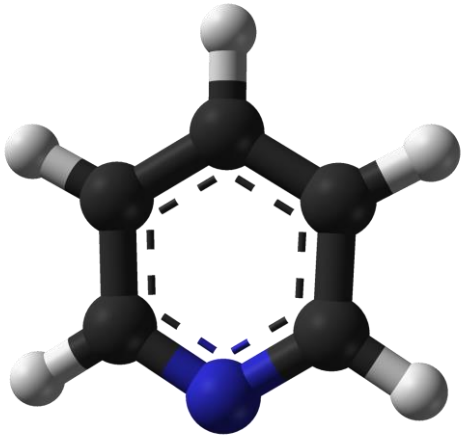
2302687 – Heterocyclic Compounds – Part I

Lecture 3-3

Reactivities of Heteroaromatics – Nucleophilic Substitution



Instructor: Dr. Tanatorn Khotavivattana
E-mail: tanatorn.k@chula.ac.th

Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

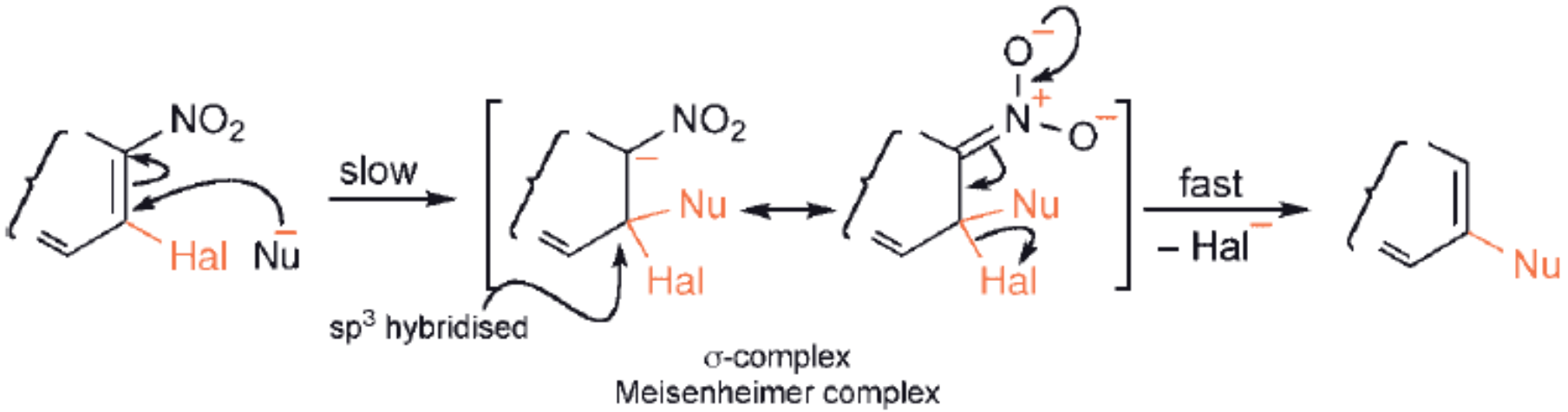
3) Substitution Reactions – Nucleophilic

- **Mechanism** : proceeds via a two-step sequence

1) **Addition** (of Nu^-) (usually ***rate determining step***)

2) **Elimination** (of a negatively charged entity, most often Hal^-)

(the **S_N(AE)** mechanism: **S**ubstitution **N**ucleophilic **A**ddition **E**limination)



It is the **stabilisation** (delocalisation of charge) of the **negatively charged intermediates** (Meisenheimer complexes) that is the key to such processes

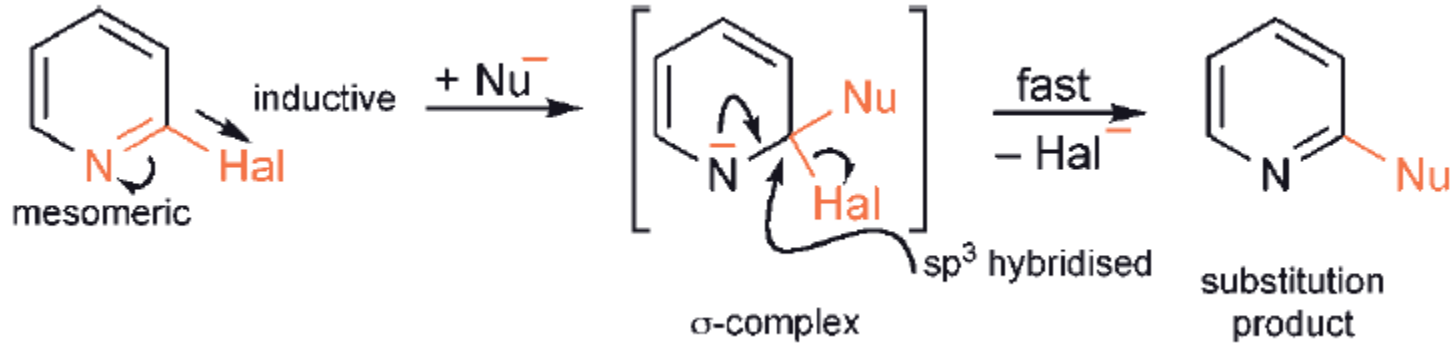
3) Substitution Reactions – Nucleophilic

3.1) Six-membered heterocycles

- The ***α-*** and ***γ-*** positions of a six-membered halo-azine (a 2-, 4- or 6- halo-pyridine being the prototype) are **activated** for the initial nucleophilic addition step by two factors:

  1) **inductive** and **mesomeric** withdrawal of electrons by the **nitrogen**

  2) **inductive** withdrawal of electrons by the **halogen**

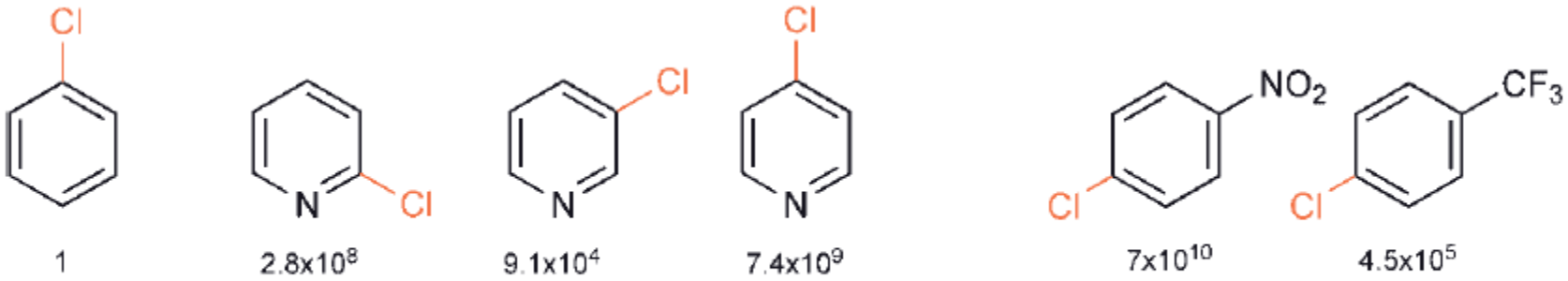


- In the intermediates formed, the negative charge resides largely on the nitrogen: *α*- and *γ*-halides are much more reactive to nucleophilic displacement than *β*-halides

3) Substitution Reactions – Nucleophilic

3.1) Six-membered heterocycles

- 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-chloro**nitro**benzene
- the *γ*-isomer somewhat more reactive than the *α*-halide



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

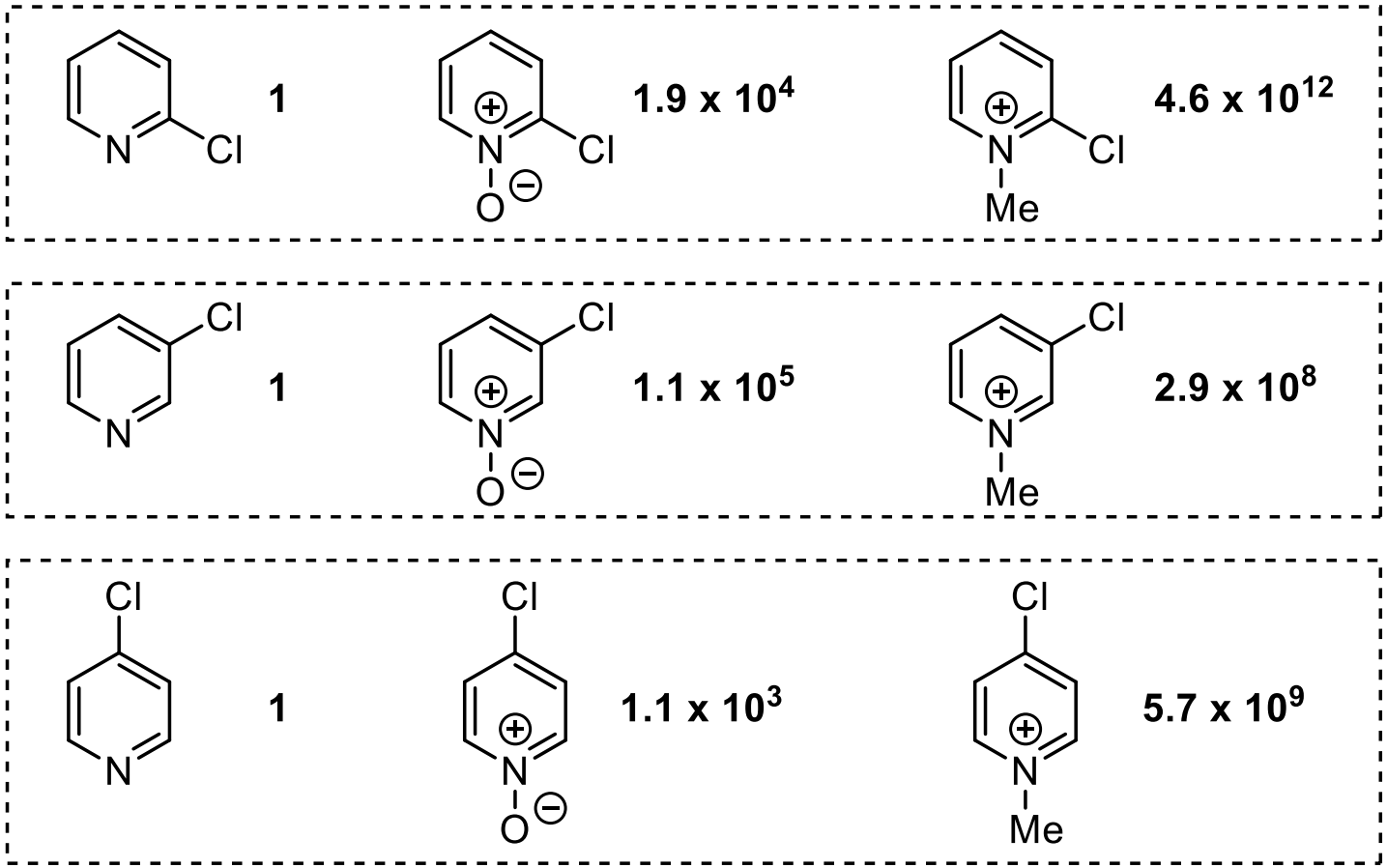
- It is notable that even 3-chloropyridine, where only inductive activation can operate, is appreciably more reactive than chlorobenzene

3) Substitution Reactions – Nucleophilic

3.1) Six-membered heterocycles

- The presence of a **positive charge on the nitrogen**, as in ***N-oxides*** and ***pyridinium salts***, has a further enhancing effect on the rate of substitution

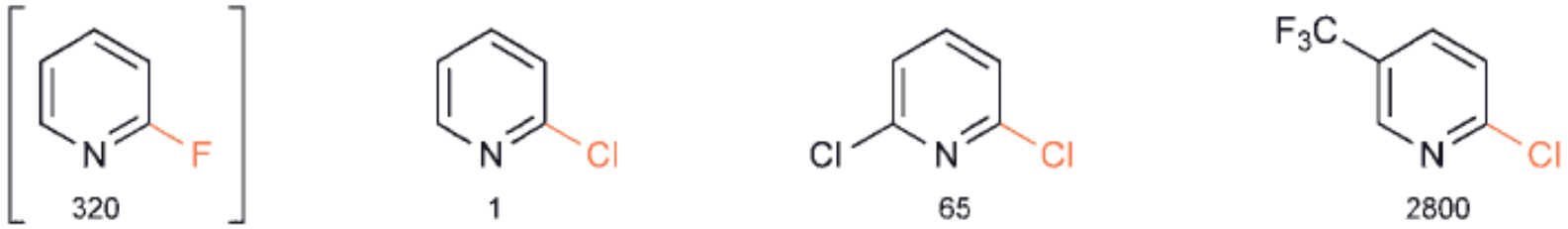
Relative rates of reaction with methoxide



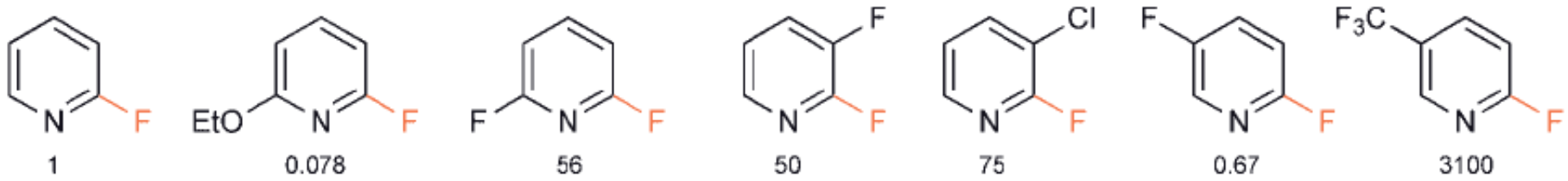
3) Substitution Reactions – Nucleophilic

3.1) Six-membered heterocycles

- ***Effects of other substituents***



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



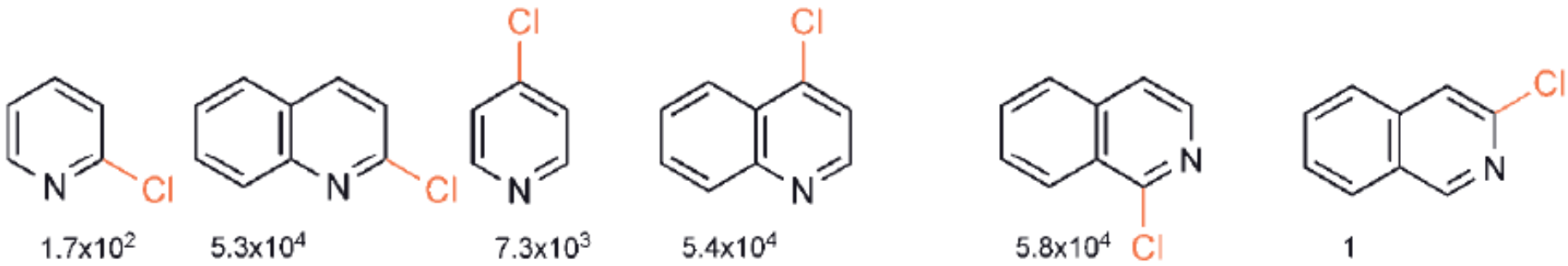
Relative rates of displacement of pyridine-2-fluoride by EtO^- in EtOH

- The activating effect of trifluoromethyl is particularly notable

3) Substitution Reactions – Nucleophilic

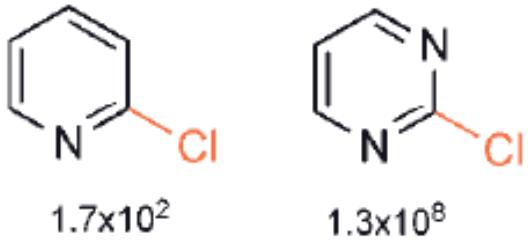
3.1) Six-membered heterocycles

- ***Bicyclic systems*** *:* a small increase in the rate of reaction relative to pyridines is found for chloroquinolines at comparable positions



Relative rates of displacement of chloride by EtO^- at 20 °C

- ***Diazines*** are much more reactive than similar pyridines

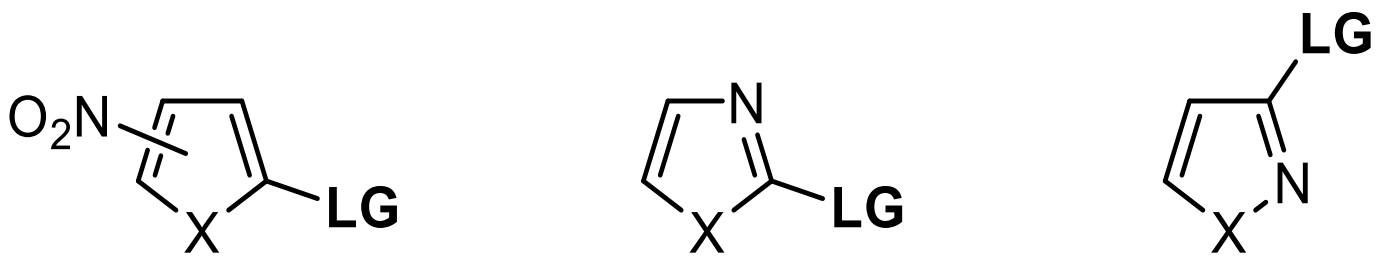


3) Substitution Reactions – Nucleophilic

3.2) Five-membered heterocycles

- The displacement of a good leaving group, often halide, by a nucleophile is a very important general process, especially for six- membered systems

- In the chemistry of **five-membered aromatic heterocycles**, such processes only come into play in situations such as where, as in benzene chemistry, **the leaving group is activated by an *ortho*- or *para*- nitro group**, or in the **azoles**, where the leaving group is attached to the carbon of the imine unit in analogy with the six-membered imines

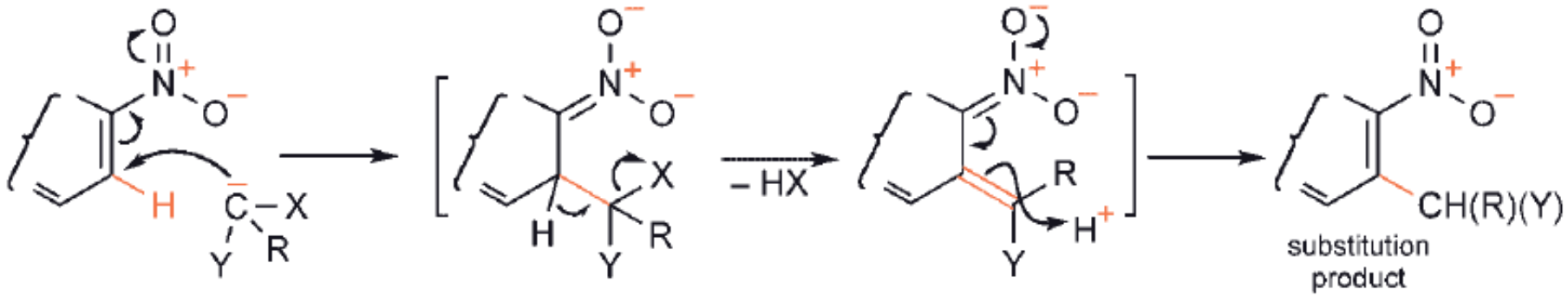


3) Substitution Reactions – Nucleophilic

3.3) Vicarious Nucleophilic Substitution (VNS Substitution)

- The process requires the presence of a **nitro group** on the substrate, which permits the addition of a **carbon nucleophile**

- The nucleophile of the form (**X**)(**Y**)(R)C^-
  - **X** is a potential **leaving group** (such as halogen) and
  - **Y** is an **anion-stabilising group** (such as arylsulfonyl, ester or benzotriazole) that permits the formation of the carbanion



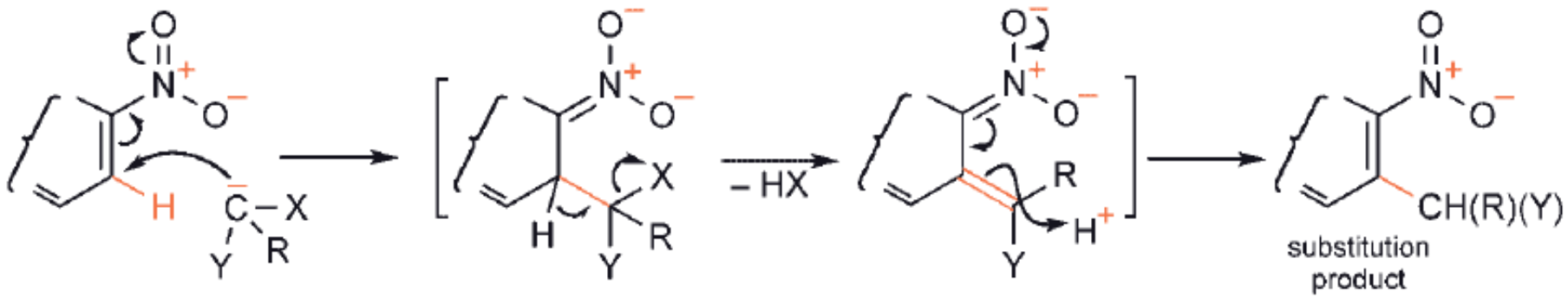
Vicarious nucleophilic substitution (VNS) of aromatic compounds

3) Substitution Reactions – Nucleophilic

3.3) Vicarious Nucleophilic Substitution (VNS Substitution)

Mechanism

1) **Addition**, *ortho* or *para* to the nitro group
2) **Elimination of HX**, forming a conjugated, non-aromatic nitronate
3) **Reprotonation** returns the molecule to aromaticity and produces the substituted product

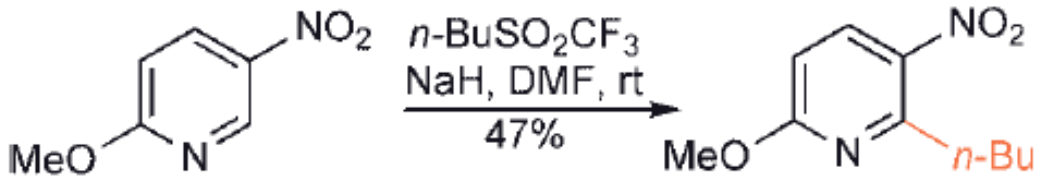


- **Excess of the base** used to generate the initial carbanion must be employed in order to drive the process forward by subsequently bringing about the **irreversible elimination of HX** from the nitronate salt

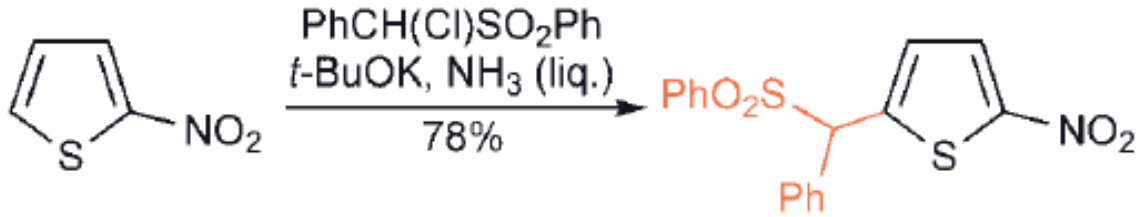
3) Substitution Reactions – Nucleophilic

3.3) Vicarious Nucleophilic Substitution (VNS Substitution)

Examples



- The anion-stabilising group (Y) **(trifluoromethanesulfonyl)** can also serve as the leaving group (X)



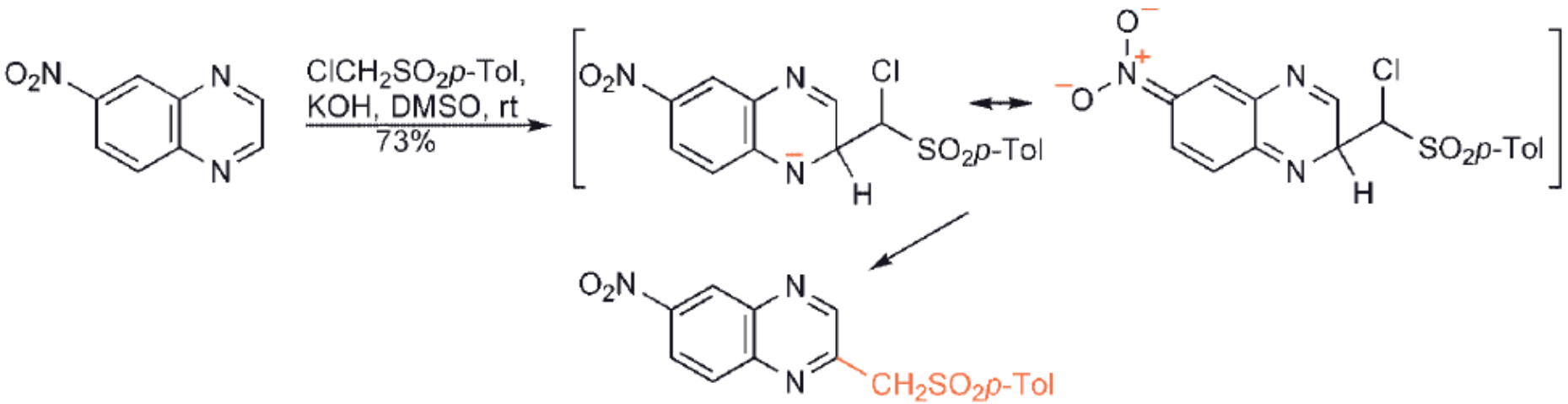
- A VNS substitution in a five-membered heterocycle with the nucleophile (X = Cl; Y = SO_2Ph) attacking at C-5, conjugated to the nitro group

3) Substitution Reactions – Nucleophilic

3.3) Vicarious Nucleophilic Substitution (VNS Substitution)

Examples

- The attacking nucleophile (X = Cl; Y = SO_2*p*-Tol) does not need to occur at the nitro-substituted ring



- Addition occurs at C-2 in 6-nitroquinoxaline, for this produces an anion stabilised by **delocalisation** involving both ***N*-1** and the **nitro group**