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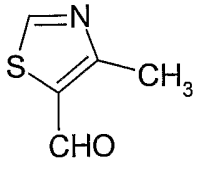
(54) Title: PREPARATION OF INTERMEDIATE FOR 3-[2-(4-METHYLTHIAZOLE-5-YL)VINYL] CEPHALOSPORINS

(57) Abstract: The present invention relates to the preparation of 4-methylthiazol-5-carboxaldehyde of Formula I, and use thereof as an intermediate in preparation of 3-[2-(4-methylthiazole-5-yl)vinyl] cephalosporins.



(I)

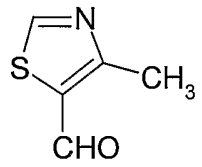
PREPARATION OF INTERMEDIATE FOR 3-[2-(4-METHYLTHIAZOLE-5-YL)VINYL] CEPHALOSPORINS

Field of the Invention

The present invention relates to the preparation of 4-methylthiazol-5-carboxaldehyde of Formula I, and use thereof as an intermediate in preparation of 3-[2-(4-methylthiazole-5-yl)vinyl] cephalosporins.

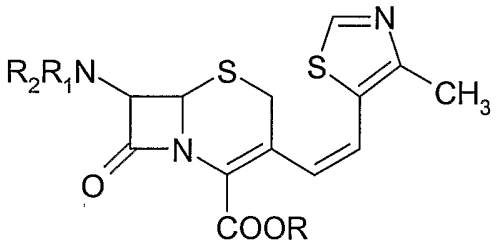
Background of the Invention

Cephalosporin antibiotics belonging to the class of 3-[2-(4-methylthiazole-5-yl)vinyl] cephalosporins have a broad spectrum of antimicrobial activity. Cefditoren pivoxil, which belongs to this class, is highly active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria. 4-Methylthiazol-5-carboxaldehyde (Formula I)



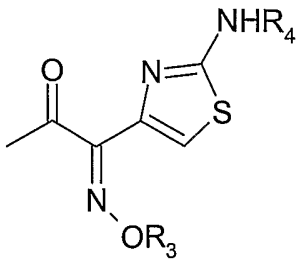
FORMULA I

is an intermediate in synthesis of 3-[2-(4-methylthiazole-5-yl)vinyl] cephalosporins such as Cefditoren pivoxil of Formula II,



FORMULA II

wherein R is pivaloxymethyl group, one of the R_1 and R_2 is hydrogen and other is a group of Formula A



FORMULA A

wherein R_3 is methyl and R_4 is hydrogen. This compound is a third-generation cephalosporin derivative developed with the aim of producing active cephalosporins with potent and broad-spectrum activity (see EP 175 610). Cefditoren pivoxil is active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria.

EP 343 640 describes a process of preparation of heterocyclic aldehydes, which comprises hydrogenating the corresponding heterocyclic carboxylic acid with molecular hydrogen in the presence of catalyst containing an oxide of at least one element selected from zirconium, yttrium, zinc, cerium, titanium and hafnium. High-pressure hydrogenation with molecular hydrogen requires a specially designed pressure vessel. The catalysts described in the patent are costly and recovery after the completion of reaction can be doubtful.

An oxidative degradation of 5-(β-hydroxyethyl)-4-methylthiazole using pyridinium dichromate in methylene chloride at room temperature to get 4-methylthiazol-5-carboxaldehyde is reported by White et al in *JACS*, 104, No. 18, 4934-4943 (1982). However, the reaction time is 24 hours and the work-up involves vacuum distillation of ethereal extract to get the desired product. The yield is only 52%.

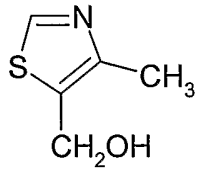
U.S. Patent No. 6,277,871 describes preparation of inhibitors of protein isoprenyl transferases wherein a process for the preparation of 4-methylthiazole-5-carboxaldehyde has been disclosed. The process follows Swern oxidation of 2-hydroxymethyl-4-methyl-thiazole in anhydrous methylene chloride and oxalyl chloride under N_2 atmosphere in anhydrous DMSO at -70 to -80°C. The product is obtained in 87% yield. The reaction requires lower temperature of about –70°C and therefore it is not commercially feasible. The intermediate 4-methyl-5-hydroxymethylthiazole has been prepared by reduction of

ethyl 4-methylthiazole-5-carboxylate using sodium borohydride and calcium chloride in ethanol in 48 hours.

US Patent Appl. No. 2003/0204095 describes a process for preparation of 4-methylthiazole-5-carboxaldehyde from 4-methyl-5-hydroxymethylthiazole using 2,2,6,6-tetramethyl-1-pyperidinyloxy free radical (TEMPO) in presence of potassium bromide, sodium carbonate, sodium hypochlorite and methylene chloride at 0-2°C and also using pyridinium chlorochromate in presence of methylene chloride at 15-30°C. Both these processes use costly catalysts and reagents and gives yield of about 60-70%. The intermediate 4-methyl-5-hydroxymethylthiazole has been prepared by reduction of methyl or ethyl ester of 4-methylthiazole-5-carboxylic using sodium borohydride and aluminium chloride in monoglyme.

Summary of the Invention

While attempting the synthesis of 4-methylthiazol-5-carboxaldehyde, the present inventors have found that when oxidation of 5-hydroxymethyl-4-methylthiazole of Formula III



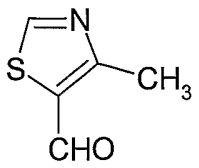
FORMULA III

is carried out in presence of an oxidizing agent, for example, manganese dioxide at relatively high temperature, the reaction proceeds efficiently and gives yields of about 80% of 4-methylthiazol-5-carboxaldehyde. The purity of the 4-methylthiazol-5-carboxaldehyde obtained is in excess of 99%, as determined, for example, by HPLC.

The intermediate 4-methyl-5-hydroxymethylthiazole can be prepared by reduction of C_{1-3} alkyl ester of 4-methylthiazole-5-carboxylic acid using lithium aluminium hydride in 2 to 3 hours in excellent yield and purity.

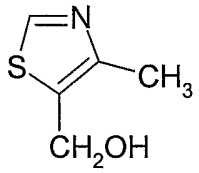
Detailed Description of the Invention

Inn one aspect, herein is provided an efficient oxidative preparation of 4-methylthiazole-5-carboxaldehyde of Formula I,



FORMULA I

wherein the process comprises oxidizing 5-hydroxymethyl-4-methylthiazole of Formula III with manganese dioxide.

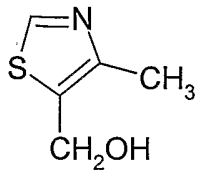


FORMULA III

The reaction can be carried out in presence of an inert organic solvent at a temperature of about 50-150°C. After completion of the reaction (as monitored, for example, by TLC or by HPLC), the reaction mass can be filtered to remove the catalyst and the solution obtained can be cooled suitably to precipitate the product. The product can then be filtered and dried to obtain 4-methylthiazole-5-carboxaldehyde as light yellowish solid having purity in excess of 99% (as determined, for example, by HPLC).

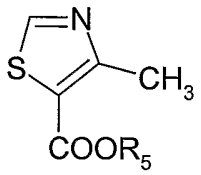
The inert organic solvent can be selected from, for example, aromatic hydrocarbons, such as benzene, toluene, xylene, substituted toluenes, substituted xylenes or substituted benzenes; chlorinated hydrocarbons, such as chloroform, or ethylene chloride; ethers, such as tetrahydrofuran, 1,4-dioxane, or diisopropyl ether; aliphatic hydrocarbons, such as hexane, heptane or petroleum ether; cylohexane; ketones, such as acetone, diisobutyl ketone, methyl ethyl ketone, or methyl isobutyl ketone; polar aprotic solvents, such as dimethylacetamide, dimethylformamide or dimethylsulphoxide; or mixtures thereof.

In another aspect, herein is provided a process for preparation of 5-hydroxymethyl-4-methylthiazole of Formula III,



FORMULA III

wherein the process comprises treating 4-methylthiazole-5-caboxylate of Formula IV



FORMULA IV

wherein R_5 is an esterifying residue selected from C_{1-3} alkyl, with lithium aluminium hydride.

The reaction of 4-methylthiazole-5-caboxylate of Formula IV with lithium aluminium hydride can be carried out in the presence of an organic solvent, such as, for example, tetrahydrofuran, diethyl ether, 1,4-dioxane, cyclohexane, hexane, heptane, toluene, benzene, xylene or mixtures thereof, at a temperature of about –50 to about 40°C.

After conversion of the starting material, the reaction mass can be quenched with water and the entire mass filtered to remove inorganic residue. The aqueous layer can be extracted with a solvent capable of substantially dissolving the compound of Formula III. After recovering the solvent from the organic layer, the product of Formula III can be obtained having purity in excess of 99% (as determined, for example, by HPLC).

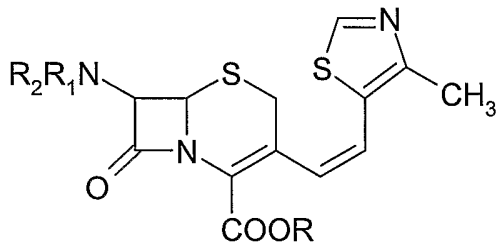
In another aspect, herein is provided a process for the preparation of 4-methylthiazol-5-carboxaldehyde of Formula I wherein the process comprises

a) reacting a compound of Formula IV (wherein R_5 is an esterifying residue selected from C_{1-3} alkyl) with lithium aluminium hydride to get compound of Formula III,

b) oxidizing the compound of Formula III with an oxidizing agent (for example, manganese dioxide), and

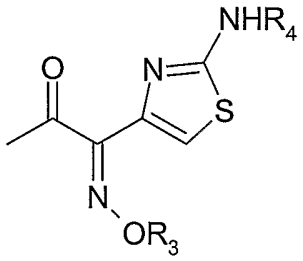
c) isolating the compound of Formula I.

In yet another aspect, herein is provided a process for the preparation of compound of Formula II;



FORMULA II

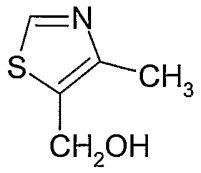
wherein R is hydrogen, esterified residue or a metal cation capable of forming a salt; R_1 and R_2 are independently selected from hydrogen, amino protecting group or combine together form a divalent amino protecting group, an optionally substituted amino acid residue or a group of Formula A



FORMULA A

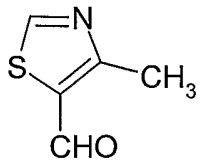
wherein R_3 is a optionally substituted lower alkyl (wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo) and R_4 is hydrogen or amino protecting group, wherein the process comprises

a) oxidizing a compound of Formula III



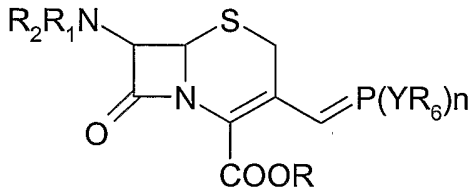
FORMULA III

with an oxidizing agent (for example, manganese dioxide) to get a compound of Formula I,



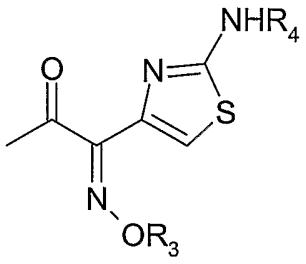
FORMULA I

b) reacting the compound of Formula I with an ylide of Formula V,



FORMULA V

wherein, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt and R_1 and R_2 are independently hydrogen, a monovalent amino protecting group or together form a divalent amino protecting group or a group of Formula A



FORMULA A

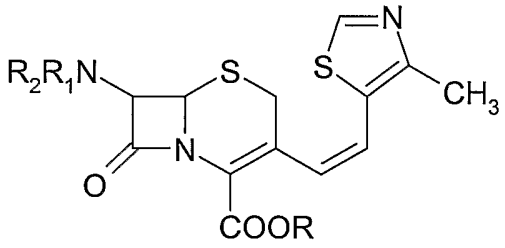
wherein R_3 is an optionally substituted lower alkyl wherein the substituents groups are selected from, for example, carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo; and R_4 is hydrogen or amino protecting group, Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R_6 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl, and

c) isolating the compound of Formula II.

The compound of Formula I can be prepared by the oxidation of compound of Formula III using, for example, manganese dioxide as described above. The isolated product can be treated with a compound of Formula V wherein R, R_1, R_2, R_3, R_4, Y, n and R_6 are as defined above in presence of an organic solvent at a temperature of about –50 to about 35°C. After completion of the reaction, it can be quenched by addition of water, followed by washing of organic layer with sodium bisulphite solution to eliminate aldehydic and related impurities generated during reaction. The compound of Formula II can then be isolated from the organic layer by suitable method of isolation, which includes evaporation of organic solvent to get the product, precipitation of the product from the organic solvent by addition of anti-solvent and the like.

The organic solvent can be selected from, for example, chlorinated hydrocarbons, such as chloroform or methylene chloride; lower alkanols, such as methanol, ethanol, n-propanol, isopropanol or n-butanol; ethers, such as tetrahydrofuran, diethyl ether, or 1,4-dioxane; esters, such as ethyl acetate, n-butyl acetate, isopropyl acetate, or the like, or ketones, such as acetone, or ethyl methyl ketone; or mixtures thereof. Chlorinated hydrocarbons containing lower alkanols can be used as a solvent mixture, for example.

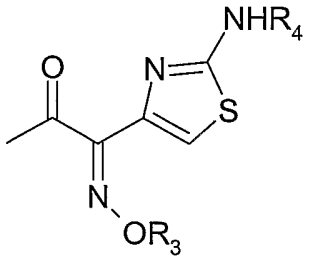
In still a further aspect, herein is provided a process for the preparation of compound of Formula II;



FORMULA II

wherein R is hydrogen, esterified residue or a metal cation capable of forming a salt; R_1 and R_2 are independently selected from hydrogen, an amino protecting group or combine

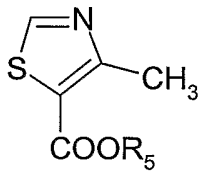
together form a divalent amino protecting group, or a group of Formula A



FORMULA A

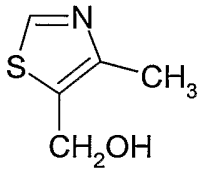
wherein R_3 is a optionally substituted lower alkyl (wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo) and R_4 is hydrogen or amino protecting group; wherein the process comprises

a) treating a compound of Formula IV



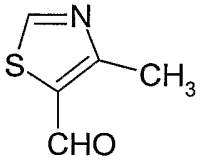
FORMULA IV

with lithium aluminium hydride to get compound of Formula III,



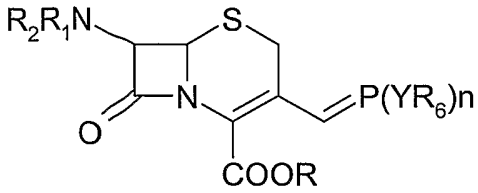
FORMULA III

b) oxidizing the compound of Formula III to get a compound of Formula I,



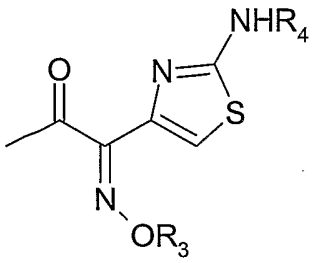
FORMULA I

c) reacting compound of Formula I with an ylide of Formula V,



FORMULA V

wherein, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group or a group of Formula A



FORMULA A

wherein R_3 is a optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and R_4 is hydrogen or amino protecting group; Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R_6 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl, and

d) isolating the compound of Formula II.

The compound of Formula III can be prepared by reducing the compound of Formula IV with, for example, lithium aluminium hydride as described above. The compound of Formula III obtained can then be converted to a compound of Formula II by a process as described above.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are within the scope of the present invention.

Example 1: Preparation of 4-Methyl-5-hydroxymethylthiazole

To a stirred mixture of lithium aluminum hydride (0.25 g) in THF (100 ml) at 5-10°C was added 4-methyl thiazole-5-caboxylic acid methyl ester (10 g) over a period of 30 minutes. The reaction mixture was stirred at 10- 15°C for 2 to 3 hours. Progress of reaction was monitored by TLC. After completion, the reaction was quenched by adding a aqueous solution of sodium sulfate. The resultant inorganic solids were filtered and the cake was washed with ethyl acetate. Filtrate was concentrated under reduced pressure to get a pale yellow solid (7.5 g), providing an HPLC Purity (% area) of more than 99%.

^{1}H-NMR (300MHz): 2.36 (s, 3H), 3.98 (s broad, 1H), 4.79 (s, 2H), 8.58 (s, 1H).

Example 2: Preparation of 4-Methylthiazolyl-5-carboxaldehyde

To a stirred mixture of 4-methyl-5-hydroxymethylthiazole (10 g) in toluene (100 ml) at 55-60°C was added manganese dioxide (50 g) in one lot. The reaction mixture was stirred at 55-60°C for 8 to 10 hours. Progress of reaction was monitored by TLC. After completion of the reaction, manganese dioxide was filtered over celite bed and washed with toluene. Filtrate was cooled below minus 20°C to get solid. The solid was filtered, and dried to get 7.0 g 4-methylthiazole-5-carboxaldehyde as a light yellowish solid, with an HPLC Purity (% area) of more than 99%.

^{1}H-NMR (300MHz): 2.80 (s, 3H), 8.99 (s, 1H) 10.15 (s, 1H).

Example 3: Preparation of Cefditoren acid, sodium salt

Step a) Preparation of 7-Amino-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cepheme-4-carboxylic acid

1,1-diphenylmethyl 7-(phenylacetamido)-3-[(triphenylphoshoranylidene)methyl]-3-cepheme-4-carboxylate (16 g) was mixed with methylene chloride (120 ml) and 1-propanol (40 ml) followed by addition of 4-methylthiazol-5-carboxaldehyde (8 g). The resultant heterogeneous mixture was stirred at 20 to 25°C for 20 to 22 hours. Progress of reaction was monitored by HPLC. After completion, reaction mixture was sequentially washed with 3% sodium bisulfite (100 ml) and water (100 ml). The organic layer was concentrated under reduced pressure to get an oily residue of 1,1,-diphenylmethyl 7-(phenylacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cepheme-4-carboxylate. To this oily residue was added phenol (60 ml) was added to the residue to get a clear solution.

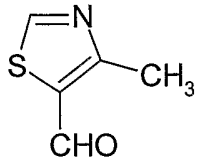
This solution was stirred at 40 to 50°C for 10 to 12 hours and n-butyl acetate (150 ml) was added to the reaction mass followed by cooling to 5 to 10°C. The organic portion was extracted with sodium bicarbonate solution (0.17 Molar, 2 x 150 ml). The aqueous layer was washed with n-butyl acetate (2 x 150 ml) to remove traces of phenol. To the aqueous layer was added Pen-G amidase (8 g wet) at 20 to 25°C. The pH of the reaction mixture was intermittently adjusted to 7.5 to 7.7 by slow addition of 5% sodium carbonate solution. After completion of reaction, enzyme was filtered and washed with deionized water. The filtrate was treated with activated carbon and then filtered at 30–35°C. The filtrate was cooled to 20–25°C and to it was added dilute HCl (2 M) to adjust the pH to 3.0 to 3.5 in order to affect complete precipitation of title compound. The product was filtered and sequentially washed with water and acetone and finally dried under vacuum to get 5.5 g of off-white title compound.

Step b) Preparation of Cefditoren acid, sodium salt

A suspension of the product obtained in Step a) (5.0 g, 15.4 mmol) and 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, S-2-benzothiazole ester (6.7 g, 18.6 mmol) in aqueous tetrahydrofuran (60 ml) was stirred at 0 to 5°C. Triethylamine (2.3 ml) was added slowly at 0–5°C over 15 to 20 minutes. The mixture was stirred at 0–5°C for 2–3 hours. The reaction was quenched by addition of dichloromethane followed by layer separation. The aqueous layer was diluted with acetone to 50 ml. Sodium 2-ethylhexanoate (3.3 g, 19.8 mmol) was added to the aqueous acetone solution at 20–25°C. After stirring the mixture for sufficient time for crystallization of the sodium salt of Cefditoren, acetone was added (50 ml) slowly to the reaction mass in order to effect crystallization. Filtered the crystallized product under suction and washed with acetone (2 x 10 ml). The product was vacuum dried to get 6.5 g of off-white title compound (Yield = 75%).

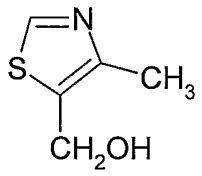
We Claim:

1. A method of preparing 4-methylthiazole-5-carboxaldehyde of Formula I,



FORMULA I

the process comprising oxidizing 5-hydroxymethyl-4-methylthiazole of Formula III.



FORMULA III

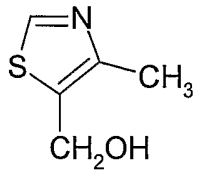
2. The process of claim 1, wherein the oxidation is carried out in presence of an inert organic solvent.

3. The process of claim 1, wherein the oxidation is carried out at a temperature of about 50-150°C.

4. The process of claim 2, wherein the inert organic solvent is selected from benzene, toluene, xylene, substituted toluenes, substituted xylenes, substituted benzenes, chloroform, ethylene chloride, tetrahydrofuran, 1,4-dioxane, diisopropyl ether, hexane, heptane, petroleum ether; cyclohexane, acetone, diisobutyl ketone, methyl ethyl ketone, methyl isobutyl ketone, dimethylacetamide, dimethylformamide and dimethylsulphoxide.

5. The process of claim 1, wherein the product of Formula I is obtained in purity of 99% or greater.

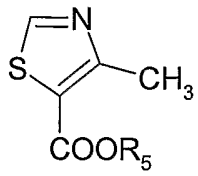
6. A process for the preparation of 5-hydroxymethyl-4-methylthiazole of Formula III,



FORMULA III

the process comprising

treating 4-methylthiazole-5-caboxylate of Formula IV



FORMULA IV

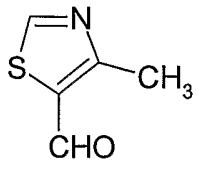
wherein R_5 is an esterifying residue selected from C_{1-3} alkyl, with lithium aluminium hydride.

7. The process of claim 6, carried out in presence of an organic solvent.

8. The process of claim 7, wherein the organic solvent is selected from tetrahydrofuran, diethyl ether, 1,4-dioxane, cyclohexane, hexane, heptane, toluene, benzene, and xylene.

9. The process of claim 6, wherein the product of Formula III is obtained in purity of 99% or greater.

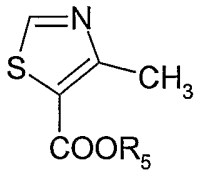
10. A process for the preparation of 4-methylthiazol-5-carboxaldehyde of Formula I,



FORMULA I

the process comprising:

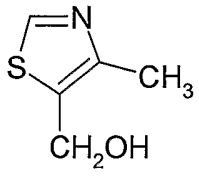
a) reacting a compound of Formula IV



FORMULA IV

wherein R_5 is an esterifying residue selected from C_{1-3} alkyl

with lithium aluminium hydride to get compound of Formula III,

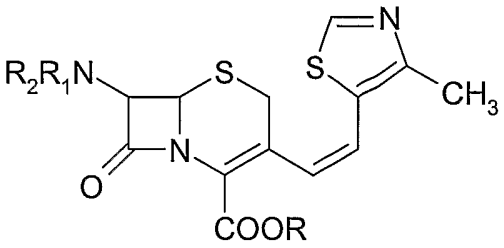


FORMULA III

b) oxidizing the compound of Formula III, and

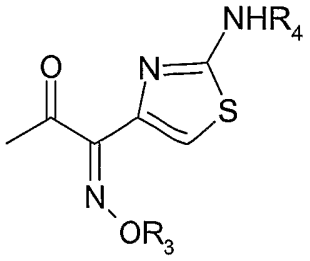
c) isolating the compound of Formula I.

11. A process for the preparation of a compound of Formula II;



FORMULA II

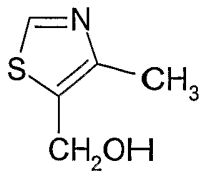
wherein R is hydrogen, esterified residue or a metal cation capable of forming a salt; R_1 and R_2 are independently selected from hydrogen, amino protecting group or combine together form a divalent amino protecting group, an optionally substituted amino acid residue or a group of Formula A



FORMULA A

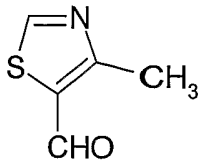
wherein R_3 is a optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and R_4 is hydrogen or amino protecting group, the process comprising:

a) oxidizing a compound of Formula III



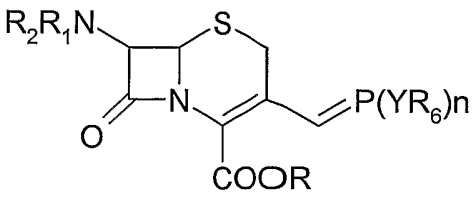
FORMULA III

to get a compound of Formula I,



FORMULA I

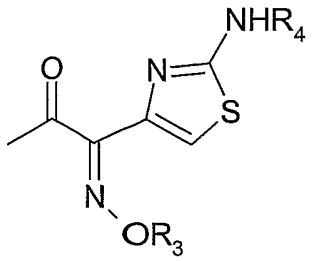
b) reacting the compound of Formula I with an ylide of Formula V,



FORMULA V

wherein, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt and R_1 and R_2 are independently hydrogen,

monovalent amino protecting group or together form a divalent amino protecting group or a group of Formula A



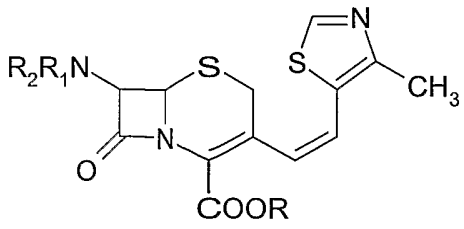
FORMULA A

wherein R_3 is a optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo; R_4 is defined as above, Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R_6 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl, and

c) isolating the compound of Formula II.

12. The process of claim 11, further comprising washing the reaction mass of step b) with sodium bisulphite.

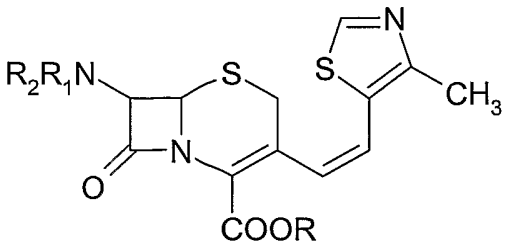
13. The process of claim 11, wherein the compound of Formula II is



FORMULA II

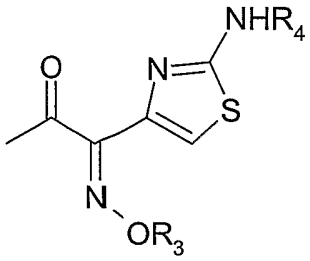
wherein R is hydrogen, esterified residue or a metal cation capable of forming a salt; R_1 and R_2 are hydrogen or amino protecting group or combine together form a divalent amino protecting group.

14. The process of claim 11, wherein the compound of Formula II is



FORMULA II

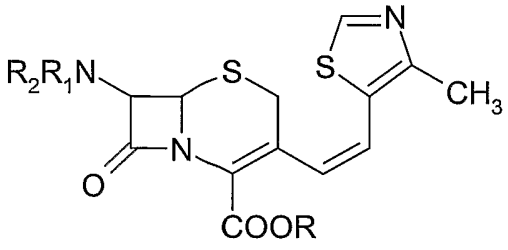
wherein R is hydrogen, esterified residue or a metal cation capable of forming a salt; one of R_1 and R_2 is hydrogen, and other is a group of Formula A



FORMULA A

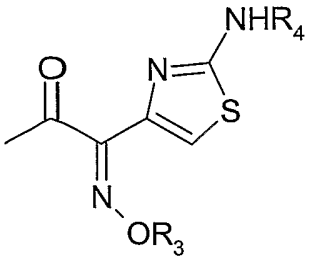
wherein R_3 is methyl and R_4 is hydrogen.

15. A process for the preparation of a compound of Formula II;



FORMULA II

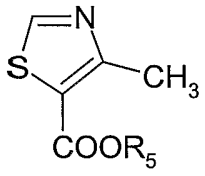
wherein R is hydrogen, esterified residue or a metal cation capable of forming a salt; R_1 and R_2 are independently selected from hydrogen, amino protecting group or combine together form a divalent amino protecting group, or a group of Formula A



FORMULA A

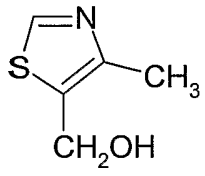
wherein R_3 is a optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo, and R_4 is hydrogen or amino protecting group, the process comprising:0

a) treating the compound of Formula IV



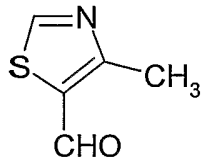
FORMULA IV

with lithium aluminium hydride to get compound of Formula III,



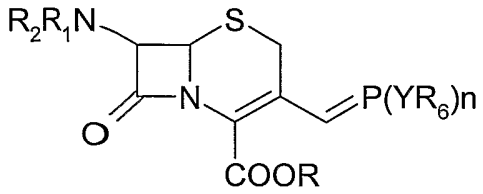
FORMULA III

b) oxidizing the compound of Formula III to get a compound of Formula I,



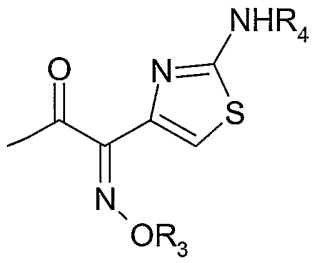
FORMULA I

c) reacting the compound of Formula I with an ylide of Formula V,



FORMULA V

wherein, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group or a group of Formula A



FORMULA A

wherein R_3 is a optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo, R_4 is as defined above; Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R_6 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl, and

d) isolating the compound of Formula II.

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/IB2005/000972

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/24 C07D501/04

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

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, BEILSTEIN Data, 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	HATANAKA ET AL: J. MED. CHEM., vol. 16, 1973, pages 978-984, XP002338157 page 982, column 2, last paragraph - page 983, column 1, paragraph FIRST -----	6-9
X	WO 03/091230 A (ORCHID CHEMICALS) 6 November 2003 (2003-11-06) figures (I),(III)-(IV)-(I) -----	1-5
X	FELL, STEPHEN C. M. ET AL: J. CHEM. SOC. PERKIN TRANS 1, 1991, pages 1361-1364, XP009051018 page 1361, column 2; figure G3 page 1362; figure 14 -----	11-14

☐ 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

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2005	08/08/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Timmermans, M

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/000972

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claim: 10

   a preparation process for 4-methylthiazole-5-carboxaldehyde starting from 4-methylthiazole-5-carboxylate derivatives

   ---

2. claims: 6–9

   A preparation process for 5-hydroxymethyl-4-methylthiazole starting from 4-methylthiazole-5-carboxylate derivatives

   ---

3. claims: 11–14

   A preparation process for cephalosporin antibiotics starting from 5-hydroxymethyl-4-methylthiazole

   ---

4. claims: 1–5

   A preparation process for 4-methylthiazole-5-carboxaldehyde starting from 5-hydroxymethyl-4-methylthiazole

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte al Application No
PCT/IB2005/000972

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03091230 A	06-11-2003	WO 03091230 A1	06-11-2003