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OPPI BRIEF

Improved Synthesis of Bepotastine Besilate

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Bepotastine besilate (**1**, Figure 1, synonymous with bepotastine besylate), is a non-sedative highly selective histamine receptor antagonist, which has a stabilizing effect on mast cells. This antihistamine can also prevent eosinophils from migrating to inflammatory tissues and thus reduce allergic inflammation.[1–5] This widely available commercial product works quickly and effectively. Methods for the synthesis of bepotastine besilate have been amply documented in the existing literature.[6–10] Among them may be found the patented route of J. I. Kita and colleagues (Scheme 1). In this route, piperidine **2** was reacted with ethyl 4-bromobutyrate **3** to obtain compound **4**. Then, butyric acid derivative **5** was prepared by hydrolysis, and bepotastine besilate **1** was finally obtained by salt formation with benzenesulfonic acid. This method has attracted our attention, and an improvement on it forms the subject of this communication.

In particular, we have focused on the preparation of compound **4**. According to the literature,[8] **2**, **3** and potassium carbonate were loaded into acetone at room temperature and then heated to reflux for 7 hours. In our hands, we found that **2** could not react completely and the volume of solution was excessive. The reaction system was not uniform. If dimethylformamide (DMF) or an acetone-water system was used as solvent, the reaction could be complete, but the waste solvent was difficult to recover. The amount of waste liquid would of course be even larger upon scale-up. We thus made an analysis of the effects of solvent and particle size of the potassium carbonate, and the results are summarized in Table 1. The best results were obtained with crushed potassium carbonate and 5 volumes of acetone (Table 1, entry 5). In the post-treatment process, we only had to filter off the inorganic salts, and the filtrate could be concentrated under reduced pressure to get **4**.

In exploring the conversion of **4** to **1**, we studied numerous approaches to the post-saponification acid treatment, and the results are summarized in Table 2. Yields were not improved until we directly used benzenesulfonic acid itself to regulate the acidity, by adding an amount of benzenesulfonic acid equal to the number of moles of base that had been used in the saponification (see Experimental section). We added acetonitrile and concentrated under vacuum to remove water from the system. The inorganic salts were filtered to obtain the mother liquor containing **5**. The mother liquor was then treated with benzenesulfonic acid to give the crude bepotastine besilate **1**. The yield was 67% (Table 2, entry 19). In further developing this good result, we enlarged

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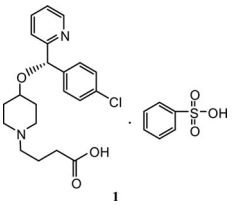
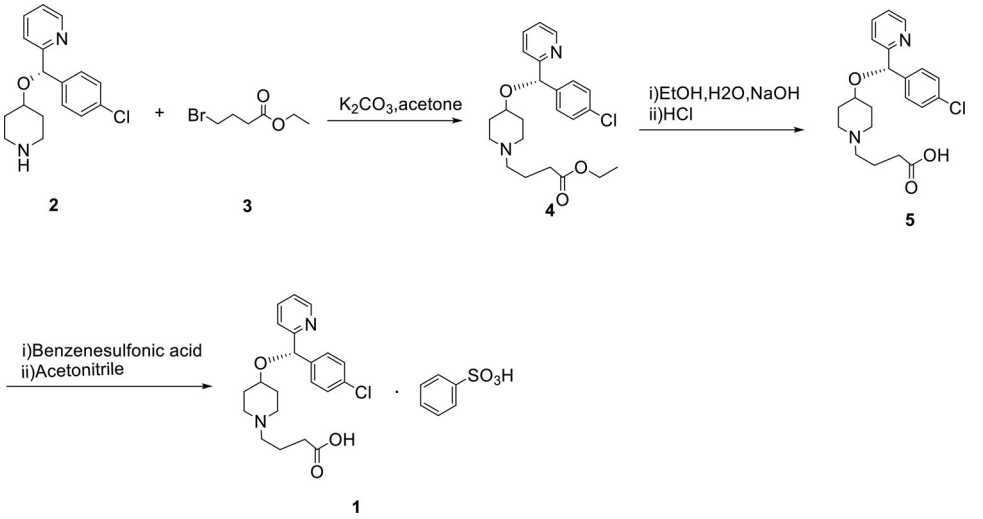


Figure 1. Bepotastine besilate.



Scheme 1. Synthesis of bepotastine besilate.

the batch to the kilogram level, and the yield was as high as 70% (Table 2, entries 20, 21).

Purity is crucial in the preparation of bepotastine besilate **1**. Recrystallization of crude **1** with such alcohol solvents as isopropanol or ethanol readily led to the formation of the corresponding esters as impurities.[11] The use of acetonitrile as solvent gave a residue of acetonitrile in the final product that would exceed the pertinent drug standard (Table 3, entry 1). Other common solvents also gave poor results. However, we found that recrystallization with a mixture of acetone and water improved the purity of **5** and also solved the problem of introducing extra impurities and residual solvents (Table 3, entry 4).

In summary, we have described here improvements in the preparation of bepotastine besilate **1**. The improvements may be suitable for industrial application. The optimized conditions have the advantages of simple operation, minimizing impurities and high yield.

Table 1. Screening of potassium carbonate particle size and solvent usage.

Entry	Particle size of potassium carbonate	The volume of acetone relative to **2**	Reaction	Reaction status
1	Flakes	11	Incomplete chemical reaction	Stirs well
2	Particles (D90 = 544μm)	11	Incomplete chemical reaction	Stirs well
3	Powder (D90 = 98μm)	11	Complete chemical reaction	Stirs well
4	Powder (D90 = 98μm)	8	Complete chemical reaction	Stirs well
5	Powder (D90 = 98μm)	5	Complete chemical reaction	Stirs well
6	Powder (D90 = 98μm)	3	Complete chemical reaction	Not easy to stir

Table 2. Optimization of conversion of **4** to **1**.

Entry	Batch	Acid	pH	% Yield
1	10 g	hydrochloric acid	6.51	35
2	10 g	hydrochloric acid	6.02	32
3	10 g	hydrochloric acid	5.82	58
4	10 g	hydrochloric acid	5.43	42
5	10 g	hydrochloric acid	5.20	40
6	100 g	hydrochloric acid	5.81	31
7	10 g	acetic acid	6.49	38
8	10 g	acetic acid	6.00	41
9	10 g	acetic acid	5.80	59
10	10 g	acetic acid	5.44	42
11	10 g	acetic acid	5.21	40
12	100 g	acetic acid	5.82	33
13	10 g	sulfuric acid	6.50	39
14	10 g	sulfuric acid	6.12	42
15	10 g	sulfuric acid	5.84	59
16	10 g	sulfuric acid	5.43	40
17	10 g	sulfuric acid	5.19	35
18	100 g	sulfuric acid	5.82	29
19	100 g	benzenesulfonic acid	–	67
20	1 kg	benzenesulfonic acid	–	70
21	2.3 kg	benzenesulfonic acid	–	70

Table 3. Screening of refining conditions.

Entry	Refinement condition	% Purity	% Yield	% Solvent Remaining	% Limit
1	Acetonitrile	99.9	85.1	0.12	0.041
2	Acetone : H_2O = 90 : 10	99.9	61.2	0.10	0.5
3	Acetone : H_2O = 95 : 5	99.9	70.5	0.13	0.5
4	Acetone : H_2O = 98 : 2	99.9	85.3	0.13	0.5

Experimental section

Compound **2** was purchased from Beijing Lianben Chemical Technology Company, and compound **3** was purchased from Shanghai Hanhong Chemical Company. Other solvents and reagents were purchased from commercial sources and used without further purification unless otherwise indicated. The reactions were monitored by analytical thin-layer chromatography (TLC) on precoated silica gel GF254 plates using 10% methanol/dichloromethane as eluting solvent and visualized under UV light (254 and 365 nm). ^{1}H and ^{13}C NMR were recorded at 500 and 300 MHz, respectively, using a Bruker Avance instrument. The chemical shifts ware reported as δ ppm using tetramethylsilane as the internal standard. We used a Waters Q-TOF mass spectrometer with ESI ionization. Elemental analysis was recorded on an Elementar Vario EL III

instrument. The HPLC analysis data was reported in area per cent, not adjusted to weight, using an Agilent 1100 instrument.

Ethyl (S)-4-{4-[(4-chlorophenyl) (2-pyridyl) methoxy] piperidine} butyrate 4

The potassium carbonate was crushed by a grinder to obtain a fine powder, as noted in Table 1. In a 30 L reactor, acetone (9.5 L) was placed, and **2** (1.90 kg, 6.27 mol), **3** (1.35 kg, 6.92 mol) and potassium carbonate (1.04 kg, 7.53 mol) were added with stirring. The mixture was heated to reflux and stirred. When TLC indicated the reaction was complete (10 hr), the mixture was cooled to 30 °C and vacuum filtered. The filter cake was washed with acetone. The mother liquor was concentrated under reduced pressure to obtain intermediate **4**, 2.62 kg, 99.9%, light yellow viscous liquid. ^{1}H-NMR DMSO-*d6*, 500 MHz) δ 1.17 (t, 3H, $J = 7.1$Hz), 1.5 (br, 2H), 1.67 (m, 2H), 1.82 (m, 2H), 2.02 (m, 2H), 2.26 (m, 4H), 2.64 (br, 2H), 3.49 (br, 1H), 4.04 (dd, 2H, $J = 7.1$Hz, 7.1Hz), 5.66 (s, 1H), 7.25 (t, 1H, $J = 5.6$Hz), 7.36 (d, 2H, $J = 8.4$Hz), 7.42 (d, 2H, $J = 8.4$Hz), 7.55 (d, 1H, $J = 7.9$Hz), 7.79 (t, 1H, $J = 7.7$Hz), 8.48 (d, 1H, $J = 4.3$Hz); ^{13}C-NMR (DMSO-*d6*, 300 MHz) δ 172.68, 161.49, 148.66, 140.89, 136.87, 136.83, 128.52 (2 × C), 128.04 (2 × C), 122.42, 120.22, 79.83, 72.92, 59.50, 56.67, 50.44 (2 × C), 31.45, 31.09 (2 × C), 21.89, 13.98. MS (M + H): Calcd for $C_{23}H_{29}ClN_2O_3$, m/z 417.1. Found, m/z 416.19.

Synthesis of (S)-4-{4-[(4-chlorophenyl) (2-pyridyl) methoxy] piperidine} butyric acid 5 and preparation of crude bepotastine besilate 1

To a 30 L reactor was added ethanol (13 L), **4** (2.60 kg, 6.24 mol), sodium hydroxide (0.50 kg 12.48 mol) and water (2.6 L). The mixture was stirred at 25 °C for 1h. Then benzene sulfonic acid (1.97 kg, 12.48 mol) in ethanol (2.6 L) was added and stirred for 45 min. The mixture was concentrated at 50 °C under reduced pressure until no further liquid could be removed. Acetonitrile (2.6 L) was added and the mixture was then concentrated at 55 °C under reduced pressure until no further liquid could be removed. Acetonitrile (13 L) was added and the mixture was stirred for 2 hours. The mixture was vacuum filtered and the filter cake was washed with acetonitrile (7.8 L). Benzene sulfonic acid (0.89 kg, 5.62 mol) was added to the mother liquor, which was heated to 80 °C and stirred for 0.5 h. The mixture was filtered and the filter cake was discarded. The mother liquor was cooled and crystallized, then centrifuged and washed with acetonitrile. The resulting solid was dried in vacuum at 45 °C to obtain crude **1**, 2.37 kg, 69.5%, white powder with a purity of 99.9%. ^{1}H-NMR DMSO-*d6*, 500 MHz, cf. reference 10) δ 1.86 (m, 6H), 2.31 (t, 2H), 3.07 (br, 3H), 3.27 (br, 3H), 3.68 (br, 1H), 5.70 (d, 1H), 7.32 (m, 4H), 7.40 (m, 4H), 7.64 (m, 3H), 7.82 (t, 1H, $J = 7.6$ Hz), 8.48 (d, 1H, $J = 4.4$ Hz), 12.00 (br, 2H); ^{13}C-NMR (DMSO-*d6*, 300 MHz) δ 173.29, 161.42, 149.36, 148.22, 140.91, 137.65, 132.61, 129.28 (2 × C), 129.20 (2 × C), 128.74 (2 × C), 128.26, 125.95 (2 × C), 123.21, 120.98, 80.69, 70.68, 55.36, 49.01 (2 × C), 31.04, 28.25 (2 × C), 19.61. MS (M + H): Calcd for $C_{21}H_{25}ClN_2O_3{\cdot}C_6H_6O_3S$, m/z 389.2. Found, m/z 388.16 + 158.00.

Purification of bepotastine besilate 1

In a 30 L reactor, acetone (9.4 L) and purified water (470 ml) were placed, and **1** (2.35 kg) and medicinal activated carbon (0.12 kg) were added with stirring, then heated to reflux and kept for 1 h. The mixture was filtered while hot and washed with acetone (13.6 L). The mother liquor was cooled down to 5 °C, then centrifuged and washed with acetone. The solid was vacuum dried at 45 °C to obtain a finished product of **1**, 1.91 kg, 81.3%, white powder with a purity of 99.97%, a single impurity of less than 0.1% and a solvent residue which met requirements.

Anal. Calcd for $C_{21}H_{25}ClN_2O_3{\cdot}C_6H_6O_3S$: C, 59.22; H, 5.46; N, 4.92. Found: C, 59.39; H, 5.54; N, 5.12.

HPLC Conditions— Column: Acclaim C18 (250mm × 4.6mm × 5μm); Detection: 220 nm; Flow rate: Adjusted so that the retention time of bepotastine was approximately 6 minutes; Temperature: 40 °C; Mobile phase: prepared by dissolving 1.0 g of sodium 1-pentane sulfonate in a mixture of 0.05 mol/L potassium dihydrogen phosphate TS (pH 3.0) and acetonitrile (7:3) to make 1000 mL; Run time: approximately 5 times as long as the retention time of bepotastine; Injection load: 20μL; Solvent: acetonitrile; t_R: 5.878 min, purity: 99.97%.

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References

1. L. Bielory, S. Duttachoudhury and A. McMunn, *Expert. Opin. Pharmacother.*, **14**, 2553 (2013). doi:10.1517/14656566.2013.849242
2. Q. J. Yang and L. X. Zhao, *Chinese. J. Med. Chem.,* **20**, 159 (2010).
3. W. W. Carr, A. S. Nayak, P. H. Ratner, J. A. Gow, T. R. McNamara and J. I. Williams, *Allergy Asthma. Proc.*, **34**, 247(2013). doi:10.2500/aap.2013.34.3671
4. G. L. Torkildsen, P. J. Gomes, J. I. Williams, J. A. Gow and T. R. McNamara, *J. Allergy Clin. Immun.*, **123**, 557(2009).
5. M. T. Bergmann, J. I. Williams and P. J. Gomes, *Clin. Ophthalmol.*, **8**, 1495(2014).
6. Z. Q. Zhao, Z. Y. Zhou and L. Z. Peng, *Chin. J. Pharm.*, **37**, 726 (2006).
7. J. Xia, Z. H. Yu and H. P. Wang, *Chin. J. Pharm.*, **47**, 8 (2016).
8. J. I. Kita, H. Fujiwara, S. Takamura, R. Yoshioka, Y. Ozaki and S. I. Yamada, US 2002026054, 2002.
9. T. J. Hu, Q. He, Z. Y. Tian, B. Yu, Q. S. Hua and D. W. Zhang, CN 104003978, 2014.
10. T. H. Ha, C. H. Park, W. J. Kim, S. Cho, H. K. Kim and K. H. Suh, US 2010168433, 2010.
11. B. Zhang, Z. Zhao, C. Z. Zou and Q. L. Mao, CN 104119314, 2014.