International Journal of Civil Engineering and Environmental Science. Volume 3, Issue 1, (2015) 38-41
http://www.cayley-nielson.com/ijcees/

An improved procedure for preparation and isolation of cefozopran intermediate, 7-ACP.HCl

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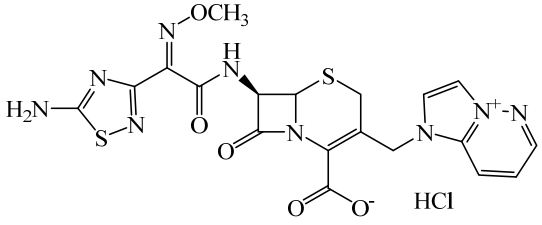
Abstract

An efficient synthesis of cefozopran intermediate, 7-ACP.HCl is described. we have developed an industrially viable process for the preparation of 7-ACP.HCl without further to column chromatography, and is cost-effective and amenable to large-scale synthesis.

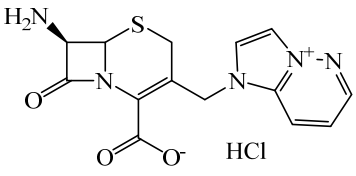
Keywords: 7-ACP.HCl; Cefozopran; preparation.

1. Introduction

Cefozopran (1) is a fourth-generation cephalosporin antibiotic having high antibacterial activity against gram-positive bacteria (including MRSA) and gram-negative bacteria (including P.aeruginosa) as compared to third-generation cephalosporins. In trails involving a broad range of infections, cefozopran has demonstrated clinical efficacy, which reflects its remarkable potential1-3.



(1)



(2)

7β-7-amino-3-(imidazo[1,2-b]pyridazinium-1-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate hydrochloride (7-ACP.HCl, **2**) is a key intermediate to the synthesis of Cefozopran, Literature survey reveals that the preparation of 7-ACP.HCl is generally from starting material 7-ACA. This method mainly involved HMDS silylation,TMSI iodation,3-position substitution by Imidazo (1,2-b) pyridazine, and deprotection, refined and recrystallization. This production contains a lot of impurities, appearing as brown color depth for further to column chromatography for the isolation of crystalline and not suitable for industrial production[3-8].

In the study of our ongoing project on the preparation of 7-ACP.HCl, we have developed an industrially viable process for the preparation of 7-ACP.HCl without further to column chromatography (Scheme 1).

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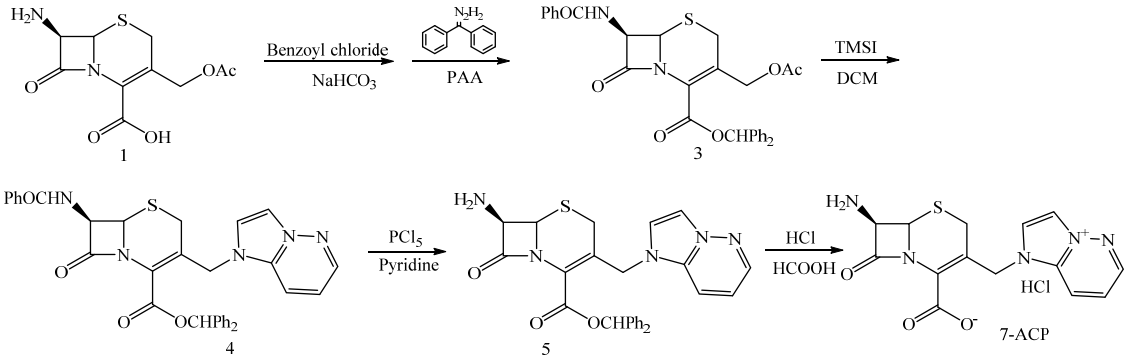
March, 2015

Scheme 1. Preparation and isolation cefozopran intermediate, 7-ACP.HCl.



2. Experimental

All reagents were purchased from commercial sources such as SCRC (www.reagent.com.cn), Aladdin (www.aladdin-reagent.com) and used without further purification. The 1H-NMR spectra (400 MHz) were measured on a DRX-400 spectrometer using DMSO-d6 as solvent and TMS as an internal standard. Chemical shifts were expressed in ppm units. Multiplicities were recorded as s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Mass spectra were obtained on a LC-MSD 1100 spectrometer with ESI.

2.1 benzhydryl (7R)-3-(acetoxymethyl)-7-benzamido-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (3).

7-ACA (63.0 g, 232mmoL) and sodium bicarbonate (42.8 g, 510mmoL) were added successively to water (800mL) and stirred at room temperature for 30min. The solution was cooled to 5~10 °C, slowly added benzoyl chloride (32.5mL, 254mmoL), then stirred for 30min. Dichloromethane (500mL) was added and followed by 2N sulfuric acid adjust the solution to pH =2~3, added 15% peracetic acid (125mL) in drops at 5~10°C, stirred for 30min, then added potassium iodide 0.05 g (3mmoL) , benzophenone hydrazone (52.0g, 256mmoL) and 15% peracetic acid (156mL) in drops respectively, stirred for 1h at 5~10 °C.

After the aqueous layer was separated, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a pale yellow oil 3 (106.7g, 85%), without further purification.

2.2 benzhydryl (7R)-3-((1H-4l4-imidazo[2,1-f]pyridazin-1-yl)methyl)-7-benzamido-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate (4).

Under an N2 atmosphere, compound 3 (99.6g, 184mmoL) was suspended in dichloromethane (500mL), added triethylamine (20mL), then stirred for 10min. The solution was cooled to 0-5°C, trimethylsilyl iodide (TMSI) (52mL, 360mmoL) in dichloromethane (200mL) was slowly added in drops at 5-10 °C, stirred for 4h. The reaction mixture was slowly added dropwise a solution of 1H- imidazo [1,2-b] pyridazine (66.0g, 550mmoL) in dichloromethane (200mL), then the reaction mixture was warmed to 30-35°C stirred for 6h. The reaction mixture was cooled to 0-5°C, added deionized water 400ml, stirred for 30min.

After the aqueous layer was separated, the organic layer was washed with saturated $NaHCO_3$, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a brown yellow oil 4 (98.8g,

82%), without further purification.

2.3 benzhydryl (7R)-3-((1H-4l4-imidazo[2,1-f]pyridazin-1-yl)methyl)-7-amino-8-oxo-5-thia-1-aza bicyclo[4.2.0]oct-2-ene-2-carboxylate (5).

Phosphorus pentachloride (38g, 182mmoL) was suspended in dichloromethane (300mL), cooled to below 0°C, added pyridine (14.5mL, 180mmoL), stirred for 30min, then added 4 (60.3g, 100mmoL) in drops, warmed to room temperature and stirred for 2~3h. The solution was cooled to -10°C, methanol (550mL) was added in drops, then reaction mixture was slowly raised to 25°C stirred for 30min.The reaction mixture was cooled to -10°C, added diethylamine (104mL) and stirred for 1h and the crystalline product was precipitated, filtrated and washed with ethyl acetate, dried under reduced pressure to give an off-white solid 5(39.4g, 79%).

2.4 7β-7-amino-3-(imidazo[1,2-b]pyridazinium-1-ylmethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate hydrochloride (7-ACP.HCl).

Compound **5** 44.9g (90mmol) was suspended in a mixture of concentrated hydrochloric acid (65mL) and 98% formic acid (65mL). The resulting reaction mixture was stirred for 1h at room temperature, then warmed to 60°C for 2h. The solution was cooled to 10~15°C, ethyl acetate (500mL) was added dropwise and the crystalline product was precipitated a white solid, filtrated and washed with ethyl acetate, dried under reduced pressure to give an off-white solid **5**(39.4g, 79%). Melting point:229-232°C. ^{1}H-NMR (400Hz, DMSO): δ3.34(m, 6H,H_8, NH_2),3.58(d,1H, H_{10}), 5.11(m,1H, H_9), 5.52(s,1H,H_7),8.14(q, 1H, H_l),8.49(d, 1H ,H_4),8.89(m, 2H,H_3,H $_6$), 9.30(m, 1H, H_2). ESI-MS: m/z = 332.27 $[M+H]^+$.

3. Results and Discussion

The present method describes the synthesis of **2** started at material 7-ACA. This method mainly involved HMDS silylation,TMSI iodation,3-position substitution by Imidazo (1,2-b) pyridazine, and deprotection, refined and recrystallization. The production appearing as brown color depth, further to column chromatography for the isolation of crystalline and not suitable for industrial production.

In optimization studies study, we have carried out the reactions to preparation and isolation of cefozopran intermediate, 7-ACP.HCl under suitable reaction conditions, thereby eliminating exhaustive workup and column chromatography.

In conclusion, a simplified, cost-effective industrial process for synthesis and isolation of **2** with improved reaction conditions is described. This process does not involve any chromatographic separation and purification steps.

Acknowledgements

This work was financially supported by Guangxi education department science research Foundation (201106LX396).

References

[1]. Ikawa, K.; Nomura, K.; Morikawa, N.et al. Pharmacokinetic-pharmacodynamic target attainment analysis of cefozopran in Japanese adult patients. *J. Infect Chemother.* 2008, 14, 130-136.

[2]. Ishikawa, T.; Iizawa, Y.; Okonogi, K. et al. Studies on anti-MRSA parenteral cephalosporins: I. synthesis and antibacterial activity of 7β-[2-(5-amino-l,2,4-thiadiazol-3-yl)-2(Z)-hydroxyiminoacetamido]- 3-(substituted imidazo [l52-6] -pyridazinium-l -yl)methyl-3-cephem-4-carboxylates and related compounds. *J. Antibiot.* 2000,

53(10), 1053-1070.

[3]. Nishimura; Shuichi; Murozumiohmachi, et al. Production of 7-aminocephalosporanic acid derivative. International patent, WO9739002, 1997-12-23.

[4]. Yoshida, K.; Nishimura, S.; Maeda, S., et al. JP Patent, JP10291993A, 1998-11-4.

[5]. Yu T.; Zhang K.L.; Wang H., et al. Synthesis of cefozopran. Chin. J. Med. Chem., 2006, 16(2)：91-92.

[6]. Chen G.H.; Ren Z.; Yang Y., Synthesis of cefozopran. *Chin. J. Antibiot.*, 2009, 34(8),479-480.

[7]. Tewari N.; Rai B.P.; Mohammad K., An Improved procedure for preparation and isolation of cephalosporin antibiotic: cefozopran as free base. Org. Process. Res. Dev, 2009, 13(5), 936-937.

[8]. Tewari; Neera; Mohammad. et al. Processes for the preparation of cefozopran, its salts and polymorphic forms thereof. International patent, WO2010089729, 2010-12-8.