O2:

Heterocyclic Systems
Revision Guide

2018/19

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C4-14

Revision guide for Heterocyclic Systems 2018/19 course

Each of the key points in the course is outlined below. This is designed to be a checklist to help with revision and knowledge of this information in this document alone is not enough to complete the exams. You should be able to justify and explain each of the points listed. For the reactions, you should be able to recall the product, mechanism (explaining any selectivity) and recognise the starting materials required. For molecules/reactivity, you should be able to recall appropriate structures and justify reactivities using mechanisms.

Heterocycle Nomenclature

- Names of key heterocycles
  - *3,4-Membered:* oxirane = epoxide, azidirine, oxetane, azetidine
  - *5-Membered*: furan, pyrrole, thiophene, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, pyrazole, oxazole, thiazole, imidazole, isoxazole, isothiazole; 1,2,3-triazole; 1,2,4-triazole; tetrazole
  - *6-Membered*: pyridine, pyridazine, pyrimidine, pyrazine, piperidine, tetrahydropyran, morpholine
  - *Fused:* indole, quinoline, isoquinoline, benzofuran
  - Use the "dihydro, tetrahydro, etc…" prefix for compounds that are (partially) saturated
- Numbering of heterocyclic systems
  - Begins at 1 with the atom with the highest atomic number
  - Continue round the ring such that the next highest or most substituted (most interesting) atoms have the lowest numbers. Skip ring junctions – label those with letters
  - Exception: isoquinolines have the same numbering pattern as quinolines so nitrogen = 2

Heterocycle Reactivity

Aromaticity Revision

- Huckel's rules: an aromatic system must be **flat; cyclic; with contiguous orbitals; with 4n + 2 electrons**

Curly Arrow Revision

- Arrows show the movement of **2 electrons**
- **Start** at lone pairs, negative charges and electrons in bonds
- **Finish** at empty orbitals, positive charges and by putting electrons in antibonding orbitals to break bonds

6-Membered Aromatic Heterocycles (-ines)

- 6-Membered aromatic heterocycles are constructed using electronegative nitrogen sp^2 orbital so are **electron poor**
- The N in pyridine, etc… does not use its **lone pair** to construct the aromatic system so it is **basic** and **nucleophilic**. *i.e.* it can form pyridinium salts easily
- Electron-poor 6 membered heterocycles can be **attacked by strong nucleophiles** e.g. RMgCl, RLi
  - The attack occurs at the **2-position**: hard / charge control
  - In pyridines the resulting anion is **oxidised** by oxygen to form the substituted pyridine
  - **Pyridinium salts react faster** with nucleophiles because they are charged
    The size of the salt can control the regioselectivity of addition
  - The **Chichibabin** reaction is the attack of $^{\ominus}NH_2$ and loss of $^{\ominus}H$ to form a 2-aminopyridine

- Electron-poor 6 membered heterocycles with leaving groups undergo **nucleophilic aromatic substitution**
  - Pyridine rates of substitution: **4** > **2** (soft / orbital control) >> **3** (can't stabilise charge on N)
  - Pyridiniums undergo substitution faster because they are positively charged species
    rates of substitution: **2** > **4** (hard / charge control) >> **3** (can't stabilise charge on N)
  - Bases such as $NaNH_2$ or $LiNH_2$ can **eliminate** leaving groups like Cl to form **pyridyne** species with very strained triple bonds. These are very reactive and nucleophiles can attack **either end** of the triple bond
- **Deprotonation α** to the electron poor heterocycle is favoured when the negative charge can be resonance stabilised by the nitrogen atom
- Electron-poor 6-membered heterocycles undergo **electrophilic aromatic substitution reactions slowly**
  - Substitution is fastest in the **3-position** to avoid destabilising resonance forms with negative charges on the electronegative nitrogen atom
  - Reactions require **harsh conditions**: $Cl_2/AlCl_3$ for chlorination, Br_2/H_2SO_4 for bromination
  - **Nitration is very slow** but can be **catalysed by S-nucleophilic** reagents (mechanism not required)
  - Pyridines substituted with **electron donating groups** (Me, OMe, etc…) **react faster** as nucleophiles
  - **Isoquinolines/quinolines are better at electrophilic aromatic substitution** because reaction occurs at the least electron poor ring (*i.e.* not the N-containing ring) and some aromaticity is retained in the mechanism
- **Reissert Reaction** (not required)
- **Lithiation of halogenated** 6-membered heterocycles turns them into good nucleophiles
- **Directed lithiation using amides** to direct deprotonation and create good nucleophiles
- **Hydroxypyridines**
  - Have electron-donating oxygen so are more **electron rich** and much **more nucleophilic**
  - **2- and 4- hydroxypyridines** undergo tautomerization between carbonyl and alcohol forms and have "less aromatic character"
  - Can be converted to chloropyridines using $POCl_3$, etc…
- **Pyridine-*N*-oxides**
  - **Formed** by reaction of pyridines with oxidants such as peracids, e.g. **MCPBA**
  - **Reduced** back to pyridines using phosphines such as **PPh_3** driven by formation of $Ph_3P{=}O$
  - **More reactive as nucleophiles** due to electron donating oxygen atom on ring
  - **More reactive as electrophiles** due to permanent positive charge on nitrogen atom

5-Membered Aromatic Heterocycles (-oles)

- 5-Membered aromatic heterocycles are constructed using high energy lone pairs so are **electron rich**
- Electron rich → **good nucleophiles** and react through the **1/5 AND 2/3** (*i.e.* all) positions
  - Reaction is preferred at the 1/5 position because the charge is stabilised over more centres in the intermediate but will occur at 2/3 when other sites are blocked
  - Undergoes **electrophilic aromatic substitution reactions** such as Friedel-Crafts
  - …also undergoes **Vilsmeier reaction**. N.B. mechanism for formation of active species from DMF/$POCl_3$
  - **Bromination** and **nitration** proceed by a double addition/single elimination mechanism
- **Indole** is most **nucleophilic** at the **3-position** to avoid breaking the aromaticity of the ring
- **Indole** reacts with formaldehyde and dimethylamine in a **Mannich reaction**
- Electron rich heterocycles promote the **leaving of leaving groups α to the ring** *i.e.* excellent at SN1
- **Porphorin synthesis**: 5-membered heterocycle is **nucleophile** to a carbonyl, then promotes loss of H_2O in SN1 with another 5-membered heterocycle nucleophile. Catalysed by acid or Lewis acid
- Indole promotes the **leaving of leaving groups α to the ring** *e.g.* ammonium salts in SN1
  Gramine is a useful for building block through this mechanism
- 5-Membered heterocycles are **lithiated at the 2-position** with *n*BuLi, etc. to form excellent nucleophiles
- 5-Membered heterocycles undergo **Diels-Alder cycloaddition**, the "diene" is locked in reactive conformation
- 5-Membered heterocycles can be **reduced with H_2**: thiophene = easy >> furan / pyrrole = hard
- **Tetrazoles** are **acidic** (pKa ~ carboxylic acids): the anion is stabilised across 4 electronegative N atoms
- **Tetrazoles** are **nitrogen rich** and can be explosive through loss of N_2

Heterocycle Synthesis

Revision

- Look back through your notes on **imine formation** and **acetal formation**
  These are very helpful mechanisms for this course
- **5- and 6-membered rings are very fast to form**: favoured by minimal strain and entropy

Condensation, Cyclisation and Dehydration

- Heterocycles can be accessed by a **condensation**, **cyclisation** and **dehydration** sequence
  Find appropriate starting materials by:
    1) Identify the backbone of the heterocycle
    2) Identify the heteroatoms needed

Can be applied across a wide-range of heterocycles:

Paal-Knorr

- Furans from 1,4-dicarbonyls using acids, e.g. PTSA (reversible)
- Thiophenes from 1,4-dicarbonyls using S-reagents: P_4S_{10} or Lawesson's (structure/mechanism not required)
- Pyrroles from 1,4-dicarbonyls and amines

Pyrazoles and Isoxazoles

- Pyrazoles from 1,3-dicarbonyls with hydrazine
- Pyrazoles from ynones with hydrazine
  (the more substituted N atom is more nucleophlic in hydrazine unless the group is aromatic or acyl)
- Isoxazoles from 1,3-dicarbonyls with hydroxylamine
- Isoxazoles from ynones with hydroxylamine

Imidazoles and Oxazoles

- Dehydration of acetylated α-iminoketones (with amines for imidazoles)
  promoted by acids / dehydrating agents

1,2,4-Triazoles

- *(Einhorn–Brunner Synthesis)* f*rom diamides and hydrazines
- *(Pellizzari Synthesis)* f*rom primary amides and hydrazides

Cascade Heterocycle Synthesis

(Feist-Benary) Furan Synthesis*

- Starting materials: **1,3-dicarbonyls** and **α-chlorocarbonyls**
- Deprotonation and **attack at carbonyl**; cyclisation by **displacement of Cl leaving group**; **dehydration**
- Can reverse the selectivity by using a better leaving group, *i.e.* swapping Cl → I using NaI

(Knorr) Pyrrole Synthesis*

- Not required

Fisher Indole Synthesis

- Starting materials: **aryl hydrazines** and **ketones**
- **Condense** to form **enamine**; **[3,3]-sigmatropic rearrangement**; 5-membered ring formation and regaining aromaticity of 6-membered ring; elimination of ammonia to form fully aromatic system
- Promotes by **acid** / **Lewis acid**
- **Selectivity** is an issue if two different enamines can be formed from the ketone

Larock Indole Synthesis

- Starting materials: **amino iodo benzenes** and **alkynes**
- Promoted by **palladium(0)** (c.f. Suzuki, etc…) N.B. Ligands, etc. on palladium not required
- **Oxidative insertion** into Ar-I bond; **carbopalladation** across alkyne; **cyclisation** of N lone pair onto Pd to form 6 membered ring; **reductive elimination**
- **Selectivity** is an issue if the alkyne is not symmetrical

Hantzsch Pyridine Synthesis

- Starting materials: **ammonia** (or ammonium salt), **aldehyde**, 2 × **1,3-dicarbonyl**
- **Aldol** between 1,3-dicarbonyl and aldehyde followed by E1Cb; **enamine formation** between ammonia and the other 1,3-dicarbonyl; **conjugate addition** of enamine to unsaturated dicarbonyl species; **cyclisation**; **dehydration**
- The product is a **dihydropyridine** and must be oxidised separately to form a pyridine
- **Selectivity** is an issue because the 1,3-dicarbonyl is used twice so only symmetrical products can be formed

Transition Metal-Catalysed 2+2+2 Synthesis of Pyridines

- Not required

Pictet-Spengler Synthesis of Isoquinolines

- Starting materials: **β-amino-electron rich arene, carbonyl**
- **Condense** amine and carbonyl; electron rich arene attacks by intramolecular **electrophilic aromatic substitution**
- The product is a **tetrahydroisoquinoline** and must be oxidised separately to form a isoquinoline

(Bischler-Napieralski) Synthesis of Isoquinolines*

- Starting materials: **β-amino-arene, acid chloride**
- Similar to Pictet-Spengler Synthesis
- Amine and acid chloride react to **form amide** (separate step); **activate amide** with dehydrating agent (e.g. $POCl_3$); electron rich arene attacks by intramolecular **electrophilic aromatic substitution**
- The product is a **dihydroisoquinoline** and must be oxidised separately to form an isoquinoline

(Combes) Synthesis of Quinolines*

- Starting materials: **electron rich aminobenzene, 1,3-diketone**
- **Enamimine formation**; intramolecular **electrophilic aromatic substitution**; **elimination**

(Conrad-Limpach-Knorr) Synthesis of 4-Hydroxyquinolines*

- Starting materials: **electron rich aminobenzene, 1,3-ketoester**
- Exactly the same as Combes but forms 4-hydroxyquinolines because of more oxidised starting material

Cycloaddition

- **1,2,3-Triazoles** can be formed by **cycloaddition** between azides and alkynes
- **Regioselectivity is poor** unless catalysed by Cu or Ru
- **Tetrazoles** can be formed by **cycloaddition** between azides and nitriles

* The names with asterisks will not be examined

Good luck in your exams!!!!!!!!