

Multistep Synthesis of Paracetamol in Continuous Flow

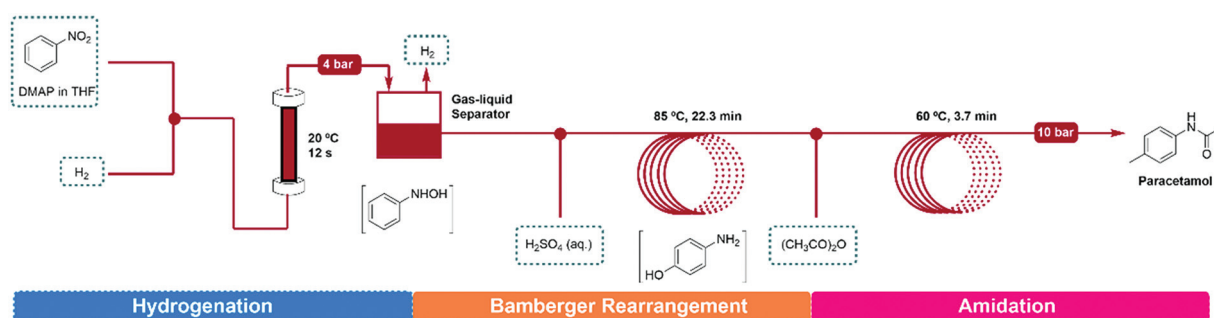
Jian-Li Chen^{1,2,*} Jing-Yu Hu¹ Qi-Fan Wang¹ Peng Ge¹ Quan-Hui Wang¹ Zi-Shuo Lou¹

¹ College of Advanced Materials Engineering, Jiaxing Nanhu University, Jiaxing, People's Republic of China

² Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education and Key Laboratory of Pharmaceutical Engineering of Zhejiang Province, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, People's Republic of China

Address for correspondence Jian-Li Chen, PhD, College of Advanced Materials Engineering, Jiaxing Nanhu University, Jiaxing 314000, People's Republic of China (e-mail: cjl329044626@163.com).

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Abstract

p-Aminophenol (AP) is the key intermediate of the traditional synthesis of paracetamol. The method of obtaining AP included a selective reduction reaction of the generation of *N*-arylhydroxylamine (AHA) using nitrobenzene (NB) as the raw material, followed by a Bamberger rearrangement reaction to transfer AHA to the target product. The generation of AHA is a key step, but due to its structural instability and the incompatibility of the two reaction systems, one-pot synthesis of paracetamol faces great challenges. Considering that using flow reactors in series may avoid the problems faced by batch reactors, the article presents the strategy to obtain paracetamol via a continuous flow technology. In particular, we focus on condition screening in total synthesis experiments, including hydrogenation, Bamberger rearrangement, and amidation in flow. The continuous three-step synthesis process used NB as a raw material to generate AHA, which entered the downstream for timely conversion, achieving *in situ* on-demand preparation of the unstable intermediate AHA, avoiding cumbersome processing and storage processes. Moreover, each step of the reaction system exhibits excellent compatibility, and the work-up is simple.

Keywords

- ▶ multistep synthesis
- ▶ paracetamol
- ▶ continuous flow

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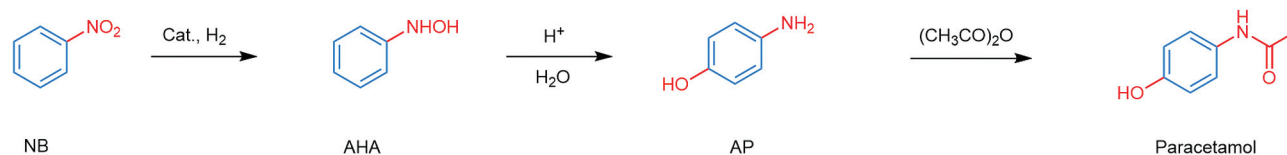
Introduction

Paracetamol is a commonly used antipyretic and analgesic drug. Meanwhile, it is also used as a key intermediate in the synthesis of drugs such as Benorilate. At present, paracetamol has become one of the most widely used drugs in the world. Especially during the COVID-19 (coronavirus disease 2019) pandemic, paracetamol remains the preferred drug for treating fever symptoms caused by the virus in many regional hospitals.¹

The traditional synthesis route of paracetamol mainly uses *p*-aminophenol (AP) as the intermediate (►Scheme 1), so the development of its synthesis process can also be seen as the development of the synthesis process of AP.^{2,3} The reported raw materials for the synthesis of AP mainly include nitrobenzene (NB), *p*-nitrophenol, and *p*-nitrosophenol.¹ However, the synthesis process using *p*-nitrophenol and *p*-nitrosophenol as raw materials does not have a cost advantage compared with NB as raw materials. The synthesis route from NB consists of two steps, namely selective reduction, and Bamberger rearrangement, which are often achieved through the “one-pot” synthesis in batch production.^{4,5}

Although there have been many reports on the synthesis routes using *N*-arylhydroxylamine (AHA) as a key intermediate, the selectivity of catalytic hydrogenation to prepare AHA remains a challenge. It is known that catalyst poisoning by adding dimethyl sulfoxide (DMSO) can improve the selectivity of AHA, but this practice is not conducive to the recovery of metal catalysts and requires a long reaction time.⁴ Amines are considered to have a good effect on enhancing reaction activity and are often used to compensate for the loss of catalyst activity.⁶ However, in the synthesis of paracetamol, the Bamberger rearrangement requires the addition of acids, making these two reaction systems incompatible.

In previous studies, we developed a 4-(dimethylamino)pyridine (DMAP)-mediated protocol for preparing AHA with Pt/C as a catalyst, in which DMAP not only improved the catalytic activity but also increased the selectivity of AHA.⁷ On this basis, using flow reactors in series can avoid the problems faced by batch reactors. Continuous flow technology has a series of advantages, such as better mass and heat transfer performance, residence time control, and inherently safer.^{8–11} The laminar flow characteristics of flow chemistry are conducive to the *in situ* on-demand preparation of unstable chemicals.^{12,13} We herein describe a fully continuous synthesis process of paracetamol via AHA intermediates. By *in situ* on-demand preparation, it is beneficial to avoid the oxidation of AHA to the azoxy compounds.



Scheme 1 Synthetic route of paracetamol.

Materials and Methods

Material

All chemicals were purchased from Sinopharm Chemical Reagent Shanghai Co., Ltd. (Shanghai, China) and were used without further purification. The T-shape mixer, back-pressure regulator, and stainless-steel tubing (SS316L) were obtained from Beijing Xiongchuan Technology Co., Ltd. (Beijing, China). Pumps (LC500P) were obtained from Hangzhou Xuyu Technology Co., Ltd. (Hangzhou, China). A packed bed (SS-98, Ø 3.0 × 50 mm) was obtained from the Dalian Baigareda Technology Co., Ltd. (Dalian, China). High-performance liquid chromatography (HPLC) analysis was performed on a United States Agilent 1100 series equipped with a C18 chromatographic column (5 μm, 4.6 mm × 250 mm, NanoMicro Technology Co., Ltd. (China). Melting points were determined on a BUCHI Melting Point B-540 apparatus (Switzerland) and were not corrected. The NMR (nuclear magnetic resonance) spectroscopy data recorded for the purified product were obtained using the BRUKER AVANCE III HD system (Bruker Bio-Spin, Rheinstetten, Germany).

Hydrogenation Experiment in Flow

The device diagram is shown in ►Fig. 1. The filled packed bed was first flushed with methanol at a rate of 0.5 mL/min over 30 minutes after being put into the continuous flow device. The solution of NB (0.1 mol/L) and DMAP (0.01 mol/L) was pumped into the flow system installed with a catalyst cartridge (5 wt.% Pt/C) under the H₂ pressure of 0.6 MPa. After purging the solution for 30 minutes, the sample was collected three times. The sampling interval was 20 minutes. The HPLC was carried out at 30°C with water and acetonitrile as the mobile phase, eluted at 60%:40% isotherm for 20 minutes. The detection wavelength and temperature are 254 nm and 30°C, respectively.

Bamberger Rearrangement Experiment in Flow

The device diagram is shown in ►Fig. 2. The solution of AHA (1.09 g, 0.1 mol/L) in tetrahydrofuran (THF) and sulfuric acid aqueous solution was pumped into the tube reactor (stainless steel, 1/8 inch) via a T-shape mixer by two pumps. After purging the solution for 10 minutes, the sample was collected three times. The sampling interval was 20 minutes. The flow rate for both pumps was set as 0.5 mL/min and a back pressure as 1.0 MPa. The adjustment of residence time is controlled by changing the length of the tube reactor. The following experimental parameters were used during sample analysis: gradient percentages of methanol were used as the eluent: 0%, 3 minutes; 0–50%, 25 minutes; 50–0%,

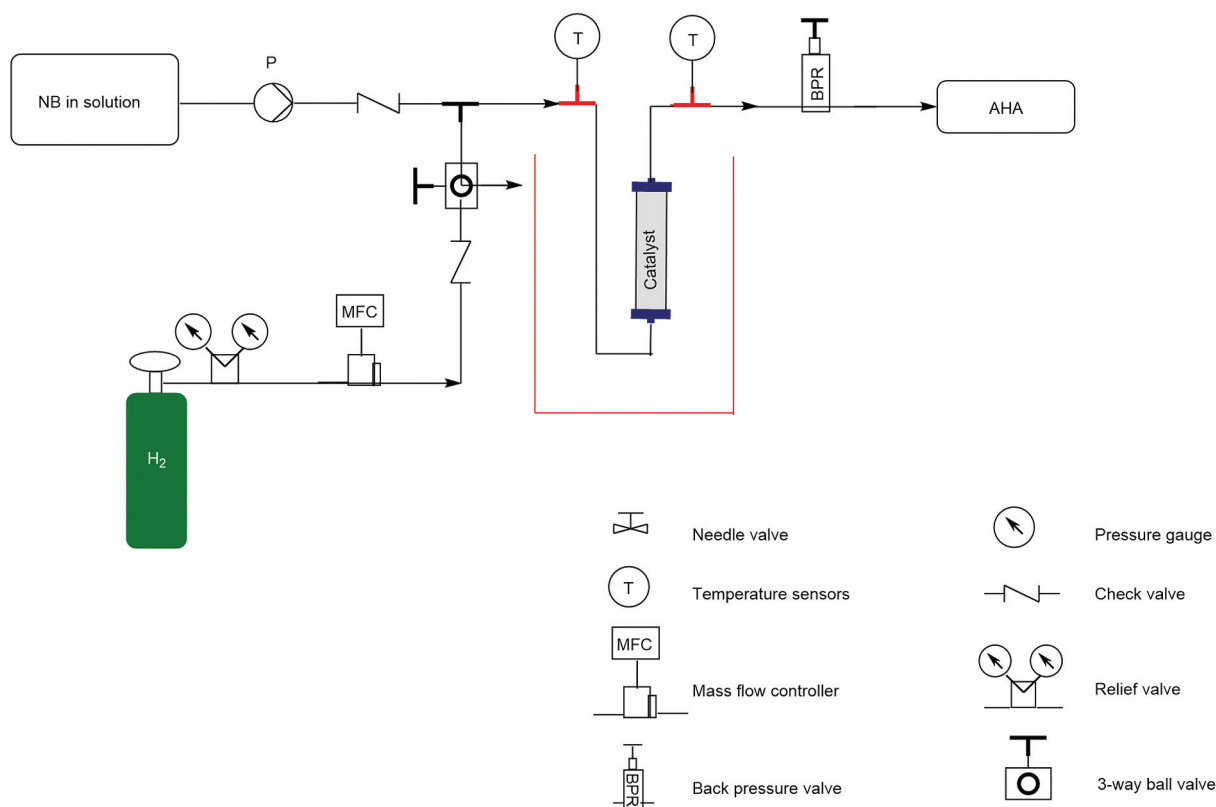


Fig. 1 Schematic diagram of continuous flow device for hydrogenation of NB. NB, nitrobenzene.

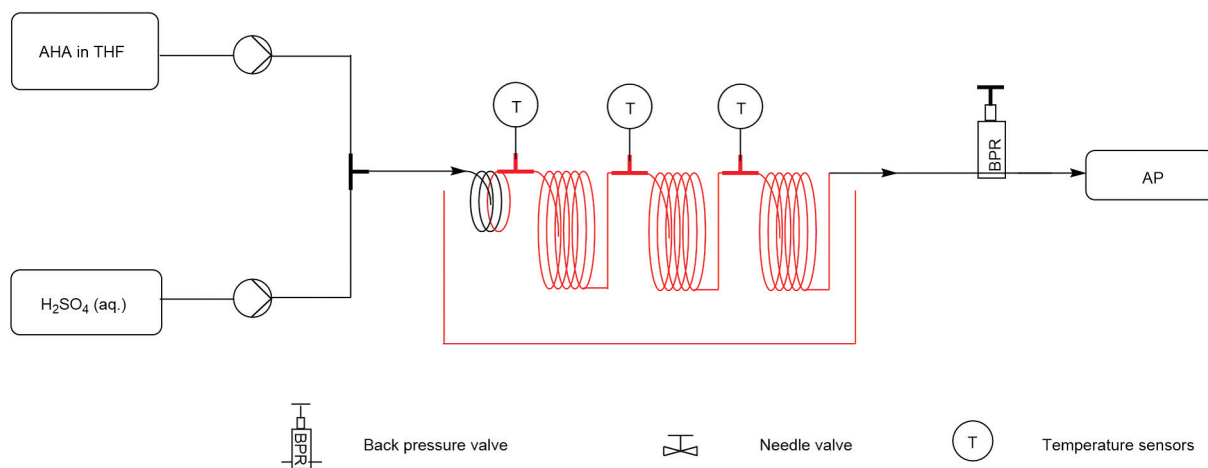


Fig. 2 Schematic diagram of continuous flow device for Bamberger rearrangement.

3 minutes; and 0%, 7 minutes. The detection wavelength and temperature are 254 nm and 30°C, respectively.

Amidation Experiment in Flow

The device diagram is shown in ► **Fig. 3**. The solution of AP (0.55 g, 0.05 mol/L) and 50.5 mL 3 wt.% H₂SO₄ (aq.) in THF and acetic anhydride were pumped into the tube reactor (stainless steel, 1/8 inch) via a T-shape mixer by two pumps. After purging the solution for 10 minutes, the sample was collected three times. The sampling interval was 20 minutes. The solution of AP has a flow rate of

1.0 mL/min and acetic anhydride has a flow rate of 0.014 mL/min. The adjustment of residence time is controlled by changing the length of the tube reactor. The following experimental parameters were used during sample analysis: HPLC-grade methanol and 1% potassium dihydrogen phosphate aqueous solution were used to prepare the mobile phase. Gradient percentages of methanol were used as the eluent: 0%, 3 minutes; 0–50%, 25 minutes; 50–0%, 3 minutes; and 0%, 7 minutes. The detection wavelength and temperature are 254 nm and 30°C, respectively.

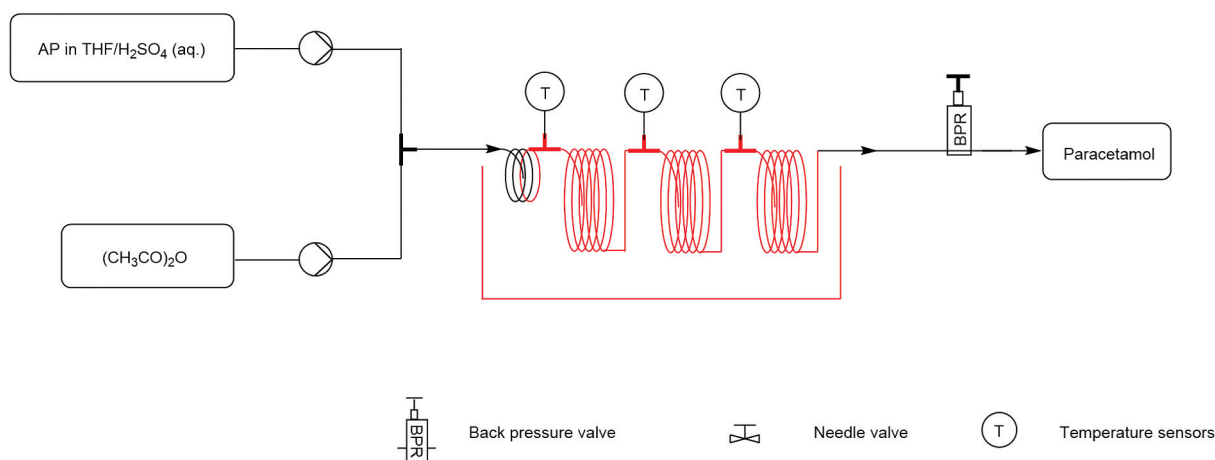


Fig. 3 Schematic diagram of continuous flow device for amidation reaction.

Total Synthesis Experiment in Flow

The device diagram is shown in ▶Fig. 4. P_1 , P_2 , and P_3 transport NB solution, 3.0 wt.% H_2SO_4 (aq.), and acetic anhydride into a continuous flow system at 0.5, 0.5, and 0.014 mL/min, respectively. The back pressure is set to 0.4 and 1.0 MPa respectively, and the hydrogen pressure is 0.6 MPa. Specific reaction conditions are as follows: T_1 , 20°C; T_2 , 85°C; T_3 , 60°C; τ_1 , 12 seconds; τ_2 , 22.3 minutes; τ_3 , 3.7 minutes. Add a three-necked flask as a gas–liquid separator after hydrogenation to avoid the impact of hydrogen on stoichiometric control. Collect the reaction solution 30 minutes after it flows out. 1H NMR (600 MHz, $DMSO-d_6$): 9.63 (s, 1H), 9.12 (s, 1H), 7.35 (d, $J=9.0$ Hz), 6.68 (d, $J=9.0$ Hz), 1.98 (s, 3H). mp: 168–170°C (lit,¹⁴ mp: 169°C).

Results and Discussions

Optimization of Hydrogenation in Flow

The optimal conditions of hydrogenation were first explored. In previous studies, we have extensively investigated the effect of solvents on conversion and selectivity using *o*-chloronitrobenzene as a model substrate.⁷ In the section, we will not conduct solvent screening because solvents have similar effects on different nitroarenes. THF was found to be a favorable solvent for the preparation of AHA. In addition, 0.1 equiv. was also determined as the optimal usage for DMAP. The effects of temperature, liquid flow rate, and EtOAc on the reaction were examined, and the results are shown in ▶Table 1. Because the subsequent two steps require water as the medium, we expect to use EtOAc as the hydrogenation reaction solvent to facilitate the work-up. Unfortunately, ethyl acetate cannot provide better selectivity than THF at 25°C (▶Table 1, entries 1 and 2). It was found that the selectivity of AHA can reach 98.2% and the reaction was completed at 20°C (▶Table 1, entry 3). However, as the temperature raised, the selectivity decreased to 81.9% at 35°C (▶Table 1, entries 4 and 5). The change in liquid flow rate also led to a significant change in the selectivity of AHA. When the liquid flow rate decreased from 0.75 to 0.1 mL/min, i.e., the residence time increased from 8 to 60 seconds, the

selectivity decreased from 99.5 to 79.1% (▶Table 1, entries 6–8). Therefore, the optimal conditions for the hydrogenation in flow were determined as follows: the solvent is THF, the temperature is 20°C, the liquid flow rate is 0.5 mL/min, and the residence time is 12 seconds.

Optimization of Bamberger Rearrangement in Flow

Due to the excellent selectivity of the reaction system combining acetic anhydride and acetic acid in the amidation reaction, we first investigated the effects of various acids on the Bamberger rearrangement in batch. Acetic acid, trifluoroacetic acid, hydrochloric acid, and sulfuric acid were investigated. The results showed that neither acetic acid nor trifluoroacetic acid could observe the occurrence of reaction conversion at 80°C, while hydrochloric acid showed lower reaction activity than sulfuric acid. Therefore, sulfuric acid was determined as the acid source. Meanwhile, no by-products were observed in the batch, so the parameter evaluation was based on conversion as the only result. The effects of molar ratio, temperature, and residence time on the reaction were examined, and the results are shown in ▶Table 2.

First, under the premise of a molar ratio of 2 between acid and AHA, the temperature was investigated, and it was found that the reaction did not occur at 70°C (▶Table 2, entry 1). It is consistent with the description in the literature that the reaction needs to be performed at high temperatures.¹⁵ This can also be observed from the reaction performed at a molar ratio of 20, even if the acid is increased by 10 times, the conversion is extremely low (▶Table 2, entry 11). Although the residence time (3.7 seconds) under this condition is very short, subsequent parameter investigations further confirm the importance of temperature. In the investigation of temperature, it was found that the conversion rate showed a gradual increase from 75°C to 85°C (▶Table 2, entries 2–4). There is no doubt that this temperature range is effective for the reaction. However, the conversion is still only 20.9% at 85°C, which is not ideal. Therefore, we attempted to increase the amount of acid. The results showed that when the molar ratio increased from 4 to 6, the conversion suddenly increased from 25.9 to 60.8%, and there was no significant

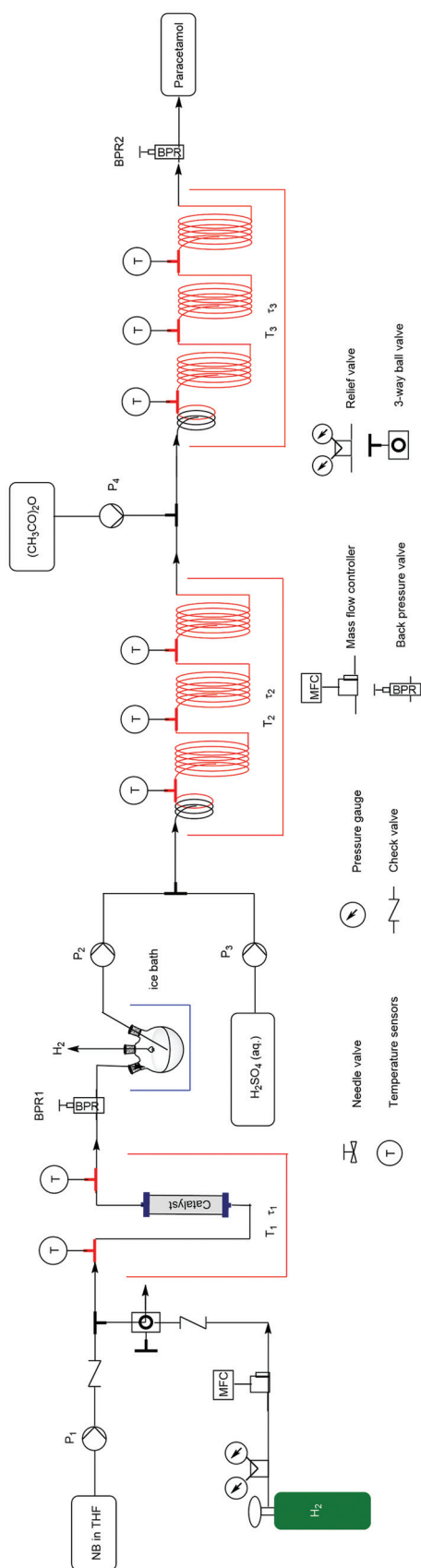


Fig. 4 Schematic diagram of continuous flow device for the synthesis of paracetamol.

change when the molar ratio increased to 8 (►Table 2, entries 5–7). It is inferred that this is similar to the effect of temperature, and the amount of acid also needs to reach a certain level to fully activate reactivity. Undoubtedly, increasing the temperature is beneficial for the rearrangement reaction, but a cooling section needs to be added later to ensure that the reaction liquid cools down and flows into the next reactor. Therefore, we choose to extend the residence time to avoid the addition of cooling sections. When the residence time increases from 11.1 to 22.3 minutes, full conversion can be achieved (►Table 2, entries 8–10). Therefore, the optimization conditions for the Bamberger rearrangement in flow are as follows: the molar flow ratio of acid to AHA is 6, the temperature is 85°C, and the residence time is 22.3 minutes.

Optimization of Amidation in Flow

In the amidation reaction of AP, the possible byproduct comes from the esterification of hydroxyl groups. According to the literature, water as the reaction medium and acetic anhydride as the acylation reagent are the most ideal choices, and this combination can ensure the quantitative conversion of the reaction. In the previous Bamberger rearrangement, using sulfuric acid as the acid source will cause the decomposition of acetic anhydride to produce acetic acid. Similarly, no by-products were observed during the reaction, so the conversion remains the only result for evaluation. In this section, a molar flow ratio of 3 between acetic anhydride and AP was selected to prevent the decomposition of acetic anhydride from affecting the reactivity, which is higher than the required stoichiometry for the reaction. The experimental results are shown in ►Table 3. It was found that higher temperatures and longer residence times were beneficial for the reaction and no by-products were observed (►Table 3, entries 1–5). To avoid a significant temperature gradient, a temperature of 60°C and a residence time of 3.7 minutes were selected as the appropriate reaction conditions for the amidation reaction in flow.

Total Synthesis of Paracetamol in Flow

Based on the previous optimal conditions, we designed a three-step continuous process for the synthesis of paracetamol. The fully continuous system runs for 4 hours under a steady state and collects the reaction solution. Apply the optimal conditions of each step to the fully continuous synthesis and collect the reaction solution that has been running steadily for 4 hours. The collected solution is concentrated by rotary evaporation and then recrystallized with water. After standing for 2 hours at a low temperature, filter to obtain a light-yellow solid. Dissolve the solid in ethanol and add activated carbon for decolorization. After filtration, the solvent is removed by rotary evaporation and recrystallized with water. After standing at a low temperature for 2 hours, a white solid was obtained by filtration and dried to weigh 1.56 g. Based on NB of 1.48 g, the yield was 86% and the purity was 99.3%.

Table 1 Optimization of reaction conditions of hydrogenation in a continuous flow

| Entry | Solvent | T (°C) | Liquid flow rate (mL/min) | τ (s) | Conversion (%) | Selectivity (%) |
|-------|---------|--------|---------------------------|------------|----------------|-----------------|
| 1 | EtOAc | 25 | 0.5 | 12 | >99.9 | 92.7 |
| 2 | THF | 25 | 0.5 | 12 | >99.9 | 94.6 |
| 3 | THF | 20 | 0.5 | 12 | >99.9 | 98.2 |
| 4 | THF | 30 | 0.5 | 12 | >99.9 | 89.8 |
| 5 | THF | 35 | 0.5 | 12 | >99.9 | 81.9 |
| 6 | THF | 20 | 0.75 | 8 | 44.7 | 99.5 |
| 7 | THF | 20 | 0.25 | 24 | >99.9 | 87.8 |
| 8 | THF | 20 | 0.1 | 60 | >99.9 | 79.1 |

Note: Conditions: DMAP (0.1 equiv.), 5 wt.% Pt/C (1 cartridge; \varnothing 3.0 mm \times 50 mm; 0.1 g), H₂ pressure (6 bar), back pressure (4 bar). All reagents were premixed before use. Conversion and selectivity were determined by HPLC.

Table 2 Optimization of reaction conditions of Bamberger rearrangement in a continuous flow

| Entry | Molar ratio (H ⁺ /AHA) | T (°C) | τ (min) | Conversion (%) |
|-------|-----------------------------------|--------|--------------|----------------|
| 1 | 2 | 70 | 11.1 | 0 |
| 2 | 2 | 75 | 11.1 | 6.4 |
| 3 | 2 | 80 | 11.1 | 16.1 |
| 4 | 2 | 85 | 11.1 | 20.9 |
| 5 | 4 | 85 | 11.1 | 25.9 |
| 6 | 6 | 85 | 11.1 | 60.8 |
| 7 | 8 | 85 | 11.1 | 61.4 |
| 8 | 6 | 85 | 15.0 | 74.1 |
| 9 | 6 | 85 | 18.5 | 89.4 |
| 10 | 6 | 85 | 22.3 | >99.9 |
| 11 | 20 | 70 | 3.7 | 5.8 |

Abbreviation: AHA, *N*-arylhydroxylamine.

Note: Conditions: flow rate of AHA solution and acid: 0.5 mL/min. All reagents were premixed before use. The conversion was determined by HPLC.

Table 3 Optimization of reaction conditions of amidation in a continuous flow

| Entry | T (°C) | τ (min) | Conversion (%) |
|-------|--------|--------------|----------------|
| 1 | 40 | 3.7 | 56.1 |
| 2 | 40 | 5.4 | 74.3 |
| 3 | 40 | 7.2 | >99.9 |
| 4 | 50 | 3.7 | 86.9 |
| 5 | 60 | 3.7 | >99.9 |

Note: Conditions: flow rate of AP solution: 0.5 mL/min, flow rate of acetic anhydride: 0.014 mL/min. All reagents were premixed before use. The conversion was determined by HPLC.

Conclusion

In summary, we have developed a three-step continuous synthesis process for paracetamol using NB as a raw mate-

rial. The addition of 0.1 equiv. DMAP in the hydrogenation system can be neutralized by sulfuric acid in Bamberger rearrangement, and both Bamberger rearrangement and acylation reactions are compatible with acid systems. In the process, the generated AHA can enter the downstream for timely conversion, which enables *in situ* on-demand preparation of AHA and avoids the cumbersome process of processing and storage. The larger scale experiment is still in progress.

Conflict of Interest

None declared.

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