The present invention relates to an improved process for the preparation of Minodronic acid. The present invention particularly relates to a process for the preparation of Minodronic acid from imidazo [1,2-a]pyridine.
FIELD OF THE INVENTION

The present invention relates to an improved, commercially viable and industrially advantageous process for the preparation of Minodronic acid.

BACKGROUND OF THE INVENTION

The bisphosphonic acids and their pharmaceutically acceptable salts are an important class of medicaments that act as specific inhibitor of Osteoclast-mediated bone resorption and are useful in the treatment of bone disorders such as Paget's disease and osteoporosis. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxy-apatite found in the bone.

Minodronic acid is a compound represented by the following formula (I), which has excellent bone resorption inhibitory activity, anti-inflammatory activity and analgesic-antipyretic activity and is useful for the treatment of diseases in which increased bone resorption participates, such as Paget's disease, hypercalcemia, bone metastasis of cancer and osteoporosis, as well as progress in the bone resorption (induction of osteoporosis) caused by inflammatory joint diseases such as rheumatoid arthritis and the like.

Few processes for the synthesis of Minodronic acid have been described in the literature. EP03 54806 disclose process for preparation of Minodronic acid as below.
China medical industry magazine 35 (4), 2004, 193-194 disclose

CN101531681 describes process as below.

CNI 02020676 also disclose process for preparation of Minodronic acid.

The above processes for preparation of Minodronic acid require many numbers of steps and involve unfriendly reagents. The process is less economical, relatively less safe and time-consuming. Hence such technology is not readily suitable for commercial production.
Several methods for making bisphosphonic acids or its pharmaceutically acceptable salts have been disclosed. The synthesis are based on reacting a carboxylic acid with a mixture of phosphorous acid and one of the following phosphorus halides: phosphorus trichloride (PCI₃), phosphorus oxychloride (POCl₃), phosphorus pentachloride (PCI₅), phosphorus tribromide (PBr₃), phosphorus oxybromide (POBr₂), or phosphorus pentabromide (PBr₅), then quenching the reaction mixture with water or a non-oxidizing aqueous acid, followed by heating to hydrolyze the phosphorus intermediates to the final product.

U.S. Pat. No. 4,407,761 describes the synthesis of 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid (alendronic acid) and other bisphosphonic acids. The reaction has been carried out in the presence of diluent, e.g. chlorinated hydrocarbons, especially chlorobenzene, which does not solubilize the reaction components and serves only as a heat carrier. The reaction starts as a two-phase system, in which the melted phase gradually thickens into a non-stirrable mass. This semi solid sticky mass finally turns into a hard, rigid material, thereby coating the walls of the reaction vessel and thus preventing the smooth heat transfer and complicating the product work-up. The overall yield of this process is variable i.e. 45% to 56%. The solvent i.e. chlorobenzene used in the reaction is carcinogenic in nature and thus not recommendable for industrial scale.

U.S. Pat. No. 4,922,007 and U.S. Pat. No. 5,019,651 reveal a solution to the solidification. Methanesulfonic acid (MSA) is used to solubilize the reaction components and keep the reaction mixture stirrable up to completion of the reaction. The optimum temperature of phosphorylation reactions using phosphorus trichloride is 90°C. or high. Although the problems with physical characteristics of the reaction appeared solved, a safety problem surfaced. Methanesulfonic acid reacts with phosphorus trichloride and under adiabatic conditions, i.e. above 85°C, the reaction mixture becomes uncontrollably exothermic, which is accompanied by high pressure and, therefore, is not very safe on large-scale production.

U.S. Pat. No. 5,908,959 employs poly alkylene glycols as reaction solvent for synthesizing bisphosphonates. The use of poly alkylene glycols on industrial scale is not very feasible as they are difficult to recover in pure form for reuse.
US Patent Application No. 20040043967 A1 describes the preparation of bisphosphonic acids by using the diluents other than halogenated hydrocarbons, but overall yield of the process is 56% to 80%. On the other hand U.S. Pat. No. 6,562,974 describes the preparation of bisphosphonates in an overall yield of 77% by using phosphorous acid as a reactant/solvent in presence of base. The disadvantage of this process is that the reaction mixture becomes very viscous without a solvent.

Apart from above mentioned process patents; polymorph patents and patent applications are available. US5480875 describes different crystalline forms of Minodronic acid hydrate, Minodronic acid anhydrous and Minodronic acid sodium salt and their process for preparation. This patent describes two Minodronic acid hydrate polymorph as crystal D and crystal E. Both the crystals show similar XRD pattern but having different TG-DSC curves. This patent describes the monohydrate crystals D and E can be produced by dissolving the crystals in aqueous hydrochloric acid solution with specific conditions of cooling and stirring. But, these processes can not reproducibly giving single polymorph crystal D.

Based on the aforementioned drawbacks, prior art processes find to be unsuitable for preparation of Minodronic acid at lab scale and commercial scale operations. Hence, a need still remains for an improved and commercially viable process of preparing pure Minodronic acid that will solve the aforesaid problems associated with process described in the prior art and will be suitable for large-scale preparation, in lesser reaction time, in terms of simplicity, purity and yield of the product.

SUMMARY OF THE INVENTION

The present inventors have focused on the problems associated with the prior art process and has developed an improved process for the preparation of Minodronic acid.

Therefore, in one aspect present invention provides a process for preparing Minodronic acid or a salt thereof, comprising a step of converting a compound of formula II in to compound of formula III which is further converted in to compound of formula (VI),
wherein R1 is a halogen or a carboxy-activating group and R2 is C1-C6 alkoxy, aralkoxy or phenoxy (both optionally substituted with C1C6 alkyl or alkoxy);

\[
\text{N} \quad \rightarrow \quad \text{O} \quad \rightarrow \quad \text{N} \\
\text{I} \quad \rightarrow \quad \text{II} \quad \rightarrow \quad \text{III} \quad \rightarrow \quad \text{IV} \quad \rightarrow \quad \text{V} \quad \rightarrow \quad \text{VI}
\]

In another aspect the present invention provides process for producing a bisphosphonic acid compound which process comprises reaction of a carboxylic acid compound or as salt thereof with phosphorous acid and phosphorous trichloride in presence of tetramethylurea as a solvent.

In another aspect the present invention provides a purification process for crude Minodronic acid which comprises acid base treatment with crude Minodronic acid.

In yet another aspect the present invention provides a process to obtain pure Minodronic acid using acid base treatment and also provides the process to obtain pure crystal D of Minodronic acid.

The present inventors have found that employing process of the present invention for the preparation of Minodronic acid, overcomes the drawbacks of the prior art and may be prepared and subsequently converted to Minodronic acid in high yield and purity.

**BRIEF DESCRIPTION OF THE DRAWINGS:**
Fig 1 is the SS-NMR of the crystalline Minodronic acid hydrate before micronisation.
Fig 2 is the SS-NMR of the crystalline Minodronic acid hydrate after micronisation.

**DETAILED DESCRIPTION OF THE INVENTION:**
Aspects, advantageous features and preferred embodiments of the present invention will be described in further detail below, noting however that such aspects, advantages features as well as embodiments and examples are presented for illustrative purposes only and shall not limit the invention in any way.
The use of ethyl oxalyl chloride to prepare Minodronic acid intermediate-Imidazo [1, 2-a] pyridine-3yl acetic acid hydrochloride is a significant point of the present invention, which distinguish over every prior art. Use of tetramethylurea as a solvent for phosphorylation is also a crucial point over prior art.

A further significant advantage of the present invention relates to achievement of purity of the final compound as per JP grade by using simple acid base treatment with high yield.

In one embodiment the present invention provides a process for preparation of Minodronic acid of formula I comprising the steps of:

a. reacting a imidazo [1, 2-a] pyridine of formula II with an ethyl oxalyl chloride to obtain compound of formula (III):

![Formula II](image)

![Formula III](image)

b. treating compound of formula III with base and hydrazine hydrate to obtain compound of formula VI:

![Formula VI](image)

c. reacting the resulting carboxylic acid compound of formula VI with phosphorous acid and a phosphorous chloride selected from PCI 3, PCI 5 and POCI 3, in an aprotic polar solvent.
In one embodiment present invention provides process where Imidazo [1,2-a]pyridine reacts with oxalyl derivative in presence of suitable solvent. Oxalyl derivative may contain on one end any halogen such as Cl, Br or I or any leaving group such as mesyl, tosyl, etc at the other end any ester group such as substituted or unsubstituted alkyl, aryl or aralkyl group which can subsequently convert into acid group. Suitable solvents used during reaction are high boiling non polar solvents like toluene, xylene etc. Reaction is carried out at a temperature of 50-150°C, more preferably 100-110°C. The reaction time may between 5 hours to 50 hours, specifically about 20 hours to 30 hours.

In one embodiment, the acylated compound of formula III is isolated from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti solvent to the solution, evaporation, vacuum distillation or a combination thereof. In another embodiment, the reaction mass containing the acylated compound of formula III obtained is concentrated and then taken for next step.

In one embodiment, the base used in step -(b) is selected from the group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, magnesium hydroxide, calcium hydroxide, sodium hydride, lithium hydride, potassium hydride, sodamide, lithium amide, potassium amide, sodium methoxide, potassium tert-butoxide, sodium tert-butoxide, sodium tert-pentoxide, lithium tert butoxide. After hydrolysis of ester group Wolff-Kishner reduction is carried out with hydrazine hydrate in presence of base. Reaction is carried out at reflux temperature and its required long time about 20 to 30 hrs for completion.

In another embodiment Imidazo [1, 2-a] pyridine-3yl acetic acid is isolated as hydrochloride salt in a pure form which is an important intermediate of Minodronic acid.

In one embodiment, the solvent used in step -(c) is selected from the group consisting of aprotic polar solvents such as N,N'-dimethyleneurea (DMEU), N,N'-dimethyl
propylene urea (DMPU), 1-methyl-2-pyrrolidone (NMP), Tetramethylurea (TMU), acetonitrile or a mixture of two or more thereof.

The most often used reaction of obtaining Minodronic acid is the reaction of Imidazo [1,2-a] pyridine-3yl acetic acid with the phosphonating agent such as H₃PO₃/PCI₃ or H₃PO₃/POCI₃. Also for this reaction the number of publications implicates the problem of dense and heterogenic reaction mass that is not even stirrable which is solved by use of suitable solvents. However, the use of those solvents deteriorates the profitability of the process, makes isolation and purification of the product more difficult which results in complication of process implementation into the industrial scale.

Unexpectedly, it was found that the use of tetramethylurea as a solvent leads to obtaining Minodronic acid and simultaneously ensuring the stirrable reaction mixture. Moreover, such solution allows for simplification of the process to a greater extent, which is advantageous for implementation in to the industrial scale. Additionally, tetramethylurea is a higher boiling, less toxic solvent and can be recoverable solvent.

The conventional process of Minodronic acid provides end product with more non-polar impurities which is difficult to remove and requires additional purification, thereby not suitable for commercial point of view. The same has been avoided by the present invention by simple acid base treatment.

The Three main known impurities of Minodronic acid hydrate are:
(i) 2-Aminopyridine (Impurity-I) which has the following structure:

\[
\text{Impurity-I} \quad \text{with relative retention time (RRT) of 1.64.}
\]
(ii) Imidazo [1,2-a] pyridine-3-yl acetic acid hydrochloride (Impurity-II), which has the following structure:

![Structure of Impurity-II](image)

Impurity-II is detected and resolved from Minodronic acid hydrate by HPLC with an RRT of 2.77.

(iii) Imidazo [1,2-a] pyridine-3-yl (oxo) acetic acid (Impurity-III), which has the following structure:

![Structure of Impurity-III](image)

The impurity-III is detected and resolved from Minodronic acid hydrate by HPLC with an RRT of 5.31.

(iv) An unknown impurity at 1.28 RRT, which m/z found to be as 291[M+H] by LC-MS/MS.

The Unknown impurity at 1.28 RRT is detected and resolved from Minodronic acid hydrate by HPLC with an RRT of 1.28.

Surprisingly the Minodronic acid obtained from this present invention contain less than 1% particularly less than 0.5% of impurity and more particularly less than 0.1% of total impurity.

No prior art teaches or motivates the invention provided in the present application, and constitute novelty of the present invention. Thus the present invention provides the robust process to eliminate the non polar impurities particularly at 1.28 RRT which is otherwise
requires additional purification. Accordingly the present invention provides a purification process for crude Minodronic acid which comprises acid base treatment with crude Minodronic acid.

In another embodiment process for purifying Minodronic acid involves preparation of disodium salt by stirring wet crude Minodronic acid with NaOH solution at pH 6.5-7.0. Stirring with methanol and then filtering product which removes all impurities in filtrate. Pure disodium salt is now converted into Minodronic acid by refluxing with HCl solution.

In yet another embodiment present invention gives process to prepare only crystal D. The method according to this invention involves dissolving Minodronic acid in dilute HCl solution (4.0 lit.) at reflux temperature and then cooling 70-80°C very slowly. Further allowing it to stir at this temperature for more than 5 hrs at 100-110 RPM and then slowly cooling to room temperature gives pure crystal D.

Further Minodronic acidhydrate obtained as per the present invention can be further micronized, milled or sieved to get the desired particle size required for pharmaceutical composition to achieve the desired dissolution profile.

The main embodiment of the present invention is described in the scheme I.

The invention will be further described with reference to the following non limiting examples.
Example-I: preparation of Imidazo[1,2-a]pyridine.
Charged 2-Aminopyridine (100.00 g), Dichloromethane (1000ml) and sodium bicarbonate (98.17 g) into the reactor. Slowly added Chloroacetaldehyde aqueous solution (205.85 g, Assay: 48.58%) into reaction mixture at temperature between 10-25°C. Stirred the reaction mixture for 6 hours at room temperature. After completion of the reaction, charged process water (300 ml) into reaction mixture and extracted product in dichloromethane. Removed dichloromethane atmospherically below 60°C and then distilled product under vacuum, (yield-75%)

Example-II: Imidazo [1, 2-a] pyridine-3yl acetic acid hydrochloride
Charged toluene, Imidazo [1,2-a]pyridine (100.0 g) and Ethyl oxalyl chloride (288.91 g) in to the reactor. Stirred the reaction mixture for 24 hours at 113±3°C. After completion of the reaction, distilled off toluene under vacuum below 80°C and then charged water (800 ml) into reaction mass. Cooled the reaction mass to room temperature and then adjusted the reaction mass pH between 6.5 and 7.5 by using aqueous potassium hydroxide solution (-300 ml, 30%). Charged Potassium hydroxide (71.20 g) into the reaction mass and heated the reaction mixture for 2 hrs at 52±3°C. After completion of the reaction, distilled off solvent and added hydrazine hydrate (63.5 g, 80 % solution in water) into reaction mass. Stirred the reaction mixture for 24 hours at 102±2°C. After completion of reaction, adjusted the reaction mixture pH between 10.5-11.0 by using cone. HCl solution (-200 ml). Charged activated charcoal (10.0 g) and stirred the reaction mixture for 30 mins. Filtered the reaction mixture through hyflo bed; washed the hyflo bed with process water (200 ml). Adjusted the reaction mixture pH 6.0-6.5 with cone. HCl solution (-100 ml). Filtered the reaction mixture and washed the wet cake with acetone in centrifuge bag (200 ml). Charged ethyl acetate.HCl [(8%), 464 g] and Ethyl acetate (200 ml) and wet cake in to the reactor. Heated the reaction mixture to 53±2°C. Stirred the reaction mixture for 4 hours at 53±2°C. Cooled the reaction mixture to 3±2°C. Filtered the reaction mixture and washed with chilled ethyl acetate (200 ml). Dried the material under vacuum for 8 hours at 53±2°C. (Yield:75.00%)
Example-III: Preparation of 1-Hydroxy-2-(Imidazo [1, 2-a] pyridine-3-yl) ethane-1, 1-bis (phosphonic acid) monohydrate

Charged Tetramethylurea (600 ml), Phosphorous acid (115.68 g) and process water (30.0 ml) in to the reactor. Charged Imidazo [1, 2-a] pyridine-3yl acetic acid hydrochloride (100.0 g) into reaction mass and stirred the reaction mass for 15 minutes. Cooled the reaction mass to 17±3°C and added Phosphorous trichloride (290.64 g) into the reaction mass below 40°C. Heated the reaction mixture to 63±3°C and stirred the reaction mixture for 3 hours. After completion of reaction, distilled off phosphorous trichloride under vacuum. Cooled the residual mass to room temperature and added 20-24 % aqueous HCl solution (800 ml) to the reaction mixture below temperature 80°C. Stirred the reaction mixture for 4 hours at 95±2°C. Cooled the reaction mixture to 75±2°C and charged toluene (500 ml) into the reaction mixture. Stirred the reaction mixture for 30 minutes at 75±2°C. Separated the lower aqueous layer. Charged aqueous layer into another reactor and cooled the reaction mass to room temperature. Adjusted the reaction mass pH between 1.1-1.8 by using aqueous sodium hydroxide solution (30%, ~1200 ml) below 30±5°C to precipitate the product. Stir the reaction mixture for 3 hours. Filtered the product and washed with water. Charged wet cake into water and adjusted the reaction mixture pH between 6.5-7.0 by using aqueous sodium hydroxide solution (~150 ml, 30%). Added methanol (15 vol.) into the reaction mass slowly at 23±3°C and stirred the reaction mixture for 3 hours. Filtered the reaction mixture and wash the wet cake with methanol. Charged 7.0-8.0 % HCl solution and the wet cake in another reactor. Heated the reaction mixture to 95±2°C for 60 minutes. Cooled the reaction mixture to 13°C and stirred the reaction mixture for 4 hrs. Filtered the reaction mixture and washed with water. Dried the material for 8 hours at 50-5.5°C under reduced pressure. (Yield: 73.00%)

Example-IV: Preparation of 1-Hydroxy-2-(Imidazo [1, 2-a] pyridine-3-yl) ethane-1, 1-bis (phosphonic acid) monohydrate

Charged 3.5-4.0 % HCl solution (4.0 lit.) and stage-III (100.0 g) into the reactor and heated the reaction mixture to 99°C for 20 minutes to get the clear solution. Filtered hot the reaction mixture through cartridge filter and then allowed to cool the reaction mixture
to 77±2°C at a cooling rate of 1°C / 5 minutes at 100-110 RPM. Stirred the reaction mixture at 77±2°C for 5 hrs at 100-110 RPM. Cooled the reaction mixture to 27±3°C at a cooling rate of 2°C / 5 minutes at 100-110 RPM. Stirred the reaction mixture for 3 hrs at 27±3°C at 100-110 RPM. Filtered the reaction mixture and washed the wet cake with process water (100 ml) at 27±3°C. Dried the material for 8 hours at 53±2°C under reduced pressure, (yield 90.00%)

Experimental

The LC system, used for method development and forced degradation studies and method validation was Waters-Alliance (manufactured by Waters India Ltd) LC system with a photo diode detector. The output signal was monitored and processed using Empower software system (designed by Waters India) on IBM computer (Digital Equipment Co).

The chromatographic column used was a Waters make X-bridge C18 (250 mm x 4.6 mm) with 5.0µm particles. The mobile phase consists 32.3 g of dipotassium hydrogen phosphate anhydrous, 3.0 g of EDTA-disodium salt, and 2.0 g Tetrabutyl ammonium dihydrogen phosphate into a suitable container. Dissolve the contents in 800 mL of water. Pipette out 2.0 mL of concentrated Hydrochloric acid into the same container, dissolve and mix well. Adjust the pH of the solution to 7.5. Transfer the contents to 1000 mL measuring cylinder and dilute to 960 mL with water. Transfer the contents to a suitable container and mix well. Add 40 mL of methanol into the same container and mix. The flow rate of the mobile phase was kept at 1.0 ml/min. beginning with the Isocratic elutions. The column temperature was maintained at 35°C and the wavelength was monitored at a wavelength of 280 nm. The injection volume was 10 µL for related substances determination. Mobile phase was used as diluent during the standard and test samples preparation.

Preparation of impurity stock solution:

Weigh and transfer about 5 mg each of Impurity-I, Impurity-II and Impurity-III standards into a 100 mL volumetric flask, add about 30 mL diluent and sonicate to dissolve. Make up the volume with diluent and mix well.

Weigh and transfer about 50 ± 5 mg of Minodronic acid hydrate reference standard into a 25 mL volumetric flask. Add about 10 mL diluent into the same volumetric flask and sonicate to dissolve. Make up to the volume with diluent and mix well.

**Standard stock preparation**

Pipette out 1.0 mL of the above solution to 100 mL volumetric flask and make up to the mark with diluent.

**Reference solution - (a) preparation (Minodronic acid hydrate and each impurity is @ 0.1%).**

Pipette out of 5.0 mL of standard stock preparation and 2.0 mL of Impurity stock solution into a 50 mL volumetric flask. Make up to the volume with diluent and mix well.

**Reference solution-(b) preparation (Minodronic acid hydrate @ 0.1%):**

Pipette out 5.0 mL of standard stock preparation into a 50 mL volumetric flask and make up the volume with diluent and mix well.

**Spiked solution (Minodronic acid hydrate + 0.10% of each Known impurity spiked solution) @ 280 nm.**
Sample solution (Minodronic acid + Unknown impurity at 1.28 RRT) @ 280 nm.
Claims:

1. A process for preparing Minodronic acid compound of formula (I) or a salt thereof,

which process comprises reacting a compound of formula II with a compound of formula V to form compound of formula III

wherein, R_i is a halogen or a carboxy-activating group, R_2 is Ci-C_6 alkoxy, aralkoxy or phenoxy (both optionally substituted with Ci-C_6 alkyl or alkoxy).

2. A process for preparing Minodronic acid compound of formula (I) or a salt thereof,

which process comprises converting a compound of formula III in to compound of formula VI

in which R_2 is Ci-C_6 alkoxy, aralkoxy or phenoxy (both optionally substituted with Ci-C_6 alkyl or alkoxy).
3. A process for producing a bisphosphonic acid compound which process comprises reaction of a carboxylic acid compound or as salt thereof with phosphorous acid and a phosphorous chloride selected from PCI₃, PCI₅ and POCI₃ in presence of tetramethylurea.

4. A process for producing a Minodronic acid which process comprises reaction of a carboxylic acid compound of formula (VI) with phosphorous acid and phosphorous trichloride in presence of tetramethylurea.

$$\text{(VI)}$$

5. A process for preparation of Minodronic acid of formula I comprising the steps of:

a. reacting a imidazo [1, 2-a] pyridine of formula II with an ethyl oxalyl chloride to obtain compound of formula (III):

$$\text{(II)}$$

$$\text{(III)}$$

b. treating compound of formula III with base and hydrazine hydrate to obtain compound of formula VI:

$$\text{(VI)}$$
c. reacting the resulting carboxylic acid compound of formula VI with phosphorous acid and a phosphorous chloride selected from PCI₃, PCI₅ and POCI₃ in an aprotic polar solvent.

6. A process according to claim 5, wherein the base used in step-(b) is selected from alkali metal hydroxide, carbonates, alkaline earth hydroxides or carbonates, alkoxide bases; preferably potassium hydroxide.

7. A process according to claim 5, wherein an aprotic polar solvent used in step-(c) is selected from N,N’-dimethylethyleneurea (DMEU), N,N’-dimethylpropyleneurea (DMPU), 1-methyl-2-pyrrolidone (NMP), Tetramethylurea (TMU), acetonitrile or a mixture of two or more thereof.

8. A process for purifying Minodronic acid of formula I comprising the steps of:
   a. stirring the Minodronic acid in water;
   b. adjusting the pH more than 6.0 using aqueous NaOH solution;
   c. adding methanol in the reaction mixture;
   d. filtering the product;
   e. mixing the product with dil. HC1 solution;
   f. heating the reaction mixture to 80-95°C;
   g. cooling the reaction mixture below 20°C;
   h. filtering the product and washing with water;
   i. optionally recrystallising above Minodronic acid using suitable solvent system.

9. A process for preparing pure crystal D of Minodronic acid comprising the steps of:
   a. dissolving Minodronic acid in dilute HC1 solution (4.0 lit.) at reflux temperature;
   b. optionally filtering the hot solution;
   c. slowly cooling the reaction mixture at 70-80°C;
d. stirring the reaction mixture at 70-80°C for more than 5 hrs at 100-110 RPM;

e. slowly cooling the reaction mixture to room temperature;

f. filtering the product and washing with water;

g. drying the material under vacuum.

10. A process for producing a Minodronic acid which process comprises reaction of a carboxylic acid compound of formula (VI) with phosphorous acid in presence of tetramethyurea where addition of Phosphorous trichloride into the reaction mass below 40°C.