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An Eight-Step Continuous-Flow Total Synthesis of Vitamin B₁

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ABSTRACT

Vitamin B₁ is widely applied in the healthcare and food industry as an antineuritic and antioxidant to maintain the normal functioning of nerve conduction, the heart, and the gastrointestinal tract. This study reports on an integrated eight-step continuous-flow synthesis of vitamin B₁ from commercially available 2-cyanoacetamide. The proposed continuous-flow process is based on advances in chemistry, engineering, and equipment design, and affords improved performance and safety compared with batch-mode manufacturing. Several challenges were precisely investigated and controlled, including mixing, unexpected clogging, solvent switches, an exothermic reaction, and the prevention of side reactions, using various micro-channel flow reactors, mixers, separators, and continuous filters. Vitamin B₁ was produced with a separated yield of 47.7% and high purity, with a total residence time of about 3.5 h. This eight-step continuous-flow protocol enables technology involving up to six of the key principles of green chemistry. Hence, the application of flow technology is of paramount importance for improving security, reducing waste, and, in particular, improving the efficiency of batch operations that require several days for manufacturing.

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1. Introduction

Vitamin B₁ (denoted herein as **1**; Fig. 1), is an antineuritic vitamin that can improve glucose metabolism. It plays an essential role in the metabolism of branched-chain amino acids and carbohydrates [1]. Commonly, vitamin B₁ is used to treat thiamine deficiency and to prevent its related disorders, including beriberi, Korsakoff's syndrome, and psychosis [2,3]. It is also broadly applied as a supplement in the food industry and is extensively used in cosmetic products and in the healthcare industry as an antioxidant [4]. The global thiamine mononitrate (vitamin B₁) market is estimated to be 680 million to 710 million USD and is expected to grow at a compound annual growth rate (CAGR) of 5.0%–6.8% over the forecast period of 2023–2035 [5,6]. This growth of the market can be attributed to the increasing demand for vitamin B₁ supplements. Huazhong Pharmaceutical, Brother Enterprises, DSM, and Zhejiang Tianxin Pharmaceutical share a majority of the thiamine

hydrochloride market. These companies mainly focus on the advancement of new technologies and devices, expanding from their territories to grab a vital share of the global market [6].

Since the isolation of vitamin B₁ (**1**) from yeast by Windaus in 1932, this compound has been synthesized via different strategies over the past 80 years [7–12]. An industrial method for the synthesis of **1** using Grewe diamine (**5**; Fig. 2) as the key building block, patented by Matsukawa and coworkers in 1951, has been applied till now. As shown in Fig. 2, the diamine **5** reacts with a chloroketone (**6**) and carbon disulfide, giving ketodithiocarbamate (**7**), and afterwards thiothiamine (**8**), which is then oxidized and transformed into **1** [13]. After the 1950s, intensive efforts were made to modify and improve the approach for operation on a manufacturing scale [7,14–17]. The normal starting materials to prepare **5** are acrylonitrile and malononitrile. However, malononitrile is an essential cost causal factor in the production of **5**, while many strategies beginning with the cheaper acrylonitrile are cumbersome, which has led to many chances for the formation of byproducts that can exist in the final product [7]. Recently, our group reported a short and efficient route to prepare **5** from 2-cyanoacetamide (**2**) [18]. However, the operation complexity of

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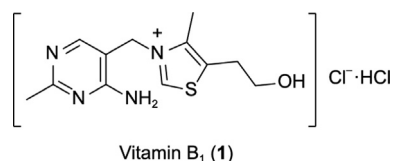


Fig. 1. Chemical structure of vitamin B₁ (1).

the multi-step synthesis and the batch-mode protocol offer great possibilities for enhancements in production.

Recently, the development of integrated continuous-flow manufacturing has gained increasing attention in both the pharmaceutical and fine chemical industries, due to its potential for faster, cheaper, and more flexible production [19–23]. For example, Snead and Jamison [24] described a 3 min synthesis and purification of ibuprofen using an integrated continuous-flow system, and Tsubogo et al. [25] reported a successful multi-step continuous-flow synthesis of (*R*)- and (*S*)-rolipram. Moreover, Cole et al. [20] developed a kilogram-scale continuous synthesis platform for prexasertib monolactate monohydrate that involves eight continuous unit operations. Inspired by these excellent cases, our group investigated the synthesis of **5** and **6** by means of a multi-continuous-flow process [26,27]. The operations were substantially improved by using a simplified reaction process, and the reaction time was greatly reduced (from days to hours), significantly enhancing the mixing and reaction efficiency. Hence, we postulated that a wise choice of reactants and solvents in the reaction route would allow for an efficient synthesis of vitamin B₁ from the starting material via a continuous-flow process [28–32]. Thus, in this study, we developed an eight-step continuous-flow synthesis of **1** using a variety of devices. We envisaged that the target product **1** might be accessible via continuous-flow synthesis by subsequently combining a series of flow devices such as micro-channel flow reactors, online mixers, and separators, as well as surge vessels in between for dispositions.

Our synthetic route to **1** in this study is depicted in Fig. 2. In our pathway, the flow process suppresses side reactions with milder conditions, reduces the operation time, and results in good product quality with high productivity.

2. Experimental section

2.1. General information

The solvents were purified through standard methods prior to use. All chemicals except 3-chloro-4-oxopentyl acetate (**6**) were obtained from commercial companies in China (i.e., Sinopharm,

Bidepharm, Macklin, and Picasso-e). The side chain **6** was prepared via a continuous-flow process reported earlier [27]. Modified Raney nickel (Ni; 20–40 mesh, in water) was obtained according to a method described in our previous work [26].

2.2. Characterization

During the flow operations, samples were collected from the outlet of the reaction system after two residence times. The equivalence for each flow reaction was controlled by the solute concentration and the flow rate of the reactants. For each reaction step, the reaction kinetics were valuated as follows:

$$-r_A = r_P = -\frac{dC_A}{dt} = \frac{dC_P}{dt} \quad (1)$$

where r_A ($\text{mol}\cdot(\text{L}\cdot\text{min})^{-1}$) is the consumption rate of the reactant; r_P ($\text{mol}\cdot(\text{L}\cdot\text{min})^{-1}$) is the generation rate of the product; and C_A ($\text{mol}\cdot\text{L}^{-1}$) and C_P ($\text{mol}\cdot\text{L}^{-1}$) are the concentrations of the reactant and product at a certain reaction time t (min), respectively. The conversion of the reactant (x_A , %) was calculated according to Eq. (2):

$$x_A = \frac{C_{A0} - C_{Af}}{C_{A0}} = 1 - \frac{C_{Af}}{C_{A0}} \quad (2)$$

where C_{A0} ($\text{mol}\cdot\text{L}^{-1}$) is the initial concentration of the reactant, and C_{Af} ($\text{mol}\cdot\text{L}^{-1}$) is the final concentration of the reactant in the solution. Based on these calculations, the overall isolated yield for the desired product was calculated as follows:

$$\text{Isolated yield} = \frac{N_p}{C'_{A0} \times x'_A \times F_r \times t'} \times 100\% \quad (3)$$

where N_p (mol) is the molecular amount of the desired product separated from the collected sample during a certain time period t' (min), where t' (min) is the time used for collecting the sample; C'_{A0} ($\text{mol}\cdot\text{L}^{-1}$) is the initial concentration of the starting material; x'_A (%) is the conversion of the starting material; and F_r ($\text{L}\cdot\text{min}^{-1}$) is the flow rate of the reactant solution. It should be noted that, in this work, a reactant conversion of no less than 98% was achieved for each reaction step before proceeding to the next step; thus, the value for x'_A was approximately 1 in our study.

The compound concentration, reactant conversion, and product purity were obtained using liquid chromatography–mass spectrometry (LC-MS) or gas chromatography–mass spectrometry (GC-MS). The GC-MS analysis employed an Agilent 7820 gas chromatograph system and an Agilent 5977B electron ionization mass detector. An Agilent HP-5ms capillary column was used with helium as the carrier gas at a flow rate of $0.9 \text{ mL}\cdot\text{min}^{-1}$ with a split ratio of 20:1; the injector temperature was kept at $250 \text{ }^\circ\text{C}$. The column temperature was started at $80 \text{ }^\circ\text{C}$, then held for 2 min, and

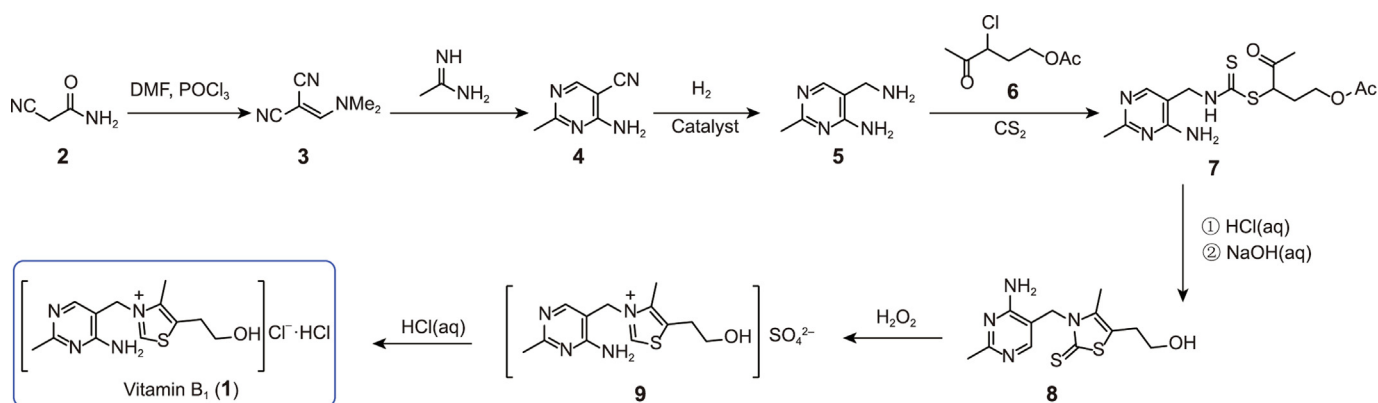


Fig. 2. The proposed eight-step continuous-flow total synthesis route to **1**. DMF: dimethylformamide; aq: aqueous.

then increased at a rate of $20\text{ }^{\circ}\text{C}\cdot\text{min}^{-1}$ until reaching $280\text{ }^{\circ}\text{C}$, at which it was held for 7 min. The LC-MS analysis employed an Agilent 6545 LC/quadrupole time-of-flight (Q-TOF) Agilent 1260 Infinity II, Eclipse Plus C18, RRHD Eclipse Plus C18, $2.1\text{ mm} \times 50\text{ mm}$, $1.8\text{ }\mu\text{m}$ threaded column. In addition, ^1H nuclear magnetic resonance (NMR) spectra were recorded at 400 MHz (Bruker Avance 400). For the ^1H NMR spectroscopy, the chemical shifts were reported in parts per million (ppm) downfield from deuterated chloroform (CDCl_3 ; $\delta = 7.26\text{ ppm}$) and deuterated dimethyl sulfoxide (DMSO-d_6 ; $\delta = 2.50\text{ ppm}$).

2.3. Continuous-flow system

The continuous-flow system included commercially available feeding equipment, continuous reactors, a process control unit, and so on. The details of the devices used are provided below:

- Feeding equipment: syringe pump (Fusion 4000 and Fusion 101, Chemyx, USA), pre-calibrated high-performance liquid chromatography (HPLC) pump (MPF0502C, Sanotac, China), precalibrated peristaltic pump (L/S Easy-Load II, Masterflex, Germany);
- Continuous reactors: stainless steel fixed-bed reactor (1 cm i.d., 20 cm length, MF200, Shenzhen E-Zheng Tech. Co., Ltd., China), Coflore Agitating Cell Reactor (ACR-P200, AM Technology, UK), polytetrafluoroethylene (PTFE) coiled reactor (0.8 mm i.d., 1.6 mm o.d.; 1.6 mm i.d., 3.2 mm o.d.), T-mixer and cross-mixer (2.0 mm i.d.), PTFE fittings (Runze Fluid, China), stainless steel coiled reactor (1/8 inch i.d., 1 inch = 2.54 cm), and stainless steel fittings (Shanghai X-Tec Fluid Tech. Co., Ltd., China);
- Process control unit: stainless steel one-way valve (SS-CVG01A-K1F, Shanghai X-Tec Fluid Tech. Co., Ltd.), back-pressure valve (2.5, 7, and 10 bar, 1 bar = 10^5 Pa ; IDEX Co., USA), gas mass-flow controller (MFC; CX-GMFC-CXB-4-R4-D-A1-F2, Shenzhen E-Zheng Tech. Co., Ltd.), and thermostat (Integral XT150, Lauda, Germany).

3. Results and discussion

The highly promising continuous-flow synthesis of Vitamin B₁ (1) was first established using 2-cyanoacetamide (2) from an eco-

nomic perspective. This synthesis was originally developed by our group as a highly efficient route to generate 2-(dimethylaminoethylidene)propanedinitrile (3) in batch mode [18]. We began by mixing the starting material 2 ($4.5\text{ mol}\cdot\text{L}^{-1}$, 1.0 equiv) and an organic base (pyridine, 0.1 equiv) in dimethylformamide (DMF, 2.0 equiv) with POCl_3 through a T-mixer to the PTFE coiled reactor I at $0\text{ }^{\circ}\text{C}$ (Fig. 3). A Vilsmeier reaction then proceeded with 96% conversion into compound 3 when the mixed stream flowed to the PTFE coiled reactor II at $25\text{ }^{\circ}\text{C}$ with a total residence time of 5 min and a back-pressure of 2.5 bar. Further optimization revealed that reduced flow rates at the same temperature resulted in the complete conversion of 2-cyanoacetamide into 3 with a residence time of 10–15 min (Table 1). The optimized process provided the desired product 3 in a separated yield of 94% and a purity of 98% after online neutralization by inducing saturated sodium bicarbonate solution through another T-mixer and online extraction through an online liquid–liquid membrane separator.

A continuous-flow cyclization process was then investigated to convert compound 3 into the desired 4-amino-2-methylpyrimidine-5-carbonitrile (4) in an Autichem flow reactor (10 mL work volume), as shown in Fig. 4. The reaction conditions, such as flow rate and temperature, were carefully controlled in the flow operation to prevent clogging. Blockages were observed within 30 min when we initially performed the flow cyclization reaction in flow, where a dichloroethane (DCE) solution of compound 3 ($0.95\text{ mol}\cdot\text{L}^{-1}$, 1.0 equiv) and an acetamidine MeOH solution ($3.3\text{ mol}\cdot\text{L}^{-1}$, 1.2 equiv) prepared from acetamidine hydrochloride and sodium methoxide were streamed to the flow reactor at $75\text{ }^{\circ}\text{C}$ with a residence time of 5–7 min (Table 2, entries 1 and 2). This clogging probably resulted from solvent evaporation at the high temperature, because no back-pressure regulator was attached in the flow protocol, resulting in elevated proportions of the solid inside the reactor, which attenuated the flowability of the reaction mixture. A further investigation was performed by decreasing the reaction temperature to $65\text{--}70\text{ }^{\circ}\text{C}$, which solved the problem (entries 3–5). The cyclization reaction was found to be satisfactory when proceeding at $70\text{ }^{\circ}\text{C}$ in almost full conversion with a residence time of 5 min. The desired product 4 was generated in a separated yield of 91.2% with 99.2% purity after filtering and drying the reaction slurry (entry 6).

Subsequently, a methanol solution of 4-amino-2-methylpyrimidine-5-carbonitrile (4, $0.075\text{ mol}\cdot\text{L}^{-1}$) and aqueous ammonia

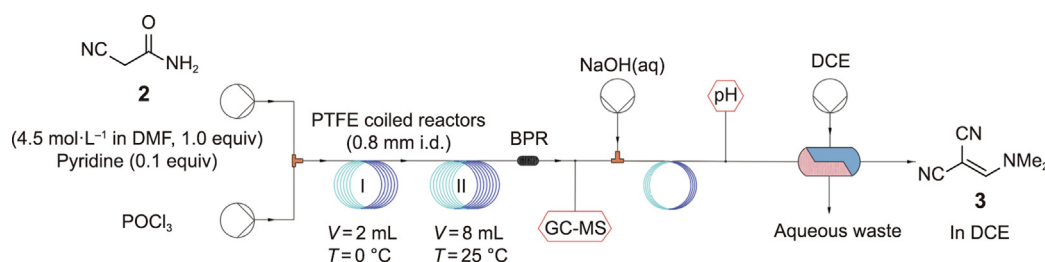


Fig. 3. Continuous-flow synthesis of 3. BPR: back-pressure regulator; DCE: dichloroethane.

Table 1
Optimization of the flow conditions for the synthesis of 3.

Entry	F_1^a ($\text{mL}\cdot\text{min}^{-1}$)	F_2^a ($\text{mL}\cdot\text{min}^{-1}$)	V (mL)	T ($^{\circ}\text{C}$)	Residence time (min)	Purity (%)
1	0.9	1.1	10	25	5	96
2	0.5	0.5	10	25	10	98
3	0.3	0.4	10	25	15	98
4	0.2	0.3	10	25	20	95
5	0.9	1.1	10	25	5	97

^a F_1 and F_2 stand for the flow rates of 2 in DMF solution and POCl_3 , respectively.

(25 wt%) was pumped through a packed-bed reactor (20 mm × 100 mm; filled with modified Raney Ni catalyst) and treated with hydrogen gas at 100 °C with a residence time of 2 min under a back-pressure of 16 bar (Fig. 5). Performing the hydrogenation in continuous flow made it possible to flexibly control different reaction parameters, such as the liquid and gas flow rates and the reaction pressure (Table S4 in Appendix A). The desired product **5** was observed from the outlet of the flow system with the full conversion of **4** once the liquid flow rate was lower than 2 mL·min⁻¹ and the gas flow rate was no less than 40 standard cubic centimeters per minute (sccm).

After successfully establishing a dependable flow protocol for the synthesis of **5**, we shifted our efforts to the chlorination and decarboxylation/acylation steps to produce the 3-chloro-4-oxopentyl acetate (**6**) side chain, as outlined in our previous study [28]. This reaction was conducted with the isolated chlorination of acetyl butyrolactone with chlorine gas in a corrosion-resistant SiC flow reactor; the raw product was then mixed with the acetic acid solution in a cross-mixer and streamed to a coiled reactor to generate the desired product **6** (Fig. S11 in Appendix A).

With the methanol solution of the pyrimidine ring product **5** and the side chain **6** in hand, our next work was to develop a continuous-flow process for the synthesis of **7**. As shown in Fig. 6, the reactant **6**, **5** (0.29 mol·L⁻¹) in methanol, and a stream of CS₂ were transferred into an Autichem flow reactor heated at

40 °C. An incomplete conversion of **5** into **7** was found in the reaction with a residence time of 7 min (92%, Table 3, entry 1). The residence time was then investigated further. Table 3 shows that the conversion rate increased to 98% when the residence time was increased to 15 min (entries 2 and 3). It should be noted that blockage occurred when the reaction temperature was increased to 50 °C after running for 4–5 residence times (entries 4–6). This may have been due to the high concentration of solids produced by the reaction. Further investigation was performed by reducing the reaction concentration of **5** to 80% of the initial concentration and decreasing the reaction temperature to 45 °C. The product was provided with incomplete conversion of the reactant **5** (entries 7 and 8). We then extended the reaction time by reducing the flow rates of the feedings; however, clogging issues occurred, possibly due to the attenuated mixing (entries 9 and 10). At last, final optimized conditions were achieved that favored a stable continuous-flow synthesis of **7**, resulting in a complete conversion of **5** with 98% purity, 86% isolated yield, and a residence time of 7 min (entry 11). Increasing the molar ratio of compound **6** to compound **5** gave the same result (entry 12). Moreover, the NH₄OH from the last step could be used directly in this continuous-flow protocol, and no extra addition was needed.

After successfully obtaining compound **7** in solid form after filtration, an aqueous solution of hydrochloric acid (1 mol·L⁻¹) was pumped into the reaction vessel heated at 75 °C (see Fig. S13, setup 2, in Appendix A). It was found that the hydrolysis reaction of **7** achieved a complete conversion after 10 min in a stirring vessel, giving a clear solution that was continuously pumped to be neutralized with a stream of sodium hydroxide solution (20% w/w) in a tubing reactor at room temperature. The target compound **8** was produced in a slurry with full conversion of **7** and a 92% isolated yield with 99% purity (Table S5 in Appendix A).

We then focused on establishing the last two steps in the flow sequence for the formation of **1** (Fig. S15 in Appendix A). With the aqueous slurry of **8** (0.29 mol·L⁻¹) in hand, an Autichem flow reactor was employed for the synthesis of **9** at 25 °C with a residence time of 25 min, giving a separated yield of 88% and 98% purity by means of LC-MS analysis. The effluent was then filtered and reacted with the methanol solution of hydrochloric acid (40% v/v)

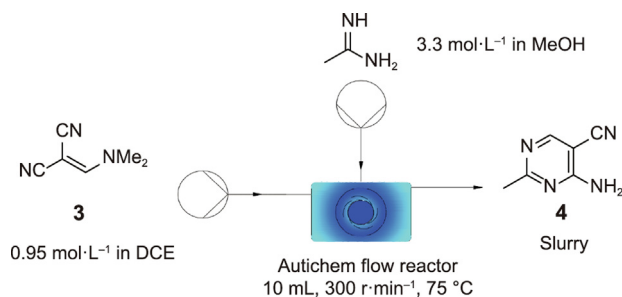


Fig. 4. Continuous-flow synthesis of **4**.

Table 2
Optimization of the flow conditions for the synthesis of **4**.

Entry	F_3^a (mL·min ⁻¹)	F_4^a (mL·min ⁻¹)	T (°C)	Residence time (min)	Yield (%)	Purity (%)
1	0.35	1.15	75	7	Blockage	95.6 ^b
2	0.46	1.54	75	5	Blockage	99.1 ^b
3	0.12	0.38	65	20	–	98.7
4	0.23	0.77	65	10	–	92.3
5	0.35	1.15	70	7	88.4	94.6
6	0.46	1.54	70	5	91.2	99.2

^a F_3 stands for the flow rate of the DCE solution of **3**; F_4 stands for the flow rate of the methanol solution of acetamidine.

^b Purity data obtained before clogging took place in the reactor; however, it is not representative.

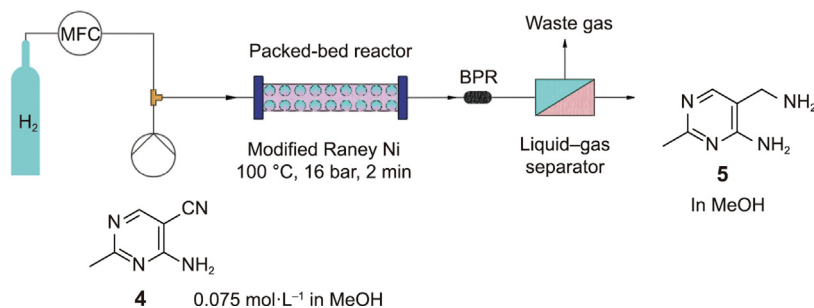


Fig. 5. Continuous-flow synthesis of **5**.

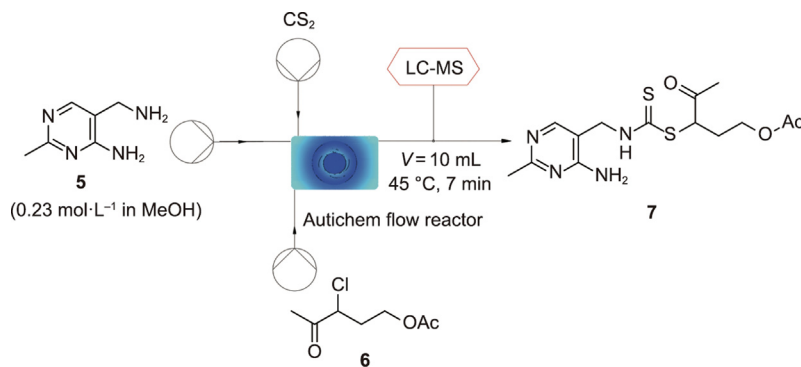


Fig. 6. Continuous-flow synthesis of 7.

Table 3
Optimization of the flow conditions for the synthesis of 7.

Entry	F_5^a (mL·min ⁻¹)	F_6^a (mL·min ⁻¹)	$F_{CS_2}^a$ (mL·min ⁻¹)	T (°C)	Residence time (min)	Purity (%)
1	1.18	0.12	0.090	40	7.0	92
2	0.80	0.08	0.060	40	11.0	98
3	0.60	0.04	0.040	40	15.0	98
4	1.18	0.12	0.090	50	7.0	98 ^b
5	0.80	0.08	0.060	50	11.0	98 ^b
6	0.60	0.04	0.040	50	15.0	Blockage
7	3.78 ^c	0.20	0.100	45	2.5	80
8	1.89 ^c	0.10	0.050	45	5.0	95
9	0.95 ^c	0.05	0.025	45	10.0	Blockage
10	0.63 ^c	0.04	0.020	45	15.0	Blockage
11	1.40 ^c	0.08	0.040	45	7.0	98
12	1.40 ^c	0.10	0.050	45	7.0	98

^a F_5 stands for the flow rate of **5** in methanol solution; F_6 stands for the flow rate of **6**; F_{CS_2} stands for the flow rate of CS_2 .

^b Blockages occurred after the process ran for about 1 h.

^c The concentration of **5** in MeOH was $0.23 \text{ mol}\cdot\text{L}^{-1}$, which was 0.8 times the initial concentration of **5**.

at 65 °C for 25 min in a continuous stirring reactor. The final product **1** was generated with an isolated yield of 95% and 99% purity as an off-white solid. The NMR data for the final product is presented in Fig. S17 in Appendix A.

After step-by-step optimizations, a continuous-flow synthesis of **1** from commercially available starting materials was achieved. The sequential combined eight-step chemical transformation was conducted smoothly in flow. In the multi-continuous-flow protocol, each step was monitored using the inline sampling method, as shown in Fig. 7. The startup and shutdown transitions for the whole continuous process were simplified by the flexible combination of surge vessels and valves, allowing uninterrupted running for sequential unit operations. Based on mass balance calculations (Table S7 in Appendix A), the starting material 2-cyanoacetamide (**2**) underwent a flow Vilsmeier reaction with DMF and pyridine in the PTFE coiled reactors I and II. The reaction solution was neutralized using NaOH solution and was then extracted using DCE solvent in a membrane liquid–liquid separator. The organic effluent was collected in surge vessel I; then, the solution was pumped to mix with a methanol solution of acetamidine in the Autichem flow reactor I to obtain compound **4** in slurry. Subsequently, a continuous filtering reactor I was applied for the solvent switching and dilution. A stainless steel column packed with a modified Raney Ni catalyst was used for the hydrogenation of **4**. The reaction mixture from the outlet was separated using a gas–liquid separator, and the liquid was collected in surge vessel II. The side chain 3-chloro-4-oxopentyl acetate (**6**) was prepared from chlorinate acetyl butyrolactone through a continuous-flow protocol. Then, the raw product of **6** was directly reacted with **5** in methanol from surge vessel II and CS_2 in Autichem flow reactor II. An integrated platform consisting of filtering reactor II and coiled reactor IV was followed to

produce a slurry of **8**, which was transferred to Autichem flow reactor III and proceeded to undergo flow oxidation with H_2O_2 . The slurry of **9** from the outlet was filtered and reacted with a methanol solution of HCl in the filtering reactor III to implement the subsequent one-pot displacement reaction. Eventually, the target product **1** was obtained after filtration and drying with an overall isolated yield of 47.7% and 98% purity over eight steps. The residence time of the whole operation was about 3.5 h with an approximate productivity of 127 g per day.

4. Conclusions

In this study, we established an integrated eight-step continuous-flow process for the synthesis of vitamin B₁ from cost-effective 2-cyanoacetamide with a total yield of 47.7% and a whole residence time of approximately 3.5 h. The main strengths of this continuous-flow technology for synthesizing vitamin B₁ are its flexible and efficient operations with short reaction times (from days to hours), simple operations (i.e., fewer workups), improved safety, and superior potential for industrial manufacturing compared with traditional batch synthesis. This eight-step continuous-flow protocol includes up to six of the key principles of green chemistry. Furthermore, this is the first example of the successful use of a fully innovative conversion from batch mode into the continuous-flow synthesis of a drug or biologically important compound. We are now working on the whole continuous-flow process for industrial applications on a kilogram scale. Real-time analysis may be conducted using a series of process analytical tools such as online liquid chromatography, gas chromatography, or Fourier-transform infrared spectroscopy while performing manufacturing activities in the future.

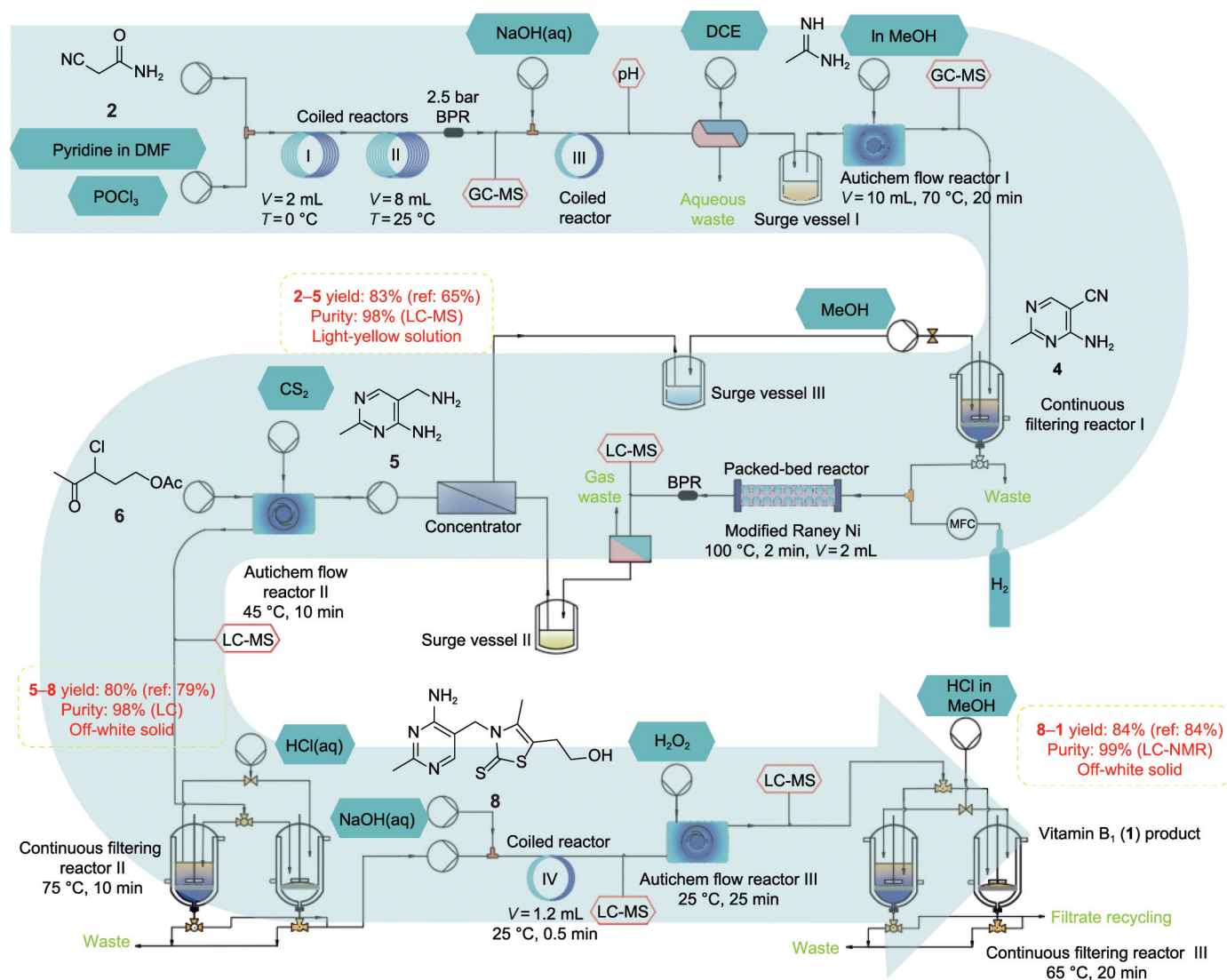


Fig. 7. Eight-step continuous-flow total synthesis of 1. LC: liquid chromatography.

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Compliance with ethics guidelines

Meifen Jiang, Minjie Liu, Weijian Li, Yingqi Xia, and Fen-Er Chen declare that they have no conflict of interest or financial conflicts to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.eng.2023.01.016>.

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