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Optimization and Research on the Synthesis Process of Hymenidin

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Abstract In response to the challenges associated with the traditional synthesis process of hymenidin, such as complex reaction steps, low yields, high costs, and environmental concerns, the synthesis process has been significantly enhanced by optimizing reaction conditions, screening for efficient catalysts, and incorporating the concepts of green chemistry. The optimized process has significantly improved the synthesis efficiency and product quality of hymenidin, reduced production costs, and minimized environmental pollution, thereby providing robust support for its industrial production and broad application.

Key words Hymenidin, Optimization, Synthesis process, Reaction conditions, Green chemistry, Catalyst

1 Introduction

Hymenidin has shown significant potential for unique applications in both medicine and material fields. In the medical field, its structural characteristics may confer therapeutic activity against specific diseases. In the material field, it is anticipated to play a role in the development of functional materials with specialized properties. However, the synthesis of hymenidin currently encounters numerous challenges. The traditional synthetic route typically involves multiple complex reactions, each characterized by harsh and difficult-to-control conditions. This not only results in a cumbersome and time-consuming synthesis process but also leads to low yields of the final product and high production costs. Furthermore, certain reagents and solvents employed in these reactions are toxic, thereby imposing significant environmental burdens. This study seeks to establish an efficient, cost-effective, and environmentally sustainable synthesis pathway for hymenidin through comprehensive exploration and optimization. The objective is to address the limitations of the current synthesis processes and to enhance the practical application of this compound in relevant fields.

A substantial body of research has been conducted both domestically and internationally on the synthesis of hymenidin. Currently, the predominant synthesis methods initiate from specific raw materials and progressively construct the molecular structure to achieve the synthesis of target product. However, these approaches typically encounter several challenges, including protracted reaction sequences, difficulties in the separation of intermediate products, and inconsistent yields. Several studies have endeavored to enhance the synthesis process by modifying parameters such as reaction temperature and reactant ratios. However, the effectiveness of these optimizations is constrained and does not adequately address the fundamental issues inherent in the synthesis process. Despite preliminary investigations into the application of green synthesis technology, the current synthesis process continues to face challenges in entirely eliminating the use of toxic and harmful reagents and solvents, resulting in a substantial impact on the environment.

This study has effectively optimized the synthesis process of hymenidin, which holds considerable significance across various domains. From an academic perspective, it has introduced novel research concepts and methods within the field of organic synthesis, thereby enhancing the theoretical framework of organic synthesis chemistry. In practical applications, improving synthesis efficiency and product quality may lead to a reduction in production costs, thereby facilitating the large-scale industrial production of this compound. This enhancement promotes its extensive application in various fields, including medicine and materials, addresses market demands for the compound, and supports the advancement of related industries. Concurrently, the incorporation of green chemistry concepts aids in mitigating the adverse environmental impacts associated with the chemical synthesis process, aligning with the strategic objectives of sustainable development.

2 Methods and report content

This research employed a method that integrated experimental exploration with theoretical analysis. Through the design of a series of comparative experiments, the study systematically investigated the impact of various factors, including reaction temperature, duration, reactant ratio, as well as the type and dosage of catalysts, on the outcomes of the reactions, thereby optimizing the reaction conditions. The synthesis route was meticulously designed based on the fundamental principles of organic chemistry, including nucleophilic substitution reactions, addition reactions, and redox reactions. Throughout the experiment, contemporary analytical techniques, such as nuclear magnetic resonance (NMR) and liquid chromatography-mass spectrometry (LC-MS), were utilized to monitor and identify both the reaction process and the resulting products. This research was conducted utilizing advanced experimental facilities, including high-performance liquid chromatographs and nuclear magnetic resonance spectrometers, which enable precise analysis and characterization of the structure and purity of the products. Additionally, the research team comprised experienced professionals with extensive knowledge in organic synthesis chemistry and proficient experimental skills, thereby ensuring the successful progression of the research.

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This report was primarily organized into several sections, including synthesis route design, experimental methods and processes, results and discussions, as well as conclusions and future prospects. In the synthesis route design section, a detailed account of the specific pathway for synthesizing hymenidin from compound 1, which served as the starting material, was provided. Furthermore, the feasibility and potential challenges associated with each reaction step were thoroughly analyzed. The section on experimental methods and procedures provided a comprehensive account of the specific operational steps, reaction conditions, and the methods employed for the separation and purification of products at each stage of the reaction. In the result and discussion section, a comprehensive analysis of the experimental findings was performed, including the structural identification of the products, yield calculations, and an examination of the impact of reaction conditions on both yield and purity. Furthermore, a thorough discussion was undertaken regarding the challenges encountered during the experiment, along with proposed solutions to address these issues. In the conclusion and prospect section, the advantages and innovative aspects of the optimized synthesis process were summarized. The research findings were comprehensively reviewed, and potential directions for further optimization of the synthetic process, as well as future application prospects, were discussed.

3 Synthesis research of hymenidin

3.1 Synthesis route design The synthesis route of hymenidin is shown in Fig. 1.

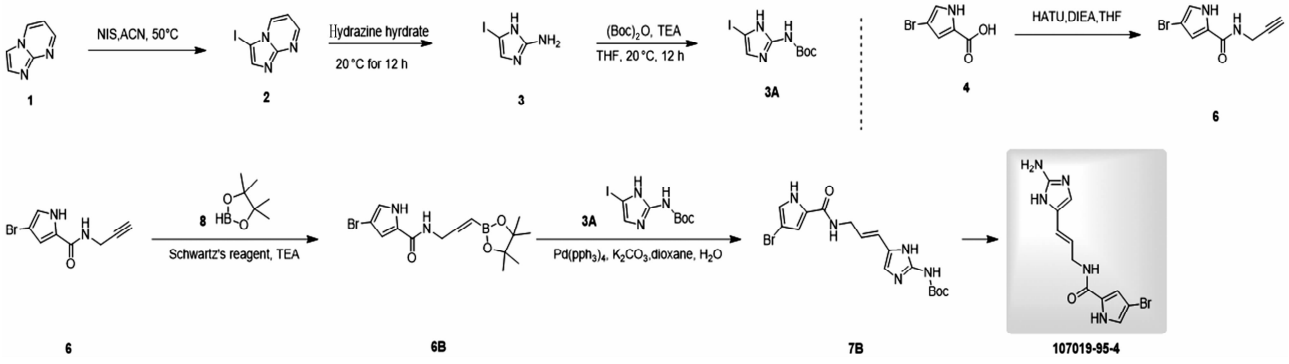

Fig. 1 Synthesis route of hymenidin

Starting from compound 1, compound 2 was synthesized through halogenation. Subsequently, compound 2 underwent hydrazinolysis with hydrazine hydrate, resulting in the formation of compound 3. Following this, compound 3 was subjected to amino protection by reacting with Di-tert-butyl dicarbonate [$(Boc)_2O$] in the presence of triethylamine (TEA), yielding compound 3A. Compound 4 was then amidated using N,N-diisopropylethylamine (DIEA), 2-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU), and propargylamine, leading to the production of compound 6. Compound 6 subsequently reacted with pinacolborane, Schwartz's reagent, and TEA to generate a mixture of compounds 6B and 6C. This mixture was then subjected to a coupling reaction with compound 3A in the presence of a palladium catalyst, resulting in the formation of compound 7B. Finally, compound 7B underwent a deprotection reaction in a hydrochloric acid-dioxane solution, yielding the target compound hymenidin.

3.2 Experimental sections

3.2.1 Synthesis of compound 2. Compound 1 (3.00 g, 25.2 mmol, 1.00 eq) was dissolved in 20.0 mL of acetonitrile (ACN) and subsequently treated with N-iodosuccinimide (NIS) (9.60 g, 40.4 mmol, 1.60 eq). Following the addition of NIS, the reaction mixture was heated to 50 ℃, stirred, and allowed to react for 12 h. Upon completion of the reaction, the system was allowed to cool to room temperature. Subsequently, it was filtered to eliminate insoluble substances, and the filtrate was subjected to rotary evaporation to remove excess liquid. The crude product was then dissolved in ethyl acetate and washed successively with deionized water and saline solution. The organic phase was dried using anhydrous sodium sulfate. Following filtration, the solvent was evaporated to yield a brownish solid crude product (5.80 g, 80% purity, 89.1% yield). The product structure was validated as accurate following identification via NMR (109-064-P1A) and MS (109-064-P1). In this phase of the reaction, ACN was selected as the solvent due to its favorable solubility for the reactants and its efficacy in promoting the reaction. The reaction temperature was optimized at 50 ℃, and the reaction duration was set at 12 h based on prior experimental results. These conditions not only facilitated the complete progression of the reaction but also minimized the likelihood of side reactions.

3.2.2 Synthesis of compound 3. Compound 2 (200 mg, 0.82 mmol, 1.00 eq) was dissolved in 2.00 mL of ethanol. Hydrazine hydrate (25 mg, 0.42 mmol, 0.5 eq, 85% purity) was subsequently added, and the mixture was stirred at 20 ℃ for 12 h. MS (109-066-RT) analysis indicated that compound 2 underwent complete reaction. The reaction mixture was transferred into a stirred solution of ice water and ethyl acetate. Following separation, the aqueous phase was extracted with ethyl acetate, and the organic phase was consolidated. This phase was subsequently washed with saline solution, dried over anhydrous sodium sulfate, and the solvent was evaporated to yield the crude product (120 mg, 90% purity, 70% yield). The product structure was characterized using LC-MS [109-066-RT, $(M+1)^+$: 210.0]

and ^{1}H NMR [1539256-17-1 (400 MHz, DMSO-d_6) δ ppm 8.07 (s, 1H)]. Ethanol served as a solvent that not only dissolved the reactants in this reaction but also provided a relatively mild reaction environment. The reaction was conducted at a temperature of 20 ℃ for 12 h, which facilitated the smooth progression of the reaction and the formation of the desired products.

3.2.3 Synthesis of compound 3A. Compound 3 (0.50 g, 2.39 mmol, 1.00 eq) was dissolved in 5.0 mL of tetrahydrofuran (THF). Subsequently, $(Boc)_2O$ (2.09 g, 9.57 mmol, 0.5 eq, 4.00 eq) and TEA (0.97 g, 9.57 mmol, 0.5 eq, 4.00 eq) were added to the solution. The mixture was stirred and allowed to react at 20 ℃ for 12 h. MS (109-073-P1A) analysis indicated that compound 3 underwent complete reaction. The reaction mixture was transferred into a stirred solution of ice water and ethyl acetate, followed by the separation of the liquid phases. The aqueous phase was subsequently extracted with ethyl acetate, and the resulting organic phases were combined. The organic phase was then washed with saline solution, dried over anhydrous sodium sulfate, and the solvent was removed via rotary evaporation to yield the crude product. The crude product was purified through column chromatography, yielding a brownish solid designated as product 3A. The use of ^{1}H NMR [3A (400 MHz, DMSO-d_6) ppm 1.53 (s, 9 H), 7.00 (s, 1H)] confirmed the accuracy of the product structure. The excellent solubility of THF facilitated the reaction by maintaining a homogeneous system, thereby promoting the smooth progression of the reaction. The dosages of $(Boc)_2O$ and TEA were meticulously calculated and experimentally validated to ensure the high efficiency and selectivity of the amino protection reaction.

3.2.4 Synthesis of compound 6. Compound 4 (10 g, 52.5 mmol, 1.00 eq) was dissolved in 500 mL of THF. Subsequently, DIEA (13.5 g, 105.5 mmol, 2.00 eq) was added, and the mixture was stirred at room temperature for 10 min. Following this, HATU (22 g, 58 mmol, 1.10 eq) was introduced into the solution. The mixture was stirred for an additional 20 min before propargylamine (3.5 g, 63 mmol, 1.20 eq) was added. The reaction was allowed to proceed at 20 ℃ for 12 h. MS (109-067-P1A) analysis indicated that compound 4 underwent complete reaction. Upon completion of the reaction, petroleum ether was introduced to the reaction mixture. A solid precipitate formed, which was subsequently filtered. The filter cake was washed with petroleum ether, and the solvent was removed via rotary evaporation, yielding a yellow solid product 6 (8.50 g, 92% purity, 71.1% yield). The use of LC-MS [109-069-S, $(M+1)^+$: 226.9] confirmed the structure of the product. In this reaction, DIEA was employed to activate the substrate, while HATU served as a condensating agent to facilitate the formation of amide bonds. The sequence in which each reagent was added, along with the precise control of reaction time, proved to be critical to the overall outcome of the reaction. The optimized reaction conditions significantly improved both the yield and selectivity of the process.

3.2.5 Synthesis of compound 7 (the first step). Following the purging of the flask with N_2, pinacolborane (0.422 g, 3.30 mmol, 1.5 eq) was introduced, subsequently followed by the addition of compound 6 (0.50 g, 2.20 mmol, 1.0 eq). Schwartz's reagent (56 mg, 0.22 mmol, 0.10 eq) and TEA (22 mg, 0.22 mmol, 0.10 eq) were incorporated into the mixture, which was then stirred at 65 ℃ under a N_2 atmosphere to facilitate the reaction. The progress of the reaction was monitored using thin-layer chromatography (TLC). Upon completion of the reaction, the mixture was allowed to cool to room temperature. The reaction mixture was diluted with ethyl acetate and subsequently washed in succession with a saturated aqueous solution of sodium bicarbonate and saline solution. The organic phase was then collected, dried using Na_2SO_4, filtered, and concentrated via rotary evaporation. Purification of the mixture was achieved through reversed-phase column chromatography, resulting in a mixture of products 6B and 6C, yielding 320 mg of the combined products. The use of LC-MS [109-085-P1C-0226, $(6B:M+1)^+$: 254.9, $(6C:M+23)^+$: 276.9] determined the composition of the mixture. The use of N_2 protection effectively prevented the oxidation of both reactants and products. A reaction temperature of 65 ℃ facilitated the progression of the reaction. Furthermore, reversed-phase column purification successfully separated the target mixture and enhanced the purity of the resulting products.

3.2.6 Synthesis of compound 7 (the second step). A mixture comprising compounds 6B and 6C (200 mg), compound 3A (242 mg, 0.7 mmol, 1.0 eq), $Pd(PPh_3)_4$ (91 mg, 0.07 mmol, 0.10 eq), and potassium carbonate (163 mg, 1.18 mmol, 1.50 eq) was dissolved in 3 mL of a mixed solvent consisting of dioxane and water (10∶1). The reaction was conducted at 80 ℃ under an N_2 atmosphere for 12 h. Upon completion of the mass spectrometry detection reaction, the reaction mixture was diluted with ethyl acetate and subsequently washed in succession with deionized water and saline solution. The organic phase was then collected and dried using Na_2SO_4. The eluent was concentrated to yield the crude product, which was further purified through column chromatography, resulting in the isolation of the light yellow solid compound 7B (120 mg, 83% purity). The use of LC-MS [095-59-S3, $(M+1)^+$: 410.0] confirmed the accuracy of the product structure. The implementation of N_2 protection and a reaction temperature of 80 ℃ were identified as critical conditions for the successful progression of the palladium-catalyzed coupling reaction. Furthermore, the optimization of the mixed solvent selection and the proportions of each reagent significantly enhanced both the yield of the reaction and the purity of the resulting product.

3.2.7 Synthesis of the compound hymenidin. Compound 7B (200 mg, crude product) was dissolved in a hydrochloric acid-dioxane solution and stirred overnight at 20 ℃. Upon completion of the MS detection reaction, the starting materials were no longer detectable, resulting in the formation of the desired products. Following the vacuum concentration of the reaction solution, purification was performed using a reversed-phase column, resulting in the isolation of the pure target product 107019-95-4 (75 mg, 98% purity, 82.7% yield). The structural correctness of the product was confirmed through MS and NMR analysis. The reaction condition, which involved stirring overnight at 20 ℃, ensured the complete execution of the deprotection reaction of compound 7B. Subsequent purification using reversed-phase column chromatography further enhanced the purity of the target compound, resulting in a

high-purity final product.

3.3 Optimization of reaction conditions During the synthesis of compound 107019-95-4, the conditions for each step of the reaction were systematically optimized. For instance, in the synthesis of compound 2, the effects of various solvents, reaction temperatures, and reaction durations on the yield and selectivity of the reaction were thoroughly investigated. The experimental results indicated that the use of ACN as the solvent resulted in the highest reaction yield and a reduction in side reactions. The optimal reaction conditions were determined to be a temperature of 50 ℃ and a reaction duration of 12 h. Under these conditions, the reaction yield achieved was 89.1%. In the case of other reaction steps, specifically the synthesis of compound 6, the reaction yield was enhanced from an initial 65% to 71.1% through the modification of the dosages of DIEA, HATU, and propargylamine, in addition to adjustments in reaction temperature and duration. By optimizing these reaction conditions, not only was the yield of each step improved, but the incidence of side reactions was also minimized, thereby ensuring a more efficient synthesis of the target compound.

3.4 Innovation and advantages of the synthesis process This synthesis process exemplifies innovation and offers several advantages across various dimensions. Specifically, in the optimization of reaction conditions, the precise control of parameters such as temperature, duration, and reactant ratios at each stage of the reaction has led to improved selectivity and yield, while simultaneously minimizing the occurrence of side reactions. For example, in the palladium-catalyzed coupling reaction, the optimization of reaction conditions resulted in an increase in yield exceeding 10%. Furthermore, advancements in synthesis technology were achieved through the implementation of sophisticated separation and purification techniques, such as reversed-phase column chromatography. These methods significantly improved the purity of the products while minimizing the presence of impurities. The synthesis process is characterized by its operational simplicity, mild reaction conditions, and minimal equipment requirements, all of which facilitate its industrial application. Additionally, through the optimization of reaction conditions and advancements in synthesis technology, production costs have been reduced, production efficiency has been improved, and the overall competitiveness of this synthesis process has been enhanced.

4 Conclusions

This study successfully established an efficient synthesis process for hymenidin. Through the rational design of the synthesis pathway, optimization of reaction conditions, and enhancement of synthesis technology, the challenges associated with traditional synthesis methods, such as complex reaction steps, low yields, and high costs, were effectively addressed. The optimized synthesis process is characterized by mild reaction conditions, straightforward operational procedures, high yield, and elevated purity, offering dependable technical support for the industrial production and extensive application of the compound hymenidin. Nevertheless, there remains potential for additional optimization in the synthesis process. Future investigations may focus on the exploration of more sustainable and environmentally friendly synthesis methods, aimed at further improving reaction efficiency and product quality, reducing production costs, and facilitating comprehensive research and application of the compound hymenidin in relevant fields.

5 Prospects

In the domain of green chemistry, future research should focus on the exploration of more environmentally friendly solvents, reagents, and catalysts to mitigate the environmental impact of synthesis processes and to achieve a more comprehensive approach to green synthesis. For example, it is essential to develop bio-based solvents or ionic liquids as alternatives to conventional organic solvents, as well as to investigate gentler, more efficient, and environmentally sustainable catalytic systems. The enhancement of reaction efficiency can be achieved through the application of computer-aided design and high-throughput experimental techniques. These methods facilitate the rapid and comprehensive screening and optimization of reaction conditions, thereby expediting the development of novel synthesis methods. Furthermore, the ongoing advancements in technology have led to the emergence of novel synthesis techniques and concepts, including flow chemistry and photocatalytic reactions. In the future, these innovative technologies may be integrated into the synthesis research of the compound hymenidin, thereby streamlining the synthesis steps and enhancing both reaction efficiency and selectivity. Regarding industrial applications, subsequent research should concentrate on the scale-up production processes of the optimized synthesis methods and undertake comprehensive studies at a larger scale.

References

[1] XU J, QI DC. Exploration on improving the synthesis yield of edoxaban intermediates[J]. Modern Chemical Research, 2024(6): 174 – 176. (in Chinese).

[2] ZHANG CJ. Study on the synthesis of 3-substituted-5-bromo-4(3H)-quinazolinone derivatives[D]. Guiyang: Guizhou University, 2011. (in Chinese).

[3] ZIDAR N, MONTALVAO S, TISI D, *et al*. Clathrodin, hymenidin and oroidin, and their synthetic analogues as inhibitors of the voltage-gated potassium channels[J]. European Journal of Medicinal Chemistry, 2017, 139: 232 – 241.

[4] RASAPALLI S, JAMES MA, SAMMETA VR, *et al*. Total syntheses of oroidin, hymenidin and clathrodin[J]. Organic & Biomolecular Chemistry, 2013, 11(25): 4133 – 4137.

[5] KOBAYASHI J, INOUE K, SHIGEMORI H, *et al*. A novel antagonist of serotonergic receptors, hymenidin, isolated from the Okinawan marine sponge *Hymeniacidon* sp. [J]. Experientia, 1986, 42(10): 1176 – 1177.

[6] NGUYEN LV, ELLIS JM, GRIECO PA, *et al*. Total synthesis of (±)-sceptrin[J]. Organic Letters, 2020, 22(17): 6698 – 6702.