Abstract:
The present invention relates to an industrially advantageous, cost-effective, and reproducible process for preparation of pure minodronic acid, including salts, hydrates and polymorphs thereof, by using ecofriendly process for preparation of key intermediate, in high yield and high purity.

Title: AN IMPROVED PROCESS FOR PREPARING PURE MINODRONIC ACID AND INTERMEDIATES THEREOF
TITLE OF THE INVENTION
An improved process for preparing pure minodronic acid and intermediates thereof

FIELD OF THE INVENTION
The present invention relates to an industrially advantageous, cost-effective, reproducible and improved process for preparation of pure minodronic acid of formula I including salts, hydrates and polymorphs thereof.

Formula I

The present invention also provides an ecofriendly process for the preparation of key intermediates of minodronic acid in high yield and high purity.

BACKGROUND OF THE INVENTION
Minodronic acid of formula I, is a third-generation bisphosphonate drug for the treatment of osteoporosis, and is chemically known as (1-hydroxy-2-(imidazo[1,2-a]-pyridin-3-yl)ethyldene)bisphosphonic acid.

Formula I

The drug has been jointly developed by two Japanese companies, Ono Pharmaceutical Co. Ltd. and Astellas Pharma Inc; and marketed under the brand name RECALBONO/Bonoteo®.

Minodronic acid, as a product was first disclosed in US patent US4,990,503 [hereinafter US'503], wherein, minodronic acid is prepared from 2-(imidazo[1,2-a] pyridine-3-yl)acetic acid as shown below in scheme:
In US'503 minodronic acid is prepared by the reaction of 2-(imidazo[1,2-a]pyridine-3-yl) acetic acid with phosphorous acid in the presence of phosphorous trichloride in chlorobenzene, heated at 110°C and after adding phosphorous trichloride, reaction mass is stirred for 8 hours and the obtained product i.e., minodronic acid is recrystallized from water-methanol. Further patent is silent about the preparation of intermediate 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid.

Several processes for the synthesis of minodronic acid have been reported in literature, wherein 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid is used as a key intermediate. For example in US patent US7,038,083, preparation of minodronic acid is generically disclosed by reaction of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid with phosphorous acid and halophosphorous compound in the presence of diluents such as aromatic hydrocarbon or a silicone fluid, however, preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid or minodronic acid is not exemplified. Similarly, US patents US7,361,761; US7,528,280; US7,872,144 disclose preparation of minodronic acid by reacting 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid with phosphorous acid in the presence of halophosphorous compound in different solvent system.

Here too, neither process for the preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid nor the crystal nature of minodronic acid has been disclosed.

In quest of preparing minodronic acid in high yield and high purity, emphasis is given on the preparation of highly pure key intermediates in fairly good yields. There exist few patents/publications which disclose the preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid, a key intermediate in the synthesis of minodronic acid.

A Chinese patent publication CN101531681A discloses a synthesis of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid, as represented below:

The process involves reaction of 2-aminopyridine with 3-bromo-4-oxo-ethylbutyrate in presence of aprotic solvent such as dimethyl formamide, tetrahydrofuran, or dioxane to give 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid ethyl ester which upon hydrolysis gives 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid with yield in the range of 29-31% which is then further converted to minodronic acid.

In an another Chinese patent publication CN101973993A, an alternate synthesis of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid is disclosed, as shown below.
In the disclosed process, 2-aminopyridine is condensed with 4-chloroacetoacetic ester in presence of triethylamine in dioxane and the resulting ester compound is hydrolyzed to give 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid further, its conversion to minodronic acid is not disclosed.

The similar process for preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid is also reported in CN102153585A, wherein 4-chloroacetoacetic acid is condensed with 2-aminopyridine in presence of ethanol to obtain 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid ethyl ester, which upon hydrolysis gives 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid. The yield of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid from corresponding 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid ethyl ester reported is more than theoretical yield and patent is silent about the purities of ester as well as acid compound. It leaves the assumption that in the claimed reaction conditions pure material is not obtained, since yield obtained is more than the calculated theoretical yield, which is not practical, and hence makes the process unattractive.

Another Chinese patent publication CN101812062A, discloses a process for the preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid employing reaction of 2-aminopyridine with 4-oxo-but-2-enio acid ethyl ester in presence of solvents such as methanol, ethanol, isopropanol, dioxane, tetrahydrofuran or acetone as represented below:

In the exemplified processes, a solution of 2-aminopyridine in a suitable solvent, like ethanol or dioxane, is cooled, and 4-oxo-but-2-enio acid ethyl ester is added dropwise and the temperature is maintained to -5°C, thereafter temperature of reaction mass is raised to 70-80°C and maintained for further 2.5 hours. After work up, the resulting ester product is hydrolyzed using caustic soda in ethanol and after work up produces 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid, which is further purified using alcoholic solvents. The reported yields of crude compound are between 47.3-54.5% which further decreased upon crystallization to an overall yield in the range of 26-43%. Such a low yield is not worth for commercial scale and makes the process
unattractive from cost point of view. Further in this patent publication preparation of minodronic acid is not given.

A very similar process is disclosed in another Chinese patent publication CN102344463A, wherein 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid ethyl ester is prepared by reaction of 2-aminopyridine with 4-oxo-but-2-enoic acid ethyl ester in acetonitrile at reflux temperature for a period of 5-6 hours. The resulting ester upon alkaline hydrolysis using 10% caustic soda solution produces 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid in 95% yield, leading to an overall yield of 47.5%. Major drawback of this process is refluxing for longer hours during condensation step and distillation of solvent from reaction mass, which may lead to decomposition and results in low yields.

US patent US7,405,305 also discloses similar process for preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid ethyl ester by reacting 2-aminopyridine and 4-oxo-but-2-enoic acid ethyl ester in presence of acetonitrile. In exemplified process, a reaction mixture containing 2-aminopyridine and 4-oxo-but-2-enoic acid ethyl ester in acetonitrile is heated at 80°C for 6 hours. Thereafter, solvent is removed under reduced pressure and the resulting oily product is purified using flash chromatography to give impure corresponding ester as brown solid containing 2-aminopyridine, in 50% yield. Further, the patent does not disclose conversion of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid ethyl ester to 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid.

It is clear from reported literature that 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid, isolated in low yield about 26% to 47.5%, is generally prepared via hydrolysis of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid ethyl ester which in turn prepared by condensation of 2-aminopyridine with 3-bromo-4-oxo-ethylbutyrate or 4-chloroacetoacetic ester or 4-oxo-but-2-enoic acid ethyl ester in presence of organic solvents such as alcohols, acetonitrile, dimethyl formamide, tetrahydrofuran, dioxane or acetone. We have not found any reference wherein organic solvent is not used during said condensation. Usually, organic solvents are used in much larger quantities than the solutes they carry and have a tendency to escape into the environment through evaporation and leakage. Use of solvent also adds cost to the process. In addition to this, use of organic solvent in synthetic reactions also requires the control of the solvent to be shown in the final API like minodronic acid.
In view of the above, present invention provides a process for synthesis of compound of formula II, by condensation of 2-aminopyridine with 4-oxo-but-2-enolic acid alkyl ester in the absence of an organic solvent, which makes the process eco-friendly, cost-effective and economically viable.

Apart from the above mentioned process patents/publications wherein preparation of key intermediates of minodronic acid and their conversion to minodronic acid is disclosed; there is one another patent US 5,480,875 [hereinafter US'875] which disclose different polymorphic forms of minodronic acid and its sodium salt along with their preparation. The patent US'875, mainly describes two hydrated forms D and E of minodronic acid, both of which show similar XRD but are differentiated by their TG-DSC thermograms. In the patent both forms are prepared by dissolving the crystals in aqueous hydrochloric acid solution with specific conditions of cooling and stirring. Particularly crystal form D is prepared by dissolving the minodronic crystal in 37-40 times of volume of IN hydrochloric acid, agitating at 110 rpm, gradual cooling, filtering and drying at 40-60°C. Contrary to this crystal form E is prepared by dissolving the crystal in 37-40 times of volume of IN hydrochloric acid, agitating at such as low rate that the liquid surface does not create a whirlpool, gradual cooling, filtering and drying at 40-60°C. In patent disclosure itself, it is mentioned that above conditions may sometimes result in the formation of crystal D or a mixture of crystal D and E, depending upon slight changes in the synthesizing scale, equipment, agitating and cooling condition and advised to adjust each of the conditions appropriately to obtain the specific form. Such a strict control of conditions is not always possible at industrial scale and hence makes process unattractive. Further major drawback of this disclosure is that even after adjusting the above specified parameters, most of the time resulting compound is a mixture of both forms D and E, and difficult to obtain pure form.

In one recent PCT publication WO2014/091386, a process for preparation of crystal form D is disclosed wherein minodronic acid is dissolved in dilute hydrochloric acid solution at reflux temperature, cooled at 70-80°C very slowly, stirring at the same temperature for more than 5 hours at 100-110 rpm and then slowly cooling to room temperature gives crystal form D.

There are some Chinese patent publications exist in art, which disclose different polymorphic forms of minodronic acid and incorporated herein as reference. In Chinese publication CN102268042A, a new crystalline form II of minodronic acid is mentioned. In CN102850401A, a dihydrate crystal form of minodronic acid is claimed. In CN103183709A, a
new crystal form of minodronic acid is disclosed. Although no efforts have been made to develop an alternate process to prepare pure crystal forms D and E, in consistent manner. Hence there is an urgent need in art to develop a process which can produce any of pure polymorphic form in consistent manner. Therefore, present invention aims to solve this problem by developing an alternate process to produce pure polymorphic forms D and E of minodronic acid in consistent and reproducible manner at any synthesizing scale.

OBJECTIVES OF THE INVENTION

It is the foremost objective of the present invention to provide industrially advantageous, cost-effective, reproducible and improved process for preparation of minodronic acid, including salts, hydrates and polymorphs thereof.

Another objective of the present invention is to provide a process for the preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester.

Another objective of the present invention is to provide an ecofriendly process for the preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid.

Another objective of the present invention is to provide a process for the conversion of said imidazo intermediates into minodronic acid.

Yet another objective of the present invention is to provide an improved process to prepare pure polymorphic forms D and E of minodronic acid in consistent and reproducible manner at any synthesizing scale.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides an industrially advantageous, ecofriendly, cost-effective, reproducible and improved process for the preparation of minodronic acid of formula I including salts and hydrates thereof,

![Formula I](image)

using intermediates such as 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II
and 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester of compound of formula III.

wherein R is C1-C4 alkyl,

According to one embodiment, the present invention provides a process for preparation of minodronic acid of formula I including salts and hydrates thereof, comprising the steps of;

5 a), reacting 2-aminopyridine with 4-oxo-but-2-enoic acid alkyl ester of formula IV

wherein R is C1-C4 alkyl

in presence of demineralized water and at a suitable temperature to obtain 2-(imidazo[1,2-a]-pyridine-3-yl)acetic acid alkyl ester of compound of formula III;

b). hydrolyzing the resulting 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester compound of formula III with a suitable hydrolyzing agent to obtain 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II;

c). phosphorylatmg 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II to obtain minodronic acid of compound of formula I.
According to one another embodiment, the present invention provides a process for preparation of minodronic acid monohydrate, comprising the steps of:

a) reacting 2-aminopyridine with 4-oxo-but-2-enolic acid alkyl ester of formula IV

\[
\begin{align*}
\text{Formula IV} \\
H_{\text{OR}}
\end{align*}
\]

wherein \( R \) is \( \text{C1-C4 alkyl} \)

in presence of a demineralized water and at a suitable temperature to obtain 2-\(\text{imidazo[1,2-a]pyridine-3-yl} \)acetic acid alkyl ester of compound of formula III;

\[
\begin{align*}
\text{Formula III} \\
N_{\text{OR}}
\end{align*}
\]

wherein \( R \) is \( \text{C1-C4 alkyl} \)

b) hydrolyzing the resulting 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester compound of formula III with a suitable hydrolyzing agent to obtain 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II;

\[
\begin{align*}
\text{Formula II} \\
N_{\text{OH}}
\end{align*}
\]

e) phosphorylating 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II to obtain minodronic acid of compound of formula I;

\[
\begin{align*}
\text{Formula I} \\
N_{\text{OP(OMe)2}}
\end{align*}
\]

d) purifying the minodronic acid using acid-base treatment;

e) converting resulting minodronic acid to desired minodronic acid monohydrate.
According to one another embodiment, the present invention provides a process for preparation of pure polymorphic form D of minodronic acid, comprising the steps of:

a) providing a solution of minodronic acid in aqueous hydrochloric acid at temperature of 80-100 °C;

b) cooling the solution at suitable temperature of 55-65 °C;
c) adding seed of form D of minodronic acid monohydrate,
d) diluting the reaction mass with a suitable solvent;
e) stirring the resulting reaction mixture for sufficient time for complete crystallization,
f) cooling the reaction mixture below 20°C
g) isolating pure polymorphic form D of minodronic acid monohydrate.

According to one another embodiment, the present invention provides a process for preparation of pure polymorphic form E of minodronic acid, comprising the steps of:

a), providing a solution of minodronic acid in a mixture of concentrated hydrochloric acid and water at temperature of 80-100 °C;

b) cooling the solution at suitable temperature of 55-65 °C;
c) adding seed of form E of minodronic acid monohydrate,
d) diluting the reaction mass with a suitable solvent;
e) stirring the resulting reaction mixture for sufficient time for complete crystallization,
f) cooling the reaction mixture below 20°C
g) isolating pure polymorphic form E of minodronic acid monohydrate.

According to another embodiment, the present invention provides a process for preparation of pure 2-(imidazo[l,2-a]pyridine-3-yl)acetic acid of compound of formula Π, comprising the steps of:

a), reacting 4-oxo-but-2-enoic acid alkyl ester of formula IV

wherein R is C1-C4 alkyl

with 2-aminopyridine in the presence of demineralized water, at a suitable temperature to prepare 2-(imidazo[l,2-a]pyridine-3-yl)acetic acid alkyl ester of formula III;
b) optionally isolating 2-(imidazo[l,2-a]pyridine-3-yl)acetic acid alkyl ester of formula III;
c) adding alkali hydroxide to 2-(imidazo[l,2-a]pyridine-3-yl)acetic acid alkyl ester of formula III in demineralized water;
d) stirring the reaction mass for sufficient time;
e) adjusting the pH of reaction mass to 4-6 using a suitable acid; and
f) isolating pure 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II.

According to one other embodiment, the present invention provides 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II having purity greater than 99% by HPLC with ROI [residue on ignition] in less than 1% and in more than 94% overall yield.

BRIEF DESCRIPTION OF DRAWINGS
Figure-1 represents DSC thermogram of polymorphic form D of minodronic acid Figure-2: represents DSC thermogram of polymorphic form E of minodronic acid

DETAILED DESCRIPTION OF THE INVENTION
As used herein, "pure polymorphic form D of minodronic acid monohydrate" refers to minodronic acid monohydrate form D having 2% or less of other polymorphic forms of minodronic acid monohydrate, preferably no detectable quantity of other polymorphic forms of minodronic acid monohydrate.

As used herein, "pure polymorphic form E of minodronic acid monohydrate" refers to minodronic acid monohydrate form E having 2% or less of other polymorphic forms of minodronic acid monohydrate, preferably no detectable quantity of other polymorphic forms of minodronic acid monohydrate.

As used herein, "pure 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of formula II" refers to purity of acid compound of formula II greater than 99% by HPLC with residue on ignition [ROI] in less than 1%.

The present invention provides an industrially advantageous, cost-effective, reproducible and improved process for the preparation of minodronic acid of formula I including salts, hydrates and polymorphs thereof. Particularly the present invention provides an eco-friendly process for preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of formula II with high purity and high yield. Generally 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid can be prepared by condensation of 2-aminopyridine with 4-oxo-but-2-enoic acid alkyl ester, followed by hydrolysis of resulting ester. Specifically, the process comprises addition of a solution of 4-oxo-but-2-enoic acid alkyl ester to a solution of 2-aminopyridine in demineralized water, slowly, at suitable temperature and maintaining the reaction mass at a suitable temperature for sufficient time.
The suitable temperature for reaction can be varied from 15-70°C and preferably room temperature may be most suitable. The reaction time can vary from 30 minutes to 24 hours preferably reaction time may not be more than 90 minutes and more preferably the reaction can be completed in 60 minutes and most preferably reaction can be completed in less than 60 minutes. In a preferred embodiment of invention, a solution of 2-aminopyridine in demineralized water is heated to room temperature and a solution of 4-oxo-but-2-enoic acid ethyl ester is slowly added to 2-aminopyridine solution, and reaction is completed in about 45 minutes. Generally, after completion of reaction, the resulting ester intermediate of formula III can be isolated from the reaction mixture using a suitable techniques known in the art. For the purpose of present invention, the resulting compound of formula III i.e., 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester can be insitu converted to compound of formula II i.e., 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid. This makes the process ecofriendly, operationally efficient, superior as well as commercially more competitive.

In a specific preferred embodiment of the present invention, the ester compound of formula III, can be obtained in high yield and high purity and can be converted insitu to an acid compound of formula II i.e., 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid. Alkyl ester can preferably be selected from C1-C4 ester and can be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl or like. Further the ester compound of formula III as such can be carry forward to the next stage without further purification, leading to acid compound of formula II.

Use of demineralized water for a particular condensation reaction is a novel and inventive part of present invention as it not only provides the mild reaction conditions such as reaction can be performed at room temperature but also enhanced the product quality; particularly in terms of purity, as use of water facilitate the removal of any unwanted inorganic salts or materials which may be produced or are generated during the reaction and subsequently during hydrolysis reaction, and this makes the product free of inorganic impurities. Further use of demineralized water not only allow the mild reaction conditions but also made possible to avoid the use of organic solvents which are expensive, toxic and proves to be hazardous to men, machinery and environment. Thus, the present invention provides a green chemistry based process for the preparation of minodronic acid via condensing the 2-aminopyridine and 4-oxo-but-2-enoic acid alkyl ester in demineralized water without using any organic solvent. Thus process is avoiding use of organic solvents, produces product in high yield and purity and hence greener, cost effective and environment friendly.
Specifically compound of formula II is obtained having purity greater than 99% by HPLC, residue on ignition [ROI] in less than 1% preferably less than 0.5%. and in more than 94% overall yield.

For the purpose of the invention 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester of compound of formula III can be hydrolyzed by using hydrolyzing agent by methods known in the art such as acidic or basic hydrolysis conditions. Generally, the acidic hydrolysis can be carried out using an inorganic acid such as hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid, or like; organic acid such as methane or ethane sulphonic acid, formic acid, acetic acid, trifluoroacetic acid or like; and/or basic hydrolysis can be carried out using inorganic base such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, or like.

In a preferred embodiment, ester of compound of formula III can be hydrolyzed under basic conditions which can be carried out in a suitable solvent for providing the reaction media and can be selected from water, C1-C4 alcohols such as methanol, ethanol, isopropyl alcohol, n-butanol and like or mixtures thereof. Usually hydrolysis can be carried out at a temperature of 0°C to 80°C for a period of 30 minutes to 10 hours. For the purpose of present invention hydrolysis reaction is performed in water in the presence of potassium hydroxides. In a general course of reaction, after the completion of hydrolysis reaction, reaction mass is neutralized to isolate desired acid compound. In case of base assisted hydrolysis the reaction mass is acidified to obtain the compound of formula II. The acid used can be selected from hydrochloric acid, sulfuric acid, acetic acid or like. Acid compound of formula II can be isolated from the reaction mixture by a suitable technique such as filtration or centrifugation or like.

The resulting product can optionally be purified using a suitable solvent system or can be directly used for the next stage for the preparation of minodronic acid.

The solvent selected at this stage can be C1-C4 alcohol such as methanol, ethanol, isopropyl alcohol, n-butanol or like; water, C1-C4 alkyl nitriles such as acetonitrile, propionitrile, butyronitrile or like; aliphatic ester such as ethyl acetate, propylacetate or like; aliphatic ethers such as isopropyl ether, methyl tertiary butyl ether or the like or mixtures thereof.

The starting materials, 2-aminopyridine and 4-oxo-but-2-enolic acid alkyl ester compound used in present invention can be prepared by methods known in the prior art or can be procured from commercial source.

The compound of formula II i.e., 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid can be converted to minodronic acid by methods known in the art or the methods as described herein. Preferably,
minodronic acid can be prepared by reacting compound of formula II with phosphorous acid in
the presence of phosphorous halide. In a preferred embodiment, 2-(imidazo[1,2-a]pyridine-3-
yl)acetic acid of compound of formula II is reacted with phosphorous acid in the presence of
phosphorous halide, in the absence of any solvent or in the presence of a neutral non alcoholic
solvent such as alkyl nitriles, like acetonitrile, propionitrile at temperature of 40-90°C, preferably
75-80°C till phosphorylation is completed, preferably for a period of about 1-12 hours. The phosphorous halide can be selected from the group comprising phosphorous trichloride, phosphorous tribromide, phosphorous pentachloride, phosphorous pentabromide, phosphorous oxychloride, phosphorous oxybromide or the like. After completion of reaction, optionally solvent is distilled off and the reaction mixture is cooled and quenched with demineralized water. The resulting solid, can be isolated from the reaction mixture by a suitable techniques such as filtration or centrifugation or like. In case wherein reaction is performed in the absence of solvent, the reaction mass is refluxed at suitable time till phosphorylation is complete. After completion of reaction, reaction mixture is cooled and quenched with demineralized water. The resulting solid, can be isolated from the reaction mixture by a suitable techniques such as filtration or centrifugation or like.

The resulting crude product i.e., minodronic acid, thus prepared, can be optionally purified using acid base treatment and/or charcolization. Particularly the crude solid can be treated with base to adjust pH above seven, optionally the resultant reaction mass is charcolized to decolorize the reaction mass and further treated with mineral acid to bring down the pH to around 1-2.

The base used can be selected from alkali hydroxides, carbonates or bicarbonate preferably alkali metal hydroxides such as sodium hydroxides, potassium hydroxides or like are used. The mineral acid can be selected from the inorganic acids such as hydrochloric acid or like.

The above purification process can be repeated if required to get the product of desired purity. After achieving the product of desired purity greater than 99%, minodronic acid is converted to minodronic acid monohydrate by the method known in the art.

In a preferred embodiment of invention, the resulting minodronic acid is dissolved in hydrochloric acid by heating it to reflux temperature for a sufficient time till the complete dissolution of minodronic acid. The hydrochloric acid used can be dilute or concentrated. The heating temperature can be varied between 60-120°C, preferably between 90-105°C is most suitable. The heating time can vary from 30 minutes to 2 hours preferably heating time may not be more than 90 minutes and more preferably it is 60 minutes. If required, reaction mass can be
diluted with demineralized water. The compound is crystallized by lowering the temperature of reaction mass, preferably cooling below to 20°C, most preferably cooling in the range of 0-5°C is sufficient. The crystallized product, thus formed, can be isolated by using simple filtration techniques. Minodronic acid monohydrate, prepared by using process of present invention is highly pure having purity greater than 99.5%, more preferably greater than 99.8%, most preferably greater than 99.9%.

In one another preferred embodiment, the present invention provides an improved process to prepare pure crystal forms D and E of minodronic acid monohydrate by incorporating step of seeding of pure desired form during crystallization step, in consistent and reproducible manner. In process of present invention, minodronic acid can be dissolved in aqueous hydrochloric acid [a mixture of concentrated hydrochloric acid and demineralized water] by heating at about 60-120°C. The hydrochloric acid used can be dilute or concentrated and can be used in volume ranging between 2 to 8 times of minodronic acid used. The heating temperature can be varied from 60-120°C, preferably between 80-100°C is most suitable so that minodronic acid can dissolved completely. Temperature is lowered preferably in the range of about 70-75°C before filtration to get clear solution. The solution is further cooled to 55-65°C. The seeds of minodronic acid monohydrate Form D or E, as desired, is added to the clear solution and stirred at 50-65°C for sufficient time and reaction mass can be diluted with a suitable solvent preferably water to induce crystallization and further stirred for sufficient time. The product can be further cooled to 0-30°C, preferably at 0-10°C for complete crystallization. The resulting crystallized product may be then isolated by filtration. It is advantageous to add seeds of pure form D or form E, to obtain desired polymorph in pure and consistent manner. Seeding a solution with a crystal of the product is a well-established technique to induce crystallization. It has also been used to encourage the formation of particular polymorph consistently. Seeding is preferably used to obtain crystals of high polymorphic purity, and especially with very high perfection and desired crystal orientation in consistent and reproducible manner. Using the seeding process during crystallization to prepare form D or form E of minodronic acid monohydrate forms an inventive part of the present invention, which overcome the drawbacks for preparation of pure form D or form E of minodronic acid monohydrate, mentioned in prior art.

The Form D and E of minodronic acid monohydrate as prepared herein, can be characterized by X-ray powder diffraction pattern. Thus, the X-ray diffraction patterns were measured on PAN analytical, X'pert PRO powder diffractometer equipped with goniometer of ΘΘ configuration.
and X'Celerator detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-40.0°. One with ordinary skills in the art understands that experimental differences may arise due to differences in the instrument, sample preparation and other factors. The X-ray powder diffraction pattern of minodronic acid monohydrate polymorphic crystal form D and form E as obtained by following the process of present invention, matches with the X-ray powder diffraction pattern disclosed in literature viz.; US 5,480,875.

The DSC measurements of form D and E of minodronic acid monohydrate were carried out on METTLER STAR® SW 8.1 instrument. The experiments were performed at heating rate of 5 or 10.0°C/min over a temperature range of 50°C to 250°C purging with nitrogen at a flow rate of 50ml/min. The DSC thermograms of minodronic acid monohydrate polymorphic form D and Form E are shown in Figures 1 and 2.

It is not the limitations of present invention to use these intermediates for the preparation of minodronic acid only. The process as presented in present invention can be suitably accommodated to prepare the equivalent intermediates used in various bisphosphonic acids, reported in literature.

The main advantage of the present invention is that it provide an industrially advantageous, cost-effective, reproducible and improved process for the preparation of minodronic acid via improved and ecofriendly process of key intermediate, 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid, which is prepared in high yield of greater than 94% and high purity of greater than 99% using environment friendly solvent water. Further advantage of the present invention is that it provide an improved process for the preparation of pure polymorphic forms D and E of minodronic acid monohydrate in consistent and reproducible manner at any synthesizing scale.

It is against this and other backgrounds, which shall be filed in a detailed manner in complete specifications, in due course, the present invention is brought out and explained in following non-limiting examples.

EXAMPLES:
Example 1: Preparation of 2-(imidazo[1,2-a]pyridine-3-yl) acetic acid
To a solution of 2-aminopyridine (50g) in demineralized water (650ml) at 25-30°C, 4-oxo-but-2-enoic acid ethyl ester (70g) was added slowly and the reaction mass was further maintained
at 25-30°C for 45 minutes. After completion of reaction, [monitored by UPLC] potassium hydroxide solution (40g in 50ml demineralized water) was added and the reaction mass was stirred at temperature of 20-30°C for 1 hour. The pH of reaction mass was adjusted to 5.0-6.0 with hydrochloric acid and the reaction mass stirred for further 60 minutes at 20-30°C. The resulting product was filtered, washed successively with water (2x50ml), and ethanol (150ml) and dried at 55-65°C to afford 83.80g of title compound having purity 99.09% by HPLC.

Example 2: Preparation of minodronic acid

Method A: To a refluxing solution of 2-(imidazo[1,2-a]pyridine-3-yi)acetic acid (80g) and phosphorous acid (89.5g) in acetonitrile (800ml); phosphorous trichloride (168g) was added slowly and the reaction mass was further refluxed for 6 hours. After completion of reaction, [monitored by HPLC], solvent was distilled off under reduced pressure and demineralized water (180ml) was added and distilled under reduced pressure. Demineralized water (640ml) was again added and the reaction mass was stirred at reflux temperature for further 12 hours. Thereafter, the reaction mass was cooled to 25-30°C, stirred for 2 hours, filtered and washed with demineralized water (800ml). The resulting solid was further taken in demineralized water (320ml) and 33% aqueous sodium hydroxide solution was slowly added to reaction mass to adjust the pH around 10.5-11.5. After complete dissolution, activated charcoal (8g) was added, stirred for 30 minutes at 50-60°C, filtered through hyflo and the bed was washed with demineralized water (320ml). The filtrate was acidified using hydrochloric acid to adjust pH between 1-2. The reaction mass was cooled to 0-5°C and stirred for further 1 hour. The product, thus crystallized, was filtered, washed with demineralized water (320 ml) and dried at 50-60°C to afford 95g of title compound.

Method B: To 2-(imidazo[1,2-a]pyridine-3-yi)acetic acid (50g, having m/c 25.30%), phosphorous acid (44.8g) and phosphorous trichloride (84g) were successively added at 25 to 30°C and the reaction mass was refluxed for 6 hours. The reaction mass was cooled to 25-30°C, demineralized water (320ml) was added to the reaction mass and refluxed at 95-100°C for 12 hours thereafter it is cooled to 20-30°C, stirred for 120 minutes. The solid was filtered, washed with demineralized water (160ml). The resulting solid was further taken in demineralized water (160ml) and 33% aqueous sodium hydroxide solution was slowly added to reaction mass to adjust the pH around 10.5-11.5. After complete dissolution, activated charcoal (4g) was added, stirred for 30 minutes at 50-60°C, filtered through hyflo and the bed was washed with demineralized water (160ml). The filtrate was cooled to 20-30°C and acidified
using hydrochloric acid to adjust pH between 1-2. The reaction mass was further cooled to 0-5°C and stirred for 1 hour. The product, thus crystallized, was filtered, washed with demineralized water (160ml). The resulting solid was further taken in demineralized water (80ml) and concentrated hydrochloric acid (80ml) and heated to 95-100°C and stirred for 1 hour. To the reaction mass demineralized water (385ml) was slowly added, temperature was maintained to 55-60°C and stirred for 1 hour. The reaction mass was further cooled to 0-5°C and maintained at this temperature for 120 min. The resulting solid was filtered and washed with demineralized water (130ml) and suck dried for 30 minutes to afford 27.2g title compound having purity 99.91% by HPLC.

**Example 3: Preparation of minodronic acid monohydrate Form D**

**Method A:** Minodronic acid (130g) is taken in demineralized water (325ml) and concentrated hydrochloric acid (325ml) was added. The reaction mass was heated to 95-100°C and stirred for further 60 minutes till complete dissolution. Thereafter, the reaction mass was cooled to 70-75°C and filtered to remove suspended particles. The filtrate was further cooled to 60°C±5°C, seed of minodronic acid Form D (6.5g) was added and the reaction mass was stirred for 60 minutes at 55-60°C. Demineralized water (1560ml) was slowly added to reaction mass and further stirred for 60 minutes at 55-60°C. The reaction mass was further cooled to 0-10°C and stirred further for 60 minutes. The solid was filtered, washed with demineralized water (1300ml) and suck dried for 10 minutes and further dried at 55-60°C for 16 hours to afford 128g of pure minodronic acid monohydrate Form D.

**Method B:** Minodronic acid (40g) is taken in demineralized water (100ml) and concentrated hydrochloric acid (100ml) was added. The reaction mass was heated to 75-85°C and further stirred for 15 minutes to dissolve the solid. The reaction mass was cooled to 65-75°C and filtered. The filtrate was further cooled to 55-60°C, seed of minodronic acid Form D (2g) was added and the reaction mass was stirred for 60 minutes at 55-60°C. Demineralized water (480ml) was slowly added to reaction mass and further stirred for 60 minutes at 55-60°C. The reaction mass was further cooled to 0-10°C and stirred further for 60 minutes. The solid was filtered, washed with demineralized water (400ml) and suck dried for 20 minutes and further dried at 55-60°C for 16 hours to afford 38.45g of minodronic acid monohydrate Form D.
Example 4: Preparation of minodronic acid monohydrate Form E

Minodronic acid (146g), demineralized water (365ml) and concentrated hydrochloric acid (365ml) were charged in a round bottomed flask and the reaction mass was heated to 90°C, further stirred for 30 minutes to dissolve the solid. The reaction mass was cooled to 58°C, seed of minodronic acid Form E (3 g) was added and the reaction mass was stirred for 60 minutes at 55-60°C. To the reaction mass, demineralized water (1752ml) was slowly added at 55-60°C and further stirred for three hours at 55-60°C. The reaction mass was cooled to 0-10°C and stirred for another 60 minutes. The solid was filtered, washed with demineralized water (1460ml) and further dried at 55-60°C for 15 hours to afford 136g of pure minodronic acid monohydrate Form E.
We Claim:

1. An **improved process for the preparation** of minodronic acid of formula I, comprising of:

   ![Formula I](image1)

   **Formula I**

   **d.** reacting 2-aminopyridine with 4-oxo-but-2-enoic acid alkyl ester of formula IV, in the presence of demineralized water at a suitable temperature,

   ![Formula IV](image2)

   **Formula IV**

   **wherein** R is C1-C4 alkyl

   to obtain 2-(imidazo[1,2-a]-pyridine-3-yl)acetic acid alkyl ester of compound of formula III;

   ![Formula III](image3)

   **Formula III**

   **wherein** R is C1-C4 alkyl

   e. hydrolyzing the resulting 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester compound of formula III with a suitable hydrolyzing agent in a suitable solvent to obtain 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II;

   ![Formula II](image4)

   **Formula II**

   f. phosphorylating 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II with phosphorous acid in the presence of phosphorous halide, at a temperature of 40-90 °C, 

   g. isolating minodronic acid of formula I.

2. The process as claimed in claim 1, wherein in step a) the suitable temperature is between 15-70°C. in step b) the suitable hydrolyzing agent is inorganic base; or inorganic acid; or organic acid; in step b) the suitable solvent is selected from water and C1-C4 alcohols or mixtures thereof.
3. The process as claimed in claim 1, wherein in step c) phosphorylation is carried out in the
presence of neutral non-alcoholic solvent.
4. The process as claimed in claim 1, wherein in step c) phosphorylation is carried out in the
absence of solvent.
5. The process as claimed in claim 1, wherein minodronic acid is further purified by
comprising the steps of:
   a) treating minodronic acid with a suitable base to adjust pH above 7
   b) optionally charcoalizing the resulting solution in step a);
   c) acidifying resulting clear solution of step b) using hydrochloric acid;
   d) isolating pure minodronic acid.
6. The process as claimed in claim 6, wherein in step a) the suitable base is alkali hydroxide,
   alkali carbonate or alkali bicarbonate.
7. The process as claimed in claim 1, wherein minodronic acid is further converted to
   minodronic acid monohydrate by treating with hydrochloric acid.
8. A process for preparation of pure polymorphic form D of minodronic acid, comprising of:
   a) providing a solution of minodronic acid in aqueous hydrochloric acid at temperature of 80-
      100 °C;
   b). cooling the solution to a temperature of 55-65°C;
   c). adding seed of form D of minodronic acid monohydrate,
   d). diluting the reaction mass with a suitable solvent;
   e). stirring the resulting reaction mixture for sufficient time for complete crystallization,
   f). cooling the reaction mixture below 20°C
   g). isolating pure polymorphic form D of minodronic acid monohydrate.
9. A process for preparation of pure polymorphic form E of minodronic acid, comprising of:
   a). providing a solution of minodronic acid in a mixture of concentrated hydrochloric acid and
      water at temperature of 80-100 °C;
   b). cooling the solution at suitable temperature of 55-65 °C;
   c). adding seed of form E of minodronic acid monohydrate,
   d). diluting the reaction mass with a suitable solvent;
   e). stirring the resulting reaction mixture for sufficient time for complete crystallization,
   f). cooling the reaction mixture to a temperature of below 20°C
   g). isolating pure polymorphic form E of minodronic acid monohydrate.
10. A process for the preparation of 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II,

\[
\begin{array}{c}
\text{Formula II} \\
\end{array}
\]

comprising the steps of

a), reacting 2-aminopyridine with 4-oxo-but-2-enoic acid alkyl ester of formula IV

\[
\begin{array}{c}
\text{Formula IV} \\
\end{array}
\]

wherein \( R \) is \( C_{1-4} \) alkyl

in presence of demineralized water at a suitable temperature to obtain 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester of compound of formula III;

\[
\begin{array}{c}
\text{Formula III} \\
\end{array}
\]

wherein \( R \) is \( C_{1-4} \) alkyl

hydrolyzing the resulting 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid alkyl ester compound of formula III with a suitable hydrolyzing agent in a suitable solvent to obtain 2-(imidazo[1,2-a]pyridine-3-yl)acetic acid of compound of formula II.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
C07D4 71/04, C07F9/65 61, 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)
C07D, 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 practicable, search terms used)

PATSEER, IPO- INTERNAL DATABASE, STN: process, preparation, Minodronic acid, 2-aminopyridine, phosphorous acid, phosphorous halide, polymorph.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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