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Fully Continuous Flow Synthesis of 5-(Aminomethyl)-2-methylpyrimidin-4-amine: A Key Intermediate of Vitamin B_1

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Cite This: https://doi.org/10.1021/acs.oprd.1c00253

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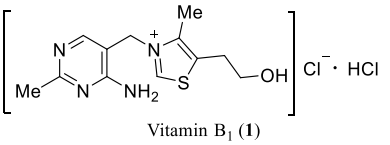
ABSTRACT: Herein, we demonstrate an expeditiously fully continuous flow synthesis of 5-(aminomethyl)-2-methylpyrimidin-4-amine, a key intermediate for vitamin B_1. The process is accomplished via three chemical transformations in six sequential continuous flow devices from an economical starting material, 2-cyanoacetamide. First, single step continuous flow synthesis is demonstrated in a certain type of flow reactor for each reaction step, with a yield of 94, 90, and 99%, respectively. Then, fully continuous flow synthesis of 5-(aminomethyl)-2-methylpyrimidin-4-amine is demonstrated in 84% total yield with a total residence time of 74 min and 0.92 g/h throughput.

KEYWORDS: *vitamin B_1, 5-(aminomethyl)-2-methylpyrimidin-4-amine, continuous flow synthesis, continuous extraction, microchannel flow reactor, continuous hydrogenation*

1. INTRODUCTION

5-(Aminomethyl)-2-methylpyrimidin-4-amine (**2**) is a key intermediate for vitamin B_1 (**1**) (Figure 1) production.[1]



Vitamin B_1 (**1**)

Figure 1. Structure of vitamin B_1 (**1**).

Vitamin B_1, which is also known as thiamine chloride, is an antineuritic vitamin and can promote normal glucose metabolism. In addition, vitamin B_1 is also essential to maintain the normal function of nerve conduction, heart, and gastrointestinal tract for the growth and well-being of humans and animals.[2,3] According to the global "Vitamin B_1 (Thiamine Mononitrate) Market 2020" research report, the global vitamin B_1 market revenue was USD 648.8 million in 2020 and has been projected to reach USD 854.7 million by 2026.[3] To date, a considerable amount of effort has been devoted to the synthesis of vitamin B_1 by utilizing different strategies.[2] Currently, the synthetic strategy via the key intermediate **2** remains a reliable approach toward **1** in industry.[2] The synthesis of the intermediate **2** has been described in a plethora of literature;[4−19] four procedures including our previous work in batch operation were selected as routes for the industrial production of **2** and discussed, and the comparison result is summarized in Table 1.

All these procedures mentioned above are, to some extent, associated with drawbacks such as long reaction time, formation of byproducts, and tedious purification. Most of these problems are inherent to the use of traditional batch technology. Continuous flow synthesis is known to overcome some of the challenges, exhibiting unique benefits in better mass and heat transfer, good extreme reaction conditions and hazard control, lower plant footprint, production flexibility, etc.[20−22] Furthermore, continuous flow technology allows for telescoping of reactions, leading to rapid production and more environmentally benign processes by avoiding intermediate purification and workup. Driven by the potential to improve control over quality, reduce costs, enhance process safety, and significantly reduce the timelines, successful innovation and adoption of a continuous flow process is essential in industry's future.[23−26]

Therefore, we envision that **2** can be synthesized efficiently and cost-effectively in a continuous flow system to demonstrate rapid fully continuous flow synthesis in the production of APIs. Leaning on the 2-cyanoacetamide approach (Scheme 1), we report an expeditiously fully continuous flow synthesis for the desired compound **2**.

2. EXPERIMENTAL SECTION

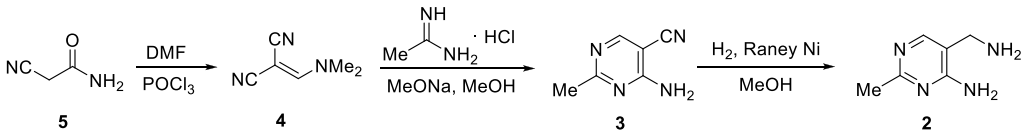
2.1. General Information. All chemicals were purchased from commercial sources and were used without further purification. 2-Cyanoacetamide (MW 84 g/mol; purity, 98%), dimethylformamide (MW 73 g/mol; purity, 99.8%), phosphorus oxychloride (MW 153 g/mol; purity, 99%), pyridine (MW 79 g/mol; purity, 99.5%), acetamidine hydrochloride (MW 94.5 g/mol; purity, 97%) ammonia (25−28% w/w), triethylamine (MW 101 g/mol; purity, 99.0%), sodium methoxide (MW 54 g/mol; purity, >98%), and dichloromethane (MW 85 g/mol; purity, >98%) were bought from Sinopharm Chemical

Received: June 24, 2021

Table 1. Simple Summary of the Reported Routes for the Synthesis of Intermediate 2

	Hoffmann-La Roche Co. process[4−8]	UBE Co. process[9−12]	Chinese producers' process[13−18]	our previous work (Scheme 1)[19]
method	carbonitrile pyrimidine approach	formyl pyrimidine approach	formamide pyrimidine approach	2-cyanoacetamide approach
starting material	malononitrile	acrylonitrile	acrylonitrile	2-cyanoacetamide
steps	4	6	5	3
yield	79%	61%	66%	65%
strengths	high overall yield			the minimum number of steps
limitation	1.8 equiv of expensive ethyl acetimidate hydrochloride is required for the cyclization of **5** in the actual production process	long synthetic route	uses *o*-chloroaniline as the amine, which is highly carcinogenic;traces of *o*-chloroaniline have been found in the end-product vitamin B_1	

Scheme 1. Synthesis Route for 5-(Aminomethyl)-2-methylpyrimidin-4-amine (2)



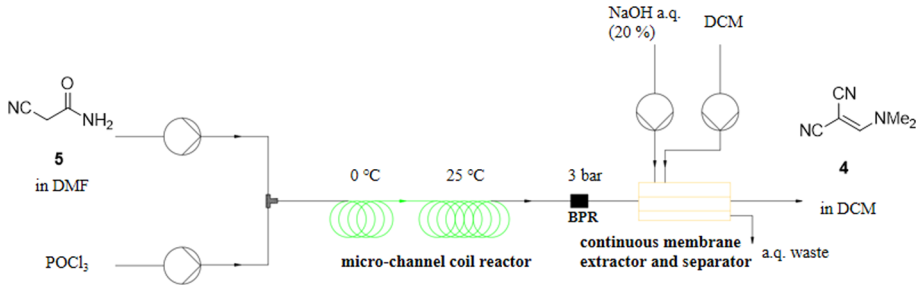


Figure 2. Continuous flow synthesis of 2-(dimethylaminomethylidene)propanedinitrile (**4**) from 2-cyanoacetamide (**5**).

Reagent Co, Ltd., Beijing. Raney Ni (20−40 mesh, in water) was acquired from bidepharm.com. Formalin (36−38% w/w) was purchased from Shanghai Titan Chemical Company. The purchased Raney Ni was modified by mixing with formalin and water (mass ratio 5:12:0.36) at room temperature for 30 min.

Precalibrated MPF0502C pumps (SANOTAC, China) were applied together with polytetrafluoroethylene (PTFE) tubings (0.08 mm i.d., 0.16 mm o.d.). Polyether ether ketone (PEEK) fittings with PEEK ferrules and T-junctions (0.025 mm i.d.) were used in conjunction. For each data point, three samples were collected from the outlet of the reaction system over at least two residence times (steady state).

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded at room temperature as solutions in deuterated dimethyl sulfoxide (DMSO-d6). HPLC analysis was performed by a standard method on a Kromasil 100-5-C18 column, 250 mm × 4.6 mm (5 μm); λ = 245 nm; mobile phase: MeOH/H_2O = 60/40. An Agilent GC−MS system equipped with a 7820A gas chromatograph and a 5977B electron ionization mass detector was also used to analyze samples. 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 and 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, then heated from 80 to 280 °C at a rate of 20 °C/min, and held for 7 min. The temperatures of the MS transfer line, the source, and the quadrupole were 280, 230, and 150 °C, respectively.

3. OPERATIONS, RESULTS, AND DISCUSSIONS

3.1. Continuous Flow Synthesis of 2-(Dimethylaminomethylidene)propanedinitrile (4). We began by mixing 2-cyanoacetamide (**5**) in DMF (dimethylformamide) with $POCl_3$ in the presence of an organic base (pyridine) in a PTFE coil reactor (Figure 2). The operation procedures and analysis are given as follows:

2-Cyanoacetamide (**5**) (1 equiv) and pyridine (0.1 equiv) were predissolved in DMF (2 equiv) at 40 °C. Then, the mixture was treated with $POCl_3$ (2 equiv) in a 10 mL PTFE coil reactor (0.8 mm i.d.) (Figure 2). The PTFE was held at 0 °C (2 mL) and 25 °C (8 mL) in water baths. The effects of temperature, pressure, and residence time were investigated for reaction optimization. The samples were neutralized by NaOH solution, extracted with DCM (dichloromethane), and then analyzed by GC/MS. For spectroscopic characterization, about 10 mL of sample was collected under the optimum condition, after neutralization and extraction, DCM and excess DMF were removed in vacuo to afford **4** as orange oil (Figure S4) (94% yield, 96% purity by GC/MS, containing 2.8% of DMF) ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.65 (s, 1H), 3.19 (s, 3H), 3.16 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 159.0, 118.2, 116.5, 46.8, 37.9; *m*/*z* (GC−MS): 121(M+), 106, 79, 54; GC/MS retention times: **4**, 8.65 min; DMF, 2.55 min.

The Wilsmerele reaction occurs once the DMF solution comes in contact with $POCl_3$ liquid, which generates heat intensely. The exothermic reaction presents great challenges in a batch reactor; however, on translating this synthesis into a

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Scheme 2. Impurites[19]

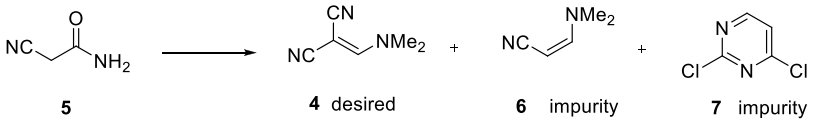

Table 2. Results for the Flow Synthesis of 4 under Different Conditions

entry	residence time (min)	temperature (°C)		pressure (bar)	conversion (%)	purity (%)	yield (%)
		coil 1	coil 2				
1	18	0	40	0	100	77.5	
2	18	0	30	3	100	90.6	
3	18	0	25	0	100	98.1	93.0
4	18	0	25	3	100	99.5	94.7
5	18	0	15	0	93.2	92.5	
6	18	0	15	3	94.0	93.3	
7	12	0	25	0	98.4	97.9	
8	12	0	25	3	99.7	98.2	93.6

continuous flow process, no severe temperature increase or pressure buildup is observed. Such improved reaction situations in flow are owing to the effective heat transfer in the microchannel reactors.[21] In this reactor, we employed two microchannel coil reactors at 0 and 25 °C, respectively.

In our preliminary studies, **5** and pyridine (0.1 equiv) were predissolved in DMF (3 equiv) and the mixture was treated with $POCl_3$ (3 equiv) in a 12.6 mL Protrix SiC lab reactor (Figures S1 and S2 in the Supporting Information) at 25 °C, affording unsatisfactory conversion (92%) of the starting materials in 78% yield with a residence time of 30 min (Table S1). Doubling the residence time or changing the reaction temperature did not improve the reaction yield. Moreover, it was noteworthy that by GC/MS analysis, compound **5** was converted to a cyclic chlorinated impurity (compound **7** in Scheme 2), resulting from overreacting with excess DMF and $POCl_3$ at higher temperatures. Due to the poor solubility of **5** in DMF, we used a water bath (40 °C) to dissolve compound **5** in 2 equiv of DMF effectively with 0.1 equiv of pyridine. Considering its an exothermic reaction, the mixture was pumped to mix with 2 equiv of $POCl_3$ in a 2 mL PTFE coil reactor held at a 0 °C water bath followed by an 8 mL PTFE coil reactor at 25 °C. This afforded compound **4** in full conversion in 18 min residence time. We then performed comprehensive investigations to optimize the reaction in continuous flow (Table 2).

Following preliminary investigations, the use of 2 equiv of DMF and $POCl_3$ generated **4** in full conversion in 18 min residence time under no pressure at 25 °C (Table 2, entry 3). Increasing the temperature of coil 2−30 and 40 °C gave the same results (Table 2, entries 1 and 2), though producing more impurities. On the other hand, decreasing the temperature of coil 2 to 15 °C gave insufficiently converted **4** (Table 2, entries 5 and 6). However, it was notable that a higher back pressure for the reaction resulted in a slight increase in the desired conversion of **4**. Less satisfactory results were generated after reducing the residence time to 12 min with a nearly full conversion (Table 2, entries 7 and 8). The best result was found when 3 bar back pressure was applied to the preliminary settings (Table 2, entry 4), and **4** was afforded in full conversion and 94.7% isolated yield with 99.5% purity. This continuous flow procedure was more efficient compared to Zhao's 12 h batch process[19] at −10 °C, which produced **4** in 74% yield (Table 3). Moreover, there were two impurities (**6** and **7**) observed in Zhao's research as shown in Scheme 2.

Table 3. Comparison between Batch and Continuous Procedures for the Synthesis of 4

operation type	batch[19]	continuous
residence time (min)	720	18
temperature (°C)	−10	0 and 25
purity (%)	98	98
yield (%)	74	94

They claimed that the impurity **6** was observed when the pH was above 3 and it could be removed at the final isolation stage, whereas the impurity **7** was formed at higher temperatures and it could be minimized by the addition of pyridine to the reaction mixture. However, neither of these impurities was observed in this continuous flow synthesis work, and it has been verified by the HPLC and NMR results. This resulted from a good and constant control over temperature and the quenching process, which actually attributed to the efficient heat and mass transfer in the microchannel reactors. PTFE tubing could also be scaled up linearly for kilogram-scale production,[27] and the flow process was much safer and easier to control in parallel.

3.2. Continuous Flow Synthesis of 4-Amino-2-methylpyrimidine-5-carbonitrile (3). Moving to the second reaction, **4** in methanol was treated with acetamidine MeOH solution to afford a compound **3** precipitate and optimized in continuous flow (Figure 3 and Table 4). The acetamidine MeOH solution was prepared by mixing acetamidine hydrochloride and sodium methoxide with a mole ratio of 1:1.1 in methanol; then, the slurry was filtered and the filtrate was collected. The precipitate formation presented huge challenges in a flow coil reactor, clogging was bound to be observed, which would definitely lead to pressure buildup and disruption of the flow process. In this reaction, we employed a Coflore Agitated Cell Reactor (ACR, 90 mL work volume) to relieve any issues that would be caused by the formation of precipitation. The operation procedures and analysis are given as follows:

2-(Dimethylaminomethylidene)propanedinitrile (**4**) (1.75 M, 1 equiv) in methanol was treated with acetamidine

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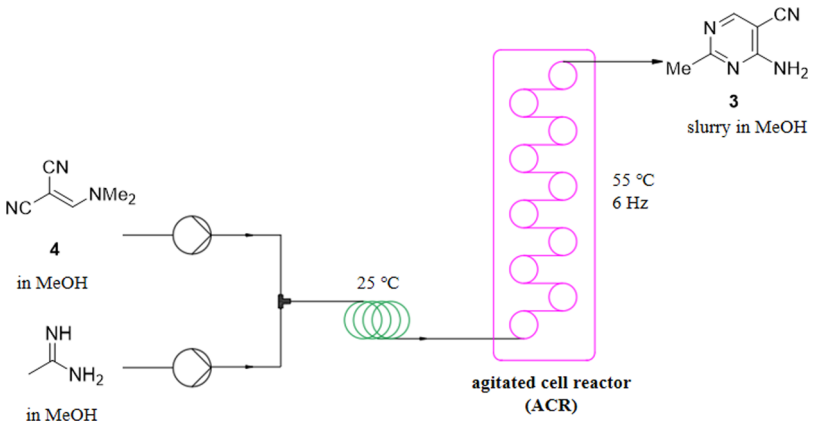

Figure 3. Continuous flow synthesis of 4-amino-2-methylpyrimidine-5-carbonitrile (**3**).

Table 4. Results for the Flow Synthesis of 3 under Different Conditions

entry	mole ratio (4:acetamidine)	residence time (min)	temperature (°C)	conc. of 4 (mol/l)	frenquency (Hz)	pressure (bar)	conversion (%)
1	1:1.1	45	40	1.75	5	0	61.8
2	1:1.1	45	45	1.75	5	0	78.4
3	1:1.1	40	40	1.75	5	0	92.1
4	1:1.1	35	50	1.75	5	0	78.5
5	1:1.1	35	55	1.75	5	0	87.3
6	1:1.1	45	55	1.25	5	0	98.7
7	1:1.1	40	55	1.25	5	0	92.3
8	1:1.1	35	55	1.25	6	0	94.6
9	1:1.1	30	55	1.25	6	0	99.2
10	1:1.1	20	55	1.25	6	0	95.6
11	1:1.1	25	55	1.25	6	0	99.1
12	1:1.1	40	40	1.15	5	0	>88
13	1:1.1	45	40	1.15	5	0	>99

MeOH solution (2.2 M, 1.1 equiv) in a Coflore ACR (90 mL reaction volume) (Figure 3). The effects of temperature, concentration, residence time, and frequency were investigated for reaction optimization. Slurry samples were filtered, dissolved in MeOH and then analyzed by GC/MS. For spectroscopic characterization, about 50 mL of sample was collected under the optimum condition after filtration and vacuum-dried to give **3** as a white solid (Figure S5) (90% yield, 99% pure by GC/MS). ^{1}H-NMR(DMSO,400 MHz): 8.50-(s,1H), 7.29(br s, 2H), 2.57(s,1H); *m*/*z*(GC−MS), 134(M+), 94, 66; GC/MS retention time: **3**, 6.73 min.

As illustrated in Table 4, the conversion to **3** increased with an increase in temperature and frequency. However, due to the poor solubility of **3** in methanol, the concentration of precipitation in slurry was depended largely on the concentration of starting materials. Clogging (Figure S3 in the Supporting Information) was observed for long residence time in an ACR with 1.75 M compound **4** reacting with acetamidine (1.1 equiv) (Table 4, entries 1−3). Deceasing residence time was helpful to remove clogging though the conversion remained unsatisfactory (Table 4, entries 4 and 5). Furthermore, a minor decrease in the concentration of **4** resulted in an increase in conversion to compound **3** with improved mixing (Table 4, entries 6−11). A major decrease in concentration of **4** led to an increase in reaction time to achieve a full conversion (Table 4, entries 12−13). Finally, the optimum conditions were found to be 55 °C, 6 Hz frequency, and 25−30 min residence time with 1.25 M compound **4** to afford **3** in nearly full conversion by GC/MS and 90% isolated yield. Our continuous flow synthesis of **3** is superior to the reported batch process by Zhao's work[19] (Table 5). This again proved that the continuous flow process exhibits unique benefits in better mass and heat transfer and good extreme reaction conditions, thus overcoming drawbacks in batch such as long reaction time.

Table 5. Comparison between Batch and Continuous Procedures for the Synthesis of 3

operation type	batch[19]	continuous
temperature (°C)	25	55
residence time (min)	720	25−30
yield (%)	90	90
purity (%)	>98	>98
melting point (°C)	249−251	249−250

3.3. Continuous Flow Synthesis of 2. Subsequent hydrogenation of **3** was accomplished by the use of a fixed-bed reactor packed with a modified Raney-type Ni catalyst (E-Zheng Technology Co. Ltd.) to afford **2** (Figure 4). The operation procedures and analysis are given as follows:

4-Amino-2-methylpyrimidine-5-carbonitrile (**3**) in MeOH (0.075 M) and ammonia or triethylamine were pumped through a fixed-bed reactor (packed with 12.4 g of modified Raney Ni, 20 mm/100 mm, 2.2 mL work volume) and treated with hydrogen at 100 °C at 16 bar back pressure (Figure 4). The mass of ammonia is 10 times that of **3**, whereas the equivalence of triethylamine is 1−2 times that of **3**. The effects

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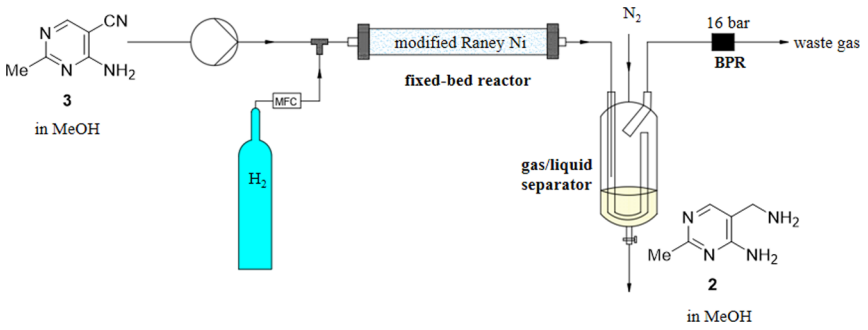

Figure 4. Continuous flow synthesis of 5-(aminomethyl)-2-methylpyrimidin-4-amine (**2**).

Table 6. Results for the Flow Synthesis of 2 under Different Conditions

entry	3 (g)	MeOH (mL)	$NH_3 \cdot H_2O$ (g)	triethylamine (g)	three liquid flow rates (mL/min)	H_2 gas flow rate (mL/min)	conversion (%)	purity (%)
1	2	200		1.5	0.5	20	>99	>99
2	2	200	20		1.0	25	>99	>99
3	2	200	20		1.5	30	>99	>99
4	2	200	20		2.0	30	70	
5	2	200	20		1.5	40	>99	>99
6	2	200	20		2.0	40	60	
7	2	210	10		1.0	30	>99	>99
8	2	1500		2.5	1.0	15	>99	>99

of residence time and reactant equivalence were investigated for reaction optimization. Samples were collected from the outlet of gas/liquid separator and analyzed by HPLC. For spectroscopic characterization, about 20 mL of sample was collected under the optimum condition, methanol was removed in vacuo, and the product was vacuum-dried to produce **2** as an off-white solid (Figure S6) (99% yield, 98% purity by HPLC). ^{1}H NMR(DMSO, 400 Hz): δ = 2.28 (s, 5H), 3.53 (s, 2H), 6.67 (s, 2H), 7.88 (s, 1H); ESI-MS: 139[M + 1]$^+$; HPLC retention time: **2**, 1.22.

As shown in Table 6, pumping a methanol solution of compound **3** (0.075 M) and a certain amount of ammonia or triethylamine into a fixed-bed reactor held at 100 °C for 2 min residence time gave a full conversion of **3** (Table 6, entries 1 and 2). Increasing the liquid flow rate to decrease the residence time reduced the conversion (Table 6, entries 3 and 4 and entries 5 and 6). An increase in the gas flow rate, as well as a drop in concentration of **3**, presented no obvious changes in conversion. In addition, both ammonia and triethylamine worked well as a base catalyst in hydrogenation. Optimum conditions were found at 100 °C and 1.5−2 min residence time to afford **2** in a constant yield and >99% purity. The comparison between batch and flow processes is shown in Table 7. The space yield from the continuous procedure (2.23 moL/L/h, i.e., 307 g/L/h) was almost 15 times of that from the batch operation (0.15 moL/L/h, i.e., 20.7 g/L/h). Notably, the production rate of the flow process in this work was only 0.15 g/h considering the operation scale, which is 2.7 times less than that of the batch process (0.41 g/h). However, the continuous flow process showed impressive reproductivity and stability in repeated experiments, so the production rate of flow operation could be linearly expanded by running continuous reactions in parallel.

Table 7. Comparison between Batch and Continuous Procedures for the Synthesis of 2

operation type	batch[19]	continuous
pressure (bar)	30	16
temperature (°C)	110	100
residence time (min)	300	1.5−2
purity (%)	>98	>97
melting point (°C)	132−134	132
space yield (mol/L/h)	0.15	2.23

3.4. Fully Continuous Process for the Overall Synthesis Route. With the optimum conditions for individual steps determined, and guided by them, we went on to combine them into a fully continuous process (Figure 5). It should be noted that the fully continuous setup herein referred to a continuous producing process without extra interruptions, though surge vessels were applied for intermediate storage, solvent switching, and redissolving. All operations were performed in continuous or at least multicontinuous manners. This was referenced to the work of Cole et al. when synthesizing prexasertib monolactate monohydrate under continuous flow conditions in a kilogram scale,[27] based on which we also previously reported a fully continuous process for the synthesis of 3-chloro-4-oxopentyl acetate.[28]

The continuous synthesis of compound **2** was performed in three flow units including six connected flow devices. In flow unit 1, **5** (1 equiv) and pyridine (0.1 equiv) in DMF was treated with $POCl_3$ in a PTFE coil reactor (0.08 mm i.d.) at 0 °C (2 mL) and 25 °C (8 mL) for 18 min residence time at 3 bar back pressure. Excess sodium hydroxide solution (20% w/w) was subsequently used to quench the reaction mixture using a T-junction for micromixing. The effluent was then collected in a surge vessel and effectively extracted via DCM using a continuous inline extractor from CINC Deutschland GMBH and Co. at room temperature (Figure S7). Then, the organic phase (compound **4** in DCM) was subsequently pumped into a continuous concentrator at 45 °C to switch solvent so as to afford a compound **4** MeOH solution in situ. In flow unit 2, compound **4** in MeOH (1.75 M, 1 equiv) was treated with acetamidine MeOH solution (2.2 M, 1.1 equiv) in an ACR reactor held at 55 °C for 30 min residence time to

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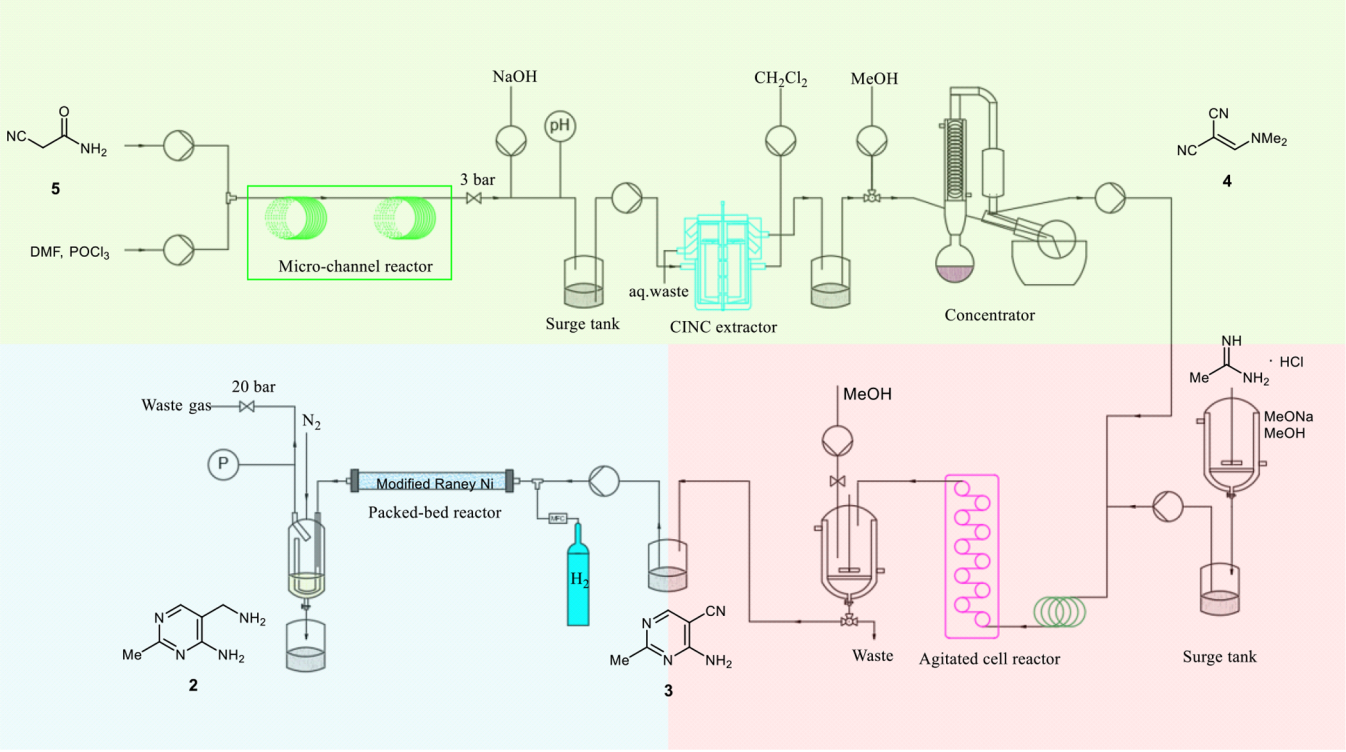

Figure 5. Fully continuous flow synthesis of 5-(aminomethyl)-2-methylpyrimidin-4-amine (**2**).

produce **3** as a slurry, which was subsequently delivered to a continuous filter device. After this, MeOH was used to dissolve the filter cake once the filtrate was removed to afford a fresh methanol solution of compound **3**. In flow unit 3, **3** in MeOH (0.075 M) and excess hydrogen gas were pumped through a fixed-bed reactor packed with a modified Raney-type Ni catalyst and held at 100 °C for 2 min residence time at 16 bar back pressure. After continuous hydrogenation, compound **2** was generated after vacuum-drying as an off-white solid in 84% total yield with a total residence time of 74 min and 0.92 g/h throughput. Overall, our fully continuous flow procedure demonstrated improved reaction conditions and time economy in the total synthesis of **2**.

4. CONCLUSIONS

We successfully synthesized **2** by a fully continuous flow process accomplishing three chemical transformations over six continuous flow devices from an economic starting material (2-cyanoacetamide). First, single step continuous flow synthesis was demonstrated in specific flow devices, and optimum conditions were determined with a yield of 94, 90, and 99%, respectively. At last, we demonstrated a fully continuous flow synthesis of **2** in 84% total yield with a total residence time of 74 min and a 0.92 g/h throughput without offline intermediate purification and isolation. In this research, the inline workup procedure could be incorporated in flow to neutralize excess acid and concentrate the desire compound before carrying out further workup processes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00253.

Continuous flow synthesis of **4** in a Protrix microchannel reactor; clogging in the flow synthesis of **3** in a Coflore ACR; products from three single continuous flow synthesis; and continuous extraction in a CINC model continuous inline extractor (PDF)

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https://doi.org/10.1021/acs.oprd.1c00253
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Fundamental Research Funds for the Central Universities.

■ ABBREVIATIONS

ACR, agitated cell reactor; DMF, dimethylformamide; DCM, methylene chloride; PTFE, polytetrafluoroethylene; PEEK, polyether ether ketone

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https://doi.org/10.1021/acs.oprd.1c00253
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