Heterocyclic Chemistry

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Course Overview

Videos

https://www.youtube.com/watch?v=MztulKZC33E&list=PLwrBgrbEpTE9vHyqzF3fccieK8-qDmE-o

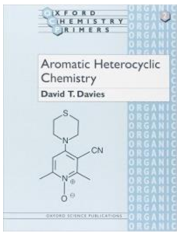
1 – Introduction and Revision
    Video 01 - Introduction to Heterocyclic Chemistry [06:46]
    Video 02 - Revision of Key Concepts [14:09]
2 – Nomenclature and Aromaticity
    Video 03 - Heterocycle Nomenclature [18:47]
    Video 04 - Aromaticity [07:48]
3 – Reactivity
    Video 05 - Reactivity of 6-Membered Aromatic Heterocycles - Part 1 [29:07]
4 – Reactivity
    Video 06 - Reactivity of 6-Membered Aromatic Heterocycles - Part 2 [16:57]
    Video 07 - Reactivity of 6-Membered Aromatic Heterocycles - Part 3 [12:40]
5 – Reactivity
    Video 08 - Reactivity of 5-Membered Aromatic Heterocycles [19:01]
    Video 09 - General Reactivity of Heterocycles [27:06]
6 – Synthesis
    Video 10 - Strategy for Heterocycle Synthesis: Cyclisation and Dehydration [29:39]
    Video 11 - Synthesis of Furans and Pyrroles [14:41]
7 – Synthesis
    Video 12 - Synthesis of Pyridines [14:49]
    Video 13 - Synthesis of Isoquinolines and Quinolines [22:39]
8 – Synthesis
    Video 14 - Synthesis of Indoles [10:25]
    Video 15 - Heterocycle Synthesis by 1,3-Dipolar Cycloaddition [11:42]

Handout

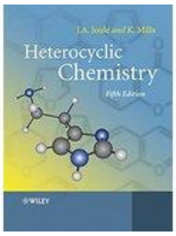
This PDF accompanies the video lecture series.
The numbers in the top right of the video correspond to the pages in this handout.

Information Sources

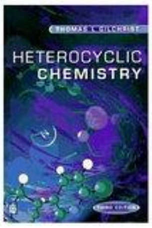
Books



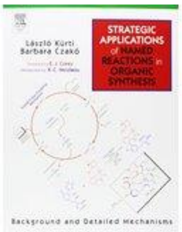
Aromatic Heterocyclic Chemistry
Oxford Chemistry Primer, Davis
[Primers No 8]
Online - Bibliu



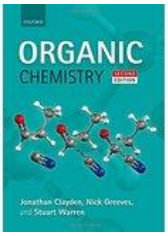
Heterocyclic Chemistry
Joule & Mills
[K270 2010-J2]



Heterocyclic Chemistry
Gilchrist
[K270 1997-G]



Strategic Applications of Named Reactions in Organic Synthesis
Kurti & Czako
[K210 2005-K]



Organic Chemistry Second Edition
Clayden, Greeves, Warren
[K210 2012-C]
https://read.kortext.com/reader/epub/125690

Online Resources

Chem Tube 3D
http://chemtube3d.com
Interactive animations of computed reaction mechanisms

Organic Chemistry Portal
http://www.organic-chemistry.org/
Online database curated by a chemistry professor in the USA

Wikipedia
https://en.wikipedia.org
Lots of people have carefully copied information (much of it from the books described previously) onto Wikipedia for free access! Be careful because there can be mistakes and people who write entries can be biased

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Google / Bing / etc...
If you perform web searches for names of heterocycles you will find many lectures, PDF handouts, book sections, etc…

Introduction

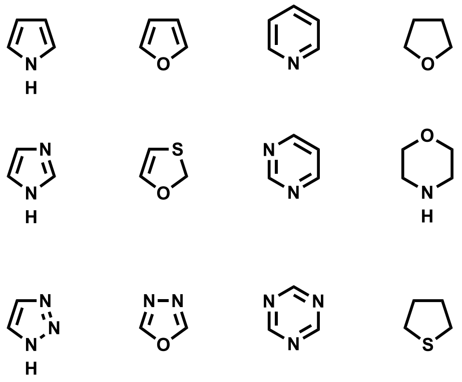
What is a Heterocycle?

"cyclic compounds having as ring members atoms of at least two different elements"

INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

hetero → at least two different elements
cycle → cyclic compound

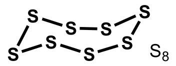
Some heterocycles: ✓



Not heterocycles: ✗


benzene

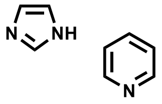
- Benzene is cyclic but all the atoms are carbon

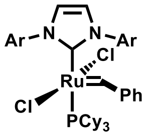


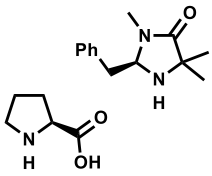
- S_8 is cyclic but all the atoms are sulfur

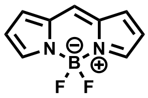
Importance of Heterocycles:

- **Chemistry**
  Heterocycles are key components of reagents, catalysts and chemical tools

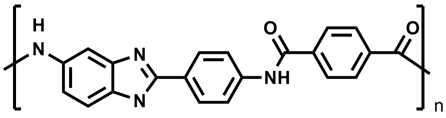

nucleophilic catalyst and base

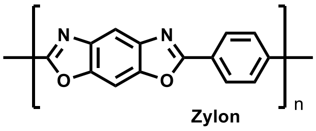

ligand
(Grubbs II metathesis)


organocatalysts


molecular imaging
(bodipy)

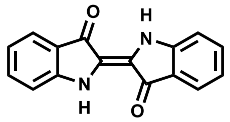
- **Polymers**
  Heterocycles are the key component in many important polymers


polybenzimidazoles
(flame retardent material)

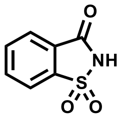

Zylon
(very strong fibres)

4 Heterocyclic Chemistry

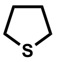
- **Everyday Items**
  Heterocycles are the key component in everyday objects



indigo
(dye)

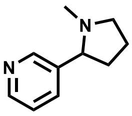


saccharine
(sweetner)

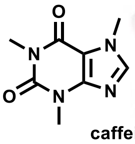


tetrahydrothiophene
(gas smell)

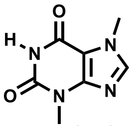
- **Natural Compounds**
  Heterocycles are the key component in natural compounds



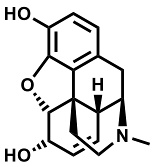
nicotine



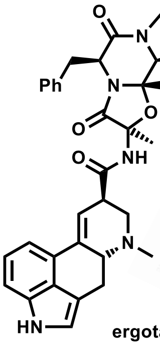
caffeine



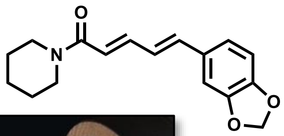
theobromine



morphine

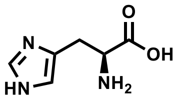


ergotamine

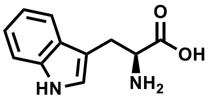


piperine
(black pepper)

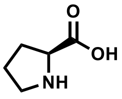
- **Nature's Building Blocks**
  Heterocycles are found in 3 of the 20 proteinogenic amino acids and in DNA/RNA:



histidine



tryptophan



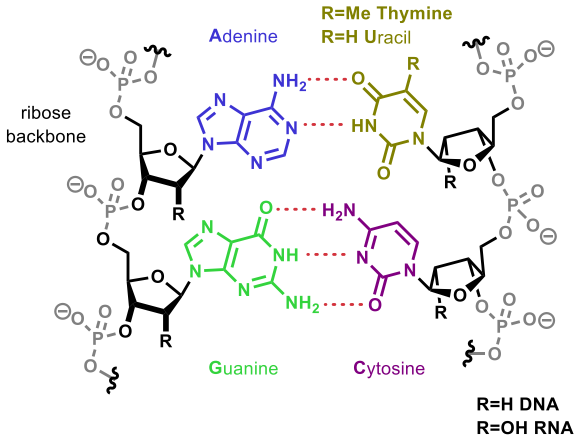
proline

Histidine:
Essential part of many enzyme active sites as nucleophilic catalyst and for H-transfer and ligand in metalloenzymes

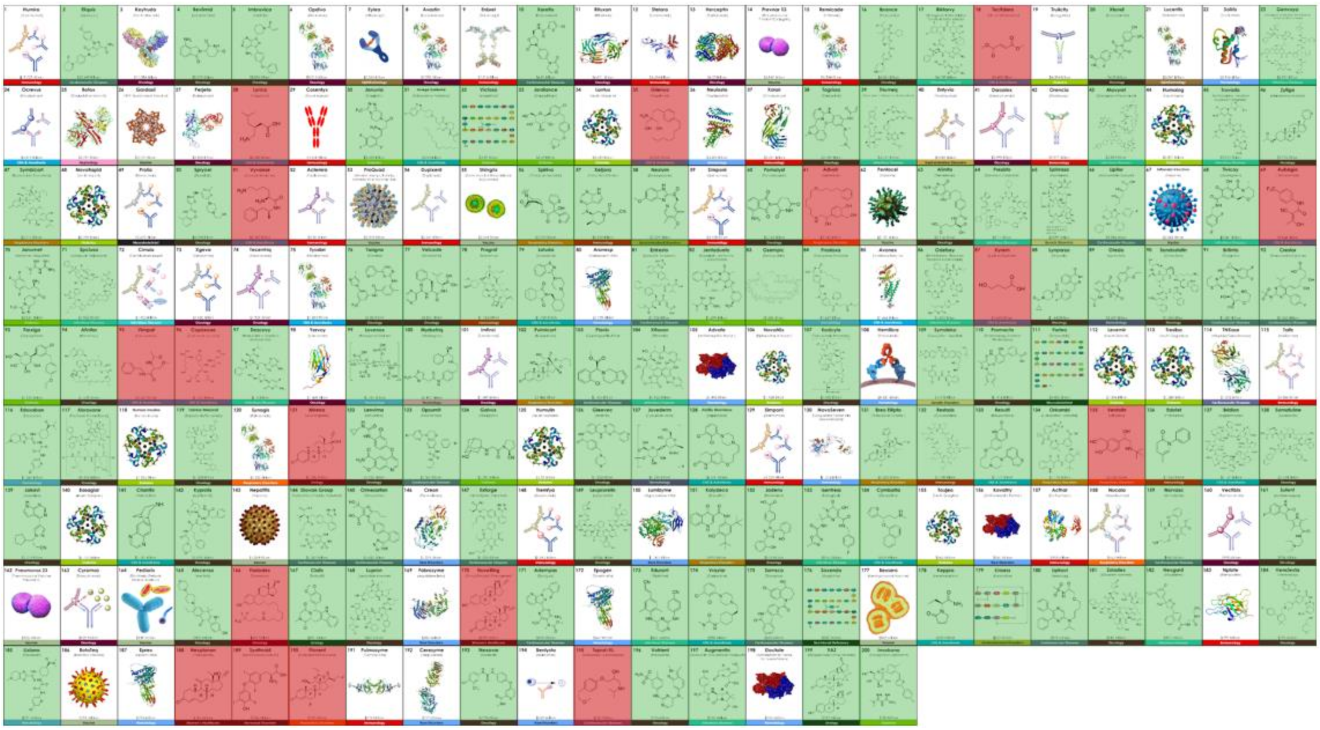
Tryptophan:
Precursor to neurochemicals
Precursor to vitamin B3

Proline:
Only secondary amine amino acid and brings added rigidity or disruption to protein structure

DNA and RNA:



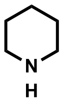
- **Drug Molecules:**
  Out of 200 top selling drugs (2019) only those in red have no heterocyclic component



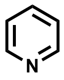
Green	**White**	**Red**
Drugs that contain a heterocycle	Biologics – proteins and antibodies that contain heterocycles as e.g. amino acids	Drugs that contain no heterocycle

Heterocycles in Drug Molecules

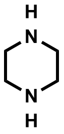
Top 5 prevalent heterocycles from 640 FDA-approved drugs:



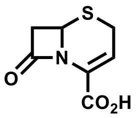
piperidine
11%



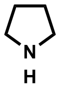
pyridine
10%



piperazine
9%



CEPHEM
6%



pyrrolidine
6%

J. Med. Chem. **2014**, *57*, 10257

Nomenclature

Heterocycles

"cyclic compounds having as ring members atoms of at least two different elements"

IUPAC Rules

Three rule systems for naming heterocycles:

- **Hantzsch-Widman Nomenclature**
  Logical system of nomenclature
- **Retained Names**
  Older heterocycles keep their traditional names
- **Carbon-Framework Substitution Nomenclature**
  For complex heterocycles

Hantzsch-Widman Nomenclature

- There is a carefully formulated system for the nomenclature of heterocycles based on **heteroatom** (start of the name), **ring size** (middle of the name) and **degree of saturation** (end of the name).

Heteroatom Element

O	***oxa***
Se	***selena***
P	***phospha***
As	***arsa***
Si	***sila***

more obvious

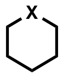
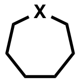
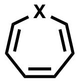
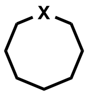
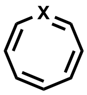
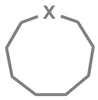
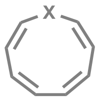
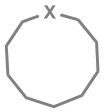
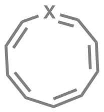
N	***aza*** *(often imid, pyr, pyrid)*
S	***thia***

less obvious

Multiple Heteroatom Elements

- Atom name prefixes can include multipliers *e.g. for* **N**: *1 = aza-, 2 = diaza-, 3 = triaza-, 4 = tetraza-, …*
- Atom name prefixes can be combined in order of BIGGEST PERIOD followed by SMALLEST ROW in the periodic table e.g. N,O = oxaza-; S,O = oxathia-; P,O = oxaphospha-; …

Ring Size

Size	Prefix	Origin	Saturated		Unsaturated	
3	**ir**	TRI, e.g. triangle		-ir**ane** -iridine for **N**		-ir**ene** -irine for **N**
4	**et**	TETRA, e.g. tetrahedron		-et**ane** -etidine for **N**		-et**e**
5	**ol**			-ol**ane** -olidine for **N**		-ol**e**
6	(in)			-**ane** -inane for **N**		-**ine**
7	**ep**	HEPTA, e.g. heptathlon		-ep**ane**		-ep**ine**
8	**oc**	OCTA, e.g. octopus		-oc**ane**		-oc**ine**
9	**on**	NONA, e.g. nonagenarian		-on**ane**		-on**ine**
10	**ec**	DECA, e.g. decade		-ec**ane**		-ec**ine**

Nitrogen-containing heterocycles have different rules, *i.e.* an **idi** in the name for some saturated compounds

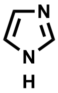
Retained Names

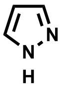
Several important heterocycles predate the Hantzsch-Widman Nomenclature and these keep their **historic names**, including:

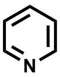

pyrrole
(azole)

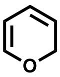

furan
(oxole)

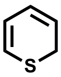

thiophene
(thiole)

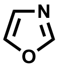

imidazole
(1,3-diazole)

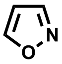

pyrazole
(1,2-diazole)

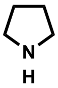

pyridine
(azine)

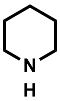

2H-pyran
(oxine)

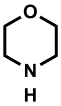

2H-thiopyran
(thiine)

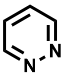

oxazole
(1,3-oxazole)

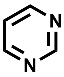

isoxazole
(1,2-oxazole)

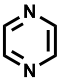

pyrrolidine
(azolidine)


piperidine
(azidine)


morpholine
(1,4-oxazinane)

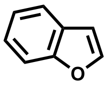

pyridazine
(1,2-diazine)

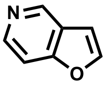

pyrimidine
(1,3-diazine)


pyrazine
(1,4-diazine)

Fused Heterocycles

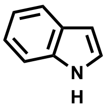
If a heterocycle is fused to another system, join the two names together with the biggest and most heteroatom-containing ring as the second part.

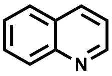

benzofuran
benzo[b]furan
(benzene fused to furan)

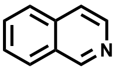

furopyridine
furo[3,2-c]pyridine
(furan fused to pyridine)

Fused Heterocycles with Retained Names

Several important heterocycles predate the Hantzsch-Widman Nomenclature and these keep their **historic names**


indole
(benzopyrrole)

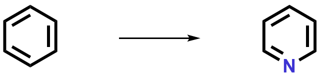

quinoline
(benzo[b]pyridine)


isoquinoline
(benzo[c]pyridine)

Carbon-Framework Substitution

Used to describe complex (multiple fused together) and large (>10 in ring) heterocycles

1. Name the all carbon version of the heterocycle - there are robust methods for describing complex all-carbon structures
2. Use substitution to describe the positions of the heteroatoms


benzene

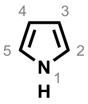
(aza-benzene)
(azinine)
pyridine

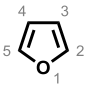
Heterocyclic Chemistry

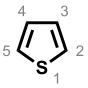
Numbering

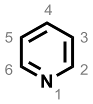
Starting at 1 = the HETEROATOM with the:

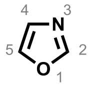
- BIGGEST PERIOD followed by SMALLEST ROW in the periodic table
- If there are multiple heteroatoms, the most saturated one takes the lowest number
- Number in a direction that gives other heteroatoms lowest numbers
- Number in a direction that gives substituents lowest numbers
- Isoquinoline takes the same numbering system as quinoline

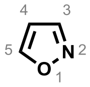

pyrrole

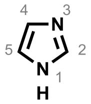

furan

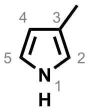

thiophene
(thiole)

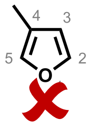

pyridine

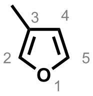

oxazole
(1,3-oxazole)

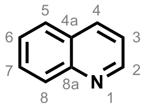

isoxazole
(1,2-oxazole)

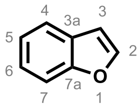

imidazole
(1,2-diazole)

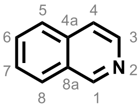

pyrrole


furan


furan


quinoline


benzofuran


isoquinoline

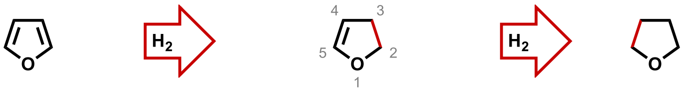
number to give any substiutent
the lowest number

numbering **SKIPS**
ring junction carbon atoms

numbering for isoquinoline
is the **SAME** as quinoline and
does not start with N=1

Degree of Unsaturation

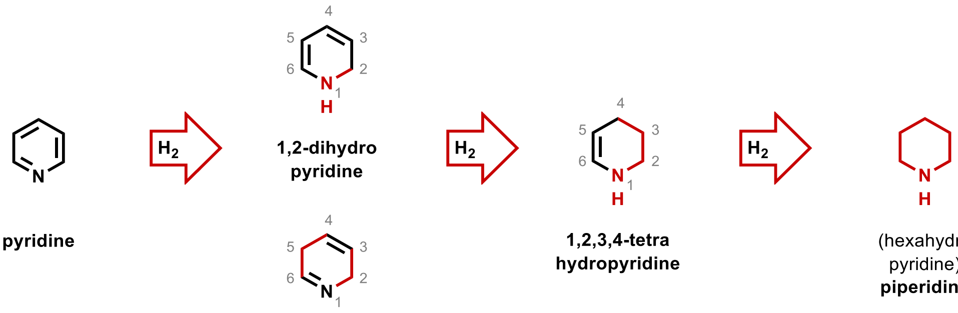
For partially unsaturated systems, start with the saturated system and describe which double bonds are missing:



furan

2,3-dihydro furan

tetrahydro furan (THF)



pyridine

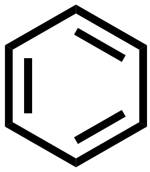
1,2-dihydro pyridine

2,5-dihydro pyridine

1,2,3,4-tetra hydropyridine

(hexahydro pyridine) **piperidine**

Aromaticity

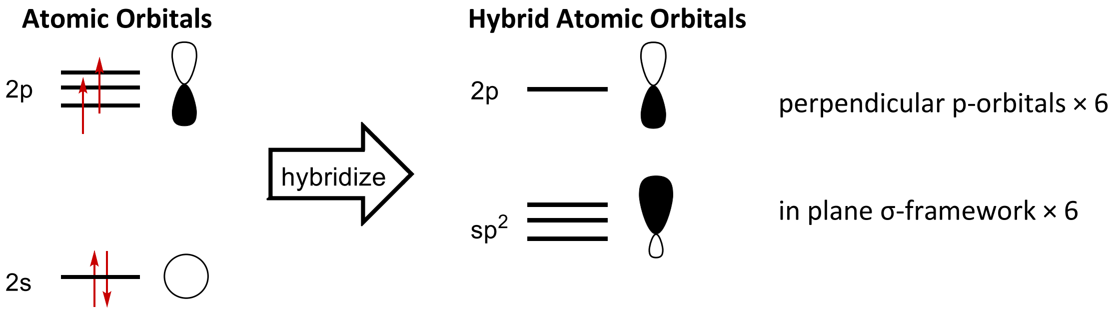


Benzene

Carbon's electronic configuration is **$1s^2$ $2s^2$ $2p^2$**

Mixing the atomic orbitals creates hybrid atomic orbitals ($2s + 2 \times 2p \rightarrow sp^2 + 2p$)

The sp^2 orbitals overlap to create the σ-bond network in the plane of benzene



2nd Year
Y3

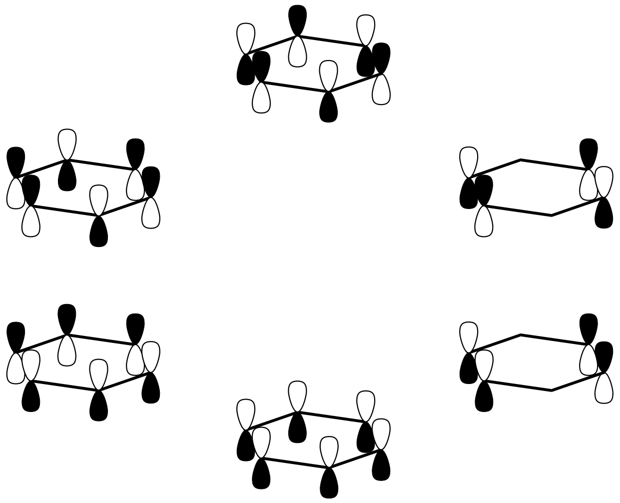
The remaining p orbitals overlap to create an **AROMATIC** system.

N.B. Hückel's rule Rules for Aromaticity

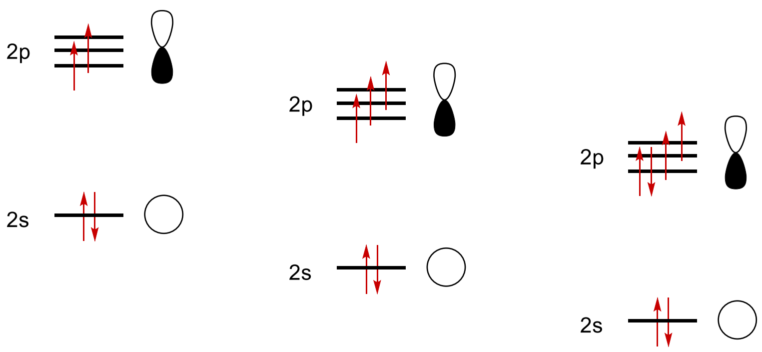
- Flat
- Cyclic
- Contiguous (non-broken) p-orbitals
- 4n+2 electrons

In benzene, all the atoms are the same so the orbitals are completely **symmetrical**

There are 6 molecular π-orbitals in benzene:

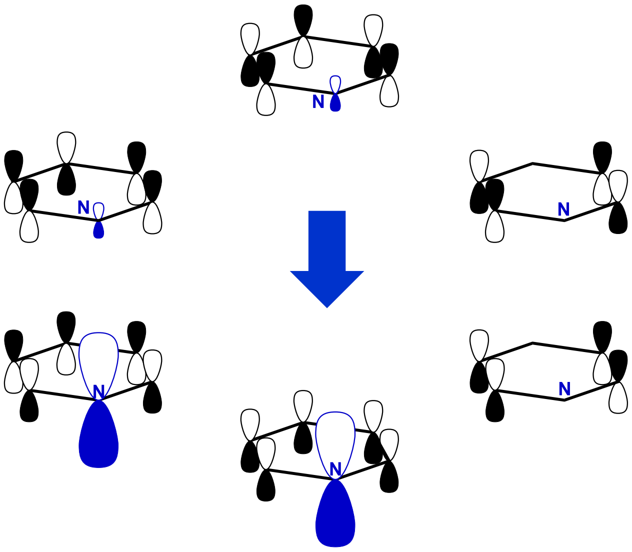


Nitrogen and oxygen are both more electronegative than carbon so have lower energy atomic orbitals



	C	N	O
Electronegativity	**2.55**	**3.04**	**3.44**

Pyridine

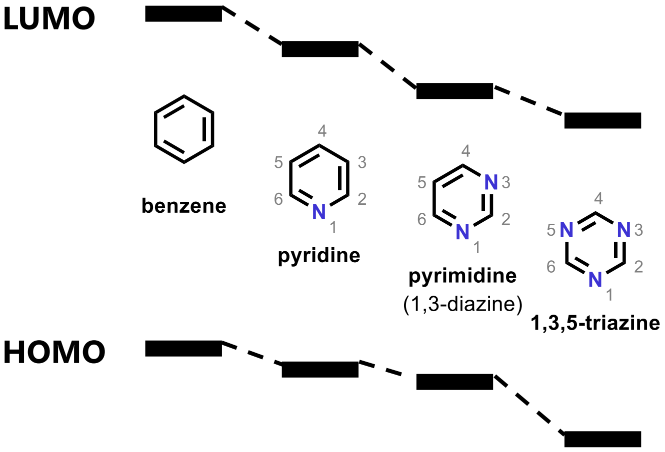


Black/Blue, White represents orbital phase

In 6-membered aromatic heterocycles, i.e. pyridine, the aromatic system includes a p orbital from electronegative N.

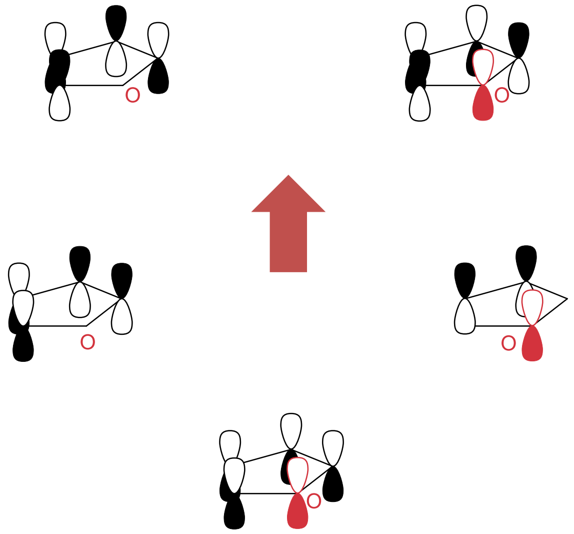
Pyridines are
BETTER ELECTROPHILES
and
WORSE NUCLEOPHILES

Azines



Having more nitrogen atoms in the heterocycle results in lower energy orbitals and therefore the behaviour of a better electrophile and worse nucleophile

5-Membered Aromatic Heterocycles



Black/Red, White represents orbital phase

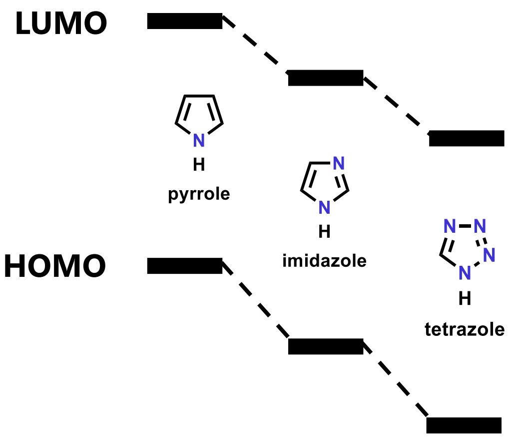
4n+2 electrons:

4 × C p-orbitals	4 electrons
1 x **LONE PAIR**	2 electrons

In 5-membered aromatic heterocycles, the aromatic system includes a higher energy lone pair from the heteroatom.

5-Membered heterocycles are
WORSE ELECTROPHILES
and
BETTER NUCLEOPHILES.

5-Membered Aromatic Multiheteroatom Heterocycles



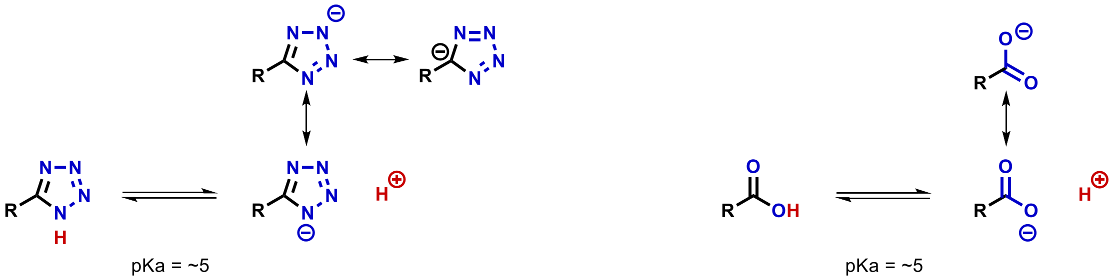
The aromatic system is built using a high energy lone pair → electron rich

The inclusion of an electronegative atom in the ring so more → electron poor

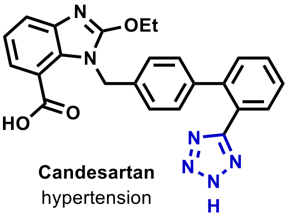
Tetrazoles

The four electronegative nitrogen atoms in tetrazole make the system very electron deficient

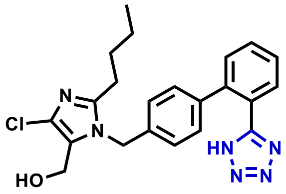
Tetrazole is acidic – the tetrazole anion well stabilised throughout the ring



Tetrazole is an **isostere** for carboxylic acids in drug compounds, for example:



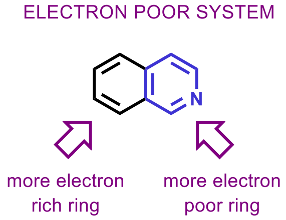
Candesartan
hypertension

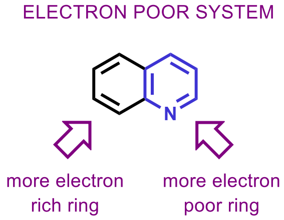


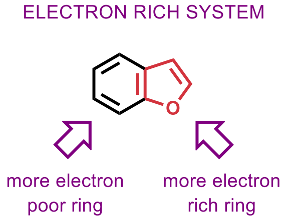
Losartan
hypertension

Fused Heterocycles

These concepts can be applied to fused heterocycles:



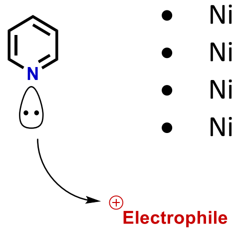




- Isoquinoline and quinoline (like pyridine) are electron poor because the aromatic system includes an electronegative nitrogen
- Benzofuran, indole and benzothiophene (like furan, pyrrole & thiophene) are electron rich because the aromatic system includes a lone pair
- The effect is most focussed on the heterocyclic ring

Reactivity of 6-Membered Heterocycles

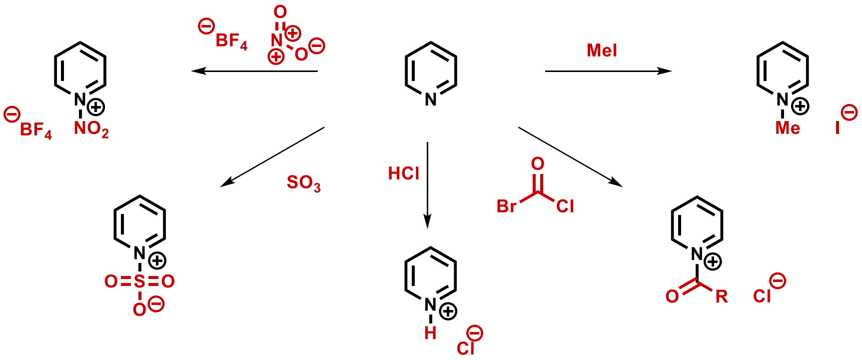
Pyridine Lone Pair



Pyridine

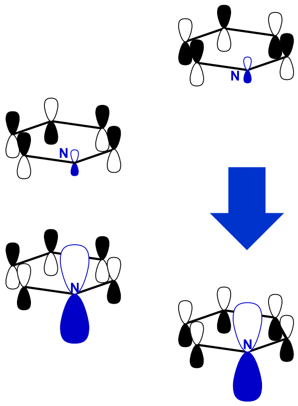
- 4n + 2 = 6 electrons from 3 double bonds
- Nitrogen lone pair is **NOT part of aromatic system**
- Nitrogen lone pair is the **HOMO**
- Nitrogen lone pair is **nucleophilic**
- Nitrogen lone pair is **basic**

- The nitrogen lone pair reacts readily with acids and electrophiles:

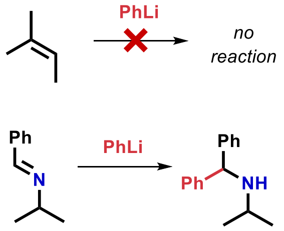


Pyridines as Electrophiles

The electronegative nitrogen lowers the energy of the aromatic system:



Consider the difference between benzene and pyridine and the difference between an alkene and an imine:

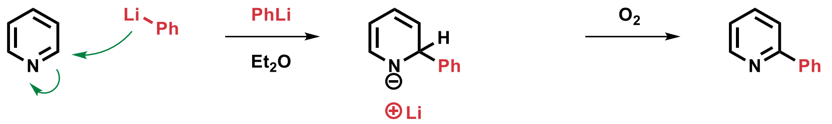


Therefore, pyridine can be expected to be an improved electrophile.

Carbon Nucleophiles

- Carbon nucleophiles attack the 2-position of the pyridine (cf. imine)
- The resulting negative charge is stabilised on the electronegative nitrogen atom
- The resulting anion is oxidised by reaction with O_2 in the air to the pyridine

negative charge stabilised on electronegative N atom



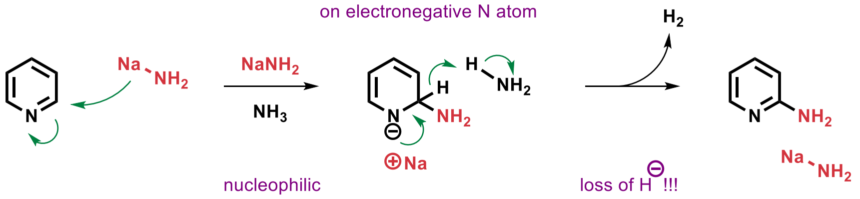
nucleophilic attack at 2-position

reaction with O_2 to restore aromaticity

Chichibabin Reaction

- Reaction with sodium/lithium amide in ammonia is known as the Chichibabin Reaction
- The amide anion attacks the 2-position of the pyridine (cf. imine)
- The resulting negative charge is stabilised on the electronegative nitrogen atom
- This reaction ends with **HYDIDE TRANSFER** (loss of H^-) i.e. oxidation
- This is one of very few examples where you see an arrow with **H^- leaving**

negative charge stabilised on electronegative N atom

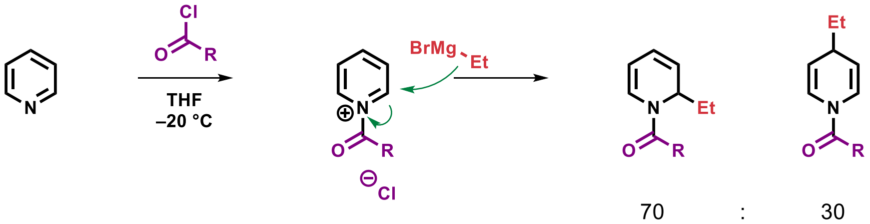


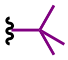
nucleophilic attack at 2-position

loss of $H^{\ominus}$!!! to restore aromaticity

Reaction of Pyridinium Salts

- Pyridines react with acyl chlorides to form acyl pyridinium salts
- The positive charge makes the pyridine more electrophilic
- The size of the acyl group can block attack at the 2-position and promote attack at the 4-position



				R
70	:	30	76%	
52	:	48	73%	

form acyl pyridinium salt (separate step)

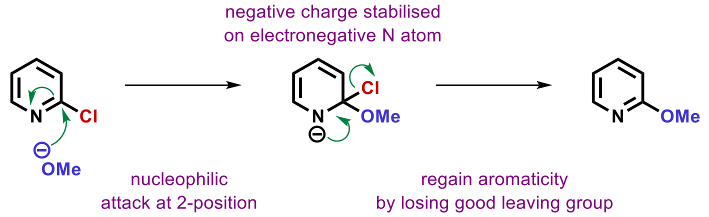
nucleophilic attack at 2-position or 4-position

Pyridines as Electrophiles: Nucleophilic Aromatic Substitution

A nucleophile attacks the electron poor pyridine, at the position of the electronegative leaving group. Then the leaving group leaves to restore aromaticity.

Nucleophilic substitution occurs fastest at the 2- and 4-positions because the negative charge in the intermediate complex is stabilised on the electronegative nitrogen atom.

2:

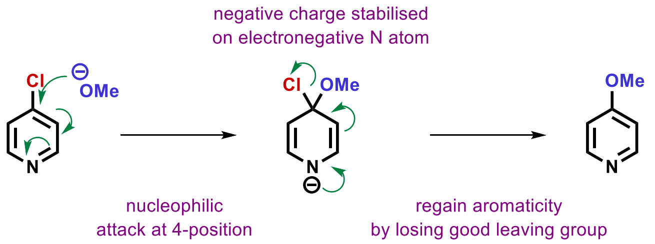


negative charge stabilised on electronegative N atom

nucleophilic attack at 2-position

regain aromaticity by losing good leaving group

4:



negative charge stabilised on electronegative N atom

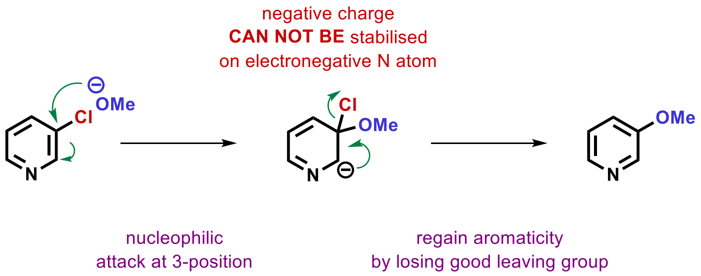
nucleophilic attack at 4-position

regain aromaticity by losing good leaving group

Nucleophilic substitution occurs slower at the 3- position because the negative charge in the intermediate complex can't be stabilised on the electronegative nitrogen atom.

HOWEVER, the aromatic system is still electron poor so substitution does occur.

3:



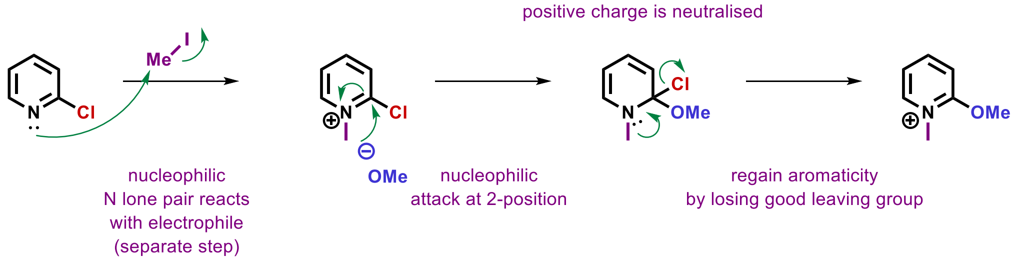
negative charge **CAN NOT BE** stabilised on electronegative N atom

nucleophilic attack at 3-position

regain aromaticity by losing good leaving group

Pyridinium

- Pyridines react with electrophiles to form pyridinium salts.
- Mechanism: nucleophilic attack with stabilisation of the negative charge by neutralisation of the positive charge followed by loss of a good leaving group to regain aromaticity.
- The permanent positive charge on the pyridinium means that the heterocycle is even more electron poor so this process is even faster.



positive charge is neutralised

nucleophilic N lone pair reacts with electrophile (separate step)

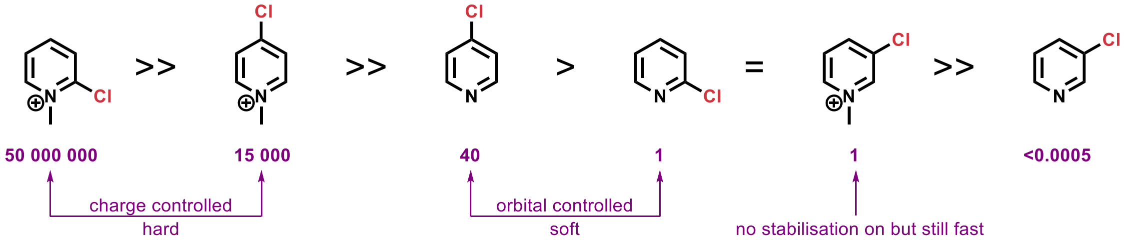
nucleophilic attack at 2-position

regain aromaticity by losing good leaving group

- Similar reaction and mechanisms for pyridiniums 4- and 3-substituted with leaving groups.

Reactivity Series

Relative rates of substitution reflect: overall charge; ability to stabilise negative charge on electronegative N atom; hard/soft interactions.



50 000 000 **15 000** **40** **1** **1** **<0.0005**

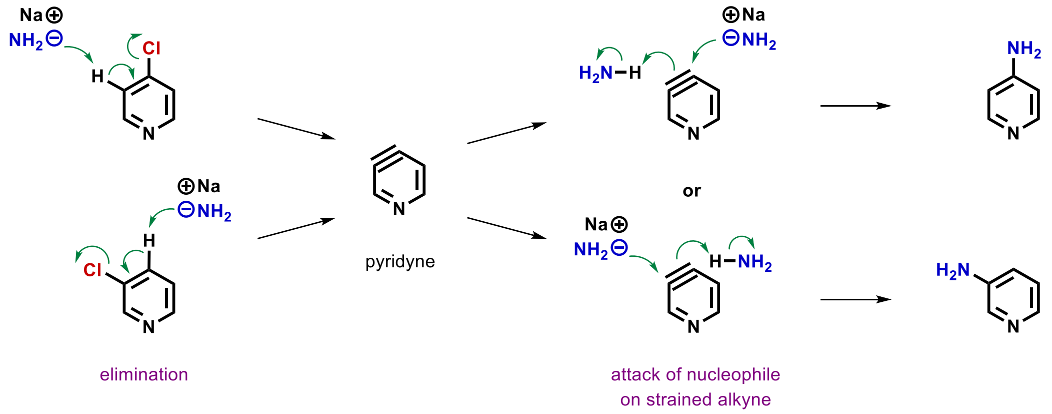
charge controlled hard

orbital controlled soft

no stabilisation on but still fast

Pyridynes as Electrophiles

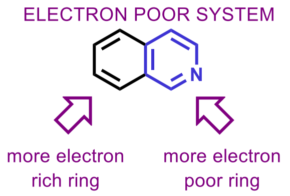
- Different substrates give same ratio of products – suggests proceeds through common intermediate.
- With some leaving groups and strong bases, there can be competition between elimination and substitution.
- Elimination of HCl to form a pyridyne – a highly strained alkyne within a 6-membered ring.
- Attack of the nucleophile can proceed at either end to form a mixture of products.

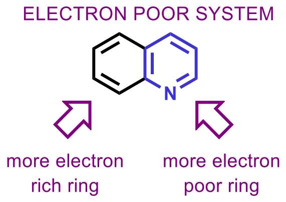


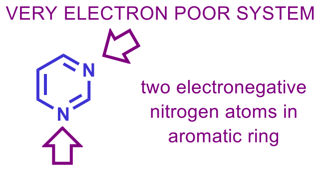
Fused Azines and Diazines as Electrophiles

In **quinolines** and **isoquinolines** a pyridine ring is fused to a benzene ring. The electronegative nitrogen atom makes the whole system electron-poor. The ring containing the nitrogen atom is more electron poor relative to the all-carbon ring that is electron rich.

In diazines such as **pyrimidine** there is an additional electronegative nitrogen atom in the ring so this system is more electron poor.

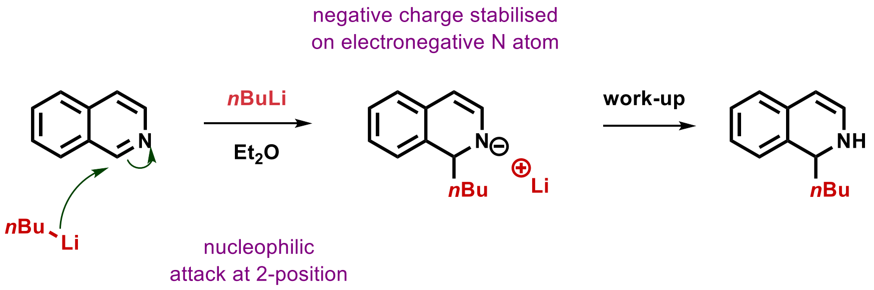






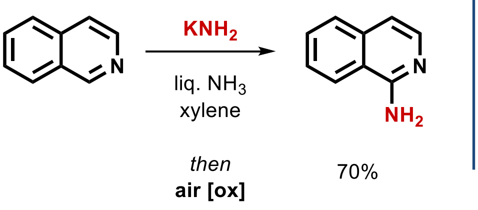
Nucleophilic Attack of C-Nucleophiles

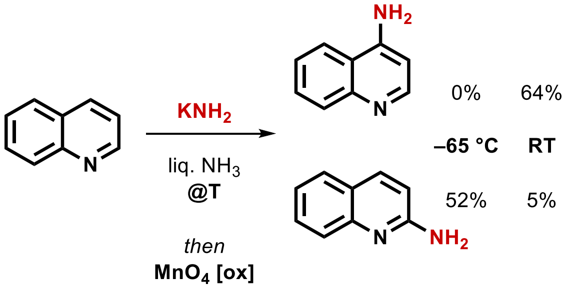
In isoquinolines, nucleophilic attack by carbanion at the 1-position to give an anion stabilised on the electronegative nitrogen atom. The reaction is on this ring because this contains the nitrogen atom. Unlike pyridine there is no *in situ* oxidation because not all the aromaticity is lost.



Chichibabin Amination

Nucleophilic attack by $^-NH2$ at the appropriate position to stabilise negative charge on the electronegative nitrogen atom. Reaction is on the more electron poor ring that contains the nitrogen atom. Unlike pyridine, there is no in situ oxidation because not all the aromaticity is lost so an external oxidant is added.

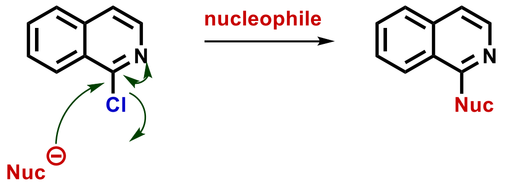


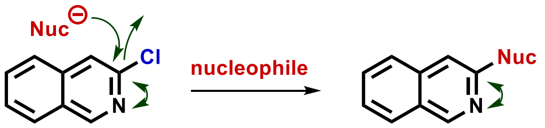


Nucleophilic Substitution

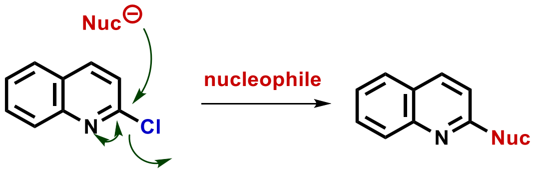
Nucleophiles react with isoquinolines and quinolines with good leaving groups (Cl, Br, F, I OMs, etc…). The nucleophile attacks the aromatic system at the leaving group with stabilisation of the negative charge on the electronegative atom followed by loss of the leaving group to regain aromaticity. The effect is mist pronounced on the ring containing the nitrogen atom.

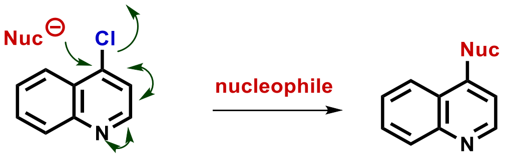
- Nucleophilic substitution of isoquinolines





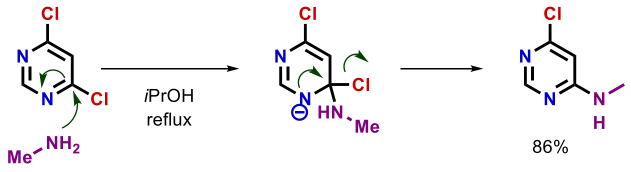
- Nucleophilic substitution of quinolines

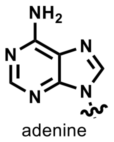




Electrophilic Aromatic Substitution of Azines

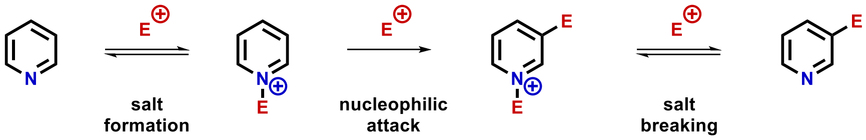
Nucleophiles react with azines with good leaving groups (Cl, Br, F, I OMs, etc…). Diazines react faster than the corresponding pyridines. The nucleophile attacks the aromatic system at the leaving group with stabilisation of the negative charge on the electronegative atom followed by loss of the leaving group to regain aromaticity. In this case, the reaction stops after one iteration because NHMe is electron donating and this is a useful reaction for the preparation of DNA base pair analogues.





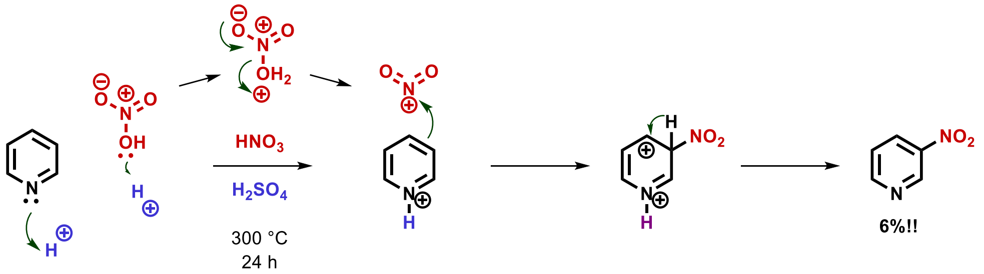
Pyridines as Nucleophiles: Electrophilic Aromatic Substitution

- 6-Membered heterocycles are electron poor so are not good nucleophiles.
- The nucleophilic nitrogen lone pair reacts first, creating a pyridinium salt whose positive charge makes the system even less nucleophilic. Then the electrophilic aromatic substitution occurs and finally, salt breaking delivers the product.

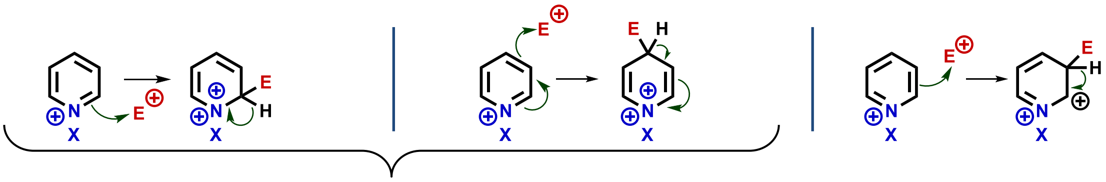


Nitration

- H_2SO_4 is a stronger acid than HNO_3 so HNO_3 is protonated and dehydrated to form the reactive species: NO_2^+
- The pyridine lone pair reacts with the acid to form a pyridinium salt
- Nucleophilic attack of pyridinium salt to the nitronium cation from 3-position
- Finally, deprotonation restores the aromaticity



- Reaction from other positions lead to extra destabilisation of the system

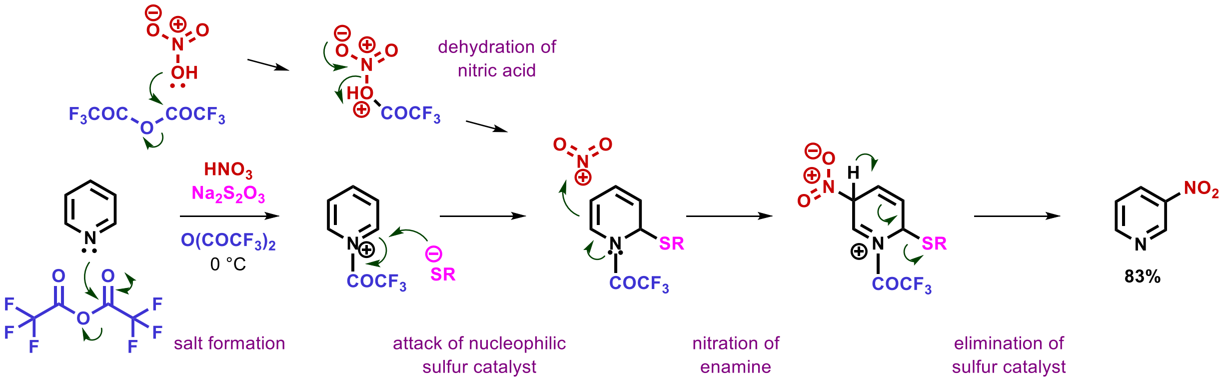


resonance puts positive charge on electronegative nitrogen → **disfavoured**

3 or β → **favoured**

Nitration of Pyridine Using a S-Nucleophilic Catalyst

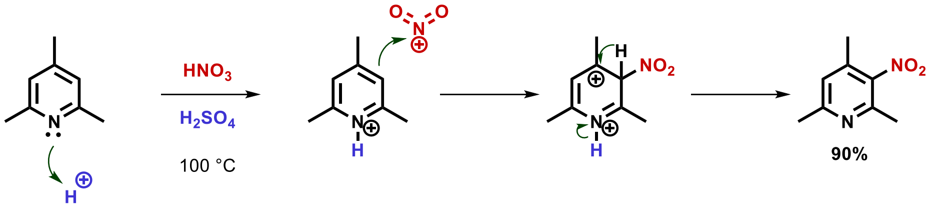
- Nitric acid is dehydrated by the **anhydride** (cf. H_2SO_4) to form the **nitronium cation** (NO_2^+)
- The pyridine lone pair reacts with the **anhydride** to form a pyridinium salt
- Nucleophilic attack of the **sulfur catalyst** to the ring, neutralising the positive charge on the pyridinium and breaking the aromatic system, resulting in an enamine
- Attack of the electron-rich enamine motif to the nitronium cation
- Elimination of the **sulfur catalyst** and restoration of aromaticity



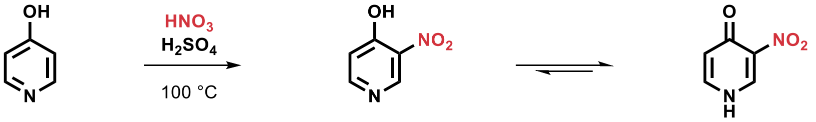
Nitration of Substituted Pyridines

Nitration of pyridines with electron donating substituents (OR, SR, NR_2, alkyl) is easier because the aromatic system is more electron rich.

- Me is electron-donating so the reaction rate is increased and *ortho*,*para*-directing so the selectivity is reinforced

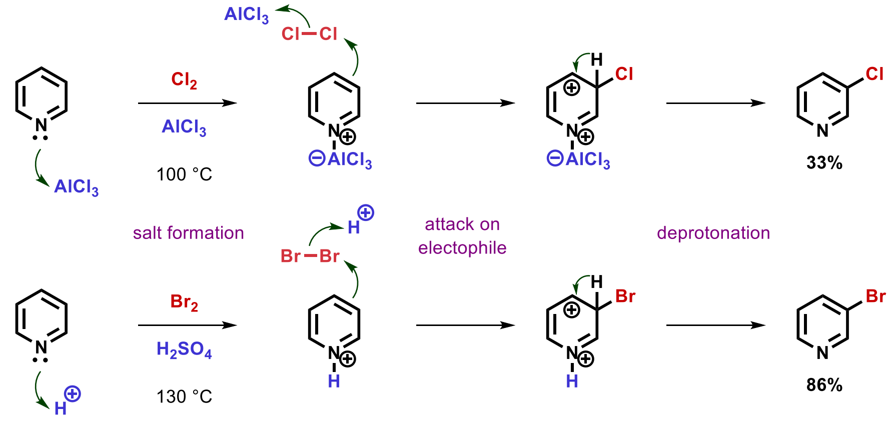


- **OH** is electron-donating so the reaction rate is increased and *ortho*,*para*- directing so the selectivity is reinforced The product tautomerises to the ketone form



Halogenation of Pyridine

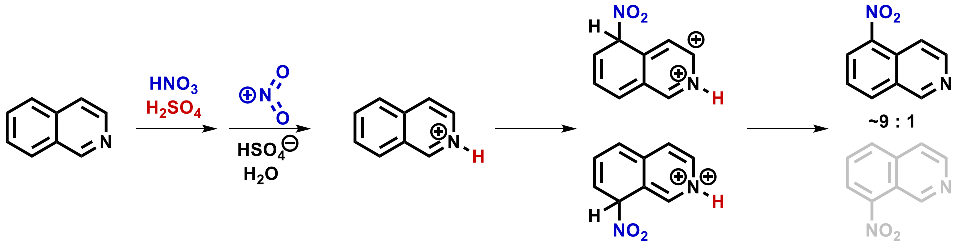
Halogenation proceeds by a similar mechanism and with similar selectivity to nitration**.** Forcing conditions are required to halogenate the electron poor system.



Quinolines and Isoquinolines as Nucleophiles: Electrophilic Aromatic Substitution

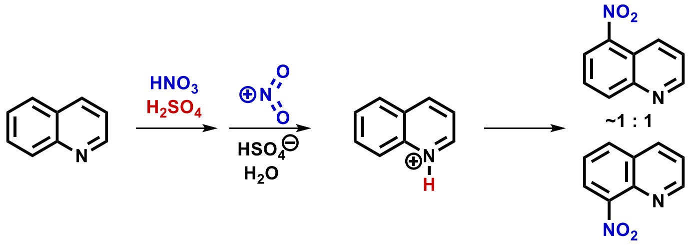
Nitration of Isoquinolines

Dehydration of nitric acid with sulfuric acid forms a nitronium cation. Protonation of nitrogen lone pair with acid forms the corresponding salt. Then nucleophilic attack by the π-system in the isoquinolinium salt from the 5-position gives least destabilisation of the positive charge and occurs on the more electron rich all-carbon ring. Finally, deprotonation to regain aromaticity delivers the product.



Nitration of Quinolines

Dehydration of nitric acid with sulfuric acid forms a nitronium cation. Protonation of nitrogen lone pair with acid forms the corresponding salt. Then nucleophilic attack by the π-system in the isoquinolinium salt from the more electron rich all-carbon ring. Finally, deprotonation to regain aromaticity delivers the product.

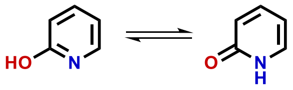


Reactions are **faster than pyridine** because the reaction is not on the nitrogen-containing ring but **slower than naphthalene** because there is still an electronegative nitrogen atom.

Oxygen-Substituted Pyridines

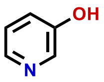
Hydroxypyridines

- Introduction of an oxygen atom next to ring changes the properties and reactivity of pyridine
- The ring is more electron rich
- There can be tautomerisation between carbonyl and hydroxy forms for 2- and 4- hydroxypyridines
- Tautomerisation does not result in an aromatic molecule for 3-hydroxypyridine
- The amine is now less basic: similar comparison between amines and amides
- The hydroxy tautomer is favoured in non-polar solvents and
  the pyridone tautomer is favoured in polar solvents

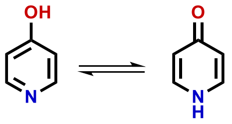


2-hydroxypyridine 2-pyridone

tautomerisation



3-hydroxypyridine

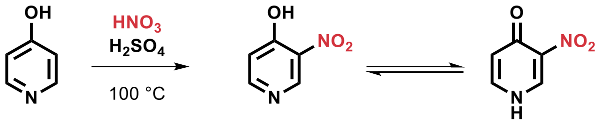


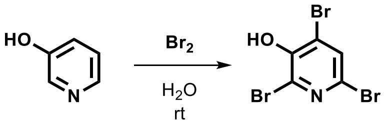
4-hydroxypyridine 4-pyridone

tautomerisation

Electrophilic Aromatic Substitution

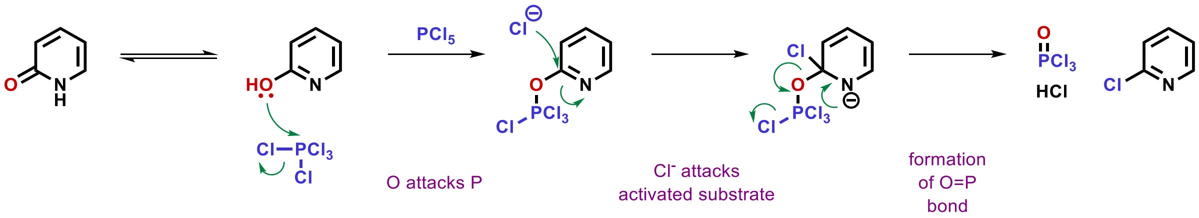
- Oxygen lone pair donation increases nucleophilicity
- Oxygen controls the selectivity → *ortho* or *para* to oxygen





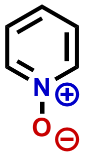
Halogenation of the Hydroxy Group

- The hydroxyl group can be converted into a halogen
- The driving force is the formation of the P=O double bond

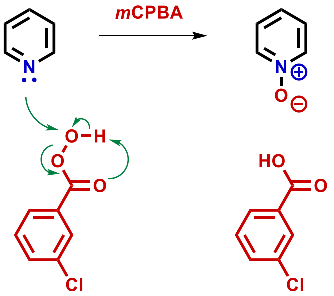


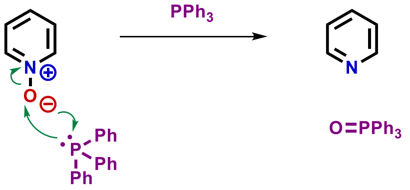
This is a common reaction in chemistry - not just for pyridines!

Pyridine *N*-Oxides



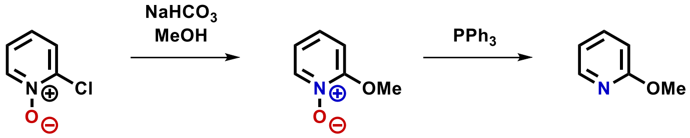
- The pyridine N atom is nucleophilic → it can also be oxidised using e.g. MCPBA
- The resulting N-oxide can also be reduced, e.g. using PPh_3
- So can serve as a **temporary activating** / **protecting** group





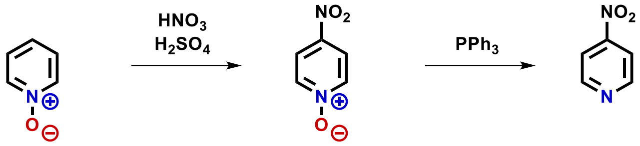
Activated Reactivity

- **More electrophilic**: N is positively charged!
  - Compare to pyridinium reactivity



  - The N-oxide can be reduced afterwards to reveal 4-substitutedpyridine

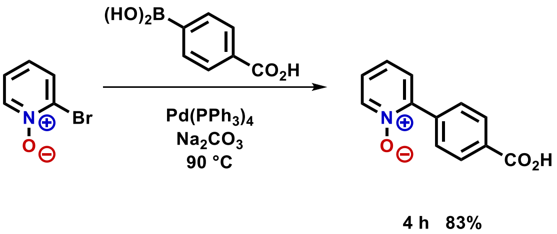
- **More nucleophilic**: oxygen lone pair donates!
  - e.g. Nitration is easier

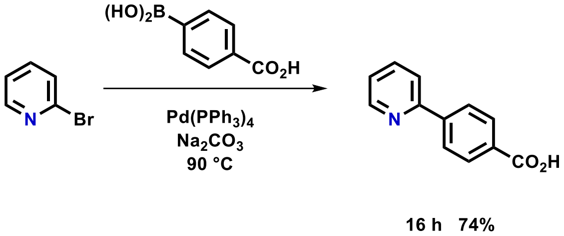


  - The N-oxide can be reduced afterwards to reveal 4-nitropyridine

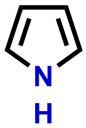
Protection of the *N* Lone Pair

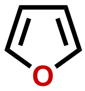
- Many modern reactions use transition metal catalysts
- The basic nitrogen lone pair can deactivate catalysts by ligating the metal
- The lone pair can be "protected" by conversion to the *N*-oxide



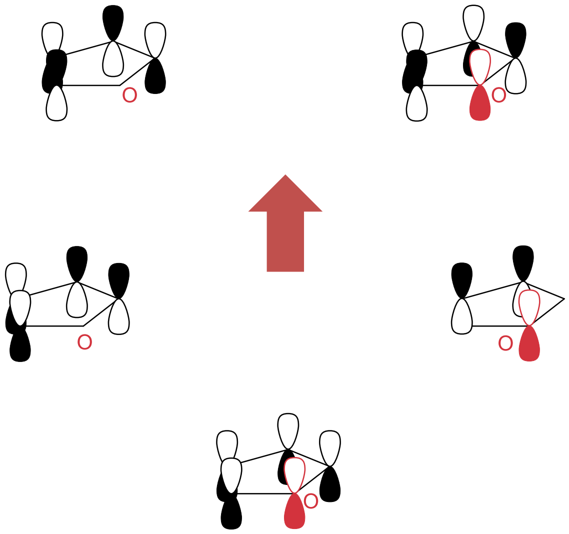


Reactivity of 5-Membered Aromatic Heterocycles





Aromaticity Recap



Black/Red, White represents orbital phase

4n+2 electrons:

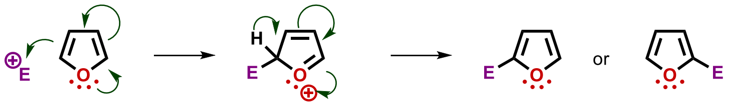
4 × C p-orbitals	4 electrons
1 x **LONE PAIR**	2 electrons

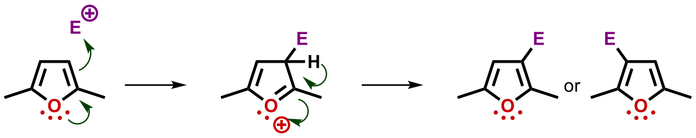
In 5-membered aromatic heterocycles, the aromatic system includes a higher energy lone pair from the heteroatom.

5-Membered heterocycles are
WORSE ELECTROPHILES
and
BETTER NUCLEOPHILES

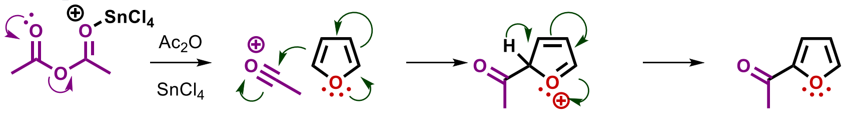
Furan General Reactivity Pattern

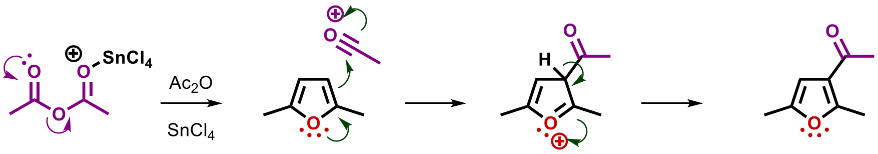
- Aromaticity includes heteroatom lone pair → **electron rich**
- Can delocalise O lone pair to attack at all the positions of the ring but attack at the 2/5 position is preferred over 3/4 because charge is stabilised over more atoms





Friedel-Crafts Acylation

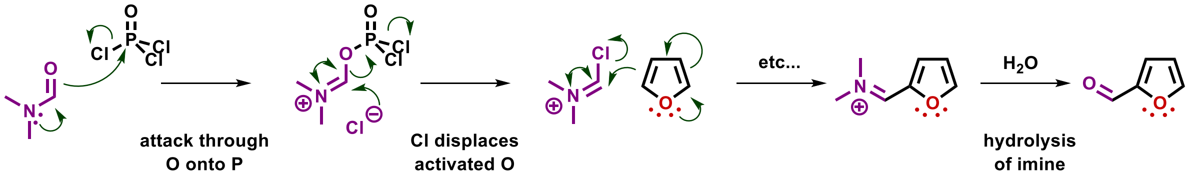




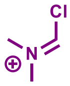
- Acylation still occurs if 2,5-position is blocked
- Activation of acyl group with Lewis acid ($SnCl_4$)
- Product is less reactive than starting material → control for mono-acylation

Vilsmeier Formylation

Furans

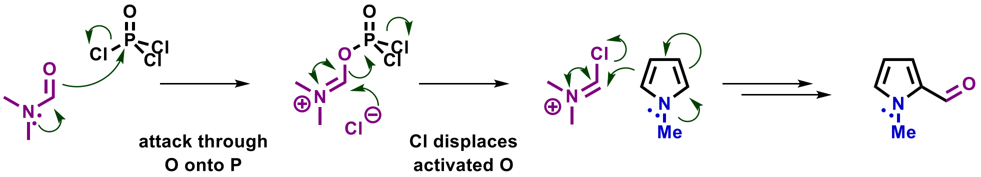


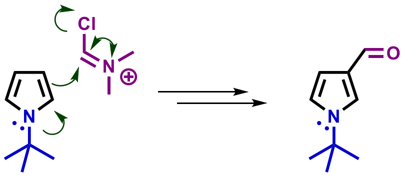
- Mechanism is the same as acylation but…
  key step is formation of the
  activated Vilsmeier reagent



Pyrroles

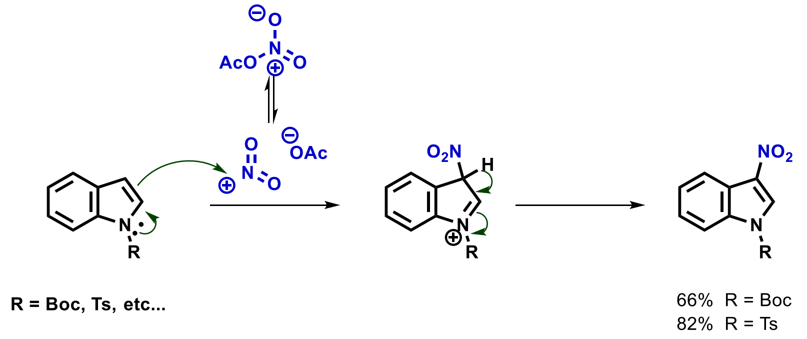
- Selectivity for reaction is driven by **size** of pyrrole *N*-substituent



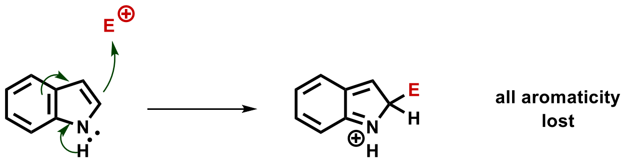


Indole Reactivity: Nitration

Unsubstituted indoles give low yield due to polymerisation

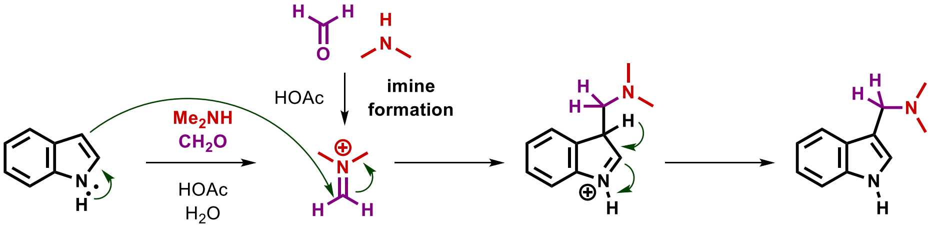


Reaction through the 2-position would break all aromaticity within the molecule



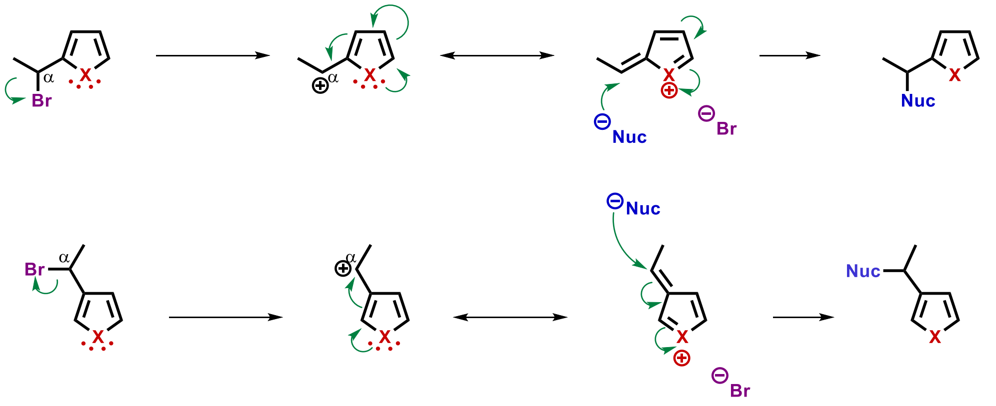
Indole Reactivity: Mannich Reaction

Indoles react preferentially through the 3-position



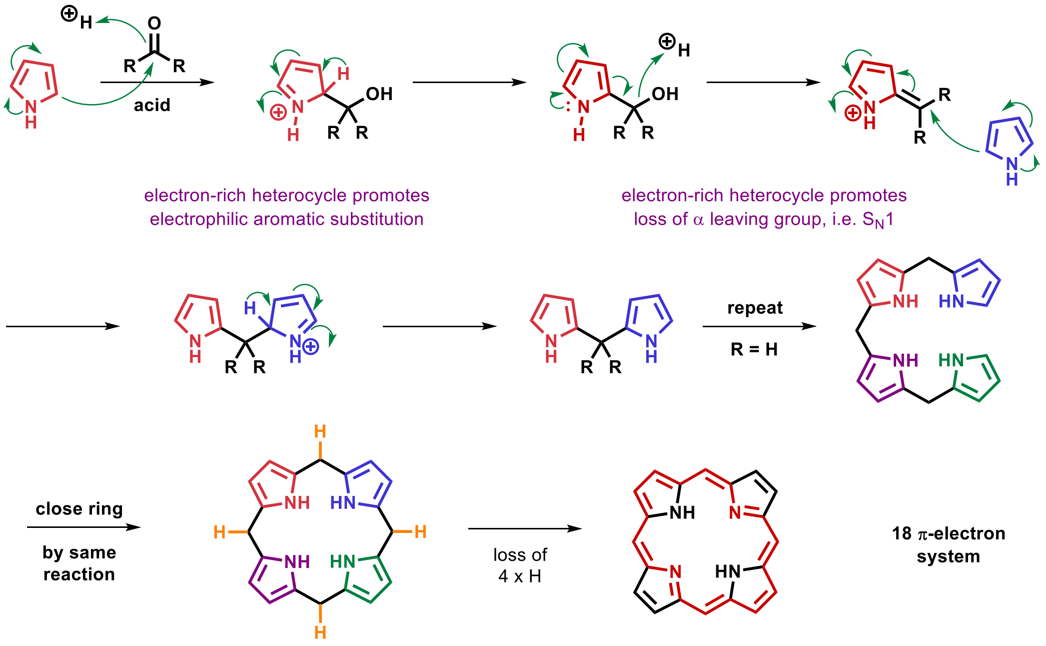
α-Reactivity of -oles

Pyrroles, furans and thiophenes are electron rich heterocycles and they can stabilise adjacent (α) positive charges. If there is a good leaving group in that position the heterocycle undergoes ready substitution reaction.



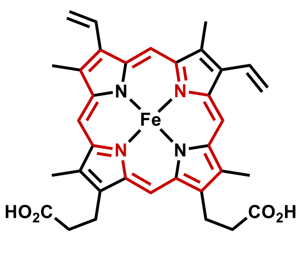
Porphyrin Formation

Electrophilic aromatic substitution and α-reactivity are combined in porphyrin synthesis



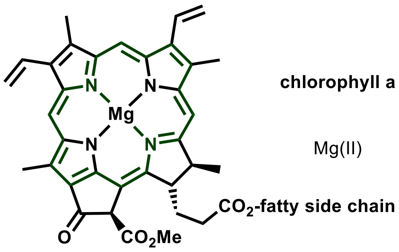
electron-rich heterocycle promotes
electrophilic aromatic substitution

electron-rich heterocycle promotes
loss of α leaving group, i.e. S_N1



haem b
haemoglobin

Fe(II)



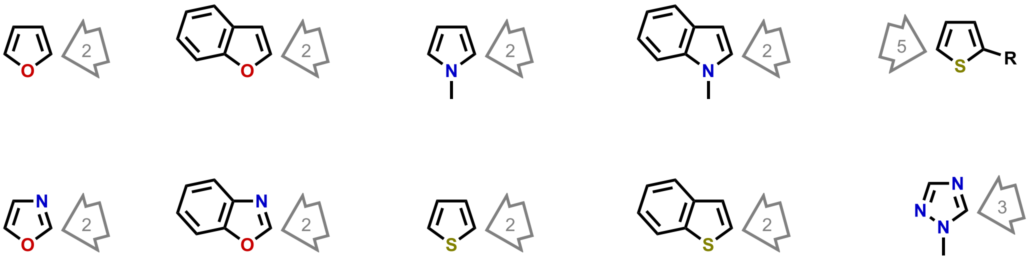
chlorophyll a

Mg(II)

General Reactivity of Heterocycles

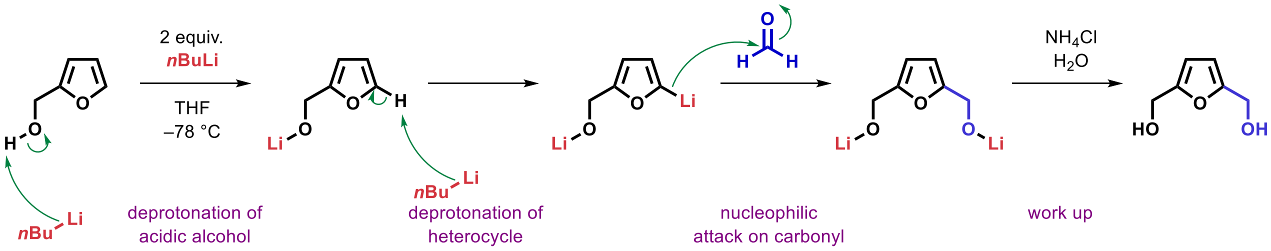
Lithiation

- 5-Membered heterocycles can be lithiated at predictable locations
- The lithiation occurs next to the electronegative atom



Furans:

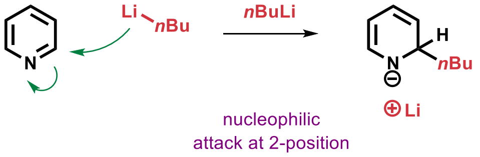
- The most acid proton is at the 2-position
- Deprotonation occurs nearest the electronegative oxygen atom
  N.B. the sp^2 C-H bond is removed leaving the aromatic system in place



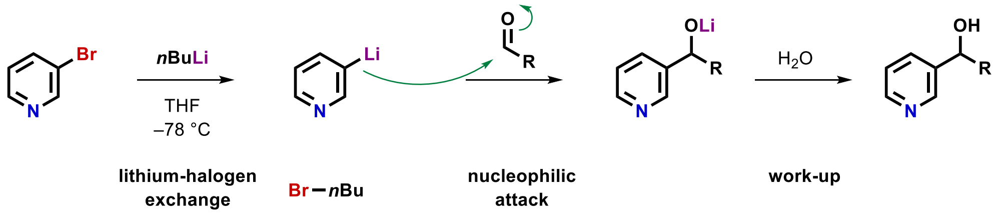
- The free OH in this example is more acidic than the furan so an excess of *n*BuLi was required

Pyridines:

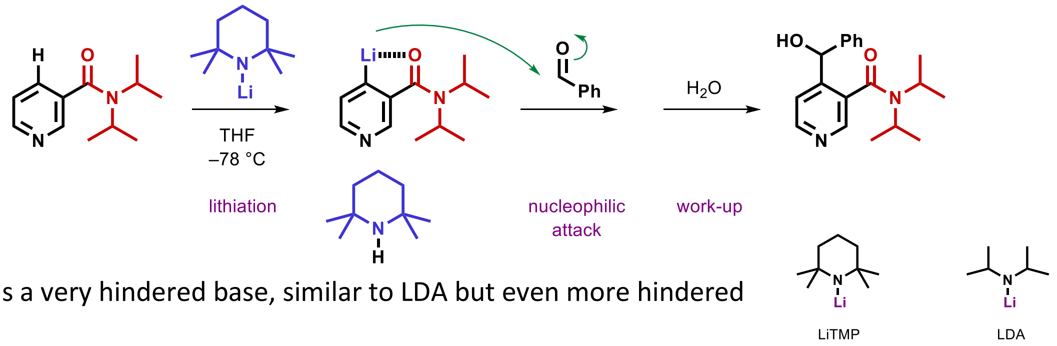
- Lithiation of pyridines does not occur and nucleophilic attack is preferred



- Lithiation of halogenated pyridines is possible
- N.B. you don't get nucleophilic substitution with C-Li nucleophiles



- Can also use directing groups to directly lithiate pyridines

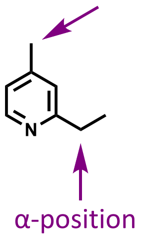


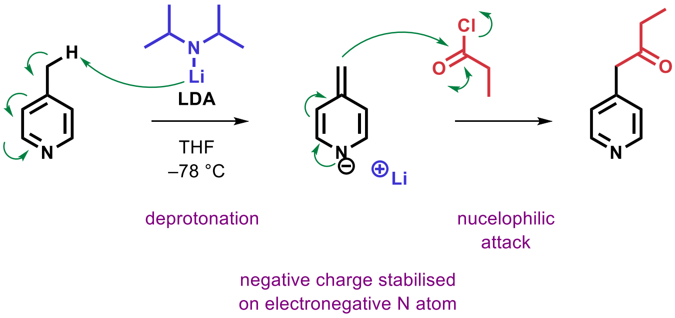
LiTMP is a very hindered base, similar to LDA but even more hindered

Deprotonation

- The electron withdrawing-pyridine makes deprotonation α- to the ring more favourable

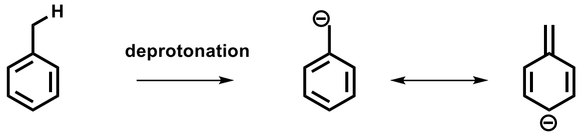
pKa = 35 in DMSO



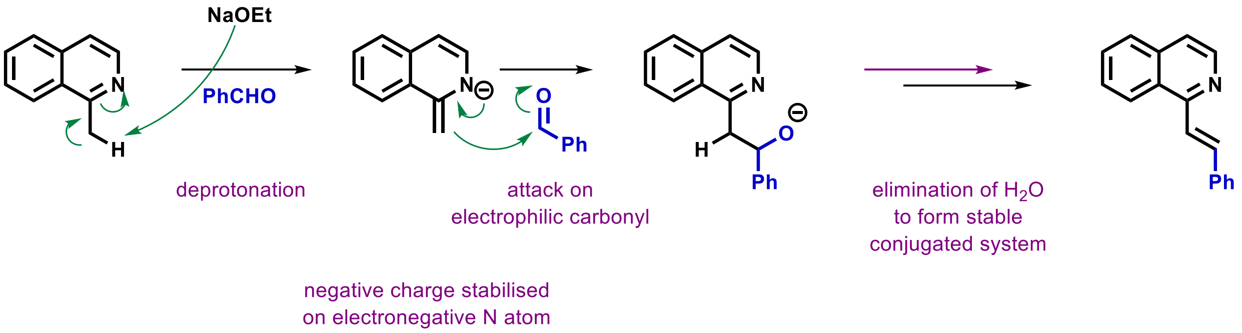


- In contrast deprotonation of toluene is much more difficult

pKa = 43 in DMSO

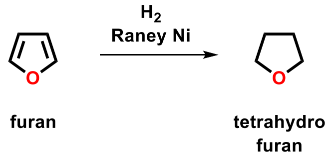


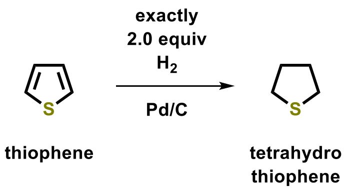
- In fused pyridines, deprotonation of the α-position occurs with the resulting negative charge of conjugate base distributed throughout aromatic system, including stabilisation on the electronegative heteroatom. Then this is a nucleophile that can attack an electrophile. Here, finally elimination of water to form a stable *trans*-conjugated system.
-

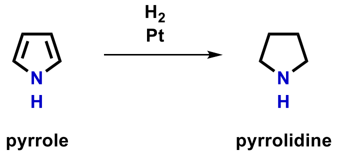


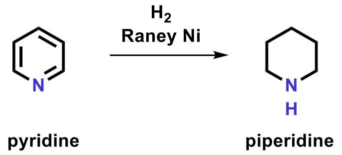
Reduction: Hydrogenation

- Hetereocycles can be reduced using H_2 and metal catalysts





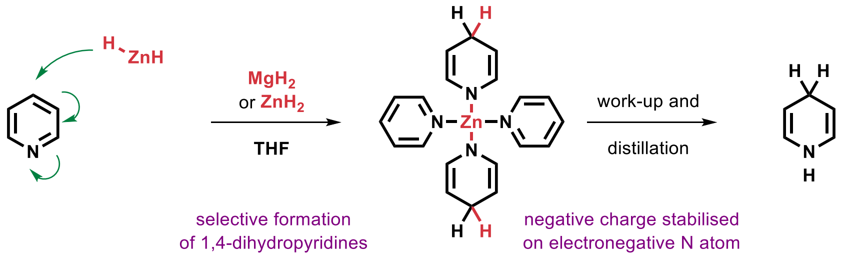




- Raney Ni and Pt are very potent metal catalysts for reduction
- The reduction of thiophene requires exactly 2.0 equivalents of hydrogen to prevent reduction of the weak C–S bond

Reduction: Hydrides

It is possible to partially reduce the heteroaromatic system using carefully controlled metal hydride conditions. Other reducing agents, such at $LiAlH_4$ give mixtures of dihydropyridines.

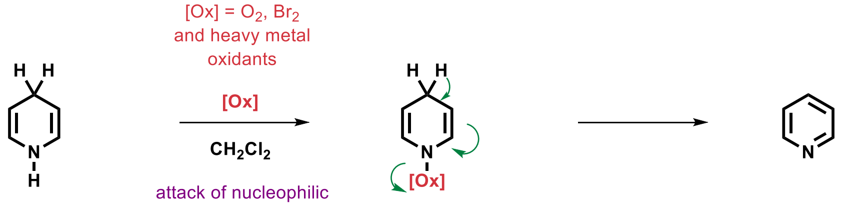


selective formation of 1,4-dihydropyridines

negative charge stabilised on electronegative N atom

Oxidation

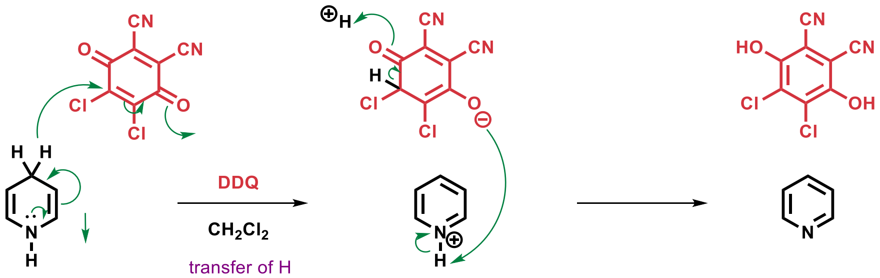
Partially saturated heterocycles are easily oxidised with a range of oxidising agents.
For agents such as oxygen, bromine and heavy metal oxidants there is attack of the nucleophilic nitrogen into the oxidant followed by elimination promoted by reduction of the oxidant, e.g. breaking the Br-Br bond.



attack of nucleophilic nitrogen onto oxidant

elimination

For DDQ, there is hydride transfer from the dihydropyridine to the very electron poor DDQ followed by tautomerisation.



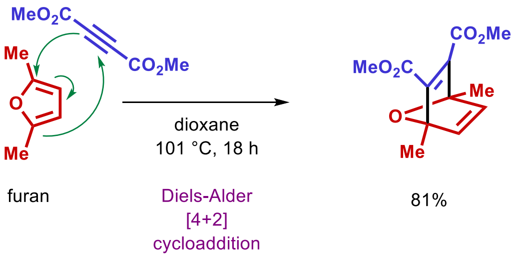
transfer of H to very electron poor DDQ

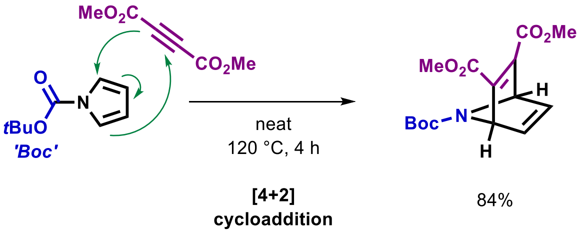
tautomerisatoin to aromatic molecule

Cycloaddition

Furans and Pyrroles

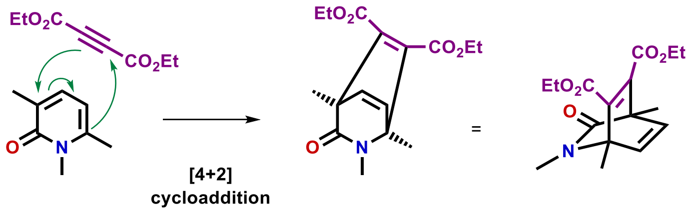
- 5-membered heterocycles contain a diene system which is permanently locked in the S-*cis* conformation requisite for Diels-Alder cycloaddition
- Electron-rich systems are ideal for reactions with electron-poor dienophiles



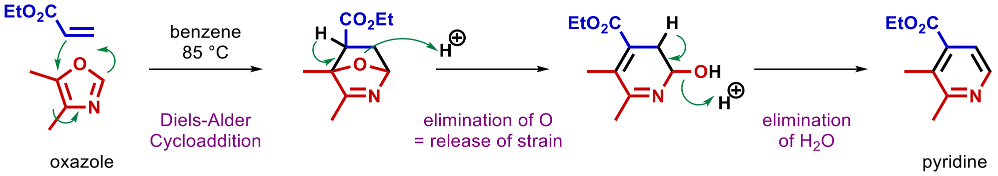


- Thiophene Diels-Alder reactions are difficult, requiring very high pressure

Pyridones



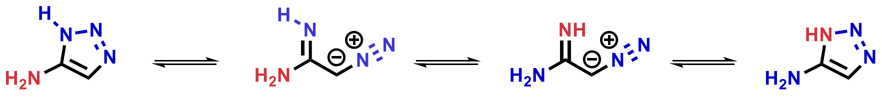
Oxazole → Pyridines



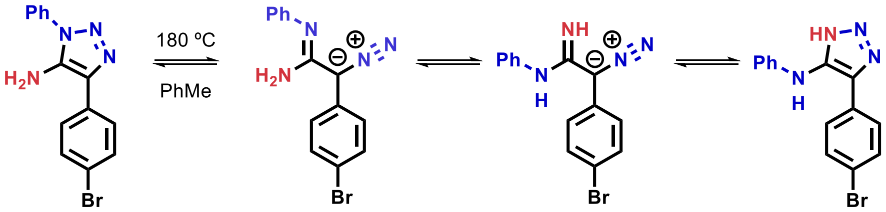
- Synthesis of one heterocycle (pyridine) from another (oxazole)
- Diels-Alder reaction is [4+2] cycloaddition
- Dieneophiles have electron withdrawing groups (CO_2Et)
- Elimination driven by release of ring strain, then loss of water

Rearrangement

- Heterocycles with certain patterns of substitution can undergo rearrangement

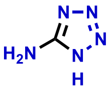


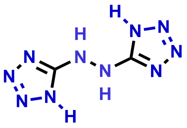
  - The ring opens to the diazo compound
  - The single bond rotates
  - The ring closes back to the triazole

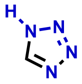


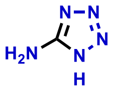
Tetrazoles: Explosive

- High nitrogen content compounds are explosives…
  they can generate a lot of energy by decomposing rapidly making a lot of very stable N2









- E.g. 4-aminotetrazole has a very high nitrogen component: CH_3N_5 ➔ C 14%; H 4%; N 82%
- This compound has been evaluated to inflate airbags

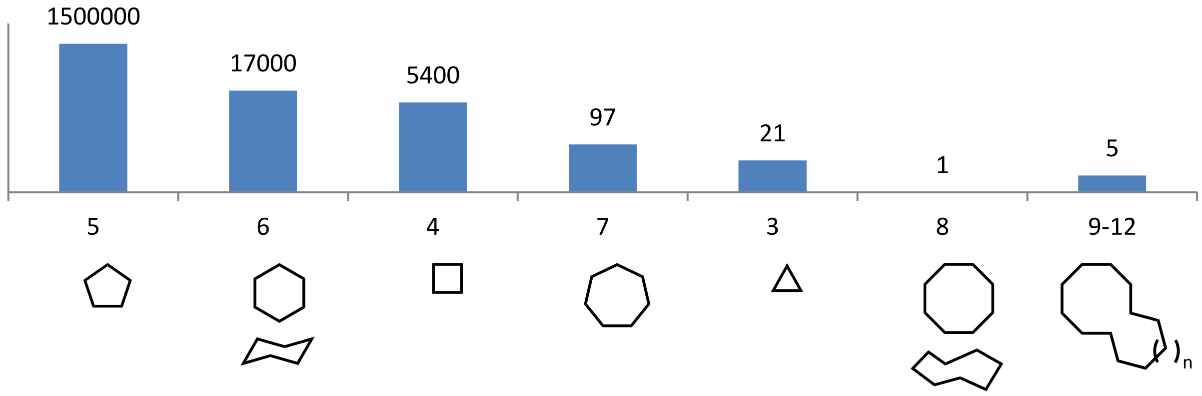
Synthesis

Rate of Formation of Different Rings

When considering rate of ring formation, there are 2 factors:

What is the strain in the system?	Unfavourable for small (<5) and medium (7-9) rings
How easy is it for the ends to meet?	Unfavourable for larger rings

5- and 6-membered rings are formed very easily!
N.B. LOGARITHMIC SCALE:



Basic Heterocycle Synthesis

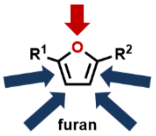
- The most basic syntheses of heterocycles are based on **DEHYDRATION** and **CYCLISATION** of linear compounds to make **FIVE** or **SIX** membered rings

Synthesis Strategy

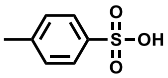
- Identify key heteroatom(s)
- Identify atoms in backbone
- Disconnect to the corresponding carbonyl species

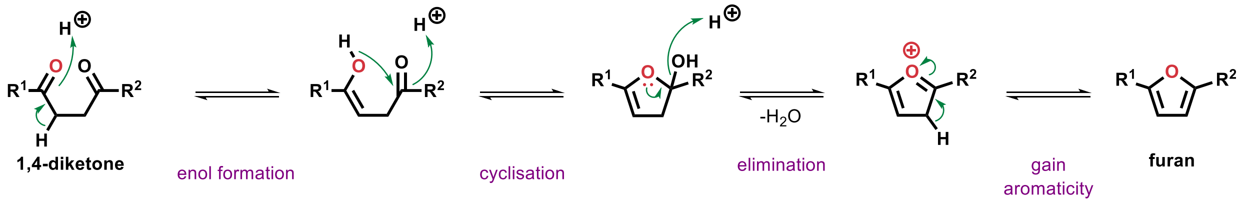
Synthesis: use carbonyl species with appropriate heteroatom source

Paal-Knorr Furan Synthesis

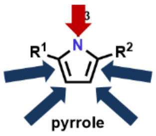


- Conditions: **acid**, e.g. para-toluenesulfonic acid (PTSA)
- Substrates: **1,4-dicarbonyl**
- Product: **furan**
- Mechanism: **dehydration and cyclisation**
- **N.B.** This is reversible to removing water gives the furan and furans can by hydrolysed to the 1,4-dicarbonyl species.

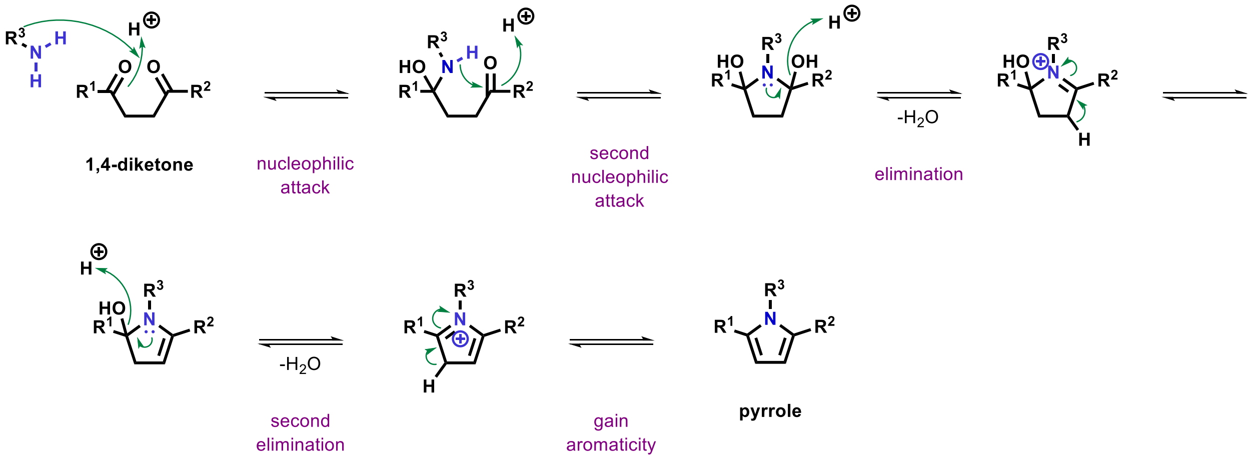




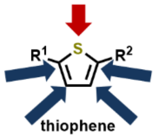
Paal-Knorr Pyrrole Synthesis



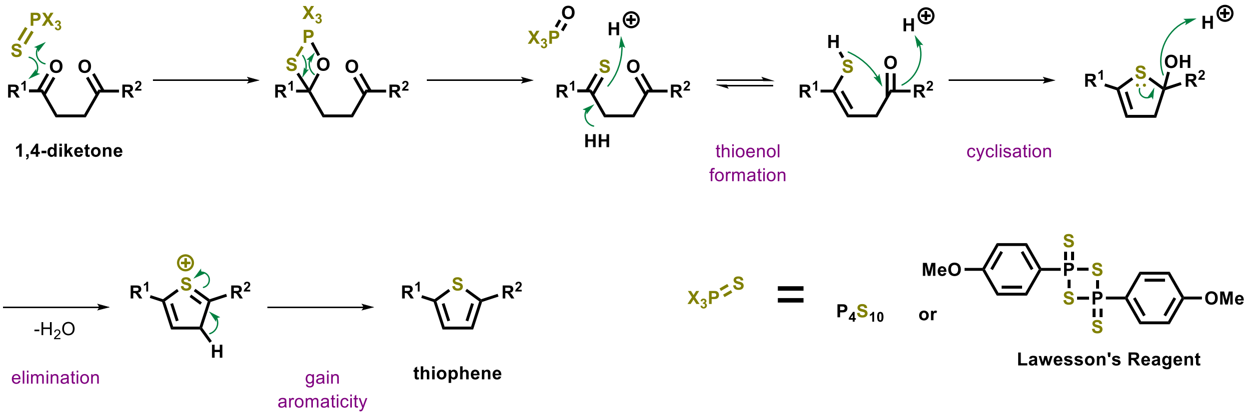
- Conditions: **acid**, e.g. para-toluenesulfonic acid (PTSA)
- Substrates: **amine** and **1,4-dicarbonyl**
- Product: **pyrrole**
- Mechanism: **dehydration and cyclisation**
- **N.B.** This is reversible



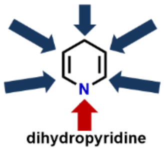
Paal-Knorr Thiophene Synthesis



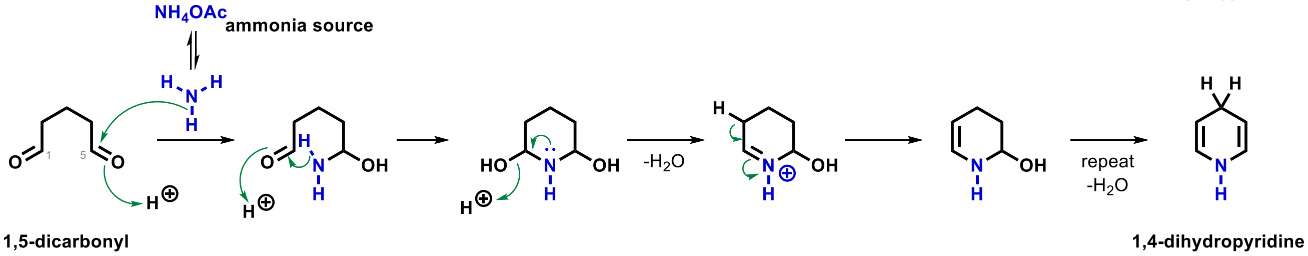
- Conditions: **P=S reagent** – converts C=O into C=S and is dehydrating
- Substrates: **1,4-dicarbonyl**
- Product: **thiophene**
- Mechanism: **dehydration and cyclisation**
- Driving force is the formation of a strong **P=O** bondS-exchange reagent also is **dehydrating** so promotes heterocycle formation



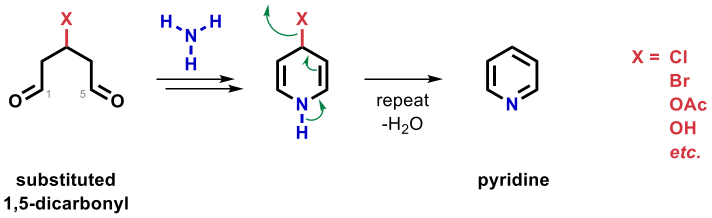
Dihydropyridine Synthesis



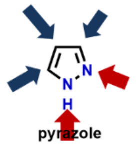
- 1,4-Dihydropyridines can be formed from the corresponding 1,5-dicarbonyl compound and an amine or ammonia or ammonia source (like ammonium acetate)



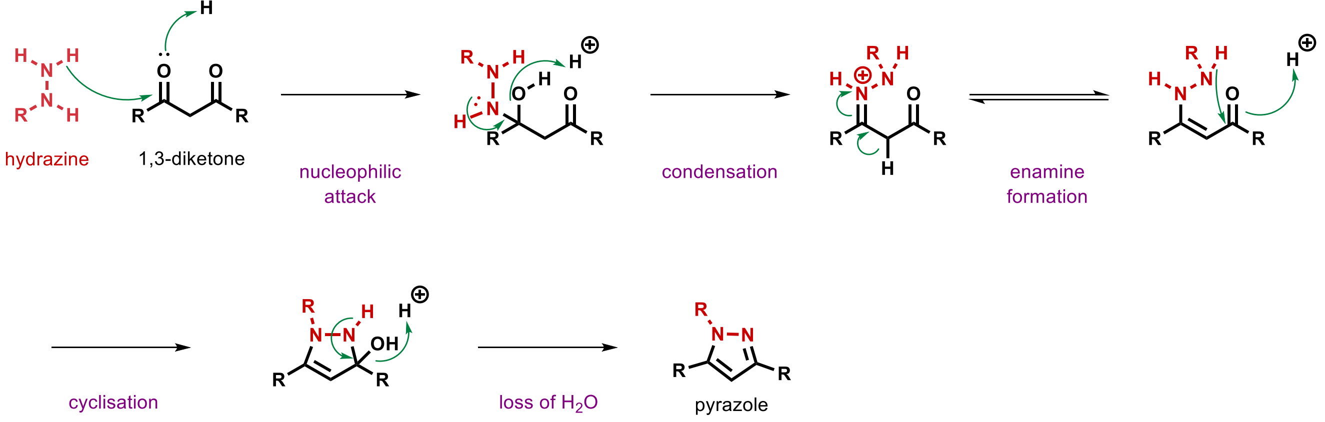
- Pyridines can be formed, driven by formation of aromaticity, if there is a leaving group on the ring



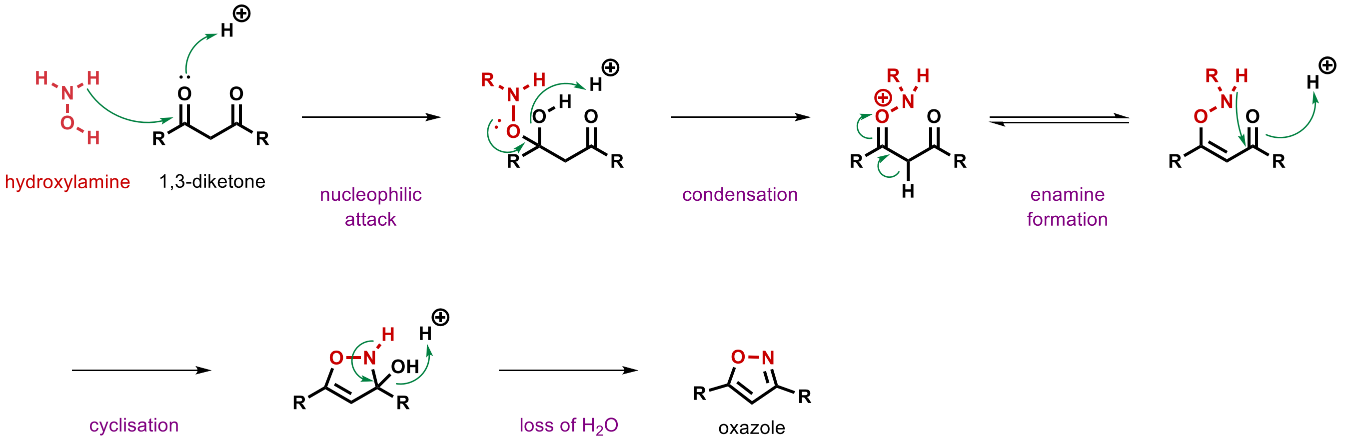
Pyrazoles and Oxazoles



Hydrazines are very good nucleophiles due to the adjacent lone pairs.
Initial attack of the nitrogen onto the carbonyl leads to dehydration and enamine formation. This is reversible so that the requisite *Z*-geometry is formed. Then cyclisation and loss of H_2O gives the pyrazole product.

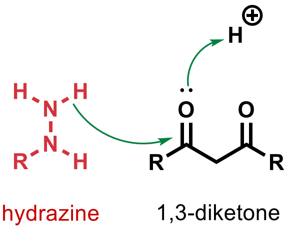


Swapping to hydroxylamine, this is still a very good nucleophiles due to the adjacent lone pairs. Initial attack of the oxygen onto the carbonyl leads to dehydration and enol formation. This is reversible so that the requisite *Z*-geometry is formed. Then cyclisation and loss of H_2O gives the isoxazole product.

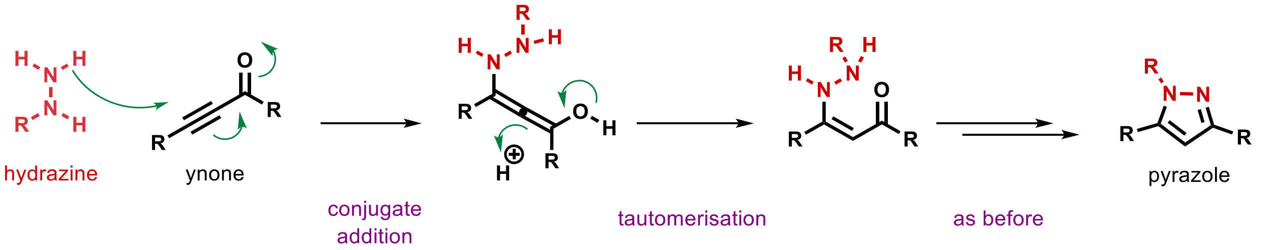


1,3-Dicarbonyl Equivalents

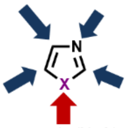
An equivalent to a 1,3-dicarbonyl species, e.g. an **ynone**, can also be used



cf.

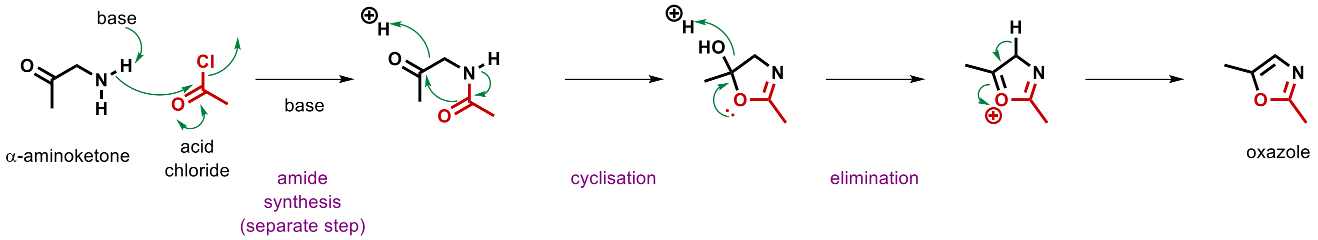


Robinson-Gabriel Oxazole Synthesis & Imidazole Synthesis



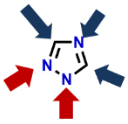
oxazole (X=O)
imidazole (X=NR)

Amides are dehydrated under acidic conditions to the oxazole
Attack of the more nucleophilic amide carbonyl onto the more electrophilic ketone carbonyl
Originally promoted by concentrated H_2SO_4, can also be promoted by dehydrating agents, e.g. PCl_5, P_2O_{10}, $POCl_3$, etc…
A similar process occurs in peptides to make oxazoles in nature



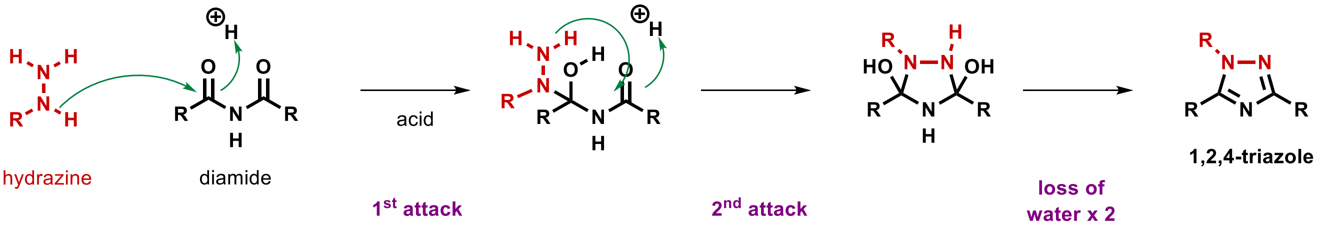
By introducing an amine RNH_2 the analogous imidazole can be synthesised.

Einhorn–Brunner Synthesis of 1,2,4-Triazoles

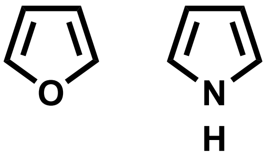


1,2,4-triazole

Using the same strategy we can condense a hydrazine with a diamide starting with double attack of the two nitrogen atoms followed by loss of two water molecules

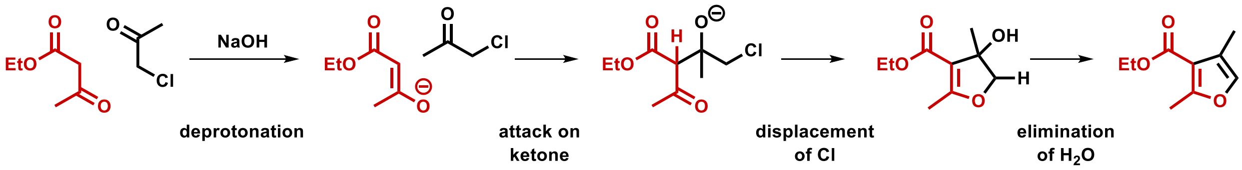


Synthesis of Furans and Pyrroles



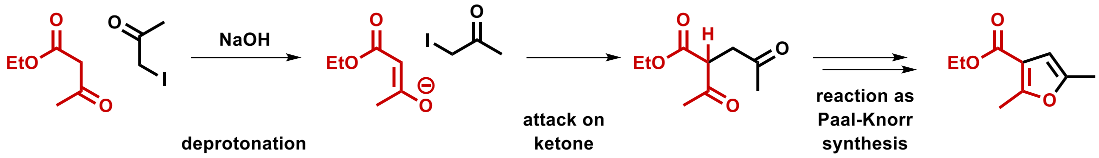
Feist-Benary Furan Synthesis

- Synthesis of furan from readily available building blocks

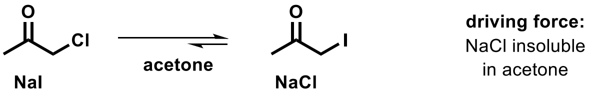


Modified Feist-Benary Furan Synthesis

- Synthesis of furan from readily available building blocks

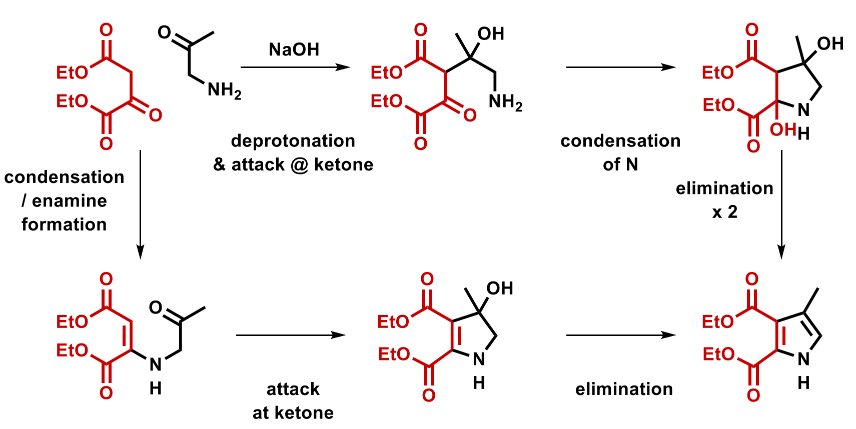


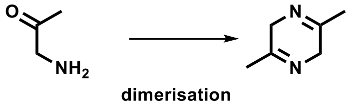
- Swapping to the **iodide reverses** the reactivity!!



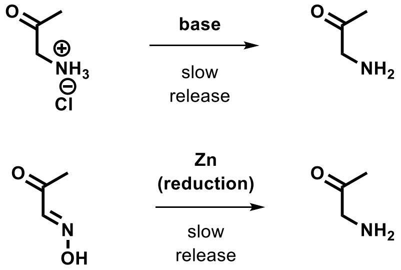
Knorr Pyrrole Synthesis

- Synthesis of pyrrole from readily available building blocks
- Order of events in mechanism does not matter → same outcome



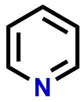


Protect free amine:

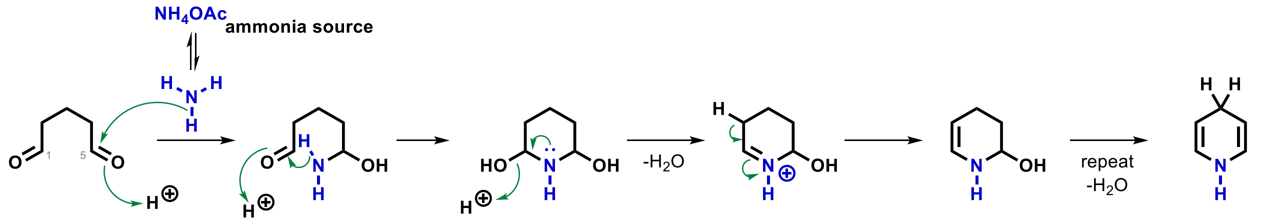


- The aminoketone can **dimerise** so is often used as its salt and converted into the free base *in situ* or using **protecting groups**

Pyridine Synthesis



Basic Synthesis Approach

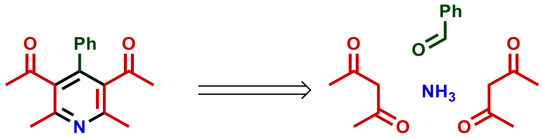


1,5-dicarbonyl

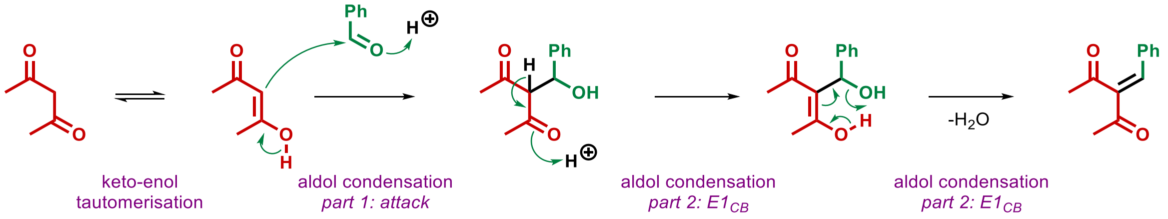
1,4-dihydropyridine

Hantzsch Pyridine Synthesis

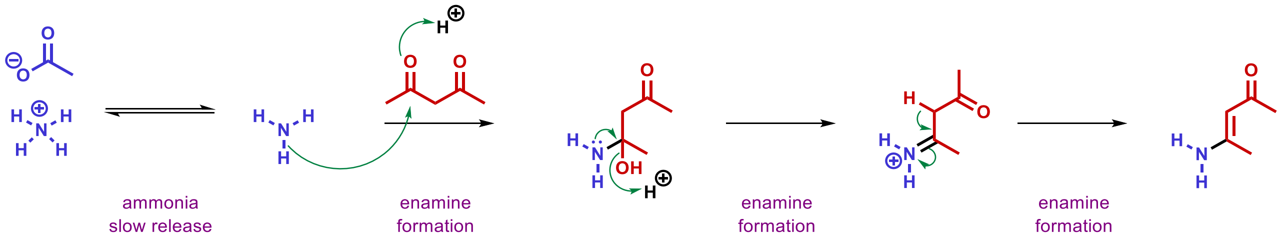
- Strategic Approach



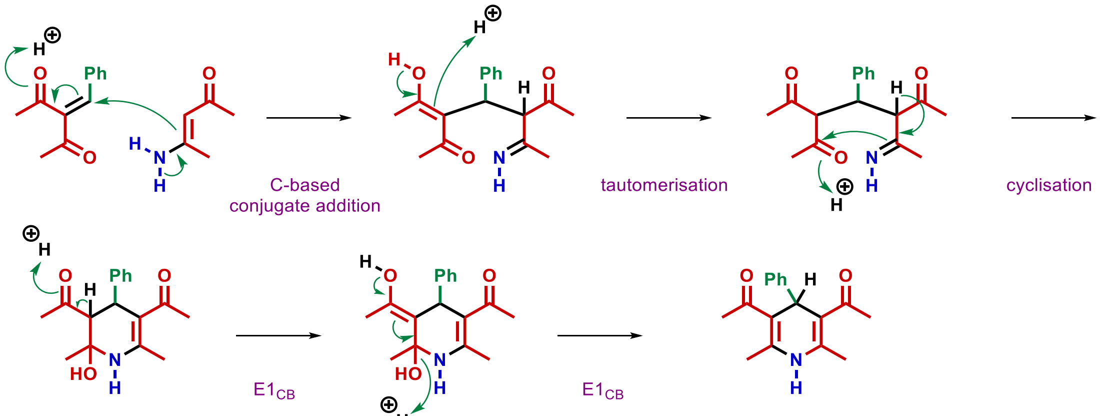
- Aldol condensation between one 1,3-dicarbonyl and the aldehyde gives a Michael Acceptor



- Enamine formation between the amine and one 1,3-dicarbonyl



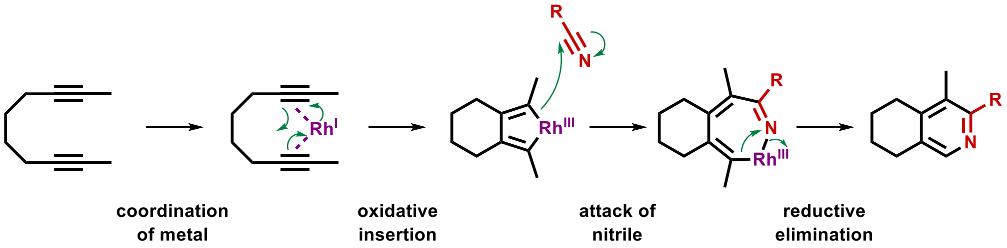
- Conjugate addition, cyclisation and dehydration delivers the diydropyridine product



1,4-dihydropyridine

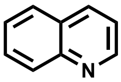
- N.B. Only symmetrical products can be formed under standard conditions
  BUT the two fragments can be formed separately

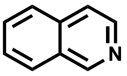
2+2+2 Pyridine Synthesis



- Works best with tethered diyne substrates
- Mechanism:
  - Both the alkenes coordinate the rhodium(I) species
  - Oxidative insertion makes new C-C bond and 2 C-Rh bonds
  - The C-Rh bond attacks the nitrile to incorporate it in the ring
    cf. C-Mg bond in Grignard reagents
  - The rhodium(III) species undergoes reductive elimination to make a new C-N bond and regenerate the rhodium(I) catalyst

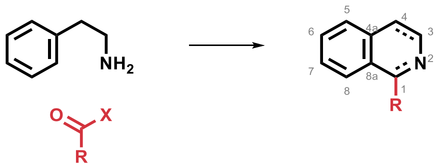
Isoquinoline and Quinoline Synthesis





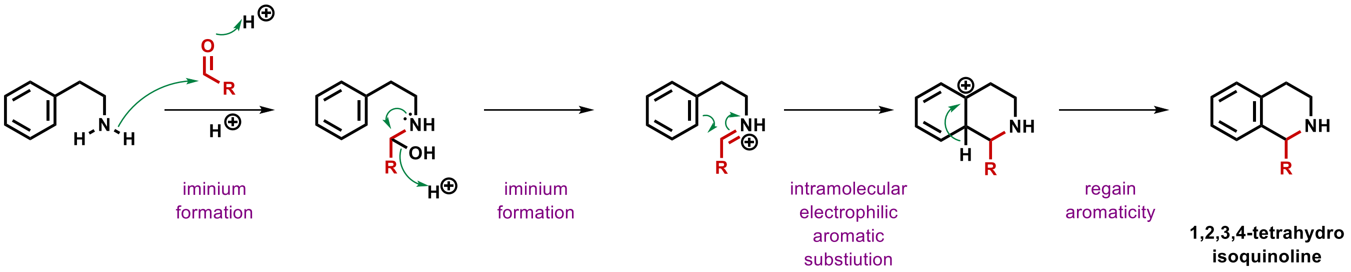
Isoquinoline Synthesis

A common general strategy for isoquinoline synthesis is the reaction between a 2-aminoethylaromatic compound and carbonyl



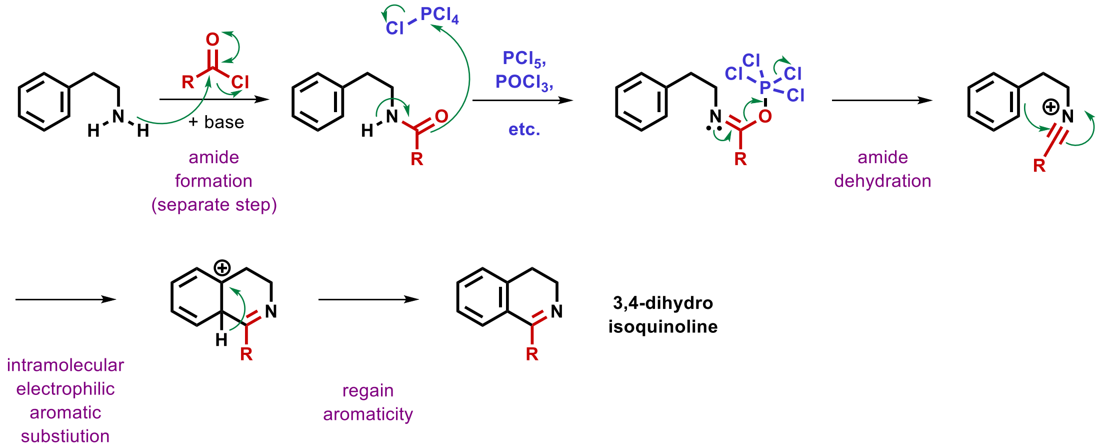
Tetrahydroisoquinoline Synthesis: Pictet-Spengler

- Rapid iminium formation between the aldehyde and the imine
- Nucleophilic attack of the π-system onto the iminium species [EAS]
- Deprotonation to regain aromaticity
- Works best with electron rich aromatic systems



Isoquinoline Synthesis: Bischler-Napieralski

- Form an amide in a separate step
- Dehydration of the amide using a phosphorus reagent, driven by strong P=O bond formation
- Nucleophilic attack of the π-system onto the positive-charged species [EAS]
- Deprotonation to regain aromaticity
- Works best with electron rich aromatic systems

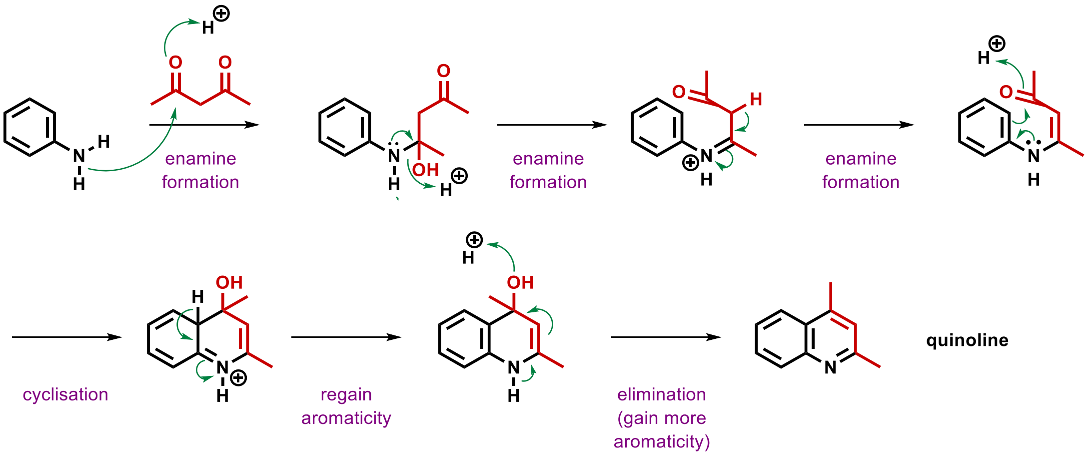


Quinoline Synthesis

A common general strategy for quinoline synthesis is the reaction between a aminoaromatic compound and 1,3-dicarbonyl species

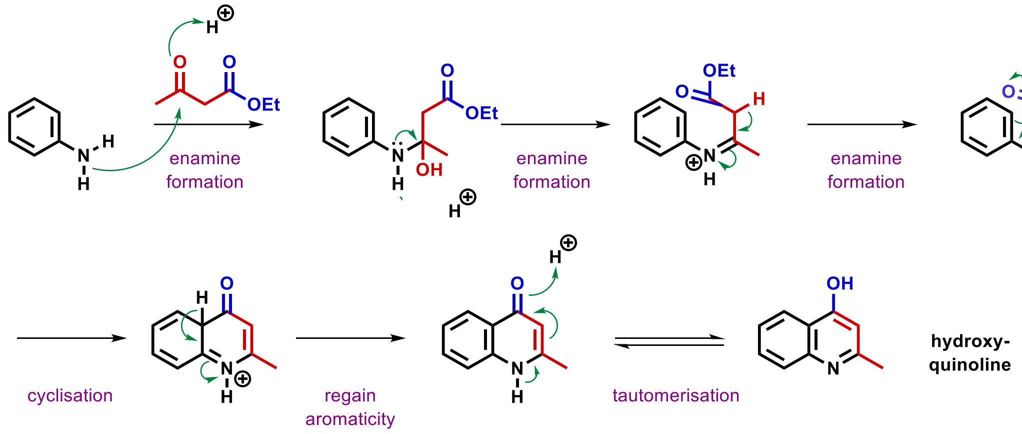
Quinoline Synthesis: Combes

Reaction between an amino-aromatic, e.g. aniline, and a 1,3-diketone to form a quinoline.
Enamine formation is followed by cyclisation similar to an intramolecular electrophilic aromatic substitution and finally elimination forms the quinoline product.



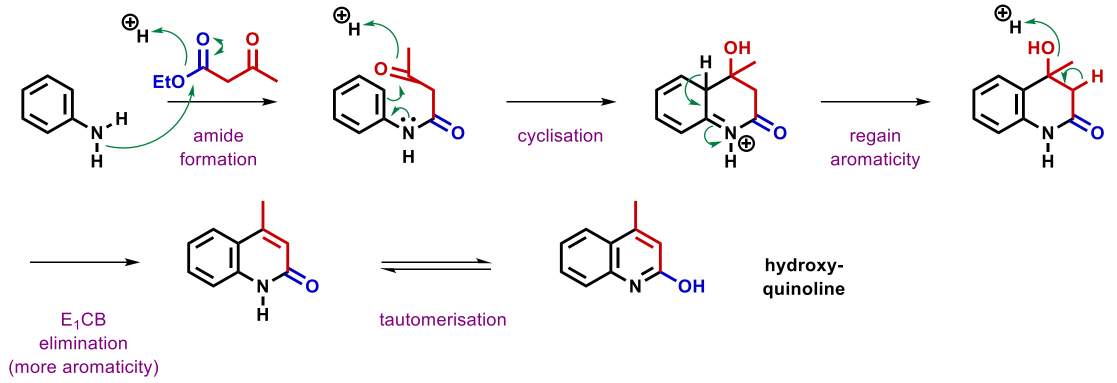
Quinoline Synthesis: Conrad-Limpach – ROOM TEMPERATURE

Reaction between an amino-aromatic, e.g. aniline, and a 1,3-ketoester to form a **2-**hydroxyquinoline. Very similar to the Combes Synthesis but using a ketoester substrate. N.B. Enamine formation at the ketone is the **kinetic** preference because ketones are more reactive than esters.

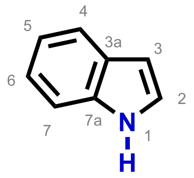


Quinoline Synthesis: Conrad-Limpach – HIGH TEMPERATURE

Reaction between an amino-aromatic, e.g. aniline, and a 1,3-ketoester to form a **4-**hydroxyquinoline. Very similar to the Combes Synthesis but using a ketoester substrate. N.B. Amide formation is the **thermodynamic** preference because amides are favoured to enamines.

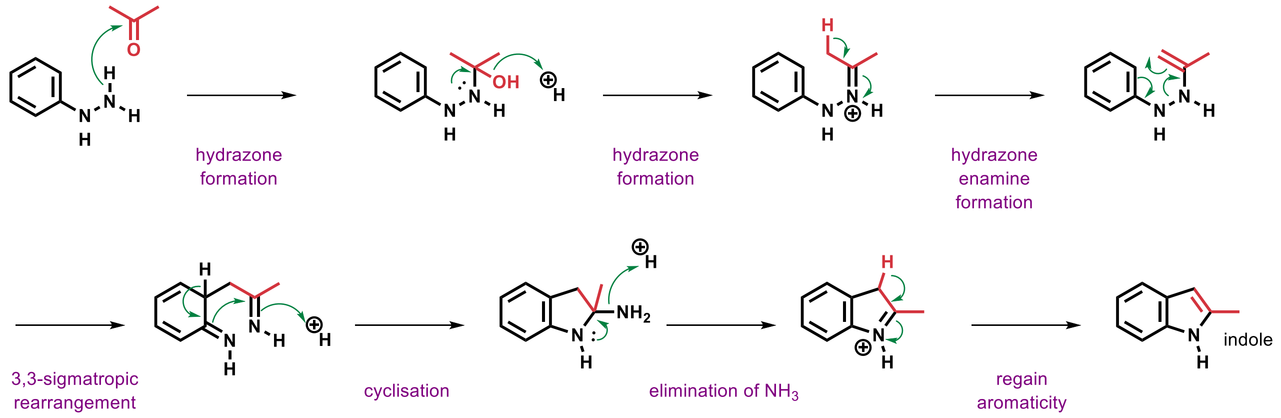


Indole Synthesis



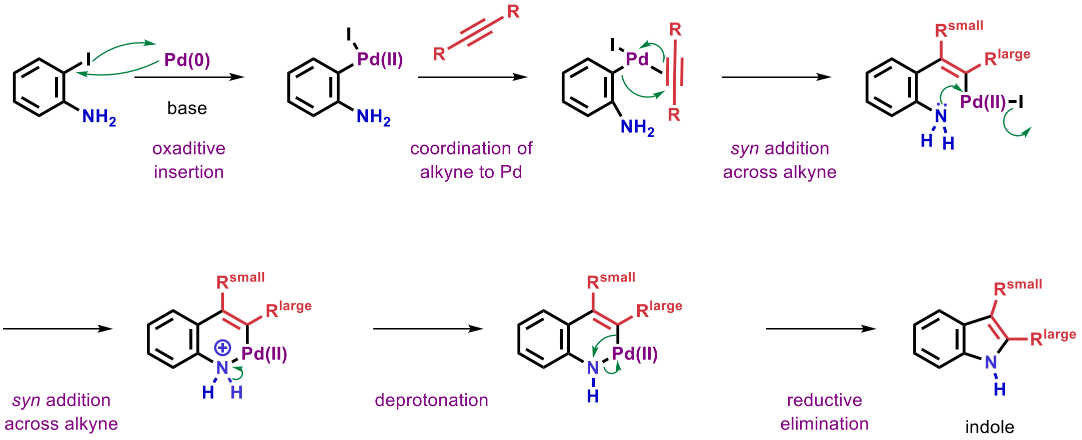
Fischer Indole Synthesis

An aryl hydrazine and ketone form an indole by rearrangement under acidic conditions.
First the hydrazine rapidly condenses with the carbonyl, then enamine formation sets up the double bond arrangement for the 3,3-sigmatropic rearrangement. Finally, cyclisation to form the 5-membered ring and loss of ammonia gives the full aromatic indole product.

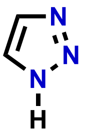


Larock Indole Synthesis

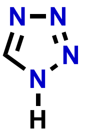
An alkyne and a 2-iodoaniline can be converted into an indole under palladium (0) catalysis.
The reaction begins with oxidative insertion followed by *syn*-carbopalladation of the alkyne. Then intramolecular displacement of the iodine by the nitrogen completes a six-membered ring. Finally, deprotonation promoted reductive elimination to generate the product and release the Pd(0) catalyst.
If the two R groups are not the same, the biggest one ends up in the indole 2-position



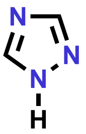
1,3-Dipolar Cycloaddition



1,2,3-triazole

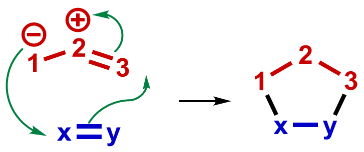


tetrazole



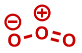
1,2,3-triazole

- 1,3-Dipolar cycloaddition occurs between a 1,3-dipole: a three atom arrangement containing both positive and negative charges
- The mechanism is a pericyclic, [4+2] cycloaddition process: 4 electrons in the dipole (two from the negative charge and two in the double bond)
  2 electrons in the dipolarophile



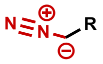
Example 1,3-dipoles:

azide



ozone

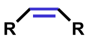
nitrile ylide



diazoalkane

Example dipolarophiles:

alkyne

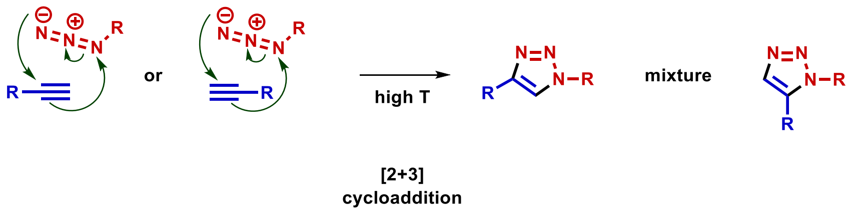


alkene

nitrile

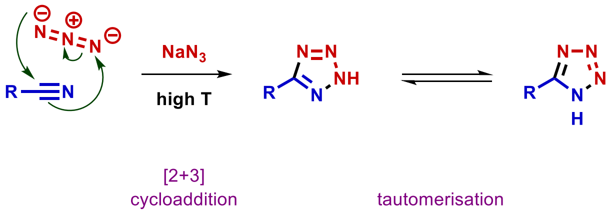
- Also called Huisgen addition.

Cycloaddition to form 1,2,3-Triazoles



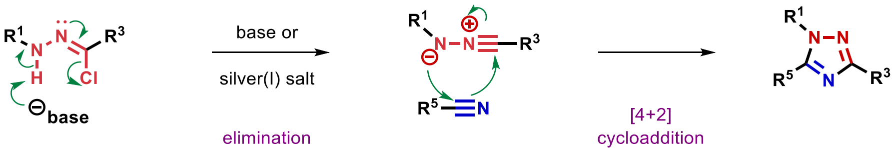
- Alkynes and azides are readily available
- **Copper** catalysts form 1,4-substituted products
- **Ruthenium** catalysts favour 1,5-substituted products

Tetrazoles



- Nitriles are readily available and sodium azide is cheap
- Can be catalysed with Lewis acids or iodine
- Each of the nitrogen atoms in tetrazole can be N-H through tautomerisation

1,2,4-Triazoles



- Elimination of HCl by base or silver (I) reagent to form 1,3-dipole
- Dipolar cycloaddition delivers 1,2,4-triazoles

Appendix A: Selected Heterocycles

3 IR

oxirene

1H-azirine

thiirene

2H-azirine

oxirane
aka epoxide

aziridine

thiirane

4 ET

oxete

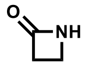
azete

thiete

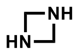
oxetane

azetidine

thietane

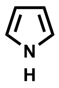


azetidin-2-one
aka β-lactam



1,3-diazetidine

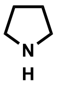
5 OL



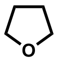
pyrrole
(not azole)

furan
(not oxole)

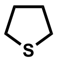
thiophene
(not thiole)



pyrrolidine
(not azolidine)

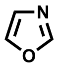


tetrahydrofuran

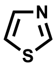


tetrahydrothiophene

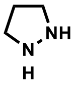
imidazole
(1,3-diazole)



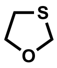
oxazole
(1,3-oxazole)



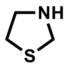
thiazole
(1,3-thiazole)



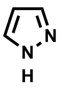
pyrazolidine
(1,2-diazolidine)



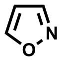
1,3-oxathiolane



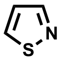
1,3-thiazolidine



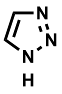
pyrazole
(1,2-diazole)



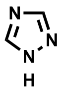
isoxazole
(1,2-oxazole)



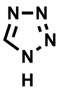
isothiazole
(1,2-thiazole)



1,2,3-triazole

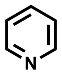


1,2,4-triazole

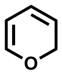


tetrazole

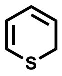
6 IN



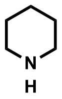
pyridine
(not azine)



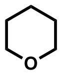
2H-pyran
(not oxine)



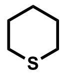
2H-thiopyran
(thiine)



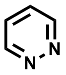
piperidine
(azinane)



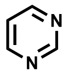
tetrahydropyran
(oxane)



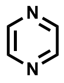
thiane



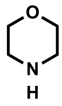
pyridazine
(1,2-diazine)



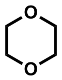
pyrimidine
(1,3-diazine)



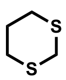
pyrazine
(1,4-diazine)



morpholine
(1,4-oxazinane)



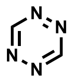
1,4-dioxane



1,3-dithiane

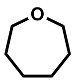
**1,2,4-
triazine**

**1,3,5-
triazine**

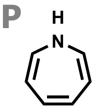


**1,2,4,5-
tetrazine**

7 EP

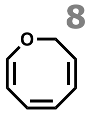


oxepane

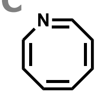


azepine

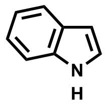
8 OC



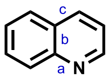
2H-oxocine



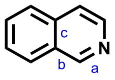
azocine



indole
(benzopyrrole)



quinoline
(benzo[b]pyridine)



isoquinoline
(benzo[c]pyridine)

Retained name in **red**, IUPAC version of retained name in (brackets).

More at:

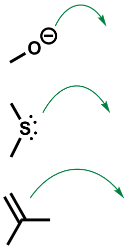
http://www.compoundchem.com/wp-content/uploads/2014/07/Heterocycles-graphic.png

https://en.wikipedia.org/wiki/Heterocyclic_compound

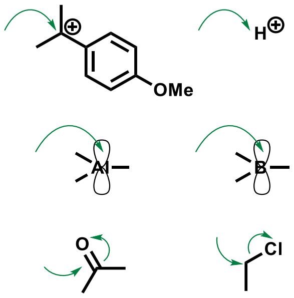
Appendix B: Revision

Curly Arrows

- **Curly Arrows**
  - Curly arrows are an essential tool when explaining reaction mechanisms
  - A curly arrow represents the movement of **TWO ELECTRONS**
  - Arrows should flow:



FROM	**TO**
Negative charge	Positive charge
Lone pair	Empty orbital
Bonding orbital i.e. a bond	Antibonding orbital i.e. bond-breaking



  - Leaving groups should be good at stabilising negative charge:
    → they are acidic (+H) → *i.e*. they have a low pKa
  - E.g. Cl^- is a good leaving group:
    → HCl is acidic ✓ → HCl pKa = −8.0 ✓

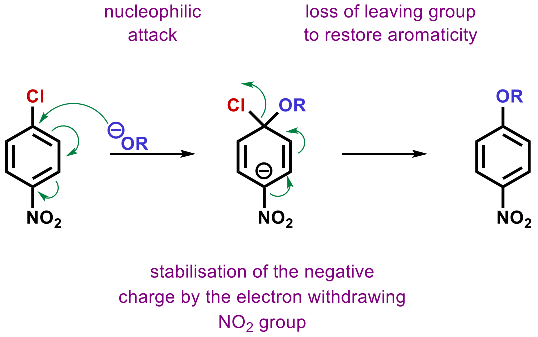
- **Make sure your charges always balance!**

- Under **acidic** conditions, all intermediates should be **positively** charged or neutral

- Under **basic** conditions, all intermediates should be **negatively** charged or neutral

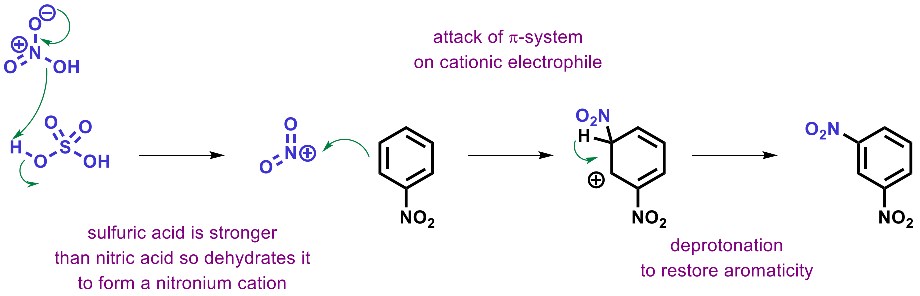
Nucleophilic Aromatic Substitution

- Electron poor aromatic rings, e.g. with NO2 groups and a good leaving group, e.g. Cl, Br, I, F can undergo substitution reactions
- The electronegative halide also accelerates the reaction which is why F gives the fastest substitution reaction
- Nucleophilic attack onto the aromatic ring with stabilisation of the resulting negative charge by the electron-withdrawing NO_2 group; followed by loss of the good leaving group



Electrophilic Aromatic Substitution

- The electrons in the π-cloud of the aromatic ring attack an electrophile
- To break the aromaticity the electrophile must be very good, i.e. posess a permanent positive charge
- Electron donating groups (NR2, alkyl, OR) are activating and ortho, para directing
- Electron withdrawing groups (NO2, SO2R, carbonyl) are deactivating and meta directing
- Halides are deactivating and ortho, para directing



attack of π-system
on cationic electrophile

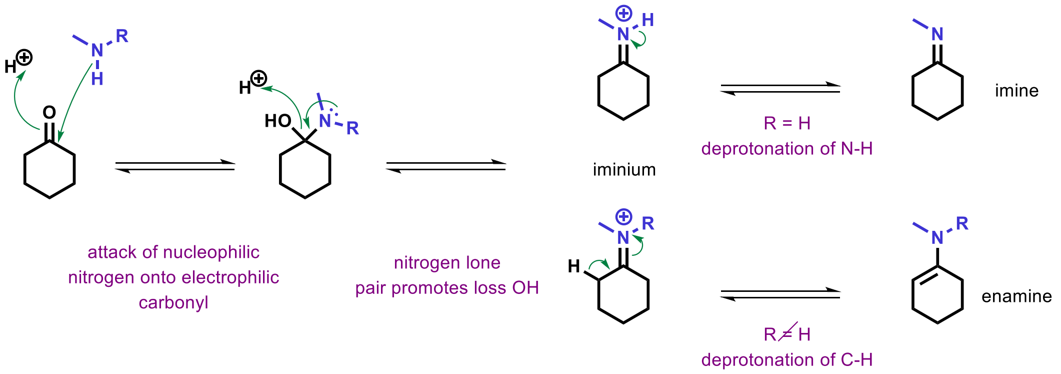
sulfuric acid is stronger
than nitric acid so dehydrates it
to form a nitronium cation

deprotonation
to restore aromaticity

A nitronium cation generated because sulfuric acid is stronger than nitric acid and dehydrates it then nucleophilic attack of the aromatic ring on the positive species followed by loss of H$^+$ restores aromaticity

Enamine and Imine Formation

Amines and ketones or aldehydes rapidly and reversibly react to form iminiums that go onto form imines or enamines. The nucleopilic nitrogen attacks electrophilic carbonyl then the nitrogen lone pair assists in loss of OH. At this stage, the iminium loses a proton either from the N-H to form an imine; or from the C-H to form an enamine.



attack of nucleophilic
nitrogen onto electrophilic
carbonyl

nitrogen lone
pair promotes loss OH

R = H
deprotonation of N-H

R ≠ H
deprotonation of C-H