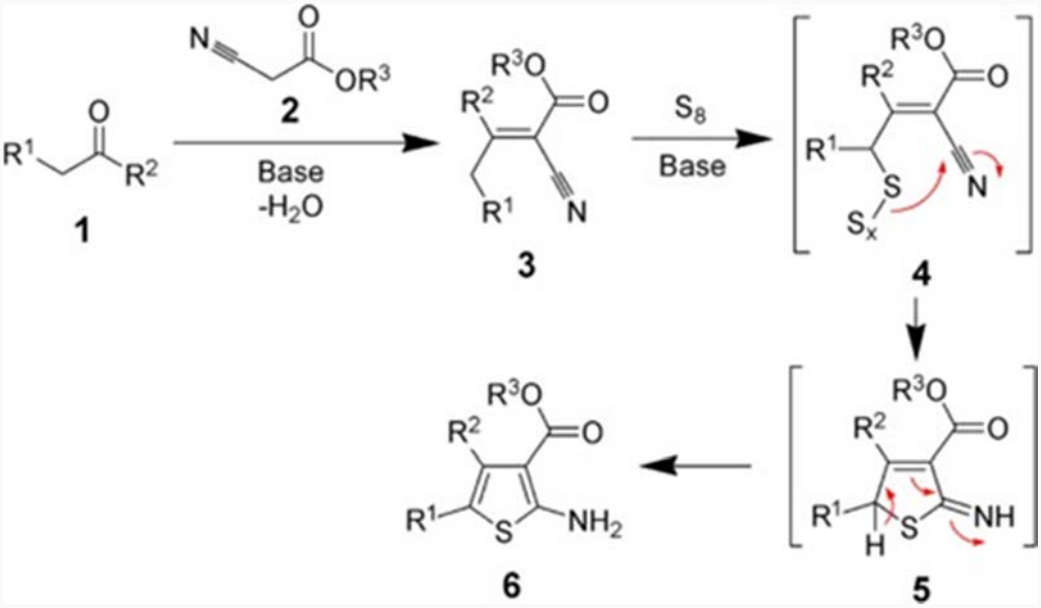


Scheme 2.10. Paal-Knorr Thiophene Synthesis.

B. Gewald Synthesis

The Gewald synthesis affords 2-aminothiophenes (thiophene-2-amines) by a three-component condensation: an α-methylene carbonyl compound (aldehyde or ketone with an active methylene), an α-cyanoester (e.g., ethyl cyanoacetate), and elemental sulfur, all in the presence of a base (morpholine, diethylamine). Step 1: Knoevenagel condensation between the carbonyl and the α-CH_2 of the cyanoester gives a Michael acceptor. Step 2: Elemental sulfur inserts into the reactive alkene via a [2+2]-type process or radical mechanism, triggering cyclization and finally aromatization to give the 2-aminothiophene.





Scheme 2.11. Gewald Synthesis (reaction and mechanism).

C. Hinsberg Synthesis

A condensation of diethyl thiodiacetate (diethyl thiodiglycolate) with an α-diketone in the presence of base (sodium ethoxide) gives thiophene-2,5-dicarboxylic acids or their esters. The mechanism involves: (1) Claisen-type enolization; (2) C-acylation; (3) intramolecular S-alkylation or S-C bond formation; (4) dehydration/aromatization. This synthesis is especially useful for preparing 3,4-disubstituted thiophenes.

D. Fiesselmann Synthesis

Condensation of thioglycolic acid ester derivatives (esters of mercaptoacetic acid) with α,β-acetylenic esters (propiolic acid esters) in the presence of a basic catalyst gives 3-hydroxythiophene-2-carboxylates. The reaction proceeds through Michael addition of the thiolate to the triple bond, followed by intramolecular cyclization.

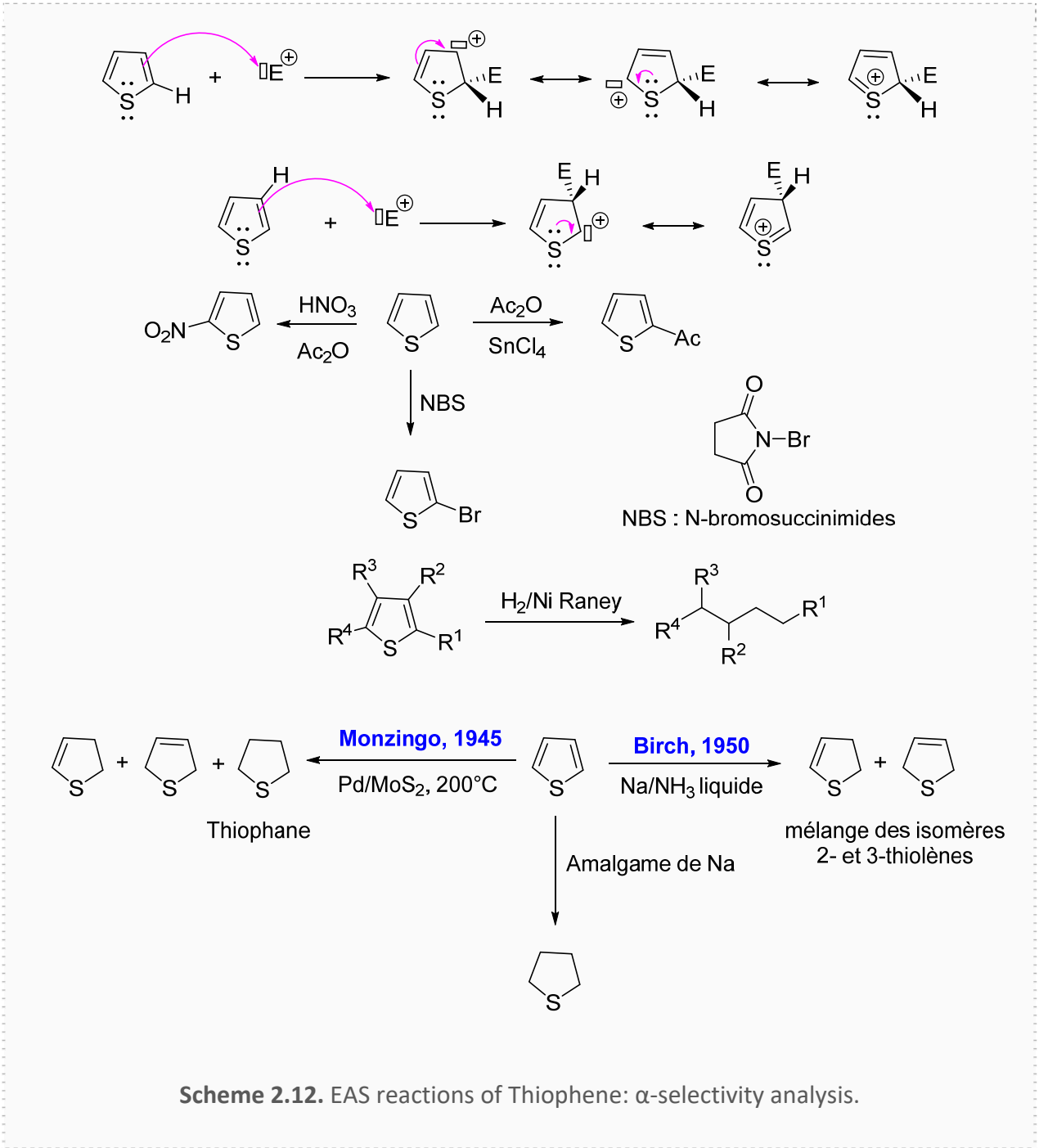
2.3.2 Reactivity of Thiophene

Electrophilic Aromatic Substitution (EAS)

Thiophene undergoes EAS much more readily than benzene but under milder conditions than furan. α-Substitution (C-2) is strongly preferred. Regioselectivity can be analyzed by comparing the stability of Wheland (arenium) intermediates for α- and β-attack: the α-attack intermediate is more stable because the positive charge in the σ-complex is delocalized over more positions, and the sulfur lone pair can stabilize the adjacent cation more effectively.

- Sulfonation: Concentrated H_2SO_4 at 25–40 °C (milder than benzene sulfonation) gives thiophene-2-sulfonic acid.

- Nitration: Acetyl nitrate gives 2-nitrothiophene; 2,5-dinitrothiophene with excess reagent.
- Halogenation: Cl_2 or Br_2 in AcOH gives 2-chloro- or 2-bromothiophene; electrophilic conditions.
- Acylation: $BF_3{\cdot}Et_2O$ or $SnCl_4$ (milder Lewis acids than for benzene) catalyse Friedel-Crafts acylation at C-2.
- Formylation: Vilsmeier-Haack ($POCl_3$/DMF) gives thiophene-2-carbaldehyde.



Scheme 2.12. EAS reactions of Thiophene: α-selectivity analysis.

2.3.3 Biological Importance of Thiophene

- Biotin (Vitamin B7/B8/H): Bicyclic compound containing a tetrahydrothiophene ring fused to a urea ring. Essential coenzyme for carboxylation reactions (fatty acid synthesis, gluconeogenesis). Deficiency causes alopecia and dermatitis.

- Clopidogrel (Plavix): Thienopyridine antiplatelet drug; an ADP receptor antagonist that prevents arterial thrombosis.
- Tenoxicam, Meloxicam: Thiophene-based NSAIDs (non-steroidal anti-inflammatory drugs).
- Tirofiban: Thiophene-containing glycoprotein IIb/IIIa inhibitor used in acute coronary syndrome.

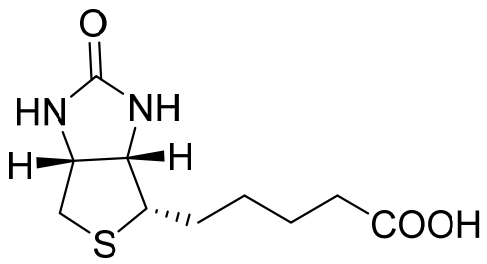


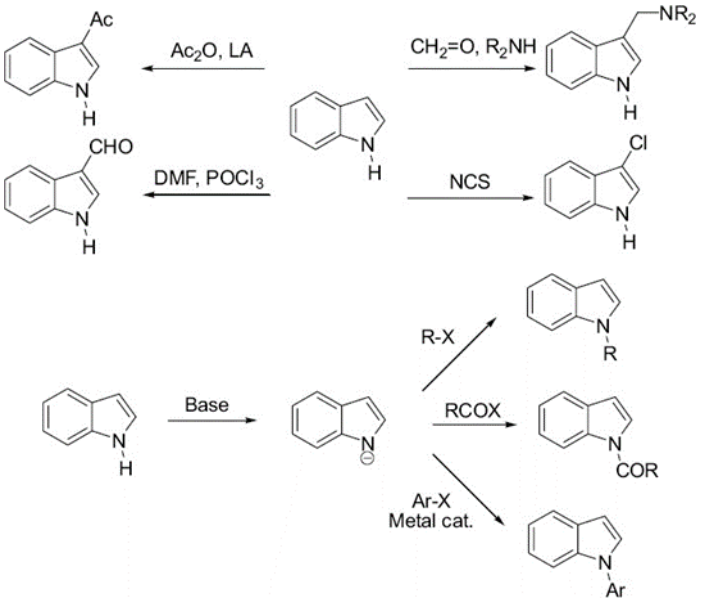
Figure 2.3. Biotin structure / other thiophene-containing drugs.

Chapter 3: Indole and Derivatives

Indole (benzo[b]pyrrole, C_8H_7N, MW = 117.15 g/mol) is a bicyclic aromatic compound consisting of a benzene ring fused to a pyrrole ring at the [b] bond (the bond between C-3a and C-7a, i.e., at the b-bond of pyrrole). The name derives from indigo (the blue dye) and oil of vitriol (oleum), since early synthetic work used fuming sulfuric acid. The structure was elucidated by Bayer and Knorr in 1869; Fischer provided the first reliable synthesis in 1883. Indole is a white solid (mp 52 °C, bp 254 °C) with a floral odour at extreme dilution but a fecal odour at higher concentration.

3.1 Electronic Structure and Aromaticity

Indole is a 10-π electron aromatic system (benzene contributes 6 electrons + N lone pair + one remaining C=C double bond = 10 electrons). Unlike simple pyrrole, the two rings are not equivalent: the benzene ring is more aromatic, while the pyrrole ring is more reactive. The nitrogen (pyrrole-type) donates electron density into the ring, making C-3 the most nucleophilic position (highest coefficient in the HOMO of indole). C-2 is the second most reactive position. N-H of indole (pKa ≈ 17) is less acidic than pyrrole-NH (17.5); the difference reflects ring-current effects.



Scheme 3.1. Resonance structures of indole showing charge distribution and electron density at C-3 > C-2

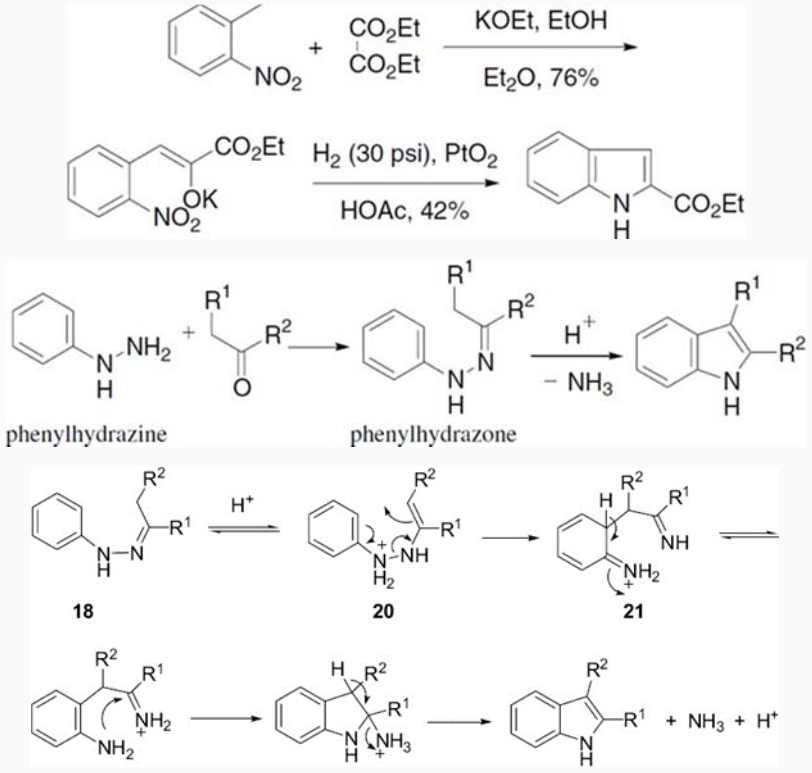
3.2 Synthesis of Indole

3.2.1 Fischer Indole Synthesis

The Fischer indole synthesis (Emil Fischer, 1883; Nobel Prize 1902) is the most extensively used method for constructing substituted indoles. A phenylhydrazine reacts with an aldehyde or ketone

under Brønsted acid catalysis (HCl, H_2SO_4, polyphosphoric acid, $ZnCl_2$) via the following mechanism:

- Step 1: Formation of an arylhydrazone by condensation of the phenylhydrazine with the carbonyl compound (loss of H_2O).
- Step 2: Tautomerization (prototropic shift) of the hydrazone to the ene-hydrazine form.
- Step 3: [3,3]-Sigmatropic rearrangement of the ene-hydrazine (through a six-membered cyclic transition state) — the key bond-forming step.
- Step 4: Rearomatization of the benzene ring; loss of NH_3 by intramolecular cyclization; formation of the C-2–C-3 bond of the indole.



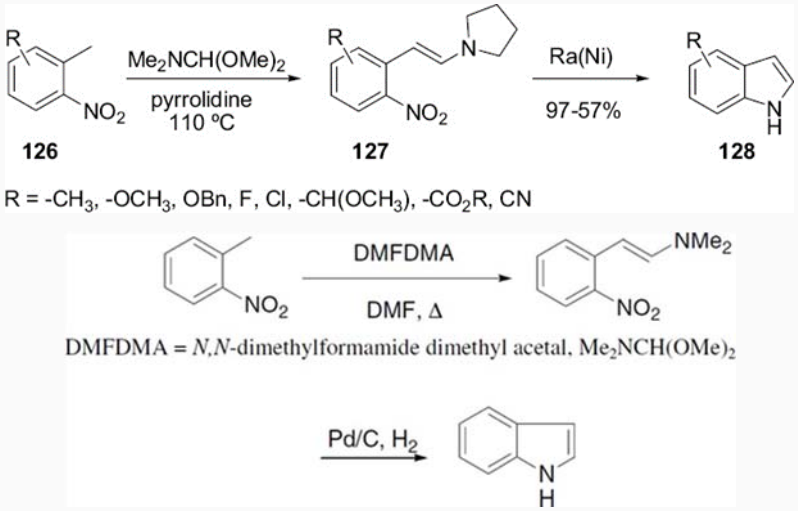
Scheme 3.2. Fischer Indole Synthesis: reaction and mechanism.

Scope: Aldehydes give 2-unsubstituted (or 2-methyl from acetaldehyde) indoles; ketones give 2-substituted indoles. Unsymmetrical ketones give mixtures of two regioisomers; the regioselectivity depends on the relative stability of the two possible ene-hydrazines and their [3,3]-rearrangement transition states.

3.2.2 Leimgruber-Batcho Synthesis

Developed in 1976 by Leimgruber and Batcho at Hoffmann-La Roche, this two-step sequence is now the preferred industrial route for indoles bearing electron-withdrawing groups or unusual substitution patterns:

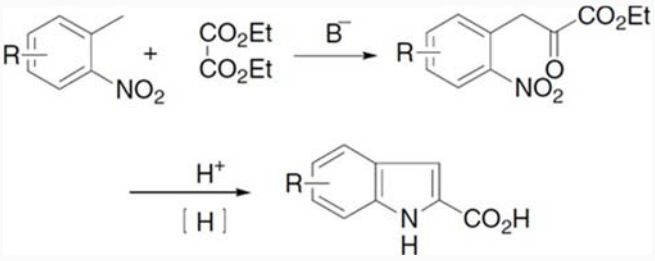
- Step 1: ortho-Nitrotoluene reacts with DMF dimethyl acetal (or DMF/acetal) and a pyrrolidine base at elevated temperature to give an enamine (β-dimethylaminovinyl intermediate).
- Step 2: Catalytic hydrogenation (Pd/C, H_2; or Fe/AcOH) reduces the nitro group to an amine, which spontaneously undergoes intramolecular condensation with the enamine to give the indole (after loss of the amine component).

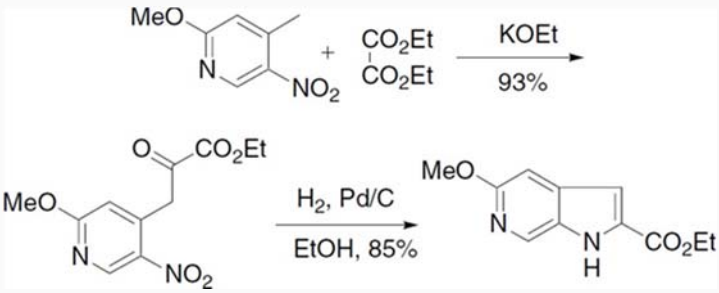


Scheme 3.4. Leimgruber-Batcho Synthesis (two steps).

3.2.3 Reissert Indole Synthesis

Starting from ortho-nitrotoluene (1) and diethyl oxalate (2): (1) Claisen condensation in the presence of NaOEt gives the α-keto ester intermediate; (2) reduction of the nitro group (Fe/AcOH or catalytic H_2) gives the indole directly via intramolecular condensation of the resulting amine with the α-keto group (loss of ethanol). This method, proposed in 1897, was one of the first to give unsubstituted indole.

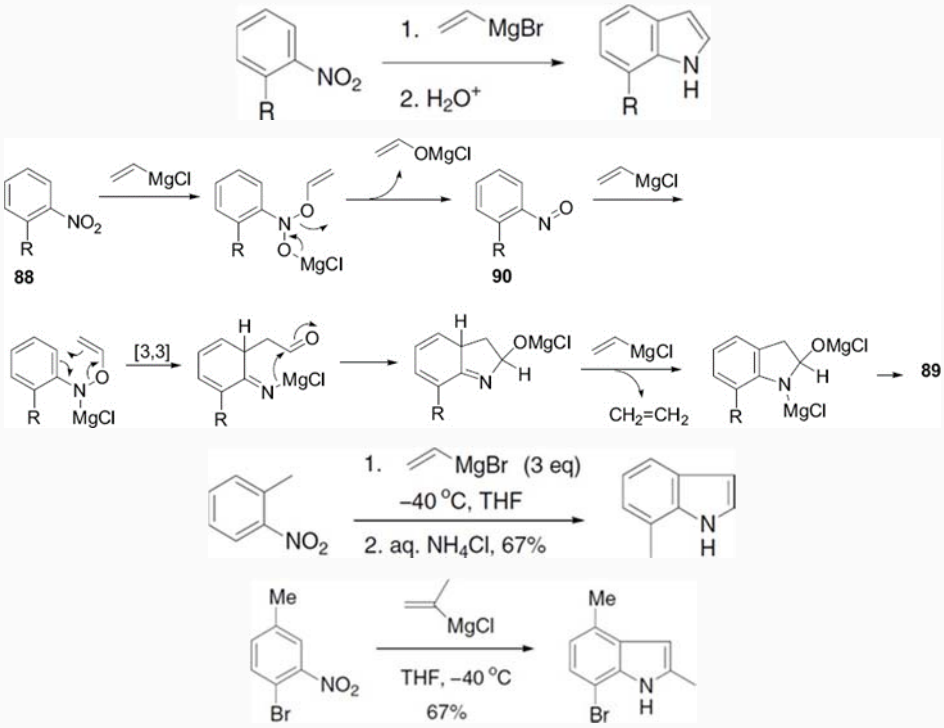




Scheme 3.5. Reissert Synthesis of Indole.

3.2.4 Bartoli Indole Synthesis

A modern method (Bartoli, 1989) based on the reaction of ortho-substituted nitroarenes with vinylmagnesium bromide (vinyl Grignard reagent, 3 equiv). The reaction proceeds through a Meisenheimer-type intermediate and gives indoles bearing substituents on the benzo ring. Particularly useful for making 7-substituted indoles (rare by other methods).

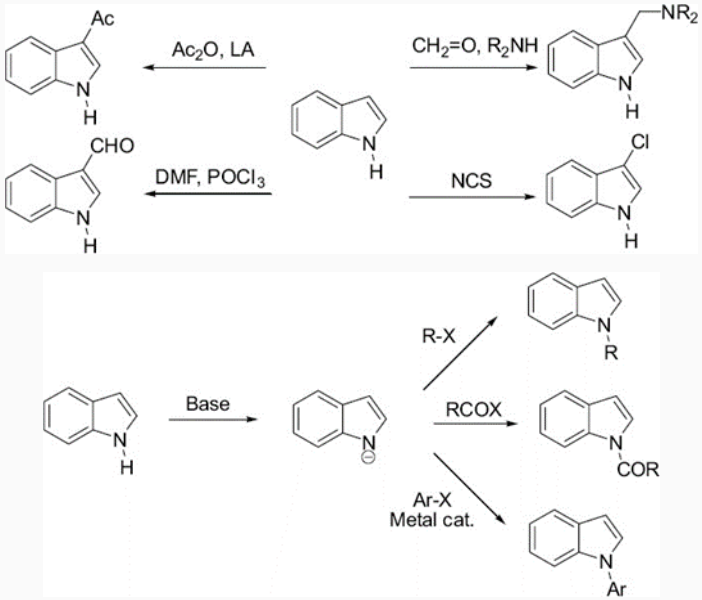


Scheme 3.6. Bartoli Synthesis of Indole.

3.3 Reactivity of Indole

Indole reacts with electrophiles preferentially at C-3 because this position has the highest electron density (HOMO coefficient). The arenium (Wheland) intermediate resulting from electrophilic attack at C-3 is stabilized by resonance with the nitrogen lone pair and the benzene ring system without disturbing benzene aromaticity.

- Formylation: Vilsmeier-Haack gives indole-3-carbaldehyde (C-3 formylation). If C-3 is blocked, N-formylation occurs.
- Alkylation/Mannich: Indole + HCHO + secondary amine → indole-3-Mannich base (used in synthesis of tryptamines).
- Acylation: C-3 acylation with acid chloride/Et_3N or anhydride. If C-3 is blocked → N-acylation.
- Nitration: Acetyl nitrate at 0 °C → 3-nitroindole; at higher T → mixture of 3-nitro and ring-nitrated products.
- Electrophilic substitution on the benzo ring: Occurs at C-5 or C-6 (meta to N in terms of electronic density) when C-3 is already occupied or when strong electrophiles are used.
- C-2 reactivity: Occurs naturally when C-3 is substituted; can be directed to C-2 by placing a group on nitrogen to block N-lone pair donation to C-3.



Scheme 3.7. Electrophilic substitution of Indole at C-3 and C-2.

3.4 Biological Importance of Indole

The indole ring is one of the most widely occurring heterocyclic scaffolds in nature:

- L-Tryptophan: Essential amino acid; precursor to serotonin, melatonin, tryptamine, and the niacin pathway.
- Serotonin (5-Hydroxytryptamine, 5-HT): Neurotransmitter in the central and enteric nervous system; mood, sleep, and appetite regulation.
- Melatonin (N-Acetyl-5-methoxytryptamine): Pineal gland hormone; circadian rhythm regulation.

- Indole-3-Acetic Acid (IAA, Auxin): Primary plant growth hormone; regulates cell elongation and tropism.
- Strychnine, Brucine: Bis-indole alkaloids from Strychnos nux-vomica; glycine receptor antagonists; extreme toxicity.
- Ergotamine, LSD: Ergot alkaloids containing the ergoline ring system (tetracyclic indole derivative).
- Sumatriptan (Imigran): 5-HT1B/1D receptor agonist; first-line treatment for migraine.
- Indomethacin: COX-1/COX-2 inhibitor; NSAID; contains a 2-methylindole with N-p-chlorobenzoyl group.
- Ondansetron: 5-HT3 receptor antagonist; antiemetic in chemotherapy; contains a carbazolone (tricyclic indole-like scaffold).

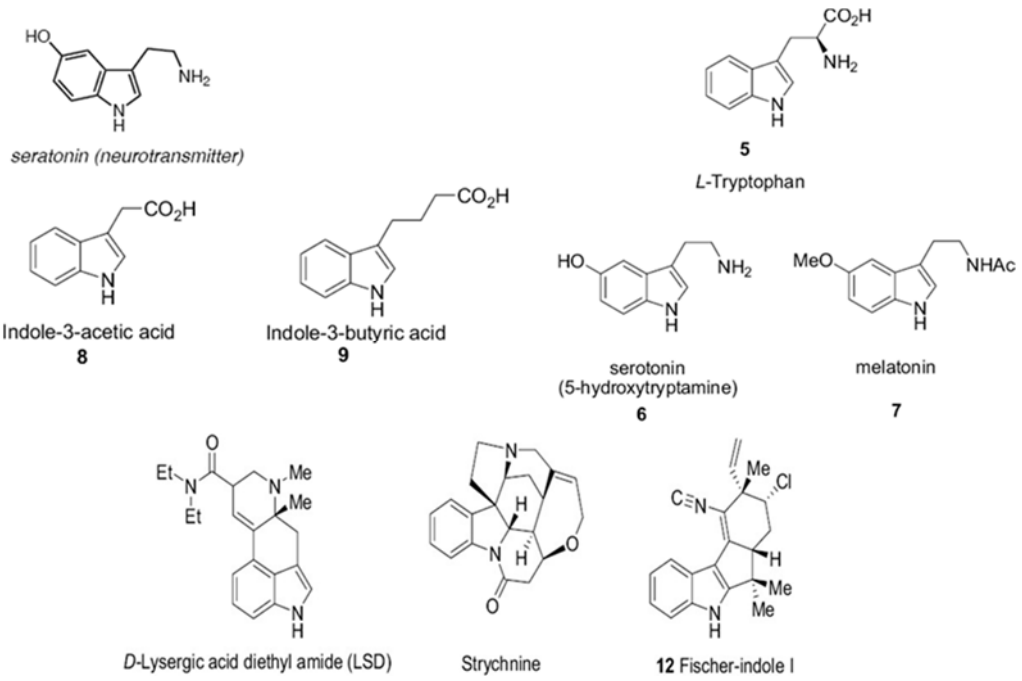


Figure 3.1. Biologically and clinically important indole derivatives: tryptophan, serotonin, melatonin, sumatriptan, indomethacin.

Chapter 4: Five-Membered Rings with Two Heteroatoms (Diazoles, Oxazoles, Thiazoles)

4.1 Imidazole (1,3-Diazole)

Imidazole ($C_3H_4N_2$, pKa 6.99) is a five-membered ring with two nitrogen atoms at positions 1 and 3. The two nitrogens play different roles: N-1 is pyrrole-type (lone pair in π ring; non-basic), while N-3 is pyridine-type (lone pair perpendicular to ring; basic). This dual character makes imidazole both an acid (N-H pKa ≈ 14.5) and a base (pKa of conjugate acid 6.99). Imidazole undergoes rapid tautomerism between 1H- and 3H-forms via proton transfer.

Biological importance: The imidazole ring of histidine is the catalytic residue in serine proteases (chymotrypsin, trypsin), ribonuclease, carbonic anhydrase, myoglobin, and hundreds of other enzymes. It acts as both a general acid and a general base because its pKa is near physiological pH. Purines (adenine, guanine) contain an imidazole ring fused to pyrimidine. Histamine (imidazole-ethylamine) mediates allergic responses and gastric acid secretion.

Drug examples: Metronidazole (antiprotozoal), omeprazole (proton pump inhibitor; contains 2-pyridyl benzimidazole), etomidate (anesthetic), clotrimazole, ketoconazole, fluconazole (antifungals).

Table 4.1 – Imidazole derivatives of pharmaceutical importance

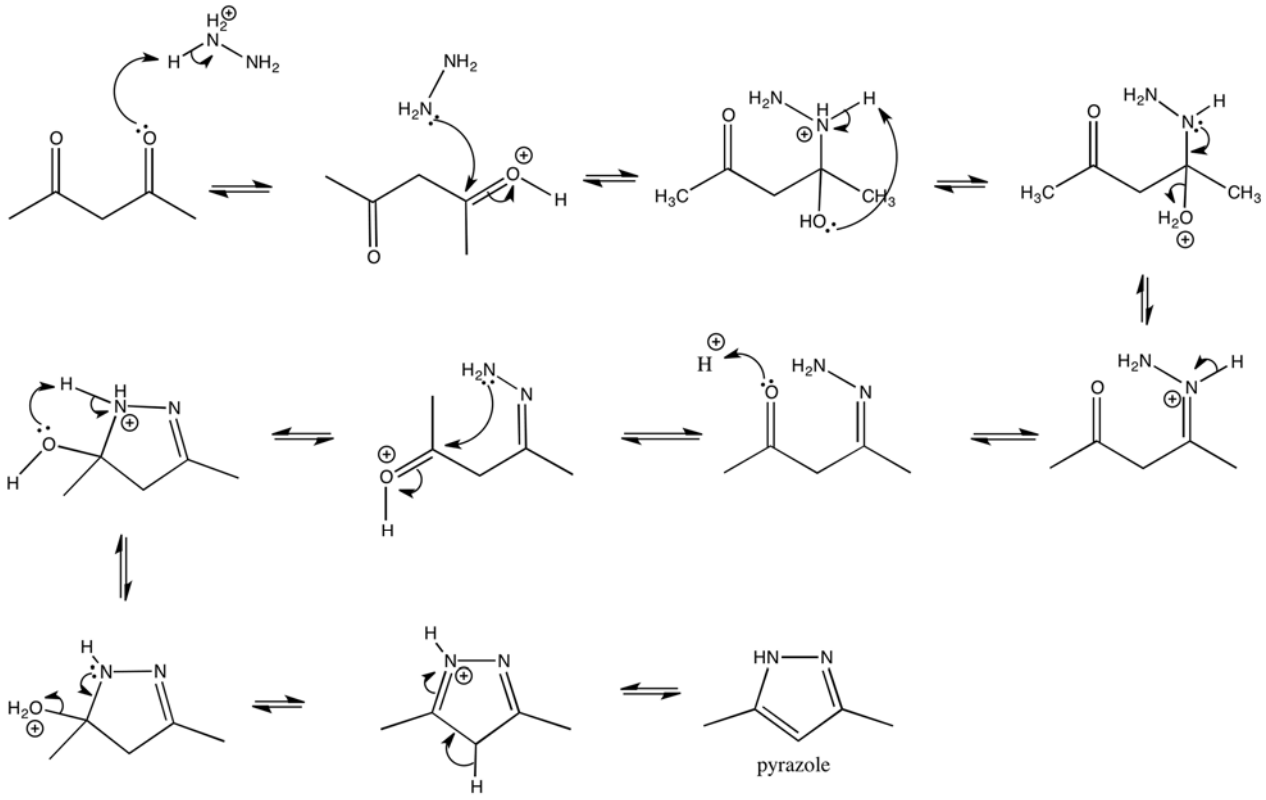
Drug Name	Heterocycle	Therapeutic Use
Metronidazole	2-Methyl-5-nitroimidazole	Antiprotozoal, antibacterial (anaerobes)
Omeprazole	Benzimidazole sulfinyl	Proton pump inhibitor (peptic ulcer)
Ketoconazole	Imidazole + dioxolane	Antifungal (systemic)
Etomidate	Imidazole ester	IV anesthetic (induction)
Histamine	Imidazole-ethylamine	Endogenous mediator (allergy, gastric acid)

4.2 Pyrazole (1,2-Diazole)

Pyrazole has two adjacent nitrogens. N-1 is pyrrole-type, N-2 is pyridine-type (pKa of BH^+ ≈ 2.5; weaker base than imidazole). The N-N bond provides additional ring rigidity. Pyrazoles are prepared from 1,3-dicarbonyl compounds + hydrazine (or substituted hydrazines) in one step;

unsymmetrical β-diketones give two regioisomeric products whose ratio depends on the reaction conditions and the substituent electronics. Pyrazole is moderately aromatic.

Drug examples: Antipyrine (phenazone, analgesic-antipyretic), phenylbutazone (anti-inflammatory), celecoxib (Celebrex; COX-2 inhibitor; pyrazole ring with CF_3 and aryl groups), rimonabant (CB1 receptor antagonist), sildenafil (Viagra; phosphodiesterase-5 inhibitor containing a pyrazolopyrimidinone core).



Scheme 4.1. Synthesis of pyrazole from 1,3-diketone + hydrazine

4.3 Oxazole and Isoxazole

1,3-Oxazole has oxygen at position 1 and nitrogen at position 3. It is aromatic but weakly basic (pKa BH^+ ≈ 0.8) and less reactive toward EAS than thiazole. Isoxazole (1,2-oxazole) has adjacent O and N; it is less aromatic and often used as a synthetic intermediate. Notable isoxazole drugs: valdecoxib, sulfamethoxazole, leflunomide (rheumatoid arthritis). Oxazole drugs: oxacillin (antibiotic), oxaprozin (NSAID).

4.4 Thiazole (1,3-Thiazole)

Thiazole contains S at position 1 (pyrrole-type: lone pair in ring) and N at position 3 (pyridine-type: basic; pKa ≈ 2.5). It is aromatic (RE ≈ 36 kcal/mol, stronger than imidazole). The most famous thiazole-containing natural compound is vitamin B1 (thiamine): a thiazolium ring linked to a pyrimidine ring; it is the cofactor for pyruvate decarboxylase and transketolase.

Hantzsch Thiazole Synthesis: α-halogenoketones react with thioamides. The S atom of the thioamide alkylates the α-carbon of the ketone; intramolecular cyclization of the nitrogen on the carbonyl carbon gives the 4,5-dihydrothiazole, which aromatizes by loss of water. Gives 2-substituted thiazoles.

Drug examples: Thiamine (B1), sulfathiazole (antibacterial), ritonavir (HIV protease inhibitor), bleomycin (antineoplastic), cefdinir (cephalosporin antibiotic containing an aminothiazole moiety at C-7).

Chapter 5: Pyridine and its Derivatives

Pyridine (azine, C_5H_5N, bp 115 °C) is the parent compound of a vast family of six-membered nitrogen-containing heterocycles. It was first isolated from coal tar in 1849 by Thomas Anderson and from bone oil by Anderson and Andersons independently. Its structure was proposed by Körner in 1869 and confirmed by Dewar using Kekulé-type arguments. The pyridine ring is the single most important heterocyclic structural motif in medicinal chemistry, found in thousands of drugs, vitamins, and alkaloids.

5.1 Structure and Aromaticity

Pyridine is isoelectronic with benzene: one CH unit is replaced by N. The nitrogen is sp^2-hybridized; its lone pair occupies an sp^2 orbital in the plane of the ring and does NOT participate in the aromatic π system. Pyridine therefore satisfies Hückel's rule with 6 π electrons (as does benzene) but the in-plane lone pair is freely available for protonation, coordination to metals, and alkylation. Because N is more electronegative than C, the four mesomeric limit structures show deficiency of electron density at C-2, C-4, and C-6 (α and γ positions relative to N). C-3 and C-5 (β-positions) retain near-benzene electron density. This asymmetric electron distribution has major consequences for reactivity (Table 5.1).

Table 5.1 — Comparison of benzene and pyridine:

Feature	Benzene	Pyridine	Explanation
Ring atoms	6 C	5 C + 1 N	N replaces one CH unit
π electrons	6	6	Both satisfy Hückel n=1
Lone pair on heteroatom	—	Yes (sp^2, in plane)	Does not contribute to aromaticity
Electron density	Uniform (δ−)	C-3 (β) highest; C-2,4,6 (α,γ) lowest	N inductively withdraws e^-
EAS rate vs. benzene	1	~10^{-7}	Highly deactivated ring
EAS position	All equivalent	C-3 (β)	Lowest deactivation at β

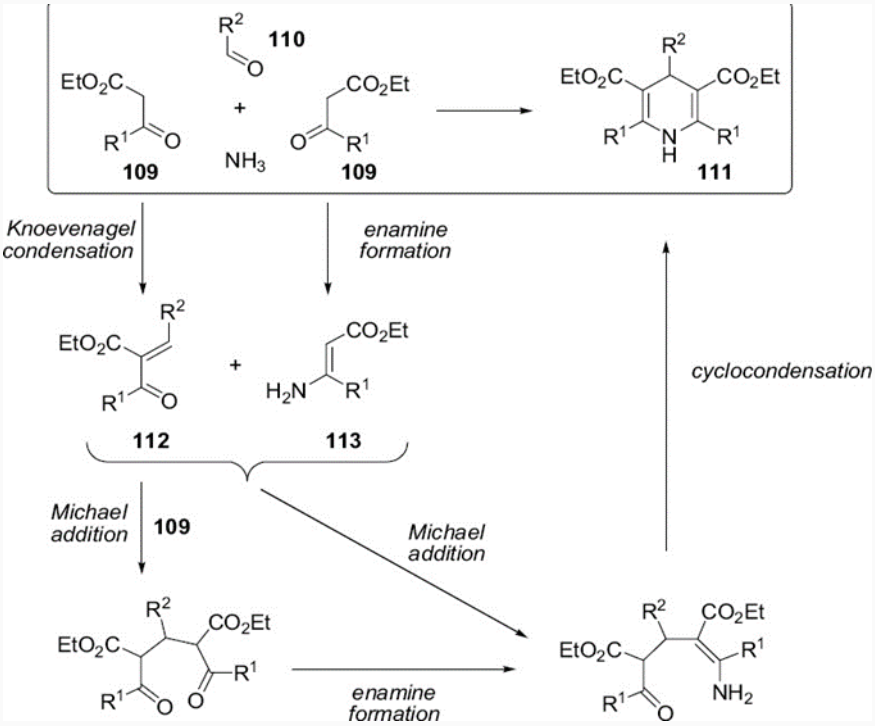
NAS	Rare	Facile at C-2/C-4	π-deficient ring promotes addition
Basicity (pKa BH^+)	—	5.23	N lone pair available
N-alkylation	—	Yes → pyridinium salts	Quaternary N salt
Oxidation of ring	Very resistant	Resistant (chain → COOH)	Ring stable; alkyl chain oxidized

5.2 Synthesis of Pyridine

5.2.1 Hantzsch Pyridine Synthesis (1882)

The Hantzsch multicomponent synthesis is the classical route to symmetrically disubstituted pyridines. The reaction involves three components: an aldehyde (1 equiv), a β-ketoester (2 equiv), and ammonia or ammonium acetate. The mechanism proceeds in four stages:

- Stage 1 (Knoevenagel): The aldehyde condenses with one β-ketoester in the presence of ammonia (or a base) to give an alkylidene β-ketoester (Knoevenagel product).
- Stage 2 (Enamine formation): The second molecule of β-ketoester reacts with ammonia/amine to give an enamine.
- Stage 3 (Michael addition): The enamine undergoes conjugate addition to the Knoevenagel product, giving a 1,4-addition product.
- Stage 4 (Cyclodehydration and oxidation): Intramolecular condensation gives a 1,4-dihydropyridine (Hantzsch ester). Oxidation with HNO_3, Ce(IV), I_2, or DDQ aromatizes this to the pyridine.

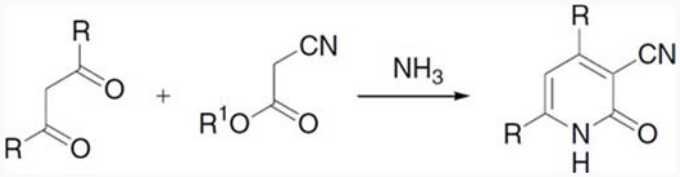


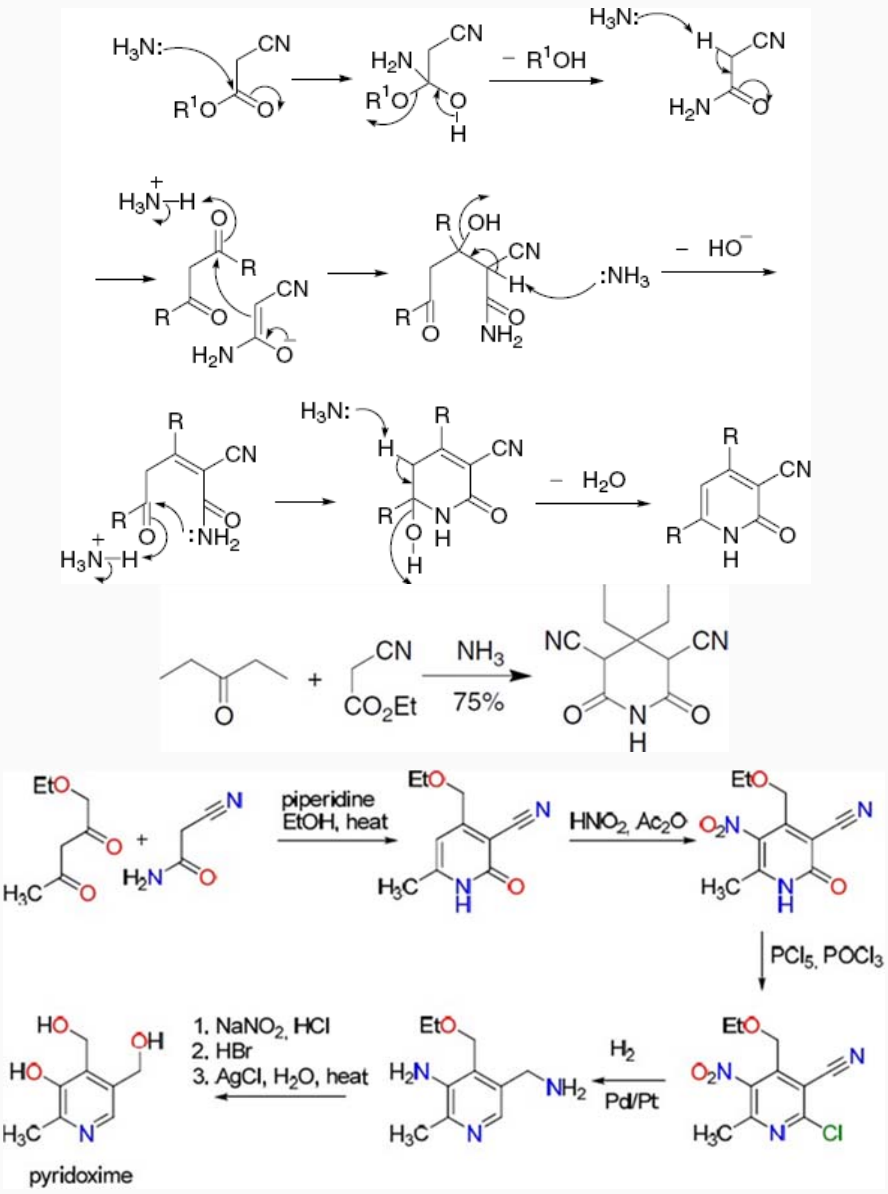
Scheme 5.1. Hantzsch Synthesis of Pyridine: full mechanistic sequence.

The Hantzsch esters (1,4-dihydropyridines) are themselves biologically important: nifedipine, amlodipine, nicardipine, and other calcium channel blockers all bear the 1,4-DHP scaffold. The Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) is a mild hydride-transfer reagent used in asymmetric organocatalysis.

5.2.2 Guareschi-Thorpe Synthesis

Cyanoacetic ester and 1,3-diketones react with ammonia to give 2-hydroxy-3-cyanopyridines (or 2-pyridones) in one step. The reaction is convergent: the cyanoacetate provides C-5 and C-6 of the ring, and the diketone provides C-2, C-3, and C-4. This synthesis was used historically for the preparation of vitamin B6 (pyridoxine) and its derivatives.





Scheme 5.2. Guareschi-Thorpe Synthesis of 2-hydroxypyridine.

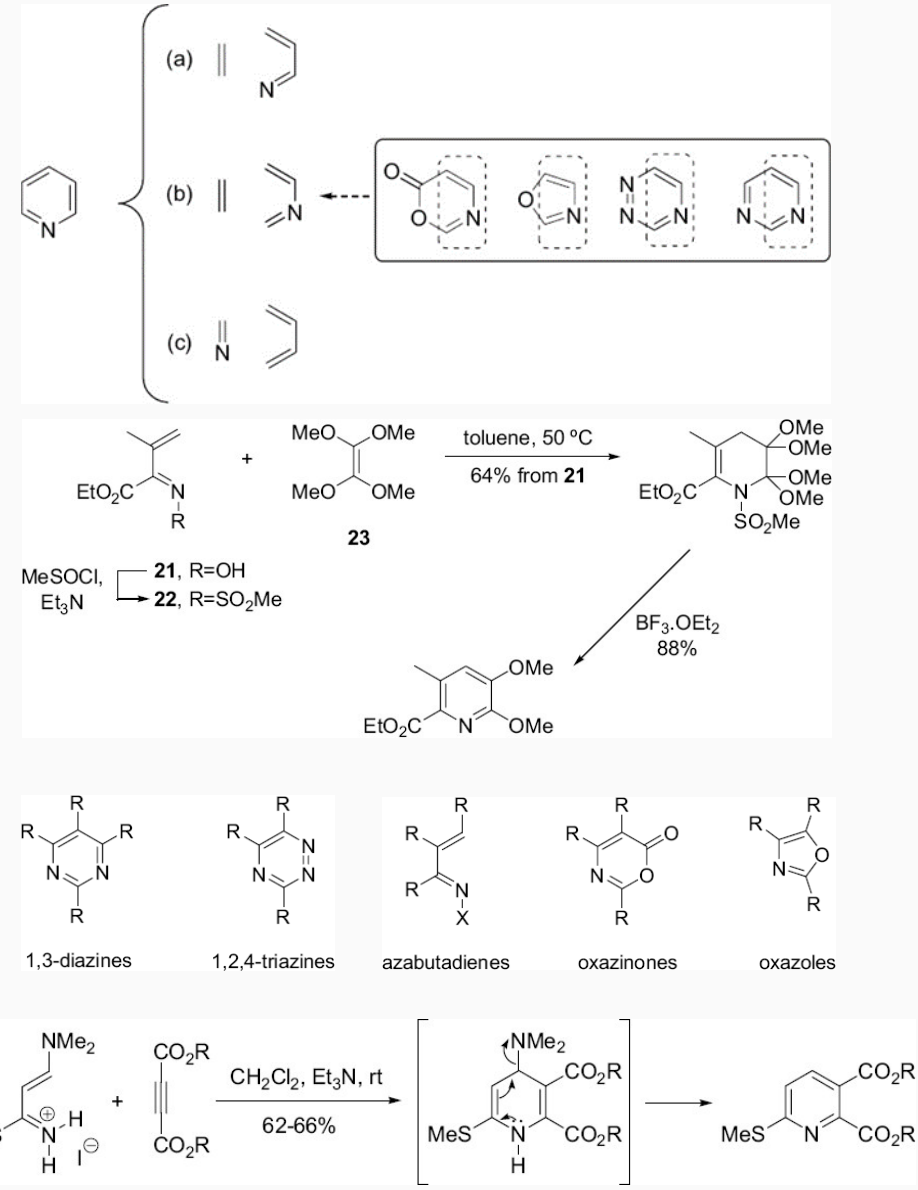
5.2.3 Zelinskyi-Borisov Method

Dehydrogenation (aromatization) of piperidine or N-substituted piperidines over Pt or Pd/C at 280–300 °C gives pyridine. This industrial method uses nicotinamide and related compounds as starting materials when the feedstock is available. It is particularly important for producing isotopically labelled pyridines.

5.2.4 Cycloaddition Approaches

Diels-Alder reactions between azadienes (nitrogen-containing 1,3-dienes or their synthetic equivalents) and dienophiles, followed by oxidation, provide an elegant approach to polysubstituted pyridines. The Diels-Alder/retro-Diels-Alder strategy with triazines (1,2,4-triazines

reacting with electron-rich dienophiles) is a powerful method for forming pyridine rings with high regiocontrol.



Scheme 5.3. Diels-Alder approach to pyridines (triazine strategy).

5.3 Reactivity of Pyridine

5.3.1 Electrophilic Aromatic Substitution (EAS)

EAS on pyridine is very difficult (the ring is ⍰10^7 times less reactive than benzene toward electrophiles). The nitrogen's electron-withdrawing inductive effect strongly deactivates the ring; the nitrogen lone pair coordinates to electrophiles/Lewis acids to form N-complexes that further deactivate the ring. When EAS does occur (usually under forcing conditions), it proceeds at C-3 (β-

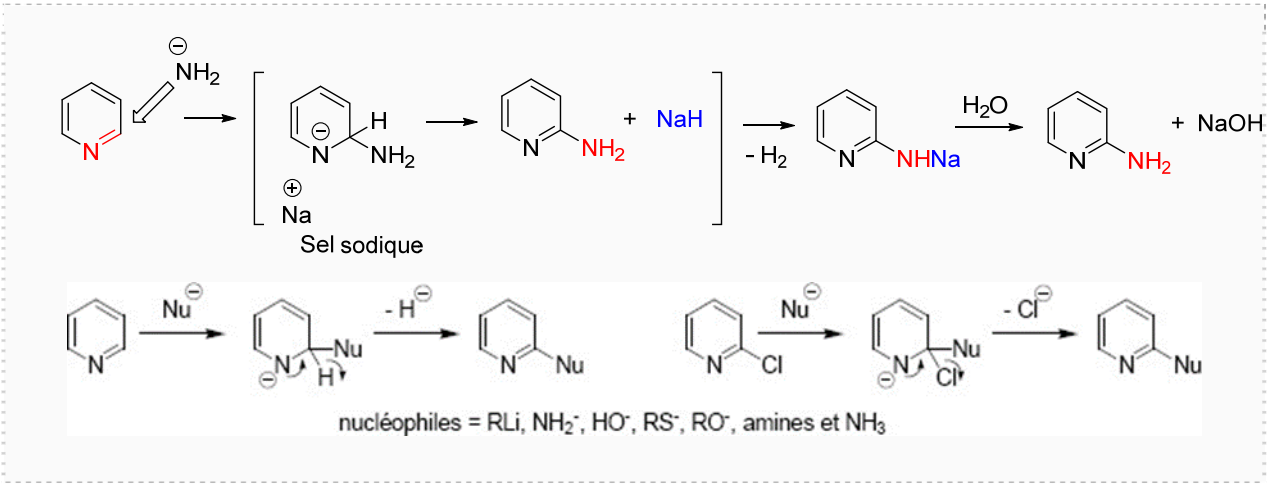
position), where the π-electron density is highest and the arenium intermediate is least destabilized.

- Sulfonation: Pyridine + SO_3 at 230 °C (or in presence of mercury sulfate as catalyst) → pyridine-3-sulfonic acid.
- Nitration: Mixed HNO_3/H_2SO_4 at 300 °C → 3-nitropyridine (only ⍰5% yield; mostly decomposition).
- N-Oxide activation: Pyridine N-oxide (from pyridine + H_2O_2/AcOH or m-CPBA) is more reactive toward EAS, giving 4-nitropyridine N-oxide with mixed acid; reduction of the N-oxide then gives 4-nitropyridine — a practical route to 4-substituted pyridines.

5.3.2 Nucleophilic Aromatic Substitution (NAS)

NAS is the characteristic reaction of electron-poor aromatics. Pyridine undergoes facile NAS at C-2 and C-4 (α and γ positions, where the partial positive charge is highest). The mechanism is addition-elimination (SNAr): the nucleophile adds to the electrophilic carbon to form a Meisenheimer complex (stable anionic adduct), then a leaving group departs. Common NAS reactions of pyridine:

- Chichibabin Amination (1914): Pyridine + $NaNH_2$ (or KNH_2) at 100–120 °C → 2-aminopyridine (+NaH, re-aromatization). The C-2 position is attacked by the amide anion; the intermediate dihydropyridine sodium salt eliminates NaH to give 2-aminopyridine. This reaction is industrially important for synthesizing sulfadiazine and other drugs.
- Meisenheimer Complex with RLi or RMgBr: Organolithium and Grignard reagents add to C-2 or C-4 of pyridine to give adducts that, after oxidation, give 2- or 4-substituted pyridines (Minisci conditions with appropriate oxidant).
- Halide Displacement: 2-Chloro- and 4-chloropyridines are readily displaced by amines, alkoxides, and thiols under mild conditions.



Scheme 5.4. Chichibabin amination mechanism and scope.

5.3.3 Basic Properties and Salt Formation

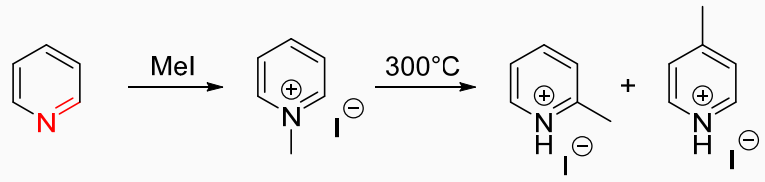
Pyridine (pKa = 5.23) reacts with strong acids to form stable pyridinium salts: with HCl → pyridinium chloride; with H_2SO_4 → pyridinium hydrogen sulfate; with RX (Menshutkin conditions) → N-alkylpyridinium salts (quaternary ammonium). Pyridinium N-oxides are formed by reaction with peracids. N-Alkylation dramatically increases the reactivity of the ring toward NAS (the positive N is even more electron-withdrawing). This strategy is exploited in the synthesis of the herbicide paraquat (methyl viologen).

5.3.4 Oxidation and Reduction

The pyridine ring itself resists oxidation under mild conditions (unlike benzene). However, alkyl substituents on the ring are oxidized to carboxylic acids by $KMnO_4$ or $K_2Cr_2O_7$. Reaction with peracids (m-CPBA) converts pyridine to pyridine N-oxide. Reduction of pyridine with H_2/Pt/C under pressure gives piperidine (full reduction); partial reduction under controlled conditions gives 1,2-dihydropyridine or 1,4-dihydropyridine.

5.3.5 Ladenburg Rearrangement

When N-methylpyridinium salts are treated with strong base at high temperature, they can undergo a rearrangement (Ladenburg, 1872) to give cyclopentadiene derivatives. The mechanism involves an azetidine intermediate formed by [2+2] cycloaddition at one face of the pyridinium ring. This rearrangement confirmed the cyclic structure of pyridine and its relationship to cyclopentadiene — a historic contribution to organic structural theory.

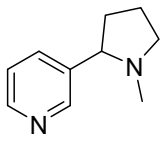


Scheme 5.5. Ladenburg Rearrangement of N-methylpyridinium.

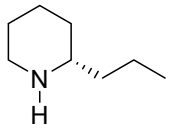
5.4 Biological and Pharmaceutical Importance

- NAD^+/NADH and $NADP^+$/NADPH: Nicotinamide adenine dinucleotide coenzymes; central to all cellular metabolism. The pyridinium/dihydropyridine redox couple transfers hydride in >400 enzymatic reactions.

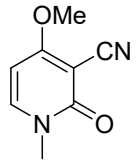
- Vitamin B_3 (Niacin/Nicotinic Acid): Deficiency causes pellagra (dermatitis, diarrhea, dementia). High doses lower LDL and raise HDL cholesterol.
- Vitamin B_6 (Pyridoxine/Pyridoxal/Pyridoxamine): Cofactor for transamination, decarboxylation, and other amino acid transformations. Deficiency causes peripheral neuropathy and epileptic seizures.
- Nicotine: Alkaloid of Nicotiana tabacum; agonist of nicotinic acetylcholine receptors; triggers dopamine release in the mesolimbic pathway (addiction).
- Morphine, Codeine: Opiate alkaloids from Papaver somniferum; piperidine ring; μ-opioid receptor agonists; analgesia.
- Isoniazid, Pyrazinamide: First-line antituberculosis drugs containing pyridine rings; inhibit mycobacterial cell wall synthesis.
- Omeprazole, Lansoprazole, Rabeprazole: PPIs containing a 2-pyridyl benzimidazole scaffold; inhibit H^+/K^+-ATPase in gastric parietal cells.
- Amlodipine (Norvasc): 1,4-Dihydropyridine calcium channel blocker; antihypertensive.



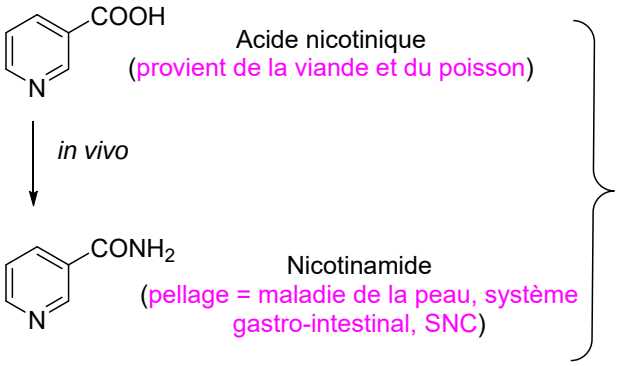
Nicotine
Alcaloide(tabac)
Toxique pour le système respiratoire

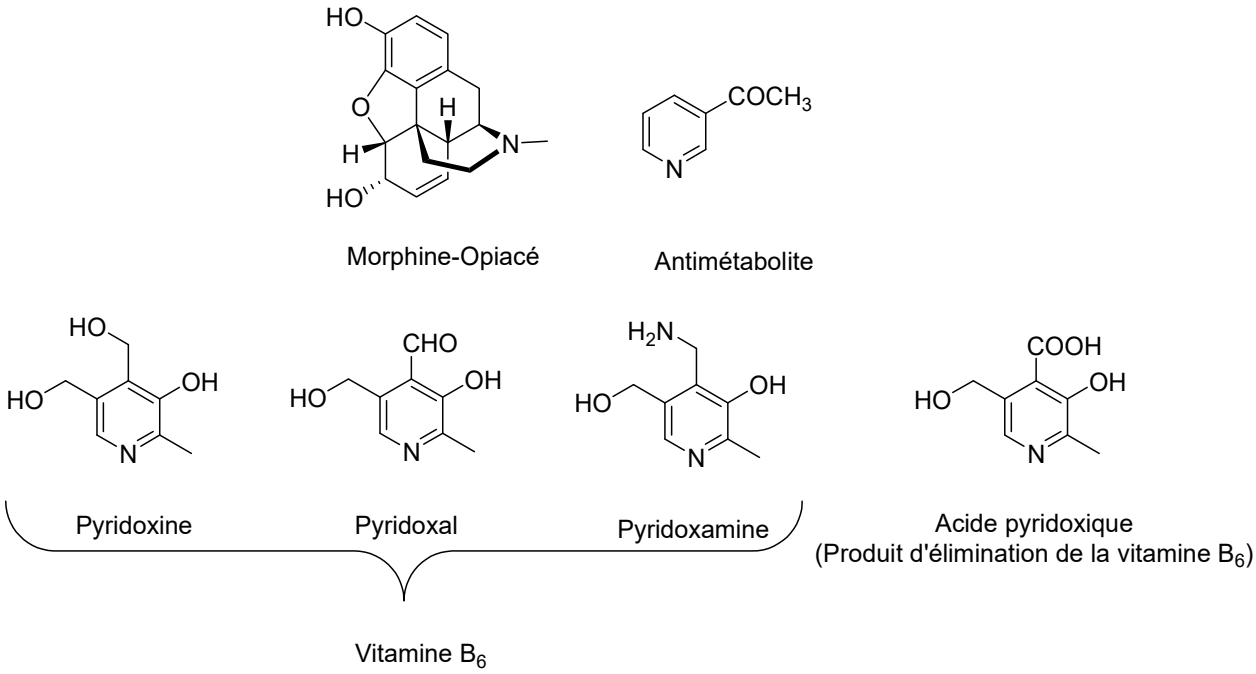


Conine
Alcaloide poison neurotoxique
(Conium muculatum)



Ricinine
Alcaloide peu toxique
(grain de Ricin)





Figures 5.1. NAD^+ structure, Morphine, Vitamin B_6, anti-metabolites.

Chapter 6: Quinoline, Isoquinoline, and Benzopyridines

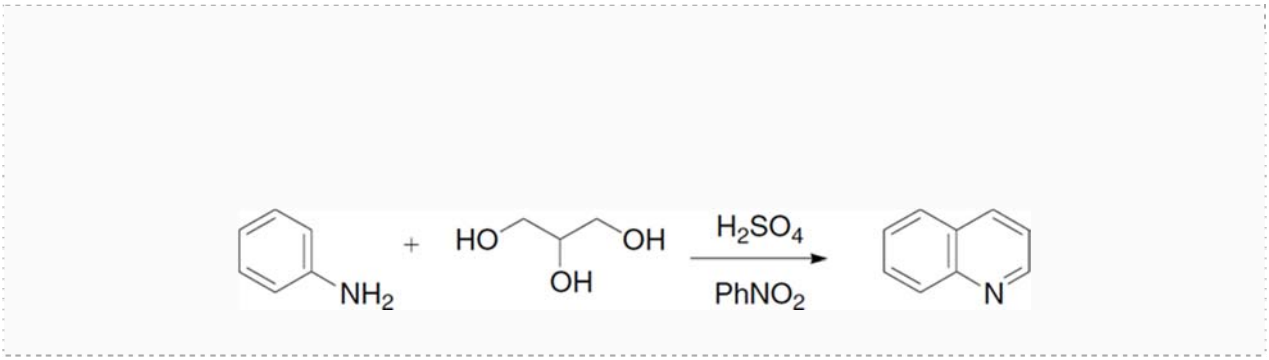
Quinoline (benzo[b]pyridine, 1-azanaphthalene, C_9H_7N, bp 237 °C) and isoquinoline (benzo[c]pyridine, 2-azanaphthalene) are the two isomeric benzopyridines. Both can be formally derived from naphthalene by replacing one CH with N: at position 1 in quinoline, at position 2 in isoquinoline. Both are colourless liquids isolated from coal tar; both are weakly basic (pKa: quinoline 4.85, isoquinoline 5.40) and electron-poor, sharing reactivity patterns with pyridine. They are quantitatively the most important benzo-fused pyridine systems in both natural products and synthetic drugs.

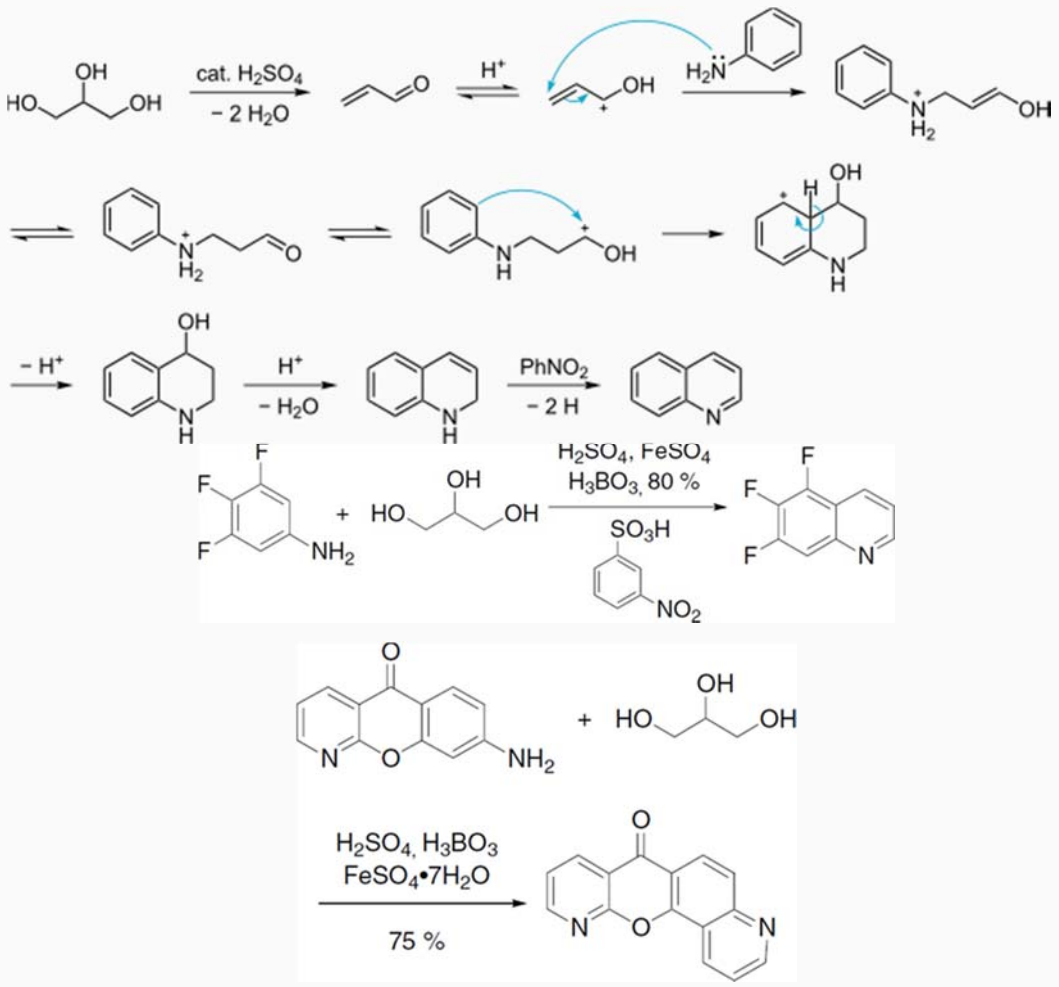
6.1 Synthesis of Quinoline

6.1.1 Skraup Synthesis (1880)

The Skraup synthesis (Zdenko Hans Skraup, 1880) is the oldest, most robust, and most industrially important method. It requires only readily available starting materials (aniline, glycerol, H_2SO_4, and an oxidant). The overall mechanism is:

- Step 1 (Glycerol dehydration): H_2SO_4 dehydrates glycerol in situ to acrolein (CH_2=CH-CHO).
- Step 2 (Michael addition): The aniline nitrogen undergoes conjugate addition to acrolein (1,4-addition) to give a β-aminoaldehyde.
- Step 3 (Cyclization — electrophilic ring closure): The aldehyde carbonyl undergoes intramolecular electrophilic attack on the benzene ring (para to NH_2), forming a dihydroquinoline after dehydration.
- Step 4 (Oxidation): The dihydroquinoline is oxidized to quinoline by nitrobenzene (acts as both solvent and oxidant) or $FeSO_4$/air. Arsenic pentoxide, p-chloranil, or other oxidants can also be used.

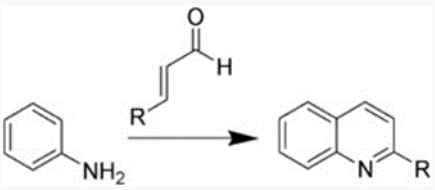


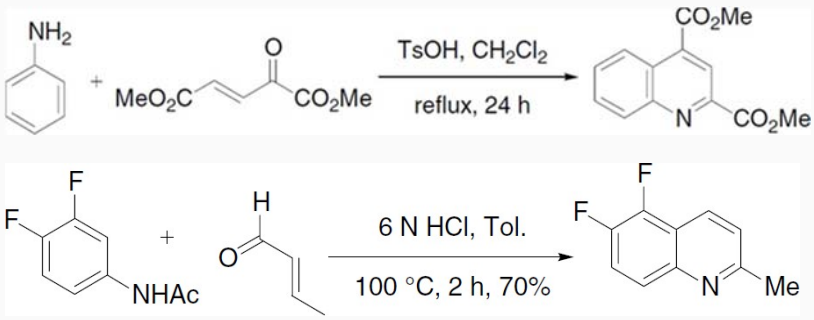


Scheme 6.1. Skraup Synthesis: mechanism and scope.

6.1.2 Doebner-von Miller Synthesis

This synthesis is a modification of the Skraup reaction. α,β-Unsaturated aldehydes or ketones (crotonaldehyde, cinnamaldehyde, methyl vinyl ketone) are used directly as the Michael acceptor instead of glycerol. Acid (HCl/$ZnCl_2$ or H_2SO_4) catalyses the reaction, and no external oxidant is needed (the initially formed 1,2-dihydroquinoline oxidizes to quinoline under the reaction conditions by loss of H_2). This method is preferred for preparing 2-methyl-, 2-phenyl-, or 2-arylquinolines.

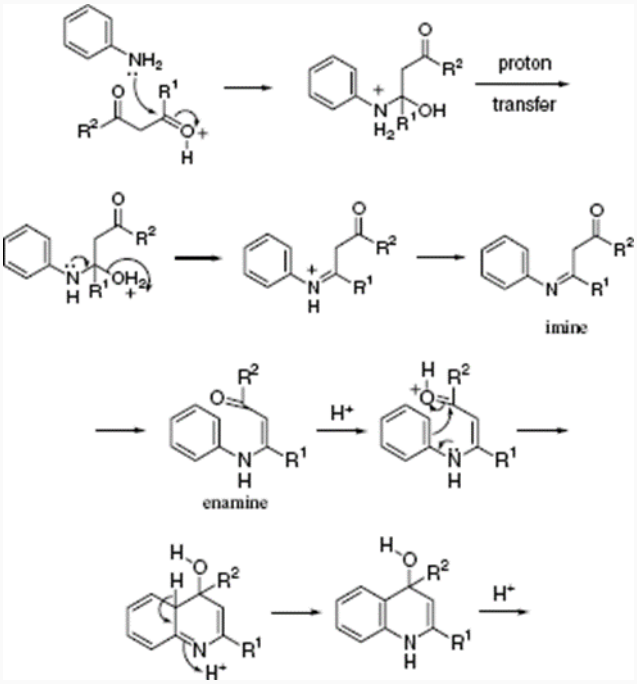


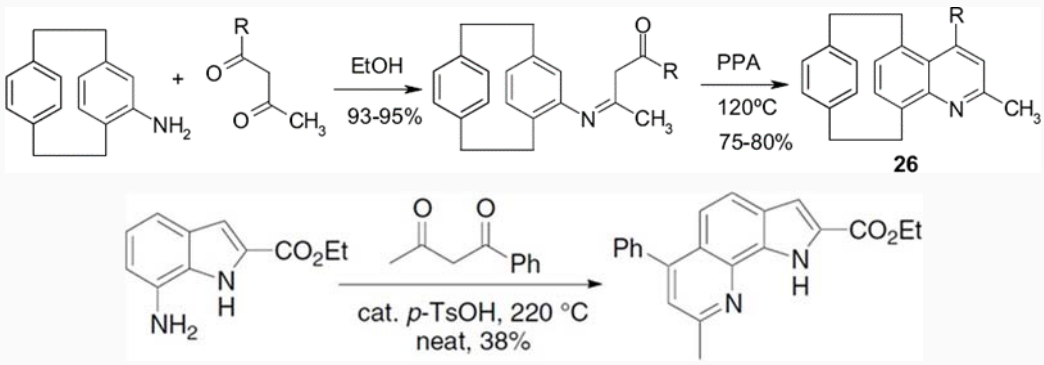


Scheme 6.2. Doebner-von Miller Synthesis mechanism.

6.1.3 Combes Synthesis

An arylamine (aniline) and a β-diketone react at room temperature to form a β-aminoenone (Schiff base product). On treatment with a strong acid (H_2SO_4, polyphosphoric acid), the β-aminoenone is O-protonated (activating it as an electrophile) and undergoes intramolecular electrophilic cyclization onto the benzene ring to give a dihydroquinolinol, which loses water to give the quinoline. This method works best with 1,3-diketones and gives 2,4-disubstituted quinolines.

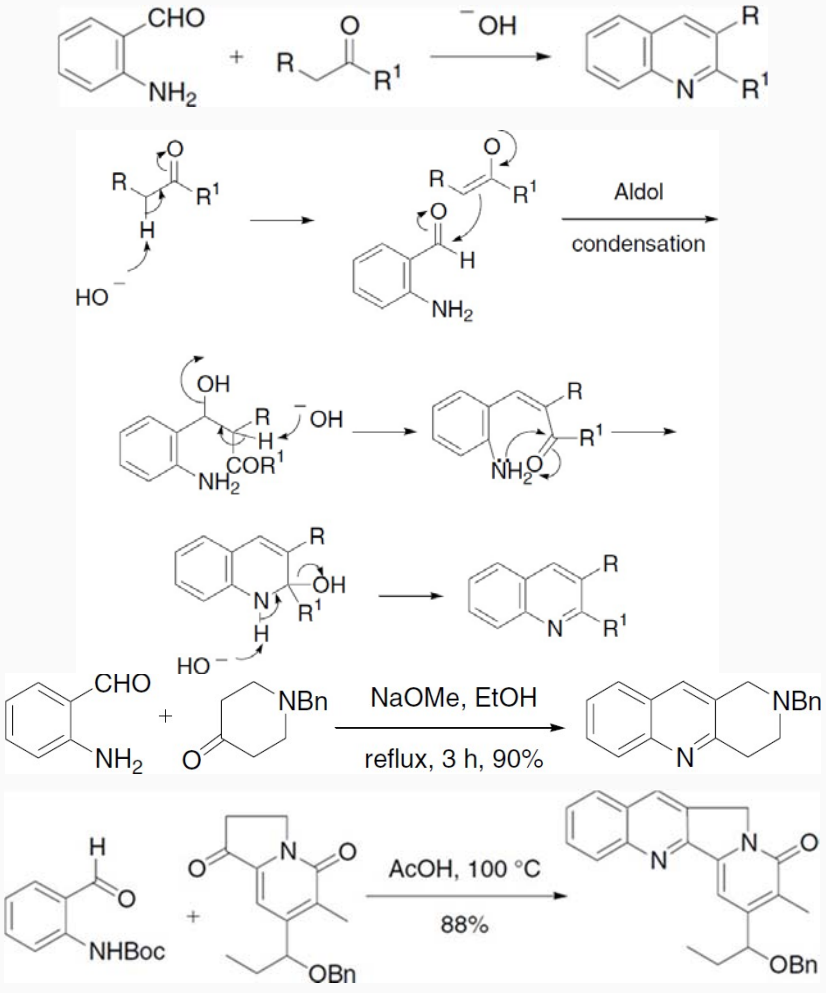




Scheme 6.3. Combes Synthesis (reaction and mechanism).

6.1.4 Friedländer Synthesis

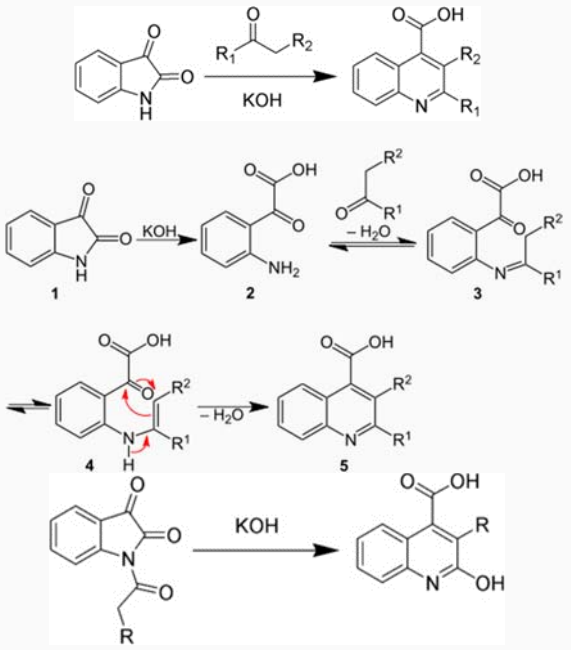
2-Aminobenzaldehyde (or 2-aminoacetophenone) and an α-methylene carbonyl compound react in the presence of base or acid to give the quinoline product directly. The mechanism involves imine formation followed by intramolecular aldol condensation and dehydration. This is one of the most versatile quinoline syntheses because the substituent pattern can be controlled by choosing appropriate carbonyl partners.



Scheme 6.4. Friedländer Synthesis (general, mechanism, and examples).

6.1.5 Pfitzinger Synthesis

Isatin (1H-indole-2,3-dione) reacts with α-methylene carbonyl compounds in alkaline medium (KOH or NaOH) to give quinoline-4-carboxylic acid derivatives (cinchoninic acid derivatives). The mechanism: (1) KOH opens the isatin ring by hydrolysis of the lactam C-3=O to give the isatinic acid anion; (2) this reacts with the enolate of the α-methylene carbonyl compound via a Claisen/aldol sequence; (3) ring closure and decarboxylation give the quinoline product.

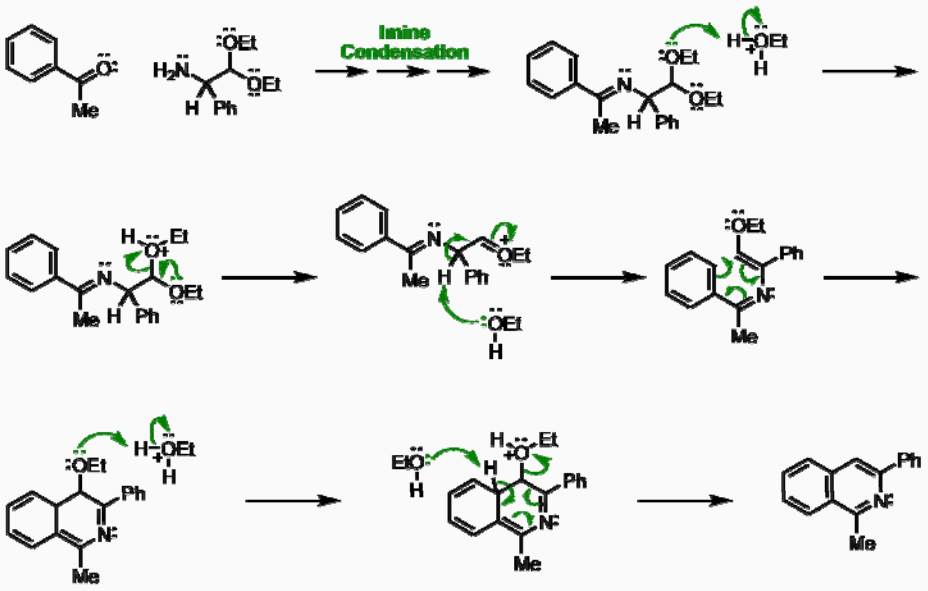


Scheme 6.5. Pfitzinger Synthesis with isatin.

6.2 Synthesis of Isoquinoline

6.2.1 Pomeranz-Fritsch Synthesis

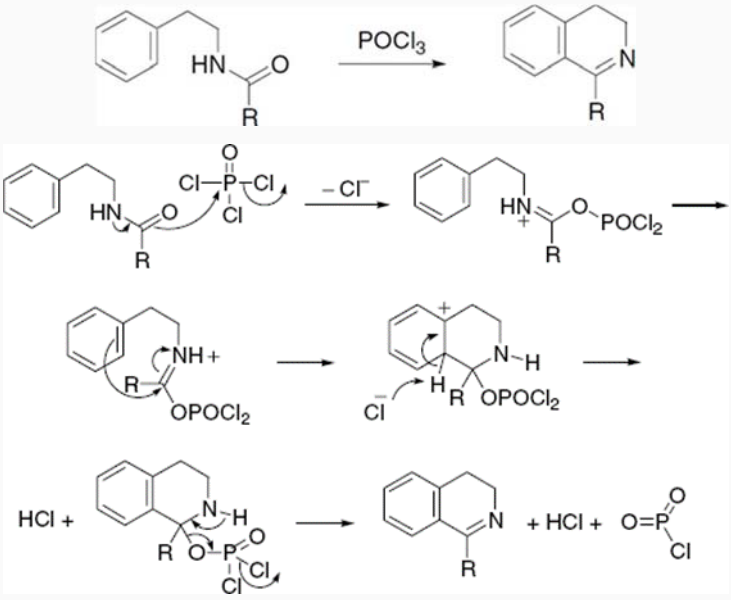
Benzaldehyde and aminoacetaldehyde dimethyl acetal react to form an aldimine (Schiff base). Treatment with H_2SO_4 or BF_3 promotes intramolecular electrophilic cyclisation of the acetal (which generates an oxocarbenium ion) onto the benzene ring, giving 1,2-dihydroisoquinoline, which is oxidised to isoquinoline. The Schlittler-Müller modification uses an N-formyl intermediate to improve yields. This method gives 1-unsubstituted or 1-substituted isoquinolines.

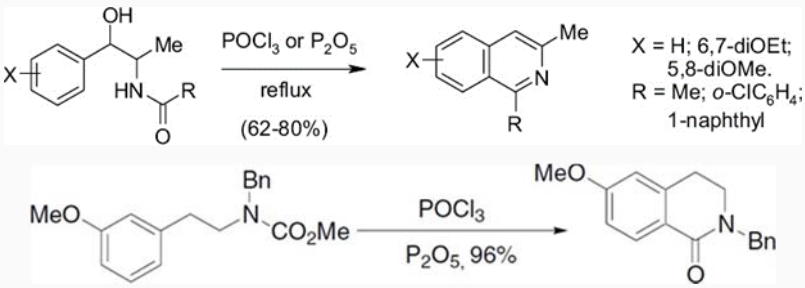


Scheme 6.6. Pomeranz-Fritsch Synthesis mechanism.

6.2.2 Bischler-Napieralski Reaction

A β-arylethylamine is first acylated with an acid chloride or anhydride to give a β-arylethylamide. Treatment with $POCl_3$, P_2O_5, or Eaton's reagent (P_2O_5/methanesulfonic acid) causes intramolecular electrophilic dehydration of the amide, generating a nitrilium or iminium ion that undergoes electrophilic attack on the benzene ring. The product is a 3,4-dihydroisoquinoline, which may be reduced ($NaBH_4$) to the tetrahydroisoquinoline or oxidized (DDQ, MnO_2) to the isoquinoline. This reaction is the basis for the biosynthesis of isoquinoline alkaloids (Pictet-Spengler condensation in the cell).

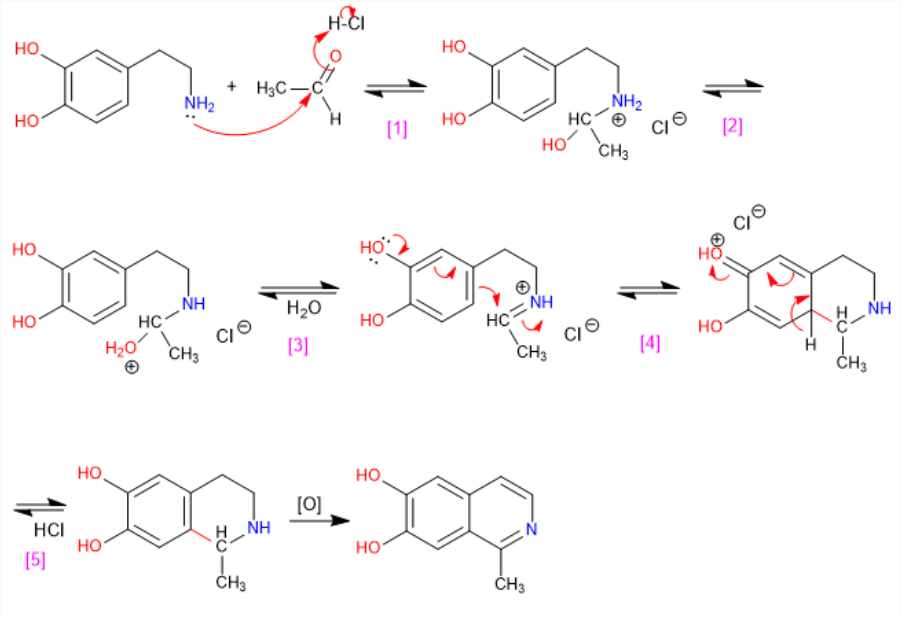




Scheme 6.7. Bischler-Napieralski reaction and examples.

6.2.3 Pictet-Spengler Synthesis

β-Arylethylamines condense with aldehydes (or ketones) under mild acid catalysis to form iminium ions (Schiff base, protonated), which undergo spontaneous intramolecular electrophilic attack on the activated benzene ring. The product is a 1,2,3,4-tetrahydroisoquinoline. This reaction is biomimetically important: it is the key step in the biosynthesis of numerous isoquinoline alkaloids (papaverine, morphine, berberine, colchicine) in plants. It is also widely used in asymmetric synthesis with chiral iminium ions to give enantioenriched products.



Scheme 6.8. Pictet-Spengler Synthesis mechanism.

6.3 Biological and Pharmaceutical Importance

- Quinine and Quinidine: Quinuclidine-quinoline alkaloids from Cinchona bark; antimalarials; quinine (antiarrhythmic); quinidine (class Ia antiarrhythmic).

- Camptothecin: Pentacyclic quinoline alkaloid from Camptotheca acuminata; topoisomerase I inhibitor. Basis of irinotecan (Camptosar) and topotecan (Hycamtin), used in colorectal and ovarian cancer.
- Chloroquine, Hydroxychloroquine: 4-Aminoquinolines; antimalarials (act by inhibiting heme polymerization in the parasite food vacuole); also used in rheumatoid arthritis and COVID-19 management (controversial).
- Fluoroquinolones (Ciprofloxacin, Levofloxacin, Moxifloxacin): Synthetic antibacterials containing a quinolone ring; inhibit DNA gyrase and topoisomerase IV.
- Morphine, Codeine, Papaverine: Isoquinoline alkaloids; μ-opioid receptor agonists (morphine, codeine); smooth muscle relaxant (papaverine).
- Berberine: Quaternary isoquinoline alkaloid; antimicrobial, anti-inflammatory, antidiabetic (AMPK activator).

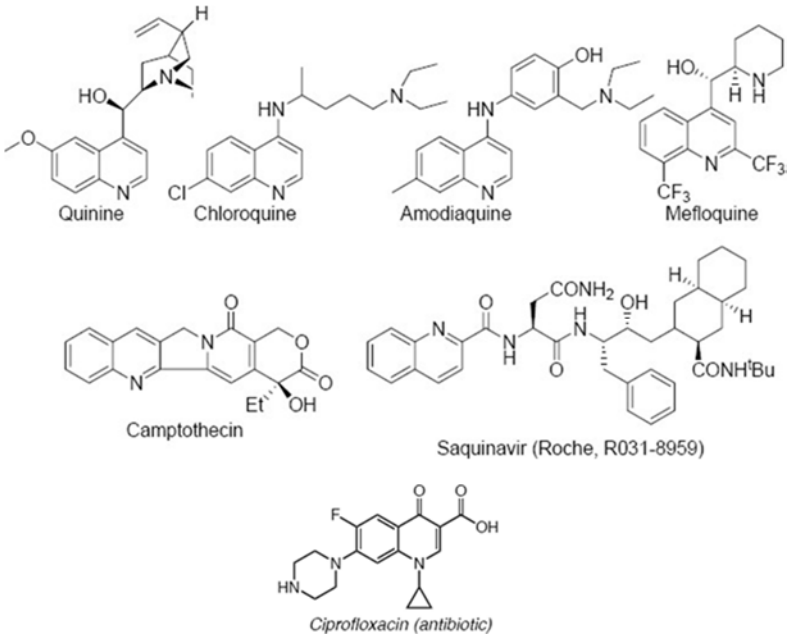


Figure 6.1. Clinically important quinoline and isoquinoline derivatives: quinine, camptothecin, ciprofloxacin, morphine, berberine.

Chapter 7: Pyrimidines and Purines — Nitrogenous Bases of Nucleic Acids

Pyrimidine (1,3-diazine) and purine are the two structural families that constitute the nitrogenous bases of DNA and RNA. They are among the most biologically significant molecules in all of chemistry: their base-pairing interactions (Watson-Crick hydrogen bonds) encode the genetic information of all known life forms, and their derivatives serve as coenzymes, second messengers, antibiotics, and drugs.

7.1 Pyrimidine

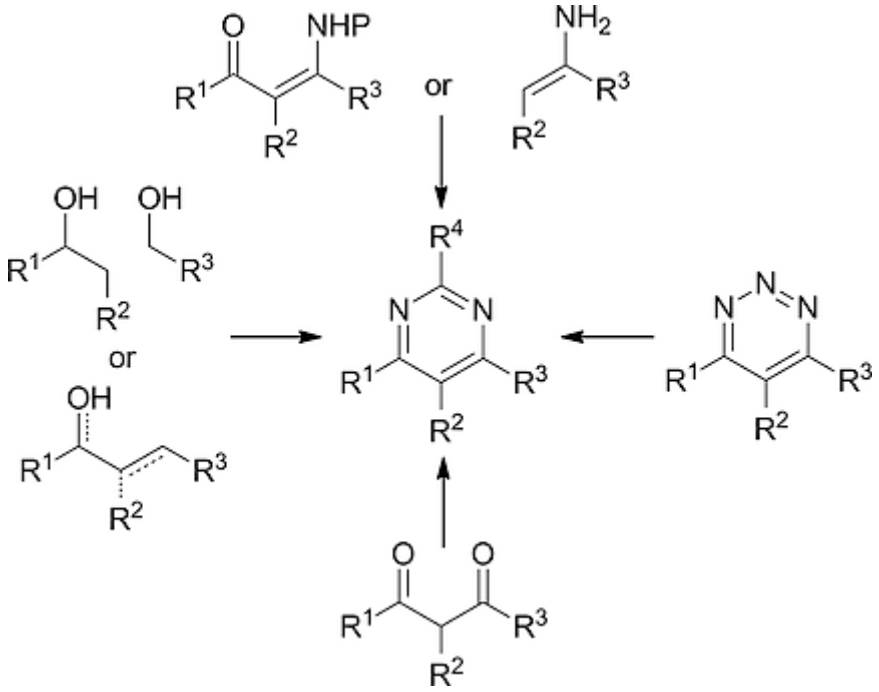
Pyrimidine ($C_4H_4N_2$, pKa $BH^+ \approx 1.3$) is a six-membered aromatic ring with two nitrogen atoms at positions 1 and 3. The two adjacent ring positions that lack nitrogen (C-4 and C-6) are both α to a nitrogen, making them highly electron-deficient. Pyrimidine is more electron-poor than pyridine; EAS is essentially impossible (only at C-5 under extremely forcing conditions). NAS at C-2, C-4, and C-6 is facile.

The three biologically essential pyrimidine bases are: cytosine (2-oxy-4-aminopyrimidine; in DNA and RNA), thymine (2,4-dioxy-5-methylpyrimidine; in DNA only), and uracil (2,4-dioxypyrimidine; in RNA only). The keto (lactam) form predominates for thymine and uracil under physiological conditions. The amino form predominates for cytosine.

Synthesis of Pyrimidines

General synthetic strategy: retrosynthetic analysis of the pyrimidine ring suggests disconnection at the C2-N1 and C2-N3 bonds. This gives a 1,3-dinucleophilic component (provides N-1, C-2, N-3) and a 1,3-dielectrophilic component (provides C-4, C-5, C-6). In practice:

- Urea/guanidine + malonic ester (Gould-Jacobs type): Urea (N-C-N, 1,3-dinucleophile) condenses with a malonate (1,3-dielectrophile) under acidic or basic conditions to give barbituric acid (2,4,6-trioxopyrimidine) or its 5-substituted derivatives (the barbiturates).
- Amidine + β-dicarbonyl: A guanidine or amidine (provides N-1, C-2, N-3) reacts with malondialdehyde or a β-diketone to give 2-amino-4,6-substituted pyrimidines.
- Biginelli reaction: Three-component condensation of an aldehyde, a β-ketoester, and urea gives 3,4-dihydropyrimidin-2(1H)-ones (DHPM compounds) in one pot; these can be oxidized to pyrimidines.



Scheme 7.1. Retrosynthetic analysis of pyrimidine and key synthesis examples.

Biological and Pharmaceutical Pyrimidines

- Cytosine, Thymine, Uracil: Constituent bases of nucleic acids; used in nucleoside analogue drugs (5-fluorouracil = 5-FU; an antimetabolite used in colorectal, breast, and skin cancers).
- Barbiturates (phenobarbital, thiopental): 5,5-Disubstituted barbituric acids; GABA-A receptor positive modulators; sedative-hypnotics.
- Sulfadiazine: Sulfonamide antibiotic containing a pyrimidine ring; competitive inhibitor of dihydropteroate synthase in bacteria.
- Trimethoprim: 2,4-Diaminopyrimidine; inhibits bacterial dihydrofolate reductase (DHFR); used with sulfamethoxazole in co-trimoxazole for UTI and Pneumocystis pneumonia.
- Zidovudine (AZT), Lamivudine: Nucleoside analogues (thymidine analogues); reverse transcriptase inhibitors; antiretrovirals against HIV.
- Cytarabine (Ara-C): Cytosine arabinoside; antileukemic drug; incorporated into DNA and inhibits chain elongation.

7.2 Purines

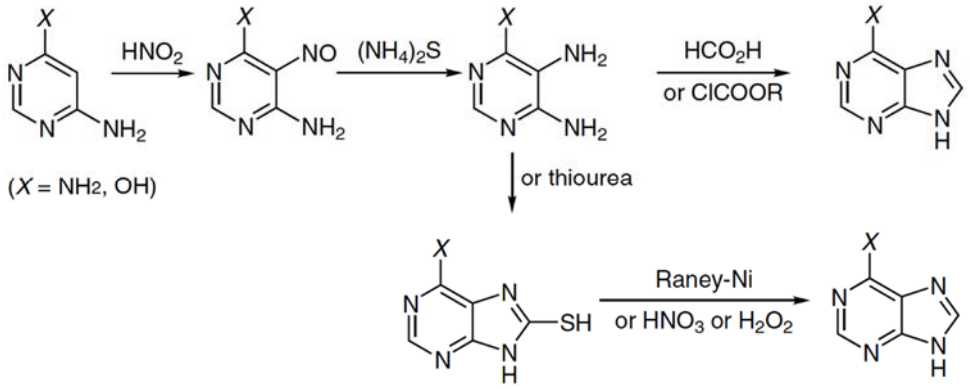
Purine ($C_5H_4N_4$) is a bicyclic compound formed by fusion of a pyrimidine ring (atoms 1–4, 6) and an imidazole ring (atoms 5, 7, 8, 9). The two nitrogen atoms of the imidazole moiety are at positions 7 (pyrrole-type; lone pair in ring) and 9 (N-H; also pyrrole-type in adenine/guanine). The total π system of purine has 10 electrons and satisfies Hückel's rule. Purine is slightly basic (pKa N-7 or N-9 protonation ≈ 2.4).

The four nucleic acid bases:

- Adenine (6-Aminopurine): Forms two hydrogen bonds with thymine (in DNA) or uracil (in RNA). Found in ATP, ADP, AMP, cAMP, NADH, FAD, and CoA.
- Guanine (2-Amino-6-oxopurine): Forms three hydrogen bonds with cytosine. Found in GTP, GMP, cGMP.

Synthesis of Purines — Traube Synthesis

The Traube synthesis (1900) starts from a 4,5-diaminopyrimidine and builds the imidazole ring in a subsequent condensation with formic acid or an orthoacid to give the imidazole C-8 atom. This approach mimics the biosynthetic pathway of purines. Steps: (1) N-formylation of one amino group; (2) cyclodehydration (acid or heat) to close the 5-membered ring. Variants using formamide or triethyl orthoformate give the unsubstituted purine in moderate yield.



Scheme 7.2. Traube Synthesis of Purine (4,5-diaminopyrimidine + HCOOH → purine)

Biological and Pharmaceutical Purines

- Caffeine (1,3,7-Trimethylxanthine): Found in coffee, tea, chocolate; non-selective adenosine receptor antagonist; CNS stimulant; mild bronchodilator.
- Theophylline (1,3-Dimethylxanthine): Adenosine receptor antagonist and PDE inhibitor; bronchodilator used in asthma and COPD.
- Allopurinol (4-Hydroxypyrazolo[3,4-d]pyrimidine): Xanthine oxidase inhibitor; reduces uric acid production; used in gout.
- Acyclovir (Zovirax): Guanosine analogue; herpes simplex virus thymidine kinase substrate → acyclovir triphosphate inhibits viral DNA polymerase; treatment of HSV and VZV.
- Azathioprine: Mercaptopurine prodrug; inhibits de novo purine synthesis; immunosuppressant in organ transplantation and autoimmune disease.
- Purine alkaloids: Adenosine (vasodilator; cardiac antiarrhythmic); inosine (muscle relaxant); xanthosine.

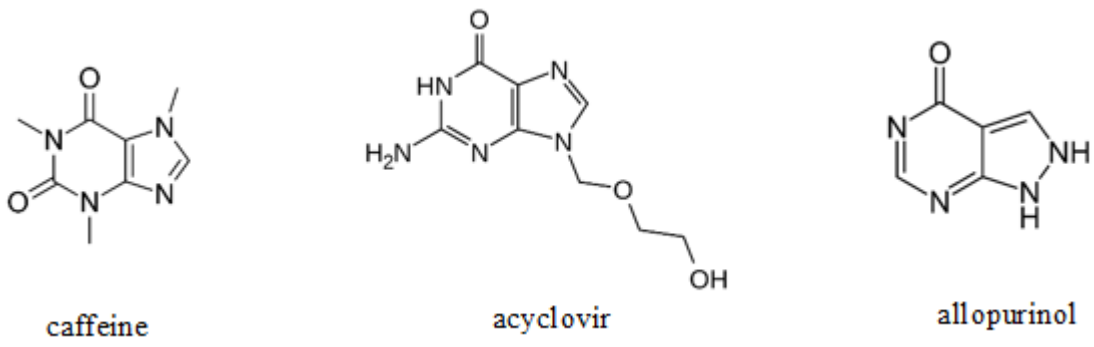


Figure 7.1. Nucleic acid bases and clinically important purine analogues: caffeine, acyclovir, allopurinol.

EXERCISES ON HETEROCYCLIC COMPOUNDS

Organic Chemistry | Tutorial Document | 6 Exercises with Detailed Solutions

01 EXERCISE 01 — Epoxide Opening — Aza-Payne and Lewis Acid Conditions

When epoxide **1** is treated under standard aza-Payne conditions, aziridine **2** is obtained as the overwhelmingly major product. However, when the same epoxide is treated in the presence of magnesium bromide ($MgBr_2$) as a Lewis acid, a mixture of products of identical molecular mass is obtained, among which compound **2** is present.

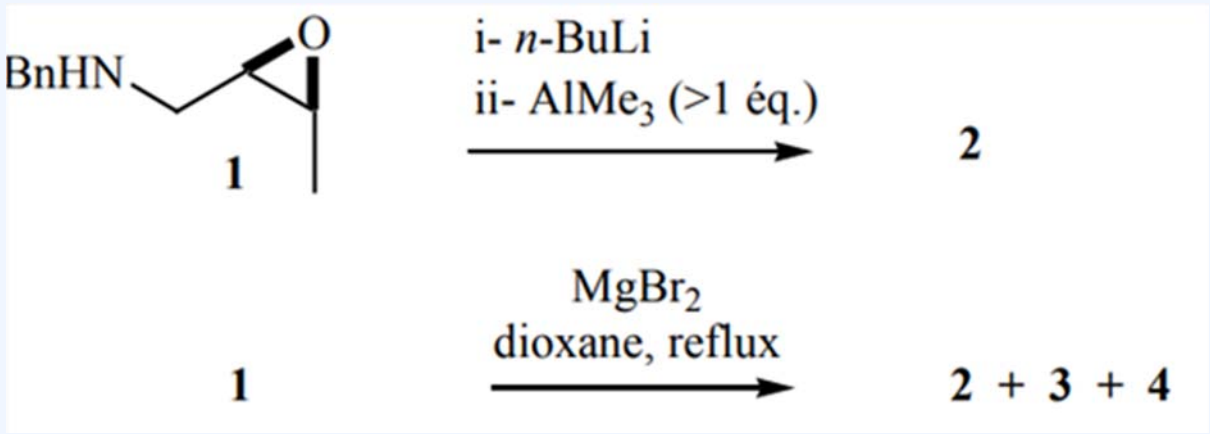


Figure 1 — Epoxide **1** structure and reaction scheme

a) Determine the structure of compound **2**.

b) Propose structures for compounds **3** and **4**, along with a brief mechanism for their respective formation.

✓ SOLUTION 01

a) Structure of compound 2:

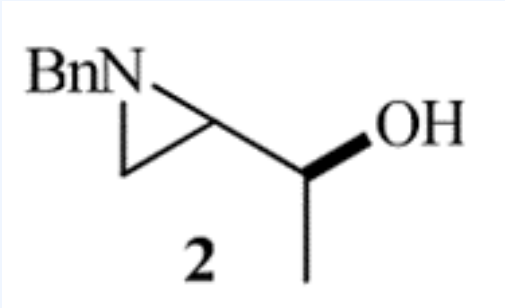


Figure 2 — Structure of aziridine **2.**

b) Structures of compounds 3 and 4 and formation mechanisms:

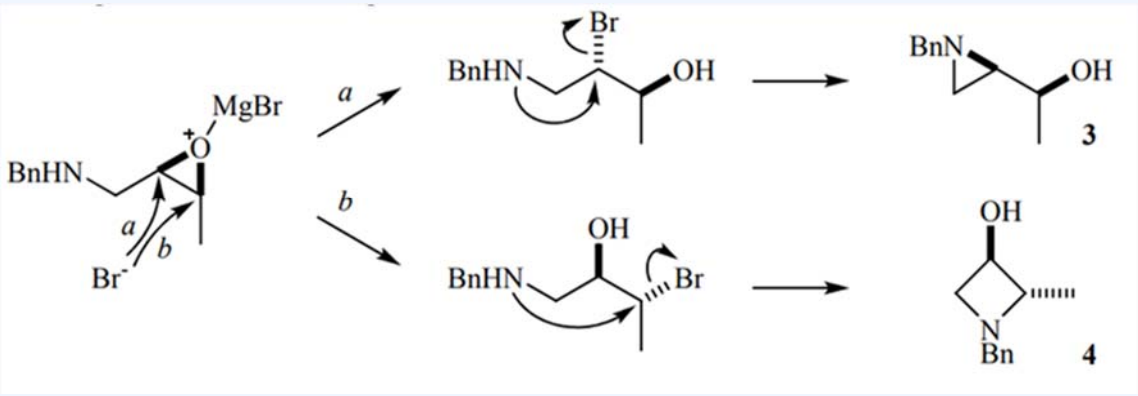


Figure 3 — Structures of **3** and **4** with mechanisms.

02 EXERCISE 02 — 1,2,3-Triazole Synthesis — Dimroth Rearrangement

Phenyl azide (PhN_3) and phenylacetonitrile ($PhCH_2CN$) are combined in the presence of sodium acetate in ethanol at room temperature. 5-Amino-1,4-diphenyl-1,2,3-triazole (**5**) is isolated in 80% yield. Upon heating compound 5 in refluxing pyridine, it undergoes the Dimroth rearrangement to give 5-anilino-4-phenyl-1,2,3-triazole (**6**).

a) Draw the structures of compounds **5** and **6**.

b) Give the mechanism for the formation of compound **5**.

c) Give the mechanism of the Dimroth rearrangement leading to compound **6**.

✓ SOLUTION 02

a) Structures of compounds 5 and 6:

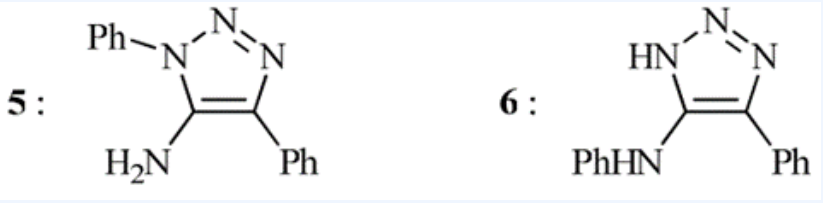


Figure 4 — Structures of triazoles **5** and **6.**

b) Mechanism of formation of compound 5:

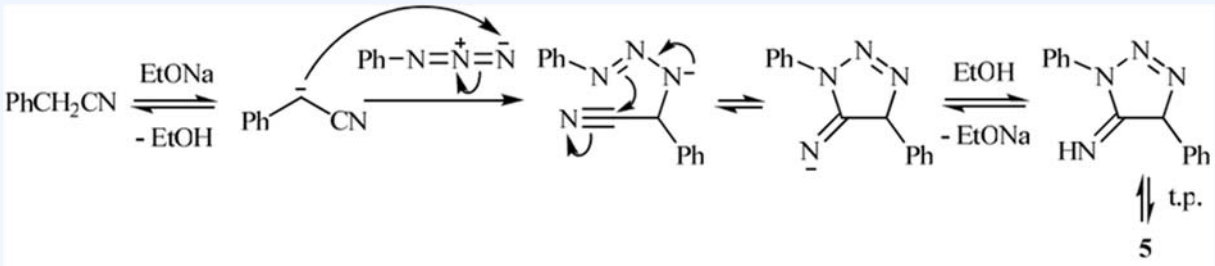


Figure 5 — Mechanism of triazole **5** formation.

c) Mechanism of the Dimroth rearrangement (5 → 6):

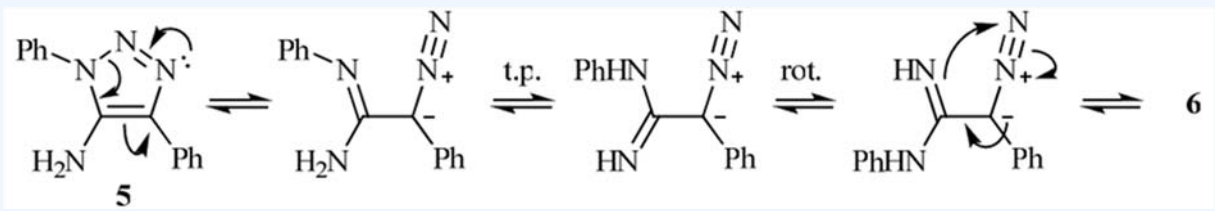


Figure 6 — Dimroth rearrangement mechanism.

03 EXERCISE 03 — Cycloaddition of Furfural with DEAD

Furfural reacts with diethyl azodicarboxylate (DEAD) to give an unexpected product **7**.

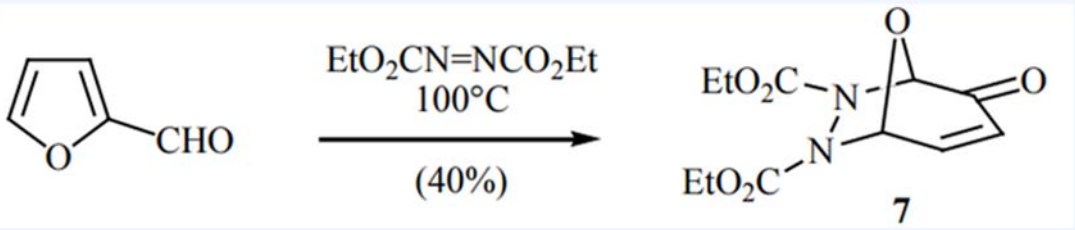


Figure 7 — Furfural + DEAD reaction scheme.

a) Propose a mechanism for the formation of compound **7**.

b) Name, in general terms, the reactions involved in your mechanism.

✓ SOLUTION 03

a) Mechanism of formation of compound 7:

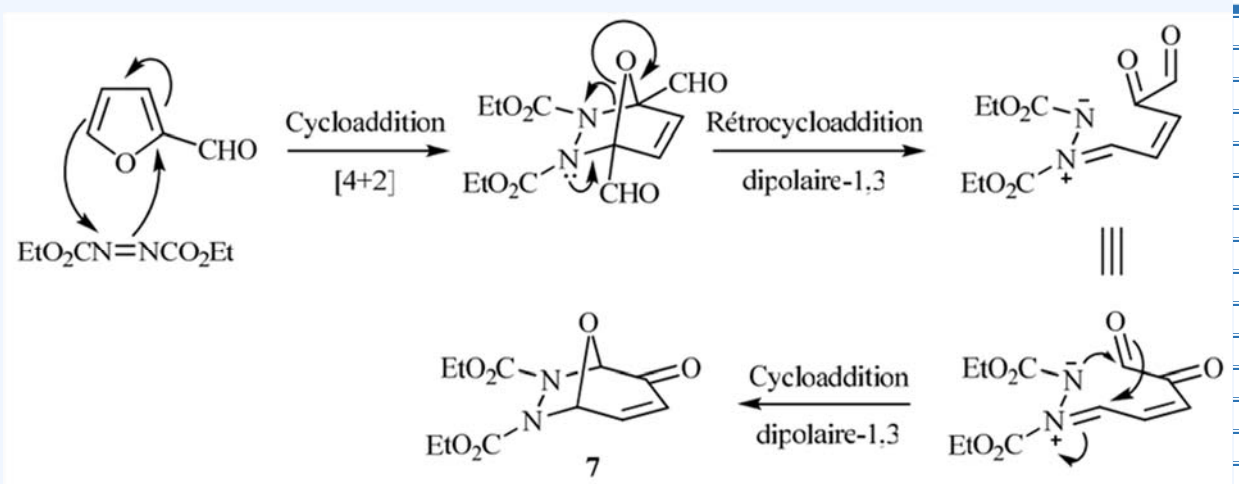


Figure 8 — Detailed mechanism for compound **7.**

b) General reaction types involved:

(See annotations within the mechanism above.)

04 EXERCISE 04 — Aromaticity and Basicity of Heterocycles

Consider the following heterocyclic compounds:

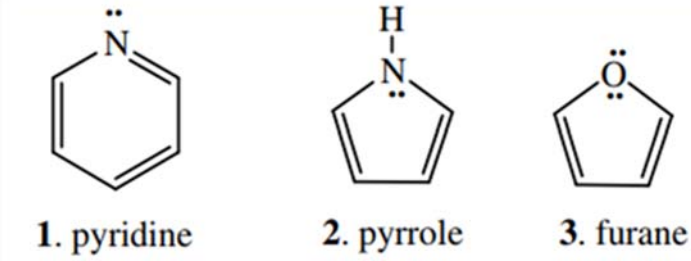


Figure 9 — Heterocyclic structures.

a) Indicate whether the lone pairs of the nitrogen and oxygen atoms participate in the aromatic system. State the hybridization of these heteroatoms.

b) Compare the basicities of pyridine and pyrrole and justify your answer.

✓ SOLUTION 04

a) Lone pair participation and hybridization:

#	Compound	Lone pair in aromatic system?	Hybridization
1	Pyridine (N)	No — lone pair in sp^2 orbital, not conjugated	sp^2
2	Pyrrole (N)	Yes — lone pair in p orbital, part of 6π system	sp^2
3	Furan (O)	Yes — lone pair in p orbital, part of 6π system	sp^2

b) Basicity comparison — Pyridine vs. Pyrrole:

Key Concept: Pyridine is more basic than pyrrole. In pyridine, the nitrogen lone pair occupies an sp^2 orbital in the plane of the ring and is not involved in the aromatic π system — it is therefore available for protonation. In pyrrole, the lone pair is donated into the π system to complete the 6-electron aromatic sextet (Hückel rule), making it unavailable for protonation and rendering pyrrole a very weak base ($pK_a(BH^+) \approx -3.8$) compared to pyridine ($pK_a(BH^+) \approx 5.2$).

05 EXERCISE 05 — Reaction Sequences — Bicyclic Heterocycles

Consider the reaction sequences below. Knowing that compounds **C** and **E** are bicyclic, draw planar structural representations of compounds **A** through **E**.

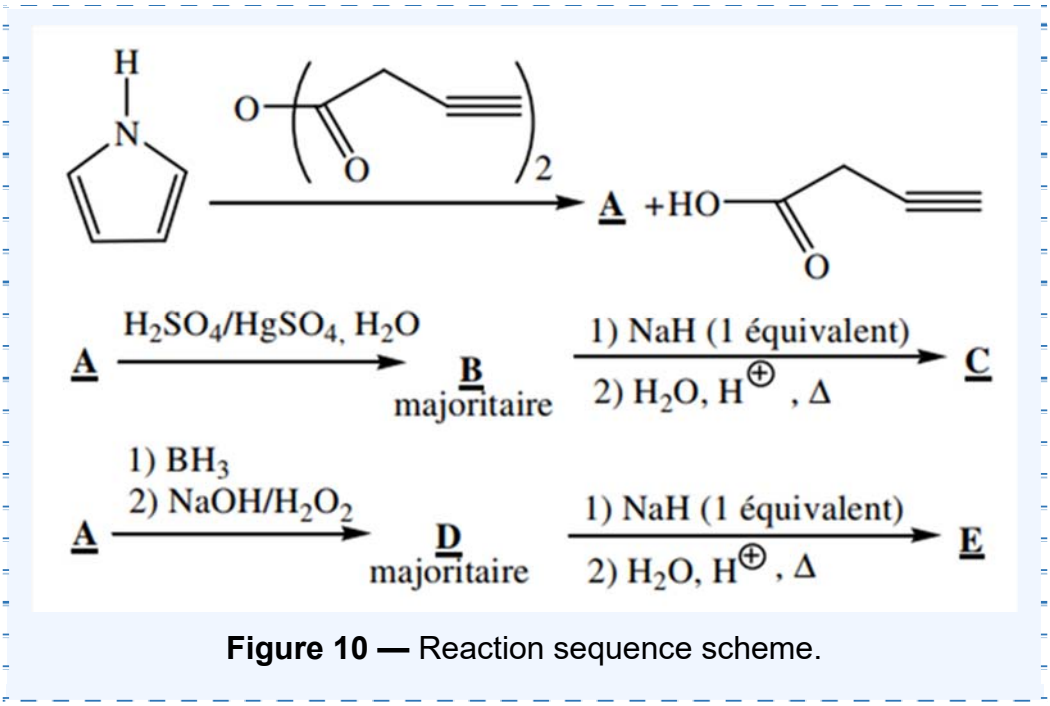


Figure 10 — Reaction sequence scheme.

✓ SOLUTION 05

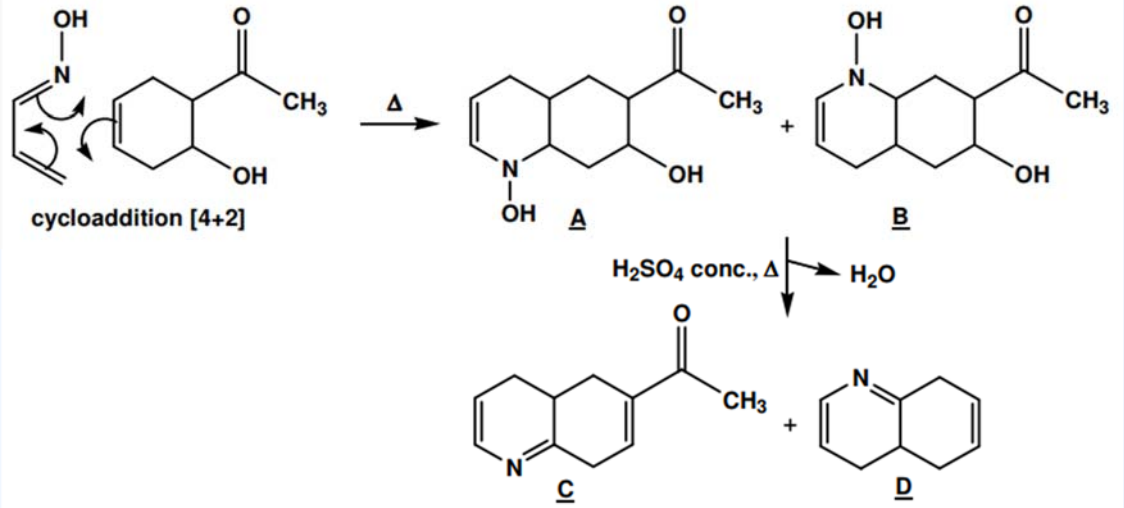


Figure 11 — Structures **A** to **E.**

06 EXERCISE 06 — Completing a Reaction Sequence

Complete the following reaction sequence by providing the missing reagents, conditions, and/or products:

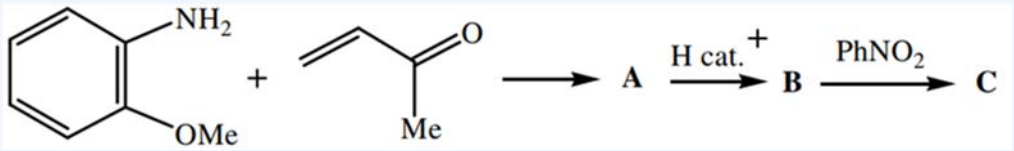


Figure 12 — Incomplete reaction sequence

✓ SOLUTION 06

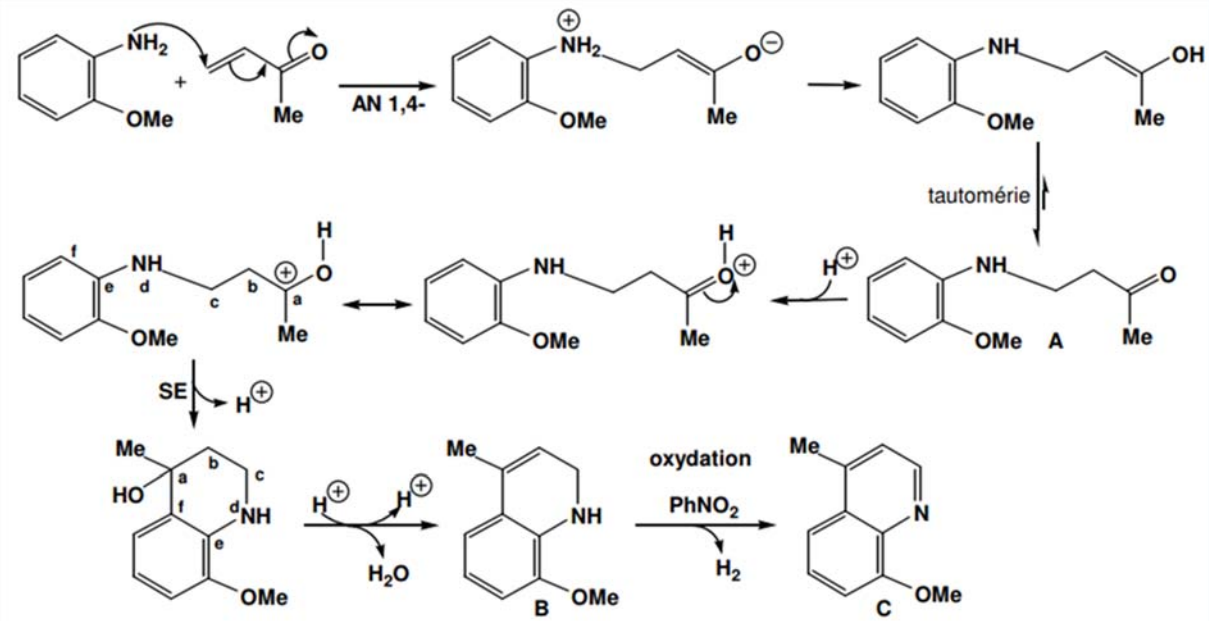


Figure 13 — Complete reaction sequence with products.

References

1. Milcent, R. Chimie Organique Hétérocyclique. EDP Sciences, 1997.
2. Milcent, R.; Barbier, F. Chimie Organique Hétérocyclique, 4th ed. EDP Sciences, 2014.
3. Katritzky, A.R.; Rees, C.W. (Eds.) Comprehensive Heterocyclic Chemistry, Vols. 1–8. Pergamon Press, Oxford, 1984; 2nd ed. 1996.
4. Pozharskii, A.F.; Soldatenkov, A.T.; Katritzky, A.R. Heterocycles in Life and Society. Wiley, Chichester, 2011.
5. Bélanger, G. Chimie Organique Hétérocyclique COR 706. Département de Chimie, Université de Sherbrooke, 2015.
6. Bekro, Y.A. Chimie Organique Hétérocyclique. LCBOSN, Côte d'Ivoire, 2017.
7. Rochais, C. Synthèse Organique Hétérocyclique — Cours résumé No. 15. Centre d'Études et de Recherche sur le Médicament de Normandie (CERMN), Université de Normandie.
8. Gaivaronskaya, L.A. Hétérochimie. Université de l'Amitié des Peuples (Lumumba), Moscou, 1983 (translated from Russian).
9. Joule, J.A.; Mills, K. Heterocyclic Chemistry, 5th ed. Wiley-Blackwell, Oxford, 2010.
10. Clayden, J.; Greeves, N.; Warren, S. Organic Chemistry, 2nd ed. Oxford University Press, 2012. [Chapters 29–32: Aromatic Heterocycles].

End of Pedagogical Document

Heterocyclic Chemistry · Master 1 Organic Chemistry · Semester 1 · 2025/2026