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A Study on Electrophilic Aromatic Substitution of Acetanilide

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Abstract: *Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic property. The literature review shows the study and preparation of acetanilide. The present work was planned to prepare acetanilide from different aldehydes. Acetanilide was prepared by reacting aniline, acetic anhydride and glacial acetic acid. The produced acetanilide is the substituted with different aromatic aldehydes.[1]*

Electrophilic Aromatic Substitution (EAS) of acetanilide involves the substitution of a hydrogen atom on the aromatic ring of acetanilide by an electrophile. In this process, the nucleophilic aromatic ring reacts with the electrophile, and one of its hydrogens is replaced by the incoming substituent. Acetanilide, with the formula C8H9NO, consists of a benzene ring attached to an amide group (-NHCOCH3).

The preparation of acetanilide from aniline via electrophilic aromatic substitution is a well-established method in organic chemistry. The process involves the activation of the aniline ring by the amino group, which makes it highly reactive toward electrophilic acetylation. Acetic anhydride is commonly used as the acetylating agent due to its higher reactivity compared to glacial acetic acid. Acetanilide remains a key intermediate in the chemical and pharmaceutical industries, underscoring the importance of this reaction in organic synthesis.[1].

Keywords: Acetanilide, Aldehyde Derivatives, Benzene, Amide group, Aniline

I. INTRODUCTION

Electrophilic Aromatic Substitution (EAS) is a crucial reaction mechanism in organic chemistry, enabling the modification of aromatic compounds by replacing one of their hydrogen atoms with an electrophilic species. The mechanism of EAS is essential for understanding the reactivity and functionalization of benzene rings, which serve as the core structure in many important organic molecules. Acetanilide, a derivative of aniline ($C_6H_5NH_2$), provides an interesting example of EAS due to the influence of the electron-donating amide group ($–NHCOCH_3$) on the aromatic ring, which significantly affects its reactivity.

Acetanilide is a white organic solid compound used primarily in organic synthesis. N-phenylacetamide, acetanilide and acetaniline are other names of this compound. It was used in the past to treat fever and headache and was known as Antifebrin by its brand name. [2]

In an electrophilic aromatic substitution, the first step involves the generation of an electrophile. Common electrophiles for EAS reactions include species like halogen ions (Cl_2, Br_2), nitronium ion (NO_2^+), sulfonium ion (SO_3H^+), or even alkyl groups (R^+). Once the electrophile is generated, it interacts with the electron-rich aromatic ring, where the amide group of acetanilide makes the ortho- and para-positions more reactive. The electrophile attacks one of these positions, forming a sigma complex, also known as an arenium ion or carbocation intermediate. This intermediate is a high-energy species in which the aromaticity of the ring is temporarily disrupted. The final step in the mechanism involves the loss of a proton (H^+), which restores the aromaticity of the ring, resulting in the formation of the substituted aromatic compound.

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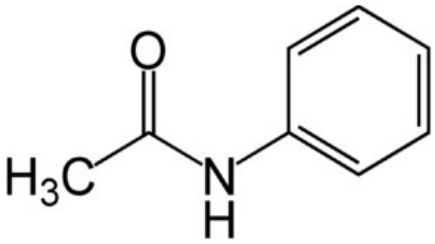
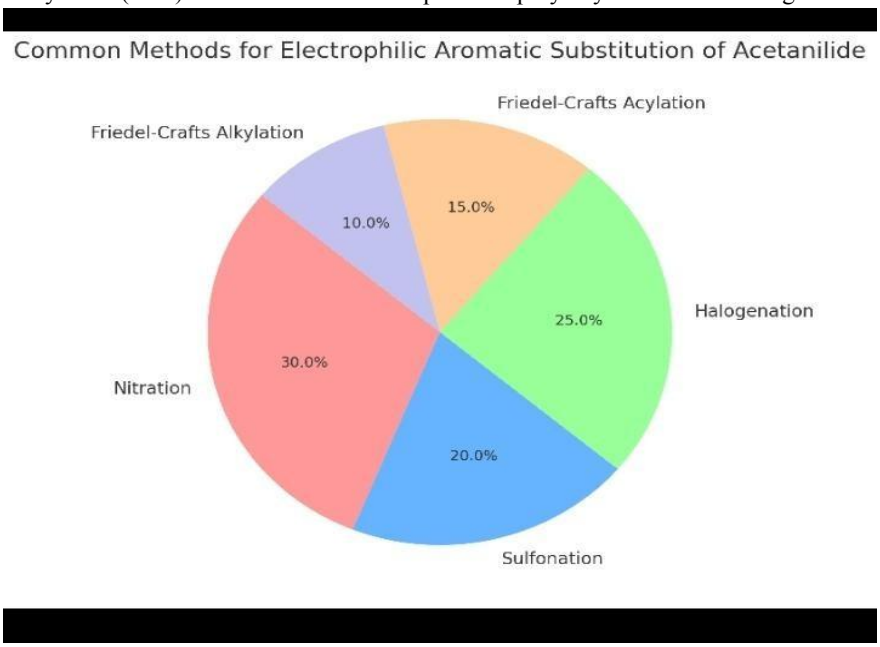


Fig.1. Structure of acetanilide [4]

Common methods for electrophilic aromatic substitution of acetanilide:

Electrophilic aromatic substitution (EAS) of acetanilide commonly occurs through the following reactions:

1. Nitration (30%) – Produces p-nitroacetanilide, useful in dye and pharmaceutical synthesis.
2. Sulfonation (20%) – Introduces a sulfonyl (-SO_3H) group, making the compound more water-soluble.
3. Halogenation (25%) – Selectively introduces halogens, crucial for agrochemicals and pharmaceuticals.
4. Friedel-Crafts Acylation (15%) – Adds an acyl group, modifying reactivity for further functionalization.
5. Friedel-Crafts Alkylation (10%) – Less common due to potential polyalkylation and rearrangements.



1. **Nitration of Acetanilide :**Nitration of acetanilide is a classic example of electrophilic aromatic substitution, where the acetamido group (-$NHCOCH_3$) directs the incoming nitro group primarily to the para position, with a lesser extent to the ortho position. The most common method employs a mixture of concentrated nitric acid and sulfuric acid, known as "mixed acid," to generate the nitronium ion (NO_2^+), the active electrophile in the reaction. Electrophilic aromatic substitution (EAS) reactions introduce electrophiles into the benzene ring of acetanilide, which is activated by the electron-donating –$NHCOCH_3$ group. The para position is typically favored due to steric hindrance at the ortho position.

2. Bromination of acetanilide :A common method for the bromination of acetanilide via electrophilic aromatic substitution involves dissolving acetanilide in glacial acetic acid and then adding a bromine solution in acetic acid. This reaction typically yields a mixture of ortho- and para-bromoacetanilide isomers, with the para isomer often being favored due to steric considerations.

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3. Sulphonation of acetanilide :A common method for the sulfonation of acetanilide involves the introduction of a sulfonic acid group ($-SO_3H$) onto the aromatic ring through an electrophilic aromatic substitution reaction. This process typically yields para-acetamidobenzenesulfonic acid as the major product due to steric and electronic effects.[7]

COMPARISON BETWEEN NITRATION OF ACETANILIDE , BROMINATION AND CHLORO-SULFONATION OF ACETANILIDE :

Reactions	Nitration of Acetanilide	Bromination of acetanilide	Chloro sulfonation of acetanilide
Reagents used	$HNO_3+H_2SO_4$	Br_2+Acetic acid	$Cl_2+H_2SO_4+SO_2CL_2$
Electrophile	NO_2^+(NITRONIUM ION)	Br^+(BROMONIUM ION)	SO_2CL^+(SULFOCHLORIDE ION)
Major product	p-nitroacetanilide	p-bromoacetanilide	p-chloro-sulfonyl-acetanilide
Minor product	o-nitroacetanilide	o-bromoacetanilide	o-chloro-sulfonyl-acetanilide
Reaction type	EAS	EAS	EAS
Otho/Para Directing	Para-directing due to the electron donating - $NHCOCH_3$ group	Para-directing due to the electron donating - $NHCOCH_3$ group	Para-directing due to the electron donating - $NHCOCH_3$ group
Deactivating or activating	Moderately activating(amide group)	Moderately activating(amide group)	Moderately activating(amide group)
Solvent used	Concentrated H_2SO_4	Acetic acid	H_2SO_4
Reaction condition	Cold condition (0-5°C) to prevent over nitration	Room temperature or slightly warm	Heated condition for better yield
Application	Used in dye and drug synthesis	Used in pharmaceuticals and agrochemicals	Used in sulfonamide drug synthesis

GENERAL MECHANISM OF ELECTROPHILIC AROMATIC SUBSTITUTION OF ACETANILIDE :

The Electrophilic Aromatic Substitution (EAS) of Acetanilide follows a general two-step mechanism:

1. Formation of the Arenium Ion (σ-Complex)

The benzene ring of acetanilide has an electron-donating amide ($-NHCOCH_3$) group, which activates the ring towards electrophilic attack. The incoming electrophile (E^+), such as NO_2^+ in nitration, attacks the ring at the para position (major product) due to resonance stabilization.

2. Restoration of Aromaticity

A base (like HSO_4^- in nitration) removes a proton from the carbon bearing the electrophile, restoring aromaticity and forming the final substituted product.[8],[9]

Mechanism of nitration of acetanilide :

The nitration of acetanilide is an electrophilic aromatic substitution reaction where a nitro group ($-NO_2$) is introduced into the aromatic ring of acetanilide. The acetamido group ($-NHCOCH_3$) is an electron-donating group that directs the nitration predominantly to the para position, yielding p-nitroacetanilide as the major product, with minor formation of o-nitroacetanilide.

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1. Generation of the Electrophile: A mixture of concentrated sulfuric acid (H_2SO_4) and nitric acid (HNO_3) is prepared. Sulfuric acid acts as a dehydrating agent, facilitating the formation of the nitronium ion (NO_2^+), the active electrophile in this reaction:

$$HNO_3 + 2H_2SO_4 \rightarrow NO_2^+ + H_3O^+ + 2HSO_4^-$$

2. Formation of the Sigma Complex (Arenium Ion): The nitronium ion attacks the electron-rich aromatic ring of acetanilide, primarily at the para position relative to the acetamido group. This forms a non-aromatic sigma complex (arenium ion).

3. Deprotonation and Restoration of Aromaticity: The sigma complex then loses a proton (H^+), and aromaticity is restored, resulting in the formation of p-nitroacetanilide.

Mechanism of chlorosulfonation of acetanilide

Chlorosulfonation of acetanilide involves the reaction of acetanilide with chlorosulfonic acid to produce p-acetamidobenzenesulfonyl chloride. The mechanism proceeds as follows:

1. Electrophilic Attack: Chlorosulfonic acid ($ClSO_3H$) acts as an electrophile. The sulfur atom, being highly electron-deficient, facilitates the generation of the electrophilic species.
2. Formation of σ-Complex: The electrophile attacks the aromatic ring of acetanilide, preferentially at the para position relative to the acetamido group due to both electronic and steric factors, forming a σ-complex.
3. Deprotonation: The σ-complex loses a proton, restoring aromaticity and yielding p-acetamidobenzenesulfonic acid.
4. Formation of Sulfonyl Chloride: Excess chlorosulfonic acid reacts with the sulfonic acid group, replacing the hydroxyl group with a chlorine atom, resulting in p-acetamidobenzenesulfonyl chloride.[16]

II. LITERATURE REVIEW

The preparation of acetanilide from aniline is a well-established and significant reaction in organic. chemistry, widely used in both laboratory and industrial settings. Acetanilide is produced by the acetylation of aniline, an aromatic amine, through electrophilic aromatic substitution (EAS). This reaction involves the introduction of an acetyl group (-COCH3) to the aniline molecule, producing acetanilide (C6H5NHCOCH3). The process is essential in the production of various chemicals, particularly in pharmaceuticals and dye industries.

The nitration of acetanilide is a fundamental reaction in organic chemistry, serving as a classic example of electrophilic aromatic substitution. This process involves introducing a nitro group ($-NO_2$) into the aromatic ring of acetanilide, resulting in the formation of nitroacetanilide isomers. Understanding this reaction is crucial due to its applications in synthesizing various compounds in pharmaceuticals, dyes, and agrochemicals.

In the nitration process, a nitronium ion (NO_2^+) acts as the electrophile, attacking the electron-rich aromatic ring of acetanilide. The reaction typically employs a mixture of concentrated nitric and sulfuric acids to generate the nitronium ion in situ. The acetamido group ($-NHCOCH_3$) present in acetanilide is an electron-donating group, which directs the incoming nitro group preferentially to the ortho and para positions on the benzene ring. However, due to steric hindrance at the ortho positions, the para-nitroacetanilide is often the major product.

Controlling reaction conditions is essential to achieve the desired product distribution and to prevent over-nitration. Maintaining low temperatures during the addition of the nitrating mixture helps minimize the formation of di-nitrated products. Additionally, the rate of addition and the concentration of reagents are carefully regulated to favor mono-nitration.

The significance of this reaction extends beyond academic interest; nitroacetanilide derivatives are valuable intermediates in the synthesis of various industrial products. For instance, they serve as precursors in the manufacture of dyes, pigments, and pharmaceuticals. Therefore, a comprehensive understanding of the nitration mechanism,

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regioselectivity, and factors influencing the reaction outcome is vital for chemists engaged in both research and industrial applications.[5]

A common approach to synthesizing chloro sulphonated acetanilide involves the stepwise introduction of chlorine and sulphonyl functional groups to the acetanilide core. Typically, chlorination is carried out using reagents such as thionyl chloride or phosphorus oxychloride, followed by sulphonation with sulfuric acid or chlorosulphonic acid Acetanilide is an organic compound commonly used as a precursor in the synthesis of various chemical compounds, including azo dyes and pharmaceuticals. It was historically used as an analgesic but has since been replaced due to safety concerns. The reaction for its synthesis from aniline is a classical example of an electrophilic aromatic substitution reaction, where an electrophile substitutes a hydrogen atom on the aromatic ring. [1]

The preparation of acetanilide from aniline is a well-established and significant reaction in organic. chemistry, widely used in both laboratory and industrial settings. Acetanilide is produced by the acetylation of aniline, an aromatic amine, through electrophilic aromatic substitution (EAS). This reaction involves the introduction of an acetyl group (-COCH3) to the aniline molecule, producing acetanilide (C6H5NHCOCH3). The process is essential in the production of various chemicals, particularly in pharmaceuticals and dye industries.

III. FUTURE SCOPE

The future scope of research into the electrophilic aromatic substitution reactions of acetanilide can focus on several aspects:

1. Green Chemistry Approaches: Developing eco-friendly solvents and reagents for EAS reactions to reduce environmental impact.
2. Substitution Pattern Modifications: Investigating how different substituents on the acetanilide molecules affect the regioselectivity of the substitution reaction.
3. Mechanistic Studies: Exploring the mechanism of EAS reactions in more detail to understand reaction pathways and intermediates.
4. Applications in Drug Synthesis: Electrophilic aromatic substitution reactions can be applied to the synthesis of pharmaceuticals and agrochemicals, where acetanilide derivatives play an
1. important role. [10], [11], [12]
5. Green Chemistry Innovations: The acetylation of aniline can be optimized by using greener reagents or solvents, reducing the use of toxic or harmful chemicals. Research into solvent-free reactions, or using alternative solvents like ionic liquids, could lead to more environmentally friendly methods of acetanilide preparation.
6. Catalysis and Efficiency: The use of catalysts in the acetylation reaction can enhance yield and selectivity. Developing more efficient catalysts or employing enzyme-based catalysts (biocatalysis) could improve the reaction's sustainability and efficiency.
7. Microreactor Technology: The use of microreactors in the synthesis of acetanilide is an emerging field. These reactors allow for precise control over reaction conditions, leading to more consistent products and potentially higher yields.
8. Optimization of Reaction Conditions: The reaction conditions (temperature, time, concentration, and solvent choice) are crucial for achieving high yields and purity of acetanilide. Future studies may focus on optimizing these parameters to reduce waste and increase efficiency.[13],[14],[15].

IV. CONCLUSION

The reaction involves the acetylation of aniline by acetic anhydride or glacial acetic acid, leading to the formation of acetanilide, an important organic intermediate. The acetanilide was isolated and purified through recrystallization, and the product exhibited a melting point of 169–170°C, which is consistent with the known value for pure acetanilide. The yield and purity of the product can be influenced by reaction conditions, but in general, this method provides a reliable and efficient way to synthesize acetanilide. [3]

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The reaction of acetanilide with chlorosulfonic acid results in the successful synthesis of chloro sulphonated acetanilide, where the introduction of both a chloro and sulfonic group enhances the reactivity of the molecule. The structure of the product is characterized by the electrophilic substitution of the acetanilide aromatic ring. This reaction provides a valuable intermediate that can be further utilized for the synthesis of various compounds in the chemical and pharmaceutical industries. The purity and yield of the product can be improved by careful control of reaction conditions, such as temperature and time, and through appropriate workup procedures like recrystallization. The electrophilic aromatic substitution reactions of acetanilide—specifically nitration, bromination, and sulfonation—demonstrate the significant influence of the acetamido group (-$NHCOCH_3$) on both the reactivity and regioselectivity of the aromatic ring.

In the nitration of acetanilide, the acetamido group, being an electron-donating substituent, activates the aromatic ring and directs the incoming nitro group to the ortho and para positions. However, due to steric hindrance at the ortho positions, the para-nitroacetanilide is predominantly formed. This selectivity is advantageous in synthetic applications where specific substitution patterns are desired. [6]

In sulfonation reactions, the acetamido group directs the sulfonic acid group (-SO_3H) to the ortho and para positions as well. However, the reaction conditions and the nature of the sulfonating agent can influence the product distribution. The para-substituted product is often favored due to similar steric considerations as observed in nitration and bromination.

In summary, the acetamido group in acetanilide plays a crucial role in directing electrophilic substitution reactions to the ortho and para positions, with para-substituted products often being predominant due to steric factors. Understanding these directing effects is essential for designing targeted synthetic pathways in organic chemistry.

REFERENCES

[1] K. P. A. A. A. R. M. G. S. S. P. G. Muthu Bhupathi, "synthesis, Characterization and antimicrobial activity of acetanilide derivative by using aromatic aldehyde and sulphonamide derivatives.," Research Journal of pharmacy and technology., vol. 9, 2016.

[2] B. B. Brodie and J. Axelrod, ". "The estimation of acetanilide and its metabolic products, aniline, N-acetyl p-aminophenol and p-aminophenol (free and total conjugated) in biological fluids and tissues",," J,Pharmacol.Exp. Ther., vol. 94, pp. 22-28, 1948.

[3] "Marri Laxman Reddy Institute of Pharmacy," Pharmaceutical Organic Chemistry-II, p. 9.

[4] l. B. Jayashree Raman, "Acetanilide structure, formula and properties," 2023.

[5] Lynch et al. "Nitrations of acetanilides by reagents of NO_2X type," Canadian Journal of Chemistry, Volume 46, pages 1141-1152. (1968)

[6] Moodie et al.,Perkin Transactions 2, Chemical Society, pages 1693-1705. 1977

[7]] P. Shashikala and D. Shruthi Keerthi, published in the Journal of Chemical and Pharmaceutical Research, 2016, pages 204-210.

[8] Clayden, Greeves, Warren, and Wothers – Organic Chemistry (2001), Page 1107 (Electrophilic Aromatic Substitution)

[9] Morrison and Boyd – Organic Chemistry (6th Edition), Page 628-630 (EAS and Acetanilide)

[10] J. E. McMurry, Organic Chemistry, 8th Edition, Brooks/Cole,, p. 821, 2011.

[11] J. D. &. C. M. C. Roberts, " Basic Principles of Organic Chemistry,," 2nd Edition, W. A. Benjamin, Inc., p. 399., 1977.

[12] G. W. &. D. M. S. Gokel, "The Mechanism of Electrophilic Aromatic Substitution Reactions in Acetanilide.," Journal of Organic Chemistry,, pp. 1210-1215, 1996.

[13]R. J. Sundberg, " Electrophilic Aromatic Substitution: Theory and Practice.," Synthesis and Reactivity in Organic Chemistry, pp. 789-803, 1996.

[14] M. B. &. M. J. Smith, " Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (5th ed.).," Wiley-Interscience.Chapter 13: Electrophilic Aromatic Substitution , pp. 504-536, 2001.

[15] " Electrophilic Aromatic Substitution.," Journal of the Chemical Society Perkin Transactions 1 , pp. 154-160.

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[16] "Chlorosulfonation of Acetanilide in a Dual-Temperature-Zone Silicon Carbide Microchannel Reactor and Synthesis of Sulfasalazine" by Zhang Zishu et al., Chinese Journal of Organic Chemistry, 2020, Volume 40, Issue 8, pages 2387-2393.