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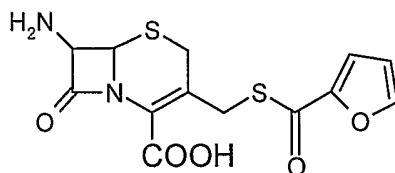
(54) Title: AN IMPROVED SYNTHESIS OF CEFTIOFUR INTERMEDIATE

(57) Abstract: The present invention relates to a process for preparation of 7-amino-3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I) by the condensation of 7-aminocephalosporanic acid (II) with furyl-2-carbonylthiol (III) in the presence of boron-trifluoride or its complex, in an organic solvent or mixture of solvents at 0-50°C.

AN IMPROVED SYNTHESIS OF CEFTIOFUR INTERMEDIATE

TECHNICAL FIELD

The present invention discloses an improved process for the preparation of 7-amino-3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I)

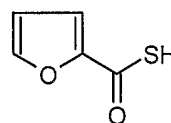


(I)

by the condensation of 7-amino cephalosporanic acid (7-ACA) represented by formula (II) with furyl-2-carbonylthiol represented by formula (III) using borontrifluoride or its complex as condensing agent.



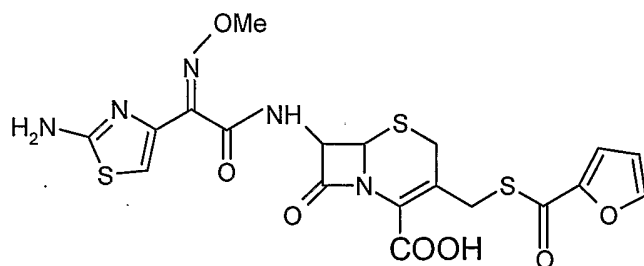
(II)



(III)

BACKGROUND OF THE INVENTION

Ceftiofur is the generic name given to compound of formula (IV)



(IV)

Ceftiofur acid, its alkali metal, alkaline earth metal and amines salts were reported for the first time in US patent no. 4,464,367. The ceftiofur is a condensation product of 7-ACA with furyl-2-carbonylthiol and 2-(2-aminothiazol-4-yl)-2-methoxyimino) acetic acid at 3 and 7 position respectively. 7-amino-3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I) is the key intermediate which decides the quality and overall yield of the process for making the ceftiofur.

To our surprise there are very few methods reported in the literature for the synthesis of 7-amino-3 - [2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid of the formula (I). The first report for the synthesis of this intermediate appeared in the US patent No. 4,464,367 where the method used for the condensation was taken from a reference from the Journal of Antibiotics 27, 573-8, (1974). These references are about the condensation carried out at a pH of 6.4 using phosphate buffer. The reaction time is very long by following this method and 47% yield is reported for the reaction. These limitations make the process unfavorable for the commercial exploitation.

Another method was disclosed in WO patent 87/01117, which is also merely an extension of the earlier mentioned patent. The condensation was affected by reaction of sodium thiofuroate and 7-ACA at a temperature of 65 °C in aqueous medium at an pH of 6.4. Cephalosporins are known to decompose at high temperature and moreover using the process using this process, the reaction is not completed and yields are also very poor (about 45 % and in addition the reaction takes longer time, for example, even after several hours the reaction is incomplete).

Looking at all these problems, a method for the condensation under non-aqueous was reported in US patent No. 5,387,679 where condensation of 7-ACA with heterocyclic thiols in the presence of complex of borontrifluoride with dialkyl carbonate was carried out to provide intermediates which are used in the synthesis of cephalosporin antibiotics. When this method was applied for the condensation of 7-ACA and furyl-2-carbonylthiol the reaction mixture was associated with several impurities which could not be separated even during the final purification step. Later on, after several experimentations we found that the stability of furyl-2-carbonylthiol in its solid form is not good, since furyl-2-carbonylthiol belongs to the class of heterocyclic thioacids and not heterocyclic thiol. The behaviour of the reaction is not similar for the thioacids as it was for thiols thereby disallowing the conditions of the US patent No. 5,387,679 to be used in the present invention.

In order to overcome the problem, the applicant provides for the first time an improved process for condensing 7-ACA with furyl-2-carbonylthiol which is generated and used *in situ* in the presence of borontrifluoride in a gaseous state or its solution in an organic solvent to obtain compound of formula (I). This process gives desired compound of formula (I) in excellent yield (90-95 %) and high purity 98-99 %).

OBJECTS OF THE INVENTION

The primary object of the invention is to provide an improved and commercially viable process for preparing 7-amino-3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid of formula (I) as an intermediate for ceftiofur.

5 Another object of the invention is to use furyl-2-carbonylthiol *in situ* without isolating it.

Yet another objective of this invention is to provide a process, this will give high yield and excellent purity of the product.

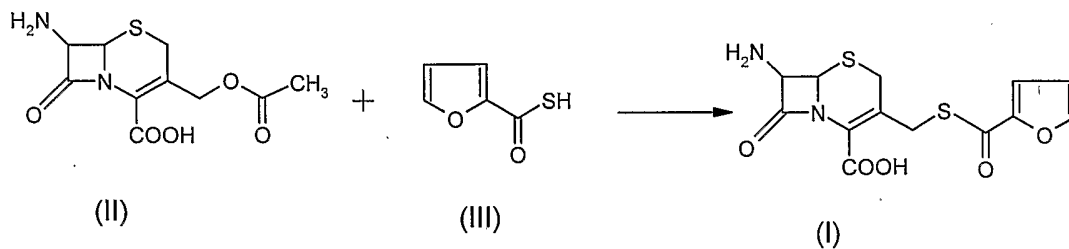
10 Still another object of the invention is to provide the use of boron trifluoride in gaseous state or its solution in an organic solvent or boron trifluoride complex for carrying out the condensation reaction at low temperature, which is convenient for commercial production.

SUMMARY OF THE INVENTION

15 Accordingly, the present invention provides the process for preparation of 7-amino-3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid (I) by the condensation of 7-aminocephalosporanic acid (II) with furyl-2-carbonylthiol (III) in the presence of borontrifluoride or its complex, in an organic solvent or mixture of solvents at 0-50 °C.

The sequence of the reaction is shown below:

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**DETAILED DESCRIPTION OF THE INVENTION**

In an embodiment the organic solvents used for the condensation is selected from tetrahydrofuran, methyl acetate, ethylacetate, n-propylacetate, iso-propylacetate, n-butylacetate, dichloromethane, toluene, diethylether, di-isopropylether, acetonitrile, acetic acid or mixtures thereof.

25 In still another embodiment, the boron trifluoride is used in gaseous state, as well as its complex with diethyl ether, in solvents such as acetonitrile, ethylacetate and other compatible solvents. Boron trifluoride is used in 4-8 mole equivalents for 1.0 moles of 7-ACA.

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In yet another embodiment the reaction is carried out preferably at a temperature in the range of 30-40°C. The reaction is monitored for completion of the reaction by measuring the content of 7-ACA in the reaction mixture. The content of the 7-ACA should be less than 1%. The content of the 7-ACA reaches to less than 1% within 3-5 hours. After completion of reaction, the mass is poured into water and pH is adjusted to 3-4 by addition of a base. The base used is selected from aqueous ammonia, ammonium hydroxide, sodium hydroxide, sodium carbonate, triethylamine, tributylamine. The solid product is filtered and washed with a solvent and water mixture. The solvent used is selected from tetrahydrofuran, methyl acetate, ethylacetate, n-propylacetate, iso-propylacetate, n-butylacetate, dichloromethane, toluene, diethylether, di-isopropylether, acetonitrile, acetic acid or mixtures thereof.

In yet another embodiment there is provided a process for the preparation of ceftiofur using the 3-[2-(furylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I) prepared by a process described above by conventional methods.

In still yet another embodiment, furyl-2-carbonylthiol is prepared *in situ* from furyl-2-carbonyl chloride/sodium sulphide or furyl-2-carbonyl chloride/sodium hydrogen sulphide.

The invention is illustrated with following examples, which are provided by way of illustration only and should not be construed to limit the scope of the invention.

20 **Example -I**

7-Amino - 3-(2-furanylcabonyl) thiomethyl]-3-cephem-4-carboxylic acid

Sodium sulfide (54.6 g) is charged to water (600ml) and furyl-2-carbonylchloride (50.0g) is added in 1.0 hr at temperature of 20 °C. Ethyl acetate is added to it and pH of the mass is adjusted to 1.0 using hydrochloric acid. The organic layer is separated, dried over anhydrous sodium sulphate, filtered to yield furyl-2-carbonylthiol in ethylacetate.

In an another flask ethylacetate (350ml) is charged and boron trifluoride gas (124.0g) is purged into it. 7-Amino-cephalosporanic acid (91.0 g) is added at 10.0 °C into this solution of borontrifluoride followed by the addition of furyl-2-carbonylthiol solution in ethylacetate (prepared above). The reaction is completed after stirring for 4 -5 hr at 30-40°C, after completion of the reaction, the mixture is poured into mixture of ice cold water. The pH of the solution is adjusted to 3.45-3.55 by addition of aqueous ammonia. The solid precipitated is filtered and washed with mixture ethylacetate to get of 7-amino-3-(2-furanylcabonyl) thiomethyl]-3-cephem-4-carboxylic acid (110.0g) with 98-99 % HPLC purity.

Example –II**7-Amino - 3-(2-furanylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid**

Sodium sulfide (36.4g) is charged to water (400ml) and furyl-2-carbonylchloride (33.3.0g) is added in 1.0 hr at temperature 20°C. Ethyl acetate is added to it and pH of the mass is adjusted to 1.0 using hydrochloric acid. The organic layer is separated, dried over anhydrous sodium sulphate, filtered to yield furyl-2-carbonylthiol in ethylacetate.

In an another flask containing acetonitrile (350ml), boron trifluoride gas (85.0g) is purged into it. 7-Amino-cephalosporanic acid (60.6 g) is added at 10.0 °C into this solution of borontrifluoride followed by the addition of furyl-2-carbonylthiol solution in ethylacetate (prepared above). The reaction is completed after stirring for 4 -5 hr at 30-40°C. After completion of the reaction mass, is poured into ice cold water. The pH of the solution is adjusted to 3.45-3.55 by addition of aq. ammonia. The solid precipitated is filtered and washed with mixture of water and acetonitrile to get of 7-amino-3-(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid (69.0g) with 97-98 % HPLC purity.

15 Example –III**7-Amino - 3-(2-furanylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid**

Sodium sulfide (54.6 g) is charged to water (600ml) and furyl-2-carbonylchloride (50.0g) is added in 1.0 hr at temperature of 20°C Ethyl acetate is added to it and pH of the mass was adjusted to 1.0 using hydrochloric acid. The organic layer is separated, dried over anhydrous sodium sulphate, filtered to yield furyl-2-carbonylthiol in ethylacetate.

In an another flask containing acetonitrile (350ml), 7-amino-cephalosporanic acid (91.0 g) is added at room temperature followed by addition of 45-48% boron trifluoride etherate (275.5ml) at 10.0°C. To this is added furyl-2-carbonylthiol solution in ethylacetate (prepared above). The reaction is completed after stirring for 4 -5 hr at 40-50°C. After completion, the reaction mixture is poured into ice cold water. The pH of the solution is adjusted to 3.45-3.55 by addition of sodium carbonate solution. The solid precipitated is filtered and washed with mixture of water and ethylacetate to get 7-amino - 3-(2-furanylcarbonylthiomethyl)-3-cephem-4-carboxylic acid (104.0g) with 97-98 % HPLC purity.

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Example –IV**7-Amino - 3-(2-furanylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid**

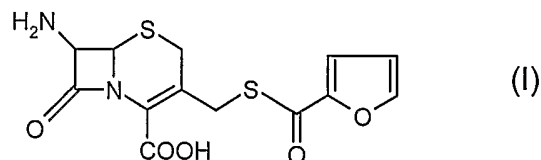
30.0 g of sodium hydrogen sulfide is dissolved in 350 ml. of water at 18-25 °C. 27.5 g of 2-furoyl chloride is added slowly in 40 to 45 mins. at 18-25°C and stir for 10

mins. at same temperature. Ethylacetate (250 ml) is added and the pH of the reaction mass is maintained below 1.0 with hydrochloric acid. Separate the organic layer and water (175 ml) is added. The pH is adjusted by sodium bicarbonate (19 g) to 7.0 to 7.5. The aqueous layer is separated and ethyl acetate (100 ml) is added. The pH is maintained adjusted to 0.9 to 1.0 with hydrochloric acid and stir for 15 min and separate the organic layer.

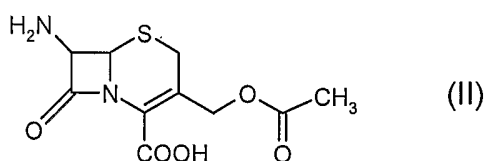
In an another flask 200ml of ethylacetate is charged and cooled to 0 C. 68.5 g boron trifluoride gas is purged into it. EDTA (1.0 g) is added to the reaction mass and the temperature is raised to 15⁰C and stirred for 10 min. 50.0 g of the 7-Amino-cephalosporanic acid is added at 10⁰C into this solution of borontrifluoride followed by the addition of furyl-2-carbonylthiol solution in ethylacetate (prepared earlier). The reaction is completed after stirring for 3-4 hr at 30-40⁰C. The mixture is then cooled to 15.degree. C. and 285 ml of cold water is added followed by freshly prepared solution of 1 g of sodium metabisulphite in 50 ml water and 0.3 g EDTA disodium in 50 ml water. pH of the solution is adjusted to 3.45-3.55 by addition of aq. ammonia. The solid precipitated is filtered and washed with ethylacetate (50 ml) to get of 7-amino - 3-(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid with 98-99 % HPLC purity.

We claim:

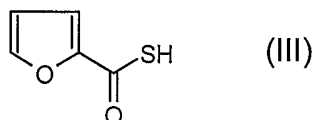
1. A process for preparation of 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I)



- 5 by the condensation of 7-aminocephalosporanic acid (II)



with furyl-2-carbonylthiol (III)



10 in the presence of borontrifluoride or its complex, in an organic solvent or mixture of solvents at 0-50 °C.

2. A process as claimed in claim 1, wherein the organic solvent used for carrying out the condensation reaction is selected from tetrahydrofuran, methyl acetate, ethylacetate, n-propylacetate, iso-propylacetate, n-butylacetate, dichloromethane, toluene, diethylether, di-isopropylether, acetonitrile or mixtures thereof.
- 15 3. A process as claimed in claim 1, wherein the borontrifluoride complex is borontrifluoride etherate.
4. A process for the preparation of ceftiofur using the 3-[2-(furylcarbonyl) thiomethyl]-3-cephem-4-carboxylic acid represented by formula (I) prepared by a process as claimed in any of the preceding claims.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 02/03268

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07D501/04 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 2002/065412 A1 (HANDA VIJAY KUMAR ET AL) 30 May 2002 (2002-05-30) the whole document	1-4
A	US 5 387 679 A (SOGLI LORIS ET AL) 7 February 1995 (1995-02-07) claims 1,5-13	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

19 December 2002

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03/01/2003

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INTERNATIONAL SEARCH REPORT

International Application No
PCI/IB 02/03268

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2002065412	A1	30-05-2002	NONE	
US 5387679	A	07-02-1995	DE 69214784 D1 DE 69214784 T2 EP 0548338 A1 KR 234442 B1 AT 144516 T DK 548338 T3 WO 9302085 A1 ES 2093267 T3 JP 6501271 T	28-11-1996 13-03-1997 30-06-1993 15-12-1999 15-11-1996 18-11-1996 04-02-1993 16-12-1996 10-02-1994