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Article

Reform of Undergraduate Thesis Project in Pharmaceutical Engineering Based on Synthesis of Fungicide Prothioconazole

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Abstract: We explored how to integrate the synthesis process of the fungicide prothioconazole into undergraduate thesis projects of the Department of Pharmaceutical Engineering of Changzhou University, China. Prothioconazole was synthesized from α-acetyl-γ-butyrolactone through a series of reactions and optimized process conditions. Recommendations for educational reform are proposed based on the result, including the introduction of microchannel reactors, improvements to experimental facilities, and strengthening of industry-university collaboration. The optimized process improves reaction yield, simplifies operational procedures, and significantly reduces costs, demonstrating strong industrial potential. The reform of the student projects based on the new process enhances students' practical abilities and employability in pharmaceutical engineering. The integration of research into education enhances the quality of pharmaceutical engineering education by preparing graduates to meet the demands of the pharmaceutical industry. The result of this study highlights the essential role of interdisciplinary knowledge and innovative practices in cultivating professionals to advance pharmaceutical technologies.

Keywords: Prothioconazole synthesis, Pharmaceutical engineering, Educational reform, Microchannel reactors, Experimental optimization

1. Introduction

Innovative teaching methods are crucial to enhance students' practical skills and industry adaptability, especially in pharmaceutical engineering. In the rapid development of the global pharmaceutical industry and the ever-changing market demands, pharmaceutical engineering education faces numerous challenges. These challenges include the need for curriculum updates due to technological advancements and the cultivation of high-quality, versatile talents with practical skills, innovative thinking, and a global perspective through educational reform (APJ, 2007). Changzhou University in China, as an institution dedicated to training pharmaceutical engineering professionals, recognizes these changes and actively promotes educational reforms to ensure that graduates can adapt to and lead the future development of the industry.

To improve teaching quality, we incorporate the synthesis process research of fungicide prothioconazole into undergraduate thesis projects. Prothioconazole is an efficient, broad-spectrum fungicide widely used in crop disease control. Optimizing its synthesis process is significant for theoretical research and provides production guidance (Chen, 2018). By integrating this cutting-edge research topic into undergraduate education, students can explore new technologies and enhance their experimental skills and research capabilities of problem-solving. This combination of theory and practice enriches students' learning experience and fosters their innovative mindset and critical thinking (Hsu, 2006).

Incorporating the prothioconazole synthesis process into undergraduate thesis projects offers substantial educational value. This approach deepens the student's understanding of complex pharmaceutical engineering processes and effectively bridges the gap between theory and practical application. While pesticide synthesis is not a cutting-edge innovation, it is essential for developing practical skills in the laboratory and equipment, thereby enriching students' engineering education. Furthermore, industry-academia collaboration allows students to engage with real practices, fostering critical skills such as teamwork, problem-solving, and innovation.

Changzhou University's pharmaceutical engineering program enrolls approximately 100 students annually, with thesis and design projects required for graduation. We explored how incorporating specific case studies such as prothioconazole synthesis into education stimulates student interest and enhances their adaptability to industry trends, improving their employability after

graduation (Ma, 2023). As pharmaceutical engineering education evolves, it is necessary to cultivate versatile talent with international perspectives, innovative thinking, and practical skills (Liu, 2008).

Globalization intensifies the challenges for pharmaceutical engineering education, necessitating interdisciplinary knowledge and international perspectives (Chien, 2024). In response, Changzhou University has integrated advanced international teaching concepts into its curriculum to provide students with broader learning platforms and development opportunities. Through these reforms, the university continues to innovate its educational philosophy and teaching methods to meet the diverse needs of the pharmaceutical industry and contribute to the sustainable growth and technological advancement of China's pharmaceutical industry.

In this study, we examined how prothioconazole synthesis can be used for educational reform to enhance teaching quality and student employability. By integrating practical research with theoretical instruction, Changzhou University's pharmaceutical engineering program aims to lead educational innovation and train students to meet the demands of the pharmaceutical industry.

2. Materials and Methods

2.1. Materials

In the synthesis, α-Acetyl-γ-butyrolactone, sulfonyl chloride, triethylamine, tetrabutylammonium hydrogen sulfate, sodium hydroxide, ethyl acetate, and other chemical reagents are used. As equipment, a reactor, a microchannel reactor (Corning Inc., USA), a steam distillation apparatus, a rotary evaporator (RE-522A, Shanghai Daiyan Instrument Co., Ltd.), a circulating water vacuum pump (SHZ-D(III), Shanghai Daiyan Instrument Co., Ltd.), an electronic balance (PL2002, Sartorius), a low-temperature cooling liquid circulating pump (AL204, Gongyi Yuhua Instrument Co., Ltd.), and a high-performance liquid chromatograph (HPLC-1260, Agilent Technologies) are used.

2.2. Methods

2.2.1 Traditional Synthesis Methods of Pyrithione

1. Zinc Grignard Reagent Method (Fig. 1)

In this method, α-acetyl-γ-butyrolactone is used as the starting material, proceeding a series of reactions including chlorination, hydrolysis, decarboxylation, substitution, Grignard reaction, nucleophilic addition, and electrophilic addition. While relatively high yields are obtained in the first two steps, the third and fourth steps result in lower yields, which significantly reduces the overall efficiency. Additionally, the high cost of raw materials restricts the feasibility of large-scale industrial applications.

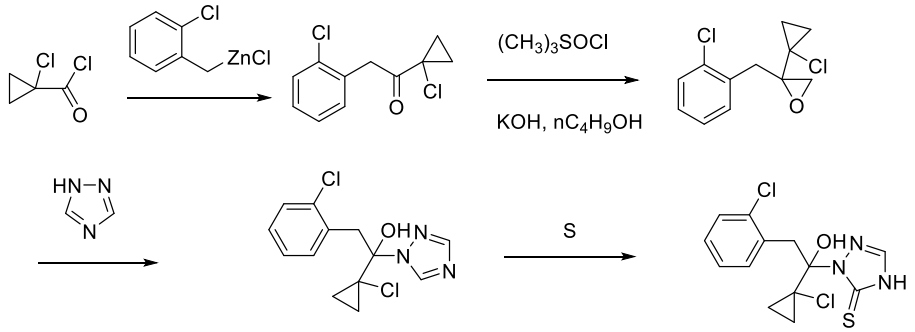

Fig. 1. Prothioconazole synthesis method 1.

2. Triazole Method (Fig. 2)

In this method, triazole is used for nucleophilic substitution. Despite the smooth progression of the first two steps, the overall yield remains low, and the high cost of raw materials limits its practicality for industrial-scale production.

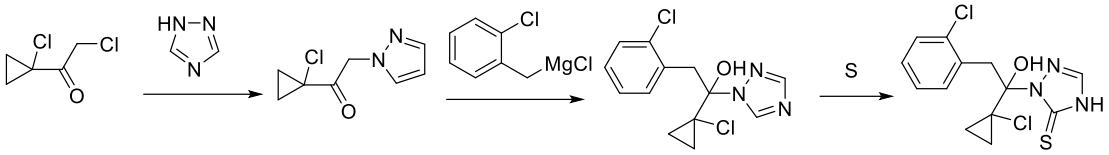

Fig. 2. Prothioconazole synthesis method 2.

3. Hydrazine Hydrate Method (Fig. 3)

This method involves reactions with hydrazine hydrate, yielding high amounts of intermediate compounds. However, the final step has extremely demanding conditions, making it challenging to execute effectively. The complexity and length of the process make it unsuitable for industrial production.

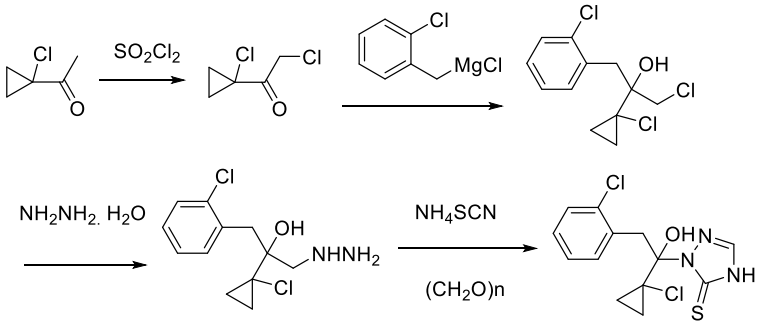

Fig. 3. Prothioconazole synthesis method 2.

2.2.2 Synthesis Method Designed for Students

To enhance the efficiency of prothioconazole synthesis, we optimized reactant ratios, catalyst selection, reaction temperatures, and times. The new process adopts α-acetyl-γ-butyrolactone as the starting material to successfully synthesize prothioconazole through chlorination, hydrolysis, decarboxylation, substitution, Grignard reaction, nucleophilic addition, and electrophilic addition (Fig. 4).

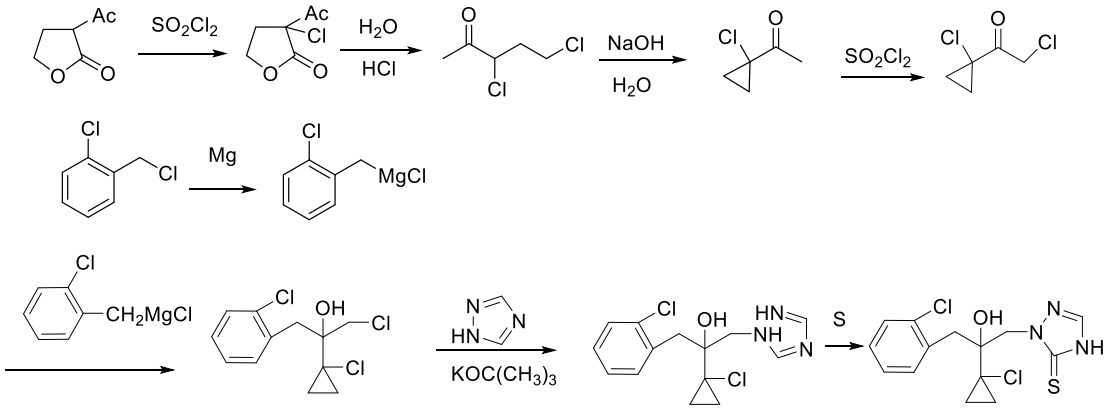

Fig. 4. Synthesis process of prothioconazole created for students.

To optimize the synthesis pathway, the ratios of reactants, types of catalysts, and reaction temperature and time were adjusted to determine the optimal reaction conditions. To enhance reaction yield and product purity, we employed a microchannel reactor, steam distillation, and phase transfer catalysts such as tetrabutylammonium hydrogen sulfate (Fig. 5).

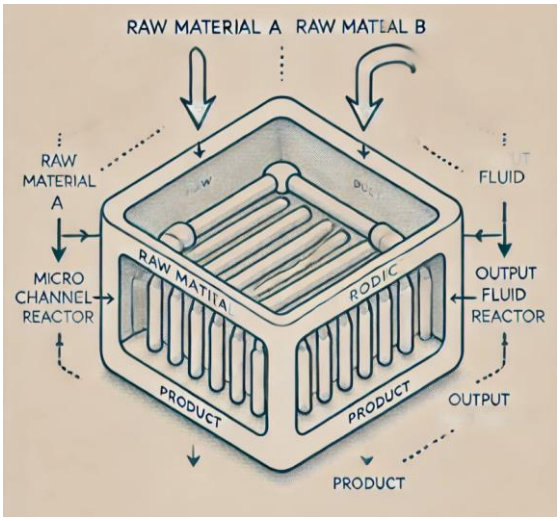

Fig. 1. Simplified schematic of the microchannel reactor process.

2.3. Synthesis of Prothioconazole

1. Synthesis of α-acetyl-α-chloro-γ-butyrolactone

In a reaction flask, α-acetyl-γ-butyrolactone (76.8 g, 0.6 mol) was added and cooled in an ice-water bath. Sulfonyl chloride (84.18 g, 0.62 mol) was slowly added, maintaining the reaction temperature around 10°C. The sulfur dioxide gas produced was absorbed using a sodium hydroxide solution. After the addition was complete, the mixture was stirred at room temperature for 1 h. Upon completion, a saturated sodium bicarbonate solution was added to adjust the pH to 6. The mixture was extracted with ethyl acetate, dried, and concentrated by rotary evaporation to yield a deep yellow transparent liquid of α-acetyl-α-chloro-γ-butyrolactone (79.27 g) with a yield of 81.7%.

2. Synthesis of 3,5-dichloro-2-pentanone

α-Acetyl-α-chloro-γ-butyrolactone (70.81 g, 0.44 mol), distilled water (106 g), and concentrated hydrochloric acid (110 mL) were added to the reaction flask. The mixture was slowly heated until no bubbles were produced, then subjected to reduced-pressure steam distillation to obtain a bright yellow transparent liquid of 3,5-dichloro-2-pentanone (52.8 g) with a yield of 86.5%.

3. Synthesis of 1-acetyl-1-chlorocyclopropane

20% sodium hydroxide solution (100 g) and 3,5-dichloro-2-pentanone (61.3 g) were added to a reaction flask. Tetrabutylammonium hydrogen sulfate (3.61 g) was added in batches. After refluxing for 1.5 h, the mixture was subjected to steam distillation. The product was concentrated by rotary evaporation to yield a colorless transparent liquid of 1-acetyl-1-chlorocyclopropane (33.9 g) with a yield of 72.1%.

4. Synthesis of 2-chloro-1-(1-chlorocyclopropyl) ethanone

1-acetyl-1-chlorocyclopropane (9.28 g, 79 mmol), sulfonyl chloride (6.7 mL, 83 mmol), and dichloromethane (15.5 mL) were added to the reaction flask and stirred at room temperature for 15 h. Saturated sodium bicarbonate was added until no bubbles were produced, maintaining the pH at around 6. After separation, the organic phase was washed with water, dried, and concentrated by rotary evaporation to yield a colorless transparent liquid of 2-chloro-1-(1-chlorocyclopropyl) ethanone (10.3 g) with a yield of 79.7%.

5. Synthesis of Grignard Reagent

Under nitrogen protection, tetrahydrofuran (20 mL), magnesium turnings (2.0 g), and four iodine crystals were added to a dry three-necked flask. Chlorobenzyl chloride (12.51 g) was slowly added, then, and the mixture was heated to 30°C to initiate the

reaction. As the reaction mixture changed from reddish-brown to grayish-white, additional tetrahydrofuran (58 mL) was added, and the temperature was maintained at 25°C. After 2 hours, a gray, cloudy Grignard reagent was obtained for further use.

6. Synthesis of 2-(1-chlorocyclopropyl)-3-(1,2,4-triazol-1-yl)-1-(2-chlorophenyl)-2- propanol

1,2,4-Triazole (7.5 g), 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)- 2-propanol (10 g), and methanol (100 mL) were added to a reaction flask. Sodium hydroxide (10 g) was then added, and the temperature was maintained at 30°C for 30 min, followed by heating and refluxing for 10 hours. After cooling to room temperature, the sodium hydroxide was removed by filtration. The mixture was concentrated by rotary evaporation to yield an orange-yellow viscous liquid, which was recrystallized from methanol to obtain a white solid of 2-(1-chlorocyclopropyl)-3-(1,2,4-triazol-1-yl)-1 -(2-chlorophenyl) -2-propanol (7.7 g) with a yield of 68.8%.

7. Synthesis of prothioconazole

2-(1-Chlorocyclopropyl)-3-(1,2,4-triazol-1-yl)-1-(2-chlorophenyl)-2-propanol (2 g), sulfur (1.7 g), and DMF (20 mL) were added to a reaction flask and slowly heated to reflux. After the reaction was complete, the mixture was cooled to 25°C, and sulfur and impurities were removed by filtration. DMF was removed by rotary evaporation, and the product was recrystallized from xylene to obtain a white solid of prothioconazole (1.7 g) with a yield of 77.2%.

In the synthesis, the use of the microchannel reactor significantly improved the precise control of the reaction, especially in key steps such as chlorination and nucleophilic addition. The reactor's small volume and efficient mass transfer properties effectively enhanced the reaction rate and selectivity, reduced by-product formation, and significantly improved the yield and purity of prothioconazole.

3. Results

3.1. Synthesis Route and Outcome of Prothioconazole

In a six-month undergraduate research project, the student successfully synthesized prothioconazole using the newly designed synthetic route and optimized reaction conditions. The process commenced with α-acetyl-γ-butyrolactone as the starting material and involved several steps, including chlorination, hydrolysis, and cyclization. This approach yielded the target compound with an overall yield of 21.6% and a purity of 95%. These results highlight the effectiveness of optimizing experimental conditions to synthesize prothioconazole that meets stringent quality standards. Key reactions were enhanced by the introduction of phase-transfer catalysts and microchannel reactors which increased yields, reduced by-product formation, and improved safety during the synthesis.

3.2. Optimization of Reaction

The application of steam distillation technology significantly improved the yield of the hydrolysis and cyclization reactions to 86.4%. This technique effectively enhanced both the quantity and quality of the product. By employing the phase transfer catalyst, tetrabutylammonium hydrogen sulfate, the yield in the nucleophilic addition reactions increased from 9% to 72.1%. This result demonstrates that the introduction of the catalyst significantly improved the reaction efficiency.

3.3. Simplification of Process

The introduction of the microreactor significantly simplifies the synthesis process. This improvement reduces the emissions of "three wastes" (waste gas, waste liquid, and waste residue) and increases production safety and efficiency, showcasing a promising industrial application potential.

3.4. Optimization Process

1. Synthesis of α-acetyl-α-chloro-γ-butyrolactone

The highest yield of 81.7% with minimal impurities was obtained when the molar ratio of α-acetyl-γ-butyrolactone to sulfonyl chloride was 1:1.03. Thus, the optimal molar ratio is 1:1.03.

2. Synthesis of 1-acetyl-1-chlorocyclopropane

In the reaction between 3,5-dichloro-2-pentanone and sodium hydroxide, the best molar ratio was 1:1 to achieve a yield of 72.1%. The introduction of the phase transfer catalyst, tetrabutylammonium hydrogen sulfate, increased the yield from 9 to 72.1% without a catalyst.

3. Synthesis of 2-chloro-1-(1-chlorocyclopropyl) ethanone

The highest yield of 79.7% was obtained when the molar ratio of 1-acetyl-1-chlorocyclopropane to sulfonyl chloride was 1:2.

4. Synthesis of 2-(1-chlorocyclopropyl)-3-(1,2,4-triazol-1-yl)-1-(2- chlorophenyl)-2-propanol

When the molar ratio of 2-(1-chlorocyclopropyl)-1-(2-chlorophenyl)-2 -propanol to 1,2,4-triazole was 1:1.15, the yield reached 68.8%

5. Synthesis of prothioconazole

The molar ratio of 1:3 of 2-(1-chlorocyclopropyl)-3-(1,2,4-triazol-1-yl)-1 -(2-chlorophenyl)-2- propanol and sulfur allowed for a yield of 77.2%. The result of ^{1}H NMR (300 MHz, $CDCl_3$) showed δ:=0.76-0.98 (m,4H,CH_2CH_2), δ=3.15-3.19(d, 1H,Ar-CH_2), δ=3.59-3.64 (d, 1H,Ar-CH_2), δ=4.44-4.49(s,1H,OH), δ=4.78-4.83(d, 1H,N-CH_2), δ=7.20-7.58 (m, 4H,Ar-H), δ=7.88(s, 1H,Triazole-H),δ= 8.30 (s,1H,Triazole-H) .

By optimizing raw material ratios, catalyst selection, solvent use, reaction temperature, and time, the optimal process conditions were determined when using α-acetyl-γ-butyrolactone as the starting material. These optimization measures laid a solid foundation for industrial production, ensuring the efficiency and stability of the synthesis process. The undergraduate students completed the experiments using these optimized conditions to obtain the desired results. Overall, the student-designed synthetic process for prothioconazole reflects significant innovation compared to traditional methods. The introduction of tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst enhances nucleophilic addition reaction efficiency, thereby reducing reaction time. By refining reaction conditions, optimal process parameters were identified and overall efficiency was improved. The microchannel reactor technology in the chlorination step increased yield and effectively mitigated safety risks.

4. Discussion

In this study, the synthesis process of prothioconazole was optimized, demonstrating the significant role of steam distillation technology and phase transfer catalysts in enhancing reaction efficiency. Furthermore, the application of microreactors in the process simplified the process, increased production efficiency, and reduced environmental impact. The yield and purity of the product were enhanced significantly and production costs were saved, showcasing promising prospects for industrialization.

4.1. Application of Steam Distillation

The application of steam distillation enhanced the efficiency of hydrolysis and cyclization reactions. By optimizing the conditions for steam distillation, the reaction yield was improved to 86.4%. This technology effectively addressed issues related to moisture evaporation and by-product management during the reaction, thus improving the overall yield and quality of the product. Steam distillation is characterized by low energy consumption and minimal environmental impact, supporting sustainable development in industrial production. Steam distillation technology was proven to be appropriate for laboratory-scale process optimization and industrial applications, especially in the modern pharmaceutical industry where efficient and green production is highly valued (Gavahian, 2018).

4.2. Phase Transfer Catalysts

The introduction of tetrabutylammonium hydrogen sulfate as a phase transfer catalyst in nucleophilic addition reactions significantly enhanced the reaction efficiency and increased the yield from 9 to 72.1%. This demonstrates the critical role of phase transfer catalysts in accelerating reaction rates and improving product yields. Phase transfer catalysts effectively facilitate the transfer of reactants between different phases, speed up the reaction process, and reduce side reactions. This result underscores the importance of phase transfer catalysts in optimizing synthesis processes and theoretically supports industrial applications, particularly in complex reaction systems to enhance reaction selectivity and rate.

4.3. Simplification of Process Using Microreactors

The introduction of microreactors was a significant innovation in this study. Compared to traditional reactors, microreactors demonstrate process flow simplification. Their efficient heat and mass transfer capabilities significantly optimize reaction conditions, reduce reaction time and energy consumption, and improve overall production efficiency (Atobe, M 2017). Additionally, microreactors effectively minimized the emission of "three wastes" (waste gas, waste liquid, and waste residue), greatly reducing environmental impact. This innovation enhances production safety and stability and showcases broad application potential in large-

scale production (Xu, 2023). In particular, the use of microreactors in the pharmaceutical industry promotes green and sustainable production, marking an important development direction in modern pharmaceutical engineering (Ashikari, 2020).

4.4. Experimental Optimization

Raw material ratios, catalyst selection, solvent use, reaction temperature, and reaction time, and the optimal process conditions using α-acetyl-γ-butyrolactone as the starting material were optmized. These optimizations increased the efficiency and quality of prothioconazole synthesis and laid a solid foundation for industrial production. The systematic process optimization effectively improved the synthesis efficiency of the target product and reduced production costs, which has significant implications for the pharmaceutical industry.

4.5. Implications for Education

Undergraduate students had experimental experience in pharmaceutical engineering, which offers important information for teaching reform. Such process optimization involves the application of multiple key technologies and theories, which serve important results in teaching, helping students understand the challenges and solutions in actual production. Additionally, it was proved that scientific experimental design and technological applications can be used for process optimization and improvement, offering guidance for related courses. Particularly, the innovative application of microreactors is a cutting-edge technology to investigate more efficient and environmentally friendly production methods in their future research. Students significantly improved their practical skills and theoretical knowledge by designing the new synthesis method. This process fosters innovative thinking in students to apply it to solve real-world problems. Specifically, the result guides how to teach green and sustainable production in pharmaceutical engineering. Students can explore cutting-edge technologies to pursue efficient and environmentally friendly production methods.

By optimizing the synthesis process of pyraclostrobin and using microchannel reactors for the first time, the effectiveness of steam distillation technology and phase transfer catalysts were verified in enhancing reaction efficiency. These findings hold theoretical and practical significance for the industry and provide a reference in the teaching and practice of pharmaceutical engineering.

5. Conclusions

We integrated the research on the synthesis process of prothioconazole into an undergraduate thesis project, achieving significant results and providing a reference for pharmaceutical engineering education. Various possibilities can be sought for improving teaching methods based on the results. The synthesis process was optimized to enhance students' practical skills and enable them to systematically master skills from process design to experimental optimization. This hands-on experience significantly improves their experimental abilities and problem-solving skills, thereby strengthening their overall quality and research capabilities. The optimized synthesis process, including the application of steam distillation technology, phase transfer catalysts, and microreactors, significantly improved the efficiency and quality of prothioconazole synthesis. The process enhanced the efficiency and consistency in the production of prothioconazole. Students acquired complex experimental skills and understood the importance of green processes in modern pharmaceutical engineering, laying a solid foundation for their future careers.

The pharmaceutical engineering program at Changzhou University has the following features in nurturing innovative talent.

1. Practice-Oriented Teaching Model

The program integrates cutting-edge technologies with real-world production, employing a practice-oriented teaching model to help students enhance their skills in authentic experimental environments. The introduction of advanced equipment, such as microreactors, enhances students' understanding and application of modern pharmaceutical processes, better preparing them for future careers.

2. Integration of Industry, Academia, and Research

The program strengthens collaboration with pharmaceutical companies, incorporating actual technical needs and production cases into graduation projects and thesis work. This application-oriented teaching approach enhances students' job readiness and market competitiveness and shortens their transition from the classroom to the workplace while providing valuable practical experience.

3. Application and Promotion of Green Processes

The program emphasizes the development of green processes, focusing on environmental protection and resource conservation. By applying green technologies such as steam distillation and phase transfer catalysts, students learn advanced synthesis techniques and understand the importance of green chemistry in reducing environmental impact, fostering environmental awareness and sustainable development concepts.

4. Cultivation of Innovative Thinking

The curriculum and experimental design foster innovative thinking and encourage students to explore new methods when solving problems. By researching and applying new technologies, students enhance their experimental skills and their innovative abilities, laying the groundwork for future research and work in advancing technology and scientific innovation.

Based on the results of this study, targeted teaching reform suggestions were made, including the introduction of more modern experimental facilities, such as microreactors and high-performance liquid chromatography, to enhance students' understanding and application of cutting-edge technologies and prepare them for future industrial practices. Additionally, by deepening industry-academia-research collaboration, strengthening cooperation between universities and pharmaceutical companies, and incorporating actual technical needs and production cases into graduation projects and theses, students' job readiness and market competitiveness can be enhanced. Reinforcing education on green processes and integrating the principles and technologies of green chemistry into courses and experiments help students better understand the importance of environmental protection and sustainable development, contributing positively to their future careers and the development of the pharmaceutical industry.

The optimized synthesis process of prothioconazole shows the effectiveness of teaching reform measures practice. These reforms contribute to fostering students' innovative thinking and practical abilities, advancing teaching reforms in pharmaceutical engineering, and experience and references for future innovations in teaching models. The education model with practical application enhances students' research abilities and job readiness in the pharmaceutical industry.

6. Patents

Although the patent protection period for prothioconazole has expired in several countries, its synthesis process still holds substantial potential for research and optimization. The process optimization described in this study has significantly improved the synthesis efficiency and product quality of prothioconazole, demonstrating promising prospects for industrial application. To protect the intellectual property of the synthesis process, we have applied for a Chinese invention patent titled "Nanopesticide Loaded with Prothioconazole Oligomers - Polycaprolactone - Polyethylene Glycol and Its Preparation Method and Application." The application of this patent not only marks a significant advancement in translating process optimization research into practical applications but also establishes a solid foundation for technology transfer and market promotion. Patent protection effectively safeguards technological innovations, prevents imitation or infringement, protects economic interests, and enhances the project's market competitiveness, attracting more industry partners. The process optimization presents a major technical breakthrough and, through the patent application, its intellectual property is protected for the future application of prothioconazole and advancing technological progress in the pharmaceutical field.

Author Contributions: Conceptualization, D. Xu; methodology, D. Xu; software, D. Xu; validation, D. Xu and H. Hu; formal analysis, D. Xu; investigation, D. Xu; resources, G. Wu; data curation, D. Xu; writing—original draft preparation, D. Xu; writing—review and editing, D. Xu; visualization, H. Hu; supervision, D. Xu.

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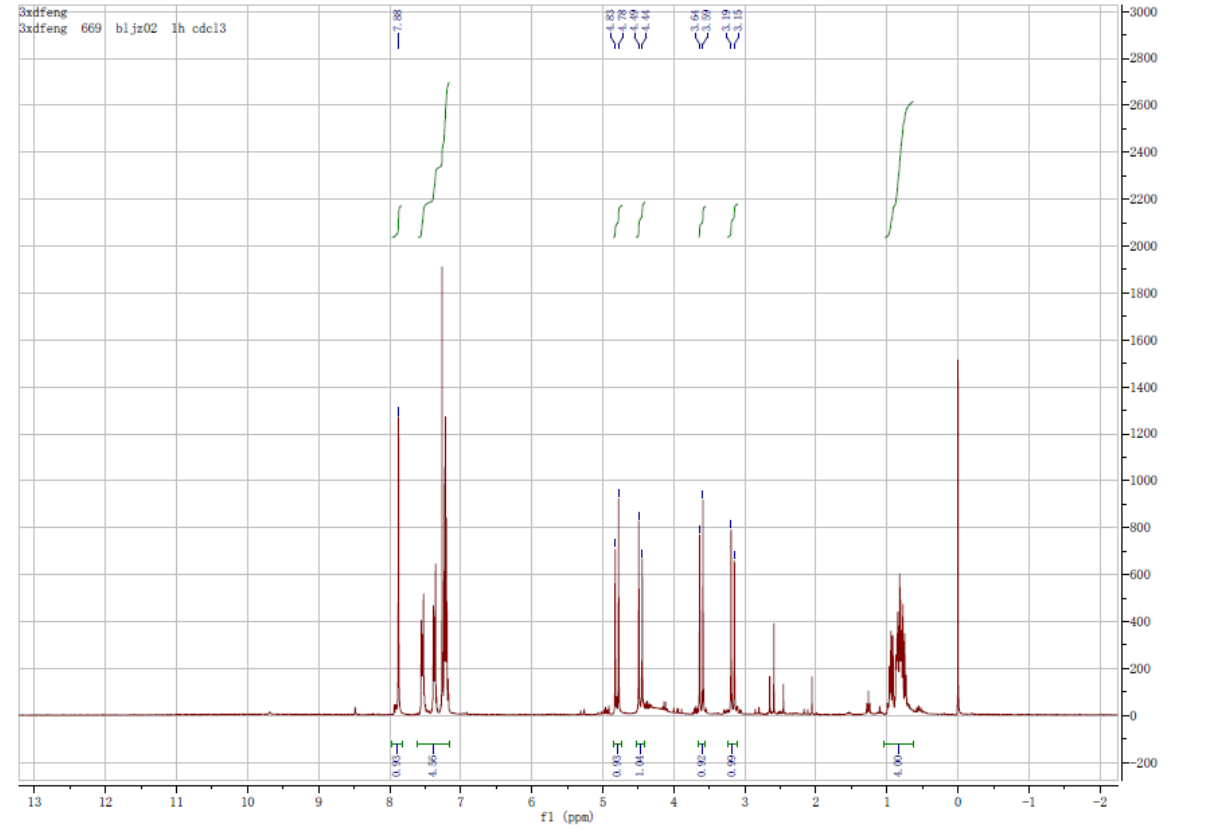
Conflicts of Interest: The authors declare no conflict of interest.

Appendix

^{1}H NMR Spectrum of Propiconazole



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