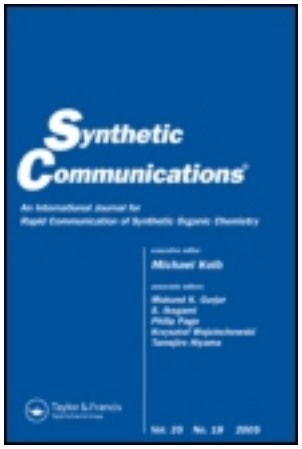

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ONE-POT SYNTHESIS OF CEFPIROME SULFATE FROM GCLE

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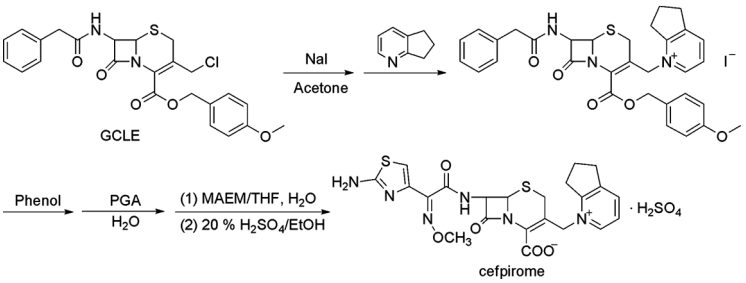
GRAPHICAL ABSTRACT



Abstract *Cefpirome was synthesized in 37.7% overall yield from 3-chloromethyl-7-phenylacetylamino cephalosporanic acid* p-*methoxybenzyl ester (GCLE) by sequential substitution of C-3 chloride with iodide and 2,3-cyclopentenopyridine, followed by a one-pot procedure including deprotection of carboxyl group, hydrolysis of 7-phenylacetamido, and reaction with 2-mercaptobenzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate (MAEM). The reaction conditions were as follows: obtained from GCLE at low temperature (−5 to 0°C) and absence of light, 3-iodomethyl-7-phenylacetylamino cephalosporanic acid* p-*methoxybenzyl ester (GILE) without purification was reacted directly with 2,3-cyclopentenopyridine, in which the molar ratio of GCLE, NaI, and 2,3-cyclopentenopyridine was 1:2:4, and the molar ratio of the resulting compound* p-*methoxybenzyl 7-phenylacetylamido-3-(2,3-cyclopenteno-1-pyridinio)methyl-3-cephem-4-carboxylate iodide and MAEM was 1:1.1. The structure of the intermediate and the target compound obtained were determined by nuclear magnetic resonance spectra and mass spectroscopy.*

Keywords Antibiotics; cefpirome; GCLE; onepot

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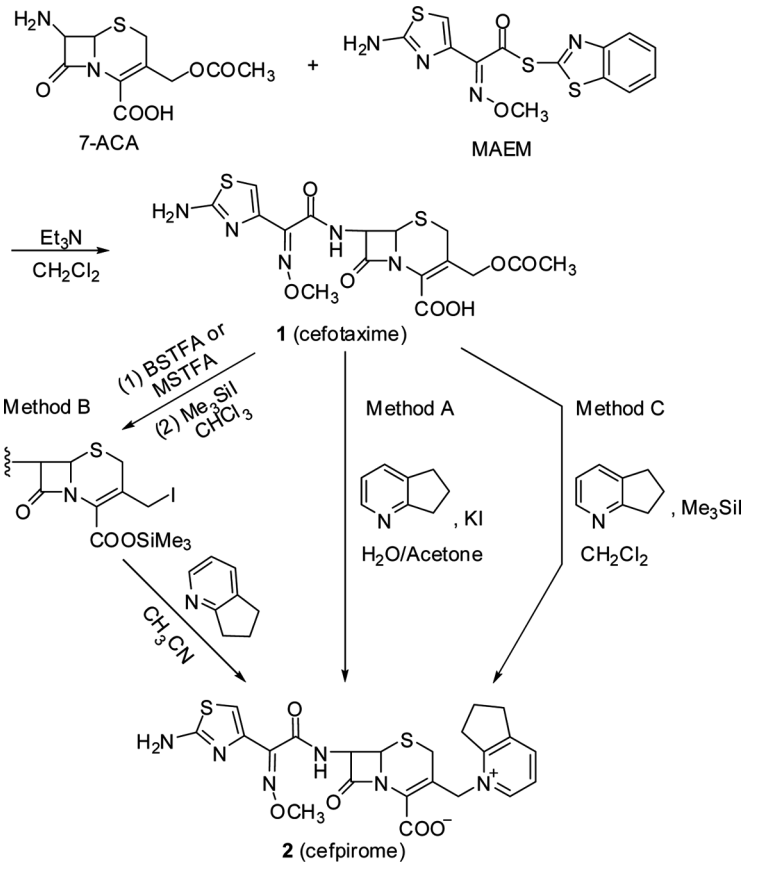
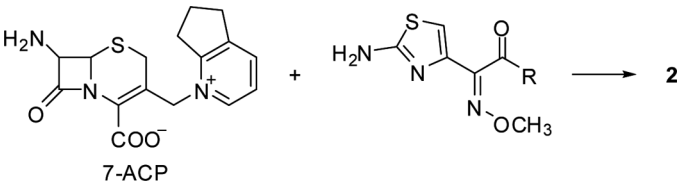
INTRODUCTION

Until now, the synthesis of cefpirome has always used cephalosporin compounds containing the 7-aminocephalosporanic acid nucleus as starting materials,[1] through the introduction of the 2,3-cyclopenteno-1-pyridinio group at the *C*-3′ position and the 2-syn-methoxyimino-2-(amino-4-thiazolyl)-acetyl group at the 7β position. These synthetic methods could be summarized in two approaches.

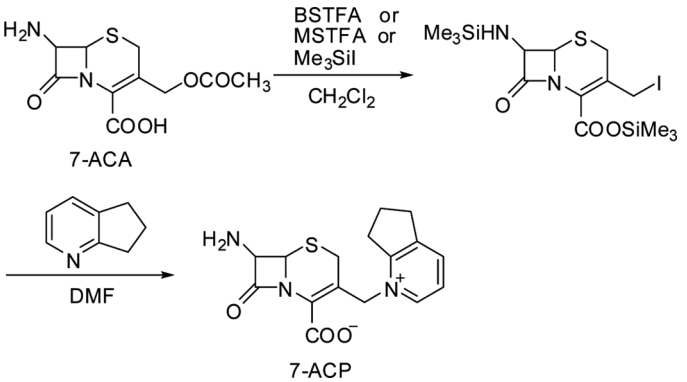
In one approach, cefotaxime **1** is obtained first by a coupling reaction of 2-mercaptobenzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate (MAEM) and 7-aminocephalosporanic acid (7-ACA),[2] and then the 2,3-cyclopenteno-1-pyridinio group is introduced at the *C*-3′ (methods A, B, and C, shown in Scheme 1). Among them, method A is applied generally for introducing *C*-3′-substituted pyridine homologs, but its yield was poor. Single-step yield was 10% to 30%, and the overall yield of cefpirome preparation was 23%. Despite the good yield of method B in the preparation of cefpirome, more than 50% for pyridine homologs with different substituents, it had disadvantages of the use of acetonitrile and the requirement for expensive *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA)



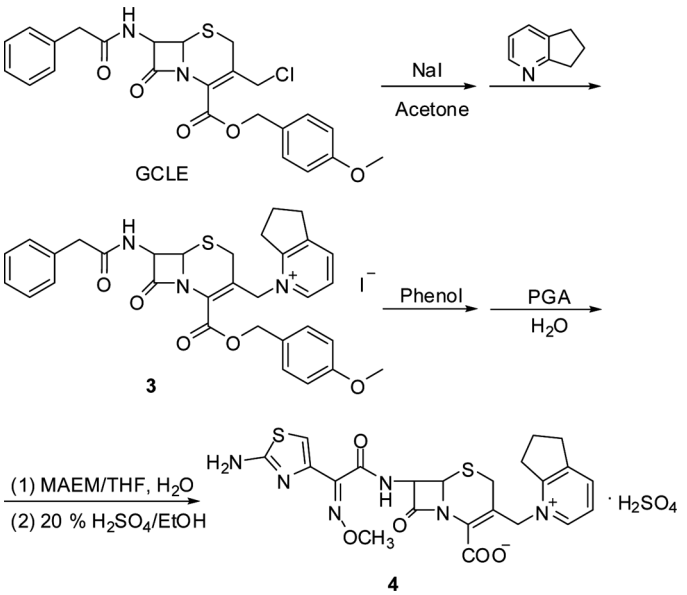
Scheme 1. Synthesis of cefpirome from cefotaxime.



Scheme 2. Synthesis of cefpirome from 7-ACP.



Scheme 3. Synthesis of 7-ACP.



Scheme 4. Synthesis of cefpirome from GCLE.

or bis(trimethylsilyl)trifluoroacetamide (BSTFA) as silylating agents. Methods B and C had the same principle. Amino and carboxyl groups of cefotaxime were protected with trimethylsilyl before the *C*-3′ chloride was replaced by iodine, and then the 2,3-cyclopenteno side chain was introduced. However, with the less active iodide reagent, the yields of method C had significant variation for pyridine homologs with different substituents, which limited its universal application.

In the other approach, 7-ACP is prepared first and then reacted with 2-(2-aminothiazole-4-yl)-2-methoxyiminoacetic acid (ATMA) or its derivatives such as acylchloride, acid anhydride, and active ester (Scheme 2). This method is easy to operate. ATMA or its active ester, particularly the widely used MAEM, was commercially available. The key to this approach was the effective synthesis of 7-ACP.

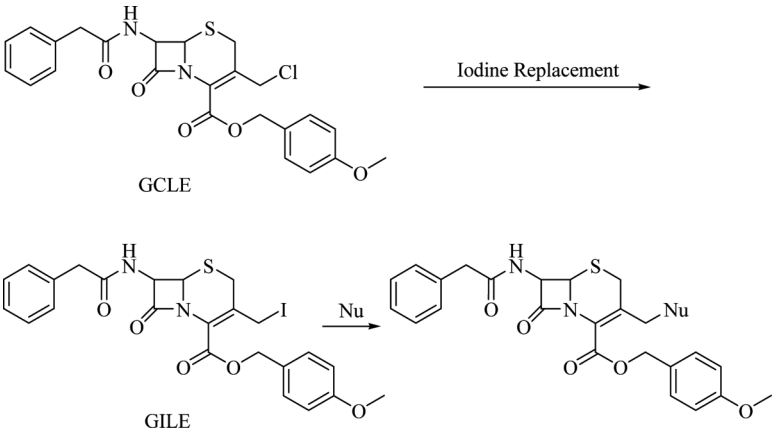
The current synthesis of 7-ACP from 7-ACA is shown in Scheme 3. Similar to methods B and C, this method also depends on the use of MSTFA, BSTFA, or iodotrimethylsilane, so its prospect of application is very limited.

Because of the availability of raw materials, cost, and operational convenience, cefpirome was synthesized from 3-chloromethyl-7-phenylacetylamino cephalosporanic acid *p*-methoxybenzyl ester (GCLE) in this article (Scheme 4). The scheme has advantages of commercially available reactants, ease of operation, low cost, and so on.

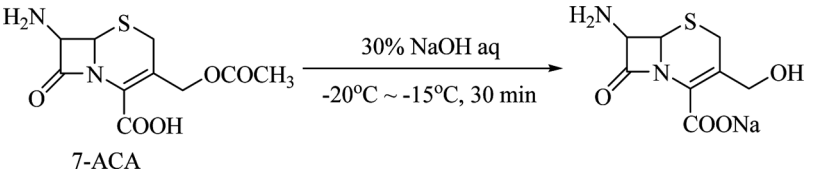
DISCUSSION

Modification of the *C*-3′ Position of GCLE

3-Iodomethyl-7-phenylacetylamino cephalosporanic acid *p*-methoxybenzyl ester (GILE) could be prepared by the replacement of chlorine at the *C*-3′ position of GCLE with iodine. Because iodine is less electronegative than chlorine, which enhanced the polarization degree of the C-I bond and made the iodine atom a better leaving group, the activity of GILE was enhanced, and *C*-3′ electrophilic substitution with tertiary amines or pyridine derivatives could take place easily. The modification of *C*-3′ of GCLE is shown in Scheme 5.



Scheme 5. Modification of *C*-3′ of GCLE.



Scheme 6. Hydrolysis of ester bond of 7-ACA.

Methyl ethyl ketone,[3] methyl isobutyl ketone,[4] or acetone[5] could be used as solvents in the iodine replacement reaction, and sodium iodide or potassium iodide could be used as iodination agents. Acetone and sodium iodide were used in this study.

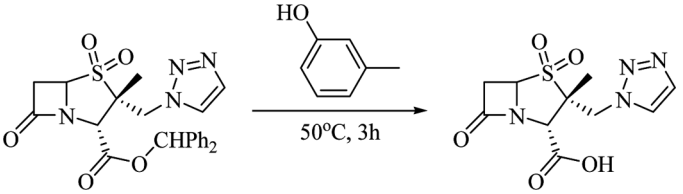
Deprotection of Ester

It is known that ester hydrolysis is a classic reaction that can be achieved in many ways, including acid hydrolysis and alkaline hydrolysis. Different conditions were adopted according to specific purposes in the synthesis of drugs or intermediates containing the β-lactam ring. For example, alkaline conditions were applied in the hydrolysis of 7-ACA into 7-amino-3-hydroxymethyl-cephalosporin acid (Scheme 6),[6] but acidic conditions were applied in the synthesis of tazobactam (Scheme 7).[7]

It was reported that the use of formic acid/dilute hydrochloric acid[3] or phenol/hydrochloric acid mixture to remove the methoxy benzyl group was easy to operate and had a good yield. We studied phenol and acid/dilute hydrochloric acid for the deprotection of the ester and successfully removed the ester by phenol with good yield.

Removal of Phenyl Acetyl Side Chain

The phenyl acetyl side chain could be removed by chemical or enzymatic reactions. Chemical reactions had many disadvantages such as more steps, longer reaction time, higher cost, and serious waste pollution, while microbial enzymatic methods could remove the acetyl side chain with high specificity and selectivity. In this study, we used penicillin G acylase (PGA) to remove the phenyl acetyl side chain and achieved good results.



Scheme 7. Synthesis of tazobactam.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV400 spectrometer using tetramethylsilane (TMS) as internal standard. Gas chromatography/mass spectrometry (GC/MS) analyses were carried out on an HP5890 gas chromatograph, coupled with an HP5971A mass spectrometer. The purity analysis of cefpirome was performed on an Agilent 1100 high-performance liquid chromatographic (HPLC) system with a Zorbax SB-C18 column (5 μm, 4.6 × 150 mm). Melting point (mp) was determined on a YRT-3 melting-point apparatus (Precision Instrument Plant, Tianjin University) and is uncorrected. PGA was purchased from Hunan Flag Biotechnology Co., Ltd., China.

p-Methoxybenzyl 7-Phenylacetylamido-3-(2,3-cyclopenteno-1-pyridinio)methyl-3-cephem-4-carboxylate Iodide (3)

To a suspension of NaI (3.07 g, 20.5 mmol) in acetone (60 mL) at −5 °C, GCLE (5.00 g, 10.3 mmol) was added. The mixture was stirred at −5 to 0 °C under N_2 in the dark for 5 h. Ethyl acetate (60 mL) and water (40 mL) were added. The two phases were separated, and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic phase was washed with 10% sodium thiosulfate solution (2 × 80 mL) and saturated saline (80 mL), dried with Na_2SO_4, and filtered. The filtrate was cooled to −5 °C, and a solution of 2,3-cyclopentenopyridine (4.90 g, 41.1 mmol) in ethyl acetate (10 mL) was added dropwise under N_2 protection. The resulting solution was stirred at −5 °C for 10 h and filtered. The filter cake was washed with ethyl acetate and dried in vacuo. Yield 5.04 g (75.4%) of a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.10–2.17 (m, 2H), 3.10–3.17 (m, 4H), 3.48–3.57 (m, 4H), 3.75 (s, 3H), 5.15–5.17 (m, 2H), 5.29 (d, J = 6.0 Hz, 1H), 5.48 (s, 2H), 5.79 (dd, J_1 = 4.8 Hz, J_2 = 8.0 Hz, 1H), 6.91 (d, J = 4.2 Hz, 2H), 7.21–7.33 (m, 7H), 7.89 (t, J = 7.2 Hz, 1H), 8.40 (d, J = 4 Hz, 1H), 8.56 (d, J = 3 Hz, 1H), 9.14 (d, J = 4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.88, 25.33, 30.45, 31.33, 41.50, 55.15, 57.65, 58.13, 59.38, 67.81, 113.78 (2C), 119.44, 125.50, 126.45 (2C), 127.82, 128.15 (2C), 128.91 (2C), 130.56 (2C), 135.63, 141.00, 141.11, 145.31, 159.43, 161.11, 161.61, 165.06, 170.86.

Cefpirome Sulfate (4)

A solution of compound **3** (1.80 g, 2.58 mmol) in phenol (10 g) was stirred at 50 °C for 4.5 h before acetone (10 mL) was added, and the mixture was poured into a beaker. Ether (120 mL) was added slowly while stirring, during which time a precipitate formed. The resulting suspension was stirred for 30 min. The precipitate was filtered and washed with a mixture of acetone (30 mL) and ether (60 mL). The filter cake was dissolved in sodium acetate solution (20 mL, pH 8.2) and stirred. The pH value of the mixture was adjusted to 8.0–8.5 at 37 °C using 13% ammonia water. PGA (1.50 g) was added, the pH value was maintained at 8.0–8.5 for 2 h using 5% ammonia water, and then PGA was filtered. The filtrate and tetrahydrofuran (THF, 50 mL) were added into a flask. After adjusting the pH value to 6.8–7.2 using hydrochloride (2 mol/L), MAEM (1.00 g, 2.85 mmol) was added, and the reaction

was stirred at 25 °C for 6.5 h. The mixture was extracted with ethyl acetate (2×40 mL). The aqueous phase was cooled to 5 °C, and the pH value was adjusted to 1–2 using 20% H_2SO_4. A large amount of ethanol was added while stirring. After standing in a refrigerator for 2 h, the precipitate formed, was collected by filtration, and was dried in vacuo. Yield 0.79 g (50.0%) of a white solid: mp > 200 °C; analytical HPLC: 98.72%; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.19–2.25 (m, 2H), 3.11–3.15 (m, 2H), 3.25–3.29 (m, 2H), 3.40 (s, 2H), 3.81 (s, 3H), 5.17 (d, $J = 2.4$ Hz, 1H), 5.50 (AB, $J = 15.2$ Hz, 2H), 5.86 (dd, $J_1 = 5.2$ Hz, $J_2 = 8.4$ Hz, 1H), 6.72 (s, 1H), 7.25 (d, $J = 3.6$ Hz, 2H), 7.93 (t, $J = 7.2$ Hz, 1H), 8.43 (d, $J = 3.8$ Hz, 1H), 8.64 (d, $J = 3.2$ Hz, Hz, 1H), 9.62 (d, $J = 4.2$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.99, 25.09, 30.51, 31.43, 57.53, 58.29, 58.90, 61.86, 108.84, 118.81, 125.61, 128.87, 141.14, 141.33, 142.12, 145.32, 148.75, 161.93, 162.82 (2C), 163.73, 168.39; MS: $m/z = 612.6$ $(M + H_2SO_4)^+$.

ACKNOWLEDGMENT

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