

Supporting Information

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

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1. General Information

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 Beijing 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. ^1H 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 \times 4.6 mm, particle size 5 μm) at 30 °C using mobile phases 80% (224 mg of ammonium acetate was dissolved in 325 mL of pure water, with acetic acid adjusted pH to 4.7, added 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.

Caution: All reactions should be carried out in an efficient fume hood; the reactor should be placed in a spill tray, and a safety blast shield should be used. Prior to performance of any high-T/P flow reaction, the apparatus must be checked with an inert solvent to ensure correct functionality of all valves and safety infrastructure.

2. Continuous Flow Setup

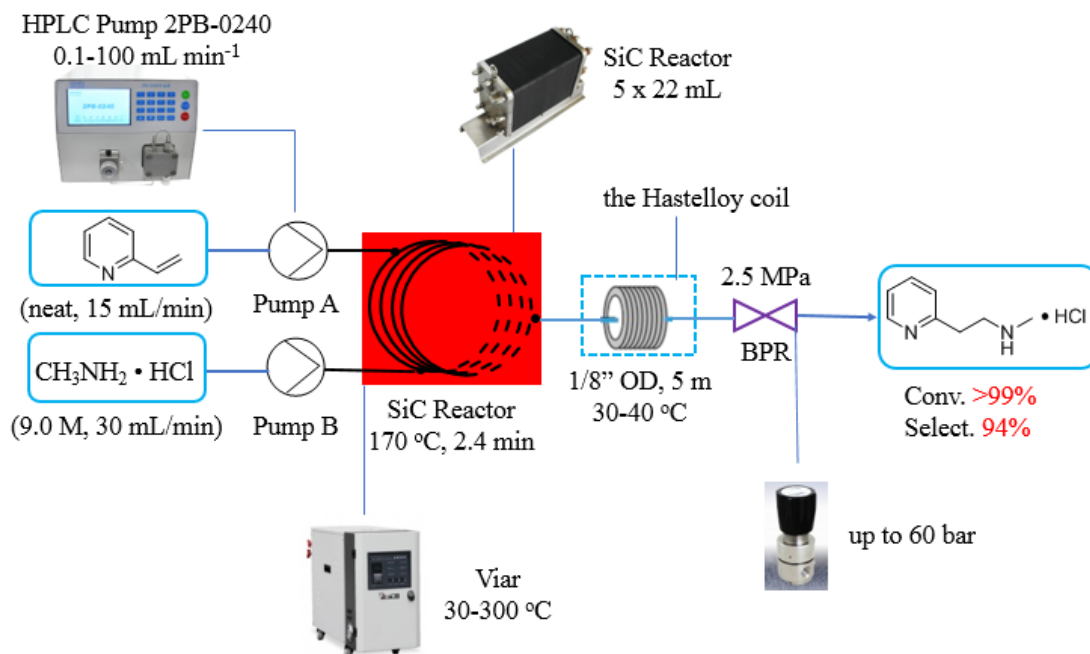


Figure S1. Continuous flow setup for the synthesis of betahistine.

Temperature control: Thermal regulation of the heating zone was carried out using a Viar thermostat VMC-H480L (30-300 °C). Thermal regulation of the cooling zone to 30-40 °C was carried out with water, re-circulated using an aquarium pump.

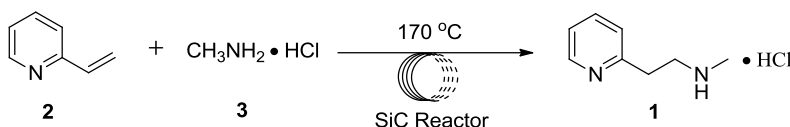
Pumps: The feed solution was pumped using SZWEICO HPLC Pump 2PB-0240 (0.1-100 mL min⁻¹).

Flow reactor: The SiC flow reactor from JINDE NEW MATERIAL, it was a standard unit to allow higher temperatures and pressures ($T < 300\text{ °C}$, $P < 50\text{ bar}$). For the heating zone, five SiC microreactor (volume = 22 mL x 5) modules were used.

Back pressure regulator: The BPR from Beijing Xiongchuan Technology Co., Ltd. was used, which was adjustable up to 60 bar.

3. Continuous Flow Synthesis of Betahistine in the Long Run

Table S1. Continuous Flow Synthesis of Betahistine in the Long Run

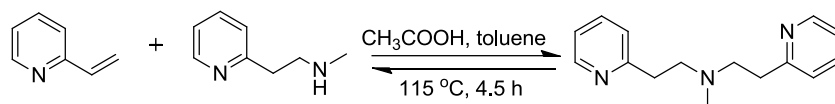


| entry | sampling time (min) | Conv. (%) ^a | Select.(%) ^a | area % ratio ^a (2:1: impurities) |
|-------|---------------------|------------------------|-------------------------|---|
| 1 | 10 | >99 | 94 | 0: 94: 6 |
| 2 | 20 | >99 | 95 | 0: 95: 5 |
| 3 | 30 | >99 | 94 | 0: 94: 6 |
| 4 | 40 | >99 | 94 | 0: 94: 6 |
| 5 | 50 | >99 | 95 | 0: 95:5 |
| 6 | 60 | >99 | 95 | 0: 95:5 |

^aMonitored by HPLC.

The reaction conditions: pump A: 2-Vinylpyridine (neat, 15 mL min⁻¹), pump B: saturated methylamine hydrochloride solution (9.0 M, 30 mL min⁻¹, 1.9 equiv.), the reaction temperature of 170 °C, retained volume of SiC reactor 110mL (22 mL x 5) and a system pressure of 25 bar.

4. The Synthesis of Impurity 4 (*N*-Methylbis[2-(2-pyridylethyl)]amine)



A mixture of 2-vinylpyridine (1.05 g, 10 mmol), betahistine (2.04 g, 15 mmol), and glacial acetic acid (0.6 g, 10 mmol) in 25 mL of toluene at 115 °C under nitrogen for 4.5 hours. The reaction mixture was cooled, and the toluene, 2-vinylpyridine and acetic acid were removed by rotary evaporator. The product was then treated with 10 mL of 15% NaOH and extracted with ethyl acetate (3 x 10 mL) followed by solvent evaporation. The crude oil was purified by column chromatography on alumina and eluted with a mixture of 98/2 (v/v) ethyl acetate/MeOH to afford *N*-Methylbis[2-(2-pyridylethyl)]amine as light yellow liquid (1.98 g, 8.2 mmol) (82% yield). ¹H NMR (400 MHz, CDCl₃): δ 8.47 (d, *J* = 4.0 Hz, 2H), 7.53 (td, *J* = 7.7, 1.9 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.08–7.04 (m, 2H), 2.95–2.91 (m, 4H), 2.84–2.80 (m, 4H), 2.36 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 160.5 (2C), 149.2

(2C), 136.3 (2C), 123.2 (2C), 121.1 (2C), 57.3 (2C), 42.0, 35.9 (2C). HRMS (ESI) m/z calcd for C₁₅H₁₉N₃ [M+H]⁺: 241.1579, found: 241.1545.

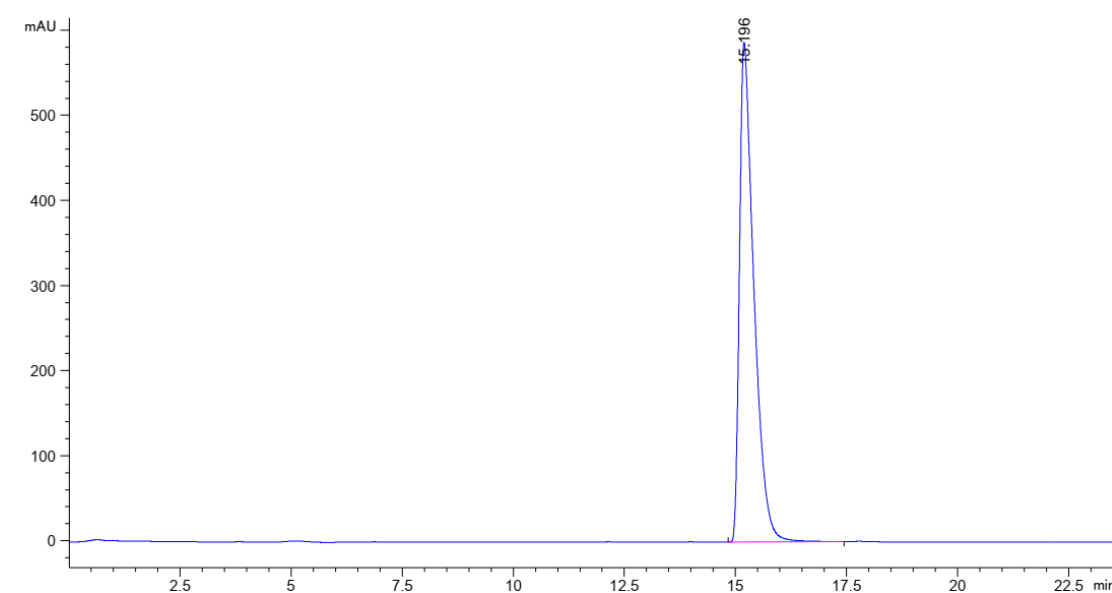
5. Process Mass Intensity (PMI)

Table S2. Detailed calculation for PMI of betahistine under batch and continuous flow process

| Components | Amount (batch) | Amount (continuous flow) |
|---------------------------------|----------------|--------------------------|
| 2-vinylpyridine | 1.10 kg | 0.86 kg |
| methylamine hydrochloride | 1.47 kg | 1.05 kg |
| toluene | 5.3 kg | - |
| water | 2.1 kg | 1.7 kg |
| 36 wt % HCl | 0.49 kg | - |
| 30 % aqueous NaOH | 4.2 kg | 2.5 kg |
| CH ₂ CH ₂ | 12.5 kg | 7.4 kg |
| Total Input | 27.2 kg | 13.5 kg |
| betahistine | 1.0 kg | 1.0 kg |
| PMI (Input / Output) | 27.2 | 13.5 |

6. Spectra

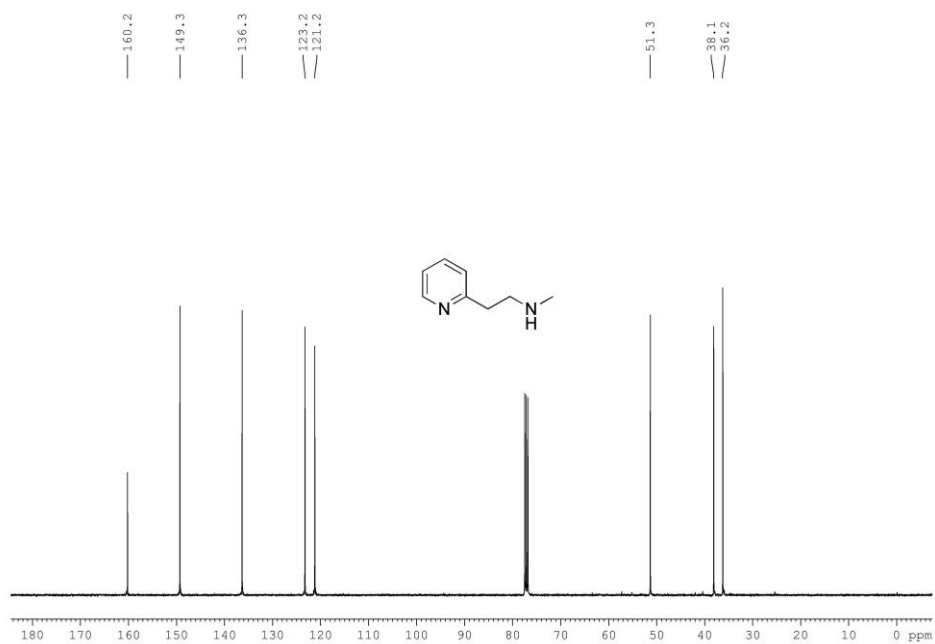
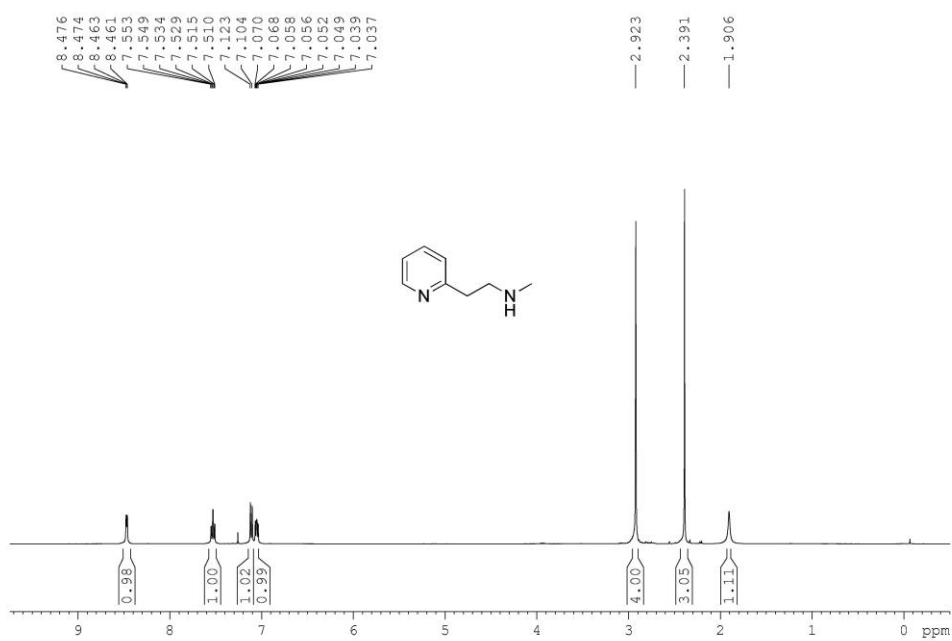
1. The HPLC analysis of betahistine (Purity: >99.9%)



| peak | retention time (min) | peak width (min) | peak area (mAU*s) | peak height (mAU) | peak area (%) |
|--------|-------------------------|---------------------|----------------------|----------------------|------------------|
| 1 | 15.196 | 0.3295 | 1.32512e4 | 586.75867 | 100.0000 |
| Total: | | | 1.32512e4 | 586.75867 | |

2. ^1H NMR and ^{13}C NMR Spectra

Betahistine



N-Methylbis[2-(2-pyridylethyl)]amine

