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Article

Continuous Flow Process for the Synthesis of Betahistine via Aza-Michael-Type Reaction in Water

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ABSTRACT: A continuous flow process for the preparation of betahistine with a 90% isolated yield has been reported. 2-Vinylpyridine and saturated methylamine hydrochloride aqueous solution were used as starting materials to achieve excellent results in the silicon carbide flow reactor, which can tolerate the corrosion of chloride ions at high temperature (170 °C) and pressure (25 bar). In the continuous flow process, the product can be obtained in 2.4 min with excellent conversion (>99%) and product selectivity (94%). The throughput can reach 1.06 kg h^{-1}, and the purity of the final product was greater than 99.9% by distillation, which were in accordance with the needs of production. This new process using environmentally friendly water as the solvent is energy-efficient, time- and cost-economic, and offers a 50% reduction in process mass intensity compared to the batch process.

KEYWORDS: *betahistine, continuous flow, process intensification, energy-efficient, environmentally friendly*

INTRODUCTION

Betahistine (**1**), which acts as an orally active histamine H1 receptor agonist and partial H3 receptor antagonistic,[1−4] is mainly used to treat various diseases such as cluster headaches, vertigo syndrome, and Meniere's syndrome.[5−9] It has two special merits: excellent safety profile and unique pharmacological properties. Besides, the pharmacokinetic results of radioisotope labelled drugs showed that betahistine could be quickly absorbed by human body after oral administration. 2-Pyridine ethylamine and 2-pyridine acetic acid were the main metabolites of betahistine, and the latter was mainly excreted in urine. At the same time, the metabolites can be completely excreted within 24 h. The evidence suggested 2-pyridine ethylamine may also be active and play a similar role to betahistine on ampullary receptors in vivo.[10]

Ever since the first synthesis of betahistine by Loffler and Kirschner in 1904,[11] various protocols have been developed.[12−18] As shown in Scheme 1, one of the most practical methods is the nucleophilic addition between methylamine (**3**) and 2-vinylpyridine (**2**) via aza-Michael reaction (a, Scheme 1).[12,13,15,16,18] In the previous reports, longer reaction time (>8 h) was required to improve conversion (b, Scheme 1).[12] Because of impurities generated from side reactions, high purity product (>99.9%) was difficult to acquire.[15] Excessive reagents and organic solvents (toluene and isopropanol) also lead to high production cost and environmental pollution (c, Scheme 1). Thus, the development of green, efficient, and cost-effective method for the synthesis of betahistine is appealing and challenging in organic synthesis.

Recently, continuous flow synthesis has become one of the most attractive technologies that can significantly affect the synthetic chemistry. This technology is characterized with precise control of reaction variables, safe process, possibility of reaction under high temperature and pressure (process intensification), automation, high repeatability, flexibility of production scale, on-line purification, smaller manufacturing plant area, and so forth.[19−23] At present, the continuous flow synthesis has successful been applied in several drug manufactures, such as ciprofloxacin,[24] dolutegravir,[25] and prexasertib.[26] Taking the advantages of continuous flow synthesis, herein, we report a continuous flow synthesis process of betahistine in water, which greatly shortened the reaction time and improved the reaction yield (d, Scheme 1). This protocol is expected to provide a more economical, reliable, and environmentally friendly method for the industrial production of betahistine.

RESULTS AND DISCUSSION

Optimization in Batch. Before the synthesis of betahistine was performed in flow, a detailed optimization study was carried out in batch. Considering the production cost and safety, methylamine hydrochloride was chosen as the amine source rather than methylamine aqueous solution. Given the requirement of avoiding the generation of any precipitates in the context of continuous flow synthesis, the solvents were screened first. Typically, the mixture of 2-vinylpyridine (0.25 g) and methylamine hydrochloride (0.41 g, 3.0 equiv) in different solvents, such as dimethylformamide (DMF), dimethyl sulfoxide (DMSO), *i*-PrOH, EtOH, and H_2O, was heated at 110 °C for 5 h in a high-pressure glass bottle. As

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Scheme 1. Schematic for the Synthesis of Betahistine

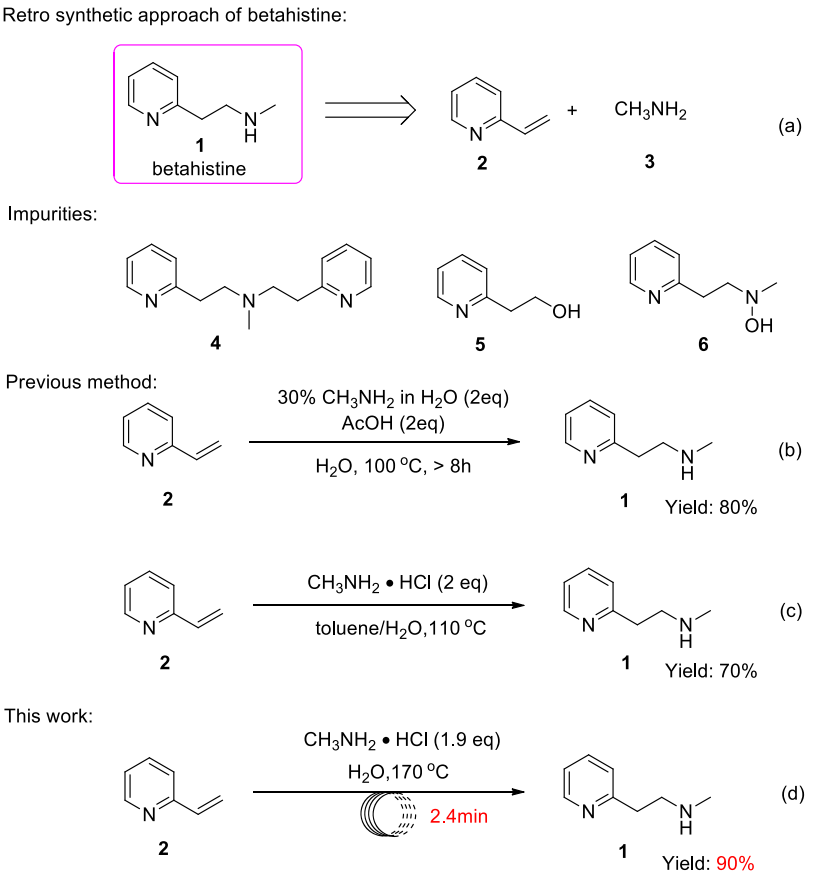
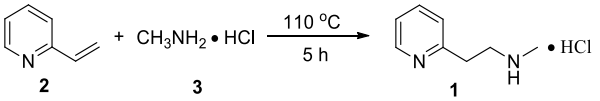


Table 1. Screening of Solvents for the Synthesis of Betahistine



entry	solvent	mL	conv. (%)[a]	select. (%)[a]	observation	area % ratio[a] (2:1: impurities)
1	*i*-PrOH/H_2O (1:1)	4	81	80	clear	19:65:16
2	toluene/H_2O (1:1)	4	81	80	clear	19:65:16
3	DMF/H_2O (1:1)	4	62	75	clear	38:47:15
4	DMSO/H_2O (1:1)	4	68	70	clear	32:48:20
5	THF/H_2O (1:1)	4	75	52	clear	25:39:36
6	EtOH/H_2O (1:1)	4	90	74	clear	10:67:23
7	H_2O	4	87	82	clear	13:71:16
8	H_2O	1	92	81	clear	8:75:17
9	H_2O	2	89	83	clear	11:74:15
10	H_2O	8	82	83	clear	18:68:14

[a]Monitored by HPLC.

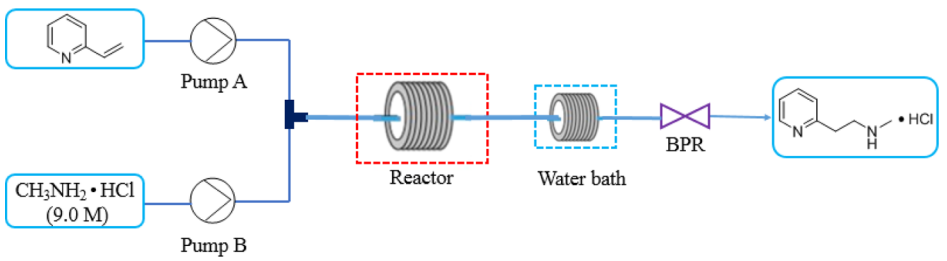


Figure 1. Continuous flow setup for the synthesis of betahistine.

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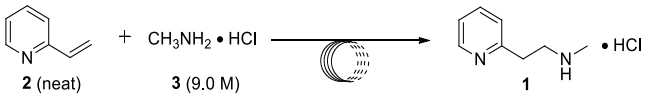
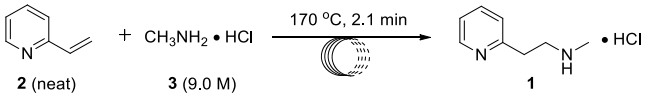
Table 2. Reaction Conditions for the Continuous Flow Synthesis of Betahistine



entry	residence time (min)	temperature (°C)	3 (equiv)	conv. (%)[a]	select. (%)[a]	area % ratio[a] (2:1: impurities)
1	2.1	130	1.3	[b]		
2	2.1	150	1.3	93	71	7:66:27
3	2.1	160	1.3	93	75	7:70:23
4	2.1	170	1.3	95	83	5:79:16
5	2.1	180	1.3	89	80	11:71:18
6	2.1	170	1.4	94	82	6:77:17
7	2.1	170	1.5	95	84	5:80:15
8	2.1	170	1.6	95	87	5:83:12
9	2.1	170	1.7	98	94	2:92:6
10	2.1	170	1.8	97	93	3:90:7
11	2.1	170	2.0	98	92	2:90:8
12	0.8	170	1.7	77	73	23:56:21
13	1.5	170	1.7	98	91	2:89:9
14	3.0	170	1.7	93	89	7:83:10

[a]Monitored by HPLC. [b]The reaction solution was two-phase, and no reaction occurred.

Table 3. Scaling-Up Experiments for the Continuous Flow Synthesis of Betahistine



entry	2 (mL min^{-1})	3 (mL min^{-1})	reactor (mL)	conv. (%)[a]	select. (%)[a]	area % ratio[a] (2:1: impurities)
1	1.0	1.8	6	98	94	2:92:6
2	1.5	2.7	9	97	94	3:91:7
3	2.0	3.6	12	98	95	2:93:5

[a]Monitored by HPLC.

shown in Table 1, no precipitates were observed in the above solvents. Surprisingly, the water was found to present the highest conversion and selectivity according to the high-performance liquid chromatography (HPLC) analysis (Table 1, entry 7). In terms of green chemistry, water is a perfect solvent to satisfy the goal of green chemistry as it is a highly accessible, nontoxic, and nonflammable solvent. Notably, the conversion (up to 92%) was positively correlated with an increase in concentration of the starting materials (Table 1, entries 7−10).

Continuous Flow Synthesis of Betahistine. Next, we turned our attention to the translation of the optimized batch toward a continuous flow process. The continuous flow setup is shown in Figure 1. Due to the high temperature and the presence of chloride ions in the reaction system, the corrosion-resistant Hastelloy reactor was chosen. 2-Vinylpyridine and a saturated solution of methylamine hydrochloride in H_2O (9.0 M) were pumped into a micromixer by an HPLC pump, respectively. The resulting solution was heated in the reactor and then cooled in a stainless steel reactor coil. The mixture was processed with an adjustable back-pressure regulator (BPR).

Table 2 shows the effects of the reaction conditions on the continuous flow synthesis of betahistine. At 130 °C, because the collected reaction solution was separated into two-phase, almost no conversion occurred within a residence time of 2.1 min (Table 2, entry 1). At 150 or 160 °C (Table 2, entries 2 and 3), the conversion of 2-vinylpyridine was comparable with that under batch conditions, but the corresponding selectivity was slightly lower. The maximum conversion of 95% with excellent selectivity of 83% was obtained at 170 °C (Table 2, entry 4), which was better than that under batch conditions. On increasing the temperature to 180 °C under similar flow conditions (Table 2, entry 5), the conversion and selectivity decreased slightly.

Then, the influence of the amount of methylamine hydrochloride was investigated (Table 2, entries 6−11). Considering the economic effect, the maximum amount of methylamine hydrochloride should be less than 2.0 equiv, and the transformation proceeded effectively at the equivalence in the range of 1.4−2.0. The conversion and selectivity reached 98 and 94%, respectively, when 1.7 equiv of methylamine hydrochloride was used (Table 2, entry 9). When the amount of methylamine hydrochloride was further increased, it resulted in the decrease in selectivity (Table 2, entries 10 and 11). In terms of the residence time, the reactants converted completely (98%) within 1.5 or 2.1 min (Table 2, entries 9 and 13). Lower yields were obtained at shorter residence times because of the incomplete conversion (Table 2, entry 12), while longer residence times also led to lower yields of betahistine (Table 2, entry 13). Therefore, the reaction residence time was set as 2.1 min. As a result, on the 3.0 mL Hastelloy reactor, the best conditions for the continuous flow synthesis of betahistine was as follows: pump A: 2-vinylpyridine (neat, 0.5 mL min^{-1}), pump B: saturated methylamine hydrochloride solution (9.0 M, 0.9 mL min^{-1}, 1.7 equiv), reaction temperature at 170 °C, residence time at 2.1 min, and system pressure at 7 bar.

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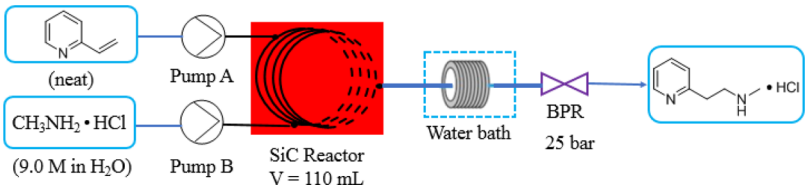
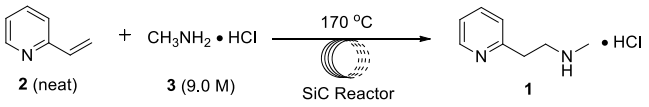


Figure 2. Continuous flow setup for the synthesis of betahistine in a SiC reactor.

Table 4. Scaling-Up Experiments for the Continuous Flow Synthesis of Betahistine in the SiC Reactor



entry	2 (mL min^{-1})	3 (mL min^{-1})	residence time (min)	conv. (%)[a]	select. (%)[a]	area % ratio[a] (2:1: impurities)
1	20	36	2.0	95	86	5:82:13
2	15	27	2.6	>99	90	0:90:10
3	10	18	3.9	>99	91	0:91:9
4	15	30	2.4	>99	94	0:94:6

[a]Monitored by HPLC.

Table 5. Comparison Between the Batch and Continuous Flow Process for the Synthesis of 1.0 kg of Betahistine

entry	2-vinylpyridine (kg)	methylamine hydrochloride (kg)	toluene (kg)	H_2O (kg)	catalyst (mL)	operation time (h)	yield (%)[a]	PMI (kg/kg)
1[b]	1.10	1.47	5.3	2.1	36 wt % HCl (420)	8.0	71	27.2
2[c]	0.86	1.05		1.7		1.0	90	13.5

[a]Isolated yield of betahistine. [b]Batch process. [c]Continuous flow process.

Scaling-Up Experiments. We further focused on establishing more practical conditions to improve productivity. In order to scale up the reaction, the flow rate was increased by increasing the retention volume of the reactor via extending the length of the Hastelloy reactor coil on the continuous flow device. Accordingly, the system pressure of 10 bar was required to achieve a stable flow. As shown in Table 3, excellent conversion (97−98%) and selectivity (94−95%) of the reaction were obtained, reflecting the good reaction scalability of continuous flow.

Due to the strong corrosive effect of the chloride ion in the reaction system under high-T/P conditions, the Hastelloy reactor coil would be corroded inevitably in industrial production during a long run. The heating operation might become more difficult and dangerous at higher flow rate, and a safer protection was required. In this regard, sintered silicon carbide (SiC) could be applied in highly corrosive reagents under harsh conditions.[27,28] SiC flow reactors have been used in the pharmaceutical industry, such as handling fluorine gas in a safe and scalable manner, as well as Wolff−Kishner reduction.[29−31] Therefore, on the scale-up synthesis of betahistine under continuous flow conditions, we used a commercially available modular SiC reactor with static mixing elements (Figure 2), which provided seamless capabilities for the manufacturing process.

As shown in Table 4, the conversion and selectivity in the SiC reactor were lower than those in the Hastelloy reactor coil at the residence time of 2.0 min with the total flow rate of 56 mL min^{-1} (Table 4, entry 1), and no change was observed in the reaction yield by increasing the mixing effect using the mixer. Hence, the flow rate was reduced via increasing the residence time to improve the reaction effect (Table 4, entries 2 and 3). At the total flow rate of 42 or 28 mL min^{-1}, maximum conversion (>99%) was obtained in good selectivity (90−91%). Increasing the amount of methylamine hydrochloride to 1.9 equiv at the total flow rate of 45 mL min^{-1} led to full conversion with the best selectivity (>99, 94%, entry 4, Table 4). Therefore, the optimum conditions for the continuous flow synthesis of betahistine in the SiC reactor was as follows: pump A: 2-vinylpyridine (neat, 15 mL min^{-1}), pump B: saturated methylamine hydrochloride (9.0 M, 30 mL min^{-1}, 1.9 equiv), reaction temperature of 170 °C, retained volume of SiC reactor 110 mL (22 mL × 5), and system pressure of 25 bar.

Long Run. With the optimized conditions in the SiC reactor in hand, 2-vinylpyridine (flow rate: 15 mL min^{-1}) and a solution of methylamine hydrochloride (9.0 M) in H_2O (flow rate: 30 mL min^{-1}) were pumped into the SiC reactor under the conditions of 170 °C and an estimated residence time of 2.4 min. During the steady state (after about 2.0 min), the reaction solution was analyzed by HPLC every 10 min per hour (see Supporting Information for details). For the analytical samples, the conversions were above 99% and the selectivity was about 94%. Thus, the reaction performed smoothly with an identical standard in the long run study, and the productivity of betahistine could reach 1.06 kg h^{-1}. Comparison of the continuous flow process to the batch process reveals dramatic improvements in economy and environmental friendliness (Table 5). In the continuous flow process, the amount of raw materials was remarkably reduced. Then, the use of organic solvents and hydrochloric acid could be avoided, and this also could simplify the post-treatment operations and reduce the amount of alkali used in post-treatment. In addition, the process operation time could be significantly shortened from 8.0 to 1.0 h. Compared with the batch process, this new continuous flow process represented a 50% reduction in process mass intensity (PMI, see the Supporting Information for details).

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Purification Process and Impurity Analysis. High-purity betahistine was generally obtained by distillation after post-treatment. It was important to select the distillation column for distillation. In Figure 3, with the Vigreux column

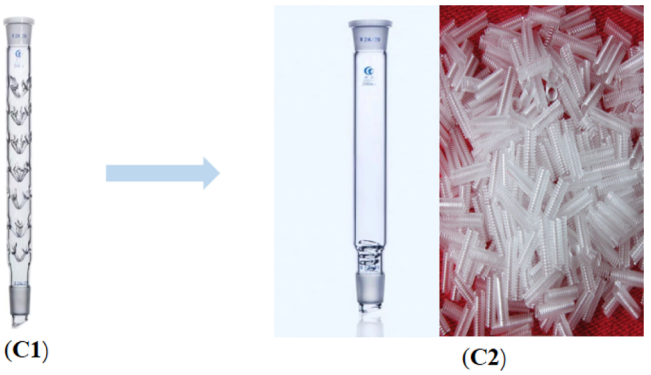


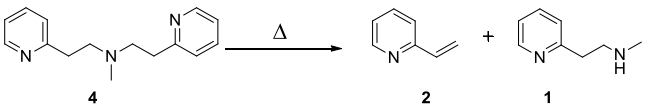
Figure 3. Distillation device in the purification process.

(**C1**), the highest purity of betahistine was only 95% at 150 °C/50 mmHg. Then, the glass spring fillers were loaded as fillers into the distillation column (**C2**) to enhance the separation efficiency. The separation purity increased to 99.1% when the number of theoretical plates reached 5.0.

Although higher purity betahistine (>99%) could be obtained by replacing the distillation column, the purity of the product still did not meet the production requirement due to the existence of a small amount of 2-vinylpyridine raw material. Furthermore, it seemed that the reaction of 2-vinylpyridine with betahistine caused the major side product, which reversibly resulted in 2-vinylpyridine at a high distillation temperature (Scheme 2). We tested 2-vinylpyridine and betahistine performed under batch conditions for 4.5 h at 115 °C, and impurity **4** was obtained in 82% yield (see the Supporting Information). The source of side products suggested a certain limitation in the reaction temperature and time in the previous optimization process of continuous flow synthesis.

The excessive side product in the reaction caused troubles in the subsequent distillation purification. High distillation temperature led to the contained 2-vinylpyridine partial from the decomposition of side product in the product fraction; while the product fraction was difficult to separate at low distillation temperature. Therefore, the stability of impurities at different temperatures was investigated (Table 6). In Table 6, the impurity obviously decomposed when the temperature was higher than 90 °C (entries 3 and 4). In this regard, the product with >99.9% purity was afforded without loss of betahistine by strictly controlling the bottom temperature of the kettle at 85 °C and the top temperature of the tower at 60 °C under a vacuum degree of 2 mmHg.

Table 6. Decomposition Temperature Test of Impurity 4



entry	temperature (°C)	time (h)	HPLC area % ratio (4:2:1)
1	60	5	100:0:0
2	80	5	98.90:0.05:0.06
3	90	5	95.50:0.25:0.20
4	100	5	83.60:8.32:8.08

CONCLUSIONS

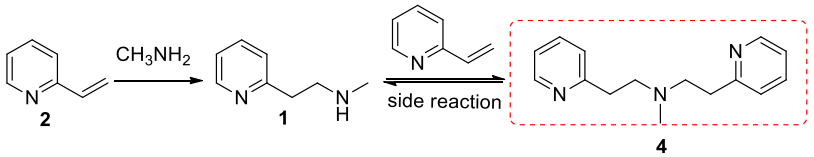
A continuous flow synthesis process of betahistine was developed and reported. The switch from a traditional batch process to a flow process allowed for the process intensification and safety security. The process was optimized in high conversion (>99%) and high product selectivity (94%) at 170 °C for 2.4 min with the total flow rate of 45 mL min^{-1} in the SiC reactor. The flow process was demonstrated steadily in an hour with a productivity of 1.06 kg h^{-1}. The high purity product (>99.9%) was obtained by optimizing the purification process of distillation. This new process using environmentally friendly water as the solvent is energy-efficient, time- and cost-economic, and offers 50% reduction in PMI compared to the batch process.

EXPERIMENTAL SECTION

General Remarks. All reagents were commercially available and used without any further purification. If not stated otherwise, reagents were weighed and handled in air at room temperature. The HPLC pumps and the Hastelloy microtube reactors were purchased from Bejing Xingda Science & Technology Development Co. Ltd. The SiC flow reactor was purchased from Jinde New Material. Thermal regulation of the heating zone was carried out using a Viar thermostat VMC-H480L (30−300 °C). The BPR was purchased from Beijing Xiongchuan Technology Co., Ltd. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz. Analytical HPLC (Shimadzu LC20) analysis was carried out on a C18 reversed-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 μm) at 30 °C using mobile phases 80% (224 mg of ammonium acetate, 325 mL of pure water, 1.44 g of sodium dodecyl sulfate, and 175 mL of acetonitrile) and 20% (acetonitrile) at a flow rate of 0.5 mL min^{-1}.

Synthesis of Betahistine in Batch. 2-Vinylpyridine (0.25 g, 2.38 mmol) was slowly added to methylamine hydrochloride (0.41 g, 7.14 mmol) in a corresponding solvent. After the reaction solution was kept at 100 °C for 5 h, it was acidified to pH >11 with NaOH aqueous solution and extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over sodium sulfate and filtered, the solvent was

Scheme 2. Formation Process of Impurity 4



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removed under reduced pressure, and the resulting crude product was used for HPLC analysis.

Large Scale Batch Synthesis of Betahistine. To a stirred slurry of 2-vinylpyridine (105 g, 1.00 mol) and 36 wt % HCl (40 mL, 0.48 mol) in toluene (500 g) at 25 °C was added 40 wt % methylamine hydrochloride aqueous solution (140 g, 2.1 mol) portionwise over 30 min. The solution was stirred at 110 °C for 8 h. After cooling to room temperature, 30% aqueous NaOH (400 g) was added to the reaction system and stirred for 10 min. The aqueous phase was extracted with dichloromethane (3 × 300 mL). The organic layers were combined, the solvent was removed under reduced pressure, and the resulting crude product was purified by distillation to give betahistine (97 g, 0.71 mol) in 71% yield.

General Flow Procedure for the Synthesis of Betahistine in a Microtube Reactor. A microreactor system consisting of two HPLC pumps, a micromixer (T-shaped tee, 1/16″ OD, 0.02″ thru hole), and a Hastelloy reactor coil was used. The temperature was controlled using an oil bath. The reaction mixture was heat to 170 °C in the Hastelloy reactor coil and rapid cooled to 30 °C in a short stainless steel coil. An adjustable BPR was positioned at the outlet of the flow reactor to allow a range of pressures (0−60 bar) to be evaluated. 2-Vinylpyridine (flow rate: 0.5 mL min^{-1}) and a solution of methylamine hydrochloride (9.0 M) in H_2O (flow rate: 0.9 mL min^{-1}) were introduced into the micromixer by an HPLC pump (PA, PB). The resulting solution passed through the Hastelloy reactor coil (1/16″ OD, V = 3.0 mL, 170 °C, t = 2.1 min) and rapidly cooled to 30 °C in a short stainless steel coil (1/16″ OD, V = 0.7 mL, 30 °C). After the pressure was adjusted to 100 psi through the BPR, fractions were collected from the reactor output, and an aliquot was taken for HPLC analysis.

General Flow Procedure for the Synthesis of Betahistine in the SiC Reactor. The continuous flow setup consisting of two HPLC pumps, an SiC reactor, and a Hastelloy coil was used. The reaction was heat to 170 °C in the SiC reactor and cooled to 30 °C in the Hastelloy coil. An adjustable BPR was positioned at the outlet of the flow reactor to allow a range of pressures (0−60 bar) to be evaluated. 2-Vinylpyridine (flow rate: 15 mL min^{-1}) and a solution of methylamine hydrochloride (9.0 M) in H_2O (flow rate: 30 mL min^{-1}) were introduced into the SiC reactor by an HPLC pump (PA, PB). The resulting solution passed through the SiC reactor (V = 110 mL, 170 °C) and rapid cooled to 30 °C in the Hastelloy coil (1/8″ OD, V = 20 mL, 30 °C). After the pressure was adjusted to 25 bar through the BPR, fractions were collected from the reactor output, and an aliquot was taken for HPLC analysis.

Purification of Betahistine. 1.5 L of product solution was collected from the SiC reactor output, and pH was adjusted to >11 with NaOH aqueous solution. The resulting mixture was extracted with dichloromethane (3 × 1.0 L). The combined organic layers were dried over sodium sulfate and filtered, the solvent was removed under reduced pressure, and the resulting crude product was purified by distillation.

Distillation process: first, the vacuum was controlled at 50 mmHg, the temperature at the bottom of the kettle was adjusted to 50 °C, the temperature at the top of the tower was 25 °C, the fraction was collected, and dichloromethane was removed; then, the vacuum was controlled at 10 mmHg, the temperature at the bottom of the kettle was adjusted to 50 °C, and the temperature at the top of the tower was 40 °C to collect fractions, and 2-vinylpyridine was removed; finally, the vacuum was controlled to 2 mmHg, the temperature at the bottom of the kettle was controlled at 85 °C, and the temperature at the top of the tower was 60 °C. The fraction was collected and the product (about 570 g, 90% yield) was obtained as a colorless oil. The purity was 99.9% by HPLC. Distillation column: Ø 30 × 300 mm packed column, Ø 5 × 8 mm glass spring fillers, 300 mm filling height. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (dd, J = 4.8, 0.8 Hz, 1H), 7.53 (td, J = 7.7, 1.8 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 7.07−7.04 (m, 1H), 2.92 (s, 4H), 2.39 (s, 3H), 1.91 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 149.3, 136.3, 123.2, 121.2, 51.3, 38.1, 36.2. HRMS (ESI) m/z: calcd for $C_8H_{12}N_2$ $[M + H]^+$, 136.1000; found, 136.1021.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00543.

Continuous flow setup, additional experimental information, PMI calculation, HPLC analysis, and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

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