Chemistry II (Organic)

Heteroaromatic Chemistry
LECTURES 2 & 3

Ring synthesis: cyclocondensations and cycloadditions

Alan C. Spivey
a.c.spivey@imperial.ac.uk

Imperial College
London

Feb 2012
Format & scope of lectures 2 & 3

• **Ring synthesis:**
  – cyclisations vs. cycloadditions

• **Cyclisation/cyclocondensation reactions**
  – essential functional group chemistry
    • imines & enamines
    • carbonyls, enols & enol ethers
    • thiocarbonyls, ene thiols & thioenol ethers
  – kinetics & thermodynamics of ring closure
  – common strategies for cyclisations
    • 5-membered rings
    • 6-membered rings
  – design considerations

• **Cycloaddition reactions**
  – 5-membered rings – 1,3-dipolar cycloadditions [3+2]
  – 6-membered rings – hetero-Diels-Alder reactions [4+2]

• **Supplementary slides 1-7**
  – some background information
Two Distinct Strategies for Ring Formation

There are 2 distinct ways in which heterocyclic aromatic compounds can be prepared:

- **stepwise** formation of linear *cyclisation precursor*
- formation of 1 new bond during ring-closure
- C-C or C-het bond
- triggered by nucleophiles, electrophiles, radicals etc.

Cyclisation reactions of acyclic substrates

- **concerted** formation of 2 new bonds
- Pericyclic mechanism
- C-C and/or C-het bonds
- convergent (efficiency, diversity)

Cycloaddition reactions

1,3-dipolar cycloadditions give 5-memb rings

hetero-Diels-Alder reactions give 6-memb rings
**Imines** – formation:

- **carbonyl** + **1° amine** → **imine**:

  ![Diagram of imine formation](image)

  - **overall**: need H\(^+\) but if too much acid is present → protonates amine → stops nucleophilic addition. pH 4.5 is a compromise. For the reverse process, low pH → fast, ~irreversible reaction (amine protonated → salt)

- **reversible**:
  - carbonyl form is thermodynamically most stable (C=O ~749 kJmol\(^{-1}\) cf. C=N ~607 kJmol\(^{-1}\))
  - need to drive off water (*i.e.* a dehydration/condensation reaction):
    - heat (>100 °C for H\(_2\)O)
    - 3 Å MS (Molecular Sieves) – zeolites
    - azeotropic distillation – ‘Dean-Stark trap’ (*e.g.* benzene – H\(_2\)O)
    - chemical dehydration – *e.g.* POCl\(_3\) or c.H\(_2\)SO\(_4\)
Enamines – formation:

- carbonyl + 2° amine → enamine:
  - last step is different:

overall:

of course, imines can also form an enamine tautomer
  - but usually the imine form is preferred thermodynamically…except in special circumstances
**Cyclisation Reactions** - *Essential Functional Group Chemistry – imines & enamines*

- **Imines & enamines** – intramolecular formation, i.e. ring-closure:
  - retrosynthetic analysis:

  ![Reaction Diagram]

  - **Imines & enamines - reactivity:**
    - *imines are ELECTROPHILES; enamines are NUCLEOPHILES:*
      
      ![Electrophile and Nucleophile Diagram]

    - *Intramolecular reactions can lead to ring-closure...*

  ![Diagrams showing different types of reactions involving imines and enamines]
**Cyclisation Reactions** - Essential Functional Group Chemistry – carbonyls & enols

- **Carbonyls, enols & enol ethers** – intramolecular formation, i.e. ring-closure:
  - retrosynthetic analysis:
    - Carbonyls, enols & enol ethers
    - reactants:
      - Carbonyls are ELECTROPHILES; enols & enol ethers are NUCLEOPHILES:

- **Intramolecular reactions can lead to ring-closure...**
  - acid and base catalysed **aldol reactions** (see supplementary slides 1-2)
Cyclisation Reactions - Essential Functional Group Chemistry – thiocarbonyls & ene thiols

- **Thiocarbonyls, ene thiols & thioenol ethers** – intramolecular formation, i.e. ring-closure:
  - retrosynthetic analysis:

  ![Thioenol Ether](image)

  ![Thiocarbonyl as electrophile](image)

  ![Ene Thiol/thioenol Ether as nucleophile](image)

  Intramolecular reactions can lead to ring-closure...

- **Thiocarbonyls, ene thiols & thioenol ethers** – reactivity:
  - thiocarbonyls are ELECTROPHILES; ene thiols & thioenol ethers are NUCLEOPHILES:

  ![Thiocarbonyl as electrophile](image)

  ![Thiol/Thioenol Ether as nucleophile](image)

  - **Intramolecular reactions can lead to ring-closure...**

  ![Thiocarbonyl as electrophile](image)

  ![Ene Thiol/thioenol Ether as nucleophile](image)

  - thiols are MORE nucleophilic than alcohols & thiocarbonyls are MORE electrophilic than carbonyls
**Cyclisation Reactions** - Essential Functional Group Chemistry – thiocarbonyls & ene thiols

- **Thiocarbonyls, ene thiols & thioenol ethers – formation:**
  - Thiocarbonyls are generally prepared from the corresponding carbonyl compounds:
    - Typically use P$_2$S$_5$ or Lawesson’s reagent (e-EROS):
      - Reactions driven by strength of P=O vs. P=S bond
  - Thiols are generally formed by substitution of a leaving group (LG):
    - CAUTION... most thiol and thiocarbonyl compounds STENCH!
**Cyclisation Reactions – Thermodynamics & Kinetics of Ring Closure**

- **Intra-molecular ring-closure vs. inter-molecular oligomerisation/polymerisation:**

  - **Entropy is the key factor:**
    - **Concentration of the reaction** – high dilution favours ring-closure
    - **Ring size formed** – smaller rings favoured (but...see below)

- **Ring-closure under thermodynamic (TD) control** *(i.e. reversible conditions):*
  - Many reactions forming heteroaromatic products are driven by:
    - Favourable $\Delta S^\circ$ due to loss of small molecule (as vapor at high temperature $\rightarrow$ irreversible)
    - *i.e.* cyclodehydration (-H$_2$O) & cyclocondensation (-H$_2$S, NH$_3$, MeOH etc.)
    - Favourable $\Delta H^\circ$ due to stability of aromatic product

- **Ring-closure under kinetic control** *(i.e. irreversible conditions):*
  - Less common when forming heteroaromatic products, but does affect the rate of TD controlled reactions:
    - Variable $\Delta S^\#$ - critically dependent on ring size & hybridisation of reacting centres - Baldwin’s rules
    (see supplementary slides 3-4)
Cyclisation Reactions – Common Strategies for 5-Membered Rings

- 2 common strategies for cyclisations:
  - TYPE I: 2 x C-X bond formation
  - TYPE II: 1 x C-X bond & 1 x C-C bond formation

- for synthetic equivalents of these ‘synthons’ and others (see supplementary slide 5)

**TYPE I: e.g. Paal-Knorr furan synthesis**

**TYPE II: e.g. Knorr pyrrole synthesis**

- the exact sequence of individual steps for most cyclocondensation reactions is unknown and will vary with reaction conditions (solvent, temperature, pH etc.) – seek plausible pathways
Cyclisation Reactions – Common Strategies for 6-Membered Rings

2 common strategies for cyclisations:

- **TYPE I**: 2 x C-X bond formation
- **TYPE II**: 1 x C-X bond & 1 x C-C bond formation

for synthetic equivalents of these ‘synthons’ and others (see supplementary slide 5)

**TYPE I: e.g. ‘Paal-Knorr’ pyridine synthesis**

**TYPE II: e.g. enamine/1,3-dicarbonyl pyridine synthesis**

*NB.* unsaturation in 1,5-dicarbonyl obviates the need for oxidation (see next slide)
Cyclisation Reactions – Design Considerations

Considerations during retrosynthetic analysis – synthesis design:

- identify strategic bond disconnections – seek maximum convergence
  - identify synthons with simple, readily available synthetic equivalents (see supplementary slide 5)
  - avoid substrates with multiple possible enol/enolate forms:

  e.g.

  \[
  \begin{align*}
  \text{H} & \text{O} \\
  \text{c} & \text{f}.
  \end{align*}
  \]

  'good'

  \[
  \begin{align*}
  \text{H} & \text{O} \\
  \text{c} & \text{f}.
  \end{align*}
  \]

  'bad'

- pay attention to oxidation level – is the degree of unsaturation correct to avoid need for oxidation?

  \[
  \begin{align*}
  \text{R} & \text{O} \text{O} \text{R'} \\
  + & \text{NH}_3
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{H} & \text{O} \\
  \text{c} & \text{f}.
  \end{align*}
  \]

  \[
  \begin{align*}
  \text{H} & \text{O} \\
  \text{c} & \text{f}.
  \end{align*}
  \]

  oxidation (-2H)

- what functional groups are required?...introduce before, or after ring formation?

Look out for different tautomeric forms of intermediates & products (see supplementary slides 6-7)
Cycloaddition Reactions – General Features

- **Cycloaddition reactions are characterised by:**
  - *concerted* formation of **2 new bonds** (C-C and/or C-het) – no reaction intermediates
  - asynchronous bond formation – *i.e.* some build up of charge in transition state as the formation of some bonds is more advanced than that of others
  - ‘aromatic’ transition state [(4n + 2) π electrons involved] – pericyclic reactions
  - convergent (efficiency, diversity) but need to control **regiochemistry** (see later)

- **5-Membered rings** are formed from **1,3-dipolar cycloadditions** {[[π₄s+π₂s] pericyclic processes]}
  - reaction of **1,3-dipole** with **dipolarophile**
  - initial products can be **aromatic** or require subsequent elimination/oxidation → **aromatisation**

- **6-Membered rings** are formed from **hetero-Diels-Alder reactions** {[[π₄s+π₂s] pericyclic processes]}
  - reaction of **diene** with **dienophile**
  - initial products are **di- or tetrahydro intermediates** – subsequent elimination/oxidation → **aromatisation**
Cycloaddition Reactions – 1,3-Dipolar Cycloadditions → 5-Membered Rings

1,3-Dipolar cycloadditions are 6 electron \([\pi_{4s} + \pi_{2s}]\) concerted pericyclic reactions:
- sometimes referred to as [3+2]-cycloadditions – this refers to the number of ATOMS (not electrons)

There are 2 main classes of dipoles used in 1,3-dipolar cycloadditions:

**Linear 1,3-Dipoles**
- Nitrile oxides
- Nitrile imines
- Nitrile sulfides
- Diazocompounds
- Azides

**Trigonal 1,3-Dipoles**
- Nitrile oxides
- Nitrile imines
- Nitrile sulfides
- Diazocompounds
- Azides

**Notes**
- 3 atom/4\(\pi\) electron species
- central atom \(\neq C\)
- always have formal charges
- charges @ 1,2- NOT 1,3-positions
- linear are: sp-sp-sp\(^2\)
- trigonal are sp\(^2\)-sp\(^2\)-sp\(^2\)
- no correlation between reactivity & geometry
- retrosynthetic ‘signature’ is \(\geq 2\) adjacent heteroatoms in the ring

Most multiple bonds can act as dipolarophiles:
- BUT usually a C=C bond...
**Cycloaddition Reactions – 1,3-Dipolar Cycloadditions – reactivity & regioselectivity**

- **Reactivity** is controlled by relative energies of Frontier Molecular Orbitals (FMOs)
  - the key interaction is between the Highest Occupied Molecular Orbital (HOMO) of one reactant and the Lowest Unoccupied (i.e. empty) Molecular Orbital (LUMO) of the other reactant
    - the closer the two interacting orbitals are in energy the faster the reaction rate
    - consequently, 2 important types can be identified:

  ![Diagram showing HOMO and LUMO interactions](image)

- **Regiochemistry** is controlled by:
  - the polarity of the frontier molecular orbitals (as for hetero-Diels-Alder regioselectivity, see later)
  - BUT, sterics can override *e.g.*:

  ![Diagram showing regioselectivity](image)

- **Example Reaction**:
  - nitrile oxide (1,3-dipole) + alkyne (dipolarophile) → 3,5- & 3,4-di-substituted isoxazoles
  - (86 : 14)

  ![Reaction equation](image)
Cycloaddition Reactions – hetero-Diels-Alder Reactions → 6-Membered Rings

- **hetero-Diels-Alder cycloadditions are 6 electron \([\pi_{4s} + \pi_{2s}]\) concerted pericyclic reactions:**
  - sometimes referred to as [4+2]-cycloadditions – this refers to the number of ATOMS (not electrons)

- **Azines are generally prepared by aza-Diels-Alder** reactions between aza-1,3-dienes and alkenes/alkynes
  - usually *inverse electron demand*
  - generally give non-aromatic heterocycle → extrusion of small molecule(s) → aromatic species

- **Most multiple bonds can act as dienophiles:**
  
\[\begin{align*}
\text{C=C} & \quad \text{C=O} & \quad \text{C=N} & \quad \text{C≡N}
\end{align*}\]
Reactivity is controlled by the relative energies of the Frontier Molecular Orbitals (FMOs)

- again, 2 important types:
  - hetero-diene + all carbon dienophile  ✓ usually inverse electron demand
  - all carbon diene + hetero-dienophile ✓ usually normal electron demand
  - hetero-diene + hetero-dienophile × rare (tend to have alternative reaction paths available)

Regiochemistry is controlled by the polarity of the frontier molecular orbitals

- electron donating and withdrawing substituents perturb energies and sizes of orbitals – most favourable reactions involve overlap of orbitals of similar size with complementary polarities:
**The acid catalysed aldol reaction:**

- Protonation of carbonyl leads to formation of enol.
- Nucleophilic enol reacts with highly electrophilic protonated carbonyl group.
- Overall:
  - $\text{aldol; can stop here but under more forcing conditions...}$
  - + get acid catalysed enolisation

**Overall:**

$$\text{aldol} + \text{aldol cat.} \rightarrow \text{aldol cat.} + \text{aldol cat.}$$
The base catalysed aldol reaction:

Base catalysed formation of enolate

Nucleophilic attack of enolate on electrophilic carbonyl compound

Protonation of alkoxide yields neutral aldol and regenerates base

Over extended time, further base catalysed enolisation and elimination can occur to give an unsaturated carbonyl compound.

Overall:
**Supplementary slide 3 – Baldwin’s ‘Rules for Ring Closure’**

- **For kinetically controlled ring closures:**
  - the relative facility of ring-closure depends critically on the ring size, the hybridisation of the reacting centres & the mode of ring-closure (*exo* or *endo*)

<table>
<thead>
<tr>
<th>nomenclature</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Exo</em> - the bond being broken in the ring closure is exocyclic <em>i.e.</em> outside the ring</td>
</tr>
<tr>
<td><em>Endo</em> - the bond being broken in the ring closure is endocyclic <em>i.e.</em> inside the ring</td>
</tr>
<tr>
<td><em>Tet</em> - electrophilic centre has sp³ hybridisation</td>
</tr>
<tr>
<td><em>Trig</em> - electrophilic centre has sp² hybridisation</td>
</tr>
<tr>
<td><em>Dig</em> - electrophilic centre has sp hybridisation</td>
</tr>
</tbody>
</table>

- **tetrahedral systems:**
  - 2 to 7-*exo-tet* are all favoured processes
  - 5 to 6-*endo-tet* are disfavoured

- **trigonal systems:**
  - 3 to 7-*exo-trig* are all favoured processes
  - 3 to 5-*endo-trig* are disfavoured; 6 to 7-*endo-trig* are favoured

- **digonal systems:**
  - 3 to 4-*exo-dig* are disfavoured processes; 5 to 7-*exo-dig* are favoured
  - 3 to 7-*endo-dig* are favoured
Supplementary slide 4 – Baldwin’s ‘Rules for Ring Closure’ cont.

- Baldwin’s rules were formulated following analysis of transition state geometries:
  - Tet - electrophilic centre has sp³ hybridisation - $S_N2$ reaction
  - Trig - electrophilic centre has sp² hybridisation - Nucleophilic addition to carbonyl/imine
  - Dig - electrophilic centre has sp hybridisation - Nucleophilic addition to nitrile/alkyne
**Supplementary slide 5 – ‘Synthons’* ↔ Synthetic Equivalents**

- **dinucleophiles:**
  - $\overset{-}{X}\overset{-}{X}$ $\rightarrow$ $\overset{-}{X}$ $\hat{\rightarrow}$ $\overset{-}{X}$ $\rightarrow$ $\overset{-}{X}\overset{-}{X}$

- **nucleophile/electrophiles:**
  - $\overset{+}{X}$ $\rightarrow$ $\overset{+}{X}$ $\rightarrow$ $\overset{+}{X}$$\overset{-}{X}$

- **dielectrophiles:**
  - $\overset{+}{X}$ $\rightarrow$ $\overset{+}{X}$ $\rightarrow$ $\overset{+}{X}$

---

*The term ‘synthon’ is used rather loosely here to denote the indicated ‘polarity assigned retrosynthetic skeleta’. For clarity and generality, these lack full indication of oxidation level unlike a true ‘synthon’ (see: Corey & Cheng ‘The Logic of Chemical Synthesis’ Wiley 1989).
Supplementary slide 6 – Tautomerism

- **Tautomerism in heterocyclic systems:**
  - many heteroaromatic compounds can exist in two or more TAUTOMERIC forms. TAUTOMERS are structurally distinct isomers in rapid equilibrium (usually). In most cases a proton shifts from one atom to another.
  - do not confuse TAUTOMERS with resonance forms
    - e.g. 2-hydroxy pyridine and 2-pyridone are TAUTOMERS and are distinct isomers which can be detected spectroscopically. Each can be represented by a series of resonance structures. The position of the tautomeric equilibrium can be different in different SOLVENTS.

- 2-hydroxy pyridine is the predominant tautomer in the gas phase
- 2-pyridone is the predominant tautomer (>9:1 in EtOH) in solution… probably due to hydrogen-bonding:
**Supplementary slide 7 – Tautomerism & Binding/Reactivity**

- **Heterocyclic tautomerism in biological systems:**
  - tautomer specific H-bonding is important in DNA/RNA base-pairing:

  ![Diagram of tautomerism in guanine and cytosine](image)

  - **N^4-amino cytosine** (a potent mutagen)

- **Tautomeric equilibria & the Curtin-Hammett principle:**
  - Curtin-Hammett principle: ‘the ratio of products formed in a kinetically controlled reaction from one starting material, present in two (or more) rapidly equilibrating tautomeric forms, depends on the relative energies of the respective transition states NOT the relative ground state energies of the equilibrating tautomers.’
    - *e.g.* methylation of 2-pyridone/2-hydroxypyridine:

  ![Diagram of tautomeric equilibria and reaction](image)