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Evolution of a Preparation Route to Sulfamoylamino Intermediates of Cephalosporin

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Abstract

Development of a convergent preparation route to sulfamoylamino intermediates of cephalosporin is described.The target molecule is assembled through an azabicyclo [2.2.1] heptane intermediate followed by condensation reaction with sulfamoylamino methylpiperidine derivatives. The preparation of azabicyclo [2.2.1] heptane intermediate by a intramolecular condensation reaction of (2S,4R)-4-Hydroxyp-yrrolidine-2-carboxylic acid. This avoids handling of column chromatography and l improves the overall yield and efficiency of the route.

Keywords

Cephalosporin; Intermediate; Preparation; Sulfamoylamino.

1. Introduction

Cephalosporins are a class of broad-spectrum semi-synthetic antibiotics1-3. Since the first cephalosporin was sold in 1960s, scientists have been improving the structure of cephalosporins to make them more effective against a wider range of bacteria4. Cephalosporins have excellent characteristic of broad-spectrum antibacterial, penicillinase-resistant, high efficacy, low toxicity and less allergic reactions compared with penicillin5-6. They played important role in anti-infective treatment. Nowadays, there are more than 60 species cephalosporins on the market7-9. However, antibiotic resistance has been an increasingly serious problem with the widespread use of antibiotics, especially abuse10. In recent years, an increased resistance of bacteria to a variety of commonly accompanied by the using of antimicrobials infections in hospitals11. One of the most effective ways to solve the problem of bacterial resistance is to find new antibacterial drugs that have novel structures different from previous antibiotics12.

In our previous work, a series of cephalosporin compounds containing sulfamoyl groups were designed and synthesized13. Among them, cephalosporin with sulfamoyl methylpiperidine structure has good antibacterial activity (Scheme 1, compound 2).

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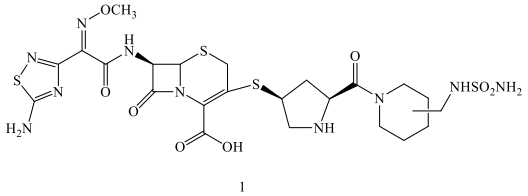

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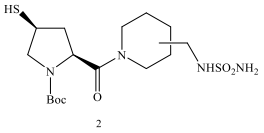
Scheme 1: cephalosporin with sulfamoylamino methylpiperidine group.

However, the synthesis of such compounds has a long route, low yield, and requires column-passing, which cannot be prepared in large quantities. Compound 2 is the key intermediate for synthesizing compound 1. The synthesis of compound 2 (Scheme 2) as an example, the synthesis process is very complicated and column chromatography is required for this process.



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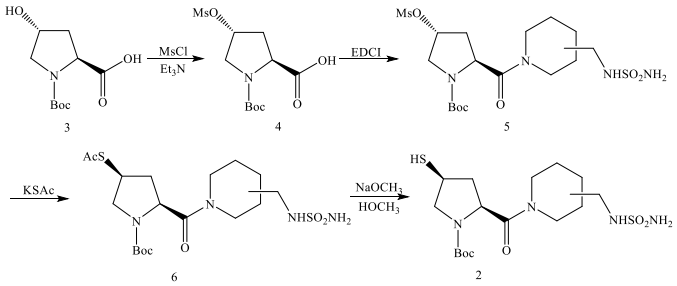
Scheme 2: The key intermediate (compound 2).

The popular synthesis route as follows (Scheme 3), (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxy-pyrrolidine-2-carboxylic acid was used as a starting material, followed by methanesulfonylation with methanesulfonyl chloride, the condensation of carboxylic acid with amines using EDCI, nucleophilic substitution reaction of potassium thioacetate. Finally, remove S-acetyl groups to obtain compound 2. However, the column chromatography is necessary in order to obtain pure product and the total yield is only 34.3%14.

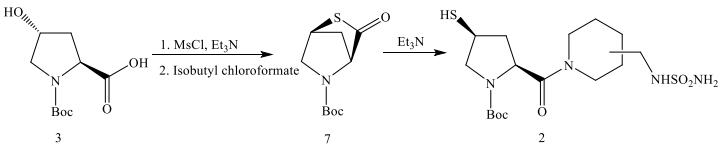


Scheme 3: The synthesis of key intermediate (compound 2).

Therefore, in order to solve the problems, the high efficiency, mild reaction conditions, no column chromatography and good to high yields are important features of this process. We have conducted in-depth research on this issue.

2. Methodology

Development of a convergent preparation route to key sulfamoylamino intermediate (compound 2) of cephalosporin is described (Scheme 4).



Scheme 4: Evolution of the process of key intermediate (compound 2).

(2S, 4R)-1-(tert-butoxycarbonyl)-4-hydroxy-pyrrolidine-2-carboxylic acid was used as a starting material, tert-butyl (1S,4S)-3-oxo-2-thia-5-azabicyclo[2.2.1]heptane-5-carboxylate (compound 7) was obtained by intramolecular condensation reaction under the condition of low temperature as a white solid. Follow closely a condensation reaction of compound 7 with amines using diisopropylethylamine catalytic to get compound 2.

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2.1 Syhthesis of tert-butyl (1S,4S)-3-oxo-2-thia-5-azabicyclo[2.2.1]heptane-5-carboxylate (compound 7)

According to Moriguchi et al15 described with slight modification. To a stirred solution of (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxy-pyrrolidine-2-carboxylic acid (50.0 g, 0.22 mol) in THF (800 mL) at −22 °C was added dropwise diisopropylethylamine (80 mL, 0.49 mol). Then, isobutyl chloroformate (30.0 g, 0.22 mol) was added dropwise. The mixture was stirred for at least 2 h, triethylamine (33 mL, 0.24 mol) was slowly added to the reaction solution and stirred for 30 min, then MsCl (18.4 mL, 0.238 mol) was added, keeping the temperature and stirred for 3 h. Sodium sulfide (55.3 g, 0.23 mol) was dissolved in water (90 mL) and pre-cool (below -5 ℃). Then, the sodium sulfide solution was poured into the reaction mixture, followed by water was added, the mixture was stirred at 25 ℃ for 6 h.

A solution of citric acid monohydrate (70.6 g, 0.336 mol) in water (130 mL) was added to the reaction mixture, stirred at room temperature for 30 min. The organic phase was separated and concentrated under vacuum at 40 ℃. The aqueous phase was extracted with tert-butyl methyl ether (TBME) (400 mL), and the extract was combined with the residue obtained by concentrating the organic phase. The organic phase was washed with water (200 mL), brine (200 mL), dried over anhydrous sodium sulfate and concentrated to 60 mL under vacuum at 40 ℃. Then, the solution was cooled to -8 °C, n-hexane (100 mL) was slowly added dropwise with stirring to crystallize the batch. Filtering, washing with mixture of n-hexane (50 mL) and TBME (22 mL) (pre-cooled to -8 °C) and dried in vacuo at 30 ℃ to afford the product 7 as a white solid (35.0 g, 70.7% yield).

2.2 Syhthesis of the key intermediate (compound 2)

Compound 7 (4.6 g, 20 mmol) was dissolved in mixture solution of dichloromethane and methanol (1:1) (100 mL), then amine (6.9 g, 30 mmol) in dichloromethane (50 mL) and diisopropylethylamine (9 mL, 52 mmol) were added dropwise in order, stirred for 5 h under the protection of nitrogen. Removed the solvent under vacuum, diluted with ethyl acetate (100 mL), washed with 1N hydrochloric acid solution (100 mL), sat. aq. NaHCO3 (50 mL), brine (50 mL), and dried over anhydrous sodium sulfate. The solvent was removed under vacuum at 40 ℃ to afford compound 2 (6.3 g, 74.6% yield) as a light yellow solid.

3. Results and discussion

The popular synthesis route for synthesizing compound 2 have the disadvantages of multiple steps, long time-consuming, column chromatography, and low yield, which limits its large-scale preparation. The evolution of a preparation route to sulfamoylamino intermediates of cephalosporin has only two steps. Compound 7 is synthesized by a one-pot method, and (2S, 4R) -1- (tert-butoxycarbonyl) -4-hydroxy-pyrrolidine-2-carboxylic acid is used as a starting material, the target product is obtained through intramolecular condensation. The target product is directly precipitated from the solvent. The advantage of this synthesis process is that shorter time and higher yield. More importance is no column chromatography and the yield is 70.7%. The preparation of compound 2 as follows, the ring-open reaction of compound 7 was carry out under basic conditions, and then condenses reaction with amine. Finally, the organic phase washed with acid and alkali to remove unreacted raw materials and obtain the target product with a yield of 74.6%.

The overall yield of this evolution of a preparation route is 52.7%. Compared with the popular synthesis route, the yield has increased significantly, what is especially important is no column chromatography. This evolution of a preparation route provides convenience for us to prepare compound 7 on large-scale.

4. Conclusion

In summary, we have described the evolution of a preparation route to key intermediate for synthesizing sulfamoylamino cephalosporin (compound 2). The compound 7 was synthesized by one-

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pot method synthesis process without column chromatography which improved the overall efficiency of the route. Starting from (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxy-pyrrolidine- 2-carboxylic acid, the overall yield of this synthesis of compound 2 is 52.7%.

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