

# Fully Continuous Flow Synthesis of 3-Chloro-4-oxopentyl Acetate: An Important Intermediate for Vitamin B<sub>1</sub>

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**ABSTRACT:** A fully continuous flow synthesis of 3-chloro-4-oxopentyl acetate (**2**), an important intermediate for vitamin B<sub>1</sub> (**1**), was developed. This continuous flow manufacturing included two chemical transformations and an inline extraction step without intermediate purification and solvent exchange. In this work, the traditional synthetic route for batch operation was efficiently simplified via a series of separated screening tests in flows under various conditions. We found that the chlorination reaction can be carried out in only 30 s at room temperature by flow. We also simplified the decarboxylation/acylation step by using a cross-mixer, so that acetic anhydride was no longer required in the acylation reaction. A computational fluid dynamics simulation was carried out to study the improved micromixing of liquid–liquid two-phase streams. Finally, 3-chloro-4-oxopentyl acetate (**2**) was obtained in a 90% isolated yield with a product purity of 96% and a total residence time of approximately 32 min. This fully continuous process was operated smoothly for 12 h, and approximately 19.1 g of the desired product was generated with a production rate of 1.79 g h<sup>-1</sup>.

**KEYWORDS:** vitamin B<sub>1</sub>, 3-chloro-4-oxopentyl acetate, continuous flow synthesis, inline extraction and separation, microchannel reactor, cross-mixer

## 1. INTRODUCTION

3-Chloro-4-oxopentyl acetate (**2**) is a vital intermediate for the synthesis of vitamin B<sub>1</sub> (Figure 1) in most industrial

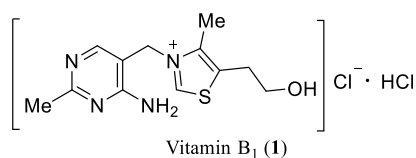


Figure 1. Structure of vitamin B<sub>1</sub> (**1**).

processes.<sup>1</sup> As an antineuritic vitamin, vitamin B<sub>1</sub> plays an important role in the metabolism of carbohydrates and branched-chain amino acids, especially for the growth of humans and animals.<sup>2</sup> According to the global “Vitamin B<sub>1</sub> (Thiamine Mononitrate) Market 2020” research report, the global vitamin B<sub>1</sub> market revenue was USD 648.8 million in 2020 and will be projected to reach USD 854.7 million by 2026.<sup>3</sup>

Driven by the potential to improve control over quality, reduce costs, enhance process safety, and significantly reduce the timelines in batch operations,<sup>4–6</sup> successful innovation and adoption of continuous manufacturing is essential in the industry’s future, exhibiting unique benefits such as better mass and heat transfer, good control over extreme reaction conditions, lower plant footprint, and production flexibility.<sup>7–10</sup>

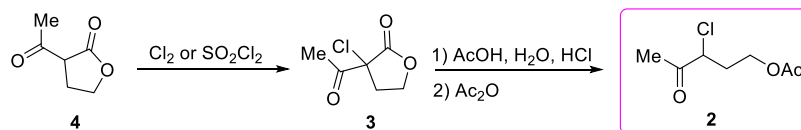
Thus, although little recent research has invested in the production of vitamin B<sub>1</sub> as a well-established treatment, improved manufacturing via continuous flow synthesis

technology is required for a more economic, safer, and greener vision.

Batch synthesis routes for 3-chloro-4-oxopentyl acetate (**2**) have been previously reported in the literature (see Scheme 1). US patent 2,932,653<sup>11</sup> reported a method in 1960, where acetyl butyrolactone was mixed with anhydrous sodium acetate and glacial acetic acid and chlorinated by chlorine gas. Then, concentrated hydrochloric acid and acetic anhydride were added subsequently to the filtrate in the presence of acetic acid in solution under vacuum distillation. Plazzi<sup>12</sup> in 1981 and Archer and Perianayagam<sup>13</sup> in 1978 produced 3-chloro-4-oxopentyl acetate (**2**) in a total yield of less than 80% using acetyl butyrolactone (**4**) and sulfuryl chloride as the starting materials. The intermediate was acylated by acetic anhydride to give the desired product. Similarly, Hawksley<sup>14</sup> in 2001 reported acetyl butyrolactone (**4**) being chlorinated with sulfuryl chloride and then decarboxylated and acetylated by heating with acetic and hydrochloric acids followed by the addition of acetic anhydride to give 3-chloro-4-oxopentyl acetate in 76% yield in total. Under similar reflux conditions, Thomas<sup>15</sup> in 2008, Herbert<sup>16</sup> in 2011, and Nemeria<sup>17</sup> in 2016 also reported the generation of compound **2** using sulfuryl chloride, followed by ring opening and acylation through refluxing with acetic anhydride in acetic acid. The product was obtained after purification with yields of 81, 77 and 63%.

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## Scheme 1. Synthesis Route to 3-Chloro-4-oxopentyl Acetate (2) in Batch Production



All of the processes mentioned above were operated in batch with massive unavoidable work-ups, limited by poor heat and mass transfer. Some reactions took several days, which was time- and cost-consuming. Therefore, efforts need to be made to improve production efficiency. Herein, we report the first example of a fully continuous flow synthesis of 3-chloro-4-oxopentyl acetate (2) from readily available starting materials. The synthesis procedures are referenced with slight modification of the methods described in the batch operation from the reported literature mentioned above. In this work, chlorine gas is applied to chlorinate acetyl butyrolactone (4), and acetic anhydride is introduced for further acylation in the second step in addition to acetic acid. This fully continuous manufacturing process of 3-chloro-4-oxopentyl acetate (2) provides a highly effective flow synthesis route and continuous operation sequence with excellent yield and purity.

## 2. EXPERIMENTAL SECTION

**2.1. Materials and Apparatus.** **2.1.1. Materials.** The reactant acetyl butyrolactone (99.68%) was acquired from [bidepharm.com](http://bidepharm.com). Chlorine gas (99%) was supplied by Jiangxi Ganzhong Chlor-Alkali Manufacturing Co., Ltd. Acetic acid ( $\geq 99.5\%$ ), hydrochloric acid (36.0–38.0%), acetic anhydride ( $\geq 99.5\%$ ),  $\text{NaHCO}_3$  ( $>99.5\%$ ), and dichloromethane (DCM, 98%) were all purchased from Sinopharm Chemical Reagent Beijing Co., Ltd.

Care should be taken when handling chlorine and reaction tail gas, as they are very toxic. Any reaction waste should be neutralized using alkali solution and put in separate waste containers.

**2.1.2. Apparatus.** Coil reactors were constructed from PTFE tubing bought from Runze Fluid Co., Ltd. with 0.8 mm i.d. An MPF0502C (Sanotac) plunger pump and F4000 (Chemyx Co. Ltd.) syringe pump were used to pump the reagents and solutions. Pressures at different stages were controlled using a 0.5–2 bar adjustable back pressure valve (Chemtrix) and 7 bar or 10 bar fixed back pressure regulator cartridges (Chemtrix), respectively. The reagent streams, reaction mixtures, and post-synthetic carrier streams were combined using Teflon T-mixers and cross-mixers with 2.5 mm i.d. (Nanjing Runze Fluid Co. Ltd.). Scheme 2 clearly presents the different stages and the key equipment used for the reaction.

**2.1.3. Protrix Reactor.** Protrix is a modular, ceramic flow reactor that is normally used for reaction screening and small-scale production (see Figure S1 in the Supporting Information). It contains three SiC modules that can be flexibly configured to deliver the required numbers of reagents, reaction volumes, and temperature zones. Each module contains a reaction channel and an integrated heat exchange layer to give optimal thermal control (see Figure S2).

**2.1.4. Inline Extractor/Separator.** The inline extractor/separator consists of three PTFE plates (designed as A, B, and C) sandwiching a 2000 mesh stainless steel screen and a PTFE membrane (pore size of  $0.45 \mu\text{m}$ ) (Figure 2). Modified from the Zefluor membrane separator,<sup>18,19</sup> identical channels were

## Scheme 2. Reaction Stages and the Key Equipment

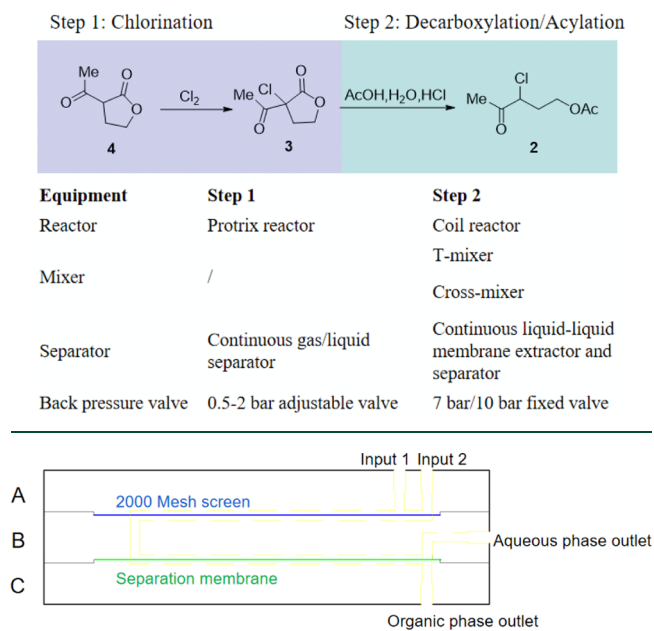
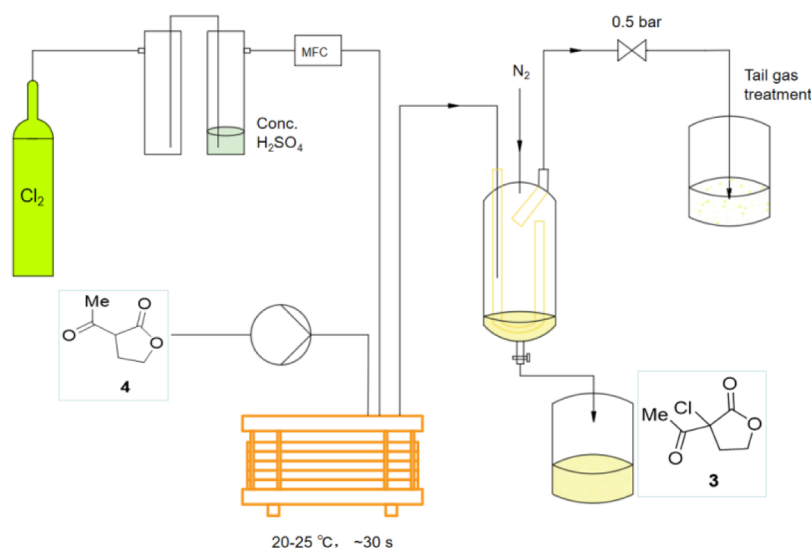


Figure 2. Continuous liquid–liquid membrane extractor/separator.

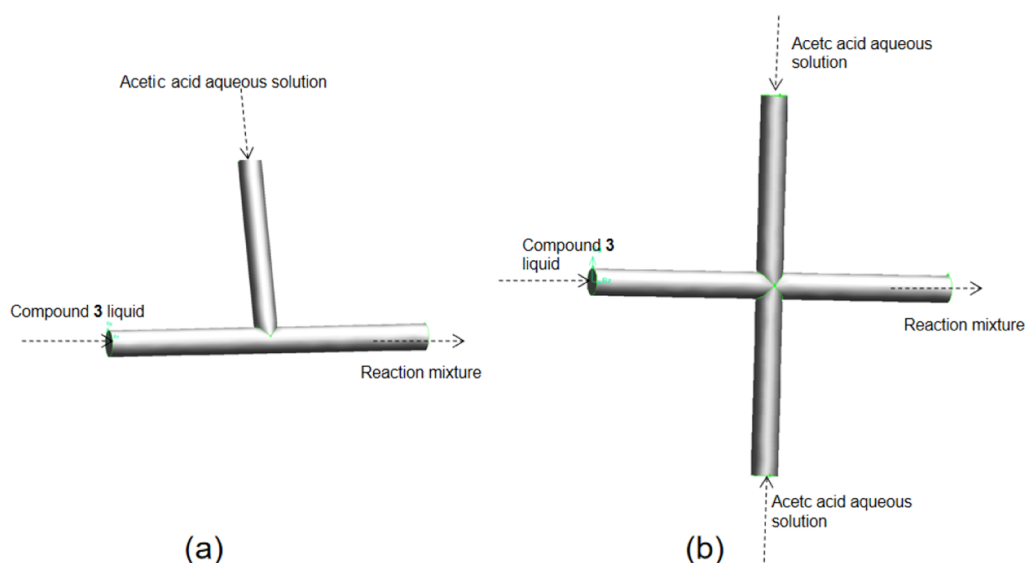
etched into each plate, causing fluid to proceed through the path in a repeating U-shaped zigzag pattern (see Figure S4 for a detailed diagram). The reaction mixture and extraction solvent (DCM) entered the mixing channel from the two entry ports on Plate A. After passing through the channel, the biphasic mixture entered the separation channel from a port at the end of the groove on Plate B. Then, the aqueous phase blocked by the PTFE membrane exited the separator via a port at the end of the groove channel on Plate B. The organic layer wetted the membrane by passing through the separation channel and exited the extraction chamber through a port at the end of the groove on Plate C.

**2.2. General Procedures.** **2.2.1. Step 1: Chlorination.** A schematic setup of chlorination is shown in Figure 3.  $\text{Cl}_2$  gas from a regulated cylinder was fed into the Protrix reactor via a mass flow controller after passing through a surge bottle and a dried bottle filled with concentrated sulfuric acid, which were used to dry the chlorine gas and to prevent back flow influence. The mass flow meter (Figure S5) was calibrated every time before the reaction to ensure an accurate value for the  $\text{Cl}_2$  gas content using an electronic soap film flowmeter (GGL-103A, Hongke Shanghai) (see S3 in the Supporting Information for details).

The liquid reagent (compound 4) was delivered by a plunger pump. The employed Protrix reactor gave a total reaction volume of 5 mL, and the outlet of the reactor was connected to a gas–liquid separator (Shenzhen E-Zheng Technology Co. Ltd.). The tail gas outlet on the separator was linked to an adjustable back pressure regulator. Nitrogen gas was introduced here to maintain the system pressure at 0.5 bar.



**Figure 3.** Continuous synthesis of 3-acetyl-3-chlorodihydrofuran-2(3H)-one (**3**).



**Figure 4.** Simulation models of the mixers: (a) three-dimensional graphics modeling of the T-mixer and (b) three-dimensional graphics modeling of the cross-mixer.

Thermal control of the reaction step was achieved using a recirculating thermal fluid controlled by Viar Temp Control (KunShan Viar Plastic Machinery Co. Ltd).

As depicted in **Figure 3**, the chlorination step was studied inside the Protrix reactor at two reaction temperatures (0 and 25 °C). The effects of the flow rate of compound **4** were investigated from 0.5 to 2 mL min<sup>-1</sup>, and the corresponding flow rate of Cl<sub>2</sub> ranged from 1:1.0 to 1:1.5.

**2.2.2. Step 2: Decarboxylation/Acylation.** The reaction between compound **3** and acetic acid was performed in a PTFE coil reactor (i.d. = 0.8 mm). Then, the reaction mixture was combined with an induced stream of acetic anhydride entering a second PTFE coil reactor (i.d. = 0.8 mm) under similar conditions for further acylation. Both coil reactors were immersed in oil baths to control the reaction temperatures.

**2.2.3. Extraction.** The effluent of the reactor from acylation was then quenched at room temperature by mixing the reaction outlet stream with a stream of saturated sodium bicarbonate aqueous solution. Then, the mixture was fed into

the membrane extractor and separator to be extracted by dichloromethane. The flow rates of the saturated sodium bicarbonate solution and dichloromethane were determined by the flow rate of effluent from step 2. After evaporation under reduced pressure (<20 mbar, 45 °C), the desired product, 3-chloro-4-oxopentyl acetate (**2**), was obtained.

**2.2.4. Sample Analysis.** After reaching the steady state (at least two residence times), product samples were collected using a scintillation vial and repeated three times. The samples were neutralized and extracted before analysis by an Agilent GC–MS system equipped with a 7820 gas chromatograph and a 5977B electron ionization mass detector. An HP-5MS capillary column (30 m × 0.25 mm I.D., 0.25 μm film thickness, J&W Scientific, USA) was used with helium as the carrier gas at a flow rate of 0.9 mL min<sup>-1</sup> with a split ratio of 20:1; the injector temperature was kept at 250 °C and the column temperature was initially set at 80 °C, held for 2 min, ramped 20 °C min<sup>-1</sup> to 280 °C, and held for 7 min. The

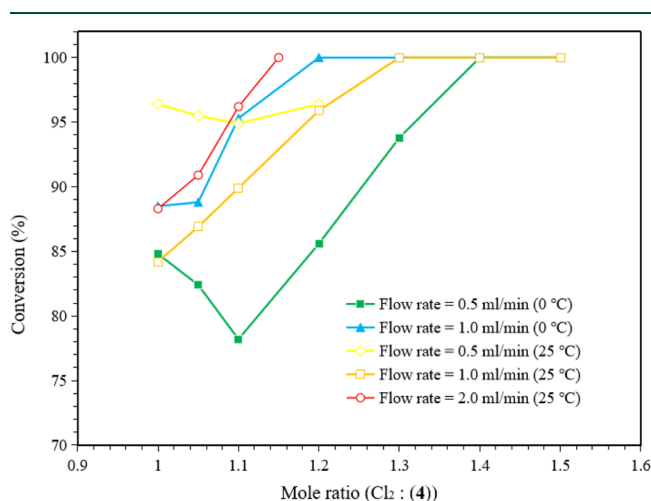
temperatures of the MS transfer line, the source, and the quadrupole were 280, 230, and 150 °C, respectively.

**2.2.5. Simulation.** The commercial software Fluent (ANSYS) was used in this work. The model of K-Epsilon [2equin] ( $k-\epsilon$  model) was applied to simulate the small scale of the coil reactor and micromixing conditions. A three-dimensional grid mesh file was created using GAMBIT software (Ansys) for each type of mixer. The simulation parameters were consistent with our continuous data in this work. Each mixer was 3.5 mm long, and the diameter of the micropores was 2.5 mm. The volume flow rates were 22.0 and 49.4  $\mu\text{L min}^{-1}$ , giving a total Reynolds number of 3.6. The mass flow rates for both the inlet and outlet were calculated for the T-mixer and cross-mixer with difference values of  $6.67 \times 10^{-6}$  and  $-7.57 \times 10^{-5}$  g  $\text{s}^{-1}$ , respectively, which met the simulation requirement. The following three-dimensional graphics models are shown in Figure 4: a T-mixing model (Figure 4a) and a cross-mixing model (Figure 4b).

### 3. RESULTS AND DISCUSSION

Operating conditions such as reaction equivalence, flow rate, reaction temperature, residence time, and pressure have been investigated comprehensively for the continuous system step by step to generate 3-chloro-4-oxopentyl acetate (2). Each condition was run for 2–5 residence times under a stable state for data collection.

**3.1. Step 1: Chlorination.** The  $\text{Cl}_2$  gas flow rate can be calculated by the calibrated equation: actual flow rate ( $\text{mL min}^{-1}$ ) = setting flow rate ( $\text{mL min}^{-1}$ ) \* 0.4953–0.6619 (see Table S1 and Figure S6). Figure 5 shows the effect of the mole ratio of  $\text{Cl}_2$  to acetyl butyrolactone (4) on the conversion results with different flow rates.



**Figure 5.** Conversion results for the flow chlorination at different mole ratios of  $\text{Cl}_2$  to acetyl butyrolactone (4).

Generally, the conversion of the starting compound acetyl butyrolactone (4) increases with the increasing equivalence ratio  $[\text{Cl}_2:(4)]$ . When the mole ratio of  $\text{Cl}_2$  to compound 4 varies from 1.1 to 1.5, the conversion gradually reaches the highest value (100%). However, fluctuations are observed when the mole ratio is lower than 1.1, especially at low temperatures. For example, the conversion of compound 4 keeps increasing for the reaction at 25 °C at 1.0  $\text{mL min}^{-1}$ , whereas it decreases first and then increases for the reaction at 0 °C with the same flow rate. In addition, the fluctuation is

more obvious for the reaction at lower flow rates under the same temperature. Presumably, this results from efficient mixing in the flow for higher flow rates generating more eddies for diffusion.<sup>18,19</sup> However, no regular trend is observed in Figure 5 regarding how the conversion changes with temperature at the same flow rate of compound 4 or with different flow rates of compound 4 at the same temperature. This is because of the fact that the dispersion of the liquid phase in the gas phase is affected by the flow rates of both gas and liquid, especially because the gas flow can be heavily influenced by temperature.<sup>20,21</sup>

Because our main aim to run the flow synthesis is to obtain the product in a much more efficient and simple way, for this chlorination reaction, the best reaction condition was obtained as follows: the temperature was room temperature (25 °C), the flow rate of acetyl butyrolactone (4) was 2  $\text{mL min}^{-1}$ , and the residence time for the flow reaction was approximately 30 s. In this way, compound 3 was produced in 93% yield with a purity of 98%.

**3.2. Step 2: Decarboxylation/Acylation.** Next, we examined the decarboxylation/acylation of 3-acetyl-3-chlorodihydrofuran-2(3H)-one (3) in the flow. The continuous flow setup is reported in Figure 6. Two individual feed streams (compound 3 and a mixture of acetic acid and hydrochloric acid solution) were introduced into a 5 mL PTFE coiled reactor (i.d. = 0.8 mm) via a T-mixer (PTFE, i.d. = 2.5 mm) by two syringe pumps. The dosages of acetic acid and 3-acetyl-3-chlorodihydrofuran-2(3H)-one (3) were consistent with their ratios in the batch process (see S5 in the Supporting Information). The reaction took place at 115 °C under 7 bar back pressure with a residence time of approximately 15 min. The desired compound 3-chloro-4-oxopentyl acetate (2) was produced with a conversion of 74–78%, and approximately 21–26% of compound 5 existed in the reaction mixture (the screening experiments can be found in Table S3).

To improve the yield of compound 2, the crude product was then passed through a second reactor coil (5 mL, i.d. = 0.8 mm) combined with an acetic anhydride stream using a T-mixer (PTFE, i.d. = 2.5 mm) at 115 °C and 7 bar back pressure. 3-Chloro-4-oxopentyl acetate (2) was isolated, obtaining 85% process yield and an average product purity of 93.25% after a residence time of 20 min (see Table S4). This is more significant than our previous batch operation result in which the desired compound 2 was generated in 60% yield with 95% purity (63% yield and 92% purity for the crude product). In the batch process, compound 3 (1.0 equiv) was mixed with acetic acid (3.2 equiv), water (1.1 equiv), hydrochloric acid (35%, 0.1 equiv), and acetic anhydride (2.0 equiv) for approximately 6 h under reflux at 120 °C, followed by vacuum distillation for purification (see Supporting Information S5 for details). Moreover, the batch results reported in the literature<sup>16,17</sup> indicated that 3-chloro-4-oxopentyl acetate (2) was generated in 60–77% yield over days of operation. Basically, the continuous run provides higher yield and purity with shorter running time than batch operation by enhancing mixing efficiency, improving heat and mass transfer, and improving reaction selectivity. Herein, the flow synthesis process shows effective reaction transformation and great efficiency.

Based on that, the reaction conditions were evaluated to enhance the desired synthesis with minimum impurity by increasing the reaction temperature, time, and equivalence. A



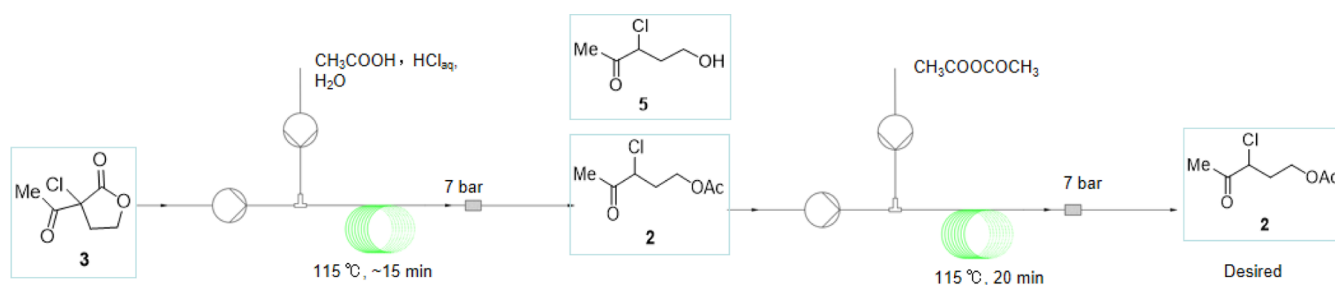


Figure 6. Decarboxylation/acylation of 3-acetyl-3-chlorodihydrofuran-2(3H)-one (3) in the flow.

series of experiments were performed under different conditions, as shown in Tables 1 and 2.

Table 1. Conversion Results in the Continuous Flow Decarboxylation/Acylation of Compound 3 with Acetic Acid in the First Flow Coil Reactor at Different Equivalences and Flow Rates<sup>a</sup>

entry	F <sub>1</sub> (mL min <sup>-1</sup> )	F <sub>2</sub> (mL min <sup>-1</sup> )	T (°C)	P (bar)	conversion (%)	AcOH equiv
1	0.02	0.05	125	10	89.3	4
2	0.022	0.0494	125	7	90.1	4
3	0.044	0.0989	125	7	90.0	4
3	0.0218	0.0614	125	7	92.2	5
4	0.0438	0.1229	125	7	91.0	5
5	0.0187	0.0527	125	7	91.4	5
6	0.0375	0.1052	125	7	91.2	5
7	0.0233	0.0655	125	7	86.6	5
8	0.0175	0.0492	125	7	88.5	5

<sup>a</sup>F<sub>1</sub>—the flow rate of compound 3 liquid (mL min<sup>-1</sup>) and F<sub>2</sub>—the flow rate of the mixture of acetic acid, hydrochloric acid, and water (mL min<sup>-1</sup>).

Table 2. Conversion Results in the Continuous Flow Acylation of Compound 3 with Acetic Anhydride in the Second Flow Coil Reactor at Different Equivalences and Flow Rates<sup>a</sup>

entry	F <sub>3</sub> (mL min <sup>-1</sup> )	F <sub>4</sub> (mL min <sup>-1</sup> )	T (°C)	P (bar)	conversion (%)	Ac <sub>2</sub> O equiv
1	0.1428	0.0403	125	7	95.7	1
2	0.1428	0.0805	125	7	96.6	2
3	0.1428	0.1610	125	7	95.6	3
4	0.1428	0.2013	125	7	96.1	4
5	0.1428	0.2818	125	7	95.7	5
6	0.2856	0.5636	125	7	80.9	1

<sup>a</sup>F<sub>3</sub>—the flow rate of the reaction mixture from the first coil reactor (mL min<sup>-1</sup>) and F<sub>4</sub>—the flow rate of acetic anhydride (mL min<sup>-1</sup>).

The flow rates F<sub>1</sub>–F<sub>4</sub> are determined by setting the reaction time and reaction equivalences between reactants. It should be noted that approximately 90% conversion of compound 3 has already been achieved at 125 °C with a residence time of 25 min after the first reaction coil (Table 1). According to Table 2, 3-chloro-4-oxopentyl acetate (2) was eventually obtained in 90% yield and >95% average purity. This result indicates that a majority of compound 5 has been converted to 3-chloro-4-oxopentyl acetate (2) with increased reaction temperature and reaction time compared with the results from the reaction process shown in Figure 6. Thus, the optimum conditions to produce 3-chloro-4-oxopentyl acetate (2) in continuous flow (Figure 7) are shown in Table 3.

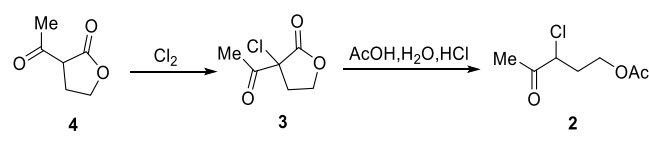
Table 3. Fully Continuous Flow Synthesis Process

compound 4 (equiv)	acetic acid (equiv)	acetic anhydride (equiv)	temperature (°C)	back pressure (bar)	reaction time (min)
1	4	2	125	7–10 <sup>a</sup>	45

<sup>a</sup>No obvious changes were observed when the pressure changed from 7 to 10 bar.

Therefore, we decided to simplify the synthesis route by eliminating the addition of acetic anhydride considering the high conversion obtained during the first decarboxylation/acylation step, as shown in Scheme 3.

Scheme 3. Modified Synthesis Route for 3-Chloro-4-oxopentyl Acetate (2)



In addition, the mixing efficiency was also considered to further improve the continuous decarboxylation/acylation

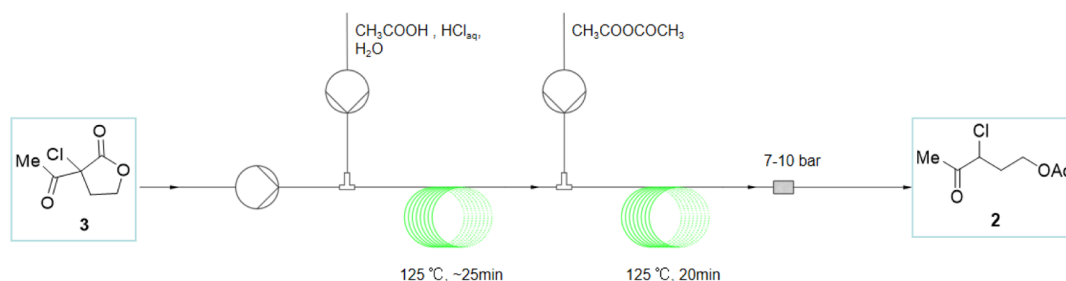


Figure 7. Continuous decarboxylation/acylation of 3-acetyl-3-chlorodihydrofuran-2(3H)-one (3).

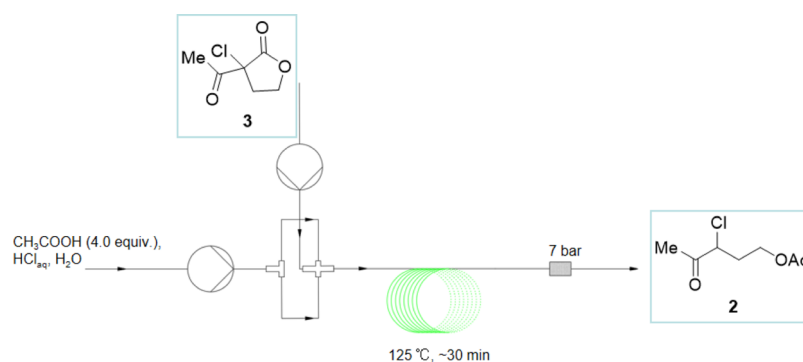


Figure 8. Improved continuous acylation of 3-acetyl-3-chlorodihydrofuran-2(3H)-one (3) using a cross-mixer.

Table 4. Conditions for Tests of the Continuous Flow Decarboxylation/Acylation Reaction with 4 equiv of Acetic Acid to Compound 3 in the Approved Process with a Cross-Mixer<sup>a</sup>

entry	F <sub>1</sub> (μL min <sup>-1</sup> )	F <sub>2</sub> (μL min <sup>-1</sup> )	T (°C)	ΔP (bar)	content in product			yield
					3 (%)	5 (%)	2 (%)	2 (%)
1	22	49.4	125	7	0	3.4	96.7	89.6
2	22	49.4	125	7	0	4.3	96.0	90.1
3	22	49.4	125	10	0	3.2	96.9	89.3
4	44	98.8	125	7	3.8	2.4	93.8	90.0

<sup>a</sup>F<sub>1</sub>—the flow rate of compound 3 liquid (μL min<sup>-1</sup>) and F<sub>2</sub>—the flow rate of the mixture of acetic acid, hydrochloric acid, and water (μL min<sup>-1</sup>).

process. The advantages of cross-mixers over T-mixers have been discussed previously by other microflow researchers with both experimental and stimulation results.<sup>18–20</sup> Therefore, a cross-mixer (PTFE, i.d. = 2.5 mm) was employed to try to enhance the two-phase liquid–liquid mixing (Figure 8).

As shown in Figure 8, 3-acetyl-3-chlorodihydrofuran-2(3H)-one (3) liquid was pumped into the cross-mixer as a separate stream, while the mixed aqueous solution of acetic acid and hydrochloric acid was divided into two streams by a T-junction. Then, three streams in total were pumped into the cross-mixer simultaneously. The decarboxylation/acylation reaction was carried out in a new reactor coil (10 mL, i.d. = 0.8 mm), and the reaction temperature was controlled at 125 °C by an oil bath. After an average residence time of 30 min, 3-chloro-4-oxopentyl acetate (2) was obtained in 89–91% yield with purity as high as 96.7% under the optimum conditions as follows: 4 equivalents of acetic acid, cross-mixer, 125 °C, and 7–10 bar back pressure (the repeated test results can be found in Table 4).

The purity results shown in Figure 9 illustrate a significant increase in the acylation efficiency by using a cross-mixer. Although there are several papers that have reported the efficiency of symmetrical structures for mixing,<sup>18–21</sup> the mixing condition varies with different flow rates in different reaction systems. In this work, the total flow rate was so low as to generate a Reynolds number of 3.6, which has not been reported previously. Moreover, the density and velocity distributions inside the micromixer were hard to measure. Therefore, computational fluid dynamics (CFD) was applied to simulate the mixing conditions in both the T-mixer and cross-mixer to obtain a better understanding of the micro-mixing process (Figure 10).

As depicted in Figure 10a,c, the velocity profiles indicate that a better regulated velocity distribution has been achieved in a cross-mixer than in a T-mixer. Figure 10b,d shows the density profiles of the compound 3 liquid and the acetic acid aqueous solution in the two micromixing systems. A stable density

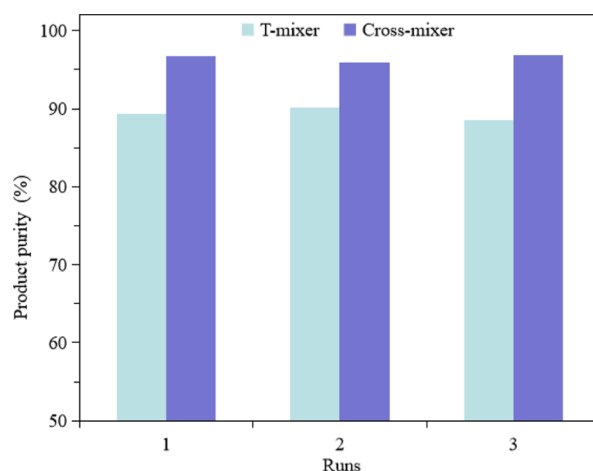
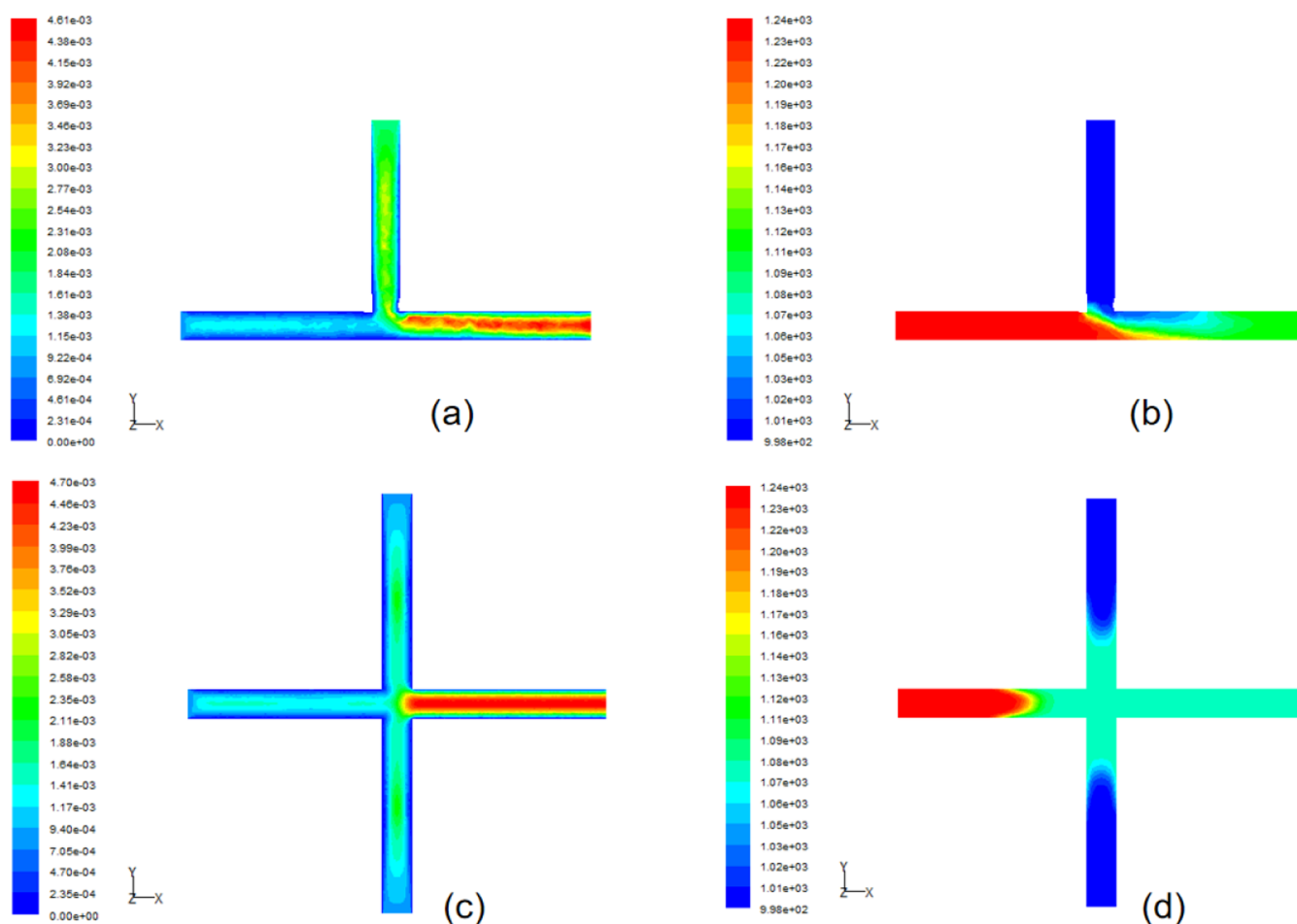
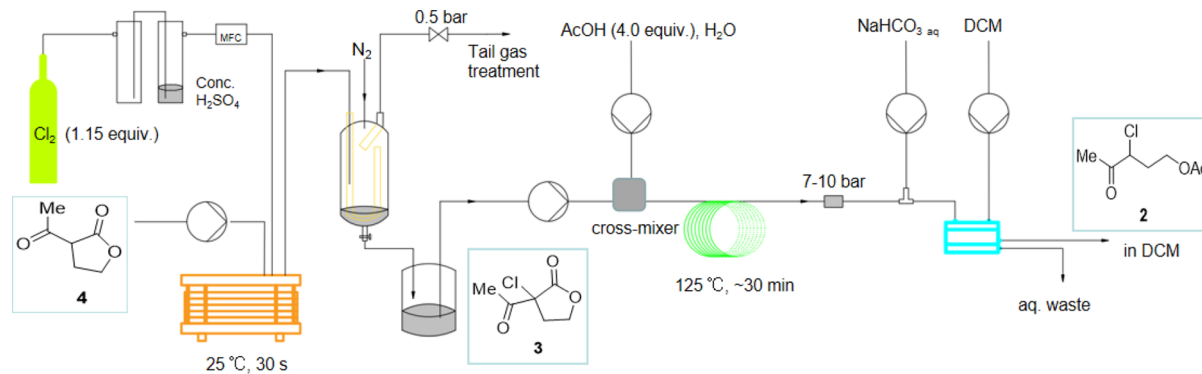


Figure 9. Product (compound 2) purity results for repeated reactions using a T-mixer and a cross-mixer at the same flow rates (F<sub>1</sub> = 22.0 μL min<sup>-1</sup> and F<sub>2</sub> = 49.4 μL min<sup>-1</sup>).

distribution is obtained in the region where the reactants are mixed in the cross-mixer, whereas in the T-mixer, a less steady state is achieved in a broader mixing region. This result agrees with the work of Luo's group,<sup>22,23</sup> where the symmetrical structure is more effective for the mixing of two phase streams even in this work with a low Reynolds number (<5). This is because in the cross-mixer, the stream of compound 3 can be adopted to mix with the acid streams from both sides in tubing flow at the same time. However, in the T-mixer, the stream flows near one side of the tubing and contacts the acid in a limited region on the other side (as shown in Figure 10a,b). Moreover, the low flow rate for the streams near tubing walls also affected the molecular diffusion efficiency. This can be explained by the equation of the Reynolds number:  $Re = d\rho v\mu^{-1}$ , where  $d$  is the tubing diameter (m),  $\rho$  is the density of the fluent fluid (kg m<sup>-3</sup>),  $v$  is the flow velocity (m s<sup>-1</sup>), and  $\mu$  is the viscosity coefficient (Pa·s). The diameter and viscosity



**Figure 10.** (a) Velocity profiles of the two phase streams mixed in a T-mixer; (b) density profiles of the two phase streams mixed in a T-mixer; (c) velocity profiles of the two phase streams mixed in a cross-mixer; and (d) density profiles of the two phase streams mixed in a cross-mixer.



**Figure 11.** Fully continuous flow synthesis of 3-chloro-4-oxopentyl acetate (2).

are regarded as the same for both mixers in this work; thus, the convective mixing in tubing is mainly controlled by the velocity and density distribution. This work to some extent verifies that the mixing performance is greatly influenced by geometric structures with a low Reynolds number.

**3.3. Fully Continuous Flow Synthesis.** With all the significant advantages in the flow process over the batch process, Figure 11 presents a fully continuous synthesis setup for 3-chloro-4-oxopentyl acetate (2) that we operate combining two steps of syntheses, flow neutralization and an inline extraction step. The operation conditions for the full continuous process are shown in Table 5.

The desired compound 2 was obtained in DCM at the exit of the membrane separator. After offline evaporation under reduced pressure, 3-chloro-4-oxopentyl acetate (2) was generated in an overall 90% yield with a purity of 96%. The production rate for the fully continuous process is approximately 1.79 g h<sup>-1</sup>, which is mainly controlled by the production rate of the decarboxylation/acylation step. It can be solved by running parallel processes. The setup was run successfully for 12 h, and approximately 19.1 g of the product was isolated. The crude product could be applied directly to the next step for the production of vitamin B<sub>1</sub> because the purity is comparable with that of the batch product after

**Table 5. Operation Conditions for the Fully Continuous Flow Synthesis of 3-Chloro-4-oxopentyl Acetate (2)**

Cl <sub>2</sub>	flow rate (mL min <sup>-1</sup> )		acetic acid solution	NaHCO <sub>3</sub> solution	DCM
	4	3			
494.1	2.0	0.022	0.0494	0.5	1.5
temperature (°C)					
Protrix reactor	coil reactor	extractor and separator		mixers	
25	125	room temperature		room temperature	
pressure (bar)					
chlorination		acylation		extraction	
0.5		7–10		0–0.1	

purification (Table 6). Therefore, the continuous flow synthesis process for 3-chloro-4-oxopentyl acetate (2) can

**Table 6. Comparison Results between Flow Operation and Batches**

operation type	reaction time (h)	isolation yield (%)	purity (%)
flow	0.5	90	96 (crude product)
batch	6	60	95 (distillation)
batch <sup>16</sup>	96	77	≥95 (column chromatography)
batch <sup>17</sup>	48	63	≥95 (column chromatography)

effectively reduce the reaction time and improve production efficiency compared with batch operations, which gives significant economic benefits for industrial operations in the future.

#### 4. CONCLUSIONS

After experimental screening tests in separated flow processes, a fully continuous flow synthesis of 3-chloro-4-oxopentyl acetate (2) was successfully developed for the first time. Compared with traditional batch processes, this study has shown several advances in the continuous operation: the safety hazards are significantly minimized because no intermediate is isolated and the reaction temperature is modest; costly acetic anhydride for further acylation is not required, while we used a cross-mixer to improve micromixing along with a CFD simulation study; and flow synthesis combined with inline extraction and separation highly enhanced productivity with significantly reduced time (from hours to minutes). Finally, the overall average residence time was approximately 32 min, and the desired 3-chloro-4-oxopentyl acetate (2) was generated in 90% yield and 96% purity with a general production rate of 1.79 g h<sup>-1</sup>. This fully continuous process ran smoothly for 12 h, generating approximately 19.1 g of the desired product. It can be easily scaled up with several high-throughput flow reactors in parallel. In the future, this continuous flow process can be adapted to the industrial manufacturing of 3-chloro-4-oxopentyl acetate (2) for vitamin B<sub>1</sub> production or other derivatives.

#### ■ ASSOCIATED CONTENT

##### Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.oprd.1c00065>.

Protrix flow reactor; inline membrane extractor and separator; inline membrane extractor and separator;

calibration of the electronic soap film flow meter and calibration curve for the Cl<sub>2</sub> gas flow meter; chlorination results of continuous flow reaction condition screening; batch operation for the decarboxylation/acylation reaction; and continuous flow screening tests for the decarboxylation/acylation of compound 3 under different conditions (PDF)

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##### Notes

The authors declare no competing financial interest.

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#### ■ ABBREVIATIONS

AcOH	acetic acid
CFD	computational fluid dynamics
DCM	dichloromethanemethylene chloride
GC–MS	gas chromatography–mass spectrometry
PTFE	polytetrafluoroethylene
Re	the Reynolds number



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