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Aromatic Substitution Reactions: An Overview

Kapoor Y[1] and Kumar K[1,2]*

[1]School of Pharmaceutical Sciences, Apeejay Stya University, Sohna-Palwal Road, Sohna, Gurgaon, Haryana, India

[2]School of Pharmacy and Technology Management, SVKM's NMIMS University, Hyderabad, Telangana, India

Abstract

The introduction or replacement of substituent's on aromatic rings by substitution reactions is one of the most fundamental transformations in organic chemistry. On the basis of the reaction mechanism, these substitution reactions can be divided into electrophilic, nucleophilic, radical, and transition metal catalyzed. This article also focuses on electrophilic and nucleophilic substitution mechanisms.

Introduction

The replacement of an atom, generally hydrogen, or a group attached to the carbon from the benzene ring by another group is known as aromatic substitution. The regioselectivity of these reactions depends upon the nature of the existing substituent and can be ortho, Meta or Para selective. Electrophilic Aromatic Substitution (EAS) reactions are important for synthetic purposes and are also among the most thoroughly studied classes of organic reactions from a mechanistic point of view. A wide variety of electrophiles can effect aromatic substitution. Usually, it is a substitution of some other group for hydrogen that is of interest, but this is not always the case. For example, both silicon and mercury substituent's can be replaced by electrophiles. The reactivity of a particular electrophile determines which aromatic compounds can be successfully substituted. Despite the wide range of electrophilic species and aromatic ring systems that can undergo substitution, a single broad mechanistic picture encompasses most EAS reactions. The identity of the rate-determining step and the shape of the reaction energy profile are specific to individual reactions, but the sequence of steps and the nature of the intermediates are very similar across a wide range of reactivity.

EAS: General Mechanism

The EAS or electrophilic substitution reaction follows the below generalized two steps:

1. In the first step, the electrophilic reagent attacks on the π electrons of the aromatic ring to form an intermediate which is known as aronium cation, the sigma complex or the pentadienyl cation as shown in Scheme 1.

2. The second step of the reaction involves the elimination of a proton from the intermediate, by an anionic species, to form a substituted aromatic compound as depicted in Scheme 2.

The reaction of benzene nucleus in the product confers stability to the substituted product. Thus, the electrophilic aromatic substitution reactions are bimolecular since the rate determining (first) step involves two step mechanisms.

Role of σ and π Complex in EAS

Formation of σ complex follows the initial formation of a π complex in which electrophile is loosely held near the π-electron cloud of aromatic ring, however in most of aromatic substitution, formation of a π-complex is found to be reversible and rapid step which is followed by the slow (rate determining) and irreversible step of σ complex formation as shown in Scheme 3.

Nitration Reaction

It is carried out with a mixture of HNO_3 and H_2SO_4 (nitrating agent) the reaction proceeds very slowly when HNO_3 alone is used which indicate that H_2SO_4 converts the HNO_3 into a form that is capable of reacting with benzene with great ease. Evidence shows that H_2SO_4 helps in converting the HNO_3 into nitronium ion which the real nitrating agent as is shown in Scheme 4.

Like H_2SO_4 other strong acids (ex., BF_3, HF) also serve the purpose (Scheme 5).

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*Correspondence:
Kapil Kumar, School of Pharmacy and Technology Management, SVKM's NMIMS University, Hyderabad, Telangana, India.
Tel: +91-8872041174
Fax: +91-1636-239515
E-mail: kapil.py@gmail.com

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Note:

• H_2SO_4 has no action on benzene itself under the conditions of nitration.

• Presence of NO_2^+ in mixture has been confirmed by the Raman spectra.

• $NO_2^+$is a powerful electrophile which attacks on the benzene ring as explained in Scheme 6.

• Each successive nitro group reduces the reactivity of ring; it is easy to control conditions to obtain a mono nitration product, if poly nitration is desired more vigorous conditions are required.

Effect of Solvent

In CH_3COOH and CH_3NO_2 formation of NO_2^+ is often the rate controlling step [1]. HNO_3 in acetic anhydride $(CH_3CO)_2O$ generates acetyl nitrate which give high ortho: para ratios [2]. A convenient procedure involves reaction of the aromatic in chloroform or dichloromethane with a nitrate salt and trifluoroacetic anhydride [3]. Presumably trifluoroacetyl nitrate is generated under these conditions as illustrated in Scheme 7.

$(CH_3CO)_2O$ and $(CF_3CO)_2O$ have been used in conjugation with HNO_3 and zeolite-β which gives excellent para selectivity (Scheme 8) [4,5]. The improved selectivity is thought to occur as a result of nitration within the zeolite pores which may restrict access to the ortho-position.

Nitration can be catalyzed by lanthanide salts (Scheme 9). For example, the nitration of benzene, toluene, and naphthalene by aqueous nitric acid proceeds in good yield in the presence of $Yb(O_3SCF_3)_3$ [6]. The catalysis presumably results from an oxyphilic interaction of nitrate ion with the cation, which generates or transfers the NO_2^+ ion [7]. This catalytic procedure uses a stoichiometric amount of nitric acid and avoids the excess strong acidity associated with conventional nitration conditions.

Catalysis results form an oxyphilic interaction of nitrate ion with the cation, which generates or transfers the NO_2^+ ion. This catalytic procedure uses a stoichiometric amount of nitric acid and avoids the excess strong acidity associated with the conventional nitration condition Scheme 10.

Salts containing the nitronium ion can be prepared and are reactive nitrating agents. The tetrafluroborate salt has been used most frequently, [8-10] but the triflurometh ane sulphonate can also be prepared readily [11], nitrogen heterocycles(pyridine, quinoline) form N-nitro salts on reaction with NO_2BF_4 [12]. These N-nitro heterocycles can act as nitrating reagents in a reaction called transfer nitration as shown in Scheme 11.

Compounds such as phenyl acetate esters and phenyl ethyl ethers, which have oxygen substituent's that can serve as directing groups, show high ortho: para ratios under these conditions [13]. These reactions are believed to involve coordination of the NO_2^+ at the substituent oxygen, followed by intramolecular transfer (Scheme 12). Scheme 13 shows some representative Aromatic nitration reactions [14-19].

Halogenation

The introduction of the halogens onto aromatic rings by electrophilic substitution is an important synthetic procedure as shown in Scheme 14. Chlorine and bromine are reactive toward aromatic hydrocarbons, but Lewis acid catalysts are normally needed to achieve desirable rates. Elemental fluorine reacts very exothermically and careful control of conditions is required. Molecular iodine can effect substitution only on very reactive aromatics, but a number of more reactive iodination reagents have been developed. It takes place in the presence of a catalyst a halogen carrier such as iron powder, $FeCl_3$, $ZnCl_2$, $AlBr_3$, iodine, pyridine etc. The function of the catalyst is to facilitate the formation of the electrophile, halonium ion Lewis Acid facilitates cleavage of halogen bond.

Rate studies show that chlorination is subject to acid catalysis, although the kinetics are frequently complex [20-23]. It is much more rapid in polar than in non-polar solvents [24]. N-Bromosuccinimide (NBS) and N-chlorosuccinimide (NCS) are alternate halogenating agents, both of which can halogenate moderately active aromatics in nonpolar solvents by using HCl [25] or $HClO_4$ [26] as a catalyst. Halogenations are strongly catalysed by mercuric acetate or trifluroacetate which generate acylhypohalites which are the active halogenating agents (Scheme 15). The trifluoroacetyl hypohalites are very reactive reagents. Even nitrobenzene, for example, is readily brominated by trifluoroacetyl hypobromite [27].

A solution of Br_2 in CCl_4 containing H_2SO_4 and mercuric-oxide is also a reactive brominating agent [28]. Fluorination can be carried out using fluorine diluted with an inert gas. However, great care is necessary to avoid uncontrolled reaction [29]. Acetyl hypofluorite can be prepared in situ from fluorine and sodium acetate [30]. It shows a strong preference for *o*-fluorination of alkoxy and acetamide-substituted rings. *N*-Fluoro-bis-(trifluoromethansulfonyl) amine (*N*-fluorotriflimide) display similar reactivity and can fluorinate benzene and activated aromatics as shown in Scheme 16 [31].

Iodination's can be carried out by mixtures of iodine and various oxidants such as periodic acid [32], I_2O_5 [33], NO_2 [34] and $Ce(NH_3)_2(NO_3)_6$ [35]. A mixture of a cuprous iodide and a cupric salt can also affect iodination as shown in Scheme 17 [36].

Iodination of moderately reactive aromatics can be affected by mixtures of iodine and silver or mercuric salts [37-41]. Hypoiodites are presumably the active iodinating species. Bis-(pyridine) iodonium salts can iodinate benzene and activated derivatives in the presence of strong acids such as HBF_4 or CF_3SO_3H [42]. Some representative Halogenations reactions are illustrated in Scheme 18 [43-50].

Friedel-Crafts Alkylation

Friedel-Crafts alkylation reactions are an important method for introducing carbon substituent's on aromatic rings. The reactive electrophiles can be either discrete carbocation's or polarized complexes that contain a reactive leaving group. Various combinations of reagents can be used to generate alkylating species. Alkylations usually involve alkyl halides and Lewis acids as shown in Scheme 19 or reactions of alcohols or alkenes with strong acids.

Owing to the involvement of carbonation's, Friedel-Crafts alkylation's can be accompanied by rearrangement of the alkylation group. For example, isopropyl groups are often introduced when *n*-propyl reactants are used as shown in Scheme 20 [51].

Alkyl groups can also migrate from one position to another on the ring [52]. Such migrations are also thermodynamically controlled and proceed in the direction of minimizing steric interactions between substitutions as illustrated in Scheme 21.

Methane sulfonate esters of secondary alcohols also give Friedel-crafts products in the presence of $Sc(O_3SCF_3)_3$ [53] or $Cu(O_3SCF_3)_2$ as shown in Scheme 22 [54].

Friedel-crafts alkylation can occur intramolecular to form a fused ring. Intramolecular Friedel-Crafts reactions provide an important method for constructing polycyclic hydrocarbon frameworks. It is somewhat easier to form six-member than five-member rings in such reactions as depicted in Scheme 23.

Limitations

1. Friedel-Crafts alkylation reaction does not proceed with aromatic reactants having electron withdrawing group substituents.

2. Each alkyl group that is introduced increases the reactivity of ring toward further substitution, so polyalkylation can be a problem. It can be minimized by using the aromatic reactant in excess Scheme 24.

Friedel-Craft Acylation

It involves reaction of acid-chlorides or anhydrides in presence of Lewis acids such as $AlCl_3$, SbF_5, or BF_3. Bismuth (III) triflate is also a very active Acylation catalyst [55,56]. For example, a combination of hafnium (IV) triflate and $LiClO_4$ in nitro methane catalyzes acylation of moderately reactive aromatics by acetic-anhydride as shown in Scheme 25.

Mixed anhydrides with trifluoroacetic acid are reactive acylating agents. Scheme 26 showed the use of a mixed anhydride in the course of synthesis of the anticancer agent tamoxifen.

Regioselectivity in Friedel-craftsacylation's can be quite sensitive to reaction solvent. In general para attack predominates for alkyl benzenes. The percentage of ortho attack increases with the electrophilicity of the acylium-ion. Moreover, by this method no rearranged alkylated product (ex.,Cumene) is formed as shown in Scheme 27.

Nucleophilic Aromatic Substitution

The replacement of hydrogen or a substitution by a nucleophilic reagent is known as nucleophilic aromatic substitution as shown in Scheme 28. It doesn't take place with the benzene itself but with its some substituted derivatives and with naphthalene. Synthetically important substitutions of aromatic compounds can also be done by nucleophilic reagents. There are several general mechanisms for substitution by nucleophiles. Unlike nucleophilic substitution at saturated carbon, aromatic nucleophilic substitution does not occur by a single-step mechanism. The broad mechanistic classes that can be recognized include addition-elimination, elimination-addition, and metal catalyzed processes.

Unimolecular substitution

Unimolecular nucleophilic substitution reactions proceed by a two-stage mechanism in which heterolysis precedes reaction with the nucleophileex, uncatalysed decomposition of aryl diazonium cation (Scheme 29). The unimolecular reaction is characterized experimentally by first-order kinetics-i.e., by a rate that depends only on concentration of the substrate (and not the nucleophile), by the absence of effects of steric hindrance, by powerful facilitation of the reaction by the presence of electron-releasing groups attached to the reaction center, and by variable, and often diagnostic, stereochemistry.

Bimolecular substitution

In bimolecular nucleophilic substitution reactions in which the substrate is attacked at a saturated carbon atom, the starting material has a tetrahedral structure, and the transition state has a trigonal bipyramidal structure. The mechanism of this reaction is characterized by entry of the nucleophilic reagent from one side of the substrate molecule and departure of the ion from the other side as illustrated in Scheme 30.

Aryl diazonium ions as synthetic intermediates

The first widely used intermediates for nucleophilic aromatic substitution were the aryl diazonium salts. Aryl diazonium ions are usually prepared by reaction of aniline with nitrous acid, which is generated in situ from a nitrite salt.Unlikealiphatic diazonium ion, which decompose very rapidly to molecular nitrogen and a carbocation, aryl diazonium ions are stable enough to exist in solution at room temperature and below. They can also be isolated as salts with non-nucleophilic anions, such as tetrafluroborate or trifluroacetate. Salts prepared with *o*-benzene disulfonimidate (Scheme 31) also appear to have potential for synthetic application [55].

The steps in forming a diazonium ion are addition of the nitrosonium ion, NO^+, to the amino group, followed by elimination of water as shown in Scheme 32.

In addition to the aqueous method for diazotization in aqueous solution, diazonium ions can be generated in organic solvents by reaction with alkyl nitrites as shown in Scheme 33.

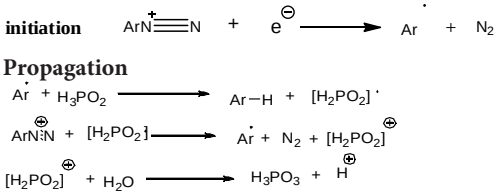
Diazonium ions form stable adducts with certain nucleophiles such as sec. amines and sulfide-anions. These compounds can be used as precursors of diazonium ion intermediates as illustrated in Scheme 34.

There are several general mechanisms by which substitution can occur. One involves unimolecular thermal decomposition of the diazonium ion, followed by capture of the resulting aryl cation by a nucleophile. The phenyl cation is very unstable and therefore highly unselective [56]. Either the solvent or an anion can act as the nucleophile as shown in Scheme 35.

Another mechanism for substitution is adduct formation followed by collapse of adduct with loss of nitrogen as shown in Scheme 36.

A third mechanism involves redox processes, and it is particularly likely to operate in reactions in which copper salts are used as catalysts as shown in Scheme 37 [57].

Reductive dediazonization: Replacement of a nitro or amino group by hydrogen is sometimes required to a synthetic operation in which the substituent was used to control the position selectivity of a prior transformation. The best reagents for reductive dediazonationare H_3PO_2, $NaBH_4$, etc. The reduction by H_3PO_2 proceeds by one electron reduction followed by loss of nitrogen and formation of the phenyl radical [58]. The hypophosphorous acid then serves as a hydrogen atom donor.



Phenols form diazonium ion intermediates: Aryl diazonium

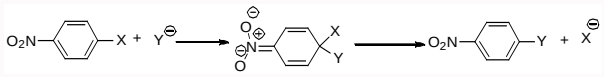


Figure 1:

ions can be converted to phenols by heating in water. Under these conditions, there is probably formation of a phenyl cation as shown in Scheme 38.

Aryl halides from diazonium ion intermediates: Aryl bromides and chlorides are prepared by a reaction using appropriate Cu(I) salt which is known as the Sandmeyer reaction. The Sandmeyer reaction occurs by an oxidative addition reaction of the diazonium ion with Cu(I) and halide transfer from a Cu(III) intermediate as illustrated in Scheme 39.

Reaction of anilines with alkyl nitrites and Cu(III) halides in Acetonitrile gives good yields of aryl-halides [59]. Fluorine substituents can also be introduced via diazonium ions. One procedure is to isolate aryl diazonium tetrafluroborate. These decompose thermally to give aryl-fluorides [60], Called the schiemann reaction, it probably involves formation of an aryl cation that abstracts fluoride ion from the tetrafluroborate anion as shown in Scheme 40 [61].

Aryl diazonium ions are converted to iodides in high yield by reaction with iodide salts. This reduction for aryl-iodide formation is initiated by reduction of the diazonium ion by iodide. The aryl radical then abstracts iodine from either I_2 or I_3^-. A chain mechanism then proceeds and consumes I^- and ArN_2 evidence for the involvement of radicals includes the isolated of cyclized products from *o*-allyl derivativesas shown in Scheme 41.

Introduction of Other Nucleophiles Using Diazonium Ion Intermediates: Cyano and azido groups are also readily introduced *via* diazonium intermediates. Reaction of diazonium salts with azide ion gives adducts that smoothly decompose to nitrogen and the aryl azide as shown in Scheme 42 and Scheme 43.

Meerwein arylation reactions: Aryl diazonium can be used to form certain types of C-C bonds. The copper-catalyzed reaction of diazonium ions with conjugated alkenes results in arylation of alkene, known as the Meerwein arylation reaction. The reaction sequence is initiated by reduction of the diazonium ion by Cu(I). The aryl radical adds to the alkene to give a new beta-aryl radical. The final step is a ligand transfer that takes place in the copper coordination sphere. An alternative course is oxidation deprotonation, which gives a styrene derivative as shown in Scheme 44.

Substitution by the addition-elimination mechanism

The addition of a nucleophile to an aromatic ring, followed by elimination of substituent results in nucleophilic substitution (Figure 1).

The addition-elimination mechanism has been used for arylation of oxygen and nitrogen nucleophiles. The pyridine family of heteroaromatic nitrogen compound is reactive toward nucleophile substitution at the C(2) and C(4) positions. The nitrogen atom serves to activate the ring towards nucleophilic attack by stabilizing the addition intermediate this kind of substitution reaction is especially important in chemistry of pyrimidines Scheme 45.

A variation of the aromatic nucleophile substitution process in which the leaving group is front of the entering nucleophile has been

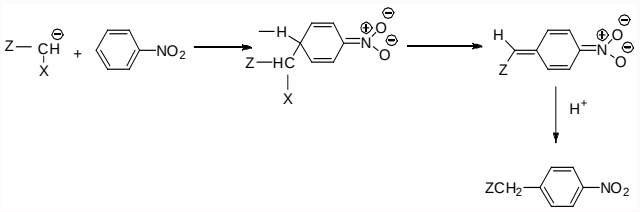


Figure 2:

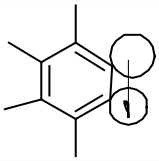


Figure 3: Benzyne molecule the sideways overlap pi sp^2 orbitals a sigma bonds out of the plane of the aromatic sigma-cloud.

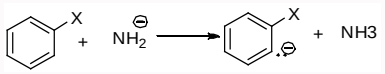


Figure 4:

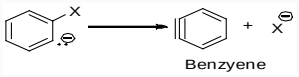


Figure 5:

developed and known as vicarious nucleophilic aromatic substitution (Figure 2).

Substitution by the elimination-addition mechanism

The elimination-addition mechanism involves a highly unstable intermediate called dehydrobenzene or benzyne as shown in Scheme 46 [62].

A unique feature of this mechanism is that the entering nucleophile doesn't necessarily become bound to the carbon to which the leaving group was attached as shown in Scheme 47 and Scheme 47(a) (Figure 3).

This new bond orbital lies along the side of the ring and has little interaction with the sigma cloud lying above and below the ring. The sideways overlap isn't very good, so bond is weak and benzyne is highly reactive molecule.

Benzyne formation elimination step involves two steps;

(1) Abstraction of hydrogen ion by the amide ion to form NH_3 and Carbanion (Figure 4).

(2) Carbanion loss halide ion to form benzyne (Figure 5).

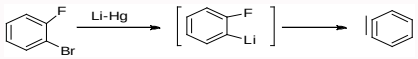
Addition steps also involve two steps as shown in Scheme 48;

(a) Attachment of amide ion to form carbanion.

(b) Carbanion abstracts a hydrogen ion form acid, NH_3.

There are several methods for Benzyne generation such as;

(1) Benzyne can also be generated from *o*-dihaloaromatic. Reaction with Li-Hg or magnesium results in the formation of transient organometallic compounds that decompose with



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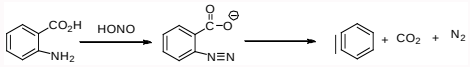
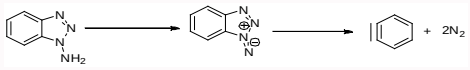


Figure 7:



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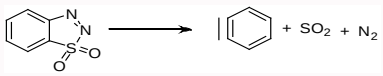

Figure 9:

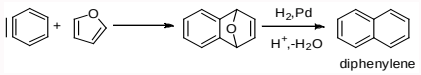

Figure 10:

elimination of lithium halide (Figure 6).

(2) Diazotization of o-amino benzoic acid, (Figure 7).

(3) Oxidation of 1-aminobenzotriazole, (Figure 8).

(4) By benzothiadiazide-1, 1-dioxide, (Figure 9).

Reactions of benzyne,

(1) With dienes[4+2] cycloaddition products are formed (Figure 10).

(2) Benzyne gives both [2+2] cycloaddition and end reaction products with simple alkenes, (Figure 11), Scheme 49.

Substitution by the $S_{RN}1$ mechanism

The distinctive feature of the $S_{RN}1$ mechanism is an electron transfer between the nucleophile and the aryl-halide the overall reaction is mainly a chain process.

Initiation: (Figure 12).

Propagation: (Figure 13).

A potential advantage of the $S_{RN}1$mechanism is that it is not particularly sensitive to the nature of other aromatic ring substitution although EWG substitution favors the nucleophile addition step.

Nucleophile which shows $S_{RN}1$ mechanism; ketone enolates, ester enolates, amide enolates, 2, 4 pentanediene dianion, pentadienyl and indenyl carbanion phenolates, phosphides and thiolates.

The reactions are frequently initiated by light, which promotes the initially electron transfer. As for other radical chain process the reaction is sensitive to substances that can intercept the propagation intermediates Scheme 50.

Conclusion

Based on our interest on organic chemistry [63A-U], we summarized the mechanism, different derivatives of aromatic

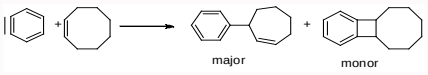

Figure 11:

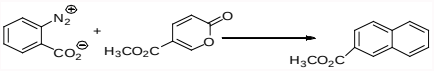

Figure 12:

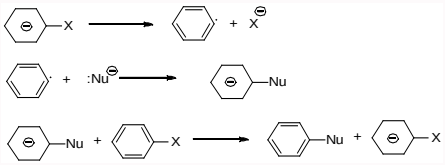

Figure 13:

substitution reaction. Different types of aromatic substitution reaction like nitration, halogenation, Friedel-Crafts alkylation and acylation reaction were also discussed. Nucleophilic aromatic substation reactions were also covered in this review article.

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Conflict of Interest

The author confirms that there is no conflict of interest for this publication.

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