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Control of Crystal Habit and Size of Cefmatilen Hydrochloride Hydrate with a Habit Modifier

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Abstract:

Control of crystal habit and size of cefmatilen hydrochloride hydrate (1) with a habit modifier is described here. One of the related substances, impurity 2, which has a diphenylmethyl group at the N3-position of the triazolyl group of cefmatilen, acts as a habit modifier. The crystal habit and size of compound 1 depended upon the amount of impurity 2 in the crystallizing system. Since the amount of impurity 2 can be controlled by the temperature during the addition of $AlCl_3$ to a suspension of compound 3 in the deprotection step, the crystal habit and size can be controlled by the temperature of addition of $AlCl_3$. The addition of small amounts of hydroxyalkylcelluloses or polyvinyl derivatives to the crystallizing system can also modify the crystal habit and size of compound 1.

Introduction

The crystal habit of a drug substance which is also called the active pharmaceutical ingredient (API) plays an important role in influencing the packing, flowability, dissolution, compressibility, and sedimentation characteristics.[1] Therefore, it should be controlled especially for oral drugs.

Cefmatilen, which was discovered by Shionogi Research Laboratories, Shionogi & Co., Ltd., Osaka, Japan, is a new oral cephalosporin antibiotic.[2] Cefmatilen hydrochloride hydrate (**1**) was chosen as a candidate. One morphic form has been found so far.[3a] At the early stage of the development,[2] the crystal habit of compound **1** was a fine needle shape (Figure 1A) and should be improved for formulation because of its lower flowability. To improve the feature of the API, the needle-shaped crystal was changed into an aggregation of a blade-shaped crystal (Figure 1B).[3] We found that important key parameters for controlling crystal shape were temperature, concentration of HCl in the crystallizing system, and agitation speed. Crystallization at higher temperatures than 35 °C in higher concentrations of HCl than 2.5 mol/L with vigorous stirring gave an aggregation of blade-shaped crystals, and crystallization under the other condition gave a needle shape. However, when recrystallization of compound **1** was repeated twice or more times under the same crystallizing conditions that would be expected to give an aggregation of blade-shaped crystals as in the previously mentioned literature[3] in order to purify it in a reprocessing step, the undesired fine needle-shaped crystal was unfortunately obtained again. Therefore, we assumed that the crystal contained an impurity which acted as a habit modifier. A habit modifier is defined as a small amount of additive introduced to a crystallizing system in order to change the crystal habit but not polymorph. For example, some water-soluble cellulose derivatives acted as habit modifiers for chloramphenicol,[4] dicyanodiamide,[5] and amino acids.[6] Before our study,[7] researchers of Fujisawa Pharmaceutical Co., Ltd. discovered that amino acids or a cephalosporin derivative acted as a habit modifier for cefazolin sodium.[8] However, there are still few examples for habit modifiers for cephalosporin crystals.

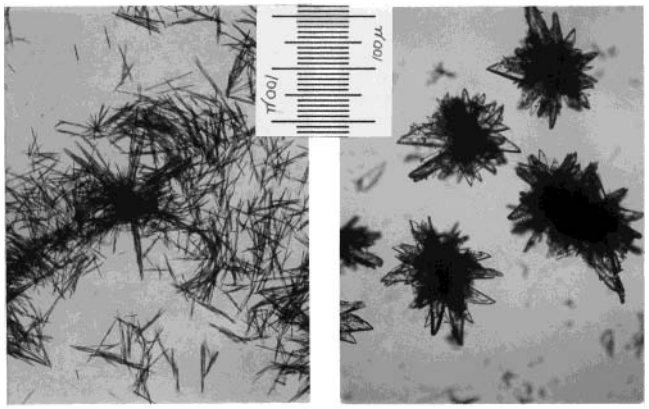

Figure 1. **Photographs of cefmatilen hydrochloride monohydrate (1).**

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(7) A portion of this study (Methods G and H) was patented. Takahashi, H.; Masui, Y. Patent Application No. JP 1994-193059.

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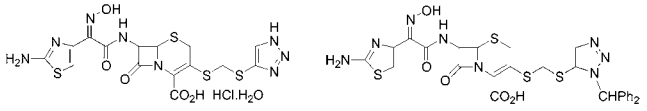
Scheme 1



1 2

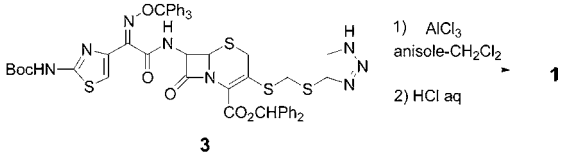
To discover a habit modifier for compound **1**, impurities in numerous pilot batches were investigated, and numerous additives were screened. We found that one of the related substances, impurity **2** (Scheme 1), which has a diphenylmethyl group at the N3-position of the triazolyl group of cefmatilen, and some water-soluble polymers such as hydroxyalkylcelluloses or polyvinyl derivatives acted as habit modifiers for compound **1**.[7]

Results and Discussion

Transformation by stirring an amorphous suspension of compound **1** under an acidic condition (1 N to 3 N HCl) in the presence of seed crystal from room temperature to 40 °C for 10 min to several hours (Method E) gave needle-shaped crystals (Figure 1A). There were three serious problems. First, the needle-shaped crystal was not desirable. Second, it was difficult to control agitation time until all the amorphous suspension changed into crystal, especially on a large scale. The longer agitation time led to the lower yield and purity because compound **1** was decomposed to give some impurities during agitation. Third, a thixotropic phenomenon was often observed during the agitation of the gelatinous slurry under the acidic condition (1 N to 3 N HCl).[9] When the phenomenon occurred, it was difficult to stir the slurry. The crystallization was developed, and the procedures (Methods E and F) were patented.[3] The slow addition of amorphous suspension (~pH 4) to 6 N HCl in the presence of seed crystal at 40 °C (Method F) gave the desired aggregation of blade-shaped crystals (Figure 1B).[3] In this case, once the amorphous suspension was dropped into the acidic solution, it was dissolved immediately before crystallization. However, when recrystallization of compound **1** was repeated twice or more times under the same crystallizing conditions (Method F), the needle shape appeared again. Those two crystal forms showed the same X-ray diffraction pattern.[3a] Therefore, both had the same morphic form.

Compound **1** was prepared by deprotection of compound **3** with $AlCl_3$ (Scheme 2). A bulk of a typical batch of compound **1** contains several impurities whose contents are smaller than 0.5% by area. After the repeated recrystallization, a decrease in impurities was observed. Therefore, we assumed that the crystals contained an impurity which acted as a habit modifier. The relationship between the content of each impurity and crystal habit was examined by reviewing

Scheme 2



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Scheme 3

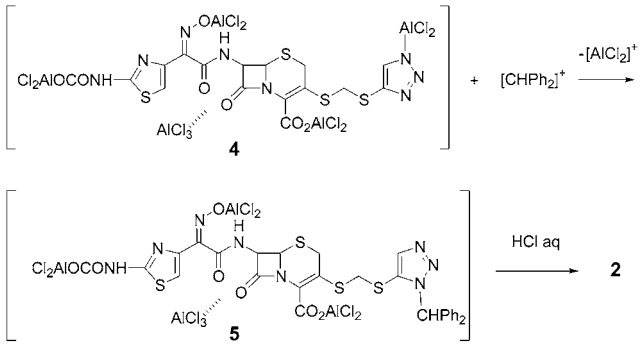

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Table 1. **Effect of Temperature, during Deprotection Reaction of Compound 3 To Give Compound 1, on the Content of Impurity 2**[a]

entry	temp,[b] °C	time,[b] min	% conversion	% content[c] of compound **1**	% content[c] of impurity **2**	% content[c] of others
1	−30	20	100	99.2	0.2	0.8
2	−12	20	100	98.9	0.5	0.6
3	0	20	100	98.7	0.6	0.7
4	20	20	100	95.5	2.1	2.4

[a] Reaction conditions: compound **3**, 27 mmol; after addition of $AlCl_3$ (5 equiv) solution, the temp was kept at 0 °C for 90 min. [b] During the addition of $AlCl_3$ solution. [c] % area measured on HPLC analysis.

production records of many pilot batches of bulk drugs. A bulk of a normal batch of compound **1** contains **2** (0.1−0.3% by area) as a usual impurity. We found that specific surface areas (measured on a Sub-Sieve Sizer) of the API were in proportion to the content of inpurity **2** in the API. Impurity **2** was isolated and identified (Scheme 1). It has a diphenylmethyl group at the N3-position of the triazolyl group and is probably generated by nucleophilic attack of the diphenylmethyl cation to triazolyl group during the deprotection reaction of compound **3** (Scheme 3).

The amount of impurity **2** formed in the deprotection reaction system depended upon the temperature during the addition of a solution of $AlCl_3$ in anisole to a suspension of compound **3** in anisole−dichloromethane (Table 1). At the end of the addition of $AlCl_3$, the conversion was higher than 80%. Most of the diphenylmethyl cation was trapped with anisole to give diphenylmethylanisole isomers. At higher temperatures, the rate of reaction increased but the selectivity was decreased. Therefore, an increase in temperature increased the content of impurity **2** in the reaction mixture.

The effect of the content of impurity **2** on the crystallization of compound **1** was examined in more detail (Table 2). For this examination, the samples of compound **1** which contained impurity **2** (0.50 and 1.24%) were prepared. When the content of impurity **2** in the crystallizing system was less than 0.1% by area, needle-shaped crystals were obtained

(8) (a) Momonaga, M.; Ohnishi, K.; Yazawa, H. Patent Application No. JP 1991-98391. (b) Yazawa, H.; Momonaga, M. *Pharm. Manuf. Int.* **1994**, 107−110.

(9) Viscosity of the gelatinous slurry during the agitation under the acidic condition (1 M to 3 M HCl) was variable not only between the runs but also in the same run. The thixotropic phenomenon depended upon the concentration of acid. When the concentration of HCl was ~0.0001 M (pH 4), no phenomenon occurred. However, a higher concentration of HCl than 1 M was necessary for crystallization.

Table 2. **Effect of Content of Impurity 2 on Crystallization of Compound 1**[a]

entry	% content[b] of impurity **2** in the crystallizing system	resulted crystals of **1**: specific surface area (SSA),[c] m^2/g	resulted crystals of **1**: % content[b] of impurity **2**	resulted crystals of **1**: crystal habit[d]
1	0.06	1.61	0.03	A
2	0.20	0.66	0.11	B
3	0.26	0.48	0.13	B
4	0.50	0.33	0.35	B
5	1.24	0.14	1.00	B

[a] Crystallization conditions (Method F) are described in the Experimental Section. [b] % area measured on HPLC analysis. [c] Measured on Sub-Sieve Sizer. [d] (A) Fine needle-shaped crystals; (B) aggregation of blade-shaped crystals.

Table 3. **Habit Modifier Screening**[a]

entry	additive (wt %)[b]	crystal habit of compound **1**
1	none	fine needle-shaped
2	hydroxypropylcellulose (HPC-M, 0.01)	fine needle-shaped
3	hydroxypropylcellulose (HPC-M, 0.1)	aggregation of needle-shaped
4	hydroxypropylcellulose (HPC-M, 0.2)	aggregation of blade-shaped
5	hydroxypropylcellulose (HPC-L, 0.2)	aggregation of blade-shaped
7	poly(vinylpyrrolidone) (0.05)	aggregation of needle-shaped
8	poly(vinylpyrrolidone) (0.2)	adhesive solid
9	poly(vinyl alcohol) (0.2)	no crystallization occurred
10	methylcellulose (0.03)	aggregation of needle-shaped
11	methylcellulose (0.1)	no crystallization occurred
12	ethylcellulose (0.05)	aggregation of needle-shaped

[a] Crystallization conditions (Method G) in the absence of impurity **2** are described in the Experimental Section. [b] Additives were dissolved in an amorphous suspension.

(Table 2, entry 1). When that was more than 0.2% by area, an aggregation of blade-shaped crystals was obtained (Table 2, entries 2−5). Interestingly, it was observed that specific surface areas (measured on a Sub-Sieve Sizer) of the resulted crystals were in proportion to the content of impurity **2** in the crystallizing system. Since the content of impurity **2** can be controlled by the temperature during the addition of $AlCl_3$ to a suspension of compound **3** in the deprotection step, crystal habit and size (specific surface area) can be controlled by the temperature of addition of $AlCl_3$. In addition, 73 mg of impurity **2** were prepared from compound **3** and were added to the crystallizing system (Method G; content of impurity **2**: initial, 0.06%; after addition, 0.2% by area) to give compound **1** as an aggregation of blade-shaped crystals (SSA: 0.79 m^2/g, compared with entry 1 of Table 2). It is obvious that impurity **2** acts as a habit modifier for compound **1**.

When API is recovered from unused drug product, the blade shape cannot be obtained because of a low level of impurity **2** in the crystallizing system. Therefore, to discover an "alien" habit modifier, numerous additives such as various water-soluble celluloses and polyvinylesters were screened (Table 3). In the absence of impurity **2**, recrystallization gave fine needle-shaped crystals (Table 3, entry 1). In the case of the addition of hydroxypropylcellulose type-M[10] (HPC-M, 0.01 wt %), no effect was observed (Table 3, entry 2). The addition of HPC-M (more than 0.1 wt %) afforded aggregation and an increase in the amount of HPC-M enlarged crystal size (Table 3, entries 3−4). Hydroxypropylcellulose type-L[10] (HPC-L) showed similar activity to HPC-M (Table 3, entry 5). Poly(vinylpyrrolidone), poly(vinyl alcohol), methylcellulose, and ethylcellulose seemed to be modifiers; however, reasonable amounts necessary to give the desired habit are probably in a narrow range between 0.03% and 0.2 wt % (Table 3, entries 7−12). In the presence of poly(vinyl alcohol) (0.2%) or methylcellulose (0.1%), no crystallization occurred (Table 3, entries 9−10). In these two cases, seed crystals were dissolved. Ethylcellulose could not be used at more than 0.1% because of its lower solubility in water. When HPC-L was used, a portion of compound **1** was sometimes separated as oil from the solution during crystallizaion; therefore, HPC-M was chosen as a modifier. Although a small amount of HPC was incorporated in the API, it was acceptable because HPC is widely used as a safe additive for food and pharmaceuticals.

Table 4. **Effect of Hydroxypropylcellulose (Type M) on Crystal Habit and SSA of Compound 1**[a]

entry	HPC-M, % by weight	method[b]	resulted crystals of **1**: specific surface area (SSA),[c] m^2/g	resulted crystals of **1**: crystal habit[d]
1	0		1.47	A
2	0.1	G	1.32	C
3	0.2	G	0.44	B
4	0.3	G	0.41	B
5	0.5	G	0.21	B
6	0.3	H	1.31	C
7	0.5	H	0.45	B

[a] Crystallization conditions in the absence of impurity **2** are described in the Experimental Section. [b] (G) Additive was dissolved in amorphous suspension; (H) additive was dissolved in 6 N HCl. [c] Measured on a Sub-Sieve Sizer. [d] (A) Fine needle-shaped crystals; (B) aggregation of blade-shaped crystals; (C) aggregation of needle-shaped crystals.

The effect of the amount of HPC-M and the procedure for the addition on the crystallization of compound **1** was examined (Table 4). When HPC-M (0.1 wt %) was dissolved in the amorphous suspension, an aggregation of needle-shaped crystals was obtained (Table 4, entry 2). When the amount was more than 0.2 wt %, an aggregation of blade-shaped crystals was obtained (Table 4, entries 3−5). Interestingly, it was observed that specific surface areas (measured on a Sub-Sieve Sizer) of the resulted crystals were in proportion to the amount of HPC-M. Therefore, crystal habit and size (specific surface area) can be controlled by the amount of HPC-M. The crystal morphology was affected similarly using impurity **2**. Since it is known that HPC is degradated in diluted HCl, it was predictable that the procedure of dissolving HPC-M in 6 N HCl (Method H) needed more HPC-M than that in the amorphous suspension (Method G). According to the data as shown in Table 4

(10) HPC is classified by the viscosity of its aqueous solution depending on its degree of polymerization. Viscosity of 2% aqueous solution at 20 °C (CPS): HPC-L, 6−10; HPC-M, 150−400.

(entries 6−7, compared to entries 4−5), Method G is preferable.

It is known that the crystal habit can be modified with additives, and the mechanism was discussed.[11] For example, benzoic acid is a habit modifier for benzamide. Benzamide molecules associates by hydrogen bonding to give dimers which develop a ribbon pattern along the crystal growth direction. The ribbons are stacked to yield crystal faces. Benzoic acid interferes with the hydrogen bonding and changes the growth rates. Similarly, impurity **2** or HPC probably interferes with intermolecular hydrogen bonding between cefmatilen molecules, which was observed by X-ray crystallography[12] of pure compound **1**.

Control of the crystal habit and size of compound **1** by the amount of impurity **2** is preferable because polymeric habit modifiers are "alien" additives. However, crystallization by addition of an "alien" habit modifier is useful because of its convenience, generality, and robustness.

Conclusions

The crystal habit and size of cefmatilen hydrochloride hydrate (**1**) can be controlled by using habit modifiers such as impurity **2** (one of related substances), hydroxyalkylcelluloses, or polyvinyl derivatives. Since the amount of impurity **2** can be controlled by the temperature during the addition of $AlCl_3$ to a suspension of compound **3** in the deprotection step, the crystal habit and size can be controlled by the temperature of addition of $AlCl_3$. A practical and robust crystallization process for compound **1** by control of the amount of impurity **2** or by addition of polymeric additives has been established.

Experimental Section

Materials and Instrumentations. [6*R*-[6α,7*β*(*Z*)]]-7-[(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-8-oxo-3-[[(1*H*-1,2,3-triazol-4-ylthio)methyl]thio]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid monohydrochloride monohydrate (**1**, cefmatilen hydrochloride hydrate) and diphenylmethyl (6*R*,7*R*)-7-[(*Z*)-2-(2-*tert*-butoxycarbonylaminothiazol-4-yl)-2-(triphenylmethyloxyimino)acetamido]-8-oxo-3-(1*H*-1,2,3-triazol-4-yl)thiomethylthio-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (**3**) were prepared according to the literature method.[3] The HPLC analysis was carried out on a COSMOSIL column (150 mm × 4.6 mm). The mobile phase was at a flow rate of 1 mL/min, and a UV detector (245 nm) was used. NMR experiments were conducted by using a MERCURY 300 NMR spectrometer (Varian). IR spectra were obtained on a MAGNA 560 FT-IR spectrophotometer (Nicolet). Specific surface areas of crystals were determined on a Model 95 Sub-Sieve Sizer (Fisher Scientific).

Separation of [6*R*-[6α,7*β*(*Z*)]]-7-[(2-Amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-8-oxo-3-[[(3-diphenylmethyl-1*H*-1,2,3-triazol-4-ylthio)methyl]thio]-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic Acid (2) from Compound 1. A bulk of a normal batch of compound **1** containing **2** (∼0.1%) as an usual impurity was used. Impurity **2** (5 mg) was separated by preparative HPLC (Develosil ODS HG 15/30, 5 cm × 50 cm, Nomura Chemical, gradient condition: aqueous solution A = 20 mM $AcONH_4$ + 0.5 mM $N(CH_2CO_2Na)_3$, B = MeCN, (time (min), A:B, hold time (min)) = (0, 80:20, 0), (30, 60:40, 5), (40, 10:90, 5), (45, 80:20,-15)). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.48 (d, 1H, J = 16.5 Hz, −SCH_2− of cephem ring), 3.64 (d, 1H, J = 16.5 Hz, −SCH_2− of cephem ring), 4.14 (d, 1H, J = 13.5 Hz, −SCH_2S−), 4.26 (d, 1H, J = 13.5 Hz, −SCH_2S−), 5.03 (d, 1H, J = 4.8 Hz, −NCHS− of cephem ring), 5.65 (dd, 1H, J = 8.1 and 4.8 Hz −CH(C=O)N− of cephem ring), 6.65 (s, 1H, −SCH= of thiazole ring), 7.10 (br s, 2H, −NH_2), 7.15−7.27 (m, 5H), 7.30−7.40 (m, 6H), 8.07 (s, 1H, 5-position of triazole ring), 9.42 (d, 1H, J = 8.1 Hz, −CONH−). The interaction between the protons of the thiomethylthio group (δ 4.14 and 4.26 ppm) and those of the phenyl group (δ 7.15−7.27 ppm) which was observed by ^{1}H−^{1}H ROESY (DMSO-d_6) suggests that the diphenylmethyl group connects at the N3-position of the triazolyl group. IR (Nujol) 1773, 1664 cm^{-1}. MS (Ion Mode: FAB^+) m/z (relative intensity) 681 (10) [M + H^+], 167 (100). MS (Ion Mode: FAB^-) m/z (relative intensity) 679 (33) [M^- − H], 266 (100), 225 (87).

Preparation of Impurity 2 from Compound 3. Compound **3** (25 g, 24 mmol) was suspended in a mixture of dichloromethane (250 mL) and anisole (20 mL). The suspension was heated to 40 °C. Then, to the suspension was added chlorodiphenylmethane (146 g, 720 mmol) with stirring. To the resulting solution was added dropwise a solution of $AlCl_3$ (33 g, 240 mmol) in anisole (80 mL) at 40 °C with stirring. The reaction mixture was stirred for 10 min. The reaction mixture was poured into a solution of methanol (213 mL), water (113 mL), and concentrated HCl (25 mL) with cooling. The layers were separated. The aqueous layer was washed with dichloromethane (100 mL × 3) and evaporated to give ∼120 mL of a suspension. Filtration followed by drying gave 12.85 g of crude product which contained impurity **2** (∼13% by area) and compound **1** (64% by area). Column chromatography on SiO_2 deactivated with oxalic acid gave crude impurity **2** (1.1 g) from 7.0 g of the mixture. The crude sample (223 mg) was dissolved in methanol (1 mL). Precipitation by adding 0.002 N HCl (2.5 g) gave 73 mg of impurity **2**. HPLC chromatogram and ^{1}H NMR spectra were compared with those of the authentic sample.

General Procedure for Preparation of Amorphous Suspension of Compound 1. According to the literature method,[3] deprotection of compound **3** by using $AlCl_3$ gave crude crystals of compound **1** which contained impurity **2** (∼1% by area). In the literature,[3] the crude crystals were not dried prior to recrystallization. However, in this report, the crude crystals were dried in order to determine the yield. To a suspension of the crude crystals of compound **1** (10.0 g, 17.6 mmol) in water (140 mL) was added dropwise

(11) (a) Mullin, J. W. In *Crystallization*, 3rd ed.; Butterworth-Heinemann: Oxford, 1997; pp 248−257. (b) Berkovitch-Yellin, Z.; Addadi, L.; Idelson, M.; Lahav, M.; Leiserowitz, L. *Angew. Chem. Suppl.* **1982**, 1336−1345.

(12) Unpublished data: A nitrogen atom of the thiazole ring is protonated. An H_2O molecule is located between the carboxylate group and triazole ring. A chloride anion is located near both the H_2O molecule and N1-position of the triazolyl group. Intramolecular hydrogen bonding between the H_2O molecule and N1-position of triazolyl group is observed. The N3-position of the triazolyl group is used for intermolecular hydrogen bonding.

aqueous 4% NaOH with the pH and the temperature kept below 6.1 and 5 °C, respectively, until most of the crystals dissolved. Cellulose powder (3.0 g) was added to the solution and stirred for 20 min. The mixture was filtered through a Buchner funnel precoated with cellulose powder and activated carbon (1.2 g), and the filter cake was rinsed with water (35 mL). The pH of the filtrate was adjusted to 4.0 with 35% HCl at 5 °C with vigorous stirring. The resulted gelatinous slurry (∼220 mL) of amorphous **1** was cooled to 0 °C and then stored overnight.

Recrystallization of Compound 1 by Addition of Aqueous HCl to Amorphous Suspension (Method E). The pH of the suspension was adjusted to 1.0 with 35% HCl at 5 °C. Then, seed crystal was added to the suspension. The suspension was warmed to 25 °C and stirred for 1 h. To the suspension was added 35% HCl (40 mL). The mixture was stirred at 25 °C until the crystallization was completed. The precipitate was collected and rinsed with water (100 mL) and dried on a Buchner funnel to give compound **1** (9.60 g, 96%) as needle-shaped crystals (Figure 1A).

Recrystallization of Compound 1 According to the Literature Procedure (Method F).[3] After approximately one-fourth of the gelatinous slurry (∼55 mL) of amorphous **1** was added to aqueous 19% HCl (220 mL) at 40 °C, seed crystal (44 mg) was added, and then the rest of the gelatinous slurry was added dropwise for ∼20 min with vigorous stirring. The resulted slurry was cooled to 20 °C. The precipitate was collected and rinsed with water (100 mL) and dried on a Buchner funnel to give compound **1** (9.60 g, 96%) as an aggregation of blade-shaped crystals (Figure 1B).

The second recrystallization (Method F was repeated) was carried out as follows. Compound **1** (9.60 g) which was prepared by Method F as shown previously was suspended in water (140 mL). To the suspension was added dropwise aqueous 4% NaOH with the pH and the temperature kept below 6.1 and 5 °C, respectively, until most of the crystals dissolved. Cellulose powder (3.0 g) was added to the solution and stirred for 20 min. The mixture was filtered through a Bucher funnel precoated with cellulose powder and activated carbon (1.2 g), and the filter cake was rinsed with water (35 mL). The pH of the filtrate was adjusted to 4.0 with 35% HCl at 5 °C with vigorous stirring. The resulted gelatinous slurry (∼210 mL) of amorphous **1** was cooled to 0 °C and then stored overnight. After approximately one-fourth of the gelatinous slurry was added to aqueous 19% HCl (210 mL) at 40 °C, seed crystals (44 mg) were added, and then the rest of the gelatinous slurry was added dropwise for ∼20 min with vigorous stirring. The resulted slurry was cooled to 20 °C. The precipitate was collected and rinsed with water (100 mL) and dried on a Buchner funnel to give compound **1** (9.10 g, 91%) as needle-shaped crystals.

Recrystallization of Compound 1 by Using a Habit Modifier (Method G). A habit modifier was dissolved in the amorphous suspension (∼220 mL). After approximately one-fourth of the suspension (∼55 mL) was added to aqueous 19% HCl (220 mL) at 40 °C, seed crystals (44 mg) were added, and then the rest of the suspension was added dropwise for ∼20 min with vigorous stirring. The resulted slurry was cooled to 20 °C. The precipitate was collected and rinsed with water (100 mL) and dried on a Buchner funnel to give compound **1**.

Recrystallization of Compound 1 by Using a Habit Modifier (Method H). A habit modifier was dissolved in aqueous 19% HCl (220 mL). After approximately one-fourth of the suspension (∼55 mL) was added to aqueous 19% HCl (220 mL) at 40 °C, seed crystals (44 mg) were added, and then the rest of the suspension was added dropwise for ∼20 min with vigorous stirring. The resulted slurry was cooled to 20 °C. The precipitate was collected and rinsed with water (100 mL) and dried on a Buchner funnel to give compound **1**.

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