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Technical Notes

An Improved and Scaleable Preparation of 7-Amino-3-vinylcephem-4-carboxylic acid

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Abstract:

A practical and efficient multikilogram-scale preparation of 7-amino-3-vinylcephem-4-carboxylic acid (7-AVCA), a key intermediate used in the synthesis of cefixime and cefdinir, is described utilizing *p*-methoxybenzyl 7-phenylacetamido-3-chloromethylcephem-4-carboxylate (GCLE) as a starting material. Reaction conditions were optimized to simplify the process, to improve the quality and to increase the yield. The process has been demonstrated on a multikilogram scale in 77% overall yield with a purity of >99%.

Introduction

7-Amino-3-vinylcephem-4-carboxylic acid (7-AVCA, **1**) is a key intermediate used in the synthesis of cefixime and cefdinir,[1−4] which are orally active third-generation cephalosporin antibiotics with broad antibacterial spectra.[5−7] Cefixime and cefdinir can be efficiently synthesized from **1** in 80% and 70% overall yields respectively.[1,3]

There are several synthetic methods reported for the preparation of 7-AVCA starting from deacetyl cephalosporin C (DCC) (Scheme 1),[8] 7-amino cephalosporanic acid (7-ACA) (Scheme 2),[8] or GCLE, (Scheme 3)[9−12] etc.

Schemes 1 and 2 have many shortcomings such as having a large number of steps, using expensive and hazardous raw materials, and being not environmentally friendly. Scheme 1 is impractical on a large scale due to the above shortcomings and the limited availability of DCC. Although some companies are producing **1** by the routes shown in Scheme 2, the above shortcomings and the low overall yield make the process uneconomical. Scheme 3 (Route B) is obviously more practical compared with other schemes due to fewer steps, easier availability of raw materials, and more environmental friendliness. However, there are still several drawbacks regarding Scheme 3 (Route B) in the reported methods,[10,11] namely: (1) the overall yield (41.4−58.5%) is low; (2) trifluoroacetic acid used in the process is relatively expensive and hazardous; (3) product purity reported by Xu, et al. is only 92.3%, which is insufficient for cefixime or cefdinir production. Although the purity has been improved to 98.3% by Du, et al., the improved process requires chromatographic purification, which is extremely inconvenient for commercial production; and (4) isolation[11] or chromatographic purification[12] of intermediate **3** makes the reported processes complicated.

To improve the quality and the yield, as well as to reduce the cost and simplify the process from a commercial aspect, we developed an improved process based on Scheme 3 (Route B). In this contribution, a simplified scaleable process with dramatically improved yield and quality for the preparation of **1** is described that uses GCLE as a starting material.

Results and Discussion

Starting from GCLE, one reported literature method[10,11] involves introduction of C-3 vinyl group by the Wittig reaction to give *p*-methoxybenzyl 7-phenylacetamido-3-chloromethylcephem-4-carboxylate (**2**), which when deprotected with trifluoroacetic acid gives 7-phenylacetamido-3-chloromethylcephem- 4-carboxylic acid (**3**). 7-AVCA (**1**) is finally obtained by enzymolysis in the presence of penicillin G amidase. In this method, the overall yield and purity of **1** are only 55% and 92.3%, respectively. **3** is isolated and dried for use in the next step. Expensive and hazardous trifluoroacetic acid is used. Furthermore, the crude product is washed with methanol, butyl acetate, and acetone sequentially to remove the impurities, making solvent recovery difficult. Another improved method[12] increases the yield and purity to 58.5% and 98.3% respectively, but trifluoroacetic acid is also used in the process, and chromatographic purification is required to improve the quality.

In the present paper, we report an improved and scaleable process with respect to improvement of yield and product quality, use of less expensive raw materials, and lower consumption of solvents. In this improved process, GCLE reacts with sodium iodide and triphenylphosphine in a mixture of

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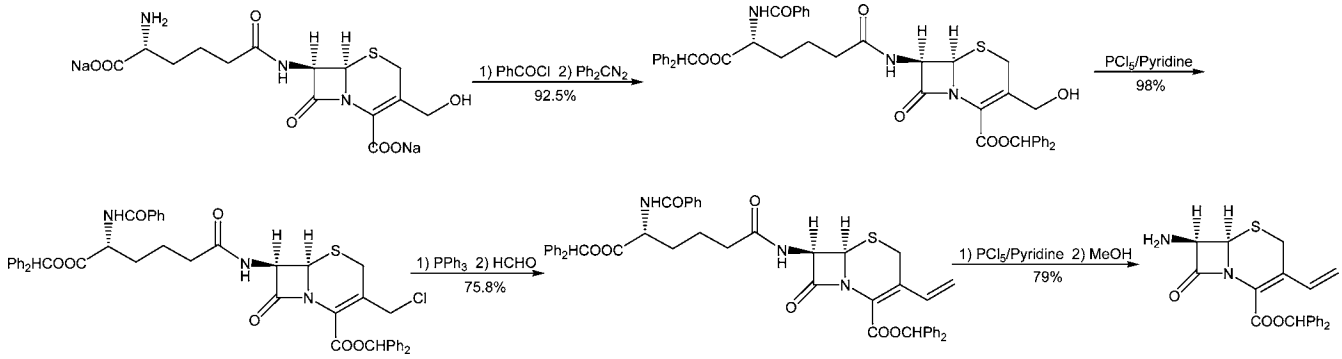
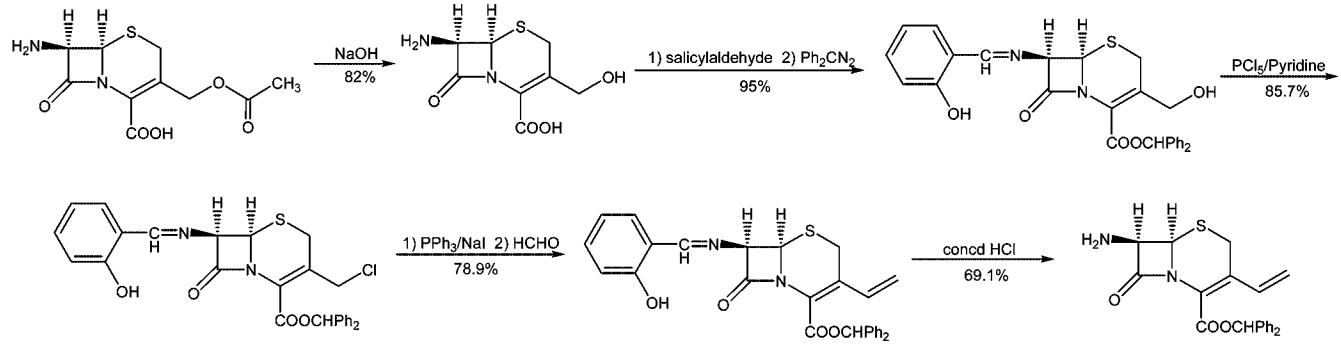
Scheme 1. **Synthesis of diphenylmethyl 7-AVCA from DCC**[8]

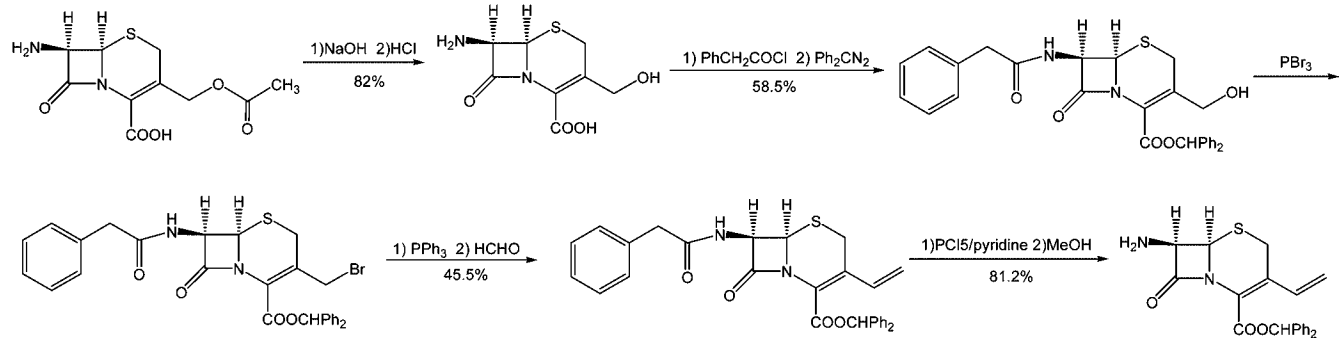


Scheme 2. **Synthesis of diphenylmethyl 7-AVCA from 7-ACA**[8]

Route A



Route B



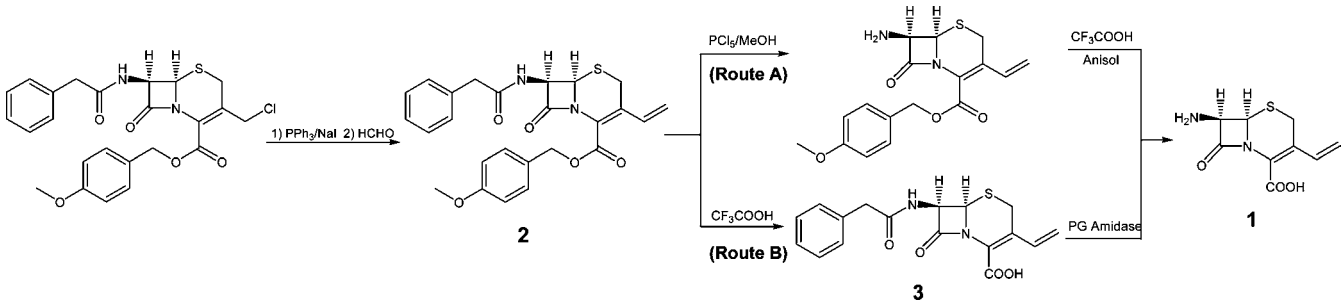
water and methylene chloride to give the phosphonium salt, which subsequently reacts with formaldehyde in the presence of base to result in **2**. The resulting **2** is then deprotected with phenol to give **3**, which when deprotected with penicillin G amidase gives **1** in an overall yield of 77% with a purity of >99%.

During the process optimization, we paid great attention to operation simplicity on a commercial scale. By controlling the purity of **2** at greater than 99%, isolation or chromatographic purification of **3** was eliminated. Two deprotection steps were carried out sequentially without isolation of **3** by aqueous phase extraction of the intermediate after the first deprotection.

Introducing a vinyl group by the Wittig reaction is a traditional method, but reported methods for preparation of **2** give low yields and purity. We studied causes for the low yield and purity during the process optimization. In the crystallization of **2**, a lower concentration of supersaturated solution gives higher product purity and lower yield; conversely, one obtains higher yield and lower purity. Further, an improved crystallization method was developed, and single-stage crystallization was optimized to multistage crystallization. Overall, this improved crystallization method dramatically improved the yield without compromising the quality.

When deprotecting the carboxyl group, expensive, hazardous trifluoroacetic acid is eliminated, making the process more cost-effective and environmentally friendly. After deprotection of the carboxyl group, **3** is extracted to water and subjected to enzymolysis directly without isolation or chromatographic purification, making the process simpler and giving better yield. Upon deprotection of the phenylacetyl group with penicillin G amidase, **1** is obtained in excellent color and purity by adjusting the pH with sulfuric acid solution without further purification, saving additional solvents and making recovery easier.

Scheme 3. **Synthesis of 7-AVCA from GCLE**[9−12]



On a commercial scale, the quality and yield of **2** are also affected by the temperature and efficiency of the distillation. Heat input and vacuum level should be controlled such that the internal temperature does not rise above 40 °C. The operational time of all workup procedures should be controlled; extended workup time compromises the quality and lowers the yields.

The present method has the following advantages over the reported methods. Consumption of solvents is minimized. The yield of **2** is dramatically improved by a multistage crystallization method without compromising the quality. The use of expensive, hazardous trifluoroacetic acid is eliminated. Isolation or chromatographic purification of **3** is avoided by extracting the intermediate into the aqueous phase. The overall yield is increased to 77% with a purity of >99%. The process has been demonstrated in pilot scale and is amenable to large-scale synthesis.

In conclusion, an environmentally friendly, cost-effective and scaleable process for the preparation of 7-amino-3-vinylcephem-4-carboxylic acid (**1**) with dramatically improved yield and quality is reported.

Experimental Section

General. Reagents were used as such without purification. Melting points were measured using a capillary melting point apparatus without correction. NMR spectra were recorded on a Bruker instrument at 300 MHz for ^{13}C and 600 MHz for ^{1}H, with tetramethylsilane as an internal standard. Infrared spectra were recorded using a Thermo Scientific Nicolet iS10 instrument. Mass spectra were recorded using an API 4000 (ABI) instrument.

HPLC methods. Reaction progress was monitored by HPLC. HPLC analysis was performed on a Waters instrument with a UV detector using a Chemsil ODS (150 mm × 4.6 mm, 5 μm) column.

HPLC analysis for triphenylphosphine complex. Mobile phase: pH 7.3 buffer/organic modifier = 40:60 (v:v) [buffer prepared as follows: dissolve ammonium dihydrogen orthophosphate (0.92 g) and disodium hydrogen orthophosphate (0.17 g) in H_2O (400 mL); organic modifier prepared as follows: dissolve tetra-heptyl-ammonium bromide (2.4 g) in acetonitrile (300 mL), add methanol (300 mL)]; flow rate: 1.0 mL/min; detection wavelength: 263 nm; injection volume: 20 μL/mL.

HPLC analysis for other reactions. Mobile phase: tetra-*n*-butyl ammonium hydroxide (TBAH) solution/acetonitrile = 50:50 (v:v), adjusted to pH 5 with phosphoric acid. [TBAH solution prepared as follows: dissolve TBAH (0.92 g) in water (500 mL)]; flow rate: 1.5 mL/min; detection wavelength: 263 nm; injection volume: 20 μL/mL.

Preparation of *p*-Methoxybenzyl-7-phenylacetamido-3-vinylcephem-4-carboxylate (2). Sodium iodide (4.65 kg, 31 mol) was added to a mixture of water (14 L) and methylene chloride (70 L), followed by adjusting the pH to 3.0 with concentrated HCl. Then GCLE (15 kg, 30.8 mol) and triphenyl phosphine (8.19 kg, 31 mol) were added. The reaction mixture was heated to 32−36 °C with hot water and stirred at this temperature until completion of the reaction as monitored by HPLC (30−60 min). Upon completion of the reaction, the mixture was cooled to 10−20 °C. Methylene chloride (28 L), dimethylformamide (21 L) and formaldehyde solution (16.2 kg, 200 mol) were added, followed by slow addition of sodium hydroxide solution (1.2 kg in 14 L water). The reaction mixture was stirred at 10−20 °C until completion of the reaction monitored by HPLC (30−60 min). After completion of the reaction, water (112 L) and concentrated HCl (0.7 kg) were added. The resulting mixture was again stirred for 30 min, and then allowed to separate. The aqueous layer was extracted with methylene chloride (14 L). The organic layers were combined and washed with water (87 L). Then methylene chloride was partly removed by distillation in vacuo while the internal temperature was maintained below 40 °C to a final volume of about 60 L. Methanol (193 L) was added, and the distillation was continued to reach a final volume of about 170 L. Water (45 L) was slowly added, and the resulting mixture was slowly cooled to 18−22 °C and filtered. The cake was washed with acetone/water (30 L/13 L) and dried in vacuo to yield **2** (12 kg, 84%). Mp 179.4−179.7 °C; HPLC purity >99%; ^{1}H NMR (DMSO-d_6): δ 9.19 (d, 1H, NH), 7.32−6.92 (m, 9H, $C_6H_{5/4}$), 6.81 (dd, 1H, -*CH* = CH_2), 5.71 (dd, 1H, -*CH*-NH), 5.65 (m, 1H, −CH=CH_2^a), 5.34 (d, 1H, −CH=CH_2^b), 5.26 (d, 1H, S−CH-N), 5.15 (m, 2H, OCH_2−), 3.75 (s, 3H, $-OCH_3$), 3.93 and 3.58 (d, 2H, O=C−CH_2), 3.50 and 3.67 (d, 2H, S−CH_2); ^{13}C NMR (DMSO-d_6): δ 171.4, 165.4, 162.2, 159.8, 136.3, 132.0, 130.8, 129.5, 128.7, 127.5, 127.0, 125.8, 124.5, 118.6, 114.3, 67.6, 59.7, 58.3, 55.6, 42.0, 23.6; IR (ν cm^{-1}, KBr): 3271 (NH), 3045 (CH=CH), 2961 (CH_2), 1775, 1714 (CO), 1659 (C=C), 1614, 1586, 1497, and 1456 (C_6H_5), 1251, 1200 (−$COOCH_2$−), 1177, 1166 (C−O−CH_3), 826 (C_6H_4), 697 (C_6H_5); MS (*m*/*e*): 465.4 $[M + H]^+$.

Preparation of 7-Phenylacetamido-3-vinylcephem-4-carboxylic acid (3). Phenol (25 kg, 266 mol) was melted with hot water and cooled to 45−50 °C followed by addition of **2** (12 kg, 25.8 mol). The reaction mixture was stirred at 45−50 °C until completion of the reaction monitored by HPLC (12−18

h). After completion of the reaction, the reaction mixture was added to a mixture of butyl acetate (108 L) and water (90 L) and cooled to 13−17 °C. Sodium bicarbonate solution (3.2 kg of sodium bicarbonate in 48 L of water) was added. The reaction mixture was stirred for 30 min at 13−17 °C, and then allowed to separate. The organic layer was extracted twice with a solution of sodium bicarbonate and sodium chloride in water (each time with 1.4 kg of sodium chloride and 0.24 kg of sodium bicarbonate in 24 L of water). The aqueous layers were combined and extracted with butyl acetate (36 L) to give water solution of **3**. If the phenol content in the aqueous layer was more than 0.5%, an additional butyl acetate (25 L) extraction was applied. The resulting solution of **3** was held for direct use in the next step. A small sample of the solution was removed and adjusted to pH 2.0 with diluted HCl, filtered, and dried in vacuo for characterization. Mp 165.4−165.6 °C; HPLC purity >99%; ^{1}H NMR (DMSO-d_6): δ 9.17 (d, 1H, NH), 7.32−7.22 (m, 5H, C_6H_5), 6.91 (dd, 1H, $-CH{=}CH_2$), 5.68 (dd, 1H, $-CH-$NH), 5.60 (d, 1H, $-CH{=}CH_2^a$), 5.32 (d, 1H, $-CH{=}CH_2^b$), 3.88 (d, 1H, S−CH−N), 3.58 (d, 1H, $-CH_2^a-C{=}O$), 3.56 (d, 1H, $-CH_2^b-C{=}O$), 3.50 (d, 2H, S−CH_2); ^{13}C NMR (DMSO-d_6): δ 170.9, 164.5, 163.1, 135.7, 131.8, 128.9, 128.1, 126.4, 125.3, 124.0, 117.2, 59.0, 57.6, 41.4, 22.9; IR (ν cm^{-1}, KBr): 3279 (NH), 3032 (CH═CH), 2956 (CH_2), 1775, 1705 (CO), 1662 (C═C), 1497 and 697 (C_6H_5); MS (*m*/*e*): 345.4 $[M + H]^+$.

Preparation of 7-Amino-3-vinylcehpem-4-carboxylic acid (1). Penicillin G amidase was added to a water solution of **3** from the previous step. The mixture was stirred at 29−33 °C while maintaining at pH 8.0 with an 8−10% sodium carbonate solution. The progress of the phenylacetyl deprotection reaction was monitored by HPLC (1−3 h). After completion of the reaction, the suspension was filtered, and the filtrate was cooled to 0−5 °C. To the filtrate were added activated carbon (0.9 kg) and chilled methanol (24 L); the resulting mixture was stirred at 0−5 °C for 20 min and filtered. The filtrate was slowly acidified to pH 4.0 with 16−18% sulfuric acid solution and filtered. The cake was washed with water (18 L), slurried with methanol (12 L), filtered, and dried under vacuum to give **1** (5.36 kg, 92% based on **2**). Mp > 200 °C dec; HPLC purity >99%; ^{1}H NMR (DMSO-d_6): δ 6.87 (dd, 1H, $-CH{=}CH_2$), 5.53 (d, 1H, $-CH{=}CH_2^a$), 5.25 (d, 1H, $-CH{=}CH_2^b$), 5.00 (d, 1H, −CH−N), 4.76 (d, 1H, $-CH-NH_2$), 3.80 (d, 1H, S−CH_2^a), 3.52 (d, 1H, S−CH_2^b); ^{13}C NMR (DMSO-d_6): δ 169.8, 163.5, 132.2, 125.8, 122.9, 116.2, 63.6, 59.1, 22.5; IR (ν cm^{-1}, KBr): 1801 (CO), 1613 (C═C); MS (*m*/*e*): 227.3 $[M + H]^+$.

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