

**CHEM 322 Organic Chemistry II - Professor Kathleen V. Kilway**  
**"Organic Chemistry" by Maitland Jones, 3rd edition**

Chapter 14 - 1, 2, 5, 7, 12, 18, 19, 22, 25, 26, 27, 29, 30, 33, 34, 36, 40, 45, 47, 48, 49, 50, 51, 53.

## CHAPTER 14 SUBSTITUTION REACTIONS OF AROMATIC COMPOUNDS

### Section 14.1

#### I. Preview

##### A- Aromatic compounds are stable

- 1- So it takes energy to destroy the aromaticity and is relatively easy to regain it.
- 2- Therefore, these compounds have high energy barriers for reactions.
- 3- In this chapter, we will learn the how and why of reaction on aromatic compounds.
- 4- In the general reaction of aromatic compounds, an **electrophile**, a "lover of electrons" (or Lewis Acid), substitutes for one of the hydrogens on a benzene ring.
- 5- The general reaction is given below. Note that the aromatic sextet is retained.

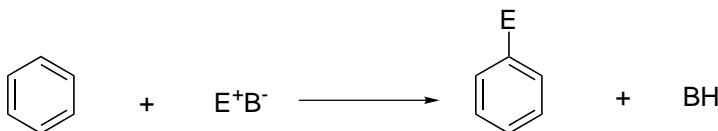


Fig 1

##### B- Essential Skills

- 1- The overall product of these reactions are substituted arenes (aromatic compounds).
- 2- All of these reactions follow a similar mechanism: generation of electrophile, attack of one of the  $\pi$  bonds of the aromatic ring with the electrophile forming a resonance-stabilized cyclohexadienyl intermediate, then regeneration of the aromatic system (6  $\pi$  electrons).
- 3- Some substituents direct the next reactants to the *ortho/para* or *meta* positions.

##### C- Important Details

- 1- It is important to understand where the positive charge resides in the cyclohexadienyl intermediate - only on three carbons of the ring - not all six.
- 2- Nitrobenzene and aminobenzene (aniline) are important intermediates in synthesis.
- 3- Carbon-carbon bonds are made in both the Friedel-Crafts alkylation and acylation.

### Section 14.2

#### II. Addition Reactions of Benzenes to give Nonaromatic Compounds:

##### Hydrogenation

##### A- Benzene is both thermodynamically and kinetically very stable.

- 1- Only high temperature, pressure and/or a very active catalyst such as rhodium or

ruthenium can hydrogenate benzene

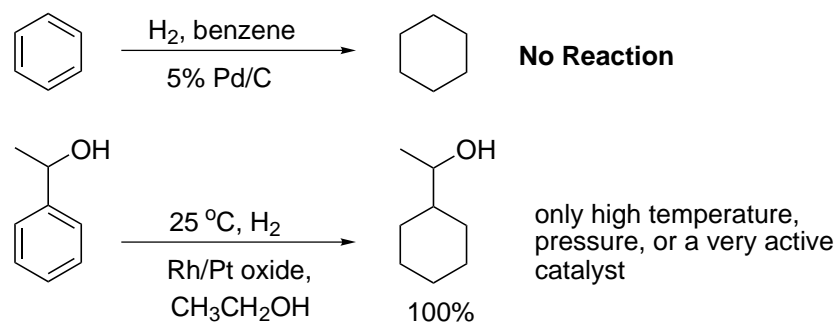


Fig 2

## Section 14.3

### III. Diels-Alder Reactions

A- Diels-Alder reactions do not normally occur with benzene.

- 1- It contains a conjugated  $\pi$  system.
- 2- The activation energy for this reaction with benzene (or any other aromatic compound) is very high.
- 3- Resonance energies of some aromatic compounds are as follows: benzene 33 kcal/mol; thiophene 29 kcal/mol; pyridine 23 kcal/mol; and furan 13 kcal/mol (Table 14.1, p 677).
- 4- This activation energy can be overcome with harsh conditions (high temperatures) and very reactive dienophiles or dienes (Fig 3).

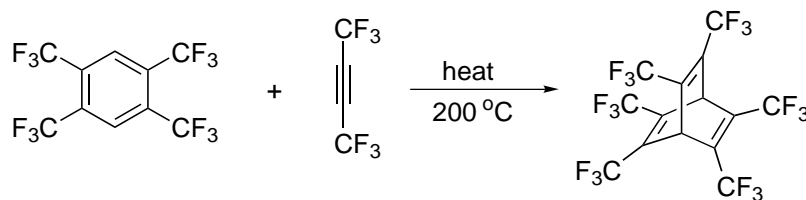


Fig 3

## Section 14.4

### IV. Substitution Reactions of Aromatic Compounds

A- Why Benzene Doesn't Undergo Simple Electrophilic Addition Reactions.

- 1- The addition of HBr to benzene logically should give a cyclohexadienyl bromide.
- 2- Although this is not the case, the speculation of how this reaction would occur shows which carbons share the delocalized positive charge generated by the hypothetical proton or halide.

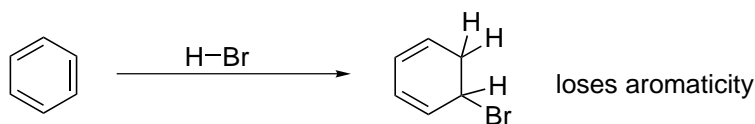


Fig 4

### B- Electrophilic Deuteration of Benzene

- 1- The way benzene and other aromatic systems *do* react is by preserving the aromatic sextet.
- 2- Benzene does not react by addition.
  - a- It would destroy the aromatic stabilization.
  - b- Aromatic compounds react by substitution reactions.
  - c- These preserve the stability of the aromatic sextet (i.e., overall it remains aromatic).
- 3- Previous example is the reaction of benzene with  $D_2SO_4$ .

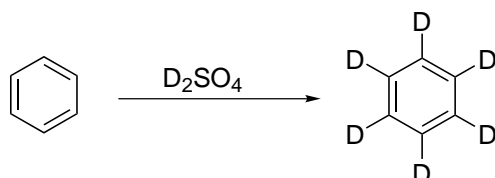


Fig 5

- a- The exchange reaction of benzene in deuterated acid is one of the simplest examples.
- b- The electrophile,  $E^+$  is the deuterated acid.
- c- The D is substituted for a hydrogen on the ring.
- d- This type of a reaction is called **electrophilic aromatic substitution**.
- e- The  $\pi$  system of the benzene ring acts as the nucleophile, and as in the exchange reaction of D for H.
- f- The reaction is completed by the removal of a proton from the intermediate cyclohexadienyl cation by a base, regenerating the aromatic benzene ring.

### C- Other Electrophilic Substitution Reactions of Benzene: The General Reaction (Figure 6)

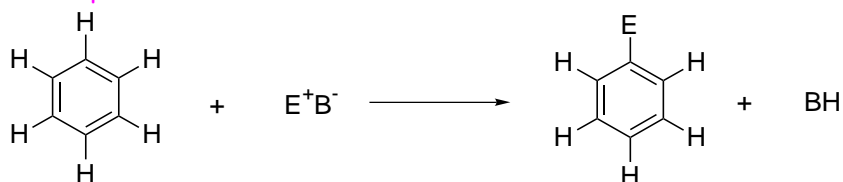


Fig 6

- 1- The general 3-step process occurs as follows:
  - a- Generate the electrophile if it is not already present.
  - b- Attack of the nucleophile ( $\pi$  bond of aromatic ring).

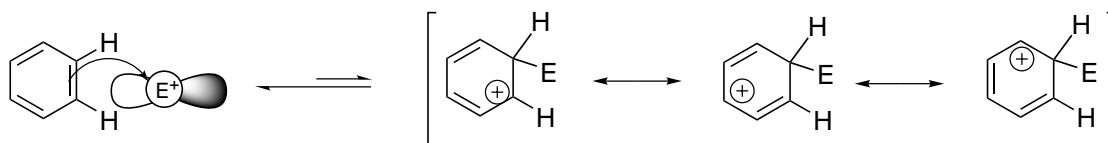


Fig 7

c- Regeneration of aromatic system.

i- Deprotonation of cyclopentadienyl cation by Lewis base.

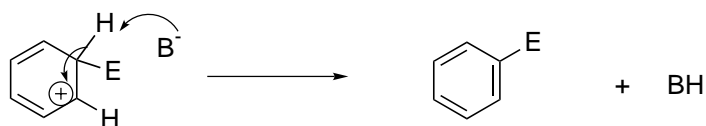


Fig 8

### D- Sulfonation

1- Benzene can be treated with a very concentrated sulfuric acid to give benzenesulfonic acid in a reversible reaction.

2- Overall reaction

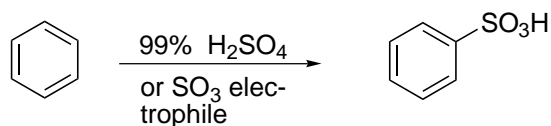


Fig 9

### 3- Mechanism

a- Step 1 - electrophile is generated

b- Step 2- nucleophilic attack

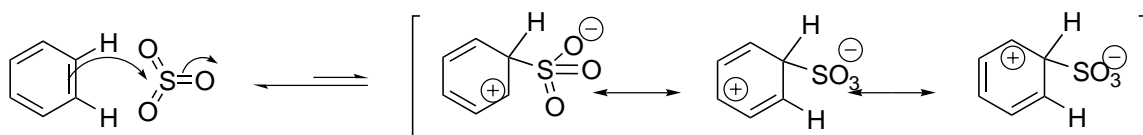
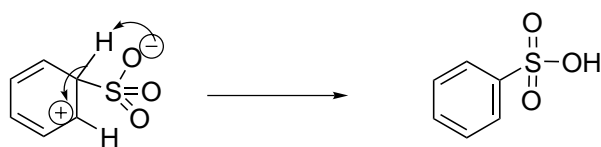


Fig 10

c- Step 3 - regeneration of aromatic system



4- This reaction is reversible.

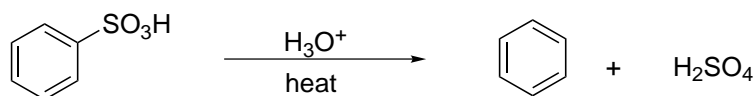


Fig 11

## E- Nitration

1- Benzene can be treated with a nitric acid to give nitrobenzene.

2- Overall reaction

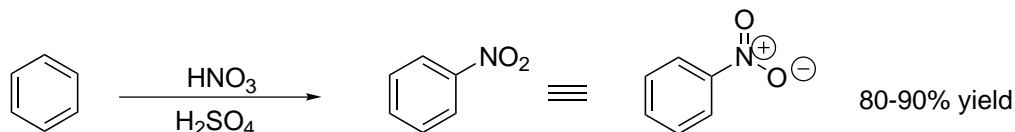


Fig 12

## 3- Mechanism

a- Step 1 - generation of electrophile

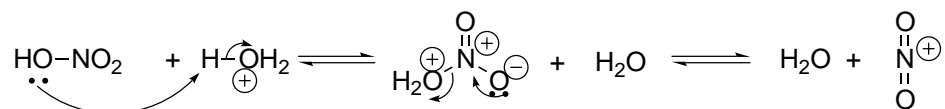


Fig 13

b- Step 2- nucleophilic attack

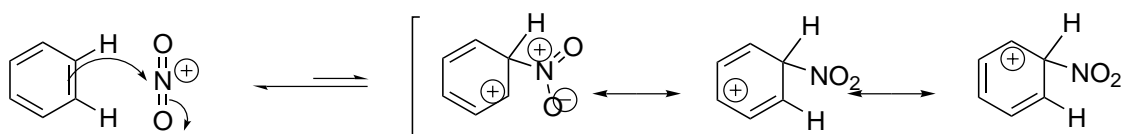


Fig 13

c- Step 3 - regeneration of aromatic system.

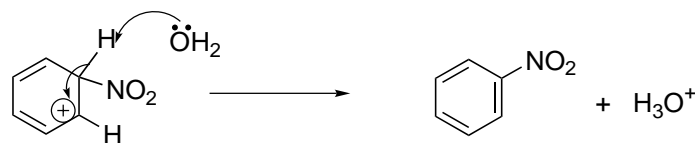


Fig 14

4- Other conditions where electrophile is generated.

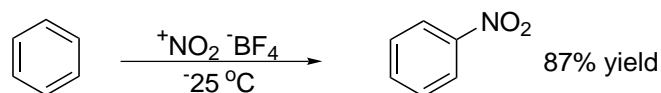


Fig 15

## F- Halogenation

1- Benzene can be treated with  $X_2$  and a Lewis acid to give halobenzene.

2- Reaction requires a Lewis acid usually where the X of the acid ( $MX_3$ ) is the same as the  $X_2$ .

3- This works because  $X_2$  is a weak acid. The Lewis acid converts the  $X_2$  to a more active acid (electrophile) which reacts with benzene.

## 4- Overall reaction.

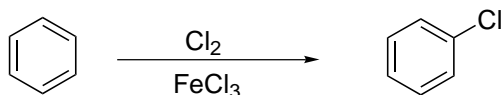


Fig 16

## 5- Mechanism

a- Step 1 - generation of electrophile

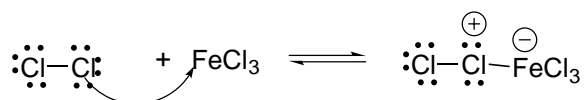


Fig 17

b- Step 2 - nucleophilic attack.

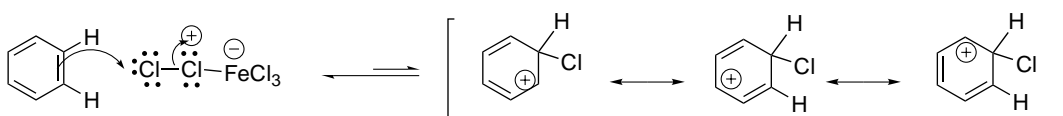


Fig 18

c- Step 3 - regeneration of the aromatic system.

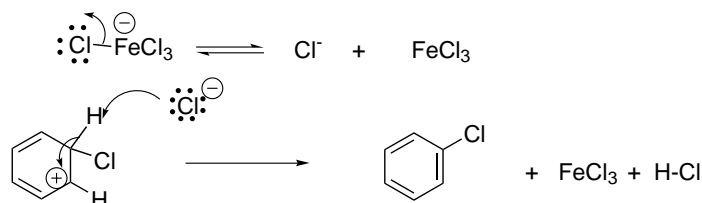


Fig 19

## Section 14.5

## V. The Friedel-Crafts Alkylation Reaction

A- Benzene can be alkylated with a variety of alkyl halides, including methyl-, ethyl-, isopropyl-, and *tert*-butyl chlorides and bromides.

1- Requires a complex (formed from the alkylhalide and a Lewis acid catalyst).

2- Typically examples of LA catalysts are FeCl<sub>3</sub> or FeBr<sub>3</sub> and the corresponding Al versions.

3- A catalytic amount of the Lewis acid is needed because it is regenerated in the final step.

## B- Overall Reaction

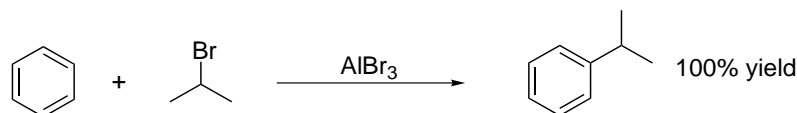


Fig 20

## C- Mechanism

a- Step 1 - generation of electrophile

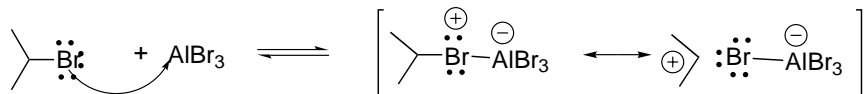


Fig 21

b- Step 2- nucleophilic attack

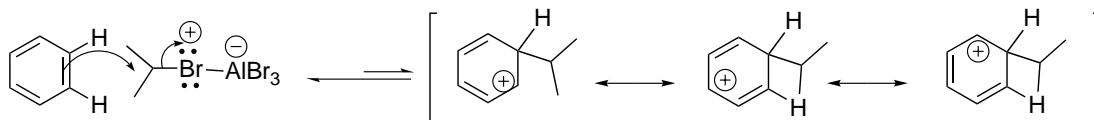


Fig 22

c- Step 3 - regeneration of aromatic system.

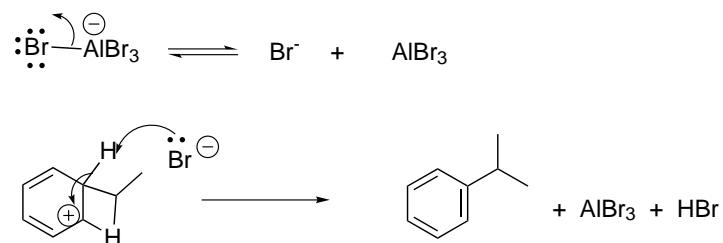


Fig 23

D- The electrophile can exist as a cation (see below).

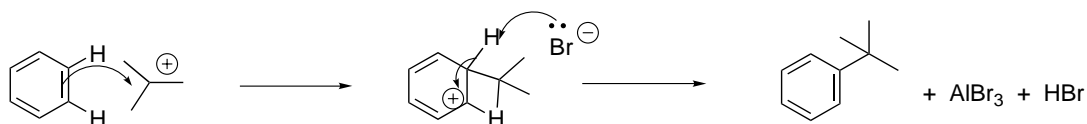


Fig 24

## E- Problems with this reaction

1- Linear alkyl halides may produce multiple products (see below).

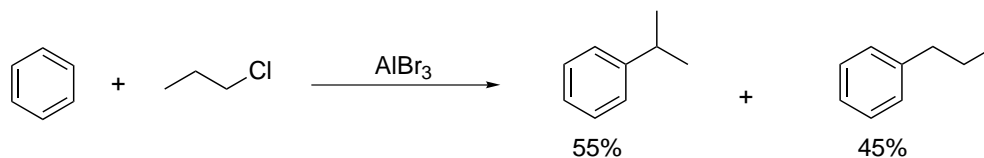


Fig 25

2- The problem is in the generation of the electrophile.

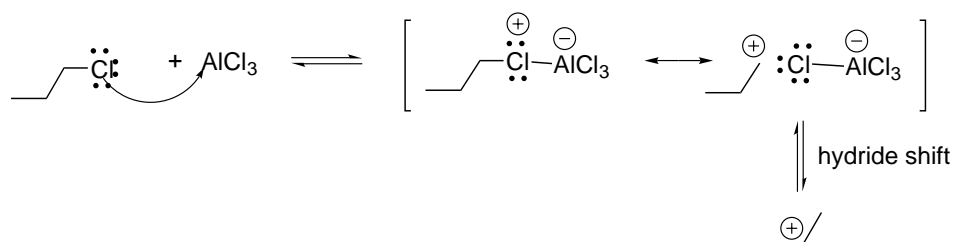
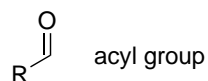


Fig 26

## Section 14.6

### VI. Friedel-Crafts Acylation

A- A reaction related to Friedel-Crafts Alkylation uses a functional group known as an **acyl group** ( $\text{RC=O}$ ) and acyl chloride ( $\text{RCOCl}$ ), also known as an **acid chloride**.



1- Acid chlorides can be synthesized by reacting carboxylic acids,  $\text{RCOOH}$ , with thionyl chloride ( $\text{SOCl}_2$ ).

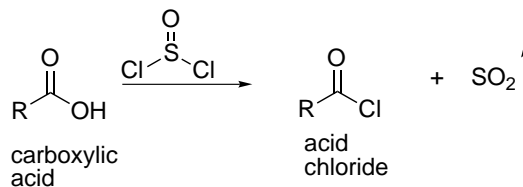


Fig 27

#### B- Overall Reaction

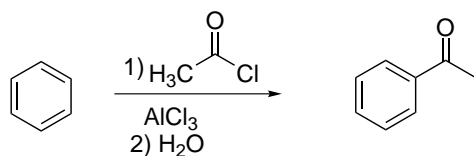


Fig 28

#### C- Mechanism

a- Step 1 - generation of electrophile (acyllium ion)

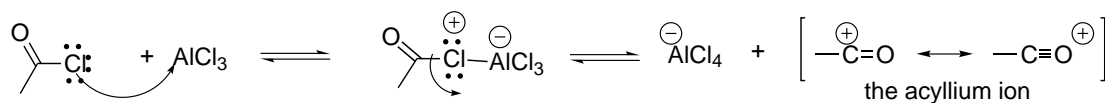


Fig 29

## b- Step 2 - nucleophilic attack

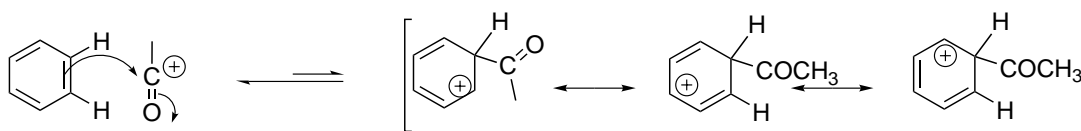


Fig 30

## c- Step 3 - regeneration of aromatic system

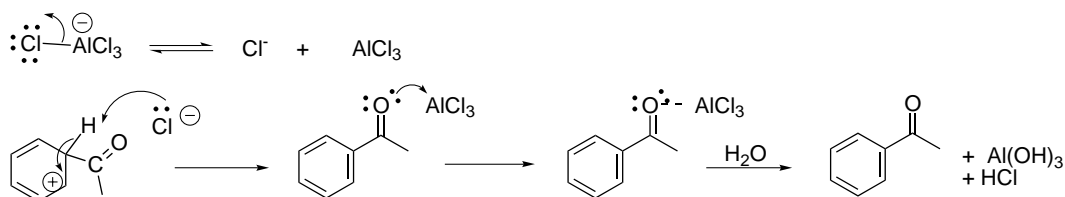


Fig 31

D- This reactions are not complicated by hydride shifts.

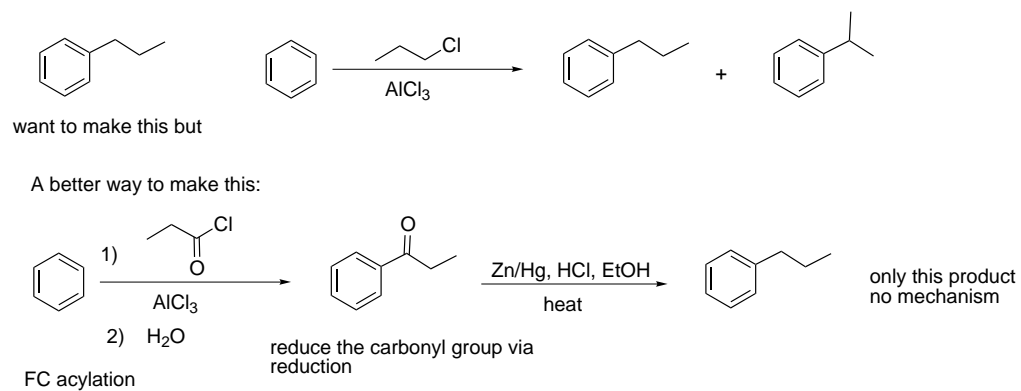


Fig 32

- 1- Acylates once.
- 2- The reduce the carbonyl by either a Clemmensen or Wolff-Kishner reduction.
- 3- No rearrangements.

## Section 14.7

## VII. Summary of Simple Aromatic Substitutions: What We Can Do So Far

A- In total, there are six EAS that you know. They are summarized below:

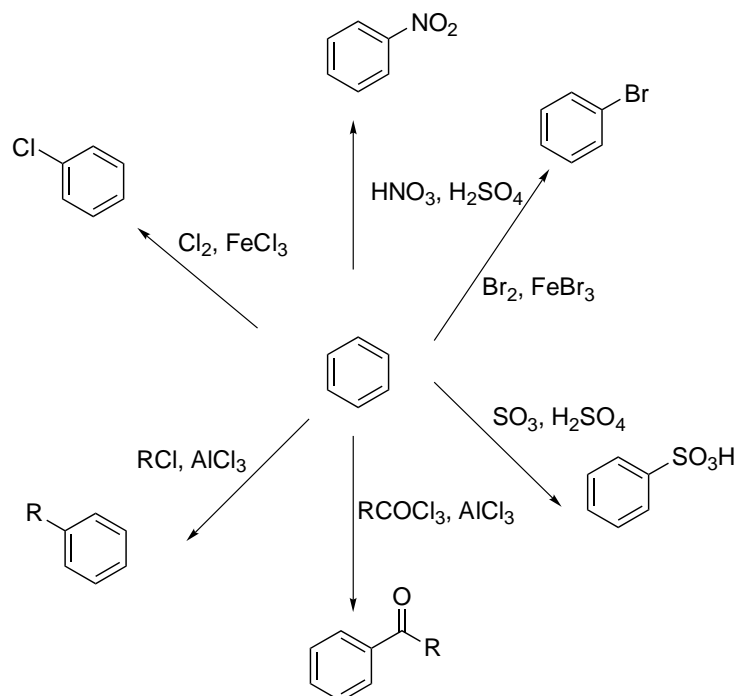


Fig 33

## B- Sandmeyer Reaction

1- An aromatic nitro group can be reduced to the amine.

2- Nitrobenzene can be reduced to aniline either by hydrogenation ( $\text{H}_2/\text{Pd}/\text{C}$  in ethanol) or metal catalyst ( $\text{Sn}/\text{HCl}$  followed by basic workup).

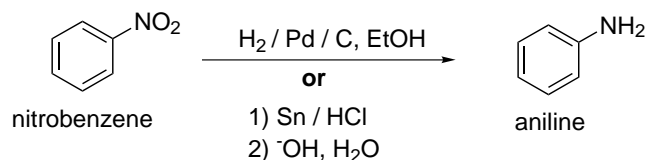


Fig 34

3- The amino group can be treated with nitrous acid ( $\text{HONO}$ ) or its sodium salt ( $\text{NaONO}$ ) and  $\text{HCl}$  to give a diazonium ion (or salt).

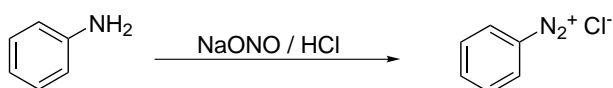
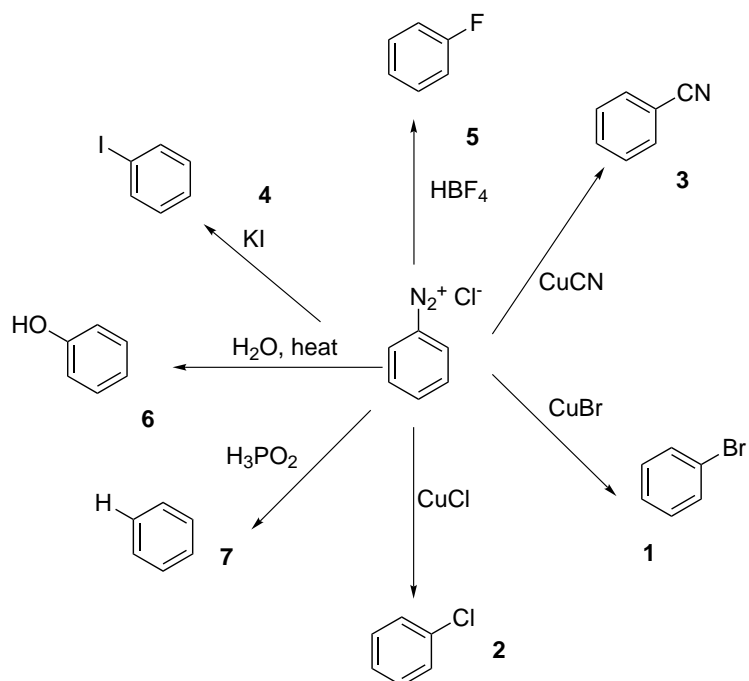


Fig 35

4- The diazonium ion is a critical intermediate, which can be converted into many other groups in the Sandmeyer reaction.



Reagent		Group
1. CuBr	----->	Br
2. CuCl	----->	Cl
3. CuCN	----->	CN
4. KI	----->	I
5. HBF <sub>4</sub>	----->	F
6. H <sub>2</sub> O	----->	OH
7. H <sub>3</sub> PO <sub>2</sub>	----->	H

Fig 35

5- Exact Mechanism is not known.

## Section 14.8

### IIX. Electrophilic Aromatic Substitution of Heteroaromatic Compounds

#### A- Reactions of Pyridine and Pyrrole.

1- The reaction products are different with heteroaromatic compounds than with benzene.

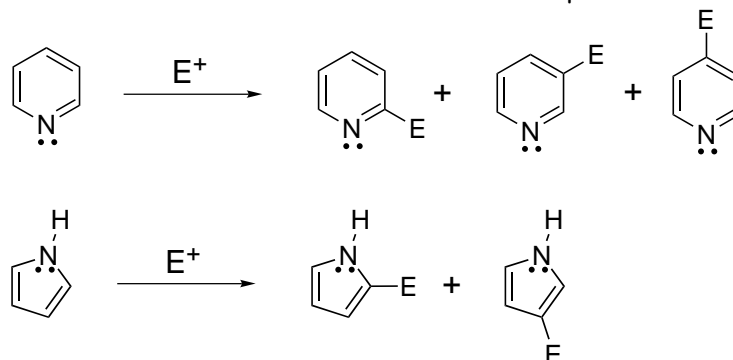


Fig 36

2- The possible products are depicted in Figure 36.

3- For pyridine, substitution at position 3 is the only product observed because there is no resonance structure which places a positive charge on the nitrogen (Fig 37).

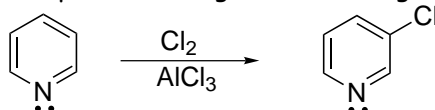


Fig 37

4- In pyrrole, substitution at position 2 is favored but substitution at position 3 is also observed (Fig 38).

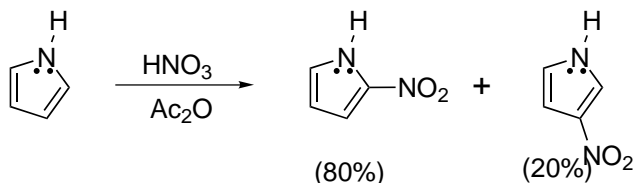


Fig 38

### B- Reactions of Furan and Thiophene

- 1- These compounds react similarly to pyrrole.
- 2- Substitution occurs first at the 2 position followed by a small amount of substitution at the 3 position (Fig 39).

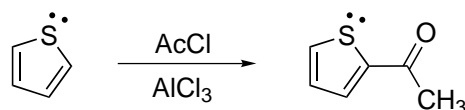
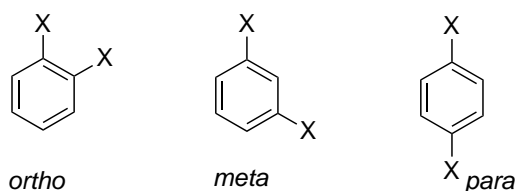


Fig 39

## Section 14.9

### IX. Disubstituted Benzenes: Ortho, Meta, and Para Substitution



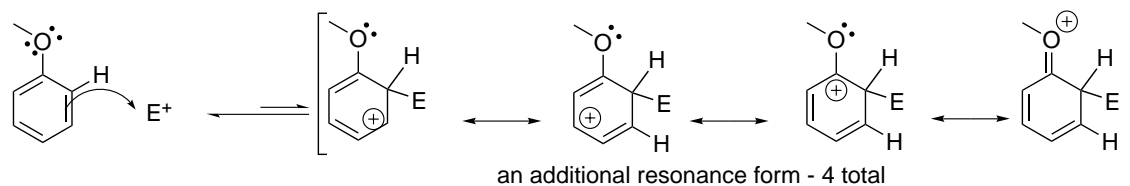
#### A- Three kinds of disubstitution patterns of benzene: ortho (1,2), meta (1,3), and para (1,4).

- 1- Nature of the groups influence where the second group will add.
- 2- Substituted benzenes that give mainly ortho or para products usually react faster than those alone.
- 3- Those that give mainly meta products react more slowly than benzene.

#### B- Electron donating groups

- 1- EDG stabilize the system inductively or donate electrons (which can be used to stabilize the cation).
- 2- Overall will give another (4<sup>th</sup>) resonance structure.
- 3- They will give ortho and/or para products.
- 4- Examples are: NR<sub>2</sub>, NH<sub>2</sub>, OH, OR, alkyl, NHOR, and halides.
- 5- Example below with resonance.

Ortho substitution with an electron donating group



Para substitution with an electron donating group

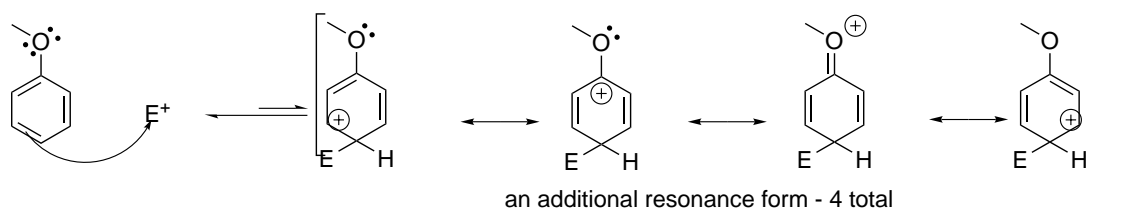


Fig 40

6- Does not go *meta* because do not have the 4<sup>th</sup> resonance structure.  
**But** Meta substitution with an electron donating group

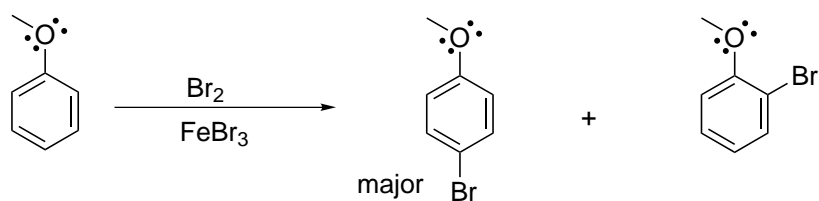
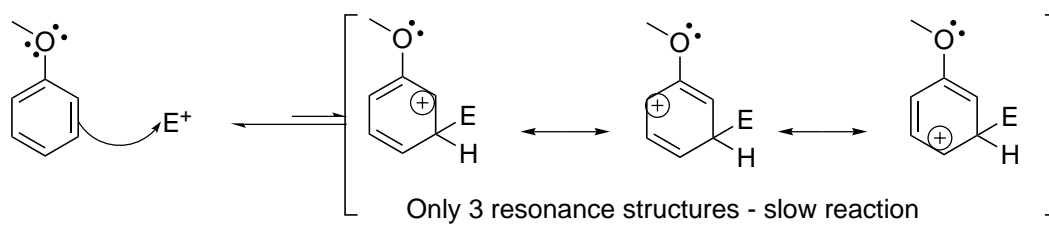
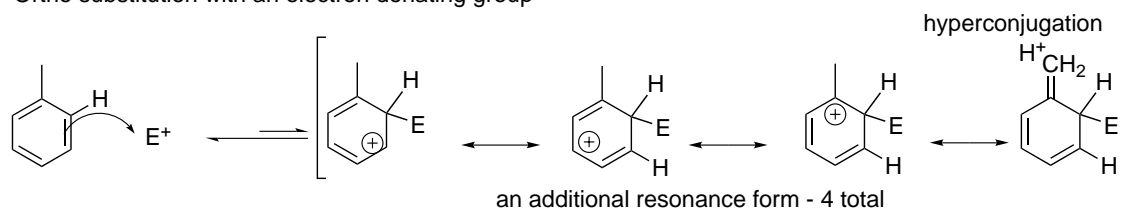


Fig 41

7- Example below EDG with inductive stabilization:

Ortho substitution with an electron donating group



Para substitution with an electron donating group

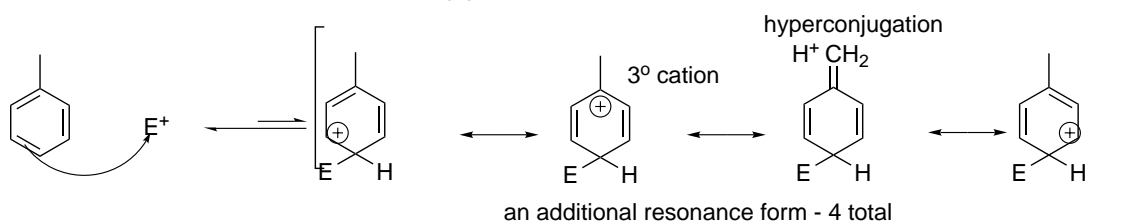


Fig 42

**But** Meta substitution with an electron donating group

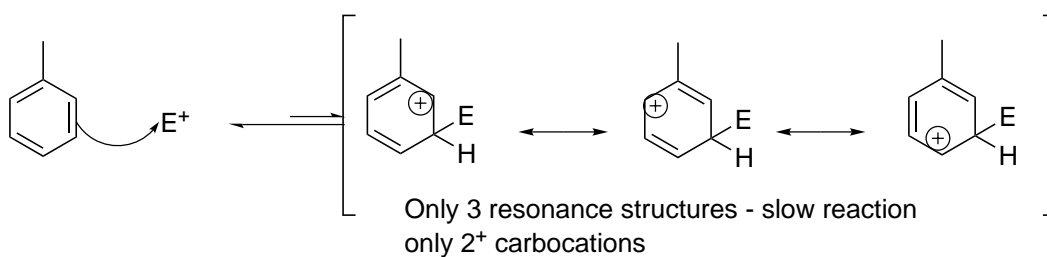
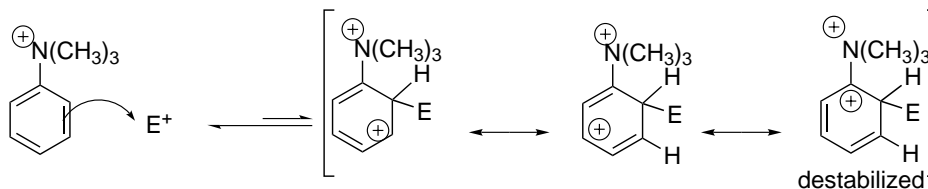


Fig 43

### C- Electron withdrawing groups

- 1- EWG destabilize 1,2 or 1,4 addition because they have either positive or partial positive charge on the atom attached to the ring.
- 2- Therefore, the second addition will go meta to the first group.
- 3- Examples are: COR, SO<sub>2</sub>OH, NO<sub>2</sub>, CN, and NR<sub>3</sub>.

Ortho substitution with an electron withdrawing group



Para substitution with an electron withdrawing

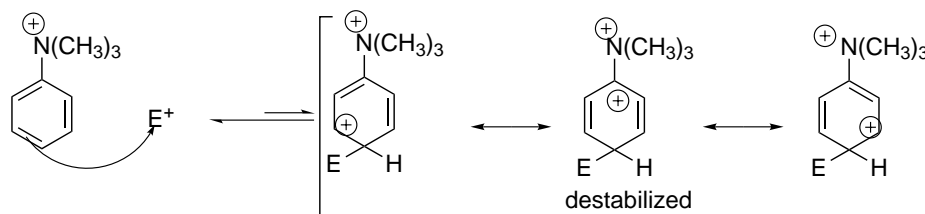


Fig 44

4- Goes meta:

**But** Meta substitution with an electron withdrawing group

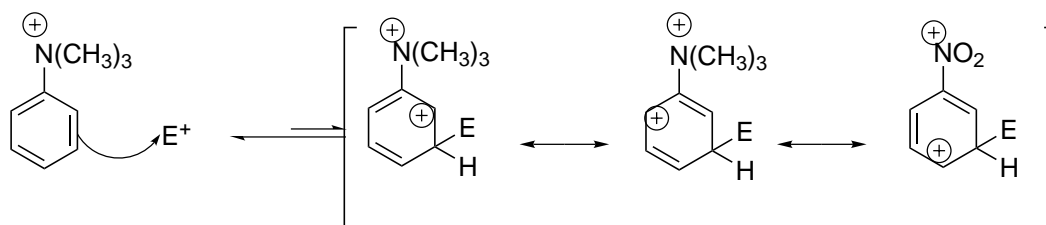
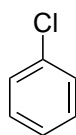


Fig 45

#### D- General Guidelines

- 1- Ortho substitution is often less favorable than para.
- 2- Halides withdraw inductively but donate electrons through resonance.



inductively withdrawing but resonance stabilizing

## Section 14.10

### X. Inductive Effects in Aromatic Substitution

#### A- Decreasing Reactivity - Slow reaction

- 1- EWGs such as  $\text{NR}_3$  and  $\text{NO}_2$  are strongly deactivating and polarized through the  $\sigma$  bond.
- 2- This makes introduction of a positive charge into the ring difficult.
- 3- Overall, slows down reaction.

#### B- Halogens and others - the competition between resonance and inductivity

- 1- The  $\sigma$  bond of electron donating groups is also polarized which makes introduction of a positive charge into the ring difficult.

- 2- But the extra resonance form available outweighs the inductive effect and the rate of reaction is very fast.
- 3- Halogens help stabilize the intermediate for ortho/para substitution through a fourth resonance form.
- 4- However the inductive withdrawing of electrons by the halogen makes substitution slow relative to benzene.

## Section 14.11

### XI. Polysubstitution of Aromatic Compounds and Synthesis of Multiply Substituted Benzenes

#### A- After disubstitution.

- 1- It is dependent on pre-existing groups.
- 2- Two *meta* directors in the 1,3 position will direct substitution to the remaining *meta* position.

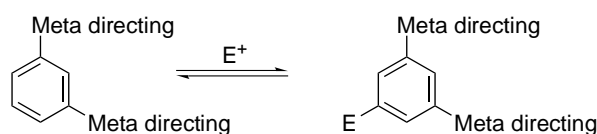


Fig 45

- 3- Specific example is depicted below.

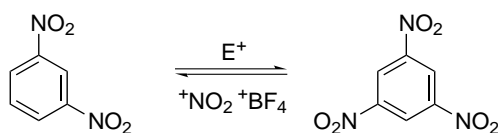


Fig 46

- 4- Whereas, *ortho/para* would direct it to remaining *ortho/para*.
- 5- The third substitution would like to follow these rules as much as possible.

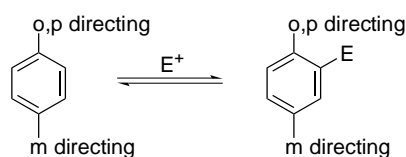


Fig 47

- 6- A specific example of this preference.

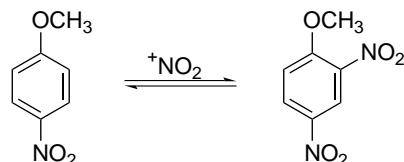
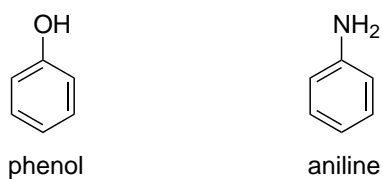


Fig 48

- 7- Electronic effects are dominant.

## B- Specially activated aromatic systems - Aniline and Phenol



- 1- Phenol is very activated so it can undergo EAS without a Lewis Acid.
- 2- It persubstitutes.
- 3- Example is depicted below.

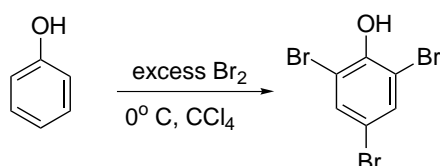


Fig 49

- 4- Aniline also persubstitutes.

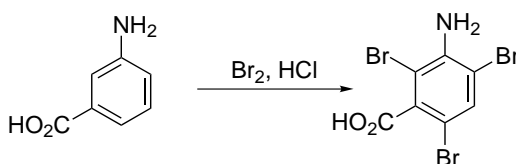


Fig 50

## C- Steric vs Electronics

- 1- Large EDG block addition *ortho* to that group.
- 2- See examples below.

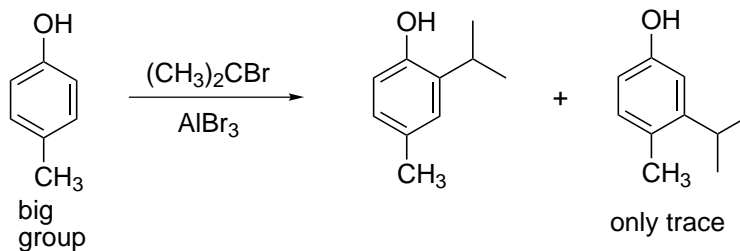
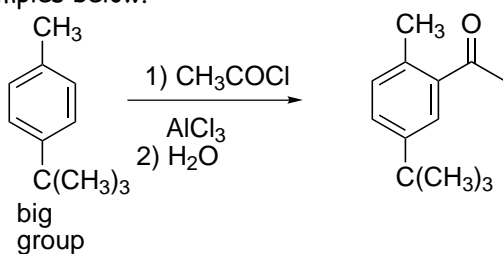


Fig 51

### D- Monosubstitution of Aniline

- 1- Acylation of amine blocks ortho position.
- 2- Can remove the group (deprotect) with base to regenerate amine.

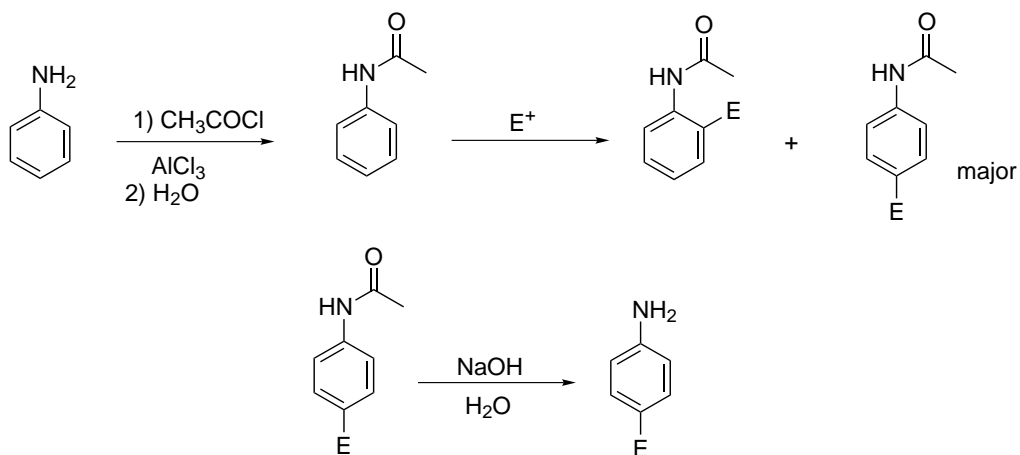


Fig 52

- 3- Example of use in synthesis.

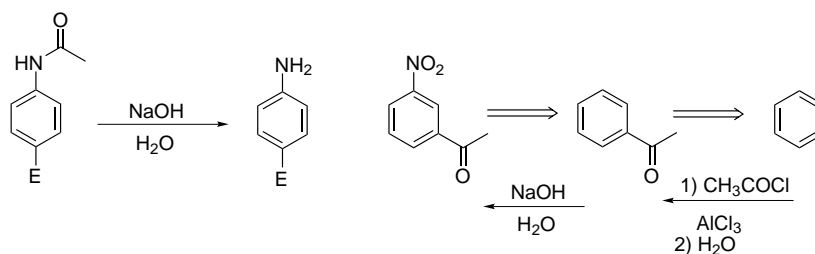


Fig 53

## Section 14.12

### XII. Nucleophilic Aromatic Substitution

A- Normally, alkenes and arenes do not undergo nucleophilic substitution but under special conditions, they do.

- 1- There are exceptions to the rule. 2,4-Dinitrochlorobenzene and *para*-nitrochlorobenzene will undergo this type of substitution.

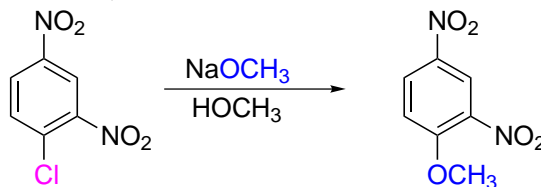


Fig 54

- 2- The mechanism is neither  $\text{S}_{\text{N}}2$  nor  $\text{S}_{\text{N}}1$ .
  - a- The first step is to add the alkoxide to the carbon bonded to the chloro group.

b- This then generates a Meisenheimer complex, which is a resonance stabilized anionic intermediate.

c- The nitro groups stabilize the negative charge so as to enable the reaction to proceed. This only occurs when the nitro group is ortho and para to the halogen. If the nitro group is meta to the halogen, then there is no resonance stabilization. The reaction does not occur.

d- The resulting anion pushes the leaving group off ( $\text{Cl}^-$ ).

e- Fluorine groups will also allow the reaction occur.

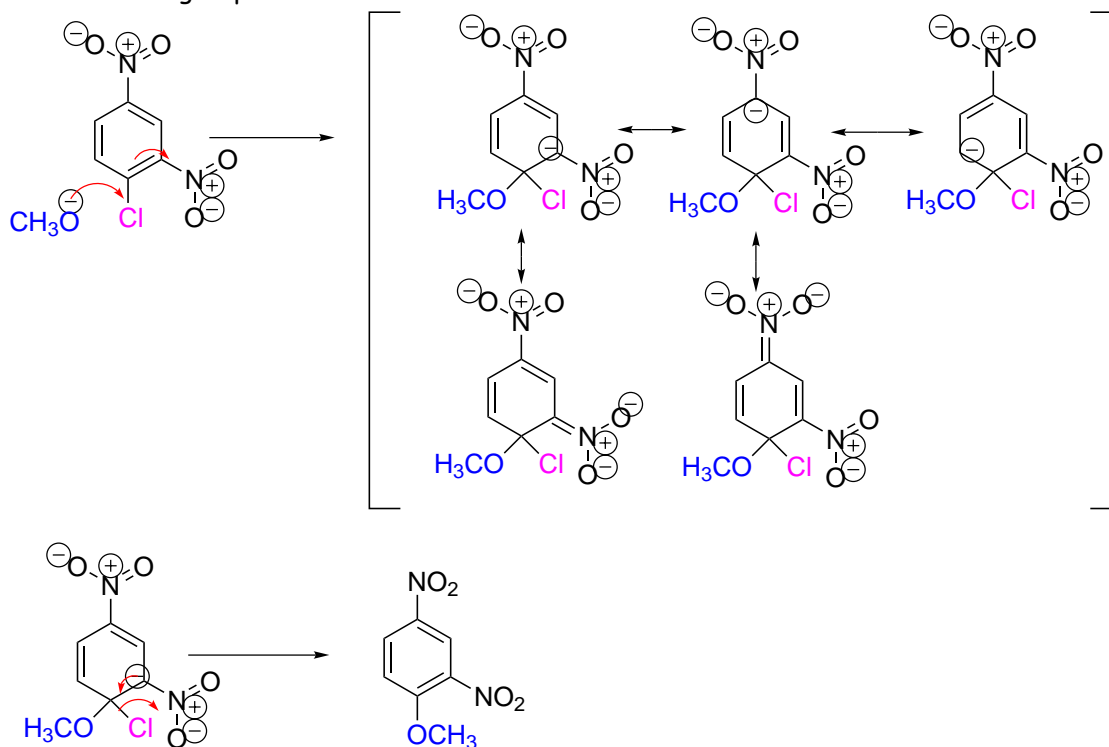


Fig 55

### B- Nucleophilic Additions to Heteroaromatics.

1- Pyridine is even more attractive than the other compounds because of the resonance stabilization. An example of this substitution is the Chichibabin reaction, which is the addition of amide to pyridine (Fig 56).

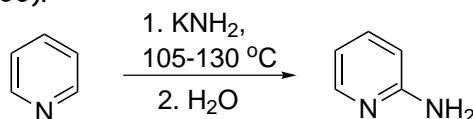


Fig 56

4- Another example of nucleophilic substitution is the addition of an alkyl lithium reagent to pyridine (Fig 57).

5- Another example is the addition-elimination reaction of pyridine (Fig 57).



Fig 57

## Section 14.13

## IIVX. Skip Special Topic: Stable Carbocations in "Superacid"

## Section 14.14

## IVX. Special Topic: Benzyne

A- Benzyne is essentially a bent acetylene.

1- Halides on benzene can be eliminated to form the alkyne.

2- Amide is a strong base which can act as a nucleophile to add to the benzyne.

B- General Reaction:

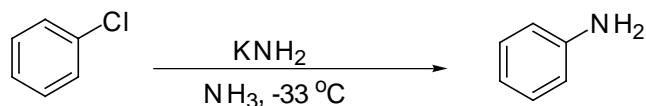


Fig 58

3- Isotopically labelled experiments:

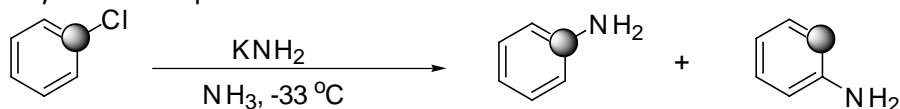
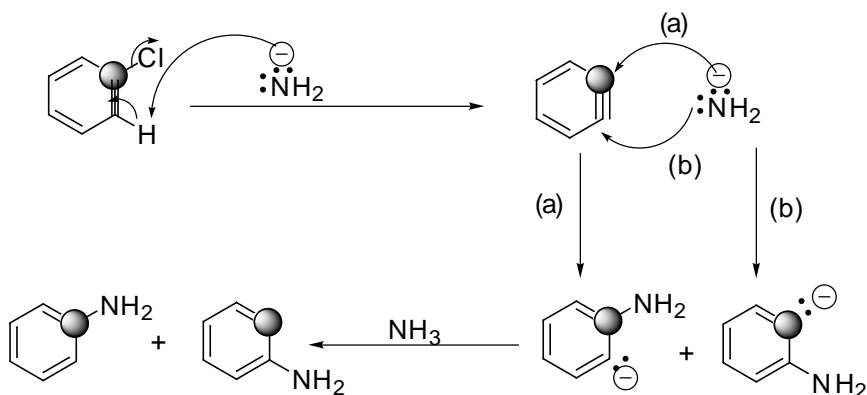


Fig 59

C- Mechanism:



- 1) Deprotonation; followed by elimination of the chloride.
- 2) Nucleophilic attack of the amide
- 3) Protonation.

Fig 60

## Section 14.15

## VX. Special Topic: Biological Synthesis of Aromatic Rings; Phenylalanine