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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 277/593 — A1

(11) International Publication Number: WO 90/15802

(43) International Publication Date: 27 December 1990 (27.12.90)

(21) International Application Number: PCT/US90/02620

(22) International Filing Date: 15 May 1990 (15.05.90)

(30) Priority data:
365,450 — 12 June 1989 (12.06.89) — US

(60) Parent Application or Grant
(63) Related by Continuation
US — 365,450 (CIP)
Filed on — 12 June 1989 (12.06.89)

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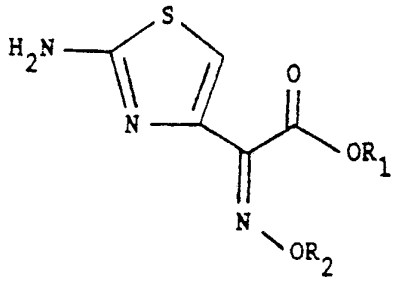
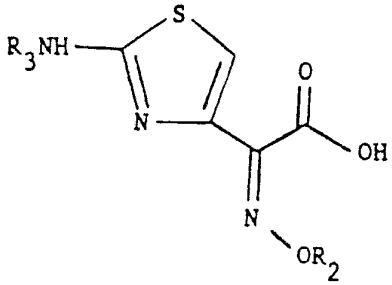
(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent)*, DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.

Published
With international search report.

(54) Title: PREPARATION OF 2-(2-TRITYLAMINOTHIAZOL-4-YL)-2-SYN-METHOXYIMINOACETIC ACID



(I)



(IV)

(57) Abstract

The process of the present invention is the conversion of an aminothiazole (I) to the corresponding thiazole acetic acid (IV) which is a precursor in the preparation of cephalosporin antibiotics.

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PREPARATION OF 2-(2-TRITYLAMINOTHIAZOL-4-YL)-2-SYN-METHOXYIMINOACETIC ACID

BACKGROUND OF THE INVENTION

1. Field of the Invention

The process of the present invention is the conversion of an aminothiazole to the corresponding thiazole acetic acid which is a precursor in the preparation of cephalosporin antibiotics.

2. Description of the Related Art

2-(2-Tritylaminothiazol-4-yl)-2-syn-methoxyiminoacetic acid is a known compound (US Patent 4,376,203, Example 3, Step C) useful in the production of a cephalosporin antibiotic, CEFTIOFUR (ceftiofur sodium, US Patent 4,464,367).

GB Patent 1,580,621 (Example 21, Stages C-F) and US Patent 4,376,203 (Example 21, Steps C-F) set forth a process the transformation of ethyl 2-(2-aminothiazol-4-yl)-2-syn-hydroxyiminoacetic acid to 2-(2-tritylaminothiazol-4-yl)-2-syn-methoxyiminoacetic acid, see Stages D-F.

Chemical Abstracts 110:57407g of December 15, 1987 reports the conversion of ethyl 2-(2-aminothazol-4-yl)-2-syn-methoxyiminoacetic acid to ethyl 2-(2-tritylaminothiazol-4-yl)-2-syn-methoxyiminoacetic acid by reacting the 2-aminothiazole with 0.8-1.6 mole ϕ_3C-Cl in the presence of a strong inorganic base at room temperature.

Chemical Abstracts 110:57653j of December 15, 1987 reports the conversion of ethyl 2-(2-aminothazol-4-yl)-2-syn-methoxyiminoacetic acid to ethyl 2-(2-tritylaminothiazol-4-yl)-2-syn-methoxyiminoacetic acid by reacting the 2-aminothiazole with $ClCH_2$-CO-Cl in the presence of an inorganic base at room temperature.

The process of the present invention is superior to the known methods of producing the thiazole acetic acid (IV) because none of the intermediates are isolated. Up to this time either the thiazole ester (II) or thiazole salt (III) or both were isolated, leading to a long process. The one-pot process of the invention can easily be accomplished, without any solvent changes, in one day giving the product in a higher yield.

SUMMARY OF INVENTION

Disclosed is a process for the preparation of a thiazole acetic acid of formula (IV)

where R_2 is -H,

C_1-C_4 alkyl,

-CO-NH-CH_3,

-CH_2-CO-CH_2,

1,2,4-triazol-5-ylmethyl,

1,2,3-triazol-5-ylmethyl,

-CH_2-CO-OCH_3,

-CH_2-COOH,

-$C(R_{2-1})(R_{2-2})$-CO-O-R_{2-3} where R_{2-1} and R_{2-2} are -H or -CH_3 and R_{2-3} is C_1-C_4 alkyl,

-$C(R_{2-1})(R_{2-2})$-COOH where R_{2-1} and R_{2-2} are as defined above;

R_3 is ϕ_3C- and Cl_2CH-CO- which comprises

(1) contacting an aminothiazole of formula (I) where R_1 is C_1-C_4 alkyl, benzyl and p-methoxybenzyl and where R_2 is as defined above with a compound of the formula R_3-X_1 where X_1 is -Cl and -Br and where R_3 is as defined above, in the presence of a non-aqueous base,

(2) hydrolyzing the product of step (1) with aqueous base and

(3) acidifying to a pH < 7, without isolation of any intermediates.

DETAILED DESCRIPTION OF THE INVENTION

While there are a number of procedures for the transformation of ethyl 2-(2-aminothazol-4-yl)-2-syn-methoxyiminoacetic acid to 2-(2-tritylaminothiazol-4-yl)-2-syn-methoxyiminoacetic acid, the process of the present invention is a one-pot process which gives improved yields.

The aminothiazole (I) is contacted with the desired alkylating agent R_3-X_1 in an organic solvent in the presence of a non-aqueous base. The particular R_2 group utilized will be chosen because of the particular R_2 desired in the final product (cephalosporin) of which the thiazole acetic acid (IV) is a portion. For example, if one desires to produce ceftiofur sodium (US Patent 4,464,367) then it is preferred that R2 is methyl. X_1 is -Cl or -Br. The non-aqueous base can be either an organic base or an inorganic base. Suitable organic bases include pyridine optionally substituted with 1-3 -CH_3, DBU, DBN, $NX_3X_4X_5$ where X_3, X_4 and X_5 are the same or different and are C_1-C_4 alkyl and where two of X_3, X_4 and X_5 are taken together with the attached nitrogen atom to form a compound selected from the group consisting of pyrrolidine, piperidine, morpholine or piperazine and

the other of X_3, X_4 and X_5 is as defined above. Preferred organic bases include pyridine and triethylamine; more preferred is pyridine. The organic base can serve as the solvent for the reaction. Suitable inorganic bases include bicarbonate (HCO_3^{-1}) and carbonate (CO_3^{-2}). Other suitable solvents include THF, N-methylpyrrolidinone, DMAC and acetone. The reaction is operable in a temperature range of about 20-100°, preferably at about 20-50°. The tritylation step is complete within about 1 hr at about 60-70° using 1.1 equivalents of trityl chloride and 5 ml of pyridine/g of reactants. During the tritylation reaction about 1-2% of the anti oxime is formed. At about 40° the reaction is still complete and no anti oxime is detected.

The product of the above step is then hydrolyzed with aqueous base. Any aqueous base which will cleave the ester is operable. Suitable aqueous bases include hydroxides, alkoxides of the formula $O\text{-}X_2^{-1}$ where X_2 is C_1-C_4 alkyl, and equivalents thereof. Preferred aqueous bases include hydroxides; more preferred are sodium or potassium hydroxide. About 3-4 equivalents of the aqueous base is preferred. If less is used the reaction rate is slowed, if more is used no advantage is observed. The hydrolysis is complete in about 3 hr at about 60° and in about 2 hr at about 70°. The temperature is not important to the yield, it only affects the rate of the reaction. Operable temperatures are from about 20-100°, preferably from about 50 to about 80°. The temperature used is affected by the amount of solvent present. With pyridine, the more solvent used the faster the reaction rate at a given temperature.

Following hydrolysis, the reaction mixture is acidified to a pH of about 2 to form the free acid. Any acid sufficiently strong is operable as is well known to those in the art. Operable acids include sulfuric, hydrochloric, phosphoric, nitric, trifluoroacetic, perchloric and equivalents thereof; preferred are sulfuric or hydrochloric. Prior to acidifying it is preferred to dilute the reaction mixture somewhat with an organic solvent such as methylene chloride. If this step is performed in less than one hr, very little of the anti oxime is formed. However, if this two phase system (organic solvent/water) is stirred for a long time at elevated temperatures the anti oxime forms in increasing amounts. Therefore, it is preferred to cool the thiazole salt (III) prior to acidifying

and allowing the heat of neutralization bring the reaction temperature to about 30-35°. At this time the layers are separated. The organic layer is washed to remove the salt of the amine base and is then worked up by known means.

For purposes of work-up the reaction mixture can be diluted with water or an organic solvent (depending on the method of work-up desired) and the thiazole acetic acid (IV) either extracted or filtered.

The anti oxime is efficiently removed by crystallization from methylene chloride or a methylene chloride/hexane mixture. It is desired to remove the anti oxime because it is very poorly active in the cephalosporin antibiotics of which the thiazole acetic acid (IV) is a part.

The thiazole acetic acids (IV) are useful intermediates in the production of cephalosporin antibiotics. More particularly, 2-(2-tritylaminothiazol-4-yl)-2-syn-methoxyiminoacetic acid (IV) is useful in the production of ceftiofur sodium (US Patent 4,464,367).

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

I. CONVENTIONS FOR FORMULAS AND DEFINITIONS OF VARIABLES

The chemical formulas representing various compounds or molecular fragments in the specification and claims may contain variable substituents in addition to expressly defined structural features. These variable substituents are identified by a letter or a letter followed by a numerical subscript, for example, "Z_1" or "R_i" or "R_i" where "i" is an integer.

Chemical formulas or portions thereof drawn in a linear fashion represent atoms in a linear chain. The symbol "-" in general represents a bond between two atoms in the chain. Thus CH_3-O-CH_2-$CH(R_i)$-CH_3 represents a 2-substituted-1-methoxypropane compound. In a similar fashion, the symbol "=" represents a double bond, e.g., CH_2=$C(R_i)$-O-CH_3, and the symbol "≡" represents a triple bond, e.g., HC≡C-$CH(R_i)$-CH_2-CH_3. Carbonyl groups are represented in either one of two ways: -CO- or -C(=O)-, with the former being preferred for simplicity.

II. DEFINITIONS

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatography.

THF refers to tetrahydrofuran.

DBU refers to 1,8-diazabicyclo[5.4.0]undec-7-ene.

DBN refers to 1,5-diazabicyclo[4.3.0]non-5-ene.

DMAC refers to dimethylacetamide.

ϕ refers to phenyl (C_6H_5).

M includes lithium, sodium and potassium.

EXAMPLES

EXAMPLE 1 2-(Tritylamino)-α-(methoxyimino)-4-thiazoleacetic acid (IV)

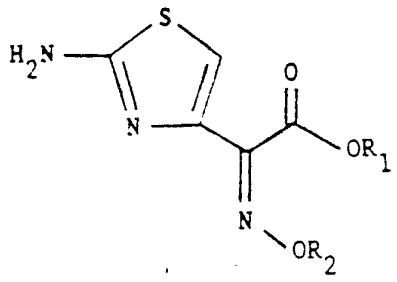
A mixture of ethyl 2-amino-α-(methoxyimino)-4-thiazoleacetate (10.0 g), trityl chloride (13.99 g), and pryidine (20.0 ml) is stirred under nitrogen at 40°. After stirring for 1 hr the reaction is checked by TLC. When the tritylation is complete, water (20.0 ml) and aqueous sodium hydroxide (50%, 8.14 ml) are added and the mixture heated at 65° for 4-5 hr. When the hydrolysis is complete (TLC) the resulting slurry is cooled to 20° and methylene chloride (100 ml) is added. This mixture is then acidified by the addition of concentrated aqueous hydrochloric acid. The layers are separated. The organic layer is washed with water (2 x 70 ml). Heptane (150 ml) is added to the organic phase with stirring. The resulting slurry is cooled to 0° and filtered. The solids are washed with heptane/-methylene chloride mixture (60/40, 200 ml) and dried under vacuum at 55° to give the title compound.

EXAMPLE 2 2-(Tritylamino)-α(methoxyimino)-4-thiazoleacetic acid (IV)

A mixture of ethyl 2-amino-α-(methoxyimino)-4-thiazoleacetate (10.0 g), dimethylacetamide (50 ml), trityl chloride (14.59 g), and triethylamine (9.12 ml) are stirred under nitrogen at 40°. When the tritylation is complete by TLC, water (20 ml) and aqueous sodium hydroxide (50%, 8 ml) are added. This mixture is heated at 65° for 2 to 2.5 hours. When the hydrolysis is complete (TLC) the resulting slurry is cooled in an ice bath and diluted with water (50 ml). This mixture is then acidified by the addition of concentrated aqueous hydrochloric acid. This slurry is filtered. The solids are washed with water and dried under vacuum. The crude solids are stirred with a mixture of heptane/methylene chloride (70/30, 77 ml). After

stirring for 30 min the slurry is filtered. The solids are washed with a mixture of heptane/methylene chloride (70/30, 150 ml) and dried under vacuum at 55° to give the title compound.

CHART A



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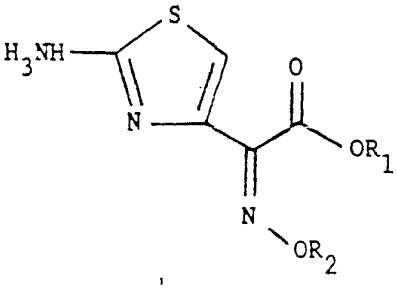

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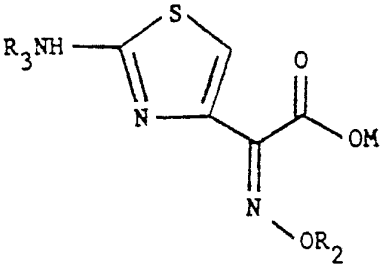

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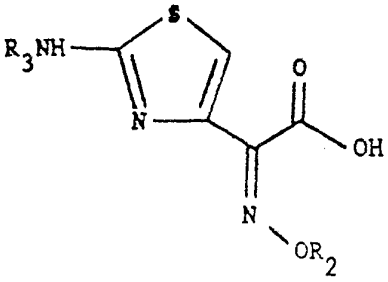
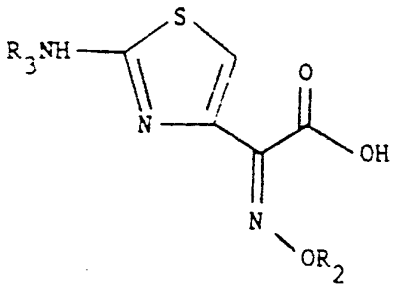


(IV)

CLAIMS

1. A process for the preparation of a thiazole acetic acid of formula (IV)



(IV)

where R_2 is -H,

C_1-C_4 alkyl,

-CO-NH-CH_3,

-CH_2-CO-CH_2,

1,2,4-triazol-5-ylmethyl,

1,2,3-triazol-5-ylmethyl,

-CH_2-CO-OCH_3,

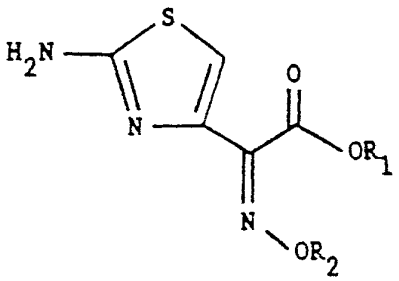
-CH_2-COOH,

-$C(R_{2-1})(R_{2-2})$-CO-O-R_{2-3} where R_{2-1} and R_{2-2} are -H or -CH_3 and R_{2-3} is C_1-C_4 alkyl,

-$C(R_{2-1})(R_{2-2})$-COOH where R_{2-1} and R_{2-2} are as defined above;

R_3 is ϕ_3C- and Cl_2CH-CO- which comprises

(1) contacting an aminothiazole of formula (I)



(I)

where R_1 is C_1-C_4 alkyl, benzyl and p-methoxybenzyl and where R_2 is as defined above with a compound of the formula R_3-X_1 where X_1 is -Cl and -Br and where R_3 is as defined above, in the presence of a non-aqueous base,

(2) hydrolyzing the product of step (1) with aqueous base and

(3) acidifying to a pH < 7, without isolation of any intermediates.

2. A process for the preparation of thiazole acetic acid (IV) according to claim 1 where the non-aqueous base is an organic or inorganic base.

3. A process for the preparation of thiazole acetic acid (IV) according to claim 2 where the organic base is selected from the group consisting of pyridine optionally substituted with 1-3 $-CH_3$, DBU, DBN, $NX_3X_4X_5$ where X_3, X_4 and X_5 are the same or different and are C_1-C_4 alkyl and where two of X_3. X_4 and X_5 are taken together with the attached nitrogen atom to form a compound selected from the group consisting of pyrrolidine, piperidine, morpholine or piperazine and the other of X_3, X_4 and X_5 is as defined above.

4. A process for the preparation of thiazole acetic acid (IV) according to claim 3 where the organic base is pyridine or triethylamine.

5. A process for the preparation of thiazole acetic acid (IV) according to claim 2 where the inorganic base is HCO_3^{-1} and CO_3^{-2}.

6. A process for the preparation of thiazole acetic acid (IV) according to claim 1 where the aqueous base is selected from the group consisting of hydroxide and $O\text{-}X_2^{-1}$ where X_2 is C_1-C_4 alkyl.

7. A process for the preparation of thiazole acetic acid (IV) according to claim 1 where the acid is selected from the group consisting of sulfuric, hydrochloric, phosphoric, nitric, trifluoracetic and perchloric.

8. A process for the preparation of thiazole acetic acid (IV) according to claim 7 where the acid is sulfuric or hyrochloric.

9. A process for the preparation of thiazole acetic acid (IV) according to claim 1 where the thiazole acetic acid is 2-(tritylamino)-α-(methoxyimino)-4-thiazoleacetic acid.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 90/02620

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: C 07 D 277/593

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	C 07 D 277/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4376203 (R. HEYMES) 8 March 1983 see columns 17,18, example 3 cited in the application	1
A	Chemical Abstracts, vol. 110, no. 7, 13 February 1989, (Columbus, Ohio, US), see page 662, abstract 57407g, & CS, A, 246443 (M. VEVERKA et al.) 15 December 1987 cited in the application	1
A	Chemical Abstracts, vol. 110, no. 7, 13 February 1989, (Columbus, Ohio, US), see page 691, abstract 57653j, & CS, A, 245873 (M. VEVERKA et al.) 15 December 1987 cited in the application	1

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"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
31st July 1990	12. 09. 90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. SOTELO

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9002620 SA 37321

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/09/90
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