Nucleophilic Aromatic Substitution:

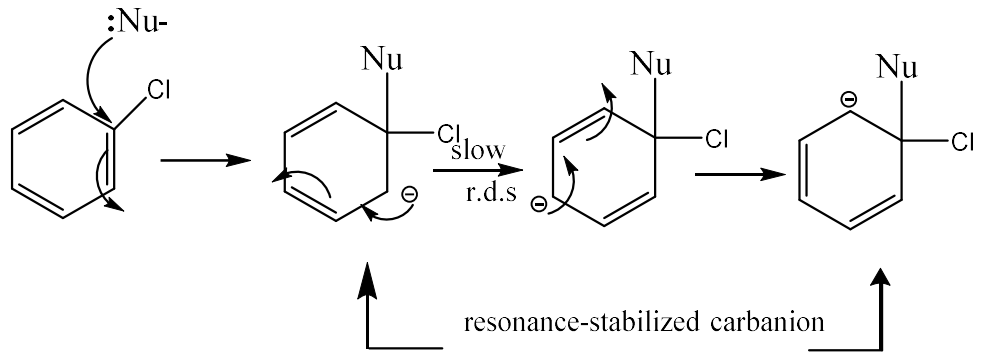
Aryl halides un active toward **nucleophilic** reagents, aryl halides undergo nucleophilic substitution readily if the **aromatic ring contain in addition to halogen certain other property place group electron-withdrawing groups (such as NO_2) on the *ortho* or *para* positions or strong base used**.

Types of mechanism in Nucleophilic Aromatic Substitution:

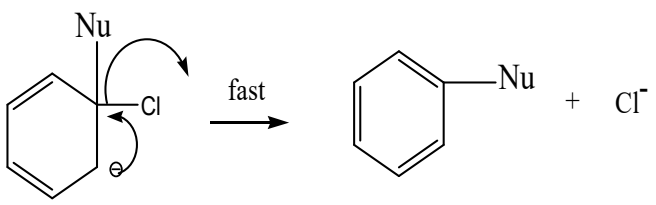
Three types of mechanism are **nucleophilic aromatic substitution** (**S_NAr**), **S_N1**, and **benzyne**.

1- **Nucleophilic Aromatic Substitution by Addition–Elimination (S_NAr):** The mechanism **involves addition** of the **nucleophile followed** by **elimination** of the **leaving group** the **addition–elimination mechanism**. These mechanisms consist of **two steps**:

Step 1: **Addition** of the **nucleophile** (**:Nu⁻**) **forms** a **resonance-stabilized carbanion** with a **new C–Nu bond three resonance structures** can be drawn, this step is **rate-determining step** (r.d.s) since the **aromaticity** of the **benzene ring** is **lost**.

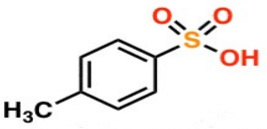
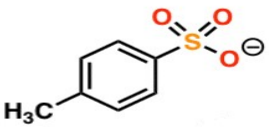
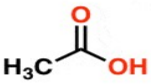
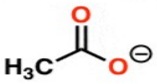
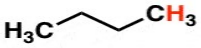
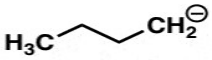


Step 2: **Loss** of the **leaving group** to **re-form** the **aromatic ring**. This step is **fast because the aromaticity of the benzene ring is restored**.



A typical nucleophilic aromatic substitution has:

1- An oxygen, nitrogen, or cyanide nucleophile.
2- A halide for a leaving group.
3- A carbonyl, nitro, or cyanide group ***ortho*** and/or ***para*** to the leaving group.

Functional group / Example		pKa	Conjugate base (Leaving group)	
Hydroiodic acid	HI	–10	$I^{\ominus}$	*Excellent leaving groups (extremely weak bases)*
Hydrobromic acid	HBr	–9	$Br^{\ominus}$	
Hydrochloric acid	HCl	–6	$Cl^{\ominus}$	
Sulfuric acid	H_2SO_4	–3	$HSO_4^{\ominus}$	
Sulfonic acids	 (p-toluenesulfonic acid)	–3		
Hydronium ion	$H_3O^{\oplus}$	–1.7	H_2O	
Hydrofluoric acid	H–F	3.2	$F^{\ominus}$	**Exception:** $F^{\ominus}$ is typically an extremely poor leaving group (forms strong bonds to carbon)
Carboxylic acids		4		*Moderate leaving groups (weak bases)*
Protonated amines	$NH_4^{\oplus}$ $Cl^{\ominus}$	9-11	NH_3	
Water	HO–H	14	$HO^{\ominus}$	*Poor leaving groups (strong bases)*
Alcohols	CH_3O–H	16-18	$CH_3O^{\ominus}$	
Amine	NH_3	~35	$NH_2^{\ominus}$	*Extremely poor leaving groups (very strong bases)*
Hydrogen	H—H	42	$H^{\ominus}$	
Alkane		~50		

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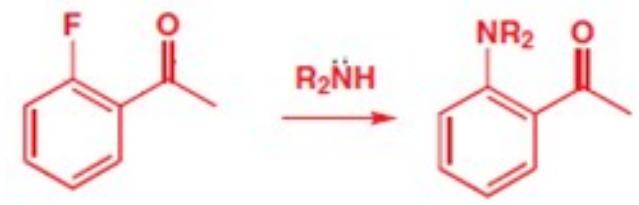
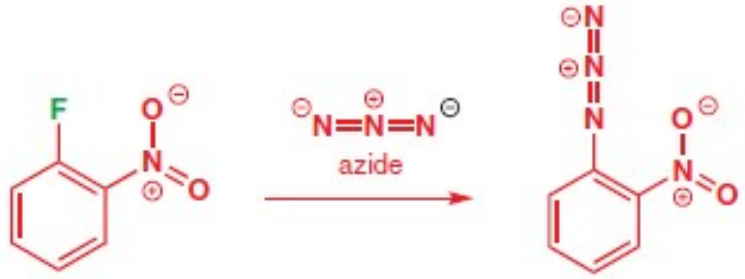


Mechanism:

Example:



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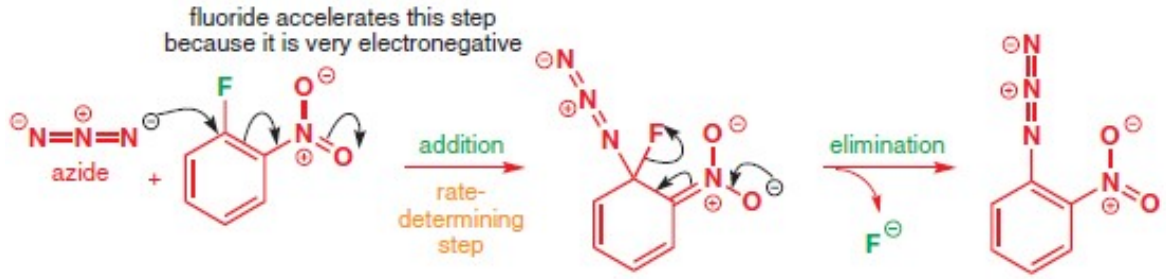

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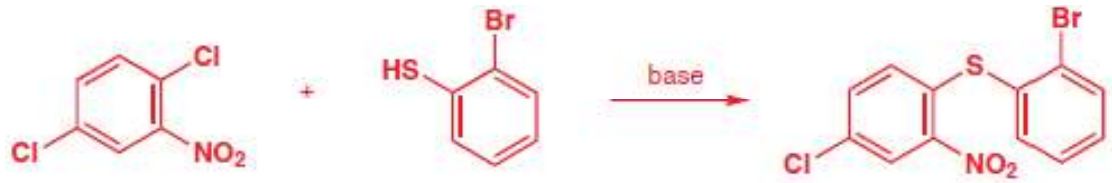
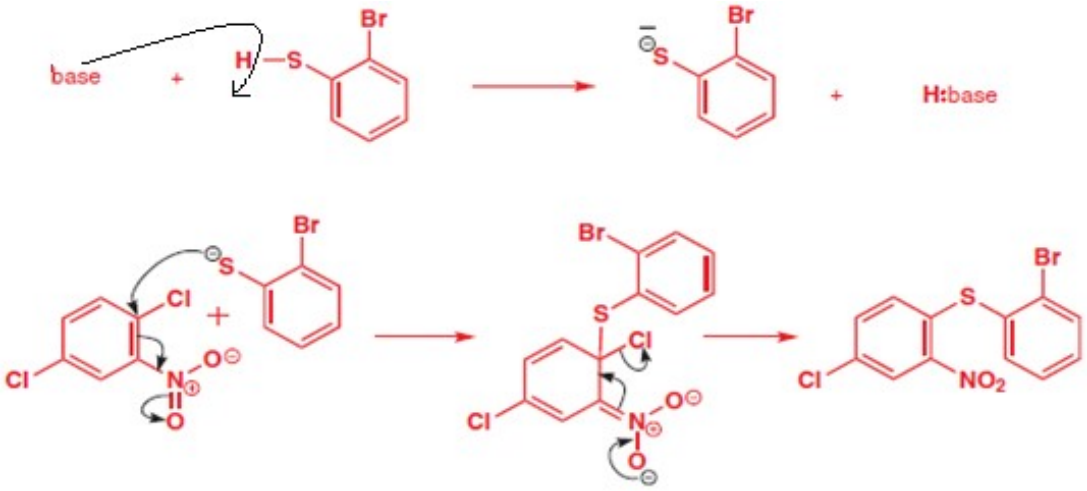
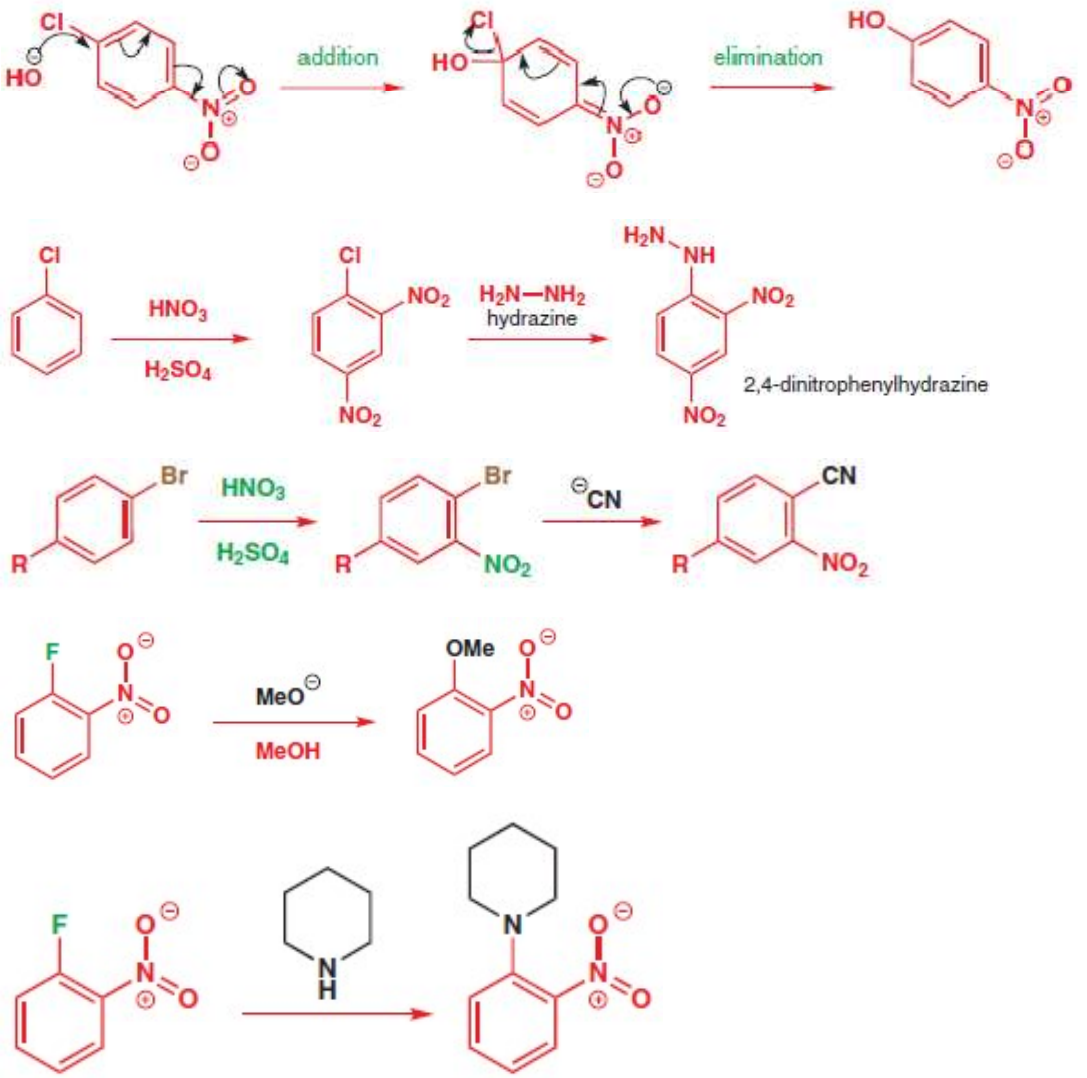


Mechanism:



Examples:

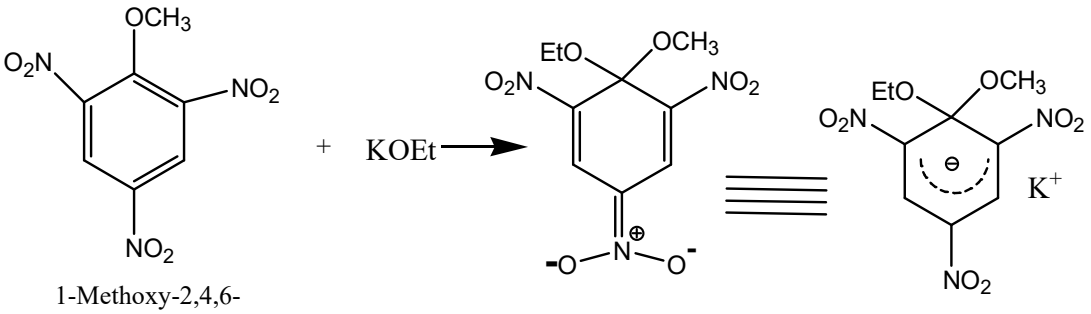


Notes:

- **Increasing** the **number** of **electron-withdrawing** groups **increases** the **reactivity** of the **aryl halide**. **Electron-withdrawing groups stabilize** the **intermediate carbanion**, **lower** the **energy** of the **transition state** that forms it.
- **Increasing** the **electronegativity** of the **halogen increases** the **reactivity** of the **aryl halide**. A **more electronegative halogen stabilizes** the **intermediate carbanion** by an **inductive effect**, making **aryl fluorides (ArF) much *more* reactive than other aryl halides**, which contain less electronegative halogens.
-A further proof for this **argument** comes from the fact that the **order of reactivity** for **halogens** is **F > Cl > Br > I** (**and not the reverse of this i.e. I > Br > Cl > F based on their leaving group ability**). This order clearly suggests that stronger bond dipoles associated with the more electronegative atom favor the addition step thus lowering the energy of activation of the nucleophilic addition step (which is r.d.s.).

Evidence of S_NAr mechanism:

1- The most convincing evidence that nucleophilic addition is a reasonable initial step was provided by the isolation of a **stable adduct** from potassium ethoxide and the methyl ether of 2,4,6-trinitrophenol (picric acid) which is called as **Meisenheimer complex** or ***Meisenheimer-Jackson* salts**, and many more have been isolated since1902. The structures of several of these intermediates have been proved by ^{1}H-NMRand x-ray crystallography.



1-Methoxy-2,4,6-trinitrobenzene (Methyl picrate)

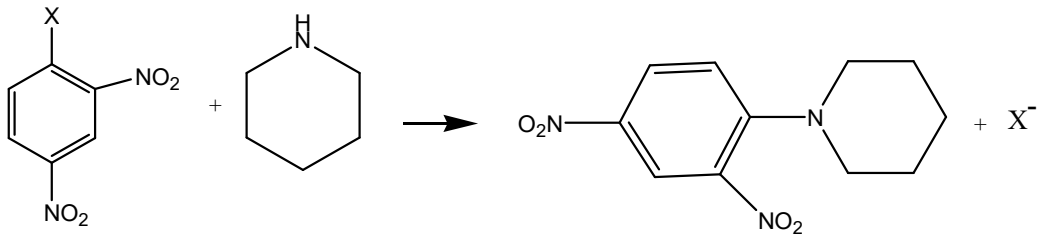
Meisenheimer complex

2- Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms, the Ar-X bond would be broken in the rate-determining step. In the **S_NAr mechanism this bond is not broken**

until after the rate- determining step (that is, if step 1 is rate-determining).We would predict from this that if the S_NAr mechanism is operating, a **change in leaving group should not have much effect on the reaction rate**.

3- When X=F, the relative rate was 3300 (compared with I =1).**The very fact that fluoro is the best leaving group** among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1 and S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens.

4- In the reaction



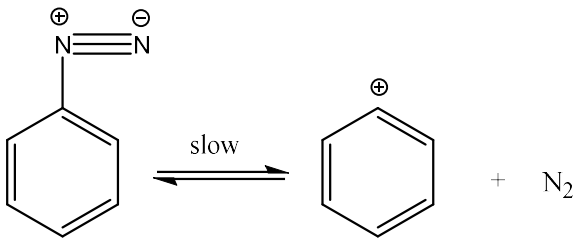
X= Cl, Br , I , SOPh

When X was Cl, Br, I, SOPh, SO_2Ph, or p-nitrophenoxy, the rates differed only by a factor of about 5 .This behavior would not be expected in are action in which the Ar-X **bond is broken in the rate-determining step**. We do not expect the rates to be identical, because the nature of X affects the rate at which Y attacks. An **increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile**.

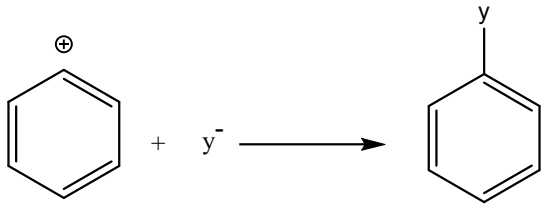
2- The S_N1 mechanism (diazonium compounds):

This mechanism is important: It is in **reactions** with **diazonium salts**, the **diazonium compound** below is so **good** at **nucleophilic aromatic substitution** that is does so even **without activating groups**, **use** absolutely the **best leaving group** of **nitrogen gas**. This mechanism consists of **two steps**: the **nitrogen** molecule just departs, **leaving behind** a **cation.**

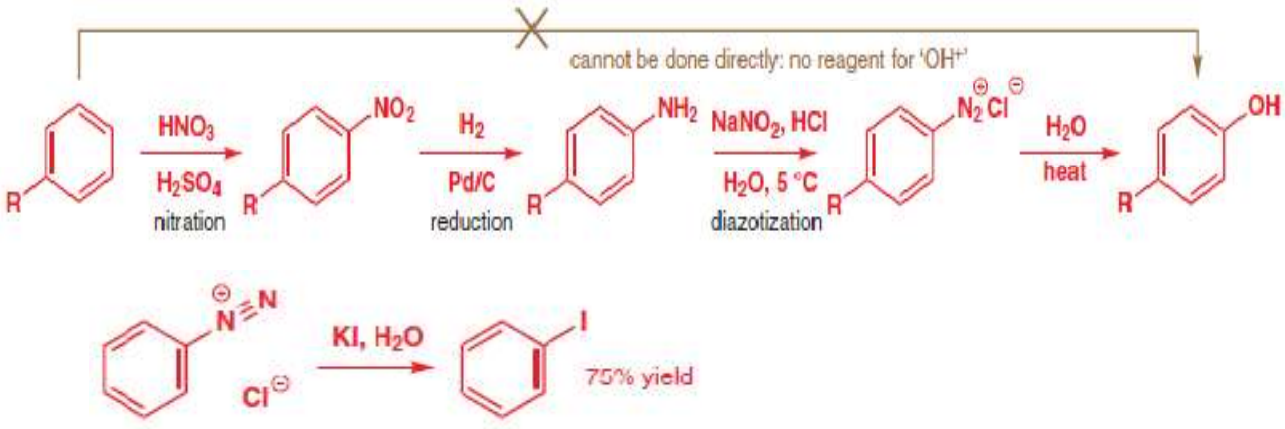
Step 1: Elimination N_2



Step 2: Addition Nu.



Examples:



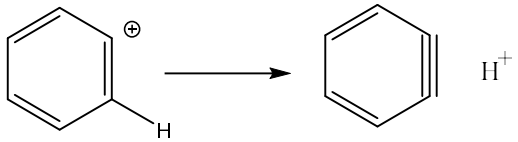
Evidence of S_N1 mechanism:

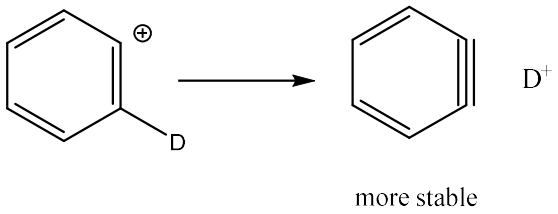
1- The **reaction rate** is **first order** in **diazonium salt** and **independent of the concentration of Y^-**.

2- When **high concentrations** of **halide salts** are added, the **product** is an **aryl halide** but the rate is **independent** of the **concentration** of the added **salts**.

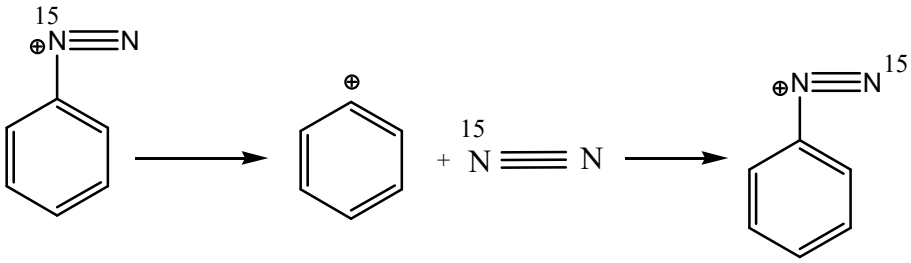
3- The **effects** of **ring substituent's** on the **rate** are **consistent** with a **unimolecular rate- determining cleavage**.

4- When **reactions** were run with substrate deuterated in the ***ortho*** position, isotope effects were obtained. It is difficult to account for such high secondary isotope effects in any other way except that an incipient **phenyl cation is stabilized by hyperconjugation which is reduced when hydrogen is replaced by deuterium**.



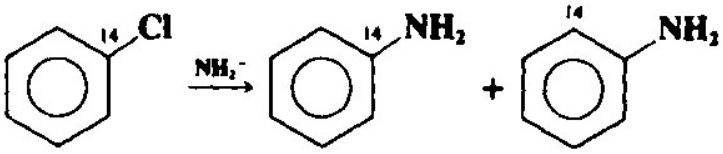


5- That the **first step** is **reversible cleavage25** was demonstrated by the observation that when Ar-N=N was the reaction species, recovered starting material contained not only Ar-15N=N but also Ar-N=15N ,This could arise only if the **nitrogen breaks** away from the ring and then returns. There is kinetic and other evidence that step 1 is more complicated and involves two steps, both reversible:



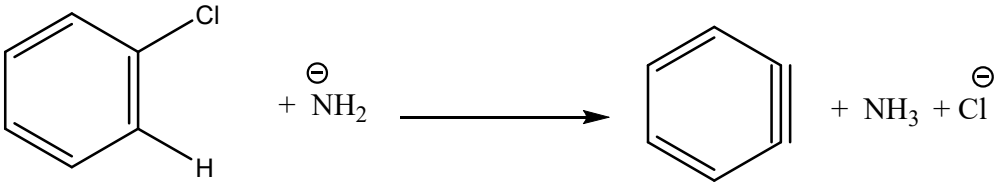
3- **Benzyne Mechanism (elimination- addition):**

Aryl halides undergo nuclophilic substitution when **treated** with **very strong bases**, The product consisted of almost equal amounts of aniline labeled in the 1 position and in the 2 position.

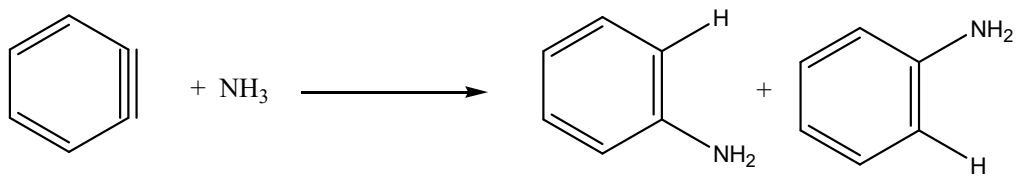


This mechanism consists of **two steps**:

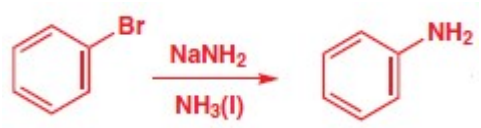
Step 1: **base remove** the ***ortho*** **hydrogen** with ions of **chlorine** (**leaving group**) to generate **intermediate** is called **benzyne**.



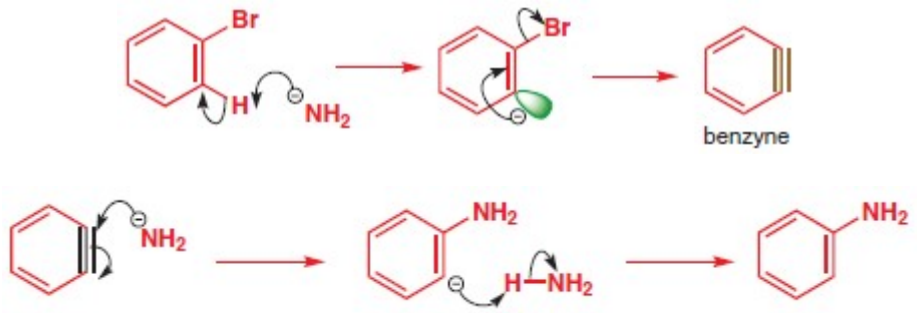
Step 2: **benzyne** is **attacked** by the **NH_3** at either of two positions.



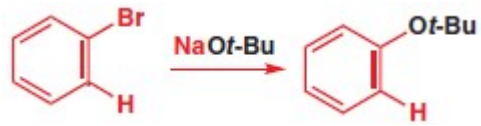
Example:



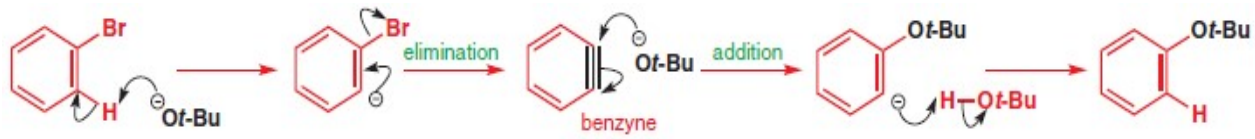
Mechanism:



Example:

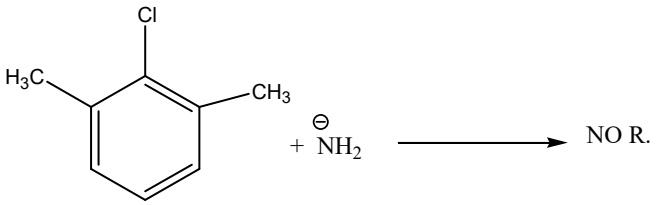


Mechanism:

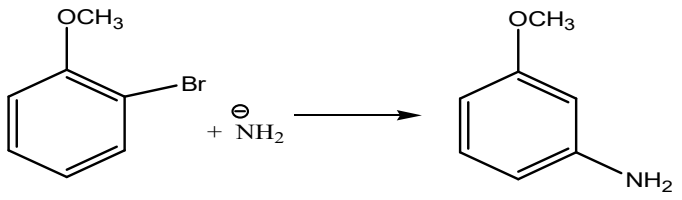


Evidence of benzyne mechanism:

1- If the **aryl halide contains two *ortho* substituent's**, the reaction should **not be able** to occur.



2- Reaction NH_2 with ***o*-bromoanisole** to **give** only ***m*-aminoanisole**.



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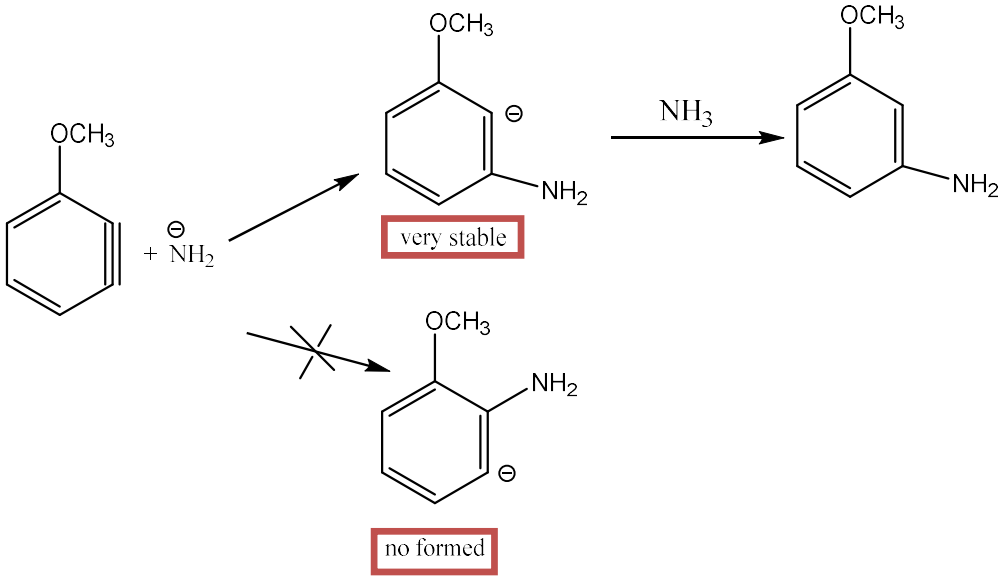

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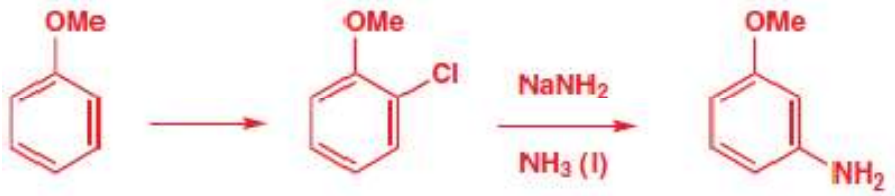
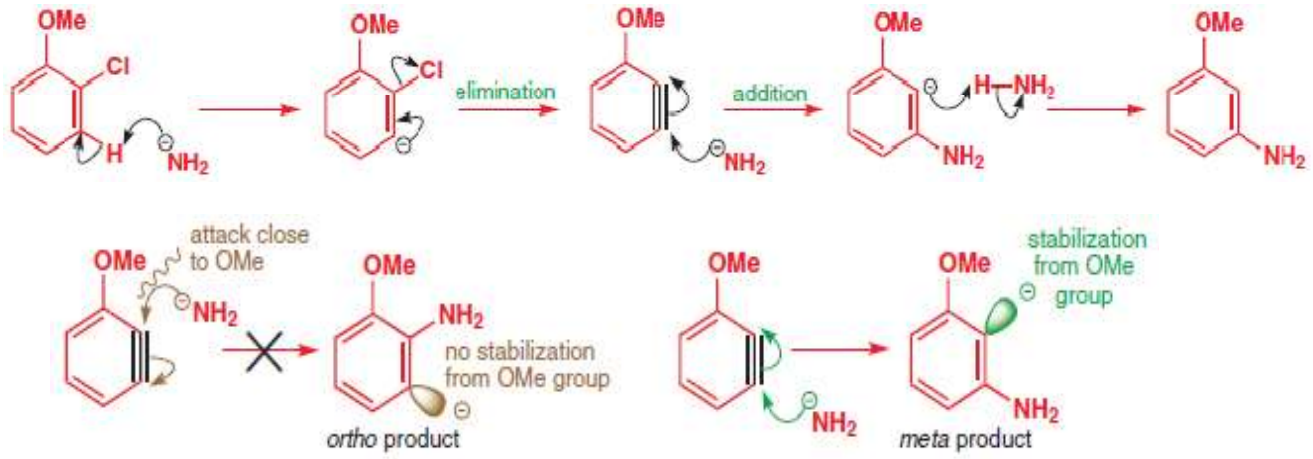
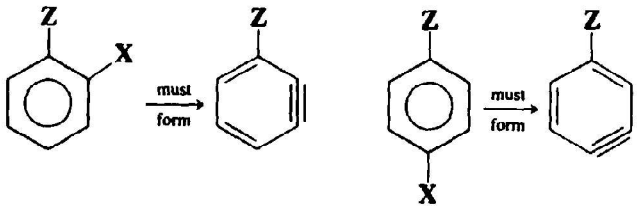


Mechanism:

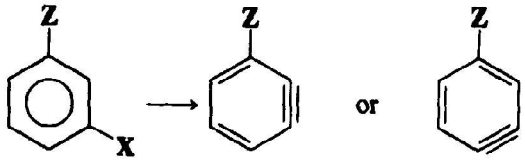


3-

Benzyne mechanism Two factors affect the positions of the incoming group, the first being the direction in which the aryne forms.[56] When there are groups ortho or para to the leaving group, there is no choice:

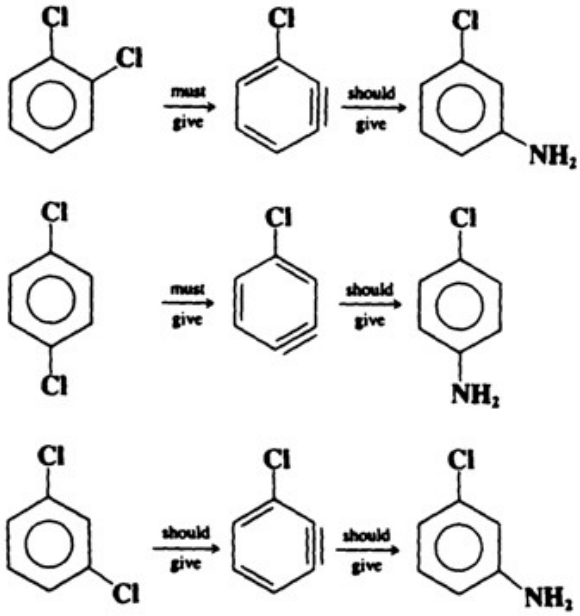


but when a meta group is present, the aryne can form in two different ways:



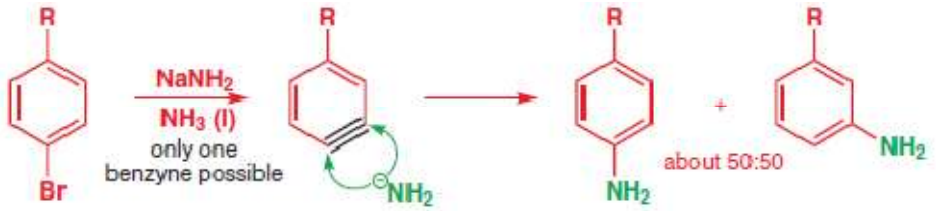
In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate, and this

in turn also depends on the field effect of Z. For $-I$ groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes with alkali-metal amides. The predicted products are

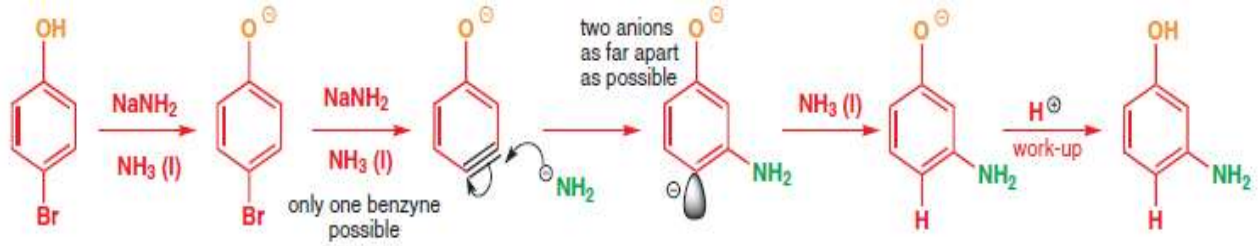
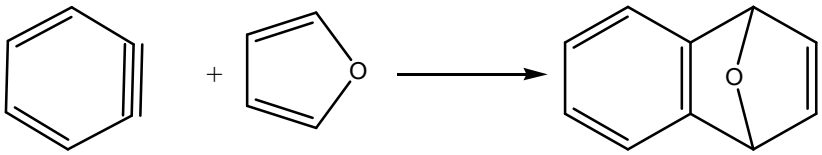


In each case the predicted product was the one chiefly formed. The obtention of *m*-aminoanisole, is also in accord with these predictions.

Example:



Mechanism:



4- **Isolation benzyne** by **Diels Alder reaction**: Wittig finds that benzyne can participate in Diels-Alder reactions as a dienophile: