(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 November 2003 (13.11.2003)

PCT

(10) International Publication Number
WO 03/093282 A1

(51) International Patent Classification[7]: C07F 9/38, 9/58, 9/6506

(21) International Application Number: PCT/IB02/04941

(22) International Filing Date:
25 November 2002 (25.11.2002)

(25) Filing Language: Italian

(26) Publication Language: English

(30) Priority Data:
MI2002A000908 29 April 2002 (29.04.2002) IT

(71) Applicant *(for all designated States except US)*: **CHEMI S.P.A.** [IT/IT]; Via dei Lavoratori, 54, I-20092 Cinisello Balsamo (IT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **DE FERRA, Lorenzo** [IT/IT]; Viale delle Province, 6, I-00162 Roma (IT). **TURCHETTA, Stefano** [IT/IT]; Piazza Vinci, 13, I-00139 Roma (IT). **MASSARDO, Pietro** [IT/IT]; Via O. Beccari, 24, I-00154 Roma (IT). **CASELLATO, Paolo** [IT/IT]; Viale del Vignola, 73, I-00196 Roma (IT).

(74) Agent: **GERVASI, Gemma**; c/o Notarbartolo & Gervasi, Corso di Porta Vittoria, 9, I-20122 Milan (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/093282 A1

(54) Title: PREPARATION OF BIPHOSPHONIC ACIDS AND SALTS THEREOF

(57) Abstract: A process for preparing bisphosphonic acids, characterized in that the reaction of synthesis is conducted in a reaction consisting of bisphosphonic acids.

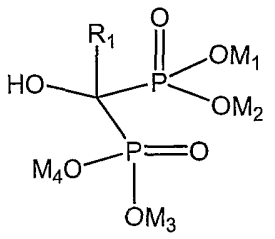
PREPARATION OF BIPHOSPHONIC ACIDS AND SALTS THEREOF

Field of the invention

The present invention relates to a process for preparing bisphosphonic acids and their pharmacologically active salts.

State of the art

The bisphosphonic acids and their salts, which form the subject of the present patent application are compounds described by the following structural formula:

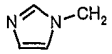
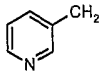
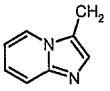
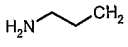
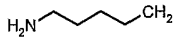
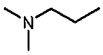
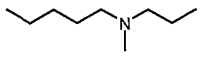


(1)

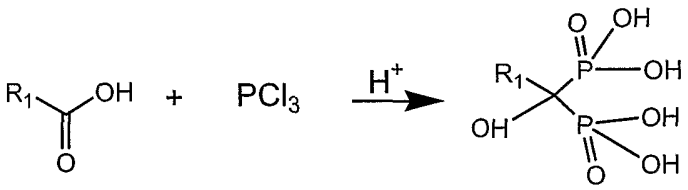
in which M_1, M_2, M_3, M_4 are selected from H, and a monovalent cation.

Belonging to this class of molecules are the following compounds used in the treatment of osteoporosis (see Table 1) according to the different meaning that R_1 may assume.

TABLE 1:

R_1= CH3,	Etidronic acid
R_1= 	Zoledronic acid
R_1 = 	Risedronic acid
R_1= 	Minodronic acid
R_1= 	Pamidronic acid
R_1 = 	Alendronic acid
R_1= 	Neridronic acid
R_1= 	Olpadronic acid
R_1 = 	Ibandronic acid

As regards the methods of synthesis, these compounds are synthesized starting from the corresponding carboxylic acid according to the synthetic scheme appearing in Diagram 1



Starting from the acid, by subsequent salification of the acid protons, the various salts may be obtained.

A problem that is commonly encountered in the preparation of these compounds is the formation, during the reaction, of very dense unstirrable masses, which render the industrial synthesis of these substances problematical.

In the literature various documents have been published which describe techniques of synthesis of the compounds listed in Table 1.

US4621077, which regards alendronic acid and neridronic acid, describes the use of chlorobenzene as the solvent in the synthesis. The application of this technique leads to obtaining solid and unstirrable masses in the course of the reaction. A

series of other patents (US4407761, US4327039, US4304734, US4267108, US4054598) envisages the use of chlorobenzene as reaction solvent, but also in these cases the drawback described above is again met with.

US4922007, US5019651 and US5510517, as well as J. Org. Chem. 60, 8310, (1995), envisage the use of methanesulphonic acid as reaction solvent. This makes it possible to obtain stirrable masses in the course of the reaction. However, this technique, as reported in J. Org. Chem. 60, 8310, (1995), involves risks of safety in that this solvent gives rise to uncontrollable reactions in the reaction conditions, when the temperature of the reacting mixtures exceeds 85°C.

WO9834940 employs polyalkylene glycols as reaction solvents for synthesizing alendronic acid; however, these solvents have a high cost and are difficult to eliminate from the finished product, given their high boiling point

In WO0049026, starting from a nitrogen-protected derivative of β-aminopropionic acid to prevent the known problems of stirrability of the reaction mixture, use is made of orthophosphoric acid as the reaction means. The derivatization of the starting product in any case renders the method of synthesis unwieldy and involves the need for introducing additional steps for protection and deprotection.

US5792885 synthesizes pamidronic acid starting from a nitrogen-protected derivative of γ-aminobutyric acid, in aromatic hydrocarbons as the reaction solvents. This method presents the same drawbacks illustrated for the method described in WO0049026.

WO0110874 regards the use of methanesulphonic anhydride as the solvent for producing alendronic acid, but the high cost of the solvent renders the method difficult to apply at an industrial level.

Technical problem

The need was thus felt to have available a general process for preparing the compounds described in Table 1 which would not present the drawbacks of the processes known to the art.

Summary of the invention

The present applicant has now unexpectedly found that, using as the reaction solvents in the synthesis of the compounds described in Diagram 1 the so-called ionic liquids, it is possible to convert the raw materials into the desired products,

avoiding the drawbacks of the processes known to the prior art.

In addition, the solvent used is economically advantageous and easy to recover and recycle.

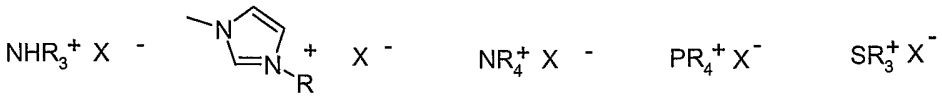
Consequently, forming the subject of the present invention are processes for preparing the active principles described in Table 1, comprising the reaction of the appropriate raw materials with phosphorous acid and phosphorus trichloride, subsequent treatment with acid water and possible final treatment with an aqueous solution of a hydroxide of an alkaline metal, characterized in that the reaction is conducted in ionic liquids at a temperature of between 15°C and 120°C.

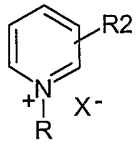
Detailed description of the invention

M_1-M_4 are preferably selected from the cations of the alkaline metals, H, cations of aliphatic or cyclolaliphatic amines, and more preferably are sodium and/or H.

The temperature at which the aforesaid ionic solvents are liquid is preferably between 20°C and 100°C. By liquid ionic solvents are meant the -onium salts selected from the group consisting of ammonium, sulphonium or phosphonium salts.

Possible examples of said solvents are given below:





in which each R may be independently H, a linear or branched C_1-C_{20} alkyl group, a cycloalkyl containing from 5 to 6 carbon atoms, alkylene aryl, or aryl; R_2 is H or a linear or branched C_1-C_{18} alkyl group, X^- is an anion selected from the group consisting of halogenide, BF_4^-, PF_6^-, or $AlCl_4^-$. Particularly preferred is tributylammonium chloride, which melts at approximately 60°C.

These solvents are moreover easy to prepare with methods of a conventional type, do not create problems of safety in so far as they do not cause uncontrollable reactions, and moreover afford the undoubted advantages that they may be recovered and re-used for several production cycles.

The following examples are provided by way of non-limiting illustrations of the process that forms the subject of the present invention.

EXAMPLE 1A

Formation of the reaction solvent (tributylammonium chloride)

A 3-litre reactor provided with a Dean-Stark trap and drip funnel is charged with 150 ml of toluene and 334.3 g of tributylamine. The solution is cooled to 25-30°C and from the drip funnel there are added 152.6 ml of 33% aqueous hydrochloric acid, in the meantime controlling that the temperature does not exceed 40°C. The homogeneous solution thus obtained is then distilled in vacuum conditions (50 mmHg) until the internal temperature reaches 80°C and no more liquid is distilled from the reactor. The mixture thus obtained consists of tributylammonium chloride and is ready for use in the subsequent reactions of formation of bisphosphonic acids.

EXAMPLE 1B

Preparation of sodium alendronate

To the liquid phase obtained in Example 1, kept at 70°C, there are added 79.5 g of phosphorous acid and subsequently 100 g of γ-aminobutyric acid. The temperature of the mixture is brought to 60°C, and from the drip funnel there are added 266.4 g of phosphorus trichloride during an interval of approximately one hour, maintaining the internal temperature between 60°C and 65°C. Subsequently, the reaction mixture is kept under stirring for two hours at 60°C, and then is cooled to 20°C. There are added 410 ml of deionized water, keeping the temperature of the reaction mixture below 40°C. At the end of addition, the temperature is brought up to 90°C and kept in these conditions for 2 hours. After cooling to 10°C, 1093 ml of 30% aqueous sodium hydroxide are added to the reaction mixture, until the final pH is 11-12. The resulting top layer, consisting of tributylamine is separated off. The tributylamine may be subsequently treated with aqueous hydrochloric acid, as described in Example 1A, to re-obtain tributylammonium hydrochlorate as the

reaction solvent.

The aqueous phase is treated with 33% aqueous hydrochloric acid to bring the pH of the solution to 4.3 ± 0.1. The aqueous phase is then dripped on 7000 ml of methanol under stirring, causing the separation of a heavy precipitate, which is then filtered and washed with 500 ml of methanol.

There are obtained 1366 g of crude sodium alendronate, which is then dissolved at 75°C in 3600 ml of deionized water. The solution is then filtered at 75°C and left to crystallize by means of slow cooling, until the mixture reaches 5°C. The crystalline solid obtained is filtered and washed with 2 x 100 ml of deionized water and then dried at 50°C for 12 hours, to obtain 97.8 g of sodium alendronate (31% yield).

EXAMPLE 2

Preparation of zoledronic acid

20 of tributylammonium chloride, prepared as in Example 1A, are put into a 100-ml flask provided with coolant, magnetic stirrer, drip funnel and thermometer. The solid is melted at 60°C, then 3.2 g of phosphorous acid and 5.0 g of 2-(1-imidazyl)-acetic acid are added. The temperature of the mixture is then brought up to 65-70°C, and from the drip funnel there are slowly added 10.9 g of PCl_3. Once the addition is completed, the mixture is brought up to 80°C and kept under these conditions for two hours, at the end of which 20 ml of deionized water are added. The mixture is brought to 90°C and is kept under these conditions for 2 hours. It is then cooled down to room temperature, and 50 ml of 33% NaOH are added to the mixture, until a pH of the mixture ≥ 12 is reached. The two phases that have formed are separated, and 20 ml of toluene are added to the aqueous bottom phase, stirring the mixture for 15 min. The phases are once more separated, and the aqueous phase is brought to pH 1 by addition of 33% HCl. The aqueous solution is then dripped on 300 ml of methanol. The solid that precipitates is filtered and washed with 50 ml of methanol.

To the filtered solid there are added 70 ml of deionized water, and the mixture is heated to 80°C and kept under these conditions for 1 hour. Then the solution is cooled to room temperature. A white solid precipitates, which is filtered and washed with 20 ml of deionized water to obtain 4.2 g of the desired product, which

is dried at 50°C under vacuum for 6 hours. The weight of the dry product is 2.8 g.

EXAMPLE 3

Preparation of risedronic acid

The same procedure of preparation as the one described in Example 3 is followed, using 5.4 g of 2.-(3-pyridyl)-acetic acid instead of 2-(1-imidazyl)-acetic acid; 3.5 g of the desired product are obtained.

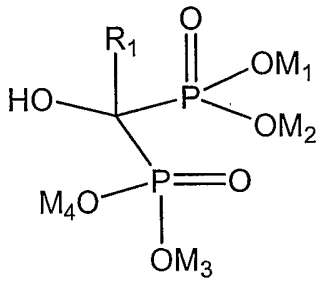
EXAMPLE 4

Preparation of sodium pamidronate

The same procedure of preparation as the one described in Example 1 is followed, using 86.4 g of β-aminopropionic acid instead of γ-aminobutyric acid; 81.5 g of the desired product are obtained.

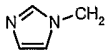
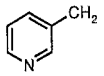
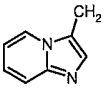
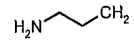
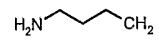
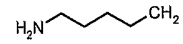
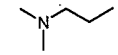
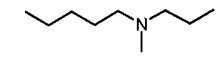
CLAIMS

1. A process for preparing bisphosphonic acids and their salts of formula (1),



(1)

in which R_1 has the meanings indicated in the following Table 1:

R_1= CH3,	Etidronic acid
R_1= 	Zoledronic acid
R_1 = 	Risedronic acid
R_1= 	Minodronic acid
R_1= 	Pamidronic acid
R_1 = 	Alendronic acid
R_1= 	Neridronic acid
R_1= 	Olpadronic acid
R_1 = 	Ibandronic acid

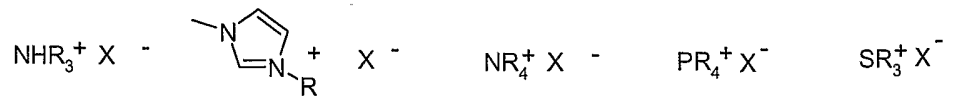
and in which M_1, M_2, M_3, M_4 are selected from H, and a monovalent cation, comprising the reaction of acids of formula R_1-CO_2H, in which R_1 has the aforesaid meanings, with acids and phosphorus trichloride, characterized in that the reaction is conducted in ionic liquids as the reaction solvents, at a temperature of between 15°C and 120°C.

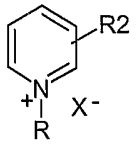
2. The process according to Claim 1, characterized in that the temperature at which the aforesaid ionic solvents are liquids is between 20°C and 100°C.

3. The process according to Claim 1 or Claim 2, characterized in that the ionic

liquids used as the solvents are selected from the group consisting of salts of ammonium, sulphonium or phosphonium.

4. The process according to Claim 3, characterized in that said -onium salts are selected from the group consisting of





in which each R may be independently H, a linear or branched C_1-C_{20} alkyl group, a cycloalkyl containing from 5 to 6 carbon atoms, alkylene aryl, or aryl; R_2 is H or a linear or branched C_1-C_{18} alkyl group, X^- is an anion selected the group consisting of halogenide, BF_4^-, PF_6^-, and $AlCl_4^-$.

5. The process according to either Claim 3 or Claim 4, characterized in that said -onium salt is tributylammonium chloride.

6. The process according to any one of Claims 1-5, characterized in that M_1-M_4 are selected from the cations of an alkaline metal, H or the cations of aliphatic or cycloaliphatic amines.

7. The process according to Claim 6, characterized in that M_1-M_4 are selected from H and/or sodium.

INTERNATIONAL SEARCH REPORT

Interr ial Application No
PCT/IB 02/04941

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/38 C07F9/58 C07F9/6506

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 C07F

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)
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	WO 01 57052 A (THE PROCTER & GAMBLE CO.) 9 August 2001 (2001-08-09) page 3, line 30-32; examples 1,2,4 ---	1-7
X	DE 37 00 772 A (INSTITUT CHIMICESKOJ KINETIKI I GORENIJA SIBIRSKOGO OTDELENIJA AKADEMI) 21 July 1988 (1988-07-21) examples 10-17 ---	1-7
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] 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
25 March 2003	08/04/2003

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	Beslier, L

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/IB 02/04941

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EZRA A. ET AL.: "A peptide prodrug approach for improving bisphosphonate oral absorption" JOURNAL OF MEDICINAL CHEMISTRY., vol. 43, no. 20, 2000, pages 3641-3652, XP002235747 AMERICAN CHEMICAL SOCIETY. WASHINGTON., US ISSN: 0022-2623 page 3042, results, paragraph 1; page 3048, left-hand column, experimental	1-7
X	US 3 366 676 A (JIMMIE K. DYER) 30 January 1968 (1968-01-30) the whole document	1-7
X	CHEMICAL ABSTRACTS, vol. 117, no. 23, 7 December 1992 (1992-12-07) Columbus, Ohio, US; abstract no. 234254, MIKHALIN, N. V. ET AL: "Method of preparation of higher 1-hydroxyalkylidene-1,1-diphosphonic acids or their mixtures or salts" XP002235748 abstract & SU 1 719 405 A (INSTITUTE OF CHEMICAL KINETICS AND COMBUSTION NOVOSIBIRSK, USSR) 15 March 1992 (1992-03-15)	1-7
E	GB 2 378 444 A (RHODIA CONSUMERS SPECIALTIES LTD.) 12 February 2003 (2003-02-12) the whole document	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/IB 02/04941

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0157052 A	09-08-2001	AU 3661301 A	14-08-2001
		BR 0107952 A	25-02-2003
		CN 1396925 T	12-02-2003
		EP 1252169 A1	30-10-2002
		NO 20023646 A	30-09-2002
		WO 0157052 A1	09-08-2001
		US 2001041690 A1	15-11-2001
DE 3700772 A	21-07-1988	DE 3700772 A1	21-07-1988
		AU 599950 B2	02-08-1990
		AU 6760787 A	21-07-1988
		BE 1000075 A4	02-02-1988
US 3366676 A	30-01-1968	BE 678619 A	29-09-1966
		CH 470417 A	31-03-1969
		DE 1250439 B	
		FR 1491248 A	11-08-1967
		GB 1093876 A	06-12-1967
		NL 6604176 A	03-10-1966
		SE 328285 B	14-09-1970
SU 1719405 A	15-03-1992	SU 1719405 A1	15-03-1992
GB 2378444 A	12-02-2003	US 2003013918 A1	16-01-2003