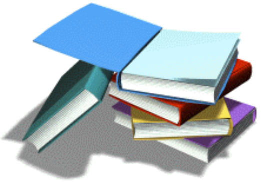
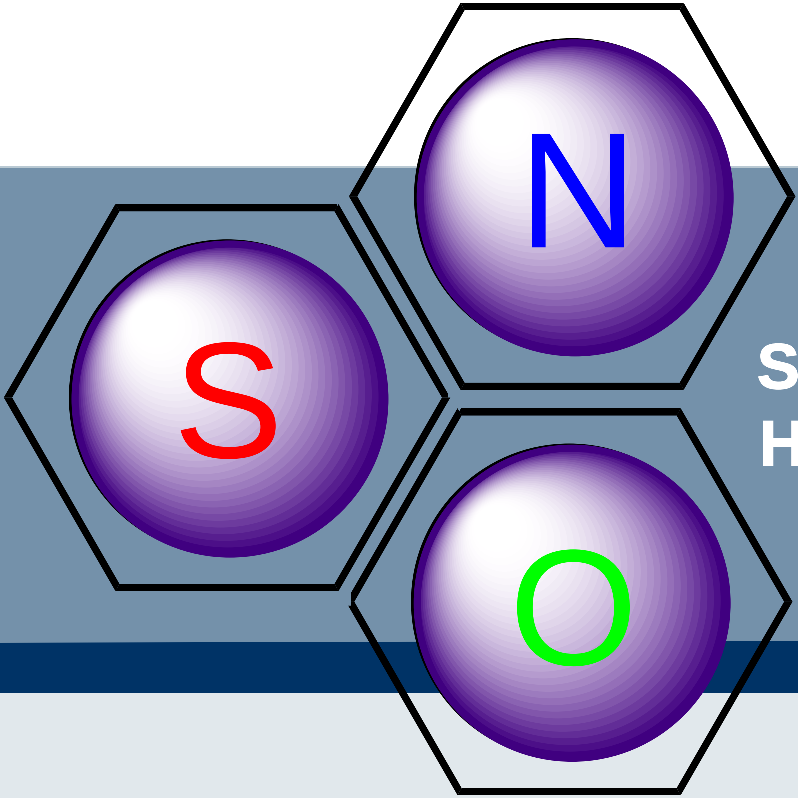


Chapter 3

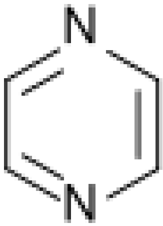


Substitutions of Aromatic Heterocycles

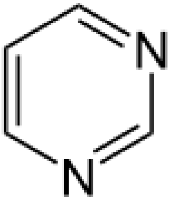
M. R. Naimi-Jamal

With special thanks to Dr. Javanshir

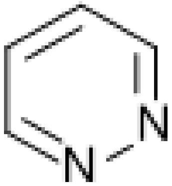
Pyridines carrying strongly electron-withdrawing substituents, or heterocycles with additional heteroatoms, diazines for example, are so deactivated that electrophilic substitutions do not take place, but again with the caveat that activating substituents do allow such substitutions in oxy – and amino - diazines.



Pyrazine



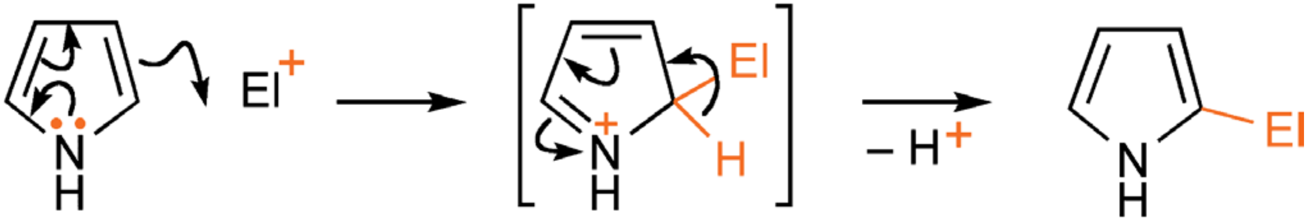
Pyrimidin



Pyridazine

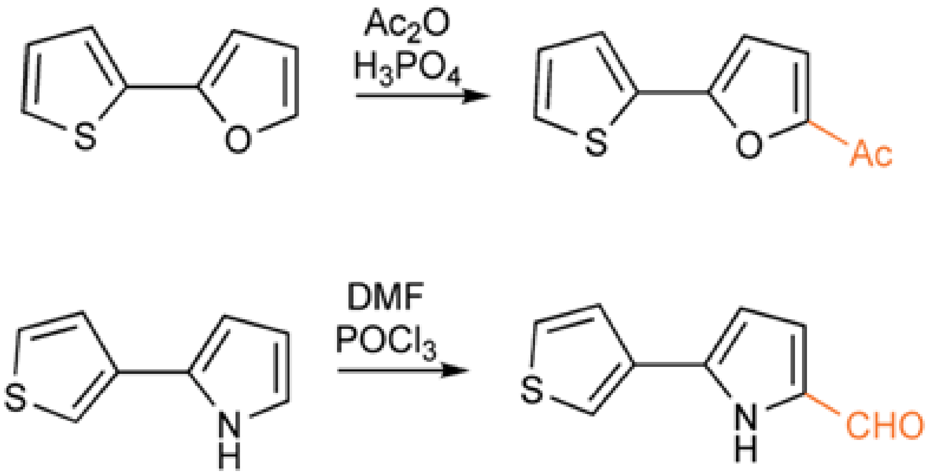
3.2.3 Five - Membered Heterocycles

- **For five-membered, electron-rich heterocycles, the utility of electrophilic substitutions is much greater.**
- **These substitutions are facilitated by electron release from the heteroatom:**
- **Pyrrole > furan > thiophene > benzene**
- **Thiophene is the most aromatic in character and undergoes the slowest reaction**

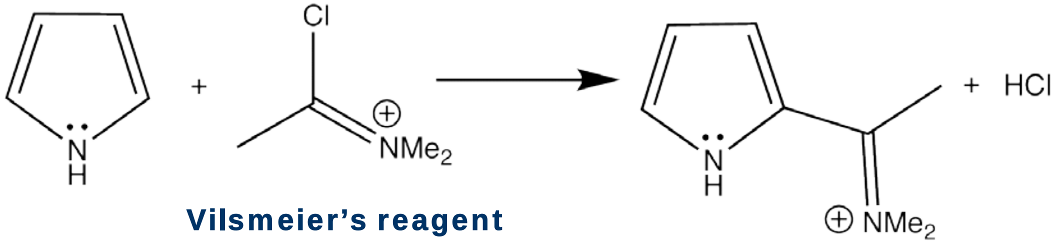


Five - Membered Heterocycles Electrophilic Substitution

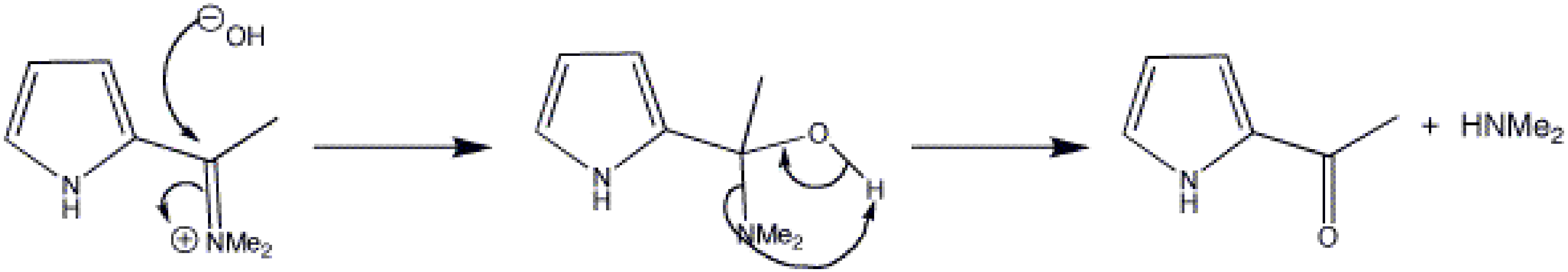
- Nice illustrations of these relative reactivities are found in acylation of compounds containing two different systems linked together.



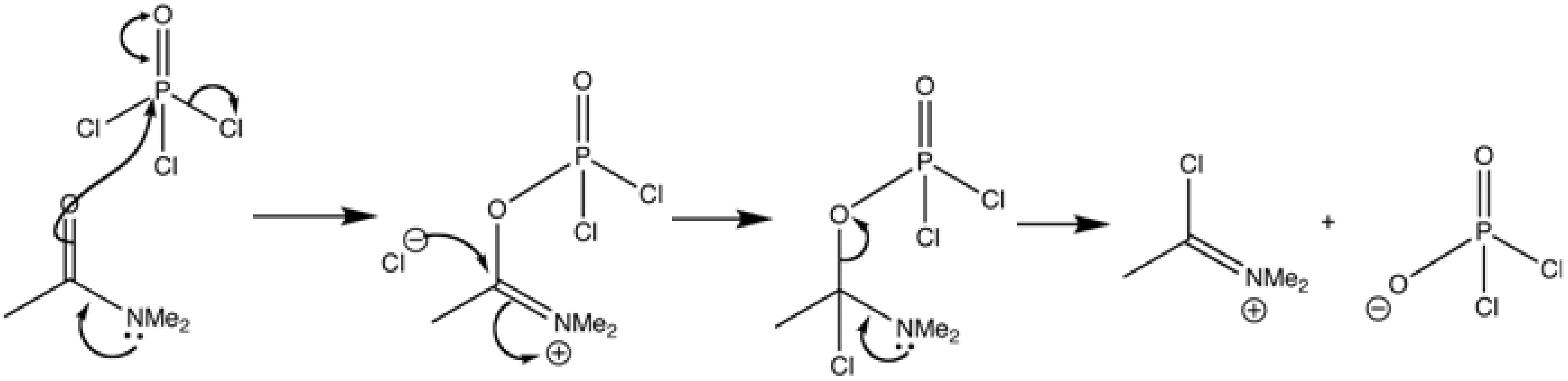
Pyrrole undergoes readily electrophilic substitution reactions, for example:



Vilsmeier's reagent



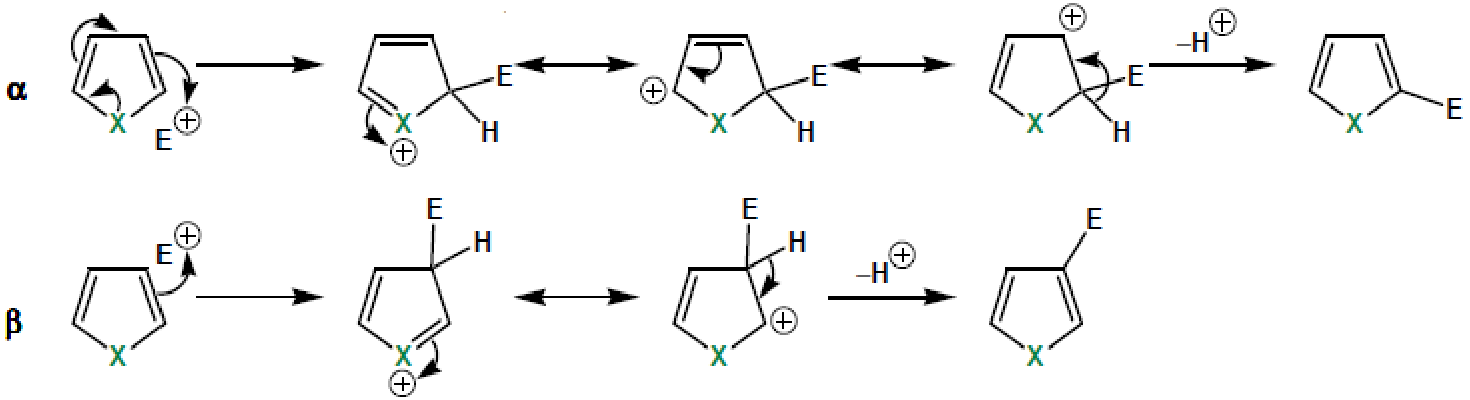
Vilsmeier’s reagent:



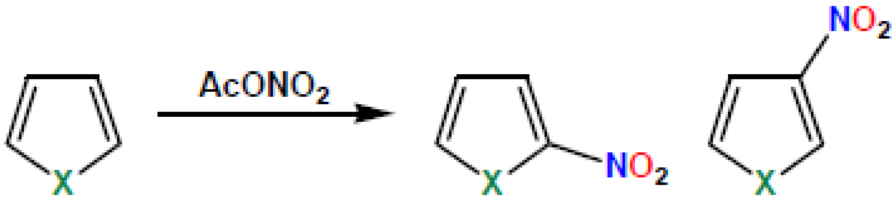
The Vilsmeier reaction is an alternative to Friedel-Crafts acylation and avoids the use of strong Lewis acids such as $AlCl_3$.

Furans, Pyrroles, Thiophenes –Electrophilic Substitution

Pyrrole and furan react under very mild conditions



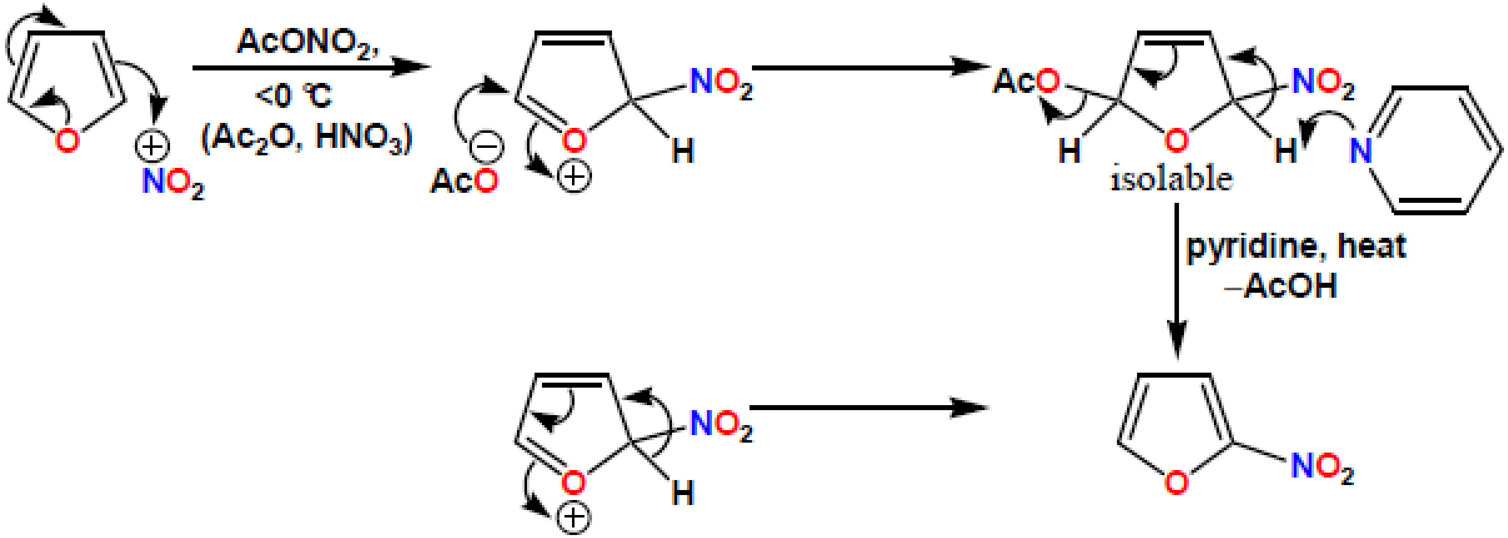
- ❖ α-Substitution favoured over β-substitution, because of more resonance forms for intermediate and so the charge is less localized (also applies to the transition state)
- ❖ Some β-substitution usually observed – depends on X and substituents



X = NH 4:1
X = O 6:1

Five - Membered Heterocycles Electrophilic Substitution

❖ Nitration of Furans



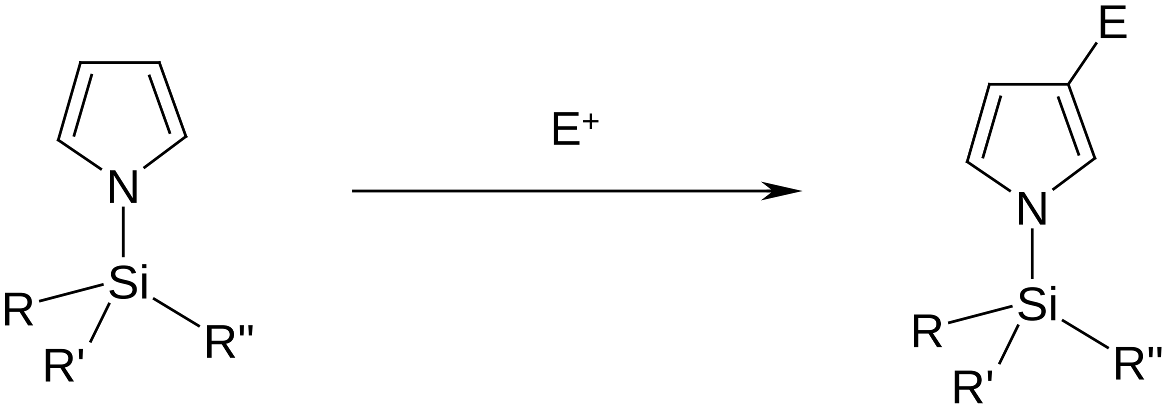
Five - Membered Heterocycles Electrophilic Substitution

Quantitative comparisons of the relative reactivities of the three heterocycles vary from electrophile to electrophile.

E^+ / Hetero	Pyrrole	Furan	Thiophene
Trifluoroacetylation CF_3CO^+	5×10^7	1.5×10^2	1
Formylation HCO^+	-	12	1
Acetylation CH_3CO^+	-	9.3	1

Five - Membered Heterocycles Electrophilic Substitution

- **The positional selectivity of attack on pyrroles can be completely altered by the presence of bulky groups on nitrogen:**
- **l-(t-butyldimethylsilyl)pyrrole and l-(tri-*i*-propylsilyl) pyrrole are attacked exclusively at their β-positions.**

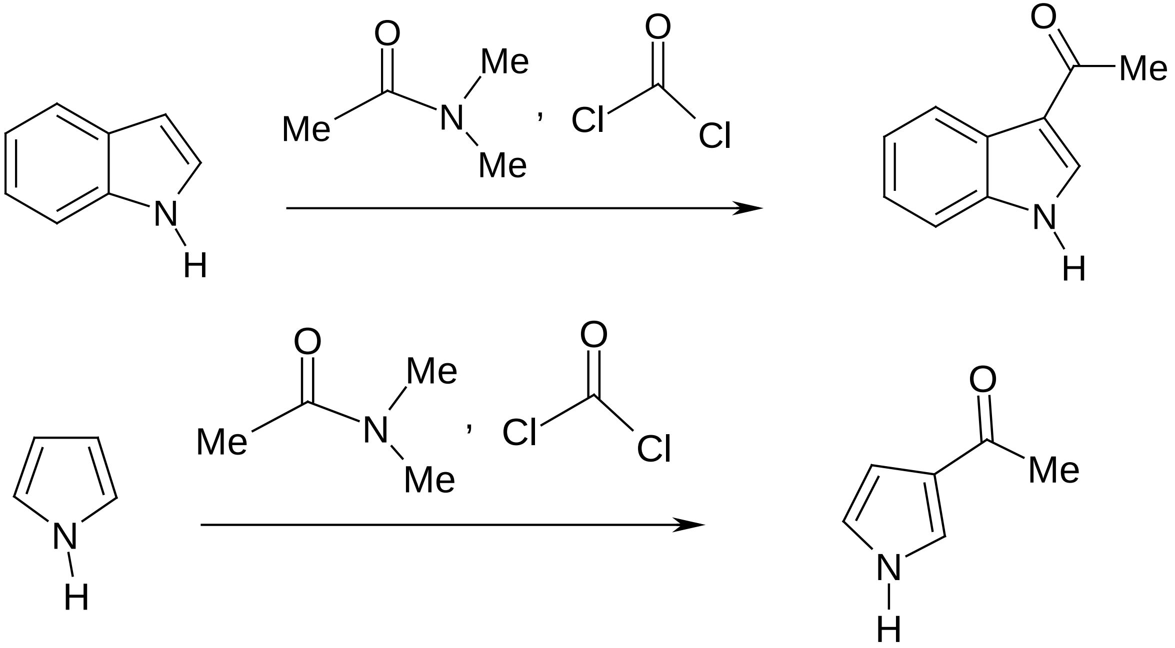


R= t-butyl; R', R''= Me

R, R', R''= *i*-Pr

Five - Membered Heterocycles Electrophilic Substitution

Indoles are only slightly less reactive than pyrroles, electrophilic substitution taking place in the heterocyclic ring, at a **β**-position: in acetylation using a Vilsmeier combination (*N*,*N*-dimethylacetamide/ phosgene), the rate ratio compared with pyrrole is 1:3.



K1

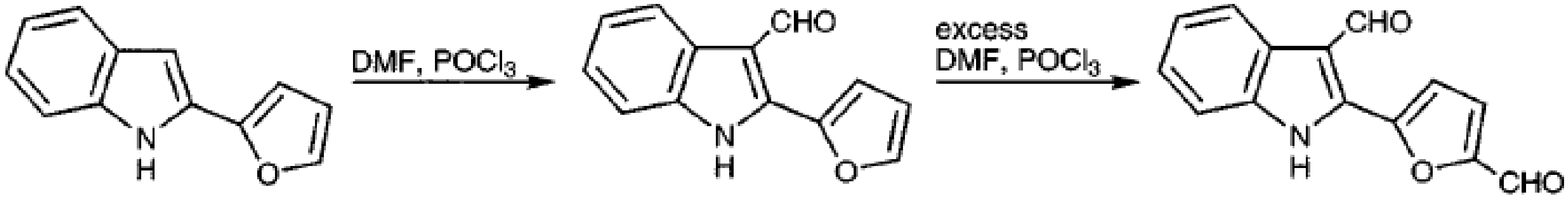
K2

K1 : K2 = 1 : 3

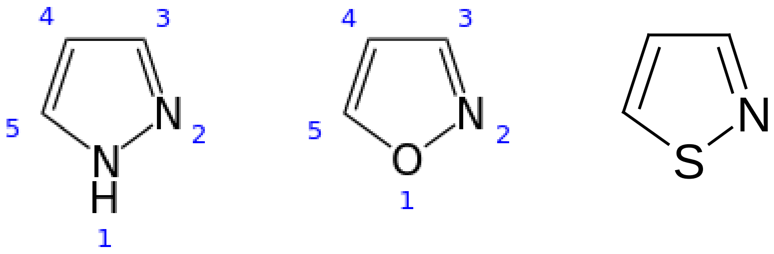
Five - Membered Heterocycles Electrophilic Substitution

1) In contrast to pyrrole, there is a very large difference in reactivity between the two hetero-ring position in indoles: 2600:1, **β:α**, *in Vilsmeier acetylation.*
2) With reference to benzene, indole reacts at its **β**-position around 5Exp13 times as fast.

Again, these differences can be illustrated conveniently using an example which contains two types of system linked together.



- In the 1,2- and 1,3-azoles there is a fascinating interplay of the propensities of an electron-rich five-membered heterocycle with an imine, basic nitrogen. This latter reduces the reactivity of the heterocycle towards electrophilic attack at carbon, both by inductive and by mesomeric withdrawal, and also by conversion into salt in acidic media.

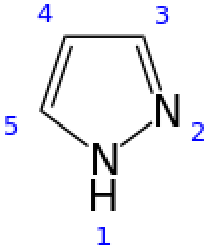


pyrazole > isoxazole > isothiazole

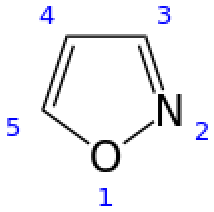
Paralleling:

pyrrole > furan > thiophene

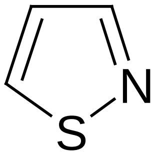
- Each diazole is much less reactive than the corresponding heterocycle without the azomethine nitrogen, but, equally, each is still more reactive than benzene . The partial rate factors for exchange at their 4-positions being 6.3×10^9 , 2.0×10^4 and 4.0×10^3 respectively.



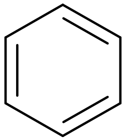
6.3×10^9



2.0×10^4



4.0×10^3



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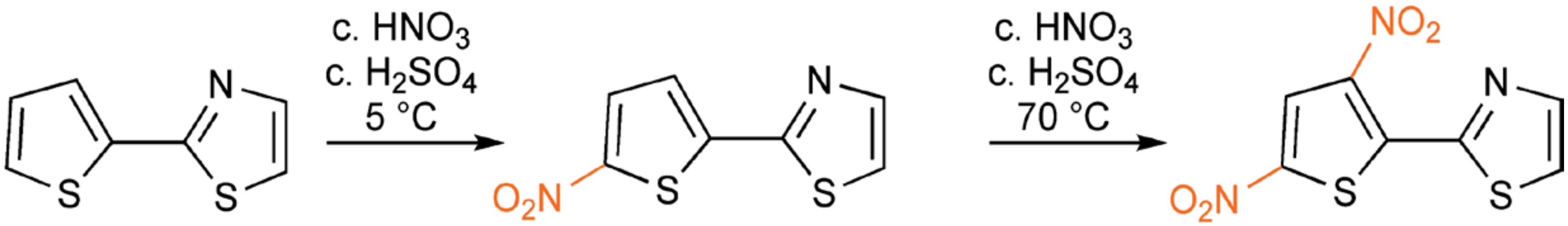
As another example, thiophene is more rapidly nitrated than thiazole. The mono - and dinitration of a 2-(thien-2-yl)thiazole illustrates the relative reactivities.

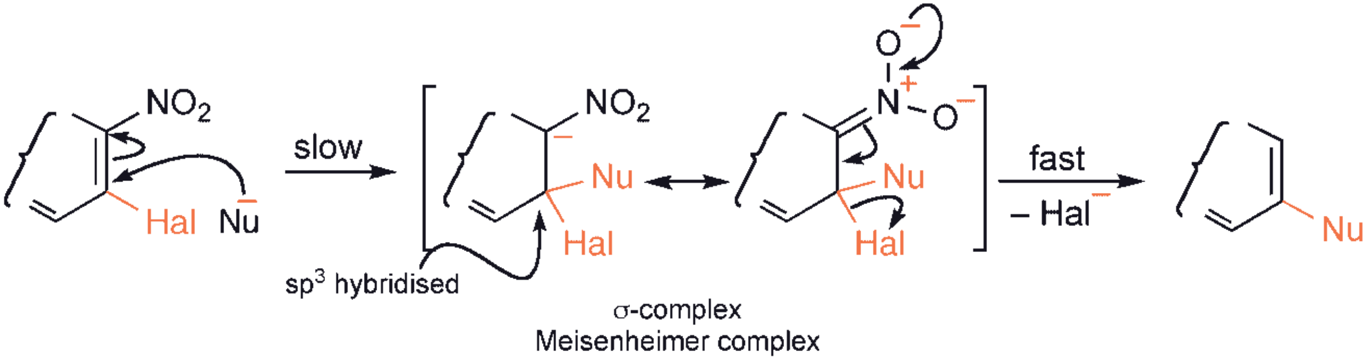


3.3 Nucleophilic Substitution at Carbon

3.3.1 Aromatic Nucleophilic Substitution: Mechanism

- Nucleophilic substitution of aromatic compounds proceeds *via an addition (of Nu⁻) then elimination (of a* negatively charged entity, most often Hal⁻) two-step sequence, of which the former is usually rate – determining (the SN(AE) mechanism: Substitution Nucleophilic Addition Elimination).

- It is the stabilisation (delocalisation of charge) of the negatively charged intermediates (Meisenheimer complexes) that is the key to such processes, for example in reactions of *ortho* - and *para* - chloronitrobenzenes, the nitro group is involved in the charge dispersal.

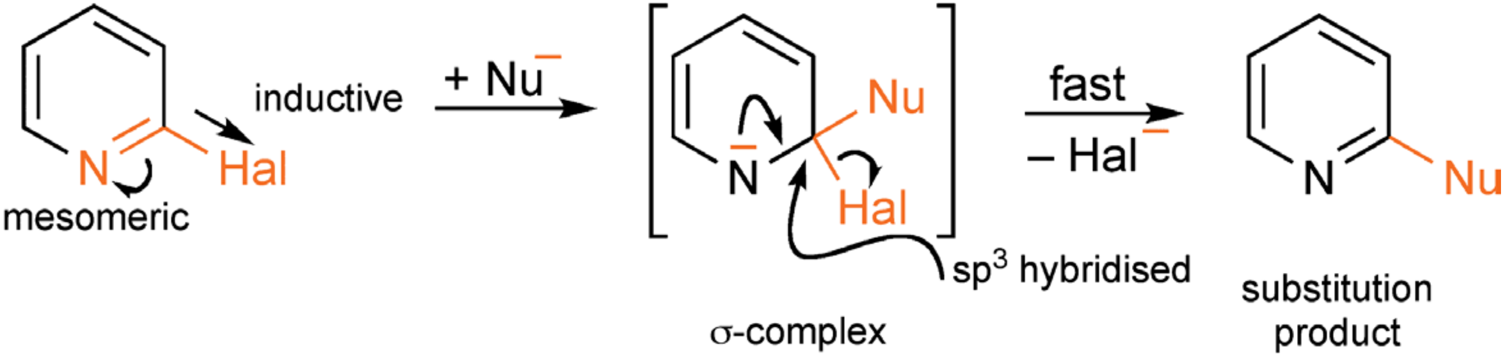


3.3.2 Six - Membered Heterocycles

- In the heterocyclic field, the displacement of a good leaving group, often halide, by a nucleophile is a very important general process, especially for six - membered systems.
- The α- and γ- positions of a six-membered halo-azine are activated for the initial nucleophilic addition step by two factors:

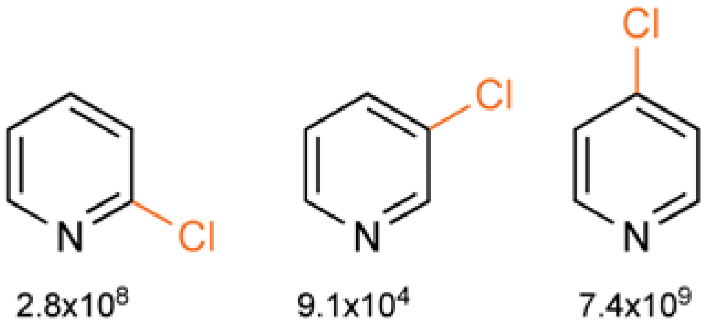
(i) inductive and mesomeric withdrawal of electrons by the nitrogen and

(ii) inductive withdrawal of electrons by the halogen.



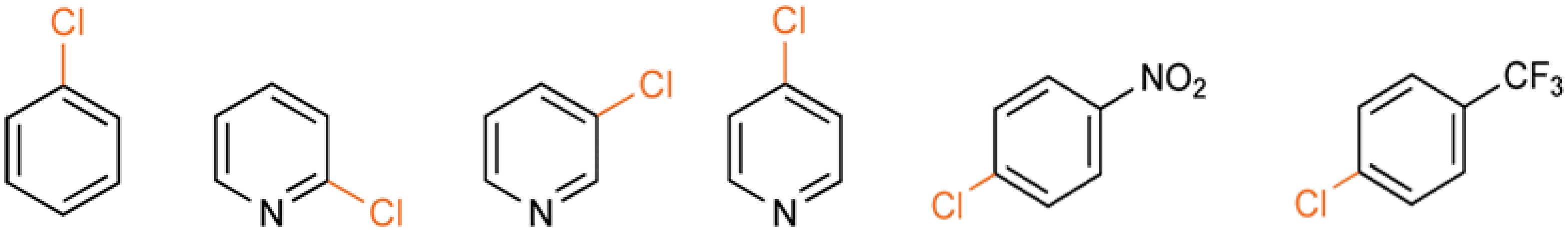
Rate of displacements of chloride with sodium methoxide in methanol

- α- and γ- halides are *much* more reactive to nucleophilic displacement than β- halides.



Rates of displacement of chloride by MeO⁻ relative to chlorobenzene, at 50 ° C

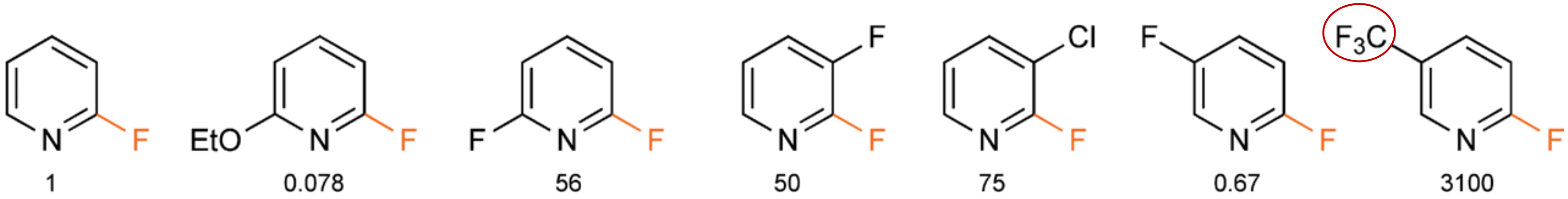
A quantitative comparison for displacements of chloride with sodium methoxide in methanol showed the 2- and 4-chloropyridines to react at roughly the same rate as 4-chloronitrobenzene, with the γ-isomer somewhat more reactive than the α-halide. It is notable that even 3-chloropyridine, where only inductive activation can operate, is appreciably more reactive than chlorobenzene.



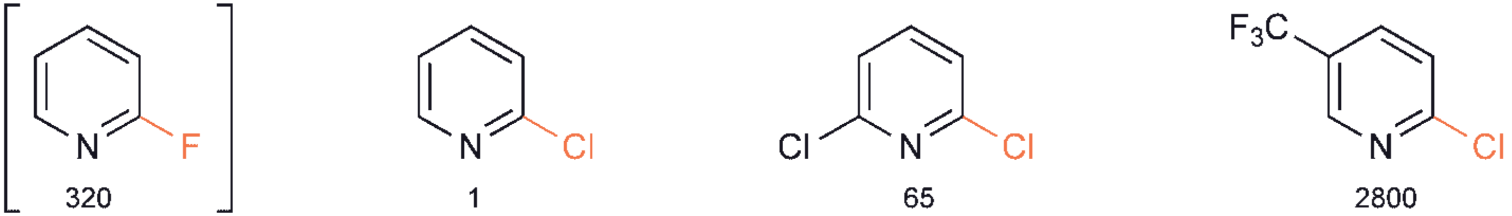
1 | 2.8×10^{8} | 9.1×10^{4} | 7.4×10^{9} | 7×10^{10} | 4.5×10^{5}

Rates of displacement of chloride by MeO^- relative to chlorobenzene, at 50 ° C

A substantial study of the activating effects of other substituents on the displacement of 2-halopyridines is very instructive and some examples are shown below. **The activating effect of trifluoromethyl is particularly Notable.**



Relative rates of displacement of pyridine-2-fluoride by EtO – in EtOH.



Relative rates of displacement of pyridine-2-chloride by EtO⁻ in EtOH

The utility of a nitro group as a leaving group (nitrite) in heterocyclic chemistry is emphasised by a comparison of its relative reactivity to nucleophilic displacement: 4-nitro-pyridine is about 1100 times more reactive than 4-bromo-pyridine.

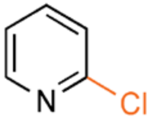
In certain situations, particularly with relatively poor nucleophiles such as anilines, reaction rates can be enhanced considerably by the addition of acids, such as HCl, CF_3CO_2H or BF_3 , to the reaction mixture, so that the much more reactive protonated haloazine is the substrate. Due to the relatively low basicity of anilines, sufficient free base is present to act as the nucleophile.

biyclic systems

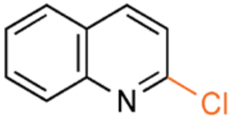
A small increase in the rate of reaction relative to pyridines is found for chloroquinolines at comparable positions.

Factor increasing the rate of nucleophilic substitution:

- **quaternization**
- **electron withdrawing group**

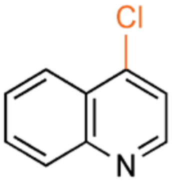


1.7×10^2

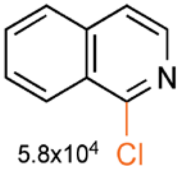


5.3×10^4

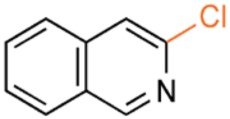
7.3×10^3



5.4×10^4



5.8×10^4



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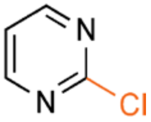

1.3×10^8