Title: NOVEL THIOESTER DERIVATIVES AND PROCESS FOR PREPARATION OF CEPHALOSPORIN

Abstract: The present invention provides new thioester derivatives of thiazolyl acetic acid of general formula (I), wherein R₁ represents H, trityl, CH₃, CR₃R₅COOR₂ (R₂ and R₅ independently of one another represents hydrogen or methyl and R₃ represents H or C₁₋₇ alkyl), also, the invention provides a process by which the said thioester derivatives is prepared by reacting thiazolyl acetic acid of general formula (IV) with 1,2,5,6 tetrahydro-2-methyl-5,6 dioxa-1,2,4-itriazin-3-thiol of the formula (V) in a solvent and in the presence of an organic base along with Wilsmeier reagent of formula (V), to obtain thioester derivatives that are further reacted with 7-amino-cephalosporin carboxylic acids of general formula (III) to produce cephalosporin antibiotic compounds having general formula (II).
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NOVEL THIOESTER DERIVATIVES AND PROCESS FOR PREPARATION OF CEPHALOSPORIN

Technical Field

The present invention relates to novel thioester derivatives of thiazolyl acetic acid of general formula (I), useful as an intermediate for the preparation of cephalosporin antibiotics having general formula (II). In addition, the present invention also relates to a process for the preparation of thioester derivatives. The present invention also provides for a process for the preparation of cephalosporin antibiotics using said thioester derivatives.

![Chemical Structures](image)

wherein, R₁ represents H, trityl, CH₃, CR₉R₈COOR₂

(R₉ and R₈ independently of one another represent hydrogen or methyl and R₂ represents H or C₁-C₄ alkyl)

R₃ is CH₃ -CH=CH₂, -CH₂OCH₃, -CH₂OCOCH₃

R₄ is H or a salt or a carboxylic protecting group or an inner salt

Background of the Invention

Use of acid chlorides, anhydrides, esters, amide etc. is reported in the chemical literature for activation of carboxylic acid of formula (IV).

![Chemical Structure](image)

wherein, R₁ as defined above

Activation in the form of acid chloride required protection and deprotection of NH₂ group.
Activation of acid (IV) is reported by SO₂Cl₂/DMF in US patent 5,856,502 and SOCl₂/DMF in US patent 5,037,988. These processes suffer the limitation of using harmful and pungent smelling chemicals like SOCl₂, SO₂Cl₂ along with solvents like benzene, toluene, etc. and involving stringent conditions for carrying out the reactions on commercial scale.

In US patent Nos. 4,576,749 and 4,548,748, the acid of formula (IV) has also been activated by reacting with 1-hydroxybenzotriazole (HOBT) or 2-mercaptobenzothiazole (MBT) in the presence of dicyclohexylcarbodiimide (DCC) to produce reactive ester of the acid (IV) which is then reacted with cephem moiety to prepare cephalosporin antibiotics, but the processes are time consuming accompanied with low yields, hence, not suitable.

US patent No. 4767852 discloses a process for production of cephems by acylating 7-amino-3-cephem-4-carboxylic acid with 2-mercaptobenzothiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate (MAEM). Similarly, US Pat.No.5026843 (1991) disclosed a process for preparing ceftriaxone disodium hemihydrate by acylation of 7-amino-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl) thiomethyl]-3-cephem-4-carboxylic acid (7-ACT) by using MAEM as acylating agents in good yield and quality. Thus MAEM has become the standard acylating agent for the preparation of cephalosporins antibiotics having an oximino group and a 2-aminothiazolyl group in 7-position of cephem compounds.

However, the synthesis of MAEM from acid (III) and 2,2'-dithio-bis-benzothiazole involves use of costly condensing agent triphenylphosphine (TPP). Moreover, during condensation of MAEM with 7-amino-3-cephem-4-carboxylic acid compound (III), a toxic compound 2-mercaptobenzothiazole (MBT) is also produced as a byproduct [Chemical Abstracts, 111, p.19243 (1989)], which is difficult to remove.

Thus, it is evident that the procedures described in the prior art for the preparation of these cephalosporin antibiotics are complex, involving protection, deprotection and also associated with generation of toxic byproduct. Hence, there is a need to develop new acylating agents which are capable of transferring the 2-aminothiazolyl moiety to cephem compounds of formula (III) in good yield, without producing this toxic byproduct. On the similar lines, a new thioester was reported by D.G.Walker, Tet. Lett. 1990, 31,6481 to acylate the cephem moiety to get cefepime sulfate but yields obtained by using this thioester were in the range of 54-73% which cannot be considered as good yield to operate a process at commercial scale. The same thioester is exploited in US patent No. 5869649 for making three more important cephalosporin antibiotics.
In the co pending application US Application No. 09/754,302, the Applicant has disclosed another novel thioester derivatives of thiazole acetic acid and its use in the synthesis of various cephalosporin antibiotics. In continuation of search for more such derivatives, the Applicant has observed that the title compound (I) works equally well and also has the similar advantages as described in the aforementioned US application.

**Objectives of the Invention**

The primary objective of this invention is to provide novel thioester derivatives of thiazolyl acetic acid of formula (I) used for the preparation of cephalosporin antibiotics of formula (II).

Another objective of this invention is to prepare new thioester derivatives of thiazolyl acetic acid of formula (I) which is better than the earlier reactive derivatives and also suitable for being used in the manufacture of cephalosporin antibiotics.

Yet another objective of the present invention is to provide a process for the synthesis of thioester derivatives of formula (I) from thiazolyl acetic acid of formula (IV) and 1,2,5,6 tetrahydro-2-methyl-5, 6- dioxo-1,2,4-triazin-3-thiol (VI).

Still another objective of the present invention is to provide a process for the preparation of cephalosporin antibiotics of general formula (II) at low temperature, which will be simple and cost effective.

Yet another objective of the present invention is to produce cephalosporin antibiotics having high purity and free from toxic byproducts.

One more objective of the present invention is to provide a process for the preparation of cephalosporin antibiotics of general formula (II) from said novel thioester derivatives.

**Summary of the Invention**

The present invention provides a new thioester derivatives of thiazolyl acetic acid of formula (I) and also provides a method by which the said thioester derivatives can be prepared by reacting thiazolyl acetic acid of general formula (IV) with the commercially available 1,2,5,6 tetrahydro-2-methyl-5,6 dioxo-1,2,4-triazin-3-thiol (VI) using Vilsmeier reagent (V) as a condensing agent. (Ber. 60B, 119 (1927)). The thioester derivatives thus obtained are reacted with 7-amino-cephem carboxylic acids of general formula (III) to produce cephalosporin antibiotic compounds of general formula (II) as described above. The cephalosporin antibiotics obtained are of high purity (95-99%). The method is workable on commercial scale without necessitating the protection of the amino group of the acylating agents, and avoiding the generation of the toxic byproduct 2-mercaptobenzothiazole.
Detailed Description of the Invention

The present invention provides novel derivatives of thiazolyl acetic acid represented by formula (I)

\[
\begin{array}{c}
\text{H}_2\text{N}-\text{N} \text{OR}_1 \\
\text{S} \text{C} \text{S} \text{N} \text{NH} \\
\text{O} \text{C} \text{N} \text{O} \\
\end{array}
\]

wherein, \( \text{R}_1 \) represents \( \text{H}, \text{trityl, CH}_3, \text{CR}_3\text{R}_2\text{COOR}_2 \) (\( \text{R}_a \) and \( \text{R}_b \) independently of one another represents hydrogen or methyl, \( \text{R}_2 \) is hydrogen or \( \text{C}_1-\text{C}_4 \) alkyl)

An embodiment of the present invention provides a process for the preparation of a new thioester of formula (I) as mentioned above. The said process comprising the step of condensing thiazolylacetic acid represented by formula (IV)

\[
\begin{array}{c}
\text{NH}_2 \\
\text{S} \text{N} \text{O} \\
\text{N} \text{C} \text{OH} \\
\text{N} \text{O} \text{R}_1 \\
\end{array}
\]

wherein, \( \text{R}_1 \) represents \( \text{H}, \text{trityl, CH}_3, \text{CR}_3\text{R}_2\text{COOR}_2 \) (\( \text{R}_a \) and \( \text{R}_b \) independently of one another represents hydrogen or methyl and \( \text{R}_2 \) represents \( \text{H} \) or \( \text{C}_1-\text{C}_4 \) alkyl).

with 1,2,5,6 tetrahydro-2-methyl-5,6 dioxo-1,2,4-triazin-3-thiol of formula (VI)

\[
\begin{array}{c}
\text{CH}_3 \\
\text{HS} \text{N} \text{NH} \\
\text{N} \text{O} \text{C} \\
\end{array}
\]

(VI)

in the presence of Vilsmeier reagent of formula (V) in an organic solvent, at a temperature in the range of \(-10^\circ\text{C} - +30^\circ\text{C}\),

\[
\{(\text{CH}_3)_2\text{N} = \text{CH} \cdot \text{O} \cdot \text{P(OCl)}_2\} \text{Cl}^-
\]

(V)
to obtain the thioesters of formula (I).
The thioester of general Formula (I) thus obtained is reacted with 7-amino cephem carboxylic acids of general formula (III) in an organic solvent in presence of an organic base to obtain cephalosporin antibiotics of general formula (II).

The reactions scheme is shown here below:

\[
\begin{align*}
\text{H}_2\text{N-} & \text{S-}\text{N-} \text{OR}_1 \\
\text{OR}_2 & \text{S-}\text{N-} \text{OR}_3 \\
\text{NO} & \text{NH} \\
\text{C} & \text{H}_3 \\
\text{NH}_2 & \text{N} \\
\text{N} & \text{O} \\
\text{C} & \text{O} \\
\text{COOR}_4 & \text{S} \\
\text{R}_3 & \text{COOR}_4
\end{align*}
\]

wherein, in formula (I), \( R_1 \) represents \( \text{H, trityl, CH}_3, \) \( \text{CR}_4\text{R}_6\text{COOR}_2 \) (\( \text{R}_4 \) and \( \text{R}_6 \) independently of one another represents hydrogen or methyl and \( \text{R}_2 \) represents \( \text{H or C}_1\text{-C}_4 \) alkyl), in formula (III) \( \text{R}_3 \) represents \( \text{-CH}_3, \text{-CH=CH}_2, \text{-CH}_2\text{OCH}_3, \) \( \text{-CH}_2\text{OCONH}_2 \),

\[
\begin{align*}
\text{H}_3\text{C} & \text{N-} \text{N-} \text{OH} \\
\text{CH}_2 & \text{S-} \text{C} \text{-} \text{C} \\
& \text{furan} \\
\text{and} & \text{N} \\
\text{C} & \text{H}_3
\end{align*}
\]

\( \text{R}_4 \) is hydrogen, salt, carboxylic protecting group or an inner salt.
\( \text{R}_5 \) is hydrogen or trialkylsilyl.

wherein formula (II), \( \text{R}_1, \text{R}_3 \) and \( \text{R}_4 \) are as defined above.

Another embodiment of the present invention provides a method by which cephalosporin antibiotics are obtained in high purity and excellent yield without the necessity for
protecting the amino group of the acylating agents and avoiding the production of toxic byproduct namely 2-mercaptobenzothiazole (MBT).

In one another embodiment of the present invention, the substituent $R_3$ in cephem compound (II) and (III) represents methyl, acetyloxymethyl, methoxymethyl, vinyl, pyridylmethyl, propenyl, 2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazine-3-thiol, furanyl-2-carboxylthiol. In general, $R_3$ represents -CH$_2$-X wherein X is a residue of any organic or inorganic nucleophilic compound, e.g., halogen, hydroxy, cyano, mercapto, azido, amino, etc. Furthermore, X may preferably represent residue of any 5 or 6 membered heterocyclic thiol.

In yet another embodiment of the present invention, the substituent $R_4$ represents hydrogen, salt, a standard carboxylic protecting group, or a inner salt. Especially it is termed as carboxylate ion when $R_3$ is pyridylmethyl, which ultimately explains the neutrality of the molecules.

Another embodiment of the invention provides the use of Vilsmeier reagent of formula (V) as condensing agent.

Still another embodiment of the invention provides acylation of (III) (when $R_5$ is H) is performed in presence of a water miscible solvent like tetrahydrofuran (THF), acetonitrile, acetone, dioxane, N,N-dimethylformamide etc. but the preferable solvents are THF and acetonitrile.

In an embodiment of the present invention, acylation of (III) (when $R_5$ is trimethylsilyl) is carried out in aprotic organic solvents like halogenated hydrocarbons, toluene, acetonitrile, alkyl ethers etc., but preferable solvent is acetonitrile and dichloromethane. More suitable silylating agents used for the reaction are hexamethyldisalazane, bis (trimethyl)silylacetamide and trimethylsilyl chloride or a mixture thereof.

In yet another embodiment of the present invention, the organic base may be selected from triethylamine, diethylamine, tributylamine, N-alkylpiperidine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, N-methylmorpholine, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylamino pyridine and mixtures thereof.

The conceptual utility of this new thioesters of 1,2,5,6 tetrahdro-2-methyl-5,6 dioxo-1,2,4-triazin-3-thiol of general formula (VI) is also tried in various coupling reactions of carboxylic acids and amines. Most of amide formation reactions have shown good results. L-alanine, 5-methylisoxazole-4-carboxylic acid, 2-thienylacetic acid, etc. are some of the compounds, which have been activated by above mentioned thiol of formula (VI). Some of the results are summarized in the following table.
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Acids</th>
<th>Amines</th>
<th>% by HPLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>H₂N−CH−COOH</td>
<td>NH</td>
<td>63 - 78%</td>
</tr>
<tr>
<td></td>
<td>CH₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>COOH</td>
<td>NH₂</td>
<td>79 - 91%</td>
</tr>
<tr>
<td></td>
<td>COOH</td>
<td>CF₃</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>CH₂COOH</td>
<td>7-Amino cephalosporanic acid</td>
<td>84 - 87%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Many other beneficial results are obtained by applying disclosed invention in a different manner or by modifying the invention within the scope of disclosure. However, since the major characteristic feature of the present invention resides in the use of novel reactive thioester derivatives of thiazolyl acetic acid of general formula (I) in preparing the cephalosporin antibiotics, the technical scope of the present invention should not be limited to the following examples.

The invention is illustrated with the following examples, which should not be construed as limiting the scope of the invention.

**Example - I**

**Synthesis of 1,2,5,6 tetrahydro-2-methyl-3-thio-5,6 dioxo-1,2,4-triazine-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (I).**

To the cold Dimethylformamide (DMF), (50g), phosphorousoxychloride (POCl₃) (84g) was added slowly in 30 min and stirred at 0-10 °C. Acetonitrile 1.0 lit was added and reaction mass cooled further to -20 to -45 °C and (Z)-(2-aminothiazol-4-yl)methoxyimino acetic acid (100g) was added and stirred for 30 min. 1,2,5,6 tetrahydro-2-methyl- 5,6 dioxo-1,2,4-triazine-3-thiol ( 96 g) followed by pyridine (198 g) was added. The reaction mixture was stirred for 30 min. After the reaction was complete, distilled water 1800ml was added to the reaction solution and the mixture was stirred for 10 min. The product was filtered, washed with water (1.0 lit) and acetone (1.0 lit) Dried to obtain 146g (yield 86 %) of the title compound as light yellow solid.
Melting point : 187° C

$^1$HNMR (DMSO-$d_6$) : 8 3.78 (3H, s, N-CH$_3$), 3.96 (3H, s, N-OCH$_3$), 7.4 (1H, s, thiazole ring proton), 7.25 (2H, bs, NH$_2$), 13.9 (1H, s, OH)

$^{13}$CNMR (DMSO-$d_6$): 845.6, 64.0, 112.3, 141.0, 144.6, 146.5, 149.3, 159.5, 169.8, 174.4.

Mass spectra : M$^+$ peak = 343

Example - II

7-[[Z]-2-(2-Aminothiazol-4-yl)2-methoxyimino]acetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl]thio]methyl]-3-cephem-4-carboxylic acid disodium hemiheptahydrate (Ceftriaxone sodium).

7-Amino-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]3-cephem-4-carboxylic acid (60g) and 1,2,5,6 tetrahydro-2-methyl-3-thio-5,6 dioxo-1,2,4-triazine-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (I) (92g) were suspended in a mixture of THF (450ml) and H$_2$O (250ml) maintained at 0° - 5°C under stirring. Triethylamine (68.7ml) was added in 2-3 hours at 5°C maintaining the pH 7.5 - 8.5. The reaction progress was monitored by HPLC. After the reaction was complete, the mixture was extracted with ethylacetate (400ml). Sodium-2-ethylhexanoate (55g) was added to the aqueous solution and acetone (1.0 lit) was added in 1 hour at 10-15°C to complete the crystallization. The product was filtered under N$_2$ atmosphere and wet cake was dissolved in mixture of water and acetone (1:2 by volume), and cooled to -10 to -15°C. Coloured impurities were separated. The solution was decanted and diluted with acetone (2500ml) at 18-20°C. Precipitated solid was filtered under N$_2$ and washed with acetone (200ml). Dried under vacuum at 40-45°C to get pure Ceftriaxone sodium, 95g which was once again crystallized in sterile area in water – acetone (1: 4 by volume) mixture to get sterile product. (85 g) (yield = 80%)

HPLC (purity) : 98-99.5%

Example - III

7-[[Z]-2-(2-Aminothiazol-4-yl)2-methoxyimino]acetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl]thio]methyl]-3-cephem-4-carboxylic acid disodium hemiheptahydrate (Ceftriaxone sodium).

7-Amino-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl]thio]methyl]3-cephem-4-carboxylic acid (20.0g) was suspended in dichloromethane (200ml). To this added hexamethyldisilazane (17.0g) and trimethylsilyl chloride
(3.0g). The suspension was refluxed for 2-3 hours to get clear solution. Cooled to 0°C and triethylamine (13.6g) was added slowly. At the same temperature, 1,2,5,6 tetrahydro-2-methyl-3-thio-5,6 dioxo-1,2,4-triazine-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (I) (20g) was added. The reaction mixture was monitored by HPLC. After completion of reaction, 200ml water was added and pH was adjusted to 7.0. The aqueous layer was separated, charcoalized and treated with sodium-2-ethylhexanoate (18.5g) in acetone, reaction was proceeded by same method as mentioned in Ex-II to get final sterile ceftriaxone sodium (28.0g)

Example - IV

3-Acetyloxyethyl-7-[(Z)-(2-aminothiazolyl-4-yl)-2-(methoxyimino) acetamido]-3-cephem-4-carboxylic acid (Cefotaxime sodium).

A mixture of THF (200ml) and water (150ml) was stirred under inert atmosphere. At 0°C - 1°C, 7-aminocephalosporanic acid (25.0g) and 1,2,5,6 tetrahydro-2-methyl-3-thio-5,6 dioxo-1,2,4-triazine-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (I) (39.8g) were added. Triethylamine (10.4g) was slowly added to reaction by maintaining pH 7.5 to 8.5. The reaction was followed by HPLC. After 4-5 hrs., the reaction mixture was extracted by ethylacetate. The aqueous layer is subjected to charcoal (0.125g) treatment. Ethylacetate was added to the filtrate and the solution was acidified with dil. HCl at 10°C to pH 3.0. The solid separated was filtered, washed with water and ethylacetate and then dried under vacuum at 40-45°C to get Cefotaxime, 40.9g (yield 98%). The Cefotaxime acid was dissolved in water at pH 6.5 using sodium carbonate. The solution was filtered through 0.2 micron under aseptic conditions & the product is crystallized by addition of acetone. Yield = 38 g

HPLC (purity)=98 - 99%

Example – V

7-[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino]acetamino]-3-methoxymethyl-3-cephem-4-carboxylic acid [Cefpodoxime acid].

7-Amino-3-methoxymethyl-3-cephem-4-carboxylic acid (24.2g) and 1,2,5,6 tetrahydro-2-methyl-3-thio-5,6 dioxo-1,2,4-triazine-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (I). (35g) were suspended in 400ml of THF and water mixture (1:1). At 10°C Triethylamine (TEA) 9.0gms added to maintain pH 7-8. The reaction was monitored and proceeded as described in example II. To the separated aq. layer, pH was adjusted to 2.7
using 16-18% sulphuric acid. Solid was cooled to 10°C, filtered and washed with water (3x50ml) and finally with acetone (20ml) to obtain the Cefpodoxime acid, 37.5g (yield 88%).

HPLC (purity) : 98.0%

Example - VI

Sodium 7-[[[(Z)-2-(Aminothiazol-4-yl)-2-methoxyimino]acetamido]-3-(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylate (sterile buffered Ceftiofur sodium)

7-Amino-3-[(2-furanylcarbonyl)thiomethyl]-3-cephem-4-carboxylic acid (30.0g, 88.2 mmol) and 2-mercapto-5-phenyl-1,3,4-oxadiazolyl-(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino acetate (47.7g, 132.0 mmol) are added to a mixture of dichloromethane (400ml) and methanol (15ml) at temperature 0-5°C. Triethylamine (25.0ml) is added to the reaction mixture in 50-60 min. After completion of reaction, the reaction mixture is extracted with water (400ml). The aqueous layer is separated and treated with charcoal (0.500g). Tetrahydrofuran (400ml) and 100g of sodium chloride is added to this solution followed by addition of (9.2ml) of hydrochloric acid (35%). The mixture is stirred for 10 min and layers are separated. Tetrahydrofuran layer is treated with charcoal and added to another 75ml solution tetrahydrofuran containing 13.5g of sodium-2-ethylhexanoate under stirring. To this solution slowly tetrahydrofuran(550ml) is added at a temperature of 20°C, white to creamish solid precipitated out in the solution, which is cooled to 0-5°C for 2.0h. Ceftiofur sodium thus prepared is filtered under inert atmosphere, washed with acetone and dried under vacuum to get 36-38g of ceftiofur sodium with HPLC (purity) of 98.0%. The ceftiofur sodium thus prepared is dissolved in water (350ml). The pH of the solution is adjusted to 7.5 by adding sodium bicarbonate. Potassium dihydrogen phosphate(1.0-1.5g) is added, the solution is filtered through a 0.2 micron filter under sterile condition and subjected to lyophilisation to obtain sterile buffered ceftiofur sodium (37-38 g).
CLAIMS

1. Novel derivatives of thiazolyl acetic acid represented by formula (I)

\[
\begin{array}{c}
\text{H}_2\text{N} - \text{S} - \text{S} - \text{N} - \text{OR}_1
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3
\end{array}
\]

wherein, \( R_1 \) represents \( \text{H}, \text{trityl}, \text{CH}_3, \text{CR}_a\text{R}_b\text{COOR}_2 \) (\( R_a \) and \( R_b \) independently of one another represents hydrogen or methyl, \( R_2 \) is hydrogen or \( \text{C}_1\text{-C}_4 \) alkyl)

2. A process of preparing thiazol-4-yl acetic acid derivatives represented by formula (I)

\[
\begin{array}{c}
\text{H}_2\text{N} - \text{S} - \text{S} - \text{N} - \text{OR}_1
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3
\end{array}
\]

wherein, \( R_1 \) is as shown above,

said process comprising the step of condensing thiazol-4-yl acetic acid represented by formula (IV)

\[
\begin{array}{c}
\text{NH}_2
\end{array}
\]

\[
\begin{array}{c}
\text{N} - \text{O} - \text{OH}
\end{array}
\]

\[
\begin{array}{c}
\text{OR}_1
\end{array}
\]

wherein, \( R_1 \) is as shown above,

with 1,2,5,6 tetrahydro-2-methyl-5,6 dioxo-1,2,4-triazin-3-thiol of formula (VI)

\[
\begin{array}{c}
\text{CH}_3
\end{array}
\]

\[
\begin{array}{c}
\text{HS} - \text{N} - \text{NH}
\end{array}
\]

\[
\begin{array}{c}
\text{O}
\end{array}
\]

\[
\text{(VI)}
\]
in the presence of Vilsmeier reagent of formula (V) and in an organic solvent

\[ \text{(V)} \]

at a temperature in the range of \(-10^\circ C\) - \(+30^\circ C\), to obtain thiazol-4-yl acetic acid derivatives represented by formula (I).

3. The process of claim 2 wherein the organic solvent is selected from the group comprising dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetone, acetonitrile, carbon tetrachloride and a mixture thereof.

4. A process of preparing cephalosporin compound of formula (II)

\[ \text{(II)} \]

wherein, \( R_1 \) represents H, trityl, CH\(_3\), CR\(_a\)R\(_b\)COOR\(_2\) (\( R_a \) and \( R_b \) independently of one another represents hydrogen or methyl and \( R_2 \) represents H or C\(_1\)C\(_4\) alkyl),

\( R_3 \) is -CH\(_2\)-, -CH=CH\(_2\)-, -CH\(_2\)OCH\(_3\)-, -CH\(_2\)OCOCH\(_3\)-,

\( R_4 \) is H or a salt or a carboxylic protecting group or an inner salt,

said process comprising the step of acylating the compound of formula (III)

\[ \text{(III)} \]

wherein, \( R_3 \) and \( R_4 \) are as defined above,

\( R_5 \) is H or trimethylsilyl
with a compound of formula (I),

![Chemical structure](image)

wherein, $R_1$ is as defined above,

in the presence of an organic solvent, an organic base and a silylating agent at a temperature in the range of $-10^\circ$C - $+30^\circ$C, to obtain the compound of formula (II).

5. The process of claim 4 wherein $R_4$ is hydrogen or an alkali metal salt or an inner salt.

6. The process of claim 4 wherein the compound of formula II is a syn isomer.

7. The process of claim 4 wherein the organic solvent is selected from the group comprising dichloromethane, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetone, acetonitrile, carbon tetrachloride and a mixture thereof.

8. The process of claim 4 wherein the organic base is selected from the group comprising triethylamine, diethylamine, tributylamine, pyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene, 1,5-diazabicyclo[4.3.0] non-5-ene, N-methyl morpholine and a mixture thereof and the silylating agent of trimethylsilyl.

9. The process of claim 4 wherein $R_5$ is H, the acylation is done in the presence of water and an organic solvent selected from the group consisting of tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide, dioxane, acetonitrile and mixtures thereof.

10. The process of claim 4 wherein $R_5$ is trimethylsilyl, the acylation is achieved by doing the reaction in an aprotic organic solvent selected from halogenated hydrocarbon, toluene, alkyl ether, acetonitrile and a mixture thereof.
11. The process of claim 4 wherein said acylation is performed in the presence of an organic base selected from the group consisting of triethylamine, N-methylmorpholine, N-methylpipridine, N-methylanilines, 1,5-diazabiclo[4.3.0]non-5-ene, 1,4-diazabiclo[2.2.2]octane, 4-dimethylaminopyridine and mixtures thereof.

12. The process of claim 4 wherein R₁ is methyl, R₃ is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, purification of this compound is achieved by dissolving the crude product in a mixture of water and water miscible organic solvent selected from the group consisting of acetone, isopropylalcohol, dioxane and a mixture thereof.

13. The process of claim 4 wherein R₁ is methyl, R₃ is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, the colour impurities are separated at a temperature ranging between -10⁰C and 0⁰C and precipitation is effected by water miscible organic solvent selected from the group consisting of acetone, isopropylalcohol, dioxane and a mixture thereof.
WE CLAIM

1. A process for preparing a compound of formula (II)

\[
\text{NH}_2 \quad \begin{array}{c}
\text{S} \\
\text{N} \end{array} \quad \text{O} \quad \begin{array}{c}
\text{N} \\
\text{H} \end{array} \quad \text{NH} \quad \begin{array}{c}
\text{S} \\
\text{O} \end{array} \quad \begin{array}{c}
\text{N} \\
\text{H} \end{array}
\]

\begin{array}{c}
\text{R}_1 \\
\text{R}_2 \\
\text{R}_3 \\
\text{R}_4 \\
\text{R}_5
\end{array}

wherein, \( R_1 \) represents H, trityl, CH\(_3\), CR\(_a\)R\(_b\)COOR\(_2\) (\( R_a \) and \( R_b \) independently of one another represents hydrogen or methyl and \( R_2 \) represents H or C\(_1\)-C\(_4\) alkyl); \( R_3 \) is CH\(_3\), -CH=CH\(_2\), CH\(_2\)OCH\(_3\), CH\(_2\)OCOCH\(_3\),

\[
\begin{array}{c}
\text{CH}_2 \quad \text{N} \\
\text{C}_6 \text{H}_{5}
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_2 \quad \text{S} \quad \text{O} \\
\text{C}_5 \text{H}_4
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_2 \quad \text{S} \\
\text{N} \quad \text{N} \quad \text{OH}
\end{array}
\]

\[
\begin{array}{c}
\text{R}_4 \quad \text{H}_2
\end{array}
\]

\( R_4 \) is H or a salt or a carboxylic protecting group or an inner salt, comprising acylating a compound of formula (III)

\[
\text{R}_5 \quad \text{NH} \quad \begin{array}{c}
\text{S} \\
\text{O} \end{array} \quad \text{R}_3 \quad \text{COOR}_4
\]

wherein, \( R_5 \) is H or trimethylsilyl; \( R_3 \) and \( R_4 \) are defined as above with a compound of formula (I)
wherein R₁ is as defined above, in the presence of an organic solvent and a base at a temperature in the range of -10°C to +30°C.

2. The process of claim 1, wherein R₄ is hydrogen or alkali metal salt or an inner salt.

3. The process of claim 1, wherein said compound of formula (II) is a syn isomer.

4. The process of claim 1, wherein when R₃ is H, the acylation is carried out in the presence of water and an organic solvent selected from the group consisting of tetrahydrofuran, N,N-dimethylformamide, dioxane, acetone, acetonitrile or mixtures thereof.

5. The process of claim 1, wherein when R₃ is trimethylsilyl, the acylation is achieved by performing the reaction in aprotic organic solvent selected from halogenated hydrocarbon, toluene, alkyl ether, acetonitrile or mixtures thereof.

6. The process of claim 1, wherein said acylation is performed in the presence of an organic base selected from the group consisting of triethylamine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylamino pyridine, diethylamine, tributylamine, pyridine, N-alkylpyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene or mixtures thereof.
7. The process of claim 6, wherein when R₁ is methyl, R₃ is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, purification of this compound is achieved by dissolving the crude product in mixture of water and water miscible organic solvent selected from acetone, isopropylalcohol, dioxane or mixtures thereof.

8. The process of claim 6, wherein when R₁ is methyl, R₃ is (2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl, the coloured impurities are separated at -10°C to 0°C and precipitation is effected by water miscible organic solvent selected from acetone, isopropylalcohol, dioxane or mixtures thereof.

9. A process according to claim 1, wherein the compound of formula (I)

![Chemical Structure](image)

wherein R₁ represents H, trityl, CH₃, CR₆R₆COOR₂ (R₆ and R₆ independently of one another represents hydrogen or methyl and R₂ represents H or C₁-C₆ alkyl), is prepared by a process which comprises condensation of thiazol-4-yl acetic acid represented by formula (IV).

![Chemical Structure](image)
with 1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-thiol of formula (VI)

\[
\text{HS} - \text{N} - \text{N} - \text{NH} - \text{O} - \text{O} \quad \text{(VI)}
\]

in presence of Vilsmeier reagent of the formula (V)

\[
\{(\text{CH}_3)_2\text{N}=\text{CH-O-P(O)Cl}_2\}^+ \text{Cl}^- \quad \text{(V)}
\]
in an organic solvent and a base at a temperature in the range of -10°C to +30°C.

10. The process of claim 9, wherein the organic solvent is selected from dichloromethane, toluene, tetrahydrofuran, dioxane, N,N-dimethylformamide, acetone, acetonitrile or mixtures thereof.

11. The process of claim 9, wherein the base is selected from the group consisting of triethylamine, N-methylmorpholine, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 4-dimethylamino pyridine, diethylamine, tributylamine, pyridine, N-alkylpyridine, N-alkylanilines, 1,8-diazabicyclo[5.4.2]undec-7-ene or mixtures thereof.

12. The process of claim 9, wherein the Vilsmeier reagent of formula (V) used is a condensing agent.

\[
\{(\text{CH}_3)_2\text{N}=\text{CH-O-P(O)Cl}_2\}^+ \text{Cl}^- \quad \text{(V)}
\]
Statement under Article 19 (1)

The present invention provides a new process for the preparation of thiazol-4-yl acetic acid derivative of formula (I) using a Vilsmeier reagent as a condensing agent, the thiazol-4-yl acetic acid derivative thus obtained is used in the preparation of cephalosporin compounds of formula (II).
**INTERNATIONAL SEARCH REPORT**

**CLASSIFICATION OF SUBJECT MATTER**

**IPC**: C07D 417/12, 501/04, 501/20

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**: C07D

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

**AT patent documents**

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

**REGISTRY and CAPLUS Databases, STN-International; WPI, EPO and PAJ Databases INTERNET**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>GB 2068957 A (RHONE-POULENCE INDUSTRIES) 19 August 1981 (19.08.81) the whole document.</td>
<td>1,4-13</td>
</tr>
<tr>
<td>A</td>
<td>the whole document.</td>
<td>2,3</td>
</tr>
</tbody>
</table>

**Further documents are listed in the continuation of Box C.**

**See patent family 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**

13 May 2002 (13.05.2002)

**Date of mailing of the international search report**

10 June 2002 (10.06.2002)

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**Authorized officer**

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