The OSCAR PUBLISHING Services
American Journal of Applied Science and Technology

VOLUME Vol.05 Issue 10 2025
PAGE NO. 65-69
DOI 10.37547/ajast/Volume05Issue10-14

Halogenation And Nucleophilic Aromatic Substitution Reactions Of Aromatic Carboxylic Acids

Karimov Javohir Sobirzoda

Assistant of the Department of Medical and Biological Chemistry, Bukhara State Medical Institute named after Abu Ali ibn Sino, Uzbekistan

Received: 19 August 2025; **Accepted:** 15 September 2025; **Published:** 17 October 2025

Abstract: This study explores the halogenation of aromatic carboxylic acids through electrophilic aromatic substitution (EAS) and their subsequent use in nucleophilic aromatic substitution (SNAr) reactions, emphasizing the preservation of the carboxylic group (-COOH). The analysis covers reaction mechanisms, empirical and theoretical approaches, and the evolution of these processes from classical methods, such as $Br_2/FeBr_3$ halogenation, to modern eco-technological innovations like NBS/carborane catalysis and electrochemical SNAr. Classical methods yield 70-90% but are limited by high waste and corrosion, while modern approaches achieve up to 95% selectivity at room temperature with minimal environmental impact. Challenges like decarboxylation and low selectivity are addressed using microwave reactors or pressurized systems. The study provides practical recommendations for selecting optimal synthesis methods based on yield, selectivity, environmental sustainability, and waste minimization, proposing the integration of NBS/carborane and electrochemical SNAr for efficient, eco-friendly organic synthesis.

Keywords: Aromatic carboxylic acids, electrophilic aromatic substitution, nucleophilic aromatic substitution, halogenation, benzoic acid, NBS/carborane catalysis, electrochemical SNAr, meta-selectivity, eco-technology, organic synthesis.

INTRODUCTION:

In the field of organic chemistry, particularly the functionalization processes of aromatic carboxylic acids such as benzoic acid and its derivatives, hold significant importance in industries like pharmaceuticals, materials science, and agrochemistry. These compounds are widely utilized due to their molecular structural flexibility and the ability to modify biological activity. This article focuses on the analysis of halogenated aromatic carboxylic acids as intermediate products formed through electrophilic aromatic substitution (EAS) halogenation reactions, their subsequent use as substrates in nucleophilic aromatic substitution (SNAr) reactions, while preserving the carboxylic group (-COOH), along with examinations of reaction mechanisms and empirical as well as theoretical approaches from the literature. A systematic review of the literature reveals that EAS and SNAr mechanisms, initially explored through the foundational works of J. F. Bunnett in the early decades of the 20th century, have significantly evolved with modern catalytic and eco-technological innovations, particularly electrochemical methods, which enhance the efficiency and selectivity of these processes. Thus, this article aims to provide practical recommendations for selecting optimal methods for new syntheses, in addition to analyzing existing literature, striving to harmonize the theoretical and practical aspects of organic synthesis.

Halogenation Reactions: Synthesis of Intermediates in Aromatic Carboxylic Acids

Halogenation reactions involving aromatic carboxylic acids, particularly through the electrophilic aromatic substitution (EAS) mechanism, represent a cornerstone in organic synthesis for producing valuable chemical intermediates. These reactions are pivotal in the preparation of compounds such as 3-halobenzoic acids, which serve as precursors in the synthesis of pharmaceuticals, agrochemicals, and other fine chemicals. The unique reactivity of aromatic carboxylic acids, such as benzoic acid, stems from the presence of

the carboxylic group (-COOH), which profoundly influences the regioselectivity and kinetics of the halogenation process.

In the context of EAS, the halogenation of aromatic carboxylic acids is characterized by the preferential substitution of halogen atoms—chlorine, bromine, or iodine—at the meta-position relative to the carboxylic group. This regioselectivity arises due to the electron-withdrawing nature of the -COOH group, which exerts a deactivating effect on the aromatic ring. The carboxylic group, being a strong electron-withdrawing substituent, reduces the electron density of the ring, thereby decreasing its reactivity toward electrophilic attack. This deactivation directs incoming electrophiles, such as halogen cations (e.g., Br^+ or Cl^+), to the meta-position, where the electron density is relatively less affected compared to the ortho and para positions. As a result, products like 3-bromobenzoic acid or 3-chlorobenzoic acid are formed with high selectivity, making this process a reliable method for synthesizing meta-substituted intermediates.

The mechanism of halogenation via EAS involves several key steps. Initially, the halogen molecule (e.g., Br_2 or Cl_2) is activated, often in the presence of a Lewis acid catalyst such as $FeBr_3$ or $AlCl_3$, to generate a more electrophilic species. For example, in bromination, Br_2 interacts with $FeBr_3$ to form a polarized complex, producing a bromonium ion (Br^+) or its equivalent. This electrophile then attacks the aromatic ring of benzoic acid, forming a sigma complex (arenium ion) as an intermediate. The stability of this sigma complex is lower at the ortho and para positions due to the electron-withdrawing effect of the -COOH group, which destabilizes the positive charge in the transition state. Consequently, the meta-position, being less affected by this deactivation, becomes the preferred site for substitution. The final step involves the loss of a proton from the sigma complex, restoring aromaticity and yielding the halogenated product.

One of the primary advantages of this halogenation process is its ability to produce well-defined intermediates while preserving the carboxylic group, which can serve as a versatile functional handle for further synthetic transformations. For instance, 3-bromobenzoic acid can undergo subsequent reactions, such as nucleophilic substitution or cross-coupling reactions (e.g., Suzuki or Heck coupling), to introduce additional functional groups, thereby expanding the molecular complexity. This makes halogenation a critical step in multi-step organic syntheses, particularly in the production of active pharmaceutical ingredients (APIs) and specialty chemicals.

Despite its synthetic utility, the halogenation of aromatic carboxylic acids presents several challenges, particularly when scaled up for industrial applications. The deactivating effect of the carboxylic group necessitates harsh reaction conditions, such as elevated temperatures, prolonged reaction times, and the use of excess halogen reagents. These conditions not only increase energy consumption but also generate significant amounts of waste, including unreacted halogens and byproducts, which pose environmental and economic concerns. Additionally, the use of strong Lewis acid catalysts can lead to safety hazards, such as the release of corrosive gases or the formation of unwanted side products. For example, over-halogenation may occur under forcing conditions, leading to di- or poly-halogenated products, which reduce the yield of the desired mono-halogenated intermediate.

To mitigate these challenges, ongoing research focuses on developing milder and more sustainable halogenation methods. For instance, the use of alternative catalysts, such as zeolites or supported metal catalysts, has shown promise in reducing the reliance on harsh Lewis acids. Additionally, greener halogenating agents, such as N-halosuccinimides (e.g., NBS or NCS), have been explored to achieve selective halogenation under milder conditions. These advancements aim to enhance the efficiency, selectivity, and environmental compatibility of the process, making it more viable for large-scale production.

In conclusion, the halogenation of aromatic carboxylic acids via electrophilic aromatic substitution is a powerful synthetic tool for generating meta-substituted intermediates, such as 3-halobenzoic acids, which are essential building blocks in organic synthesis. The electron-withdrawing effect of the carboxylic group governs the regioselectivity of the reaction, ensuring high meta-selectivity, while the preserved carboxylic functionality offers versatility for further transformations. However, the requirement for harsh reaction conditions highlights the need for continued innovation in catalyst design and reaction methodologies to improve efficiency and sustainability. By addressing these challenges, halogenation reactions can remain a vital component of synthetic chemistry, enabling the production of complex molecules with applications across diverse industries.

Mechanism

The electrophilic aromatic substitution mechanism consists of two main stages. In the first stage, a halogen molecule, such as bromine (Br_2), is converted into an electrophilic species (Br^+) under the influence of a Lewis acid catalyst, like $FeBr_3$ or $AlCl_3$. Then, the

aromatic ring attacks this electrophile, forming a resonance-stabilized sigma-complex (arenium ion), whose energy state is optimized due to the inductive and resonance effects of the carboxylic group at the meta-position. In the second stage, deprotonation of the sigma-complex results in the halogenated product, ensuring the irreversibility and meta-selectivity of the process. A classic example of this mechanism is illustrated by the following reaction equations:

$Br_2 + FeBr_3 \rightarrow Br^+ + FeBr_4^-$

Aromatic ring + Br^+ → Sigma-complex (at meta-position)

Sigma-complex + $FeBr_4^-$ → Product + HBr + $FeBr_3$

Literature highlights that the deactivating effect of the carboxylic group slows down the reaction kinetics, so protective strategies, such as converting the carboxylic group to a methyl ester followed by hydrolysis, help reduce the risk of polyhalogenation.

A in-depth analysis of the literature indicates that traditional halogenation methods, such as $Br_2/FeBr_3$, provide 70-90% yields but have limited industrial application due to their corrosive nature and high waste generation. To address this, modern approaches based on N-bromosuccinimide (NBS) and carborane catalysts are proposed, offering up to 95% selectivity at room temperature with minimal waste. For instance, 2024 studies on the NBS/carborane system demonstrated 95% yield in meta-halogenation, providing ecological and economic advantages over classical methods. To prevent ortho-halogenation, a carboxylic group protection strategy is employed, represented by the following sequence: Benzoic acid (C_6H_5COOH) is converted to methyl ester:

$C_6H_5COOH + CH_3OH \rightarrow C_6H_5COOCH_3$ (catalyst: H_2SO_4).

The esterified compound is brominated at the meta-position using NBS/carborane: $C_6H_5COOCH_3$ + NBS → $3BrC_6H_4COOCH_3$. Deprotection:

$3BrC_6H_4COOCH_3 \rightarrow$ 3-BrC_6H_4COOH (via hydrolysis).

These intermediates, such as 3-bromobenzoic acid, serve as ideal substrates for nucleophilic aromatic substitution reactions, but due to the low reactivity of meta-position halogens, additional activating groups, like nitro groups, are necessary.

Nucleophilic Syntheses: SNAr Reactions

In nucleophilic aromatic substitution (SNAr) reactions based on halogenated aromatic carboxylic acids, halogen atoms (e.g., Cl, Br) act as good leaving groups. In this process, the halogen is replaced by a nucleophile (e.g., hydroxide OH^-, amine NH_2^-, or alkoxide RO^- ions). The carboxylic group (-COOH) possesses electron-withdrawing properties, reducing the electron density of the aromatic ring, which increases the reaction rate and selectivity, especially for ortho- (position 2) or para-position (position 4) halogens.

For meta-position (position 3) halogens, SNAr reaction activity is low because the electron deficiency is less pronounced. Therefore, additional activating groups or catalysts are required to accelerate the reaction at the meta-position. However, the carboxylic group helps make the reaction conditions milder (lower temperature and pressure).

The SNAr mechanism is based on an addition-elimination process. In this: The nucleophile attacks the aromatic ring, forming an intermediate compound called the Meisenheimer complex. This complex is stabilized through resonance due to the electron-withdrawing effect of the carboxylic group at the ortho- or para-position. Then, the halogen (leaving group) is eliminated, forming the new product. The kinetics of this reaction are typically first-order, with the carboxylic group's influence lowering the activation energy, meaning the reaction occurs faster.

Alternative mechanism: Under strong bases (e.g., NaOH) and high temperatures (350°C), an elimination-addition (benzyne) mechanism operates. However, under such conditions, the carboxylic group may undergo decarboxylation (i.e., CO_2 release), reducing the reaction's efficiency.

Example: When 2-chlorobenzoic acid (C_6H_5COOH with Cl at position 2) reacts with hydroxide (OH^-), the following product is formed:

$C_6H_5COOH(2\text{-}Cl) + OH^- \rightarrow C_6H_5COOH(2\text{-}OH) + Cl^-$

In this process, chlorine (Cl) is replaced by the hydroxide group.

Starting from late 19th-century research, fluoro-substituents (F) stand out as the best leaving groups in nucleophilic aromatic substitution (SNAr) reactions. The high reactivity of the fluorine atom increases the reaction rate by 10^3–10^5 times. A systematic analysis of the literature shows that classical SNAr reactions, such as the reaction of 2,4-dinitrofluorobenzene with amines, achieve 80–95% yields but require high temperatures and harsh conditions. In the case of carboxylic acids, for example, the reaction of 4-fluorobenzoic acid with hydroxide (OH^-) is represented by the following equation:

Among modern approaches, electrochemical nucleophilic aromatic substitution (SNAr) holds particular significance. This method allows processing electron-rich fluoroarenes without catalysts, achieving up to 90% yields. This is discussed in detail in 2024 studies. To enhance SNAr activity in meta-halogens, activating groups like nitro ($-NO_2$) are added, based on

empirical data from over 150 years of research.

Challenges

Reactions face issues such as decarboxylation of the carboxylic group (CO_2 release) and low selectivity. However, microwave reactors or pressurized systems significantly mitigate these problems, thereby increasing reaction efficiency.

Selecting the Optimal Synthesis Method

For new syntheses, especially in producing pharmaceutical substances or functional materials, the following criteria are considered in selecting the optimal method:

Yield: Maximum product quantity.

Selectivity: High percentage of the desired isomer.

Environmental sustainability: Minimizing environmental harm.

Waste quantity: Minimizing by-products.

These criteria are reinforced by empirical data from literature and thermodynamic calculations. The integration of modern catalytic systems further enhances the efficiency of reaction processes.

Diagrammatic Comparison

The following table compares classical and modern SNAr methods:

Method Type	Advantages	Disadvantages	Applications
Classical EAS ($Br_2/FeBr_3$)	Provides high yield (80-90%) and inexpensive reagents, effective in simple laboratory conditions with good control over meta-selectivity.	Harsh conditions (high temperature and excess halogen) increase corrosion and waste, leading to environmental issues.	Simple laboratory synthesis and educational purposes.
NBS/Carborane-Catalyzed Halogenation	Offers high selectivity (95%) at room temperature with minimal waste, providing eco-technological superiority and 100% retention of the carboxylic group.	The cost of the catalyst and requirement for special synthesis conditions may limit scalability.	Eco-technological industrial synthesis and pharmaceutical production.
Classical SNAr (High T, NaOH)	Universal application and simple reagents provide quick results on a small scale.	Low selectivity and risk of -COOH decarboxylation at high temperatures.	Small-scale organic synthesis and fundamental research.
Electrochemical SNAr	Achieves 90% yield at room temperature without catalysts, reducing energy consumption and increasing selectivity.	Requires special electrodes and equipment, complicating industrial transition.	Modern pharmaceutical synthesis and sustainable chemistry processes.

For new syntheses, the combination of NBS/carborane-catalyzed halogenation and electrochemical SNAr is considered optimal, as it fully preserves the carboxylic group while providing over 90% yield. For example, from 3-bromobenzoic acid, nitro-activation followed by SNAr to obtain amino-hydroxybenzoic acid is performed in the following sequence:

CONCLUSION

This article analyzes the halogenation of aromatic carboxylic acids via electrophilic aromatic substitution (EAS) and their subsequent application in nucleophilic aromatic substitution (SNAr) reactions. Classical methods (e.g., $Br_2/FeBr_3$) provide high yields (70-90%) but are limited by corrosion and high waste. Modern approaches, including NBS/carborane-catalyzed halogenation and electrochemical SNAr, offer up to 95% selectivity at room temperature with minimal waste, providing ecological and economic advantages. Issues like carboxylic group decarboxylation and low selectivity are mitigated through microwave reactors or pressurized systems. In selecting the optimal synthesis method, criteria such as yield, selectivity, environmental sustainability, and waste quantity are considered. The combination of NBS/carborane and electrochemical SNAr is recommended for new syntheses, enabling over 90% yield while preserving the carboxylic group, contributing to the theoretical and practical development of organic synthesis.

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