



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) **EP 1 390 373 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

Note: Bibliography reflects the latest situation

(15) Correction information:
Corrected version no 2 (W2 B1)
Corrections, see page(s) 3

(48) Corrigendum issued on:
16.08.2006 Bulletin 2006/33

(45) Date of publication and mention
of the grant of the patent:
14.12.2005 Bulletin 2005/50

(21) Application number: **02736468.6**

(22) Date of filing: **08.05.2002**

(51) Int Cl.:
C07F 9/38 (1968.09)

(86) International application number:
PCT/TR2002/000018

(87) International publication number:
WO 2002/090367 (14.11.2002 Gazette 2002/46)

(54) **PROCESS FOR THE PREPARATION OF 4-AMINO-1-HYDROXYBUTYLIDENE-1, 1-BIPHOSPHONIC ACID**

VERFAHREN ZUR HERSTELLUNG VON 4-AMINO-1-HYDROXYBUTYLIDEN-1,1-BISPHOSPHONSÄURE

PROCEDE DE PREPARATION D'ACIDE 4-AMINO-1-HYDROXYBUTYLIDENE-1, 1-BIPHOSPHONIQUE

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU
MC NL PT SE TR**

(30) Priority: **10.05.2001 TR 200101250**

(43) Date of publication of application:
25.02.2004 Bulletin 2004/09

(73) Proprietor: **EOS Eczacibasi Ozgun Kimyasal
Urunler Sanayi Ve Ti
Caret A.S.
80640 Istanbul (TR)**

(72) Inventors:
• **DABAK, Kadir,
Buyukdere Caddesi
80640 Istanbul (TR)**

- **OZARSLAN, A., Evren,
Buyukdere Caddesi
80640 Istanbul (TR)**
- **SAHBAZ, Filiz,
Buyukdere Caddesi
80640 Istanbul (TR)**
- **ASLAN, Tuncer,
Buyukdere Caddesi
80640 Istanbul (TR)**

(74) Representative: **Sevinç, Erkan et al
Istanbul Patent & Trademark Consultancy Ltd.
Plaza-33, Buyukdere cad. No: 33/16
Sisli
34381 Istanbul (TR)**

(56) References cited:
WO-A-98/34940 US-A- 4 922 007

EP 1 390 373 B9

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

[0001] Process for the preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid or salts thereof

[0002] This invention is related with the preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid or salts thereof. The reaction of 4-aminobutyric acid with phosphorous acid and phosphorus trichloride in the presence of aralkyl or alkyl ethoxylates or triglycerides such as plant or animal oils or their derivatives and recovering of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid or salts thereof are described.

[0003] 4-Amino-1-hydroxybutylidene-1,1-biphosphonic acid monosodium salt trihydrate is used for treatment or prevent of diseases involving bone disorders, such as hypercalcemia of malignancy, Paget's disease and osteoporosis.

[0004] 4-Amino-1-hydroxybutylidene-1,1-biphosphonic acid or salts thereof are prepared basically by the reaction of 4-aminobutyric acid with a mixture of phosphorous acid and one of the three phosphorus chlorides; phosphorous trichloride, phosphorous oxychloride or phosphorous pentachloride and then quenching the reaction mixture with water followed by heating to hydrolyse the phosphorous intermediates.

[0005] Several patented methods can be found in the literature for the preparation of ω -amino-1-hydroxyalkylidene-1,1-bisphosphonic acids and especially for 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid and salts thereof. In U.S. Patent 4,407,761 (Blom et al.) the preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid besides other bisphosphonic acids are described. When using this procedure, a semisolid sticky non-stirrable mass develops which prevents smooth heat transfer. The described process might be suitable for laboratory preparations, however for industrial production it is not acceptable. In U.S. Patent 4,705,651 (Staibano, G.), a similar procedure is followed with different molar ratios and although some improvements were achieved, it is still unsuitable for industrial scale up.

[0006] Kieczkowski et al. (In U.S. Patents 4,922,007; 5,019,651 and J. Org. Chem. 1995, 60, 8310-8312) reported that the solidification problem has been solved. Methanesulfonic acid was used to solubilize the reaction components and keep them fluid throughout. By the use of methanesulfonic acid, the fluidity problems were solved however another serious safety problem surfaced. A reaction between methanesulfonic acid and phosphorus trichloride is exothermic and at certain point becomes uncontrollable.

[0007] WO-A-98/34940 describes a similar process with non-aromatic ethers.

[0008] U.S. Patent 5,908,959 (Kubela et al.) also describes the preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid or salts thereof. The reaction is carried out in poly(alkylene glycol) as a diluent, which solubilizes the reaction components, however still when the reaction mixture is decomposed with water, an agitation problem occurs. The viscous reaction mixture must be transferred into the water. To facilitate this, viscosity problem is solved by the addition of toluene. When using toluene, a safety problem arises and also an additional separation step is needed.

[0009] In the present invention; by the use of aralkyl or alkyl ethoxylates or triglycerides such as plant or animal oils or their derivatives as emulgators, the solidification and the safety problems are solved in a cheaper, safer and easily accessible way without any need of an additional solvent. These emulgators solubilize the reaction components and do not react with the reactants to cause any uncontrolled reactions. It has been found that 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid or its salts can be obtained in a safe and high yielded way without an additional purification step.

[0010] Aralkyl or alkyl ethoxylates or their derivatives are used very often in the textile, leather and metal industries as emulgators. Triglycerides such as plant or animal oils are also used very often in the food and lubricant industries. These emulgators are easily accessible, readily available and non-expensive.

[0011] The reaction of 4-aminobutyric acid with phosphorous acid and phosphorus trichloride in the presence of one of these emulgators at a suitable temperature such as between about 40 °C and about 150 °C; and hydrolysing the phosphorous intermediates by heating the reaction mixture in the presence of water and recovering of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid or salts thereof are described.

[0012] Aralkyl or alkyl ethoxylates or their derivatives may be selected from the general formula of $R-X-O-(CH_2CH_2O)_n-H$; and triglycerides might be selected from the general formula of $(RCO_2CH_2)_2CHOCOR$ wherein R represents branched or non-branched alkyl groups which contain 1 to 20 carbon atoms, X represents phenyl or naphthyl or $-CH_2-$ groups and; n is a number of between 1 and about 30.

[0013] The main feature of the invention is in the use of the above defined emulsifiers or derivatives thereof in the phosphorylation reaction. These compounds keep the mixture in homogenous form and can be separated easily from the product at the end of the reaction and can be reused. The hydrolysis of the formed phosphorous intermediates can be completed in the same reaction mixture and if desired, by adjusting the pH to about 4.3, the sodium salt of the said biphosphonic acid can be directly obtained and isolated in a pure form.

[0014] The 4-aminobutyric acid and the phosphorous acid are suspended in one of the mentioned emulgators and reacted with phosphorus trichloride at a suitable temperature for example between about 40 °C and about 150 °C, preferably at about 10 °C. The phosphorylation reaction is completed in about 3 hours at this temperature. The preferred ratio of the amino acid to phosphorous acid and to phosphorous trichloride is about 1:1:2.

[0015] As example of aralkyl or alkyl ethoxylates or their derivatives, which can be applied, are nonylphenol with 4 mol, 6 mol or 10 mol ethoxylate; and alkyl ethoxylates such as lauryl alcohol of different ethoxylate numbers. And as

example of triglycerids are sunflower oil, olive oil and corn oil, which are glyceride of oleic acid, palmitic acid, linoleic acid, stearic acid, myristic acid, behenic acid and arachidic acid in different ratios.

[0016] The reaction can be shown schematically as follows:

see Fig. 1.

[0017] Wherein R represents branched or non-branched alkyl groups which contain 1 to 20 carbon atoms, X represents phenyl or naphthyl or $-CH_2-$ groups and; n is a number of between 1 and about 30.

The following examples are introduced the practical procedures and the results without any limitations in any subject.

EXAMPLE 1

Preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid Monosodium Salt Trihydrate in Nonylphenol Ethoxylate 4 Mol (NP4) (or in Nonylphenol Ethoxylate 6 Mol)

[0018] A 2-L flask charged with 500 mL of NP 4 (or Nonylphenol Ethoxylate 6 Mol), 75.4 g (0.73 mol) of 4-aminobutyric acid and 60 g (0.73 mol) of phosphorous acid in room temperature. The system was connected to a caustic scrubber and flushed with nitrogen. After 15 minutes of stirring, 132 mL of phosphorous trichloride was added by dropwise addition over a period of 30 minutes. Then the reaction mixture was stirred at 70 °C for 4 hours. After 4 hours, the mixture was cooled to 20 °C, then 300 mL of water was added by dropwise addition over a period of 30 minutes. After completion of the addition of the water, the reaction mixture was heated at 105 °C for 4 hours, then cooled to 20 °C. The stirring was discontinued to allow the layers separate, the lower aqueous layer was separated and the pH of this solution was adjusted to 4.3 with 50% NaOH. After stirring for 13 hours, 50 mL of acetone was added and stirred for 1 hr, then the crystalline product was collected by filtration, washed with 100 mL of ice cold water and 100 mL of acetone and dried at room temperature. The yield of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid monosodium salt trihydrate was 136.5 g (57.4 %). The analysis confirmed the identity of the product and the absence of impurities.

³²P-NMR, ¹H-NMR and ¹³C-NMR analyses were recorded on a Varian Mercury 300 MHz instrument. ³¹P-NMR (D₂O), 18.794 (s); ¹³C-NMR (D₂O), 30.68 (t), 40.07(t), 73.59 (s); ¹H-NMR (D₂O), 1.84 (4H, m), 2.87 (2H, m).

EXAMPLE 2

Preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid Monosodium Salt Trihydrate in Nonylphenol Ethoxylate 10 Mol

[0019] Instead of NP4, NP10 was used as a solvent and a procedure was followed as described in Example 1 until 4-hour hydrolysis at about 110 °C and cooling to room temperature. Then pH of all the reaction mixture (because two phases were not formed at this point as described in example 1.) was adjusted to 4.3 and then two phases were formed. The lower phase was separated, after stirring for 13 hours, 50 mL of acetone was added and stirred for 1 hr. Precipitated crystalline product was collected by filtration, washed with 100 mL of ice cold water, 100 mL of acetone and dried at room temperature. The analysis confirmed the identity of the product and the absence of impurities. The yield of 4-amino-1-hydroxybutylidene-1,1-biphosphonic acid monosodium salt trihydrate was 58%.

EXAMPLE 3

Preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid in Nonylphenol Ethoxylate 4 Mol (or in Nonylphenol Ethoxylate 6 Mol)

[0020] A procedure was followed as described in Example 1 until 4-hour hydrolysis at about 110 °C and cooling to room temperature. Then stirring was discontinued to allow the layers separate, the lower aqueous layer was separated and 500 mL of acetone was added and stirred. The product firstly was separated as in oil form then was crystallised after 10 minutes stirring. The crystalline product was collected by filtration, washed with 100 mL of ice cold water and 100 mL of acetone and dried at room temperature. The yield of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid was 60 %. 1 L of acetone was added to the upper layer and the yield was increased from 60 to 65% by the filtration of precipitated product however since this second precept was not as pure as the first one, it needs an additional crystallisation. The analysis confirmed the identity of the product and the absence of impurities.

EXAMPLE 4

Preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid in Nonylphenol Ethoxylate 10 Mol

5 **[0021]** Instead of NP4, NP 10 was used as a solvent and a procedure was followed as described in Example 1 until 4-hour hydrolysis at about 110°C and cooling to room temperature. Then 1,5 L of acetone was added and stirred, the product firstly was separated as in oil form then was crystallised after 10 minutes stirring. The crystalline product was collected by filtration, washed with 250 mL of ice cold water and 250 mL of acetone and dried at room temperature. The yield of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid was 60 %. The analysis confirmed the identity of the product and the absence of impurities.

EXAMPLE 5

15 Preparation of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid Monosodium Salt Trihydrate in Lauryl alcohol Ethoxylate 6 Mol

[0022] Instead of NP4, lauryl alcohol Ethoxylate 6 Mol was used and an experiment was carried out same as it was described in Example 1. The yield of 4-amino-1-hydroxybutylidene-1,1-biphosphonic Acid Monosodium Salt Trihydrate was (59 %). The analysis confirmed the identity of the product and the absence of impurities.

EXAMPLE 6

Preparation of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate by using sunflower oil.

25 **[0023]** A 3 L flask was equipped with a mechanical stirrer, thermometer, condenser, and an addition funnel. The system was connected to a caustic scrubber and flushed with nitrogen. The flask was charged with 500 mL of sunflower oil. The temperature was brought to 75 °C. At this temperature 100 g (0.97 mol) of 4-aminobutyric acid and 79.5 g (0.97 mol) of phosphorous acid were added. The mixture was stirred for 15 minutes. Phosphorous trichloride 130 mL (1.45 mol) was added to this solution in 20 minutes by keeping the internal temperature between 70 to 75 °C. The mixture was stirred at this temperature for 3 hours and then 500 mL of water was added in portions. The mixture is stirred for 10 minutes, and transferred into a separatory funnel and separated. The aqueous phase was heated at 105 °C for 6 hours. The pH of the solution was brought to 4.3 by adding 50% NaOH. The solution was concentrated half of its volume (250 mL) and stirred for 12 hours at 25 °C. The product was collected by filtration washed with 25 mL of cold water, air dried at 25 °C to give 135 g of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate as a white solid in 43% yield. After completion of the reaction, the structure of the sunflower oil was checked by ¹H-NMR and ¹³C-NMR and no change was observed. This result showed that the oil can be reused.

EXAMPLE 7

40 Preparation of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate by using recovered sunflower oil.

[0024] A 1 L flask was equipped with a mechanical stirrer, thermometer, condenser, and an addition funnel. The system was connected to a caustic scrubber and flushed with nitrogen. The flask was charged with 100 mL of recovered sunflower oil obtained from example 1. The temperature was brought to 75 °C. At this temperature, 20 g (0.19 mol) of 4-aminobutyric acid and 15.9 g (0.19 mol) of phosphorous acid were added. The mixture was stirred for 15 minutes. Phosphorous trichloride 26 mL (0.29 mol) was added to this solution in 10 minutes by keeping the internal temperature between 70 °C to 75 °C. The mixture was stirred at this temperature for 3 hours and then 100 mL of water was added in portions. The mixture is stirred for 5 minutes, and transferred into a separatory funnel. The phases were separated. The aqueous phase was taken and stirred at 105 °C for 6. hours. The pH of the solution was brought to 4.3 by adding 50% NaOH. The solution was stirred for 12 hours 25 °C. The product was collected by filtration, washed with 25 mL of cold water, air dried at 25 °C to give 26.3 g of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate as a white solid in 42% yield.

EXAMPLE 8

Preparation of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate by using sunflower oil without separation of the phases before hydrolysis.

[0025] A 500 mL flask was equipped with a mechanical stirrer, thermometer, condenser, and an addition funnel. The system was connected to a caustic scrubber and flushed with nitrogen. The flask was charged with 50 mL of sunflower oil. The temperature was brought to 75 °C. At this temperature 10 g (0.097 mol) of 4-aminobutyric acid and 7.95 g (0.097 mol) of phosphorous acid were added. The mixture was stirred for 15 minutes. Phosphorous trichloride 13 mL (0.145 mol) was added to this solution in 5 minutes by keeping the internal temperature between 70 to 75 °C. The mixture was stirred for 3 hours at this temperature and then 50 mL of water was added. The two phases system was stirred at 105 °C for 6 hours and then transferred into a separatory funnel. The aqueous phase was taken. The pH of the solution was brought to 4.3 by adding 50% NaOH. Acetone 25 mL was added to the solution and stirred for 12 hours 25 °C. The product was collected by filtration washed with 25 mL of cold water, air dried at 25°C to give 13.2.g of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate as a white solid in 43% yield. The structure of the oil used in this reaction was checked by ¹H-NMR, the spectra showed some hydrolysis of the triglycerides under reflux condition.

EXAMPLE 9

Preparation of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate by using olive oil.

[0026] Instead of sunflower oil, olive oil was used as a solvent. The reaction was carried out with a 10 g scale following the procedure described in example 1. After filtration, 9 g of 4-Amino-1-hydroxybutylidene-1, 1-bisphosphonic acid monosodium salt trihydrate was obtained as a white solid in 36% yield..

Claims

1. A process for preparation of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof, comprising the steps of:
 - (a) reacting 4-aminobutyric acid with phosphorous acid and phosphorous trichloride in the presence of aralkyl or alkyl ethoxylates or derivatives thereof having the general formula of $R-X-O-(CH_2CH_2O)_n-H$, or in the presence of triglycerides selected from the group consisting of plant oils, animal oils or their derivatives, having the general formula of $(RCO_2CH_2)_2CHOCOR$, wherein R represents branched or non-branched alkyl or alkenyl groups which contain 1 to 20 carbon atoms, X represents phenyl or naphthyl or $-CH_2-$ and n is a number between 1 and 30, and
 - (b) recovering said 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof by the hydrolysis reaction of phosphorous intermediates.
2. The process of Claim 1 wherein the reaction is carried out in the presence of ethoxylates or triglycerides in which $R = C_4-C_{19}$ alkyl or alkenyl, $X =$ phenyl or $-CH_2-$, and $n = 4-30$.
3. The process of Claim 2 wherein the reaction is carried out at a temperature from 40 °C to 150 °C.
4. The process of Claim 2 wherein the reaction is conducted in the presence of ethoxylates in which $R = C_9$, $X =$ phenyl and $n = 4-10$ where the compounds are nonylphenol with 4 mol, 6 mol or 10 mol ethoxylate.
5. The process of Claim 2 wherein the reaction is conducted in the presence of ethoxylates in which $R = C_{11}$, $X = CH_2$ and $n = 6$ where the compound is lauryl alcohol with 6 mol ethoxylate.
6. The process of Claim 2 wherein the reaction is conducted in the presence of triglycerides in which $R = C_{12}-C_{20}$ containing one or more double bonds where the compounds are sunflower oil, olive oil or corn oil.
7. The process of Claim 4, 5 or 6 wherein the temperature is substantially around 70 °C.
8. The process of Claim 4, 5 or 6 wherein 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid or salts thereof are

recovered.

Patentansprüche

1. Verfahren zur Herstellung von 4-Amino-1-hydroxybutyriden-1,1-diphosphonsäure oder deren Salze, umfassend die Schritte:

a) Umsetzen von 4-Aminobuttersäure mit phosphoriger Säure und Phosphortrichlorid in Gegenwart von Aralkyl- oder Alkyl-Ethoxylaten oder Derivate davon mit der allgemeinen Formel $R-X-O-(CH_2CH_2O)_n-H$ oder in Gegenwart von Triglyceriden, gewählt aus der Gruppe bestehend aus Pflanzenölen, Tierölen oder deren Derivaten, mit der allgemeinen Formel $(RCO_2CH_2)_2CHOCOR$, worin R für verzweigte oder nicht-verzweigte Alkyl- oder Alkenyl-Gruppen steht, die 1 bis 20 Kohlenstoffatome enthalten, X für Phenyl oder Naphthyl oder $-CH_2-$ steht und n für eine Zahl zwischen 1 und 30 steht, und

b) Gewinnen der 4-Amino-1-hydroxybutyriden-1,1-diphosphonsäure oder deren Salze durch Hydrolysereaktion von Phosphor-Zwischenprodukten.

2. Verfahren gemäß Anspruch 1, worin die Reaktion in Gegenwart von Ethoxylaten oder Triglyceriden durchgeführt wird, in denen $R = C_4 - C_{19}$ Alkyl oder Alkenyl, $X = \text{Phenyl}$ oder $-CH_2-$ und $n = 4 - 30$.

3. Verfahren gemäß Anspruch 2, worin die Reaktion bei einer Temperatur von 40 bis 150°C durchgeführt wird.

4. Verfahren gemäß Anspruch 2, worin die Reaktion in Gegenwart von Ethoxylaten durchgeführt wird, in denen $R = C_9$, $X = \text{Phenyl}$ und $n = 4 - 10$, wobei es sich bei den Verbindungen um Nonylphenol mit 4 Mol, 6 Mol oder 10 Mol Ethoxylat handelt.

5. Verfahren gemäß Anspruch 2, wobei die Reaktion in Gegenwart von Ethoxylaten durchgeführt wird, in denen $R = C_{11}$, $X = CH_2$ und $n = 6$, wobei es sich bei der Verbindung um Laurylalkohol mit 6 Mol Ethoxylat handelt.

6. Verfahren gemäß Anspruch 2, wobei die Reaktion in Gegenwart von Triglyceriden durchgeführt wird, in denen $R = C_{12} - C_{20}$, enthaltend eine oder mehrere Doppelbindungen, wobei es sich bei den Verbindungen um Sonnenblumenöl, Olivenöl oder Maiskeimöl handelt.

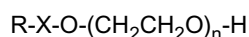
7. Verfahren gemäß Anspruch 4, 5 oder 6, wobei die Temperatur im wesentlichen bei 70°C ist.

8. Verfahren gemäß Anspruch 4, 5 oder 6, wobei 4-Amino-1-hydroxybutyriden-1,1-diphosphonsäure oder deren Salze gewonnen werden.

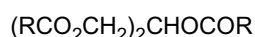
Revendications

1. Procédé de préparation de l'acide 4-amino-1-hydroxy-butylidène-1,1-diphosphonique ou de sels de cet acide, lequel procédé comporte les étapes suivantes :

a) faire réagir de l'acide 4-aminobutyrique avec de l'acide phosphoreux et du trichlorure de phosphore, en présence d'éthoxylates d'aralkyle ou d'alkyle ou de dérivés de tels composés, de formule générale:



ou en présence de triglycérides choisis parmi les huiles végétales, les huiles animales et leurs dérivés, de formule générale :

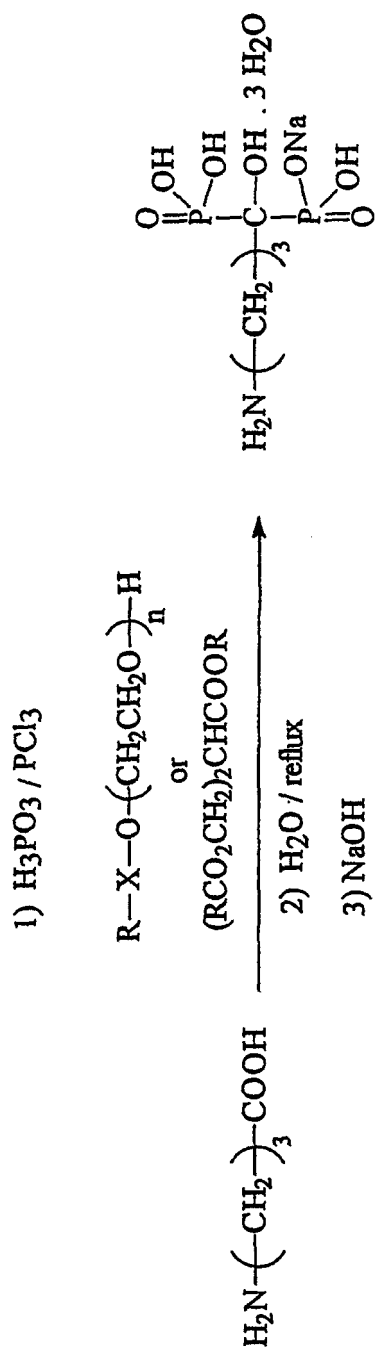


dans lesquelles formules R représente un groupe alkyle ou alcényle, ramifié ou non et comportant 1 à 20 atomes de carbone, X représente un groupe phénylène, naphtylène ou méthylène, et n représente un nombre valant de 1 à 30,

b) et le fait de récupérer ledit acide 4-amino-1-hydroxybutylidène-1,1-di-phosphonique ou un sel de cet acide,

par hydrolyse des intermédiaires phosphorés.

2. Procédé conforme à la revendication 1, dans lequel on effectue la réaction en présence d'éthoxylates ou de triglycérides chez lesquels R représente un groupe alkyle ou alcényle en C₄₋₁₉, X représente un groupe phényle ou méthylène, et n vaut de 4 à 30.
3. Procédé conforme à la revendication 2, dans lequel on effectue la réaction à une température de 40 à 150 °C.
4. Procédé conforme à la revendication 2, dans lequel on effectue la réaction en présence des éthoxylates chez lesquels R représente un groupe en C₉, X représente un groupe phényle et n vaut de 4 à 10, ces composés étant du nonylphénol tétraéthoxylé, hexaéthoxylé ou décaéthoxylé.
5. Procédé conforme à la revendication 2, dans lequel on effectue la réaction en présence de l'éthoxylate chez lequel R représente un groupe en C₁₁, X représente un groupe méthylène et n vaut 6, ce composé étant de l'alcool laurylique hexaéthoxylé.
6. Procédé conforme à la revendication 2, dans lequel on effectue la réaction en présence des tricyclérides chez lesquels R représente un groupe en C₁₂₋₂₀ comportant une ou plusieurs doubles liaisons, ces composés étant de l'huile de tournesol, de l'huile d'olive ou de l'huile de maïs.
7. Procédé conforme à la revendication 4, 5 ou 6, dans lequel la température vaut pratiquement à peu près 70 °C.
8. Procédé conforme à la revendication 4, 5 ou 6, dans lequel on récupère de l'acide 4-amino-1-hydroxy-butylidène-1,1-diphosphonique ou un sel de cet acide.



SCHEME