The Research on the Synthesis Method of Sulphonamide and the Scheme for Improving the Synthesis Technology

Tongying Liu [1, a], Mahanqi Mao [2, b]

[1] Shenzhen Senior High School, Shenzhen, Guangdong, China

[2] Beijing New Oriental Foreign Language School at Yangzhou, Yangzhou, Jiangsu, China

[a] 3408864672@qq.com, [b] mm2513@qq.com

Abstract. Sulphonamides, as one of the earliest classes of synthetic antibacterial agents, remain essential in pharmaceutical and chemical industries due to their broad-spectrum activity and versatile applications. This study reviews the classical multi-step synthesis of sulphanilamide, analyzing its reaction mechanisms, operational limitations, and environmental challenges, including high energy consumption, low yield, and the formation of toxic by-products. Through laboratory validation, the traditional route was confirmed to be feasible but inefficient, motivating the exploration of innovative synthesis technologies. Based on a comparative literature review, this paper examines three contemporary optimization strategies: continuous flow technology (CFT), green chemistry (GC), and electrochemical synthesis (ECS). Continuous flow technology improves reaction control, safety, and scalability; green chemistry promotes atom economy and environmental sustainability; and electrochemical synthesis introduces a waste-free, catalyst-efficient approach suitable for industrial application. Case studies from leading enterprises demonstrate that these methods significantly enhance product yield, reduce carbon emissions, and lower resource consumption. Despite these advancements, standardization, high equipment cost, and interdisciplinary technical barriers remain key challenges. The study concludes that integrating automation, artificial intelligence, and modular electrochemical systems may further advance sulphonamide synthesis toward sustainable industrial production.

Keywords: Sulphonamide; Green Chemistry; Continuous Flow Technology; Sustainable Pharmaceutical Production; Process Optimization.

1. Introduction

The discovery of sulfonamides was the original and most historically significant event, revolutionizing the field of medicine. The sulfonamide is primarily used as an antibacterial agent to treat various types of bacterial infections. Additionally, sulfonamides can act as diuretics, carbonic anhydrase inhibitors, and anti-inflammatories. Hence, sulfonamide plays an important role in pharmaceuticals and agrochemicals as a structural unit. Nowadays, there are various methods for synthesizing sulfonamides. To date, several issues have been identified in the synthesis of sulfonamides, including reagent stability, reaction conditions, operational steps, and environmental friendliness. For example, the classical method, the reaction between sulfonyl chloride and an amine, has highly stringent requirements for reaction conditions, as sulfonyl chloride is hydrolytically responsive and a corrosive and toxic reagent that should be handled with care. However, there are several methods for synthesizing sulfonamides, including oxidative coupling and the reaction with diphenylurea. Most have some challenges, such as function group tolerance, atomic economy, environmental impact, and cost and operation.

Hence, it is essential to optimize the traditional method by developing new reagents and processes, as well as optimizing existing conditions, to reduce the environmental impact of reagents and products, and minimize by-products, thereby increasing yield.

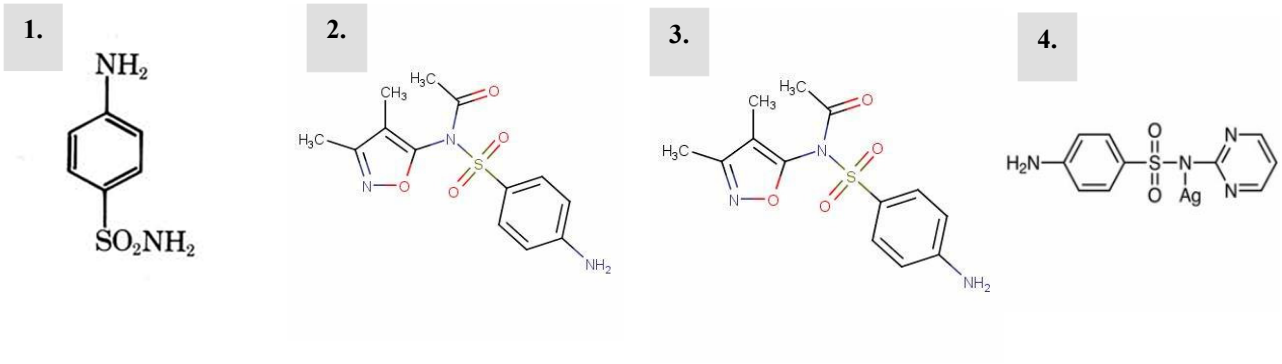

Figure 1. Common types of sulphanilamide. 1: Sulphanilamide, 2: Sulfisoxazole (SIZ), 3: Sulfamethoxazole (SMZ), 4: sulfadiazine silver

Sulphanilamide is a tertiary compound characterized by a central sulfur atom double-bonded to two oxygen atoms and singly bonded to both a substituted amine and an aniline group, forming its typical sulfonamide structure. Traditionally, it is synthesized through a five-step process: the reduction of nitrobenzene to aniline, acetylation to form acetanilide, chlorosulfonation to yield 4-acetaminobenzenesulfonyl chloride, subsequent amidation with ammonia to form 4-acetamidobenzenesulfonamide, and final acid hydrolysis to obtain pure sulphanilamide. This multi-step synthesis, while effective, involves complex reactions and multiple purification stages.

Based on this traditional method for synthesising sulphanilamide, we identified certain drawbacks and limitations associated with it. For instance, the reaction conditions are demanding, with numerous by-products generated during the process and a relatively low yield.

2. Conventional Sulphanilamide Synthesis Method

2.1 Detailed Mechanism

The synthesis of sulphanilamide follows a sequential reaction pathway involving reduction, acetylation, electrophilic substitution, amide formation, and deprotection. The process strategically employs a protecting group to ensure selective electrophilic substitution on the aromatic ring while preventing interference from the amino group.

In the first step, nitrobenzene is reduced to aniline using tin (Sn) and hydrochloric acid. During this reaction, hydrogenation targets the nitro group rather than the benzene ring because the energy barrier for nitro reduction is significantly lower. The nitro group undergoes progressive hydrogenation through hydroxylamine intermediates, eventually forming aniline.

Next, aniline undergoes acetylation with acetic anhydride to produce acetanilide. The nitrogen atom in aniline acts as a nucleophile. It attacks the carbonyl carbon of acetic anhydride, forming a tetrahedral intermediate that rearranges to release acetic acid and yield the protected amide.

The third stage involves chlorosulfonation, in which acetanilide reacts with chlorosulfonic acid ($ClSO_3H$) to generate p-acetamidobenzenesulfonyl chloride. Chlorosulfonic acid serves both as a reagent and solvent, forming electrophilic chlorosulfonic cations that attack the activated para-position of the benzene ring. The intermediate sulfonic acid subsequently converts into sulfonyl chloride ($-SO_2Cl$) under excess reagent.

The fourth stage proceeds through nucleophilic substitution, where ammonia reacts with the sulfonyl chloride to form 4-acetamidobenzenesulfonamide. The nitrogen atom of ammonia donates its lone pair to the electrophilic sulfur atom, forming a transient tetrahedral intermediate that collapses with chloride ion elimination, restoring the S=O bond.

Finally, acidic hydrolysis removes the acetyl protecting group to produce sulphanilamide. Protonation of the carbonyl oxygen enhances electrophilicity, allowing water to attack the carbonyl

carbon. The resulting intermediate decomposes, generating acetic acid and releasing the free amino group (-NH_2).

This multi-step mechanism efficiently constructs sulphanilamide by integrating protection–deprotection strategies and controlled electrophilic substitution, ensuring regioselective sulfonation while maintaining molecular integrity throughout the synthesis.

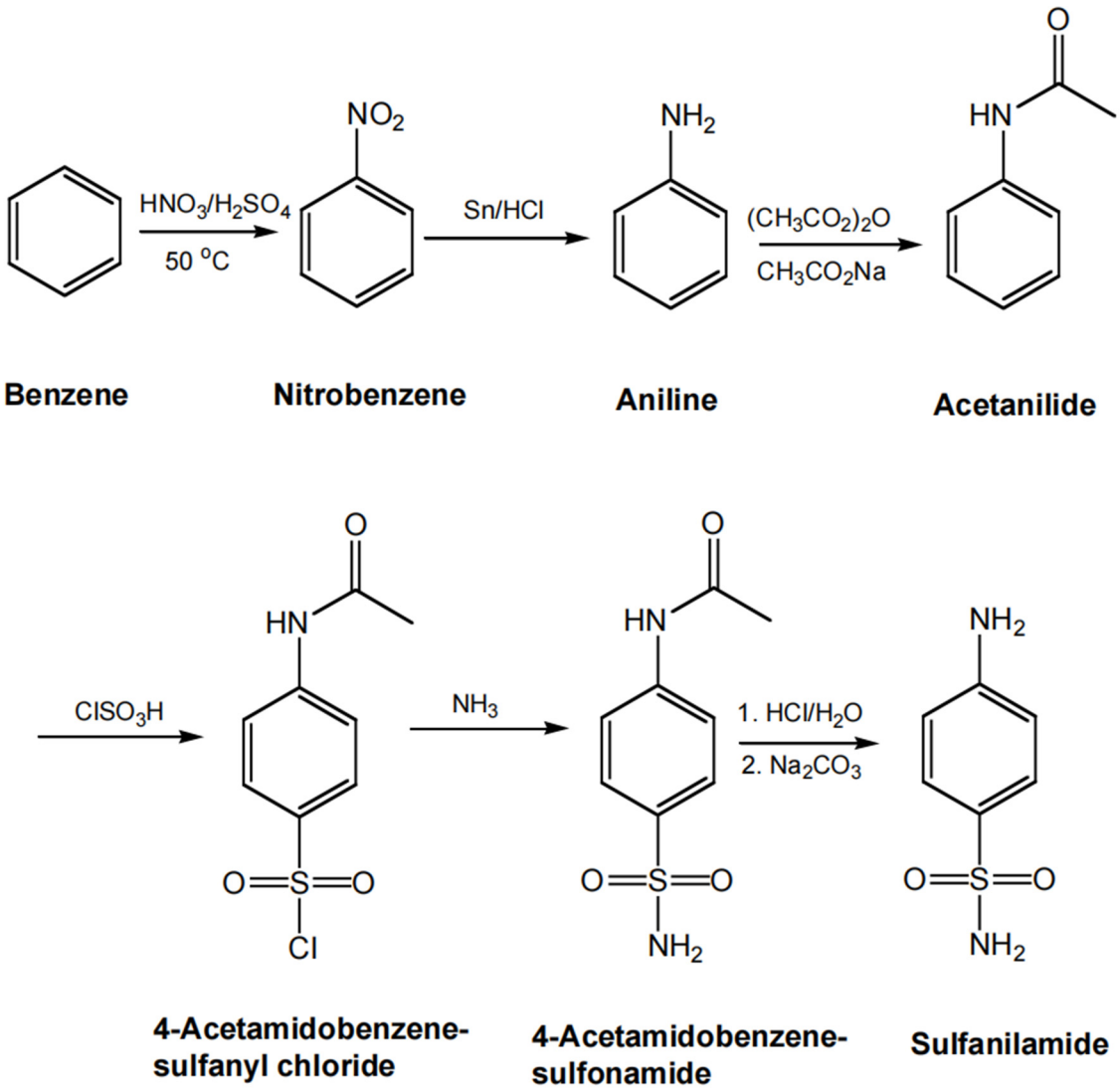

Figure 2. The pathway of sulphanilamide synthesis

2.2 Limitations of the Traditional Method

While the traditional way needs four steps of separating acetylation, chlorsulfonation, ammonolysis, and hydrolysis during the synthesis, which is quite cockamamie and needs a long time to complete the synthesis, for all products of each step, there is at least one hydrophilic group, which allows them to dissolve in water, resulting in product loss in the filtrate. Additionally, during the synthesis, many by-products, similar to those in the sulfonation reaction, can occur. The benzene ring may be substituted at the ortho and meta positions, producing a variety of by-products that increase the difficulty of separation and purification. Moreover, nitration, sulfonation, and other steps typically require high temperatures (100-200℃) or a strong amount of energy. Some reactions require control in an oxygen-free and anhydrous environment. Another disadvantage of using the traditional method is the low theoretical atomic economy of the reagent—a larger number of atoms are wasted in the form of the by-product. For example, only a portion of the sulfur element in the sulfuronation reagent is incorporated into the target product, while the remainder is discharged as waste acid. Hence the

theoretical atomic economy is about 0.504 (TAE = $\frac{total\ Mr\ of\ product}{total\ Mr\ of\ reagent} = \frac{172}{135+116.5+17+73} = 0.503$). The reaction does not meet the requirements of atom economy and sustainable development.

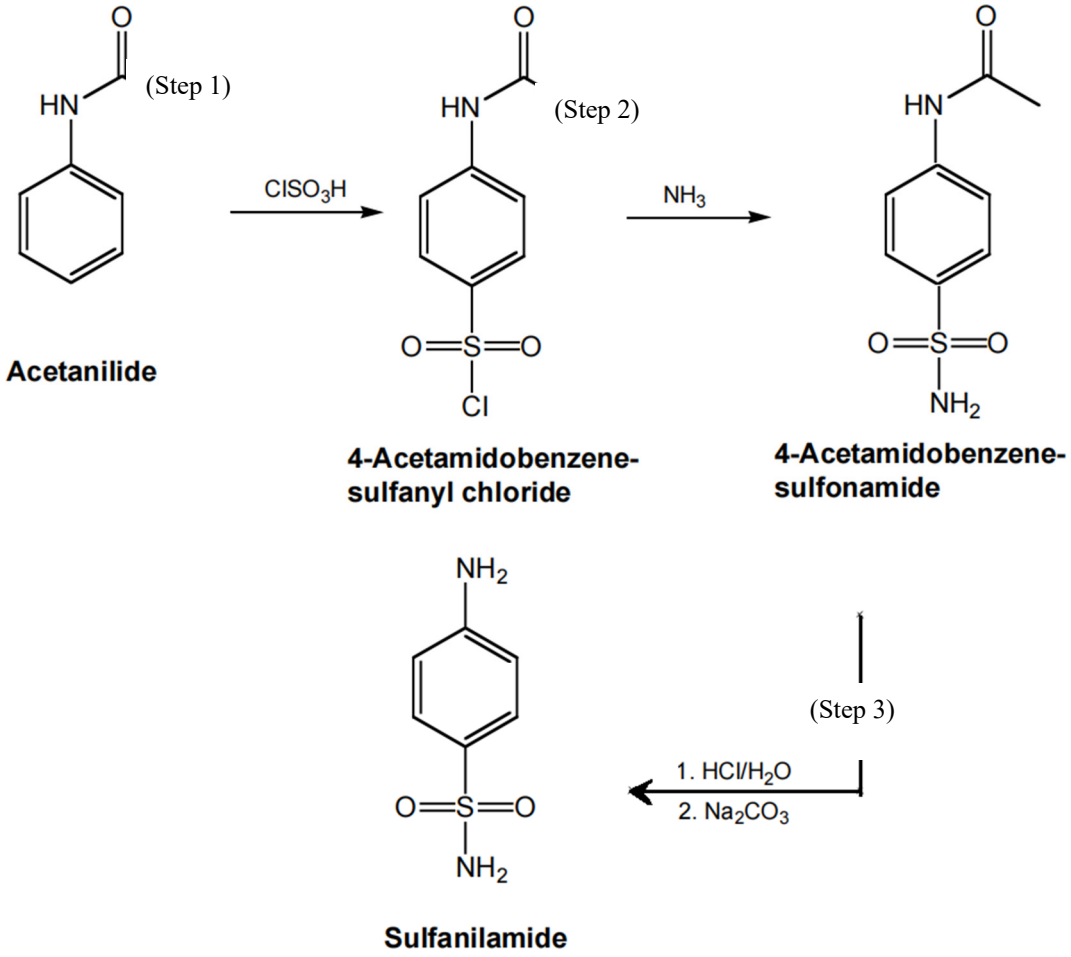

Figure 3. last two steps of sulphanilamide synthesis

In each step, numerous details must be addressed to increase yield or reduce the difficulty of separation. In step 01 much excess chlorosulfonic acid added will lead the step of washing sample to change the pH become more cockamamie; in step 02 the reaction has a highly require of the concentration of the solution of ammonia (at least 25%) ammonia to make sure the rate of the reaction not be too low; In step 03 if the acid is excess too much or the concentration of the base is too low too much water will be remained in the container which increase the difficulty of crystallizing (even need an additional step, rotary evaporation, before sucking filtration). Moreover, between steps, if the sample of product is not completely dry, it may stick to the inner wall of the sample bottle, resulting in unnecessary material waste. Furthermore, the sample experiences 3 times of sucking filtration, and some products are lost in the filtrate.

After completing several sets of experiments, the yield of the product is presented in Table 1 below. Due to the experimental conditions (the air pressure is barely able to reach the standard, which causes a difference in solubility for the product), it is not entirely the same. Hence, the extent of product loss during filtration varies. The yield in most groups is too low, as many reagents are wasted during transportation, separation, and other processes. Hence, the yield is not high.

Table 1. Yield of the synthetic product

Yield	Total
Group1	17.4%
Group2	14.5%
Group 3	34.3%
Group 4	9.3%
Group 5	32.8%
Average	21.7%

3. Research on the Improvement Methods of Sulphanilamide Synthesis Techniques

Based on our aforementioned research on the classical synthesis process of sulphanilamide, we can conclude that although the traditional method is feasible. The synthesis process is well-established; however, several problems are associated with the traditional sulphanilamide synthesis method, including a relatively low yield, high energy consumption in actual production due to stringent reaction conditions, and the presence of toxic and harmful substances during the reaction process that cause pollution and are difficult to handle. Therefore, it is necessary to develop some methods to improve the synthesis process. According to our literature review, numerous modified pathways exist based on different chemical principles. The improved solutions that have been widely adopted in recent years can be classified into three main categories based on their different principles: 1. Continuous flow technology (CFT), 2. Green chemistry, 3. Electrochemical synthesis (ECS). In the following article, we selected some typical cases from each category. Through the lens of improved chemical principles and data feedback after production, we examined the advantages of these cases over traditional synthesis methods.

3.1 Continuous Flow Technology

When synthesizing using traditional techniques, batch synthesis is usually employed. However, batch synthesis technology has several drawbacks. For instance, the mixing of reagents relies on the use of a stirring device. As the scale increases, efficiency declines, and this may also lead to an increase in by-products. Moreover, toxic substances are involved in the reaction, which may also pose safety risks. That is why the continuous flow technology is needed to optimise the traditional synthesising method.[5]

3.1.1 Case Study

To address the problems associated with traditional synthesis methods that arise from the increase in reaction scale, which lead to incomplete reactions, unstable intermediates, and difficulties in controlling heat release, Miao Yu et al. proposed a modified continuous process in 2019. With this method, the synthesis of 5-bromo-N-(tert-butyl) pyridine-3-sulfonamide can be successfully achieved. The reaction process of this technique mainly consists of three steps: 1. Using i-PrMgCl·LiCl and 3,5-dibromopyridine to react in THF to form the Grignard intermediate; 2. Sulfonation: The generated Grignard reagent reacts with SO_2Cl_2 in DCM to form sulfonic acid chloride 3. Amination: The sulfonic acid chloride solution is directly introduced into the DCM solution containing tert-butylamine to generate the target sulphonamide[6]

To be specific, the advantages of this technology can be summarised in the following aspects. First, the intrinsic safety of it should be highlighted. The traditional reaction takes place in a huge reaction vessel, where the hazardous substances stored therein are usually in tons. If the reaction gets out of control, it will lead to serious consequences. Continuous flow reactions are carried out in very small pipes. At any time, the amount of hazardous substances in the system is very small, making the danger more controllable. When a strongly exothermic reaction is initiated, the surface area of the flow reactor is larger, which can prevent heat accumulation and the occurrence of runaway reactions.

Moreover, the closed system also enables operators to avoid exposure to toxic and harmful volatile reagents while increasing the pressure inside the container, ensuring that the reactants remain in a liquid state throughout the process and thereby enhancing the reaction rate. Second, the control of the entire reaction has become more precise. The duration that the reactants remain in the container is precisely controlled, which is crucial for unstable intermediates. This ensures that they can continue to participate in the next reaction before decomposition, and the temperature and concentration within the entire system are nearly uniform, allowing for real-time monitoring. Third, the continuous flow technology circumvents the problems that arise in traditional reaction techniques, where an increase in reaction scale impacts the reaction outcome. The CFT involves increasing the number of reaction units, ensuring that the conditions in each unit are identical to those established in the laboratory.

3.1.2 Production Application

Continuous flow technology has currently been applied in production, and its improved effects have been confirmed. The '2025 China Industrial Sulfanilamide (SN) Data Monitoring Research Report' indicates that leading Chinese pharmaceutical companies such as Lu'an Pharmaceutical and Huabei Pharmaceutical have successfully applied micro-reactor technology on a large scale and achieved positive results.

The traditional synthesis of sulfonamides primarily employs batch or continuous reactions. The core problem lies in the uncontrolled high activity of intermediates and the low selectivity of the reaction. For instance, in the key chlorosulfonation step, the reaction between p-aminobenzene and chlorosulfonic acid is prone to generating polysulfonated by-products due to local overheating. After that, in the subsequent amide formation reaction, the hydrolysis loss of the sulfonyl chloride intermediate further reduces the industry average yield, which has remained at around 50%-68% for a long time. The technological breakthroughs of leading enterprises are reflected in dual-temperature zones, precise temperature control, and seamless integration of continuous flow. The yield of core products has generally exceeded 95%, directly driving the average industry yield in 2023 to rise from 78% in 2021 to 92%.

Traditional batch reactors rely on external heating to maintain reaction temperature, and the low mixing efficiency leads to reaction cycles lasting 8-12 hours, with the unit product's comprehensive energy consumption reaching as high as 1.2 tons per ton. The high specific surface area advantage of microreactors (up to 1000 times that of traditional reactors) reconfigures the heat transfer path:
In the production of sulfamethoxazole by Lu'an Pharmaceutical, a modular microchannel reactor was adopted. Through the jacketed heat transfer oil, the heat released during the reaction was removed in real time, allowing the optimal reaction temperature of 80°C to be maintained without additional heating. The reaction time per batch was reduced from 12 hours to 30 minutes, and the heating energy consumption was reduced by 40%.[7]

3.2 Green Chemistry

3.2.1 About Green Chemistry

The traditional synthetic production process is unsustainable in terms of resources, environment, and safety. The green blood transfusion is a set of theoretical and practical methods that emerged to address these issues.

According to the twelve principles of green chemistry, the core idea of green chemistry is to eliminate pollution at its source rather than dealing with it at the end of the reaction process, as is done in traditional methods.[8] There are mainly three strategies for improving the synthesis of sulfanilamide using green chemistry methods: 1. Selecting less harmful reaction media, such as preferentially using water as the reaction solvent. 2. Adopt more efficient synthesis strategies, such as one-pot synthesis methods and multi-component reactions, to reduce waste production and improve atomic economy. 3. Extensively employ catalytic methods to enhance reaction efficiency and reduce waste.[9]

3.2.2 Production Application

The '2019 Greener Synthetic Pathways Award' mentioned that Merck Company had made green chemical improvements to the production process of its antibiotic Zerbaxa. The company redesigned the synthetic route, reducing the number of reaction steps. For instance, through more efficient chemical reactions, multiple steps were integrated or replaced with simpler reactions, thereby avoiding the formation of unnecessary intermediate products. By adopting advanced crystallization purification technology, they have replaced traditional column chromatography and other separation methods. The crystallization process can more efficiently separate and purify products, thereby reducing reliance on organic solvents.

Moreover, environmentally friendly catalysts and reagents were selected to reduce the use of toxic and harmful chemicals. For instance, using biocatalysts or low-toxic chemical reagents can minimize the environmental impact and operator exposure during the production process. The synthesis route was redesigned to reduce the number of reaction steps. For example, through more efficient chemical reactions, multiple steps were integrated or replaced with simpler reactions, avoiding the generation of unnecessary intermediate products.

After the optimization, the cost of raw materials has decreased by approximately 30% - 40%. The output has increased by approximately 20% to 30% with the more efficient synthesis and purification processes. The water-saving effect is also remarkable. The consumption of water resources during the production process has been reduced by approximately 50%. The carbon footprint has been reduced by approximately 40 -50%. Energy consumption has decreased by approximately 30% to 40%.

From this, it is evident that the application of green chemical technology to optimize the production process of antibiotics has yielded significant results in multiple aspects, including resource utilization, cost control, and environmental protection. This demonstrates that green chemistry has significant application value and development potential in the production of antibiotics, enabling a win-win situation that balances economic benefits with environmental benefits.

3.3 Electrochemical Synthesis

3.3.1 Optimising with Electrochemical Synthesis

The electrochemical method achieves the conversion between electrical energy and chemical energy through electron transfer. In organic synthesis, organic electrocatalysis utilizes electrons as clean and controllable reagents to drive reactions, providing a more environmentally friendly and efficient approach to synthesis.

In 'Electrochemical Synthesis of Sulfonamide in Single-Pass Flow', Johannes Schneider, Stephan P. Blum, and Siegfried R. Waldvogel gave a detailed introduction to a new method for electrochemical flow synthesis of malonamide. Firstly, the new method utilizes electrons and achieves an atomic economy of 100%, thereby eliminating the generation of harmful waste at the source. Second, the new method does not require pre-functionalisation. It directly starts from unactivated raw materials (aromatic compounds, amines, SO2) and synthesises in one step. The raw materials are readily available and inexpensive, which not only reduces production costs but also avoids the hazardous situation caused by the instability of toxic substances. Third, electrochemical synthesis controls the reaction by precisely regulating the current density and charge quantity. Lastly, the new method does not use toxic substances such as chlorosulfonic acid, thereby enhancing safety. The downstream processing is also simpler, making it suitable for large-scale production.

3.3.2 Production Application

The 'Global Sulfonamide Industry Technology Trends and Investment Analysis in 2025' report indicates that electrochemical synthesis technology has entered the stage of large-scale validation. The non-metallic catalyst-free electrochemical multi-component synthesis process has become mainstream. For instance, the single-step continuous-flow electrochemical synthesis technology for sulfonyl amides developed by the University of Mainz in Germany, in collaboration with Merck,

generates sulfonyl chloride intermediates in situ from SO_2, thereby avoiding the use of highly toxic thiosulfuric acid in traditional processes. The yield reaches 70-92% at the pilot scale, with an electric current efficiency of over 85%.

The pilot project for the electrochemical reduction of cyanosulfonyl amide by BASF, a European chemical giant, has completed a 500 mL scale validation. The yield of the mafenide intermediate reached 80-86%. By generating hydrogen in situ instead of using high-pressure hydrogenation, the equipment investment was reduced by 20%. It is anticipated that a commercial production line with an annual output of 200 tons will be established at the Antwerp base in Belgium by 2026.

4. Remaining Issues and Future Development Prospects

These improvement methods have, to some extent, optimised the technology for the synthesis of sulphanilamide and achieved certain results. However, there are still some issues that need to be addressed urgently.

In terms of equipment and technology, the continuous flow electrochemical reactor lacks unified industry standards, which increases the risk of scaling up the process. Furthermore, the development and operation of the system require highly skilled professionals who are proficient in organic synthesis, electrochemistry, and chemical engineering simultaneously. Such specialised talents are relatively scarce. The design of a complete continuous-flow chemical synthesis system involves many components. Ensuring the efficient and accurate operation of their systems is also a crucial consideration for production companies.

At the practical production level, the initial investment of the new method is high. The original investment in equipment, such as sophisticated continuous reaction flow instruments and high-precision pumps, is significantly higher than that of traditional glass reaction vessels. Moreover, for mature pharmaceutical production, the traditional process is cost-effective and stable. The introduction of new technologies needs to be evaluated to determine if it can enhance market competitiveness, and the investment return period is uncertain.

Based on the above issues, we considered that, first of all, standardised and modularised reaction components can be developed in the future to lower the usage threshold. Secondly, it is advisable to combine with artificial intelligence technology. By using artificial intelligence to learn from the research data, predict reaction conditions, and optimise the reaction process. Thirdly, interdisciplinary technological integration can be carried out. For instance, considering the combination of electrochemistry, photochemistry, and biochemistry (enzyme catalysis) technologies could be a possible research direction. This might break through the limitations of traditional reaction pathways and enable efficient synthesis.

5. Conclusion

This study reviewed the synthesis process of sulphonamide and evaluated emerging strategies for improving its production efficiency and sustainability. Traditional multi-step synthesis methods, while chemically robust, are hindered by high costs, energy consumption, and environmental impact. Contemporary techniques—such as continuous flow technology, green chemistry principles, and electrochemical synthesis—offer viable pathways to address these limitations by enhancing yield, minimizing waste, and reducing hazardous by-products. However, challenges remain in terms of industrial scalability, equipment investment, and cross-disciplinary integration. Future research should focus on developing standardized, automated, and AI-assisted synthesis platforms that combine precision, safety, and sustainability, ensuring that sulphonamide production evolves toward environmentally responsible and economically feasible industrial applications.

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