Nucleophilic Aromatic Substitution

Dorian Didier
dorian.didier@cup.uni-muenchen.de
1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case
5. Elimination-addition mechanism
1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case
5. Elimination-addition mechanism
Chapter: Nucleophilic Aromatic Substitution

1. General considerations

2. Addition-elimination mechanism

**Nucleophilic Aromatic Substitution** = $S_N\text{Ar}$

![Diagram showing Nucleophilic Aromatic Substitution](image)

**EWG** = Electron **Withdrawing Group**

**Electrophilic Aromatic Substitution** = $S_E\text{Ar}$

![Diagram showing Electrophilic Aromatic Substitution](image)

**EDG** = Electron **Donating Group**
1. General considerations

2. Addition-elimination mechanism

**Nucleophilic Aromatic Substitution** = $S_{N}\text{Ar}$

\[
\begin{align*}
\text{EWG} & \quad \text{X} \quad \text{Nu}^- \quad \rightarrow \quad \text{EWG} \quad \text{Nu} \\
\end{align*}
\]

\[S_{N}\text{Ar} \quad \neq \quad S_{N}2\]
Chapter: Nucleophilic Aromatic Substitution

1. General considerations

2. Addition-elimination mechanism

Nucleophilic Aromatic Substitution = $S_{N}Ar$
1. General considerations

2. Addition-elimination mechanism

*Nucleophilic Aromatic Substitution* = $S_{N}Ar$

- Usually requires an EWG for stabilization of the intermediate (Meisenheimer complex)
- Exceptions to the presence of an EWG:
  - *intra* molecular reaction (*Smiles, Clayden or Neuman-Kwart rearrangements*)
  - *aryne* formation (*elimination-addition mechanism*)
  - *external* activation (*metal π-arene complex formation*)
Table of contents

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case
5. Elimination-addition mechanism
Chapter: Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

**Classical $S_{N}Ar$**

EWG $\xrightarrow{\text{Nu}^-}$ $\text{EWG} \xrightarrow{\text{Nu}^-}$ $\text{EWG}$

**Smiles rearrangement**

EWG $\xrightarrow{\text{BH}}$ $\text{EWG} \xrightarrow{\text{BH}}$ $\text{EWG}$

**Truce-Smiles / Clayden rearrangement**

EWG $\xrightarrow{\text{BH}}$ $\text{EWG} \xrightarrow{\text{BH}}$ $\text{EWG}$
Chapter: Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

Classical $S_N Ar$

\[
\begin{align*}
\text{KHMDS} & \quad \text{THF} \\
0 \degree C & \quad 16h
\end{align*}
\]

Chapter: Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

$S_N Ar$ - Smiles rearrangement

**Chapter:**
Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

**S\textsubscript{N}Ar - Cascade sequence**

\[
\begin{align*}
\text{F}_3\text{C-} & \text{O} \quad \text{NH}_{\text{Et}} \\
\text{F} & + \\
\text{Cl} & \quad \text{Br} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

\[
\text{K}_2\text{CO}_3, \text{NMP} \quad 150 \, ^\circ\text{C}, \, 2\text{h}
\]

- **step 1:**
- **step 2:**
- **step 3:**

**tricyclic structure**

Chapter:
Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

Smiles rearrangement - OH → NH₂ interconversion

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

Smiles rearrangement - OH → NH₂ interconversion
Chapter: Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

*Neuman-Kwart rearrangement - OH → SH interconversion*
Chapter: Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

Truce-Smiles rearrangement / $S_{N}Ar$

Chapter:
Nucleophilic Aromatic Substitution

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution

**Clayden rearrangement - ring expansion strategy**

Table of contents

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case
5. Elimination-addition mechanism
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case

General reaction scheme - VNS

- A “H” is substituted at the aromatic position
- Requires an EWG for stabilization of the Meisenheimer complex
- Requires a leaving group on the nucleophile
Chapter: Nucleophilic Aromatic Substitution

2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case

Application to indole synthesis

Chapter:  
Nucleophilic 
Aromatic 
Substitution 

2. Addition-elimination mechanism 
3. Vicarious nucleophilic substitution 
4. The $\pi$-arene case 

Application to substituted indoles - Fukuyama’s synthesis of (-)-Eudistomin E

Chapter: Nucleophilic Aromatic Substitution

2. Addition-elimination mechanism

3. Vicarious nucleophilic substitution

4. The $\pi$-arene case

\[ \text{M. Mąkosza et. al. - Acc. Chem. Res. 1987, 20, 282-289.} \]
Chapter:
Nucleophilic Aromatic Substitution

2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The π-arene case

**Vicarious Nucleophilic Substitution (VNS) – a summary**

- The substrate needs an electron-withdrawing group.
- Usually leads to a mixture of regioisomers.

### 3-steps sequence:
1. Nucleophilic addition
2. β-elimination
3. Protonation/Rearomatization

For more references, see:

Table of contents

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case
5. Elimination-addition mechanism
3. Vicarious nucleophilic substitution

4. The $\pi$-arene case

5. Elimination-addition mechanism

“Ar” is not electrophilic enough
No stabilization of the Meisenheimer complex

make a better electrophile of “Ar”
create an electron deficiency

“$\pi$-arene complex” or “6$\pi$-arene complex”
increases the electrophilicity of “Ar”
Chapter:
Nucleophilic
Aromatic
Substitution

3. Vicarious nucleophilic substitution
4. The \( \pi \)-arene case
5. Elimination-addition mechanism

\( \pi \)-arene systems: complexation and decomplexation

\[ \text{complexation} \]
- \( X = BF_4, PF_6 \)
- requires mixture of salts

\[ \text{difficult decomplexation} \]
- strong oxidant (DDQ...)
- reflux in coordinating solvents

\[ \text{easy decomplexation by} \]
- excess of coordinating solvent
- \( h\nu \) / oxidation
- or complexing agents (\( R_3N \), \( R_3P \)...)
Chapter: Nucleophilic Aromatic Substitution

3. Vicarious nucleophilic substitution
4. The π-arene case
5. Elimination-addition mechanism


K. Kirschke et. al. - Phosphorus 1996, 117, 293.
peptide macrocyclization - Rich’s synthesis of K-13

# Table of contents

1. General considerations
2. Addition-elimination mechanism
3. Vicarious nucleophilic substitution
4. The $\pi$-arene case
5. Elimination-addition mechanism
Chapter: Nucleophilic Aromatic Substitution

4. The $\pi$-arene case

5. Elimination-addition mechanism

---

**the first observation**

![Chemical reaction diagram](image)


---

**the rationale**

![Chemical reaction diagram](image)

Deprotonation is highly $pK_a$-dependant

Values calculated in gas-phase by DFT (B3LYP/6-31G)

4. The $\pi$-arene case

5. Elimination-addition mechanism

**Major problem** = Regioselectivity of the nucleophilic addition

![Chemical structure diagram showing reaction and regioisomers](image)

**A solution** = Intramolecular nucleophilic addition

![Chemical structure diagram showing intramolecular reaction](image)

4. The $\pi$-arene case

5. Elimination-addition mechanism

**Typical example of intramolecular nucleophilic addition on arynes**

![Chemical reaction](image_url)
Chapter: Nucleophilic Aromatic Substitution

4. The $\pi$-arene case

5. Elimination-addition mechanism

**Applications - Kametani’s synthesis of Cryptowoline**

Applications - Garg’s synthesis of (+)-tubingensin A

Chapter: Nucleophilic Aromatic Substitution

4. The π-arene case
5. Elimination-addition mechanism

Applications - Tokuyama’s synthesis of Dictyodendrin A

Knochel-Hauser base

Kumada-Tamao coupling

**Chapter:**
Nucleophilic Aromatic Substitution

4. The $\pi$-arene case

5. Elimination-addition mechanism

**Applications to $\beta_2$-adrenoceptor agonist - Fairhurst’s synthesis of S1319**

Nucleophilic aromatic substitution through aryne – a summary

need for a strong base
most acidic proton reacts first

intramolecular reactions favour regiocontrol
generated anion can react with electrophiles

For spectroscopic evidence of arynes, see:

Chapter: Nucleophilic Aromatic Substitution

Summary

**Addition-elimination mechanism**

![Reaction mechanism diagram for addition-elimination](image)

- **Meisenheimer complex**
- **Intramolecular versions:** Smiles, Truce-Smiles, Neuman-Kwart, Clayden

**Vicarious nucleophilic substitution**

![Reaction mechanism diagram for vicarious nucleophilic substitution](image)

- **Elimination-addition mechanism**

**The π-arene case**

![Reaction mechanism diagram for the π-arene case](image)

- $\eta^6$-arene-[M]
  - activates aromatic rings
  - alternative to the presence of an EWG

**Elimination-addition mechanism**

![Reaction mechanism diagram for elimination-addition](image)

- **Aryne**
  - need for a strong base
  - enables further reaction with electrophiles