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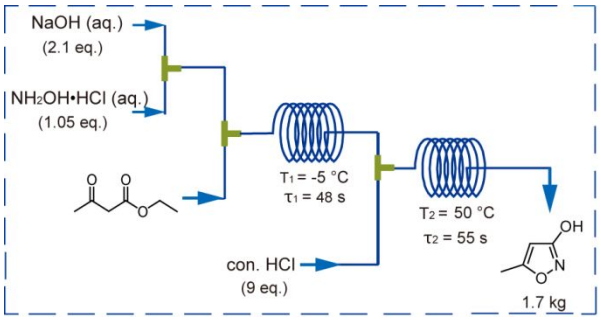

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ABSTRACT: Hymexazol is an efficient and low-toxic soil fungicide. In this paper, a fully continuous flow process for synthesizing hymexazol has been developed. This process began with combining ethyl acetoacetate and hydroxylamine hydrochloride to form the intermediate product: hydroxamic acid. The reaction solution was then quenched with concentrated hydrochloric acid to obtain the final product: hymexazol. Under optimized process conditions, the total yield of the target product reached 86%. In addition, production was successfully scaled-up to a kilogram scale. The continuous-flow method not only greatly decreases the reaction time but also significantly inhibits the side reactions.

KEYWORDS: continuous flow reaction, hymexazol, synthesis, optimization

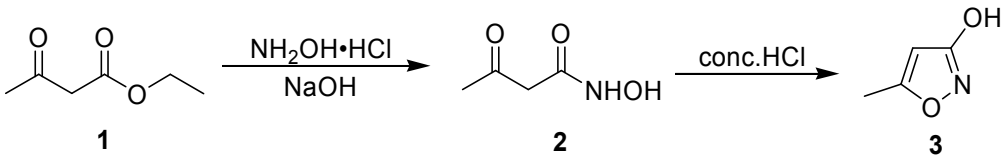
INTRODUCTION

Hymexazol, 3-hydroxy-5-methyl-isoxazole (**3**), is an excellent broad-spectrum fungicide.[1] It is used for soil sterilization and seed disinfection, and it has significant regulatory effects on plant diseases caused by various fungi such as Fusarium, Mortierella and Rhizoctonia solani.[2] In addition, this agent has little effect on bacteria and actinomycetes other than pathogenic bacteria in the soil, so, it does not affect the ecology of microorganisms in the soil, and can be decomposed into very low-toxicity compounds.[3]

Thus far, several synthetic routes to hymexazol have been reported.[4] Among these pathways, the synthetic route shown in **Scheme 1** was considered to be the most economical and practical for industrial production. This synthesis used ethyl acetoacetate (**1**) and hydroxylamine hydrochloride as starting materials to obtain hydroxamic acid (**2**), followed by quenching with an excess of concentrated hydrochloric acid. Although the synthetic route is simple and low-cost, the yield is not sufficiently high.[5] The highest yield of the target product reported in the literature

is 70%.[6] Therefore, a more efficient synthetic method for the industrial production of hymexazol is needed.

Scheme 1. Synthetic Routes of Hymexazol

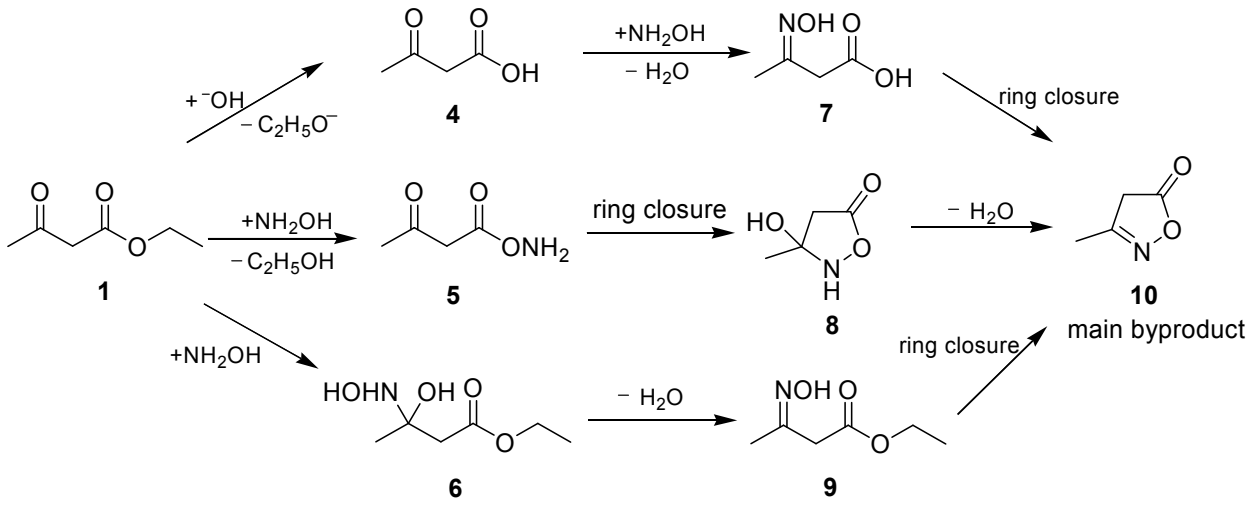


1 **2** **3**

In recent years, the application of continuous flow technology to the field of chemical synthesis has become an area of intense interest. There have been many reports addressing the applications of flow reactors.[7] The continuous flow reactor has unique features, that can enhance the mixing effect and achieve precise temperature control, as well as greatly shorten the cycle of process screening and process amplification.[8] Compared with conventional batch vessels, flow reactors can not only improve the reaction performance and reduce waste, but also improve safety.[9] From the literature we have learned that the process of synthesizing **2** from **1** has a strong dependence on alkaline and low temperature environments, and the preparation of intermediate **2** plays a crucial role in the synthesis of **3**.[5a] Therefore, we decided to introduce the reaction into a flow reactor to investigate whether a continuous flow system is beneficial to increase the yield of **3**. To our knowledge, the method of synthesizing **3** with a continuous flow reactor has never been reported. In this paper, we describe an efficient, stable and practical method for the preparation of compound **3**.

RESULTS AND DISCUSSION

Scheme 2. Main Byproduct



As shown in **Scheme 2**, the synthetic route in this study (**Scheme 1**), provides several possible attack modes of hydroxylamine on **1**; in addition to generating our target product **3**, it also leads to the formation of an undesired byproduct, 3-methyl-2-isoxazolin-5-one (**10**).[10] The amount of this byproduct is usually large, resulting in a low yield of the desired product (**3)**. In the batch reaction, we achieved a product yield of only 68%, and a by-product 10 content of 22% was detected. The key factors affecting the reaction pathway are pH and reaction temperature.[4a, 5a] At a pH of 10, hydroxamic acid **2** is the primary intermediate produced and can be acidified to **3**. Lowering or raising the pH will result in the formation of different intermediates that are not capable of forming the desired product **3**. In the batch preparation of target product **3**, the hydroxylamine hydrochloride solution was added to the sodium hydroxide solution at a low temperature to obtain a solution with a pH 9-10, and then **1** was added dropwise into the mixed solution at -5~5 °C; after 2 hours of reaction, acidification was carried out with hydrochloric acid to obtain **3**. In theory, the efficient heat transfer and mass transfer capacity of the continuous flow reactor can effectively avoid inhomogeneous pH and temperature profiles during material mixing, thereby reducing the occurrence of side reactions and the decomposition of

hydroxylamine. Therefore, our goal was to develop a continuous-flow process that reduced side reactions and increased the total yield.

1. Switch from Batch to Continuous-Flow process.

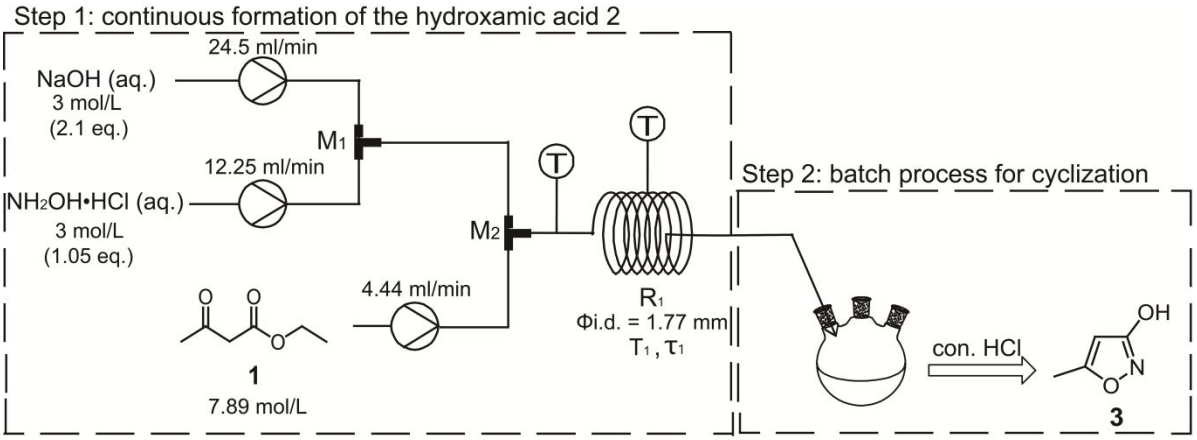


Figure 1. Semicontinuous flow process for the synthesis of hymexazol.

The process equipment we designed includes the feeding system (three plunger metering pumps), two T-shaped mixers (M_1 and M_2, Hastelloy C276, 1.77 mm internal diameter), and a tubular reactor (R_1, Hastelloy C276, 1.77 mm internal diameter). In addition, the tubular reactor and the T-shaped mixers were both submerged in a thermostatic bath to control the temperature. The pH of the reaction solution at the outlet of the reactor was measured using a pH meter. As shown in **Figure 1**, there were three streams in total. The thermostatic bath temperature was set to -5 °C. Then, two plunger pumps were used to separately introduce sodium hydroxide solution (3 mol/L) and hydroxylamine hydrochloride solution (3 mol/L) into M_1 for mixing and precooling. The solution flow rates were 24.5 ml/min and 12.25 ml/min, respectively. The combined solution was mixed with **1** (4.44 ml/min, 7.89 mol/L) in M_2, and the resulting solution was passed through R_1. After running for six minutes (at this time, residence time τ = 40 s), the system reached a steady state. The output of the reactor was collected in a flask, continuously collected for 5 minutes, and

then the collected mixture was poured into 10 equivalents (based on compound **1**) of ice-cooled concentrated hydrochloric acid, where it was allowed to react at 25 °C for 12 hours. The pH of the reaction mixture was adjusted to 3-4 with a 30 wt% sodium hydroxide solution, followed by three extractions with dichloromethane. The organic phases were combined, and the solvent was evaporated in vacuo to generate crude product **3**. The crude product was recrystallized from cyclohexane to gain pure product **3**. To our satisfaction, excellent results were obtained using this continuous process.

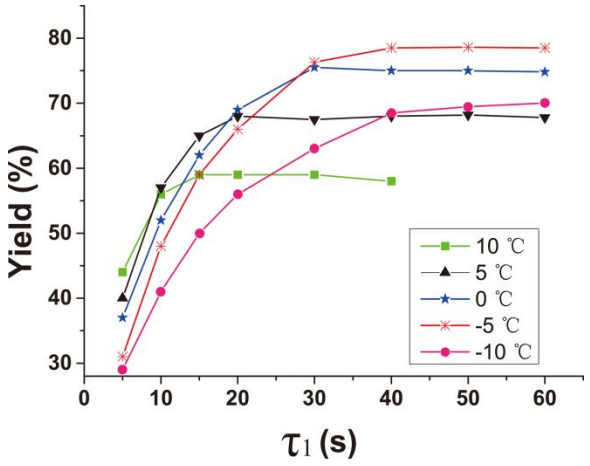


Figure 2. Effect of temperature (T_1) and residence time (τ_1) on the yield of product **3**. Yield was determined by external standard method (HPLC).

To find appropriate reaction conditions, the effects of residence time τ_1 and reaction temperature T_1 on the first reaction step were systematically investigated (**Figure 2**). As the residence time τ_1 was prolonged, the yield was increased to a constant value. Higher temperatures caused an increase in side reactions, resulting in lower yields. We found a significant increase in yield when the temperature was lowered to -5 °C, which also indicated that the lower temperature favored the main reaction. Lower temperatures caused lower

conversion rates (-10 °C), so we extended the residence time τ_1 in an attempt to increase the yield, but the results did not meet our expectations, with a yield of only 72%. Therefore, the reaction conditions of T_1 = -5 °C and τ_1 = 40 s were selected.

Table 1. Total yield of hymexazol under different reaction conditions[a]

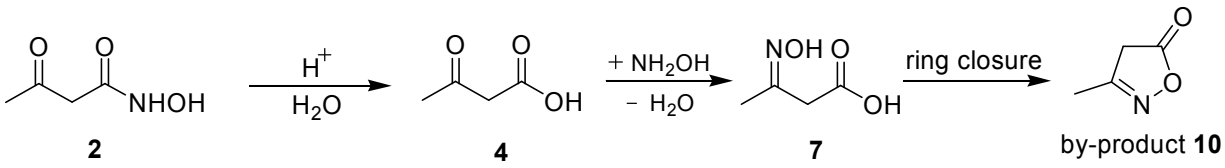
Entry	N_1: N_h: N_s [b]	PH	**10** (HPLC area %)	Yield[c] of **3** (%)
1	1:1:1.3	8.5	57.3	30.1
2	1:1:1.5	9.0	38.6	51.6
3	1:1:1.7	9.5	28.8	65.2
4	1:1:1.9	9.8	19.1	72.1
5	1:1:2.0	10.3	8.5	81.8
6	1:1:2.1	10.8	19.6	70.1
7	1:1:2.3	11.4	28.6	62.3
8	1:1:2.5	12.0	30.1	58.6
9	1:1.05:2.1	10.3	8.2	82.5
10	1:1.10:2.2	10.4	8.9	80.8
11	1:1.15:2.3	10.1	10.0	79.2
12	1:1.20:2.4	10.2	13.8	77.1

[a]All cyclization procedures were carried out with 10 equivalents (based on compound **1**) of concentrated hydrochloric acid, reacted at 25 °C for 12 hours. [b]Molar feed ratio of **1**: hydroxylamine hydrochloride: sodium hydroxide = N_1: N_h: N_s. [c]The reaction yield was determined by external standard method (HPLC).

The effect of the molar flow ratio of **1**, hydroxylamine hydrochloride and sodium hydroxide (N_1: N_h: N_s) was then investigated, in an attempt to increase the yield (**Table 1**). The amount of sodium hydroxide was varied to investigate the effects of alkaline conditions on yield (entries 1−8). It can be seen that the alkaline conditions have a strong influence on the reaction. Too much or too little sodium hydroxide was not conducive to the formation of target product **3** because hydroxylamine attacked **1** in a weaker alkaline environment resulting in the formation of compound (**6**), and the hydroxylamine was deprotonated (NH_2O^-) under overbased conditions, producing some intermediates that were incapable of forming **3**. In addition, the study shows that 1.05 equivalents of hydroxylamine hydrochloride was a good compromise because excessive hydroxylamine hydrochloride led to an increase in side reactions (entries 9−12). The results

show that N_1: N_h: N_s = 1:1.05:2.1 was the most suitable molar ratio. Therefore, we determined the optimum conditions for the continuous flow process to be τ_1 = 40 s, T_1 = -5 °C, and N_1: N_h: N_s = 1:1.05:2.1 (pH = 10.3). Under these conditions, an isolated yield of 82% was successfully obtained with a purity of 99%.

Scheme 3. Hydrolysis of hydroxamic acid



In step 2 (the cyclization process), excessive strong acid is crucial for obtaining a large amount of target product **3**.[5a] It is known from the literature that hydroxamic acid can be hydrolyzed.[11] As shown in **Scheme 3**, insufficient acidic conditions can cause hydroxamic acid (**2**) to be hydrolyzed to produce acetoacetic acid (**4**), which is then reacted with hydroxylamine to give compound **7** that is followed by cyclization to form byproduct **10**. Therefore, the cyclization process (step 2) also has the potential to generate impurities. To reduce the formation of byproducts, we have explored the cyclization process. The results are shown in **Figure 3**.When the amount of concentrated hydrochloric acid was insufficient, a large amount of byproducts was formed due to hydrolysis of **2**, resulting in low yield. As the amount of concentrated hydrochloric acid increased, the yield increased to a constant value. The results showed that the yield reached a maximum of 82% with approximately 9 equivalents (based on compound **1**) of concentrated hydrochloric acid. The effect of cyclization temperature (T_2) on the yield of product was then investigated. The highest yield was obtained at a temperature of 30 °C. Low conversion rates caused by low-temperature conditions or side reactions caused by high-temperature conditions can result in a decrease in yield. We thus achieved a maximum yield of 84.6% at T_2 =

30 °C using 9 equivalents of concentrated hydrochloric acid. Byproduct **10** was reduced to 7%. This result indicated that the continuous flow process could be successfully utilized, and the yield of product **3** was greatly improved compared with that of the conventional batch reaction.

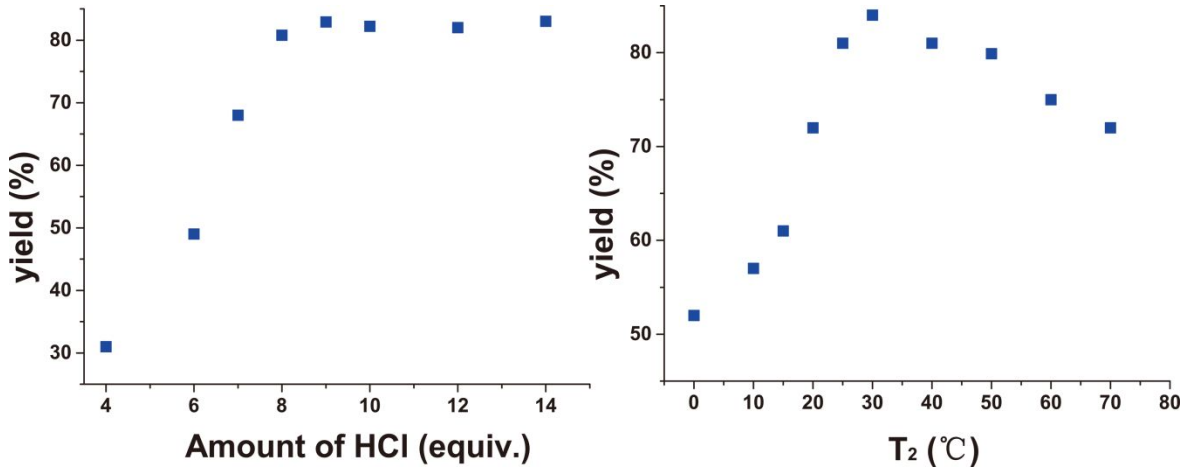


Figure 3. Effect of HCl and temperature (T_2) on the yield of product **3**.Yield was determined by external standard method (HPLC).

2. Fully Continuous Flow Process

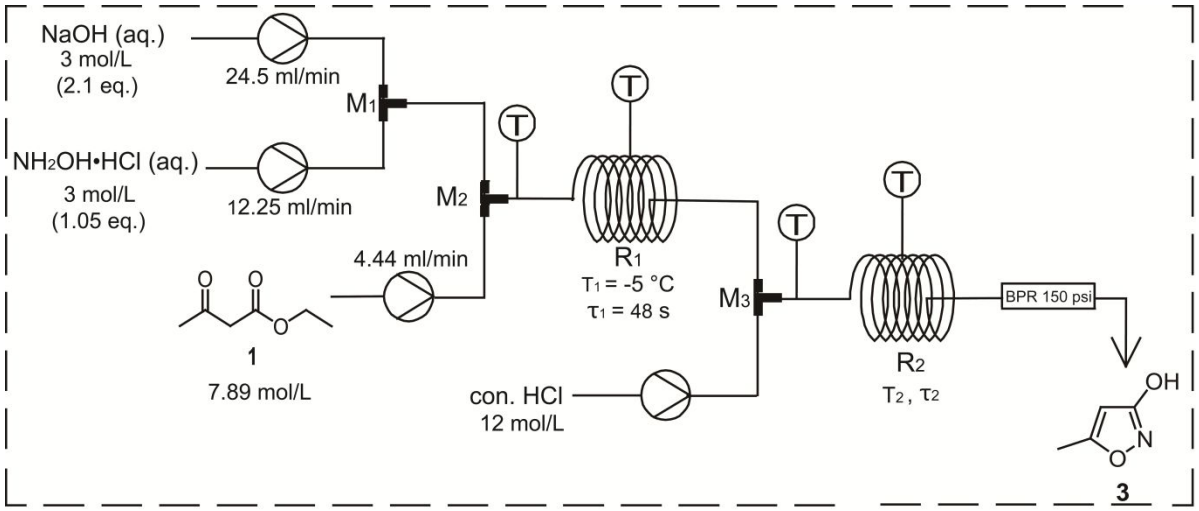


Figure 4. Fully Continuous Flow Process

Next, we attempted to establish a fully continuous flow process for the preparation of product **3**. As shown in **Figure 4**, unlike the semicontinuous process previously described, a fourth pump was introduced for the delivery of concentrated hydrochloric acid, and a tubular reactor (R_2, Hastelloy C276, 1.77 mm internal diameter) and a T-shaped mixer (M_3, Hastelloy C276, 1.77 mm internal diameter) replaced the original cyclized flask. There were four streams in total. The thermostatic bath temperature T_1 was set to -5 °C. Then, two plunger pumps were used to separately introduce sodium hydroxide solution (24.5 ml/min, 3 mol/L) and hydroxylamine hydrochloride solution (12.25 ml/min, 3 mol/L) into M_1 for mixing and precooling. The combined solution was mixed with **1** (4.44 ml/min, 7.89 mol/L) in M_2, and the resulting solution was passed through R_1. Then, the obtained mixture was mixed with the stream of concentrated hydrochloric acid (29.2 ml/min, 12 mol/L) via M_3 and pumped into R_2 for the cyclization reaction. M_3 and R_2 were immersed in a separate constant temperature bath to control the temperature T_2. After a steady state was reached, the product solution was collected. The pH of the reaction mixture was adjusted to 3-4 with a 30 wt% sodium hydroxide solution, which was followed by three extractions with dichloromethane. The organic phases were combined and the solvent was evaporated in vacuo to afford crude product **3**. The crude product was recrystallized from cyclohexane to obtain pure product **3**.

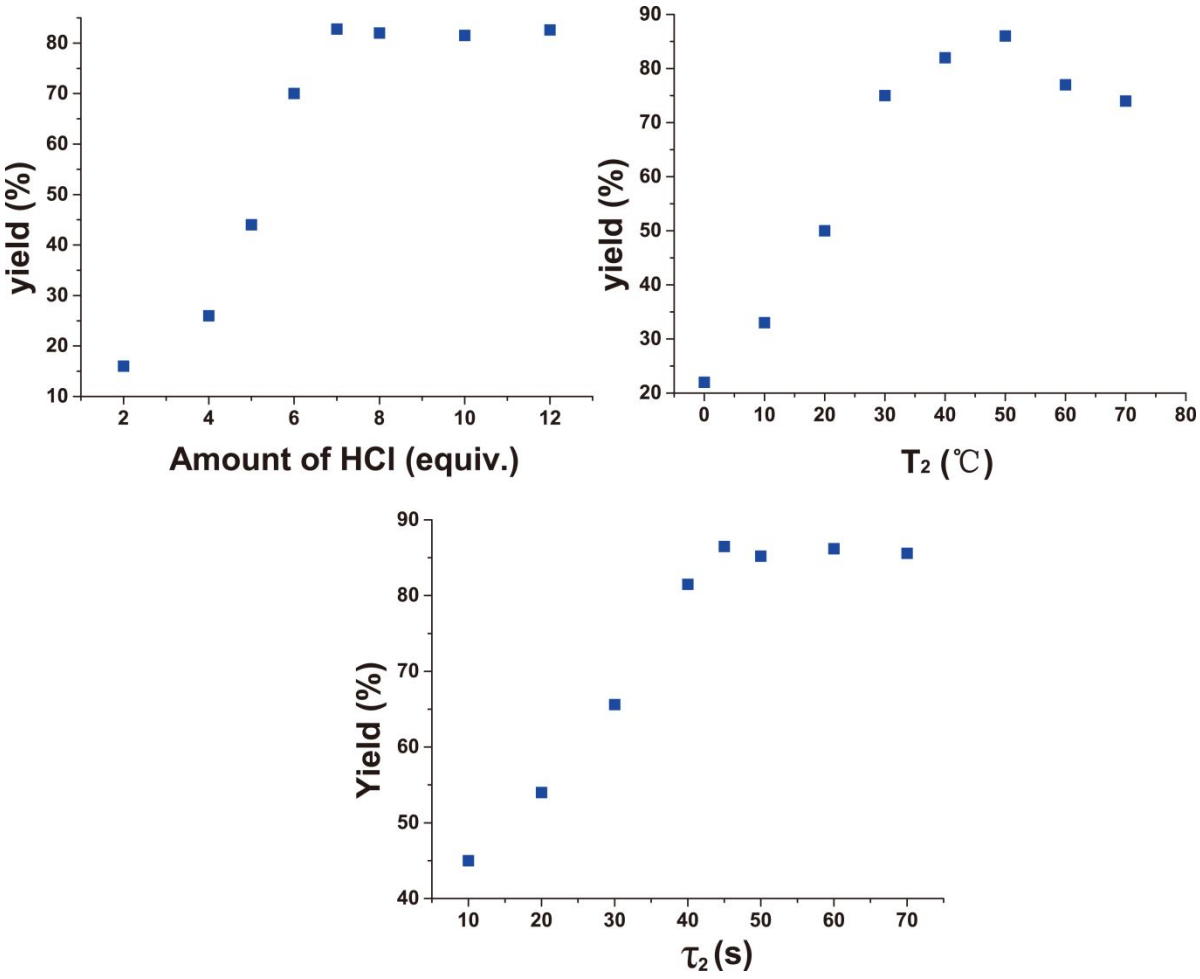


Figure 5. Effect of different reaction conditions on the yield of product **3**. Yield was determined by external standard method (HPLC).

The cyclization process parameters were systematically investigated, including testing the concentrated hydrochloric acid amount, reaction temperature T_2, and residence time τ_2, as shown in **Figure 5**. For the case in which the amount of concentrated hydrochloric acid was small, the yield of the product was lower due to the hydrolysis of **2**. As the amount of concentrated hydrochloric acid increased, the yield increased to a constant value. We found that only 7 equivalents (based on compound **1**) of concentrated hydrochloric acid were required for the yield to reach a maximum. Next, the effect of cyclization temperature (T_2) on the yield of product was

investigated. The highest yield was obtained at a temperature of 50 °C. Low conversion rates caused by low-temperature conditions or side reactions caused by high-temperature conditions can lead to a decrease in yield. Insufficient residence time led to incomplete conversion; the yield increased with the extension of the residence time τ_2 and remained essentially unchanged after 45 s. This result indicated that τ_2 = 45 s was a suitable residence time. Therefore, the optimum conditions for the continuous flow cyclization process were determined to be T_2 = 50 °C, τ_2 = 45 s, and 7 equivalents of concentrated hydrochloric acid. After the cyclization process was introduced into the continuous flow reactor from the reaction flask, we found that when the cyclization temperature was raised to 50 °C, a yield of 87% was obtained with a residence time of 45 s (τ_2), and the content of byproduct **10** was only 4%. In addition, the amount of concentrated hydrochloric acid used was reduced to 7 equivalents. The product from the fully continuous flow process was purified to give an isolated yield of 86.2%. The advantages of the continuous process were significant compared to the batch process.

To evaluate the advantages of the continuous flow process in the synthesis of **3**, we compared the optimal results of several modes of operation. As shown in **Figure 6**, in the two-step continuous flow process, the major byproduct **10** was significantly inhibited. Side reactions caused by inhomogeneous pH and temperature profiles during the mixing process can thus be effectively avoided in the continuous flow processes.

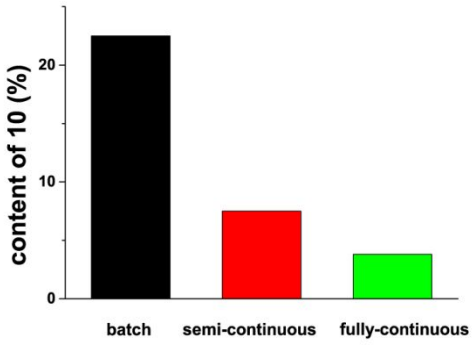


Figure 6. The content of byproduct **10** in different operation modes

As shown in **Table 2**, different results were obtained with the same synthetic route and different modes of operation. In the continuous flow reactor, the reaction time was greatly shortened compared with the batch reactor, and the yield of the final product **3** was also remarkably improved.

Table 2. Comparison of Batch and Continuous Flow

Operation manner	Total reaction time	Isolated Yield of **3** (%)
batch	2 h + 12 hours	68.0
semicontinuous flow	40 s + 12 hours	84.0
fully continuous flow	40 s + 45 s	86.2

3. Scale-Up of the Continuous Process

Finally, scaled-up production was carried out. The process equipment was changed to a larger geometry tube as shown in **Figure 7**. The inner diameters of all tubular reactors and T-shaped mixers were increased to 3 mm. To increase productivity, the flow rate of the feed was also increased. After running continuously for 3.5 hours, 1.78 kg of **3** was produced at an isolated

yield of 85%. The obtained product had a purity of 99%. The results showed the stability and utility of the continuous flow process and demonstrated its potential for industrial production.

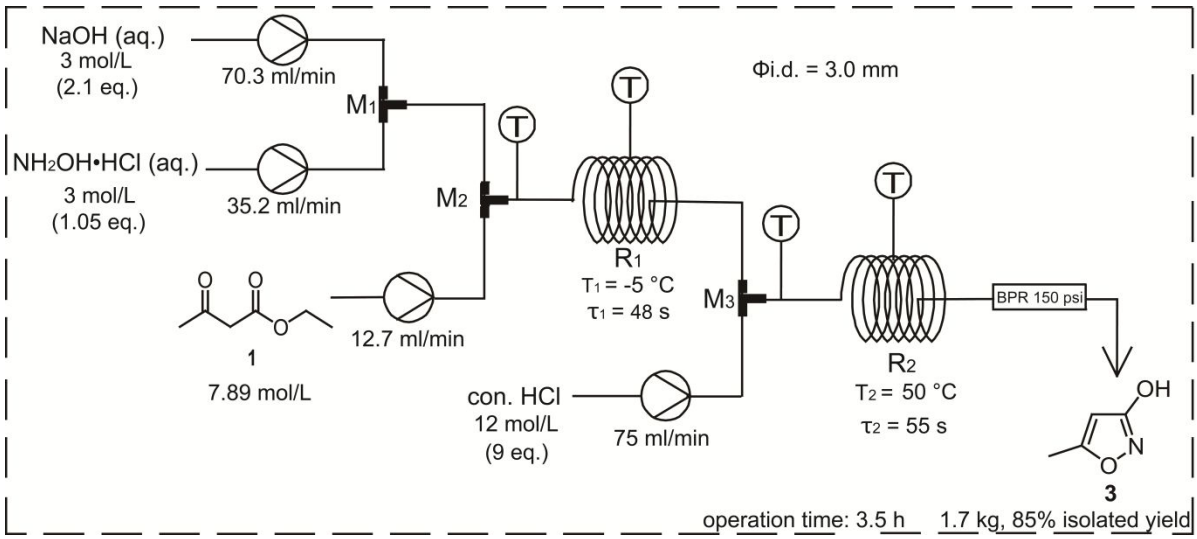


Figure 7. Scale-Up of the Continuous Process

EXPERIMENTAL SECTION

General Information.

All reagents were purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd. All pumps were purchased from Jiangsu Hanbon Science And Technology Co., Ltd. (Jiangsu, China). ^{13}C NMR and ^{1}H NMR spectra were recorded on an AVANCE III spectrometer (Bruker, Hangzhou, China) at 125 and 500 MHz NMR, respectively. MS data were recorded on a Thermo DSQ II GC-MS spectrometer equipped with an EI source and controlled by MassHunter software. Melting points were carried out on a B-545 melting point apparatus (Buchi, Hangzhou, China) and were uncorrected.

HPLC Method: The HPLC method for analyzing the yield and purity of hymexazol employed a Shim-Pack VP-ODS 250 mm × 4.6 mm (S-5μm, 12nm) column. The mobile phase consisted of

MeOH and pure water at a ratio of 60:40 and was pumped into the VP-ODS column at a total flow rate of 1.0 mL/min. Detection temperature was 25 °C, and the injection volume was 2.0 μL. Detection was carried out at 226 nm. The relative retention time of hymexazol at the time of elution was 3.48 min.

Batch Experiment

Sodium hydroxide (25 g, 0.6 mol) was dissolved in 200 ml of water, and a solution of hydroxylamine hydrochloride (3mol/l, 100ml, 0.3 mol) was added with stirring at 0 °C to achieve a solution of pH = 10; then, **1** (39.4 g, 0.3 mol) was added dropwise into the mixed solution at -5°C during 45 min, and after 2 hours of reaction, the mixture was poured into 250 mL of ice-cold concentrated hydrochloric acid , then it was allowed to stand at room temperature for 12 hours. Finally, the pH of the reaction mixture was adjusted to 3-4 with a 30 wt% sodium hydroxide solution, and then extracted with dichloromethane (3×250 g). The organic phases were combined and the solvent was evaporated in vacuo to afford crude product **3**. It was recrystallized from cyclohexane to obtain 19.5 g of white crystalline solid product **3** in 65% yield with a purity of 99%. CAS number 10004-44-1. mp 83-84 °C (lit.[5b] mp 84-85 °C); GC-MS (EI) m/z 99 ([M]+, 99); ^{1}H NMR (500 MHz, Chloroform-d) δ/ppm: 2.34 (s, 3H), 5.69 (s, 1H), 10.58 (s, 1H); ^{13}C NMR (125 MHz, Chloroform-d) δ/ppm: 12.90, 93.93, 170.38, 171.34.

General procedure for semicontinuous flow synthesis of hymexazol

As shown in **Figure 1**, aqueous sodium hydroxide (3 mol/L, 300 ml), hydroxylamine hydrochloride solution (3 mol/L, 150 ml), and ethyl acetoacetate (98%, 49.8 g, 0.38 mol) were prepared. The thermostatic bath temperature was set to -5 °C. Then, two plunger pumps were used to separately introduce sodium hydroxide solution (24.5 ml/min) and hydroxylamine hydrochloride solution (12.25 ml/min) into M_1 for mixing and precooling. The combined

solution was mixed with **1** (4.44 ml/min, 7.89 mol/L) in M_2, and the resulting solution was passed through R_1. After running for six minutes, the system reached a steady state. The output of the reactor was collected in a flask, continuously collected for 10 minutes, and then the collected mixture was poured into 292 ml (3.5 mol) ice-cooled concentrated hydrochloric acid and allowed to react at 25 °C for 12 hours. The pH of the reaction mixture was adjusted to 3-4 with a 30 wt% sodium hydroxide solution, followed by extraction with dichloromethane three times. The organic phases were combined, and the solvent was evaporated in vacuo to afford crude product **3**. It was recrystallized from cyclohexane to obtain 28.9 g of white crystalline solid product **3** with 82.5% yield and a purity of 99%.

General procedure for synthesizing hymexazol in a fully continuous flow process

As shown in **Figure 3**, aqueous sodium hydroxide (3 mol/L, 250 ml), hydroxylamine hydrochloride solution (3 mol/L, 125 ml), concentrated hydrochloric acid (12 mol/L, 300 ml), and ethyl acetoacetate (98%, 46 g, 0.35 mol) were prepared. There were four streams in total. The thermostatic bath temperature T_1 was set to -5 °C, T_2 was set to 50 °C. Then, two plunger pumps were used to separately introduce sodium hydroxide solution (24.5 ml/min, 3 mol/L) and hydroxylamine hydrochloride solution (12.25 ml/min, 3 mol/L) into M_1 for mixing and precooling. The combined solution was mixed with **1** (4.44 ml/min, 7.89 mol/L) in M_2, and the resulting solution was passed through R_1. Then the obtained mixture was mixed with the fourth stream of concentrated hydrochloric acid (29.2 ml/min, 12 mol/L) via M_3 and pumped into R_2 for the cyclization reaction. A back pressure regulator was used to adjust the pressure to within 150 psi. After a steady state was reached, the output of the reactor was collected for 10 minutes. The pH of the reaction mixture was adjusted to 3-4 with a 30 wt% sodium hydroxide solution, followed by extraction with dichloromethane (3×300 ml). The organic phases were combined,

and the solvent was evaporated in vacuo to afford crude product **3**. It was recrystallized from cyclohexane to obtain 30.4 g of white crystalline solid product **3** with 86% yield and a purity of 98%.

Scale-Up of the Continuous Process

As shown in **Figure 7**, four plunger metering pumps (PEEK, 100 ml) were used to pump four reagents. Three T-shaped mixers (M_1, M_2 and M_3, Hastelloy C276, 3.0 mm internal diameter), and two tubular reactors (R_1 and R_2, Hastelloy C276, 3.0 mm internal diameter) were used. Aqueous sodium hydroxide (3 mol/L, 14 L), hydroxylamine hydrochloride solution (3 mol/L, 7 L), concentrated hydrochloric acid (12 mol/L, 17.5 L), and ethyl acetoacetate (98%, 2675 g, 21 mol) were prepared. The thermostatic bath temperature T_1 was set to -5 °C, T_2 was set to 50 °C, and then sodium hydroxide solution (70.3 ml/min) and hydroxylamine hydrochloride solution (35.2 ml/min) were separately introduced to M_1 by two plunger pumps for mixing and precooling. The combined solution was mixed with **1** (12.7 ml/min, 7.89 mol/L) in M_2, and the resulting solution was passed through R_1. Then, the obtained mixture was mixed with the fourth stream of concentrated hydrochloric acid (75 ml/min, 12 mol/L) via M_3 and pumped into R_2 for the cyclization reaction. A back-pressure regulator was used to adjust the pressure to within 150 psi. After a steady state was reached, the product of the reactor was collected for 3.5 hours.

Procedure for Isolating **3**: The pH of the reaction mixture was adjusted to 3-4 with a 30 wt% sodium hydroxide solution, and then extracted with dichloromethane (3×25.5 kg). The organic phases were combined and the solvent was evaporated in vacuo to give crude product **3**. The crude product was recrystallized from cyclohexane to gain pure product **3** as a white solid with 85% yield (1.78 kg) and 99% purity. Dichloromethane and cyclohexane can be recycled repeatedly.

CONCLUSION

In summary, a stable and efficient continuous flow process for the synthesis of hymexazol has been developed. Significant process intensification and suppression of side reactions have been achieved compared to batch operations. After the initial scale-up of the continuous process, a productivity of 508.5 g/h was obtained, and the isolated yield was stable at approximately 85% with 99% purity. Furthermore, the utilization of continuous flow strategies provides a good alternative for the synthesis of hymexazol and offers possibilities for industrial production.

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge on the ACS Publications website.

Copies of $^{1}H/^{13}C$ NMR, HPLC and GC-MS spectra for compounds (PDF)

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Notes

The authors declare no competing financial interest.

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