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Research Progress in the Synthesis of N-Acyl Amino Acid Surfactants: A Review

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Abstract: This paper reviews the research progress in the synthesis of N-acyl amino acid surfactants, including chemical synthesis methods, enzymatic synthesis methods, chemo-enzymatic methods, and fermentation methods. Chemical synthesis is currently the main route for laboratory and industrial synthesis, including methods such as direct dehydration condensation of fatty acids, amidation of fatty acid anhydrides, carbonyl addition of fatty amides, amidation of fatty acid activated esters, amidation of fatty acid methyl esters, amidation of oils and fats, hydrolysis of fatty nitriles, and Schotten–Baumann condensation. Enzymatic synthesis has the advantages of mild reaction conditions and being green and pollution-free, but the yield is relatively low. The chemo-enzymatic method combines the advantages of enzymatic and chemical methods, but it has not been widely promoted. Fermentation methods have low production costs and are environmentally friendly but the technology is not yet mature. This paper elaborates on the principles, advantages, and disadvantages of each synthesis method and provides an outlook on future research directions.

Keywords: N-acyl amino acid surfactants; Chemical synthesis methods; Biosynthesis methods

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1. Introduction

As a new type of biomass surfactant, N-acyl amino acid surfactants possess excellent surface properties, biocompatibility, and biodegradability. They are widely used in fields such as daily chemicals, textiles, oil extraction, and lubrication [1–2]. Given the global trend of environmental protection and sustainable development, exploring green and efficient synthesis routes for N-acyl amino acid surfactants is of crucial importance. This is not only related to process optimization, cost reduction, and product quality improvement but also the key to expanding their application scope and promoting the green transformation of the surfactant industry. This paper reviews the latest progress in the synthesis research of N-acyl amino acid surfactants, aiming to jointly promote

the development of this field in a more environmentally friendly and efficient direction and provide valuable references and inspirations for the continuous optimization and innovation in this field.

2. Chemical method

There are mainly two main approaches for the chemical synthesis of N-acyl amino acid surfactants [3]. The core of the first approach lies in using natural oils and fats as starting materials. Through a series of chemical reactions, different acylating agents are obtained, and then an amidation reaction is carried out with amino acids. The second approach is to directly synthesize specific substances starting from existing chemical raw materials.

2.1. Direct dehydration condensation method of fatty acids

The direct dehydration condensation method involves carrying out a dehydration condensation reaction between fatty acids and amino acid salts at high temperatures to generate N-acyl amino acid salts (**Figure 1a**). The earliest research on this method can be traced back to 1975. Takizawa et al. made amino acid salts react with fatty acids at a high temperature above 170°C [4]. Later, Woodbury et al. improved this method [5]. For example, by using nitrogen protection and continuously removing the generated water, they successfully increased the yield of N-acyl amino acid salts. Zeng Ping et al. synthesized sodium N-lauroyl methyl taurate by using boric acid as a catalyst and liquid paraffin as a solvent and taking lauric acid and acetic acid as raw materials [6]. Under optimized operating conditions, the conversion rate can reach more than 95%. Although this method is simple to operate, it has some disadvantages. For example, the high reaction temperature may lead to the occurrence of side reactions, affecting the purity and yield of the product.

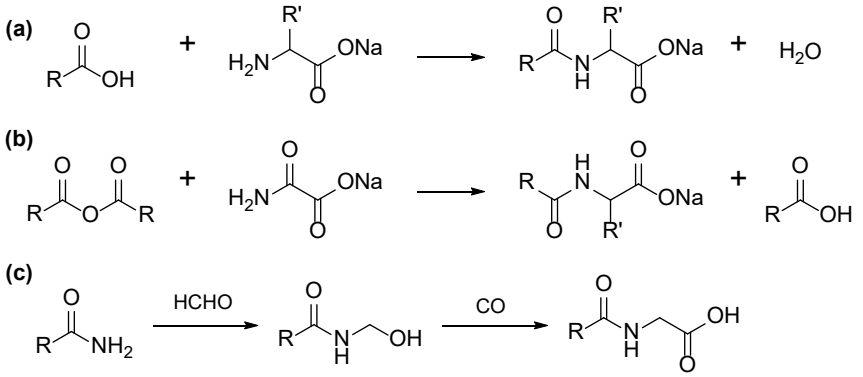

Figure 1. Synthetic route diagrams of (a) direct dehydration condensation method of fatty acids, (b) amidation method of fatty acid anhydrides, and (c) fatty acid amide carbonyl addition method

2.2. Amidation method of fatty acid anhydrides

This method was proposed as early as 1963 by Thomnas H et al. [7]. The principle is that fatty acid anhydrides react rapidly with sodium amino acid at 100°C to generate sodium N-acyl amino acid (**Figure 1b**). However, this process requires the addition of excessive anhydride and is accompanied by the generation of a large amount of fatty acid by-products. This not only increases the cost but also reduces the atomic economy of the reaction, so it is not suitable for large-scale industrial production.

2.3. Carbonyl addition method of fatty acid amides

The fatty amide carbonyl addition method is an approach where fatty amides and formaldehyde are used as raw materials to form primary amidohydrols through catalytic addition (**Figure 1c**). Then, carbonyl addition with CO occurs under the action of a catalyst to finally synthesize N-acyl amino acids. This method was first reported by Akiyama et al. [8]. Beller et al. improved it to catalytically synthesize N-lauroyl sarcosine under high temperature and high-pressure conditions, enabling a product yield of up to 99% [9]. Hancker et al. used a LiBr-loaded modified palladium halide catalyst to synthesize N-lauroyl sarcosine under high pressure and low temperature, achieving a yield of 95% [10]. However, the high cost of the catalyst limits the widespread application of this method.

2.4. Fatty acid activated ester amidation method

This method uses N, N-dicyclohexylcarbodiimide (DDC) as a dehydrating agent (**Figure 2a**). Fatty acid reacts with N-hydroxysuccinimide (NHS) to generate an activated ester intermediate, which then reacts with amino acids to generate N-acyl amino acid surfactants [11–12]. However, the use of DDC and NHS increases economic costs and product safety issues, and further post-treatment steps are required for removal. Therefore, it is not suitable for large-scale industrial production and is often used in laboratory synthesis methods.

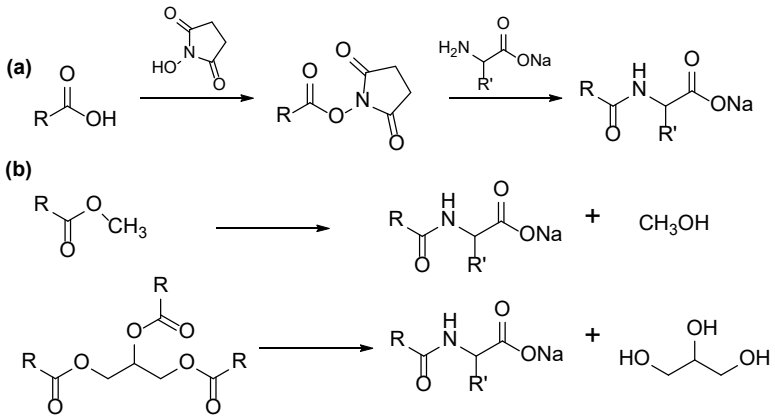

Figure 2. Synthetic route of (a) fatty acid activated ester amidation and (b) fatty acid lipid amidation method

2.5. Fatty acid ester amidation method

The fatty acid ester amidation method uses fatty acid methyl esters or glycerides as raw materials to react with amino acids to prepare N-acyl amino acid salts (**Figure 2b**). For example, Xu Baocai et al. used methyl ketone/water as a solvent and reacted sodium glutamate and methyl laurate under the action of a phase transfer catalyst to obtain sodium N-lauroyl glutamate, but its yield was only 33.1% [13]. Liu Qun et al. then improved this method. Using glycerol as a solvent, sodium methyl laurate and sodium glycinate were synthesized into sodium N-lauroyl glycinate under the catalytic action of sodium methoxide, with a yield of up to 78.7% [14]. Zhang et al. used sodium methoxide as a catalyst to successfully synthesize sodium N-cocoyl glycinate through the reaction of coconut oil and sodium glycinate, with a yield of 87% [15]. Wang et al. used natural oils from coconuts, palm kernels, and soybeans as acyl donors to react with lysine, serine, threonine, and methionine to successfully synthesize a variety of N-acyl amino acid surfactants, with yields ranging from 60% to 93% [16]. Sun et al. synthesized three kinds of sodium N-myristoyl amino acids by using polyethylene glycol 400 as a solvent and feeding N-myristoyl methyl ester and aromatic amino acids at a molar ratio of 1:1 [17].

This method has certain industrial application potential. However, the product needs to be acidified to separate unreacted oils and by-products such as methanol and glycerol. If the oil conversion rate can be further increased and the purification step can be omitted, it will greatly promote the application of such surfactants in industrial production.

2.6. Fatty nitrile hydrolysis method

The fatty nitrile hydrolysis method uses methylamine, formaldehyde, and hydrocyanic acid as raw materials [18]. Firstly, methylaminoacetonitrile is synthesized. Then, an amidation reaction occurs with fatty acyl chloride to prepare fatty nitriles with longer carbon chains (**Figure 3a**). Finally, N-acyl sarcosine is obtained through a hydrolysis reaction. This method shows extremely high selectivity and reaction efficiency. However, since highly toxic chemicals such as hydrocyanic acid (HCN) may be required in the reaction process, this not only poses extremely high requirements for the safety management of equipment and personnel but also increases operational complexity and cost, limiting its widespread application in actual production.

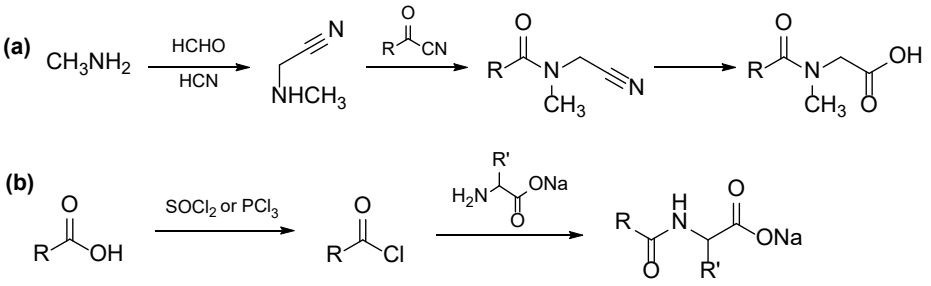

Figure 3. Synthetic routes of (a) fatty nitrile hydrolysis method and (b) Schotten-Baumann condensation reaction method

2.7. Schotten-Baumann condensation method

The Schotten-Baumann condensation reaction method is commonly used in industry for preparing N-acyl amino acid salts. It involves the reaction of fatty acyl chlorides with amino acids in a basic mixed solvent (including water and other organic solvents) (**Figure 3b**) [3, 19–21]. This method can be generally divided into two steps: First, fatty acids are converted into fatty acyl chlorides through acylating agents. Subsequently, fatty acyl chlorides undergo a condensation reaction with sodium amino acid in an alkaline aqueous solution to obtain crude N-acyl amino acid sodium products. The crude product needs to go through steps such as acidification with inorganic acid, hot water washing, liquid separation to remove impurities, and neutralization with sodium hydroxide to finally obtain a relatively pure aqueous product of N-acyl amino acid salts. It can also be made into powder products by spray drying. Although this method has been widely applied in industry, there are still problems such as high-quality requirements for acyl chlorides, easy hydrolysis, and difficult product separation. Future research can further optimize reaction conditions, explore new solvent systems, or develop new synthetic routes to improve the efficiency and product quality of this process.

3. Biosynthesis method

3.1. Enzyme-catalyzed synthesis

Currently, the enzymes used in the enzymatic synthesis of N-acyl amino acids are mainly lipases, proteases, and so on [22]. Montet et al. explored the synthesis pathway of triglycerides and lysine catalyzed by lipase to generate

N-acyl lysine and comparatively studied the effects of this reaction under different organic solvents and solvent-free conditions [23]. However, even under optimal conditions, the recovery rate of the product only reached a level of 19%. Ferjancic et al. synthesized N-acyl methionine in an organic solvent-water mixed system environment by using porcine kidney and intestinal aminoacylase, and the yield was increased to 20%–30% [24]. Soo et al. synthesized N-palmitoyl lysine salt by catalyzing palmitic acid and lysine with lipase in different solvent environments, and the highest yield could reach 40% [25]. Wada et al. synthesized a class of lauroyl amino acid salts in a glycerol-water mixed system by using porcine kidney aminoacylase I, and the highest yield could reach 44% [26]. Bourkaib et al. obtained a yield range of 6% to 23% by catalyzing the acylation reaction of various carbon chain fatty acids and different amino acids with lipase in an aqueous medium [27]. Wang Hongwei et al. successfully synthesized N-oleoyl lysine under the condition of micro-aqueous organic solvents using fatty acids as catalysts, and the highest yield reached 58% [28]. Nian Binbin synthesized N-acyl lysine by using different enzymatic syntheses in natural eutectic solvents, and the highest yield was close to 77% [29]. Bidin et al. synthesized N-fatty acyl lysine salt by catalyzing the reaction of palm oil and lysine with lipase RMIM. After process optimization, the reaction conversion rate was 89.03% [30].

Compared with the chemical method, the enzyme conversion method has the advantages of mild reaction conditions, high selectivity, and avoidance of toxic and harmful by-products, showing extremely attractive potential and thus receiving extensive attention [18, 31]. However, this technology faces problems such as low yield, high enzyme cost, and easy inactivation, which restricts its wide promotion in industrial applications [32].

3.2. Chemical-enzymatic method

The chemical-enzymatic combination method integrates the advantages of both chemical and enzymatic synthesis methods, demonstrating unique advantages. Valivety et al. once used N-myristoylserine glyceride as the substrate and achieved the synthesis of N-acylserine through an enzymatic pathway [33]. Rolland et al. successfully prepared optically pure N-acyl-α-aryl glycine by using the chemical-enzymatic method [34]. Goujard et al. synthesized N-arachidonoyl glycine from methyl N-arachidonate through a chemical-enzymatic pathway. Xia Yongmei et al. synthesized N-lauroyl-β-aminopropionitrile from laurate and 3-aminopropionitrile under the catalysis of lipase, with a raw material conversion rate reaching 96.8% [35].

The chemical-enzymatic method is known for its high selectivity. It combines the mild characteristics of enzymatic catalysis processes with the high efficiency of chemical methods, significantly improving the yield of single enzymatic synthesis. However, the limitations of this method mainly lie in the high specificity of enzymes. It is only applicable to the amidation reaction of a few organic substances. Additionally, the high cost also limits its widespread application and popularization.

3.3. Microbial fermentation synthesis method

Fermentation technology is a production technique that utilizes microorganisms such as yeast or Bacillus to convert biomass resources into acyl amino acid salts through biological metabolic pathways. It has attracted much attention due to its environmental friendliness, high cost-effectiveness, and significant industrialization potential. Reznik et al. pioneered the introduction of peptide synthetase into Bacillus subtilis (Bacillus) and successfully achieved the fermentation production of N-fatty acyl glutamic acid using cellulose-based materials such as soybean hulls [36]. Marti et al. further deepened the research on the factors affecting fermentation rate and yield and significantly increased the yield by removing solid particles from the hydrolyzate of soybean hulls [37]. Lamsal et

al. screened strains suitable for the synthesis of specific amino acids by fermentation method and compared the effects of different hydrolyzates (including switchgrass, soybean, alfalfa, and bagasse, etc.) on the synthesis of N-fatty acyl glutamic acid. Finally, under optimal conditions, a total yield of 95% was achieved [38].

Due to its mild reaction conditions, low-cost advantage, and environmental friendliness, the fermentation method is gradually becoming an indispensable and important part of the amino acid-based surfactant market [22]. However, at present, the industrialization process of the fermentation method in the synthesis of amino acid-based surfactants is still in the laboratory research stage. To achieve large-scale production, further breakthroughs in biotechnology are needed, and the production process needs to be further optimized to improve yield and purity.

4. Conclusion

N-acyl amino acid surfactants have received extensive attention due to their excellent surface activity performance, as well as outstanding biocompatibility, biodegradability, and high safety characteristics. Currently, the main synthesis method for this type of surfactant is the Schotten–Baumann condensation method. However, this method still has problems such as solvent residue, high content of by-products, and unfriendliness to the environment. To achieve the full-process green development of N-acyl amino acid surfactants, it is necessary to further study and optimize the existing synthesis methods.

In this context, the biological fermentation method with low cost and easy industrial production has become the focus of research. The development of this method will help to efficiently utilize resources and promote the carbon emission reduction process of the full life cycle of the surfactant industry. Therefore, future research should focus on optimizing the synthesis process, reducing production costs, and strengthening environmental friendliness to promote the sustainable development of N-acyl amino acid surfactants.

Disclosure statement

The authors declare no conflict of interest.

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