WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 9, 2731-2777. Review Article ISSN 2277– 7105

# AN EXHAUSTIVE METHODOLOGICAL REVIEW OF PATENTS ON THE SYNTHESIS AND PURIFICATION OF ZOLEDRONIC ACID

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Article Received on
25 April 2023,

Revised on 10 May 2023,
Accepted on 30 May 2023,

DOI: 10.20959/wjpr20239-28454

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## ABSTRACT

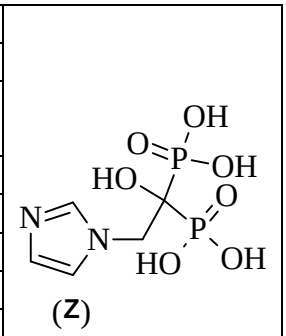
The present review work was focused on extracting the disclosed methods from patents about the synthesis and purification of Zoledronic acid. Numerous patents were filed by the researchers/organizations over the years to synthesize Zoledronic acid with significant claims. In most of the patents, synthesis and biological activities of a few related dronic acids are also demonstrated alongside Zoledronic acid. In the context, 1-*H*-imidazole, 1-*H*-imidazol-1-ylacetic acid, 1-*H*-imidazol-1-ylacetic acid hydrochloride were found to be the major key starting materials used to synthesize Zoledronic acid. Similarly, phosphoric acid/phoshorous acid and phoshorous trichloride/phosphorous oxychloride are the key *P*-reagents used for phosphorylation.

**KEYWORDS:** Zoledronic acid, 1-*H*-imidazole, 1-*H*-imidazol-1-ylacetic acid, 1-*H*-imidazol-1-ylacetic acid hydrochloride, phosphorylation, hydrolysis, recrystallization.

## INTRODUCTION

Similar to Ibandronic acid, Minodronic acid, and Risedronic acid, the drug under focus Zoledronic acid (**Z**) is a therapeutically active heterocyclic bisphosphonate compound.[1] It is a potent medication to treat and prevent numerous forms of osteoporosis,[2] hypercalcemia of malignancy,[3] multiple myeloma,[4] bone metastases from solid tumors,[5] and Paget's disease of bone,[6,7] It is a third generation, nitrogen comprising bisphosphonate that inhibits

osteoclast function and prevents bone resorption.[8] Some of the basic but essential details of (**Z**) are depicted in **Table 1**.

| **Table 1. Basic details of Zoledronic acid (Z)** |  |
|---|---|
| Generic name: Zoledronic acid | |
| IUPAC name: [1-hydroxy-2-(1-*H*-imidazol-1-yl)-1-phosphonoethyl] phosphonic acid | |
| Brand names: *Aclasta*, *Reclast*, *Zometa* | |
| Drug-Bank accession number: DB00399 | |
| CAS number: 118072-93-8 | |
| FDA approval: 2001-08-20 | |
| Water solubility: 3.27 mg/mL | |
| Chemical Formula: $C_5H_{10}N_2O_7P_2$ | |
| Molecular weight: 272.0896 | |

(**Z**)

During the mode of action, bisphosphonates bind to hydroxyapatite in bone. The bone resorption by osteoclasts causes the local acidification, which eventually releases the bisphosphonate. It is taken into the osteoclast by fluid-phase endocytosis. Endocytic vesicles become acidified, releasing bisphosphonates into the cytosol of osteoclasts where they act. Osteoclasts mediate resorption of bone. When osteoclasts bind to bone they form podosomes, ring structures of F-actin. Etidronic acid also inhibits V-ATPases in the osteoclast, preventing F-actin from forming podosomes. Disruption of the podosomes causes osteoclasts to detach from bones, preventing bone resorption.[9,10] Bisphosphonate drugs having nitrogen in their framework are renowned to impart apoptosis of hematopoietic tumor cells by inhibiting the components of the mevalonate pathway farnesyl diphosphate synthase, farnesyl diphosphate, and geranylgeranyl diphosphate. These are vital for post-translational prenylation of GTP-binding proteins like Rap1. The lack of prenylation of these proteins interferes with their function, and in the case of Rap1, leads to apoptosis.[11,12] A study related to safety, pharmacokinetics, and changes in bone metabolism associated with medication of (**Z**) was done to Japanese patients with primary osteoporosis.[13]

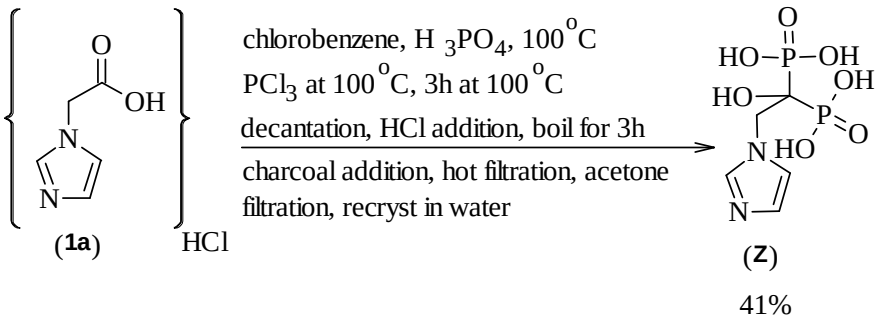
With regard to the synthesis of (**Z**), Nagy, D. I., *et al*. 2017, had compiled a review article about the mechanistic aspects behind the formation of hydroxymethylenebisphosphonic acids. This initiative had covered the synthesis and isolation methodologies of first, second and third generation dronic acids in broad.[14] Keglevich, G., *et al*. 2021, had reported the synthesis of (**Z**) using a non-hazardous solvent. The same research group compiled an article on the mechanistic study on the formation of dronic acids, which includes the discussion on the synthesis of (**Z**) from methanesulfonic acid and sulfolane.[15,16] The present review work

specifically emphasizes on the chronological survey of patents, which disclose the synthesis and purification of (**Z**) by various researchers/organizations/institutions around the globe.

## DETAILS ON THE SYNTHESIS AND PURIFICATION OF (Z)

Jaeggi, K, A., & Widler, L. 1989, had reported the synthesis and recrystallization of (**Z**) in a patent (**Table 2**). The work primarily elaborates the synthesis and pharmaceutical use of many substituted alkanediphosphonic acids. As per the disclosure, 8.60 g of 1-*H*-imidazol-1-ylacetic acid hydrochloride (**1a**), 7.1 ml of 85% phosphoric acid ($H_3PO_4$) and 25 ml of chlorobenzene were taken in reactor provided with condenser and addition funnel. It was heated to 100 $^oC$, added 13.9 ml of phosphorous trichloride ($PCl_3$) dropwise to the reaction mixture, meanwhile HCl gas evolution was occurred. Over a period of 30 min, a dense precipitation occurs in the reaction mixture and the reaction was then continued at 100 $^oC$ for further 3 h. The supernatant chlorobenzene phase was decanted to separate it from the residue. To the residue added 40 ml of 9N HCl and refluxed for 3 h, later to it added activated charcoal and hot filtered. The clear filtrate was then diluted with acetone to get the precipitation and filtered to isolate the crude product. It was then recrystallized from water to isolate (**Z**), (**Scheme 1**). Yield: 41.0%, mp: 239 $^oC$ (dec.).

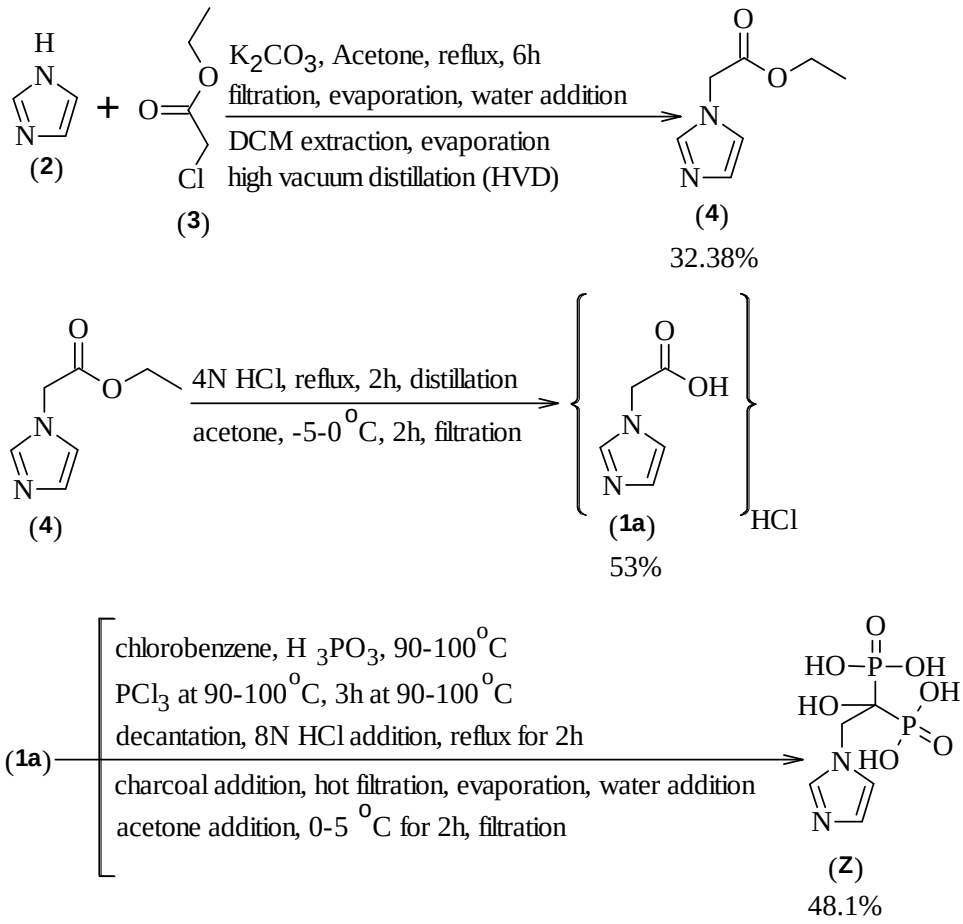
| **Table 2: Details of the patent entitled "Substituted alkanediphosphonic acids and pharmaceutical use".[17]** |
|---|
| **Application**: US31596289A, 1989-02-27 |
| **Publication**: US4939130A, 1990-07-03 |
| **Published also as**: AT72816T; AU607722B2; AU8145387A; CA1338937C; CY1827A; DD270533A5; DE10199052I1; DK174098B1; DK609587A; EP0275821A1; EP0275821B1; ES2038692T3; ES2038692T4; FI875096A; FI87570B; FI87570C; GR3003895T3; HK114894A; HU199150B; HUT46330A; IE59816B1; IE873148L; IL84497A; JP2744238B2; JPS63150291A; KR880006204A; KR960010752B1; LU90838I2; MX9427A; NL300058I1; NL300058I2; NO173446B; NO173446C; NO2001015I2; NO874856L; NZ222610A; PH24345A; PT86167A; PT86167B; SG92194G; ZA878698B. |
| **Inventors**: Jaeggi, K, A., & Widler, L. |




**Scheme 1: Synthesis of (Z) by phosphorylation to (1a) using $H_3PO_4$.**

With an intention to synthesize (**Z**) from a simple key starting material Hu, W., *et al*. 2002, had reported the use 1-*H*-imidazole (**2**) in a patent (**Table 3**). As per the disclosure, 300.0 g of 1*H*-imidazole (**2**), 450 ml of ethyl-chloroacetate (**3**), 360.0 g of anhydrous $K_2CO_3$ and 1500 ml of acetone were taken in reactor provided with a condenser. The reaction mixture was refluxed under stirring for 6 h, and then cooled to ambient temperature for filtration. The filtrate obtained was evaporated to dryness to remove the acetone, and then added 600 ml of water. The crude product mixture was extracted to dichloromethane and dried over anhydrous $MgSO_4$. Solvent was evaporated to dryness under normal pressure to get the oily residue. It was then distilled under reduced pressure (high vacuum distillation) to collect the product fraction in the range of 135-140 $^oC$ under 5 mm Hg of pressure. Yield: 32.38%, as pale yellow oily residue. In the next stage, 220.0 g of ethyl-1*H*-imidazol-1-ylacetate (**4**) and 900 ml of 4N HCl were refluxed for 2 h under stirring in a reactor. The reaction mixture was subjected to distillation under pressure until the residual volume reaches around 150 ml. To the residue added 600 ml of acetone and kept under stirring at -5-0$^oC$ for 2 h. The precipitate formed was filtered and dried at 70 $^oC$ to isolate (**1a**). Yield: 53.0%, as white flaky crystals. In the final stage, 180.0 g of (**1a**), 180.0 g of phosphorous acid ($H_3PO_3$) and 1 L of chlorobenzene were taken in reactor provided with condenser and addition funnel. It was heated to 90-100 $^oC$, added 190 ml of ($PCl_3$) dropwise to the reaction mixture. Over a period of 1 h, a dense yellow viscous mass appears in the reaction mixture and the reaction was continued at 90 $^oC$ for further 2 h. The supernatant chlorobenzene layer was removed by the decantation. To the residue added 1 L of 8N HCl and refluxed for 2 h, later to it added activated charcoal and hot filtered. The clear filtrate was concentrated under reduced pressure to get the oily residue. To it added 400 ml of water and 800 ml of acetone to get the precipitation. The mixture was allowed to stand at -5-0 $^oC$ for 2 h, meanwhile needle shaped crystal growth was observed. It was filtered and dried at 80 $^oC$ to isolate (**Z**), (**Scheme 2**). Yield: 48.1%, as white needle shaped powder.

| **Table 3: Details of the patent entitled "Synthesis of product prepared from imidazole acted with halogenated acetate ethyl ester".[18]** |
|---|
| **Application**: CN02138852A, 2002-07-30 |
| **Publication**: CN1472215A, 2004-02-04 |
| **Published also as**: None |
| **Inventors**: Hu, W., Zhang, Y., & Zhang, G |

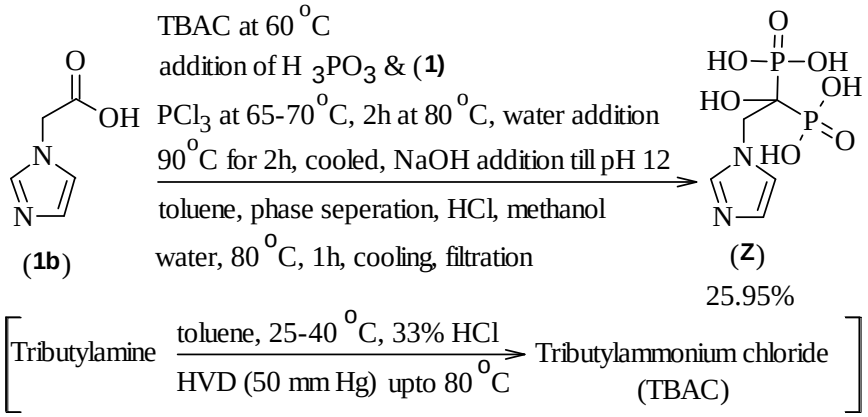



**Scheme 2. Synthesis of (Z) from (2) via condensation, hydrolysis, and phosphorylation.**

An innovative single step process was reported by De, F, L., *et al*. 2002, in a patent (**Table 4**) to synthesize (**Z**) along with three other dronic acids using tributylammonium chloride (TBAC) as the solvent instead of routinely used chlorobenzene. As per the disclosure, 20.0 g of TBAC was taken in reactor provided with a condenser and dropping funnel. It was heated to 60 $^{o}$C to melt TBAC, then 3.2 g of $H_3PO_3$ and 5.0 g of 1-*H*-imidazol-1-ylacetic acid (**1b**) were added and the mixture was stirred at 65-70 $^{o}$C. To the reaction mixture, 10.9 g of $PCl_3$ was added slowly and then it was stirred at 80 $^{o}$C for 2 h. Added 20 ml of water and the reaction mixture was heated under stirring to 90 $^{o}$C for 2 h. Reaction mixture was then cooled to ambient temperature and 50 ml of 33% NaOH solution was added till pH: 12. The alkaline mixture was allowed to settle and the two phases formed were separated. To the aqueous layer 20 ml of toluene was added and stirred for 15 min. The phases formed are again separated and the aqueous phase was acidified with 33% HCl to pH: 1. It was then added slowly to 300 ml of methanol under stirring and the precipitate formed was filtered to isolate the crude product. To the crude solid, 70 ml of water was added and heated under stirring to 80 $^{o}$C for 1h. The solution was cooled to ambient temperature to get the precipitation, and

then it was filtered to isolate (**Z**), (**Scheme 3**). Yield: 25.95%, 2.8 g as white powder. The work extends to give a process for the synthesis of TBAC, 150 ml of toluene and 334.3 g of tributylamine were taken in a reactor provided with a condenser and dropping funnel. The mixture was kept at 25-30 $^{o}$C under stirring and 156.6 ml of 33% HCl solution was added slowly by not allowing reaction mass to exceed over 40 $^{o}$C. The homogeneous mixture was concentrated under reduced pressure of 50 mm Hg, till the viscous mass reached 80 $^{o}$C. This viscous liquid was directly used for the experiments without any further purification (**Scheme 3**).

| **Table 4. Details of the patent entitled "Preparation of biphosphonic acids and salts thereof".[19]** |
|---|
| **Application**: IB0204941W, 2002-11-25 |
| **Publication**: WO03093282A1, 2003-11-13 |
| **Published also as**: AT452899T; AU2002367897A1; AU2002367897A8; EP1504012A1; EP1504012B1; EP1504012B9; ES2338540T3; ITMI20020908A1; JP2005523938A; KR20050025162A; US2005288509A1; US7332603B2; WO03093282A8 |
| **Inventors**: De, F, L., Turchetta, S., Massardo, P., & Casellato, P. |



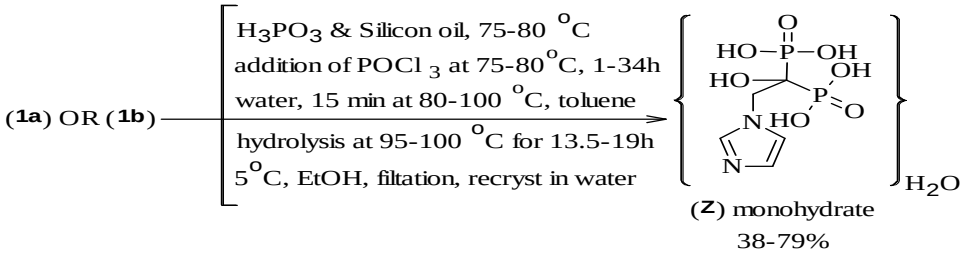

**Scheme 3. Synthesis of (Z) by the phosphorylation of (1b) in presence of tributylammonium chloride as solvent.**

To attain higher yield by avoiding the use of halogenated hydrocarbons, Lidor, H, R., *et al*. 2003, had demonstrated a process to synthesize (**Z**) and other dronic acids using a few diluents for phosphorylation in a patent (**Table 5**). The general process involves the addition of (**1a**)/(**1b**), $H_3PO_3$, and a diluent (silicon oil) to a reactor provided with condenser and dropping funnel. It was heated to 75-80 $^{o}$C and phophorous oxychloride ($POCl_3$) was added slowly. The reaction was continued at 75-100 $^{o}$C for 1-34 h, and then water was added at 80-100 $^{o}$C. It was vigorously stirred for 15 min and added toluene for proper separation of phases. The aqueous phase was separated and heated to 95-100 $^{o}$C for 13.5-19 h, for

hydrolysis. The reaction mixture was cooled to 5 $^{o}$C, added absolute ethanol to enforce the precipitation and kept under stirring at 5 $^{o}$C for 2.5-4 h. It was then filtered, dried and recrystallized from 26 vol of water to isolate (**Z**) monohydrate, (**Scheme 4**). Yield: 38-79% with LOD by TGA: 6.3-9.3%.

The general procedure was finalized after performing six different experiments using either (**1a**, for four experiments) and (**1b**, for two experiments) to synthesize (**Z**). The specific experimental conditions and the results obtained were all tabulated in **Table 6**.

| **Table 5. Details of the patent entitled "Process for making bisphosphonic acids using diluents other than halogenated hydrocarbons".** [20] |
|---|
| **Application**: US44200103A, 2003-05-19 |
| **Publication**: US7038083B2·2006-05-02 |
| **Published also as**: AT461205T; AU2003233569A1; CA2485443A1; CA2485443C; CA2657002A1; CN1665825A; EP1476451A1; EP1476451B1; JP2005526140A; JP3857706B2; KR100681282B1; KR20040111633A; PL373574A1; US2004043967A1; US2006128960A1; US2009209763A1; WO03097655A1 |
| **Inventors**: Lidor, H, R., Harel, Z., Lifshitz, L, R., & Kovalevski, I, E |



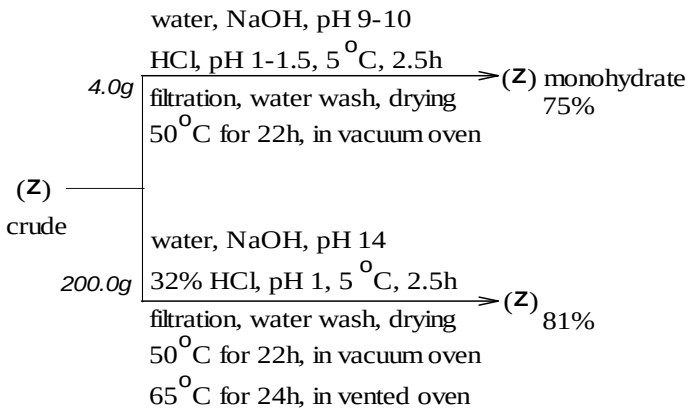

**Scheme 4. Synthesis of (Z) monohydrate by phosphorylation to (1a)/(1b) in the presence of Silicon oil using $POCl_3$.**

**Table 6: Details of experiment specific raw materials/reagents/conditions to synthesize (Z) monohydrate.**

| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** | **Exp. 4** | **Exp. 5** | **Exp. 6** |
|---|---|---|---|---|---|---|
| **(1a)/(1b)** | **(1a)** | **(1a)** | **(1a)** | **(1a)** | **(1b)** | **(1b)** |
| Batch | 5.4 g | 4.9 g | 5.9 g | 6.0 g | 12.0 g | 70.0 g |
| $H_3PO_3$ *(equiv)* | 3.6 | 3.0 | 2.0 | 4.0 | 3.0 | 3.0 |
| $POCl_3$ *(equiv)* | 4.5 | 3.75 | 3.0 | 4.0 | 3.75 | 3.75 |
| Silicon oil | 35.1 ml | 26.95 ml | 32.45 ml | 33.0 ml | 72.0 ml | 490 ml |
| Time & Temp. | 80 $^{o}$C, 24 h | 80 $^{o}$C, 22 h | 80 $^{o}$C, 23 h | 80 $^{o}$C, 11 h | 80 $^{o}$C, 17 h | 80 $^{o}$C, 34 h |
| $H_2O$ | 45 ml | 54 ml | 33 ml | 33 ml | 72 ml | 490 ml |
| Toluene | 50 ml | 54 ml | - | 33 ml | - | 490 ml |
| Hydrolysis | 19 h | 19 h | 16 h | 16 h | 16 h | 16 h |
| EtOH | 90 ml | 54 ml | 200 ml | 33 ml | - | 490 ml |
| Yield | 7.8 g, 79.0% | 6.7 g, 76.0% | 4.0 g, 38.0% | 8.2 g, 74.0% | 20.0 g, 72.0% | 95.1 g, 59.0% |

With a satisfactory yield of (**Z**) previously, the focus had shifted on to the impurity profiling of crude/crystallized (**Z**). In this context, Lifshitz, L, R., & Lidor, H, R., *et al*. 2004, had reported a crystallization method of (**Z**) by an acid-base pathway (**Scheme 5**) in a patent (**Table 7**). As per the disclosure in example 1, 4.0 g of crude (**Z**) and 40 ml of water are taken in a reactor. To this mixture, added 1.7 g of NaOH at ambient temperature under stirring until the mass becomes mild alkaline (pH: 9-10). To the clear solution, added HCl until the mass becomes acidic (pH: 1.5-2), an intense precipitation was observed during the process. It was then cooled to 5 $^{o}$C, stirred for 2.5 h, and filtered to isolate the solid. The wet cake was washed with 10 ml of water and the solid was dried in vacuum oven at 50 $^{o}$C for 22 h to isolate (**Z**) monohydrate, with a recovery of 75.0%. In example 2, 200.0 g of crude (**Z**) and 2.0 L of water are taken in a reactor. To this mixture, added 91.0 g of NaOH at ambient temperature under stirring until the mass becomes strongly alkaline (pH: 14). To the clear solution, added 300 ml of 33% HCl until the mass becomes acidic (pH: 1.5-2), an intense precipitation was observed during the acidification at 20 $^{o}$C. It was then cooled to 5 $^{o}$C, stirred for 2.5 h, and filtered to isolate the solid. The wet cake was washed with 3*100 ml of water and the solid was dried in vacuum oven at 50 $^{o}$C for 1.5 h. It was then dried in a vented oven at 65 $^{o}$C for 24 h to isolate (**Z**), with a recovery of 81.0%. The effectiveness of purification was monitored by HPLC (a%), wherein the relative retention time (RRT) of impurities in crude and crystallized sample was compared. The comparative results are tabulated in **Table 8**.

| **Table 7. Details of the patent entitled "Process for purification of Zoledronic acid".**[21] |
|---|
| **Application**: US2004005865W, 2004-02-27 |
| **Publication**: WO2004075860A2, 2004-09-10 |
| **Published also as**: CA2517387A1; EP1525207A2; US2004230076A1; WO2004075860A3 |
| **Inventors**: Lifshitz, L, R., & Lidor, H, R. |




**Scheme 5. Recrystallizarion process to get pure (Z) by acid-base method.**

| **Table 8. Impurity profile data of (Z) before and after the crystallization process.** | | |
|---|---|---|
| Relative retention time (RRT) | (**Z**) crude (a% by HPLC) | (**Z**) crystallized (a% by HPLC) |
| 0.84 | 0.57% | 0.008% |
| 1.00, for (**Z**) | 97.20% | 99.60 |
| 1.30 | 0.61% | Not detected |
| 1.90, for (**1b**) | 0.73% | Not detected |
| 2.40 for (**2**) | 0.37% | Not detected |

More serious studies on the purification arena of (**Z**) had led to the rise of a patent by Aronhime, J., & Lifshitz, L, R.. 2004, on the crystal forms of (**Z**), crystal forms of sodium salt of (**Z**) and amorphous form of sodium salt of (**Z**), **Table 9**. It was a continued part of the previous disclosure,[20] to synthesize (**Z**) using the diluent (silicon oil). A similar synthetic strategy was adopted by using diluents like chlorobenzene, toluene, and PEG-400 with mild process modifications. The individual experimental details and results are tabulated in **Table 10**. A thorough analysis of isolated (**Z**), for LOD by TGA (6.3-9.3%) and PXRD had confirmed the crystal nature to be form I of (**Z**), **Table 10** (Exp. 1-3). Furthermore, a mild modified process was reported to synthesize the form II of (**Z**) with LOD by TGA (5.2%), **Table 10** (Exp. 4). Similarly, (**1b**) and silicon oil was used to synthesize the form XVIII of (**Z**) with LOD by TGA (1.0%), **Table 10** (Exp. 5). The work continues to report numerous crystal forms of (**Z**) and its salts, by form inter-conversions, modulated drying techniques etc.

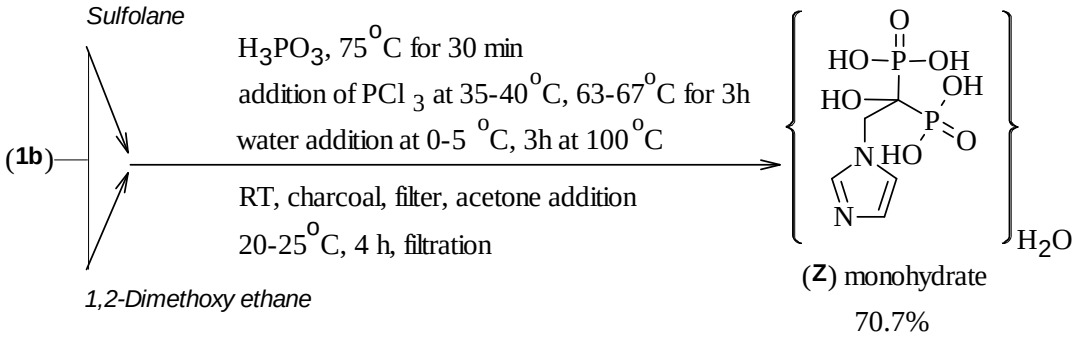
| **Table 9. Details of the patent entitled "Zoledronic acid crystal forms, Zoledronate sodium salt crystal forms, amorphous Zoledronate sodium salt, and processes for their preparation".[22]** |
|---|
| **Application**: CA2530193A, 2004-07-06 |
| **Publication**: CA2530193A1, 2005-01-20 |
| **Published also as**: AT425170T; EP1567533A2; EP1567533B1; EP1612212A1; ES2322592T3; US2005054616A1; US2007021389A1; US2007021616A1; US2007021617A1; US2007021618A1; US2007021619A1; US2007027323A1; US7435827B2; US7582768B2; US7589211B2; US7687636B2; WO2005005447A2; WO2005005447A3 |
| **Inventors**: Aronhime, J., & Lifshitz, L, R. |

| **Table 10. Details of experiment specific raw materials/reagents/conditions to synthesize (Z) in form I, II & XVIII.** | | | | | |
|---|---|---|---|---|---|
| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** | **Exp. 4** | **Exp. 5** |
| (**1a**)/(**1b**) | (**1a**) | (**1a**) | (**1a**) | (**1a**) | (**1b**) |
| Batch | 4.9 g | 4.9 g | 4.9 g | 4.9 g | 70.0 g |
| $H_3PO_3$ *(equiv)* | 3.7 | 3.0 | 3.7 | 2.0 | 3.0 |
| $POCl_3$ *(equiv)* | 3.7 | 3.0 | 3.7 | 3.7 | 3.7 |
| Chlorobenzene | 43.12 ml | - | - | - | - |
| Toluene | - | - | 43.12 ml | - | - |
| PEG-400 | | 26.95 ml | - | - | - |

| | | | | | |
|---|---|---|---|---|---|
| Silicon oil | - | - | - | 27 | 490 |
| Time & Temp. | 1 h, 100 $^{o}$C | 2 h, 75 $^{o}$C | 3 h, 100 $^{o}$C | 27 h, 80 $^{o}$C | 22 h, 80 $^{o}$C |
| $H_2O$ | 50 ml | 27 ml | 44 ml | 27 ml | 490 ml |
| Toluene | - | 27 ml | - | 30 ml | - |
| Hydrolysis | 15.5 h | 13.5 h | 16 h | 16 h | 17.5 h |
| EtOH | 50 ml | - | 200 ml | 27 ml | 490 ml |
| Acetone | - | 100 ml | - | - | |
| Yield | 8.2 g, 100% | 1.1 g, 13.4% | 6.2 g, 69.0% | 4.9 g, 58.0% | 26.0 g, 50.0% |
| Crystal form | I | I | I | II | XVIII |

To achieve higher yield, a modified process to synthesize (**Z**) monohydrate was demonstrated in a patent (**Table 11**) by Patel, V, M., *et al*. 2004. The work also covers the synthesis of three other dronic acids and their salts. As per the disclosure, 50.0 g of (**1b**), 48.7 g of $H_3PO_3$ and 180 ml of sulfolane were taken in a reactor provided with condenser and dropping funnel. The mixture was heated to 75 $^{o}$C under stirring for 30 min and then cooled to 35-40 $^{o}$C. To the mixture, added 117 ml of $PCl_3$ gradually through the dropping funnel. It was heated and maintained at 63-67 $^{o}$C for 3 h under stirring. The heterogeneous reaction mass was cooled to 0-5 $^{o}$C and 500 ml of water was added over a period of 1 h. The clear solution obtained was further hydrolyzed at 100 $^{o}$C for 3 h, the cooled to ambient temperature and charcoalized. It was then filtered, to the clear filtrate added 800 ml of acetone and stirred at 20-25 $^{o}$C for 4 h. The precipitate formed was filtered, washed with 200 ml of cold water and then with 100 ml of acetone. The solid isolated was dried in hot air oven at 55-60$^{o}$C until the water content reaches around 6.2-7.2% to get (**Z**) monohydrate. Yield: 70.7%, 81.3 g as white crystalline solid. A similar process was followed by taking 20.0 g of (**1b**) and 72 ml of 1,2-dimethoxy ethane to get (**Z**) monohydrate (**Scheme 6**). Yield: not given, as white crystalline solid, purity: 99.5% by HPLC (a%).

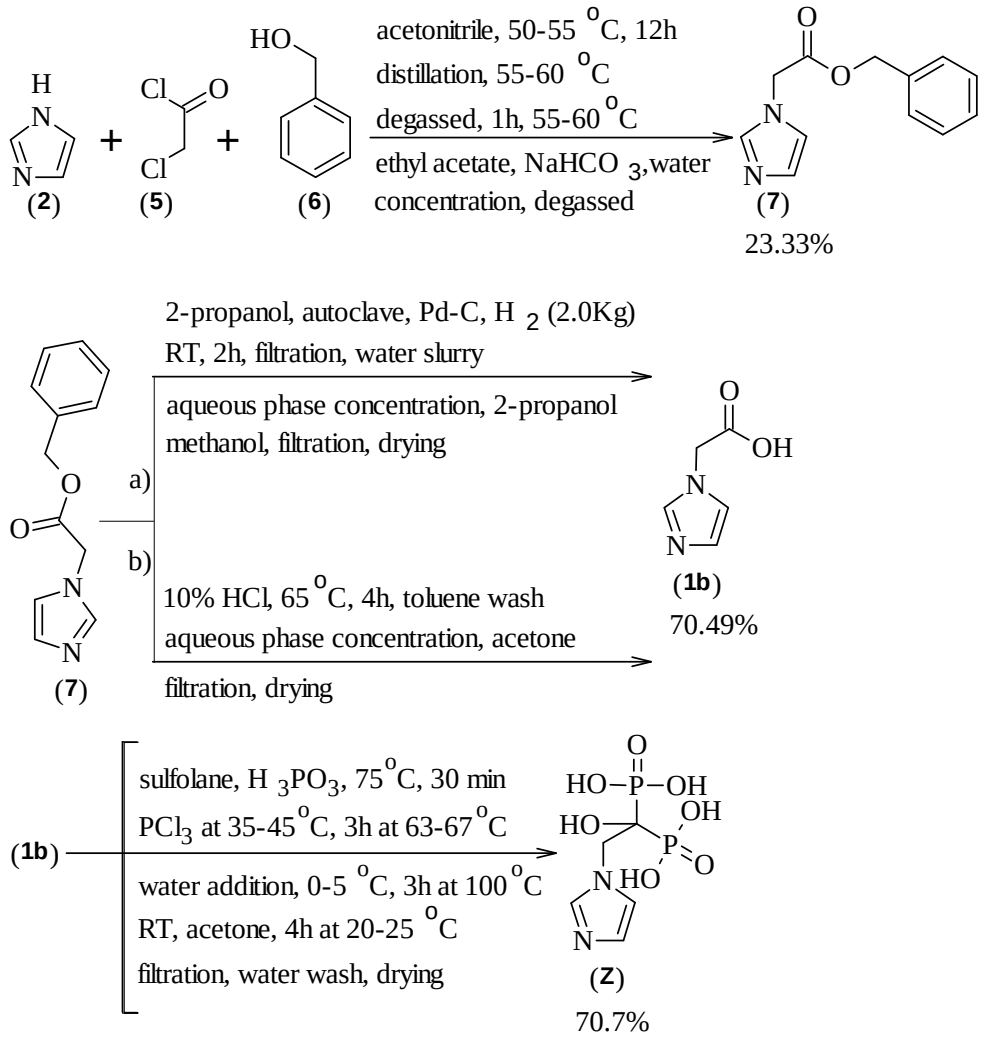
| **Table 11. Details of the patent entitled "A process for preparation of bisphosphonic acid compounds".[23]** |
|---|
| **Application**: IN2004000238W, 2004-08-10 |
| **Publication**: WO2005044831A2, 2005-05-19 |
| **Published also as**: AT451380T; CA2536229A1; CA2536229C; DK1656386T3; EP1656386A2; EP1656386B1; ES2337063T3; JP2007502810A; JP4642762B2; PL1656386T3; PT1656386E; SI1656386T1; US2006293524A1; US7411087B2; WO2005044831A3 |
| **Inventors**: Patel, V, M., Chitturi, T, R., & Thennati, R. |




**Scheme 6: Synthesis of (Z) monohydrate by phosphorylation to (1b) in sulfolane or 1,2-dimethoxy ethane.**

A refurnished process to synthesize (**Z**) from (**2**) was demonstrated in a patent (**Table 12**) by Patel, V, M., *et al*. 2004. As per the disclosure, 630.0 g of (**2**), 300 ml of benzyl alcohol (**6**) and 900 ml of acetonitrile were taken in a reactor provided with condenser and dropping funnel. The mixture was cooled to 10-20 $^{o}$C under stirring and added chloroacetyl chloride (**5**) slowly through the dropping funnel. The reaction mixture was heated to 50-55 $^{o}$C for 12 h and then the solvent was evaporated to dryness under reduced pressure at 55-60 $^{o}$C. Furthermore, it was degassed at 55-60 $^{o}$C for 1 h. To the residue added water, extracted the product to ethyl acetate, washed with 10% $NaHCO_3$ and finally washed with water. Ethyl acetate was removed completely by distillation under reduced pressure to isolate benzyl-1-*H*-imidazol-1-ylacetate (**7**). Yield: 23.33%, 467.0 g. In the next stage, 450.0 g of (**7**) and 2.25 L of 2-propanol were charged to an autoclave. To this added 22.5 g of 50% wet 5% (w/w) Pd-C and hydrogenation was done under 2 Kg pressure of $H_2$ at ambient temperature for 2 h. The mixture was filtered and the product was taken to water. It was concentrated under reduced pressure and degassed by co-distillation with 2-propanol to get the residue. To the residue added 300 ml of methanol, filtered the solid and dried to get (**1b**). Yield: 70.49%, 185.0 g with a purity of >99.0% by HPLC (a%). An alternate pathway to isolate (**1b**) was also demonstrated, wherein 25.0 g of (**7**) and 50 ml of 10% HCl were taken in a reactor and heated to 65 $^{o}$C for 4 h under stirring. The reaction mixture was washed with 50 ml of toluene and the aqueous phase was separated. The aqueous phase was concentrated under reduced pressure and degassed by co-distillation with toluene. To the residue obtained added acetone, stirred, filtered and dried to get (**1b**). Yield and purity was not mentioned. In the final stage, 50.0 g of (**1b**) was converted to (**Z**) as per the procedure demonstrated in their previous patent using sulfolane as the medium for phosphorylation [23]. Yield: 70.7%, 81.3 g as white crystalline solid (**Scheme 7**).

| **Table 12. Details of the patent entitled "A process for the preparation of 2-(imidazol-1-yl)-1-hydroxyethane-1, 1-diphosphonic acid".[24]** |
|---|
| **Application**: IN2004000320W, 2004-10-18 |
| **Publication**: WO2005066188A1, 2005-07-21 |
| **Published also as**: None |
| **Inventors**: Patel, V, M., Chitturi, T, R., & Thennati, R. |



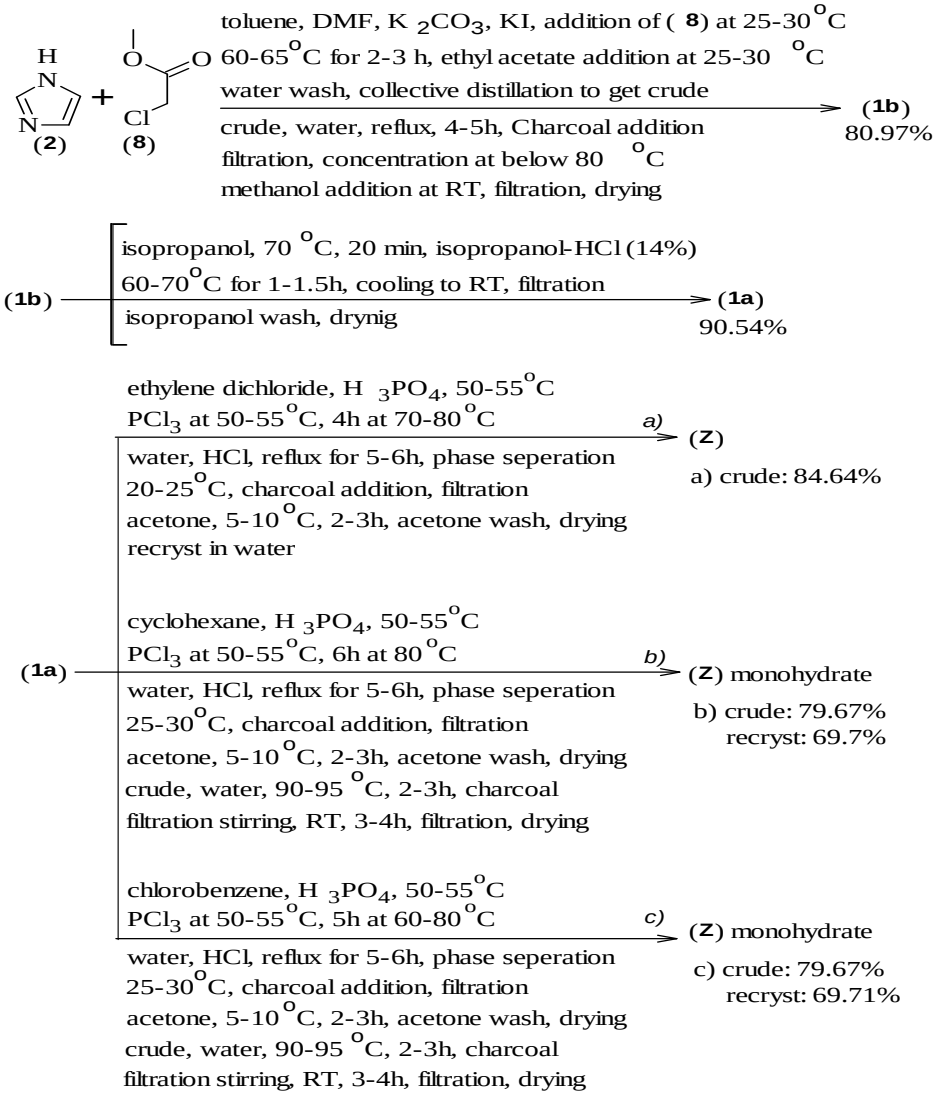

**Scheme 7: Synthesis of (Z) from (2) and the phosphorylation of (1b) in sulfolane medium.**

A promising methodology was required to overcome the numerous drawbacks in previous disclosures such as controlling the exothermicity, no control for the loss of $PCl_3$ because of vigorous HCl release, poor yield due to the formation gummy substances etc. In this regard, Pulla, R, M., *et al*. 2004, had demonstrated a scalable process to synthesize (**Z**) using (**2**) with an improved yield. As per the disclosure, 100.0 g of (**2**), 400 ml of toluene, 40 ml of dimethylformamide, 180.0 g of potassium carbonate ($K_2CO_3$) and 10.0 g of potassium iodide (KI) were taken in a reactor provided with condenser and dropping funnel. The mixture was

stirred at ambient temperature for 10 min and then 240.0 g of methyl chloroacetate (**8**) was added slowly over a period of 1.5-2 h. The reaction mixture was stirred at 25-30 $^{o}$C for 1 h, then gradually heated to 60-65 $^{o}$C and maintained for 2-3 h. After the reaction completion, it was cooled to 25-30 $^{o}$C, added 200 ml of ethyl acetate and stirred for 30 min. The top ethyl acetate layer was decanted, to the residue was extracted again with 200 ml of ethyl acetate. To the residue added 200 ml of water and stirred for 30 min and filtered to remove suspensions. The clear filtrate was extracted with 200 ml of ethyl acetate twice. All the ethyl acetate layers are combined and evaporated to dryness under reduced pressure to get the crude product. Added 500 ml of water to the crude product and refluxed in reactor for 4-5 h. Activated charcoal was added to the clear solution and filtered. Water was distilled under reduced pressure by maintaining the mass below 80 $^{o}$C. The residue formed was cooled 25-30 $^{o}$C, added 250 ml of methanol, stirred for 1h and filtered to isolate (**1b**). Yield: 80.97%, 150.0 g, as white crystalline solid, mp: 268-269 $^{o}$C and purity: 99.2% by HPLC (a%). In the next step, 60.0 g of (**1b**) and 200 ml of isopropanol were taken in a reactor provided with condenser and dropping funnel. It was heated to 70 $^{o}$C for 20 min, then added 150.0 g of isopropanol-HCl solution (14.0%) over a period of 1-1.5 h. The reaction mass was stirred at 60-70 $^{o}$C for 30 min, cooled to 25-30 $^{o}$C and stirred for additional 2 h. The mixture was filtered, washed with 50 ml of isopropanol and dried at 60-70 $^{o}$C to get (**1a**). Yield: 90.54%, 70.0 g, as white crystalline powder. In the final step, 60.0 g of (**1a**), 105.0 g of $H_3PO_4$, and 250 ml of ethylene dichloride were taken in a reactor provided with condenser and dropping funnel. It was heated to 50-55 $^{o}$C and added 152.0 g of $PCl_3$ over a period of 2-2.5 h by keeping the mass below 80 $^{o}$C. The reaction mixture was kept under stirring at 70-80 $^{o}$C for 4 h and later added 30 ml of water and 165.0 g of concentrated HCl. It was then refluxed for 5-6 h and then cooled to 25-30 $^{o}$C. The phase separation was done and the activated carbon was added to the aqueous phase. It was filtered, added 700 ml of acetone and cooled to 5-10 $^{o}$C. After 2-3 h of stirring, the precipitate formed was filtered, washed with acetone and dried at 50-60 $^{o}$C to get crude (**Z**). Yield: 84.64%, 85.0 g, as white crystalline solid, purity: 98.5% by HPLC (a%). A small portion of the crude product was dissolved in 20v of water under reflux and cooled to 25-30 $^{o}$C. It was filtered and dried to get (**Z**). Yield: not mentioned, purity: 99.4% by HPLC (a%). A similar process pathway was followed for the conversion of another 60.0g of (**1a**) in cyclohexane medium to get crude (**Z**). Yield: 79.67%, 80.0 g, as white crystalline solid, purity: 98.0% by HPLC (a%). To this added 1.6L of water, heated to 90-95 $^{o}$C and maintained for 2-3 h to get clear solution. To the solution added 10.0 g of activated charcoal and hot filtered to get clear filtrate. It was cooled to 25-30 $^{o}$C, stirred for 3-4 h and

filtered. The wet cake was washed with water and dried at 50-60 $^{o}$C until the moisture content of (**Z**) reached 6-10% to get the monohydrate for of (**Z**). Yield: 69.7%, 70.0 g, purity: 99.3% by HPLC (a%). A substantially high scale batch was done in the similar way to convert 6.0 Kg of (**1a**) in chlorobenzene medium to get crude (**Z**). Yield: 79.67%, 8.0 Kg as white crystalline solid, purity: 99.0% by HPLC (a%). It was recrystallized in water to isolate (**Z**) monohydrate (**Scheme 8**). Yield: 69.71%, 7.0 Kg, purity: 99.8% by HPLC (a%). This process reports the yield of (**Z**) close to 80%, which was around 40% in the past disclosures.

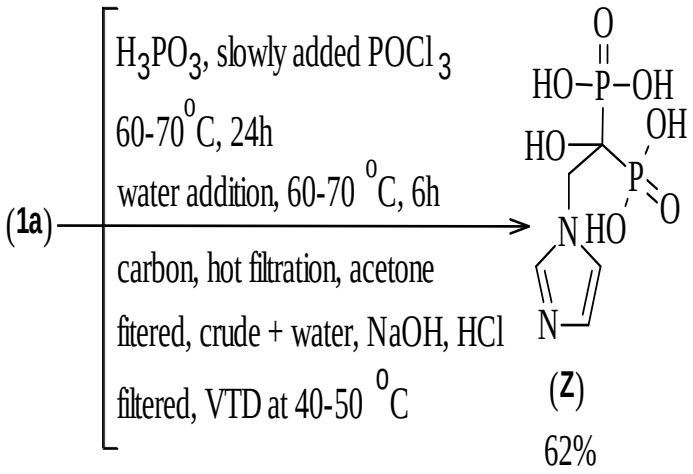
| **Table 13. Details of the patent entitled "An improved process for the preparation of Zoledronic acid".[25]** |
|---|
| **Application**: IN2004000392W, 2004-12-20 |
| **Publication**: WO2005063717A1, 2005-07-14 |
| **Published also as**: None |
| **Inventors**: Pulla, R, M., Usha, R, V., & Venkaiah, C, N. |




**Scheme 8: Synthesis of (Z) and its monohydrate from (2) in high scale with good yield.**

In previous works, variety of solvents were tried to synthesize (**Z**) but the solvent-free initiative for phosphorylation was not reported. Grassi, S., & Volante, A. *et al*, 2004, had demonstrated a process to get (**Z**) in the absence of solvent in a patent (**Table 14**). The work extends to report the synthesis of other two dronic acids and their salts. As per the disclosure, 10.0 g of (**1a**) and 47.56 g of $H_3PO_3$ were taken a reactor provided with condenser and dropping funnel. To the mixture at ambient temperature added 29.13 g of $POCl_3$ slowly under stirring. The reaction mixture was heated to 60-70 $^oC$ and maintained for 24 h. To the mixture added 60 ml of water at 60-70 $^oC$ and then refluxed for 6 h. To it added 0.3 g of activated charcoal and hot filtered to get the clear filtrate. Added 160 ml of acetone to the clear filtrate to get the precipitate and filtered to isolate the crude product. It was suspended in 50 ml of water and dissolved by adding 30% of NaOH solution till pH: 7.3-7.7. Re-precipitation was achieved by the addition of HCl till pH 0.6-1.0. The precipitate formed was filtered and dried under vacuum at 40-50 $^oC$ to get (**Z**), (**Scheme 9**). Yield: 62.0%, 10.38 g, purity: not mentioned.

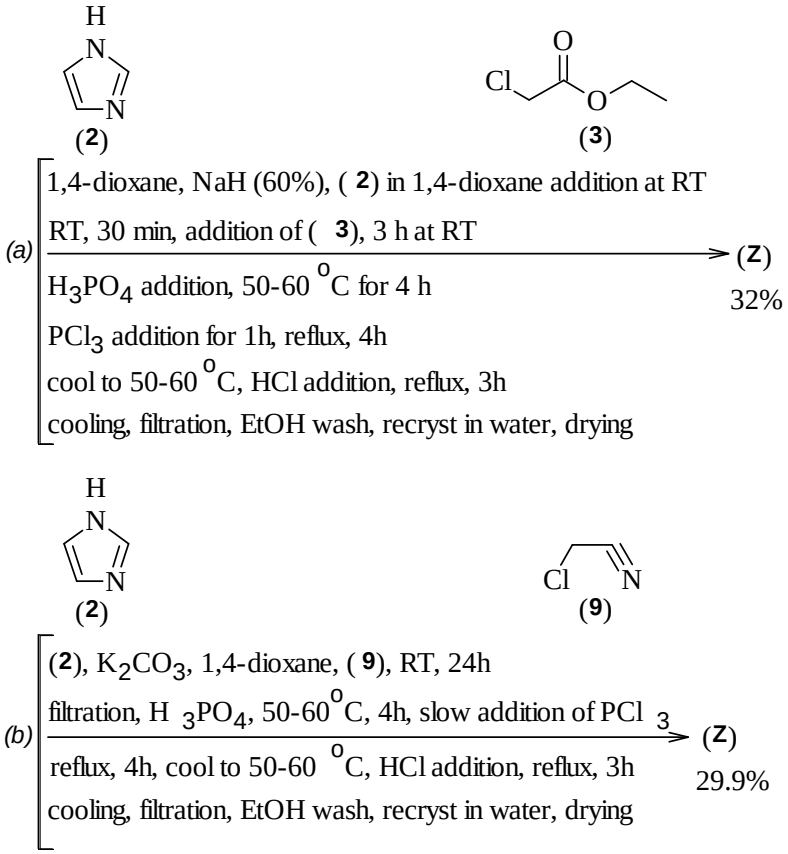
| **Table 14. Details of the patent entitled "A process for the preparation of alkyl- and aryl-diphosphonic acids and salts".[26]** |
|---|
| **Application**: EP2004014556W, 2004-12-22 |
| **Publication**: WO2005063779A2·2005-07-14 |
| **Published also as**: AT508134T; CA2551230A1; EP1716161A2; EP1716161B1; EP2206717A1; EP2206717B1; IL176487A; IL205426A; US2007112197A1; US7723542B2; WO2005063779A3; ES2365919T3; ITMI20032582A1. |
| **Inventors**: Grassi, S., & Volante, A |




**Scheme 9. Synthesis of (Z) by phosphorylation to (1a) in the absence of solvent.**

With an aim to avoid the multi step process and hazardous solvents, a new single step process to synthesize (**Z**) was demonstrated by Cai, W, Z. 2005, in a patent (**Table 15**). As per the disclosure, 500 ml of 1,4-dioxane, 40.0 g of 60% sodium hydride were taken in a reactor provided with condenser and dropping funnel. A solution of 68.0 g of (**2**) in 150 ml of 1,4-dioxane was added slowly to the reaction mixture under stirring in an ice water bath. It was stirred at ambient temperature for 30 min, then added 122.5 g of (**3**) to the mixture and stirred at ambient temperature for 3 h. To it added 200 ml of 85% $H_3PO_4$ slowly and the mixture was heated to 50-60 $^oC$ and maintained under stirring for 4 h. A controlled addition of 200 ml of $PCl_3$ was done at 50-60 $^oC$ over a period of 1 h, then the reaction mixture was refluxed for 4 h and later cooled to 50-60 $^oC$. Added 500 ml of HCl solution at 50-60 $^oC$ and then refluxed for 3 h. After the completion of hydrolysis, reaction mixture was cooled to get the precipitation. The precipitated solid was filtered, washed with ethanol and recrystallized from water to get (**Z**). Yield: 32.0%, 93.0 g, mp: 239 $^oC$ (dec.) In another example, 68.0 g of (**2**), 120.0 g of ($K_2CO_3$), 700 ml of 1,4-dioxane and 76.0 g of chloroacetonitrile (**9**) were taken in a reactor provided with condenser and dropping funnel. The mixture was stirred at ambient temperature for 24 h and later the insolubles were eliminated by filtration. To the clear filtrate added 200 ml of 85% $H_3PO_4$ slowly and the mixture was heated to 50-60 $^oC$ and maintained under stirring for 4 h. A controlled addition of 200 ml of $PCl_3$ was done at 50-60 $^oC$ over a period of 1 h, then the reaction mixture was refluxed for 4 h and later cooled to 50-60 $^oC$. Added 500 ml of HCl solution at 50-60 $^oC$ and then refluxed for 3 h. After the completion of hydrolysis, reaction mixture was cooled to get the precipitation. The precipitated solid was filtered, washed with ethanol and recrystallized from water to get (**Z**), (**Scheme 10**). Yield: 29.9%, 87.0 g, mp: 239 $^oC$ (dec.).

| **Table 15. Details of the patent entitled "Process for preparing dazoline phospho acid" [27].** |
|---|
| **Application**: CN200510038871A, 2005-04-15 |
| **Publication**: CN1693308A, 2005-11-09 |
| **Published also as**: None |
| **Inventors**: Cai, W, Z. |

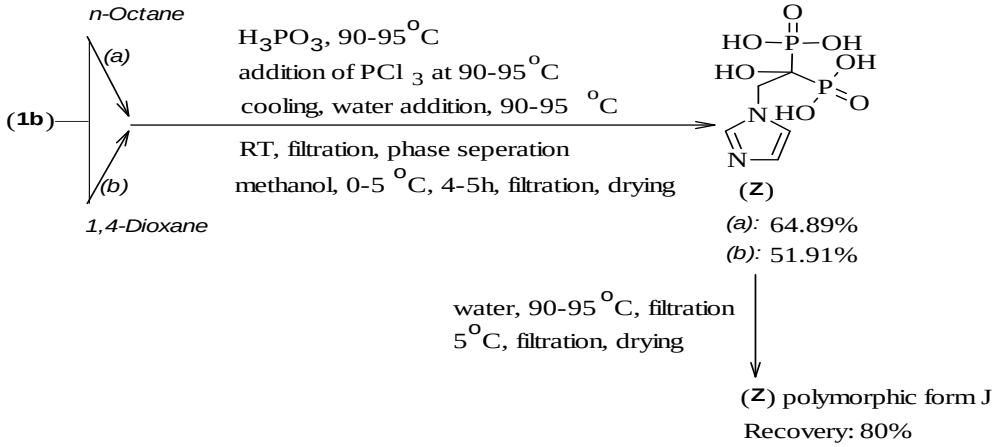



**Scheme 10. Single step synthesis of (Z) from (2) in 1,4-dioxane medium.**

In view to fulfill the demand for a safe, economical and an efficient scalable process to synthesize (**Z**) and its new polymorphs in high yields, Pandey, S, C., *et al*. 2005, had demonstrated a process to synthesize (**Z**) from (**1b**) in a patent (**Table 16**) using the solvents like n-octane and 1,4-dioxane for phophorylation. As per the disclosure, 50.0 g of (**1b**), 150.0 g of $H_3PO_3$ and 1 L of n-octane were taken in a reactor provided with condenser and dropping funnel. The mixture was heated to 90-95 $^oC$ under stirring and slowly added 250.0g of $PCl_3$ at 90-95 $^oC$. The reaction mixture was cooled and 500 ml of water was added to it. It was then heated to 90-95 $^oC$ and later cooled to ambient temperature. It was filtered through the celite bed to get clear filtrate and the aqueous phase was separated. To the aqueous layer 2 L of methanol was added for precipitation. It was kept under stirring at 0-5 $^oC$ for 4-5 h, filtered, washed with methanol and dried under vacuum to isolate (**Z**). Yield: 64.89%, 70.0 g, purity: not mentioned. A similar method was followed to convert 50.0 g of (**1b**) to (**Z**) using 1,4-dioxane as solvent. Yield: 51.91%, 56.0 g, purity: not mentioned. The work extends further to convert (**Z**) to its crystalline polymorphic form J. 50.0 g of (**Z**) and 750 ml of water were taken in a reactor and heated to 90-95 $^oC$ to get solution. It was hot filtered to get the clear filtrate and then cooled to 5 $^oC$ to get the precipitation. The solid formed was filtered

and suck dried to get the crystalline polymorph J of (**Z**). Recovery: 80%, 40.0 g, purity: not mentioned (**Scheme 11**). The works also covers the synthesis details of five other dronic acids and a few their forms.

| **Table 16. Details of the patent entitled "Process for producing biphosphonic acids and forms thereof".[28]** |
|---|
| **Application**: US92206405A, 2005-06-13 |
| **Publication**: US2009312551A1, 2009-12-17 |
| **Published also as**: EP1891081A1; EP1891081A4; EP1891081B1; US7872144B2; WO2006134603A1 |
| **Inventors**: Pandey, S, C., Haider, H., Saxena, S., Singh, M, K., Thaper, R, K., & Dubey, S, K. |

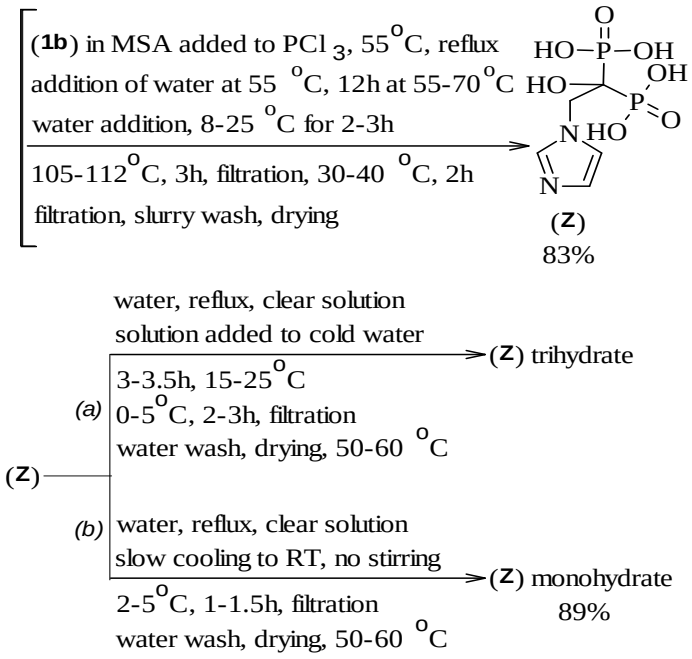



**Scheme 11. Synthesis of (Z) by phosphorylation to (1b) in n-octane/1,4-dioxane medium.**

A work from Kieczykowski, G, R., *et al*. 1995 [29], to synthesize (**Z**) under the mediation of methananesulfonic acid (MSA) had inspired Vecchioli, A., *et al*. 2006, to demonstrate a process to synthesize (**Z**) in a patent (**Table 17**) using MSA in absence of $H_3PO_3$. As per the disclosure, 200.0 g of (**1b**) was dissolved in 240 ml of MSA. This solution was added slowly to 856 ml of $PCl_3$ taken in a reactor fitted with condenser and dropping funnel. Addition was done keeping the reaction mass below 55 °C, reflux was observed. To the mixture added 171 ml of water (I lot) gradually, strong reflux was observed and the reaction mixture turned to thick viscous mass. It was maintained at 55-70 °C for 12 h and then cooled to below 25 °C. To it added 805 ml of water (II lot) at 8-25 °C, viscous mass dissolves completely. The reaction mixture was kept at 105-112 °C for around 3 h under stirring. It was filtered through the celite bed to eliminate the suspended impurities. The clear filtrate was cooled to 30-40 °C and neutralized to pH: 0.22-0.28 by the addition of 50% NaOH solution. It was then cooled to 0-5 °C and kept stirred for 2 h. The solid formed was filtered, washed by re-suspension in 500 ml water and twice in 500 ml of methanol. The humid solid was dried in hot air oven at 50-60

$^{o}$C to isolate (**Z**). Yield: 83.0%, 358.14 g, purity: approx 98% by potentiometric titration. Furthermore, 30.0 g of crude (**Z**) and 900 ml of water was taken in a reactor provided with condenser. It was heated to reflux to get clear solution and then slowly added to 50 ml of cold water between 15-25 $^{o}$C over a period of 3-3.5 h. After the completion of addition, it was cooled to 0-5 $^{o}$C and kept under stirring for 2-3 h. The solid formed was filtered, washed with 30 ml of cold water and dried in hot air oven at 50-60 $^{o}$C to get trihydrate form of (**Z**). Yield: not mentioned, purity: approx 99% by potentiometric titration, humidity (loss by dissection): 16.6%. In another example, 90.3 g of crude (**Z**) and 3.05 L of water are taken in a reactor provided with condenser. It was heated to reflux under stirring to get clear solution. Heating and stirring was stopped, gradually allowed to ambient temperature and then cooled to 2-5 $^{o}$C for 1-1.5 h. The solid formed was filtered, washed with cold water and dried in hot air oven at 50-60 $^{o}$C to get monohydrate form of (**Z**), (**Scheme 12**). Yield: 89.0%, 169.3 g, purity: not mentioned, humidity (loss by dissection): 6.8%.

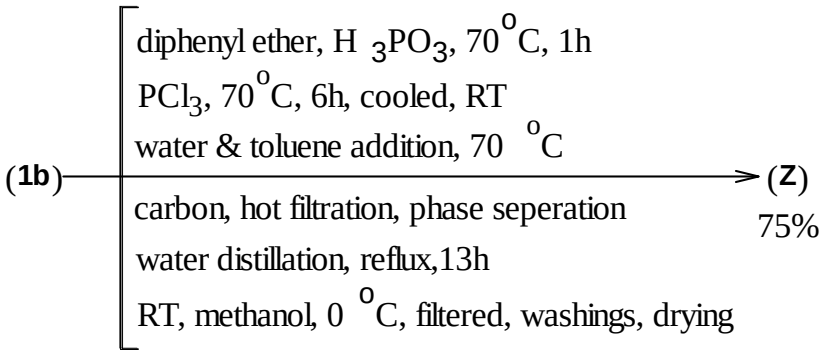
| **Table 17. Details of the patent entitled "A crystalline form of the Zoledronic acid, a process to obtain it and the pharmaceutical composition comprising it".[30]** |
|---|
| **Application**: EP2006004473W, 2006-05-12 |
| **Publication**: WO2007016982A1·2007-02-15 |
| **Published also as**: AR054673A1; AU2006278951A1; AU2006278951B2; BRPI0613924A2; CA2615418A1; CA2615418C; EP1924587A1; EP1924587B1; KR20080031475A; KR20140023949A; NZ565356A; US2008090784A1; US2010197931A1; US2010197935A1; US8338619B2; US8952172B2; ZA200800729B |
| **Inventors**: Vecchioli, A., Tombari, D., & Labriola, R. |




**Scheme 12. Synthesis of (Z) by phosphorylation to (1b) under MSA mediation.**

The complexity and high cost involved in previous disclosures to synthesize (**Z**), there was a need for an improved and commercially feasible process. In this context, Deshpande, P, B., & Luthra, P, K. 2006, had demonstrated a simple and scalable process in a patent (**Table 18**) to synthesize biphosphonic derivatives. As per the disclosure, 10.0 g of (**1b**), 19.5 g of $H_3PO_3$ and 50 ml of diphenyl ether were taken in a reactor provided with condenser and dropping funnel. The mixture was heated to 70 $^oC$ for 1 h. To it added 20 ml of $PCl_3$ slowly at 70 $^oC$ and maintained under stirring for further 6 h. Reaction mass was cooled to 25 $^oC$, added 150 ml of water and 30 ml of toluene. It was then heated to 70 $^oC$, added activated charcoal to the biphasic reaction mixture and stirred. It was then filtered through the celite bed, bed washed with 30 ml of hot water. The clear filtrate was allowed stand and the phases are separated. The aqueous phase was washed with 20 ml of toluene and combined organic phase was then back extracted with 20 ml of water. All the aqueous phases were mixed together and distilled under atmospheric pressure to remove around 140 ml of water in a span of 2 h. The remaining aqueous phase was refluxed for 13 h under stirring. It was then cooled to 25 $^oC$, added 50 ml of methanol for 1 h and stirred. The mixture was further cooled to 0 $^oC$, filtered and washed with 30 ml of chilled mixture (1:2) of water and methanol. The wet cake was dried at 60 $^oC$ to get (**Z**), (**Scheme 13**). Yield: 75%, 19.0 g, purity: not mentioned.

| **Table 18. Details of the patent entitled "Process for the preparation of biphosphonic derivatives".[31]** |
|---|
| **Application**: US49169606A, 2006-07-24 |
| **Publication**: US7439385B2·2008-10-21 |
| **Published also as**: CA2642321A1; EP1987046A1; US2006258625A1; WO2007096896A1 |
| **Inventors**: Deshpande, P, B., & Luthra, P, K. |

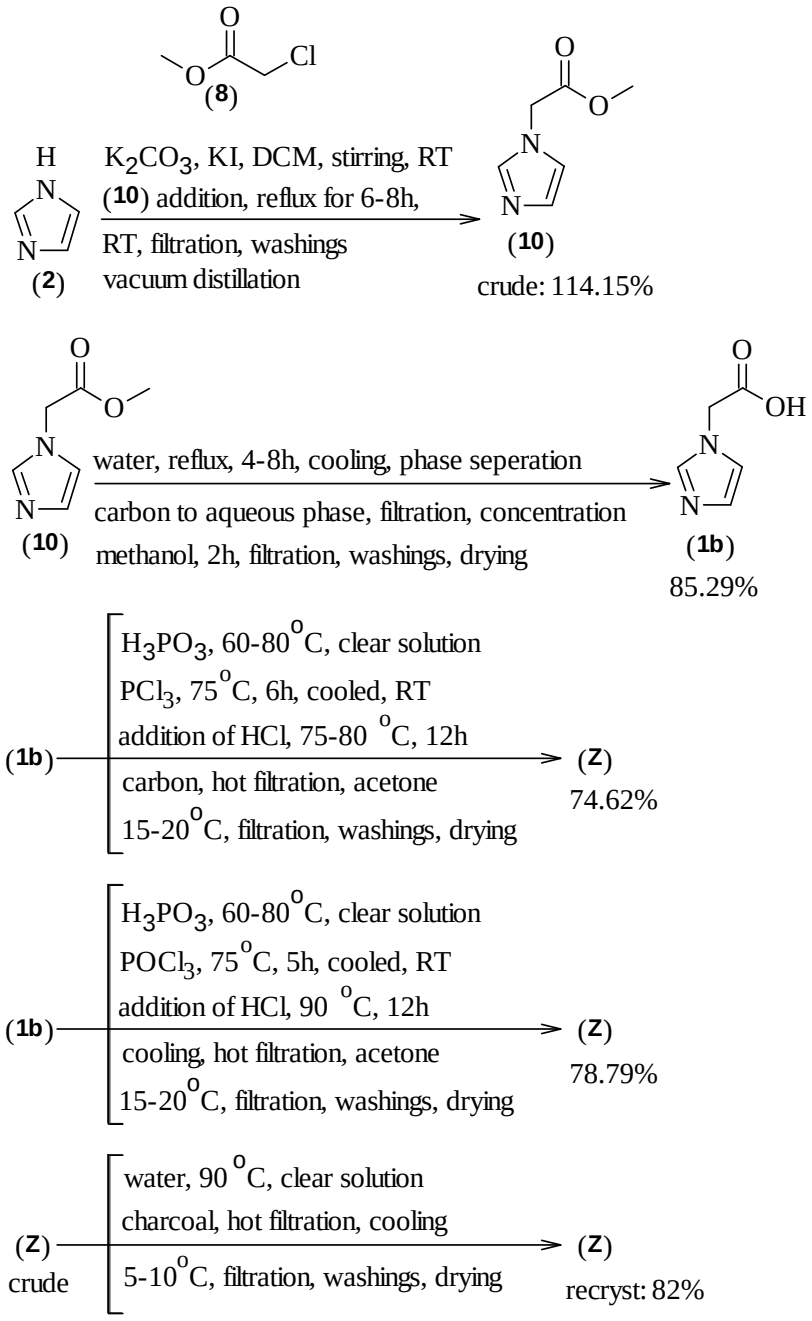



**Scheme 13. Synthesis of (Z) by phosphorylation to (1b) in diphenyl ether medium.**

Commercial $PCl_3$ has free phosphorous, which can lead to fire hazards during the workup. Hence, $POCl_3$ would be an efficient replacement for $PCl_3$ with a high boiling point of 105$^oC$. Avoiding the solvent was another prime concern, it was well negotiated by taking excess

$H_3PO_3$ during posphorylation to isolate (**Z**). By considering these aspects, Yadav, R, P., *et al*. 2006, had demonstrated a scalable multi step process in a patent (**Table 19**) to synthesize (**Z**) in good yield. As per the disclosure, 100.0 g of (**2**), 400.0 g of $K_2CO_3$, 5.0 g of KI and 2 L of dichloromethane were taken in reactor provided with condenser and dropping funnel. It was stirred vigorously, then slowly added 205.0 g of methyl chloroacetate (**8**) at ambient temperature for 30 min and heated to reflux for 6-8 h. The reaction mass was cooled to ambient temperature and filtered to eliminate the suspended residue. The residue was washed with 500 ml of dichloromethane and it was combined with the filtrate. The collective organic layer was distilled under reduced pressure to isolate methyl 1-*H*-imidazol-1-ylacetate (**10**). Yield: 114.15%, 235. 0g as crude. In the next step, 235.0 g of (**10**) and 500 ml of water was taken in a reactor provided with condenser. It was refluxed for 4-8 h under stirring. After the reaction completion, it was cooled and the phases were separated. To the aqueous phase, activated charcoal was added, hot filtered and concentrated under reduced pressure to get the residue. To the residue added 250 ml of methanol, stirred for 2 h, filtered and dried at 70-80 $^oC$ to get (**1b**). Yield: 85.29%, 158.0 g. Furthermore, 100.0 g of (**1b**), and 324.0 g of $H_3PO_3$ were taken in a reactor provided with condenser and dropping funnel. It was heated under stirring to 60-80 $^oC$ to get a uniform solution. To the reaction mass, 324.0 g of $PCl_3$ was slowly added at 75 $^oC$ under constant stirring and maintained for 6 h. Then the reaction mixture was cooled and 465 ml of 9N HCl was added over a period of 30 min, then continued the reaction under stirring at 75 $^oC$ for 12 h. To the reaction mixture, added 3.8 g of activated charcoal and filtered to get the clear solution. To the filtrate, added 1.2 L of acetone and cooled to 15-20 $^oC$ for complete precipitation. The solid formed was filtered, washed with 300 ml of acetone and dried at 50-60 $^oC$ to get crude (**Z**). Yield: 74.62%, 161.0 g, as white crystalline solid, purity: 99.92% by HPLC (a%). The work extends to provide a simple method for the purification, wherein 100.0 g of crude (**Z**) and 2.4 L of water were taken in a reactor provided with condenser. The mixture was heated under stirring to 90 $^oC$ to get clear solution. Added activated charcoal and filtered hot through celite bed to get the clear solution. It was cooled to 5-10 $^oC$ under stirring, filtered, washed with 100 ml of water and dried at 50-60 $^oC$ to get (**Z**). Recovery: 82.0%, 82.0 g as white crystals, purity: 99.9% by HPLC (a%). In another example, 100.0 g of (**1b**) was phosphorylated as per the previous method but using 364.0 g of $POCl_3$ instead of $PCl_3$. The reaction was completed in lesser time, hydrolysis was achieved at 90 $^oC$ and avoids the charcoalization process to get crude (**Z**), (**Scheme 15**). Yield: 78.79%, 170.0 g, purity: 99.92% by HPLC (a%).

| **Table 19. Details of the patent entitled "Processes for the preparation of pure Zoledronic acid".[32]** |
|---|
| **Application**: IB2006003603W, 2006-12-14 |
| **Publication**: WO2007069049A2, 2007-06-21 |
| **Published also as**: EP1963345A2; WO2007069049A3 |
| **Inventors**: Yadav, R, P., Shaikh, Z, G., Mukarram, S, M, J., & Kumar, Y. |



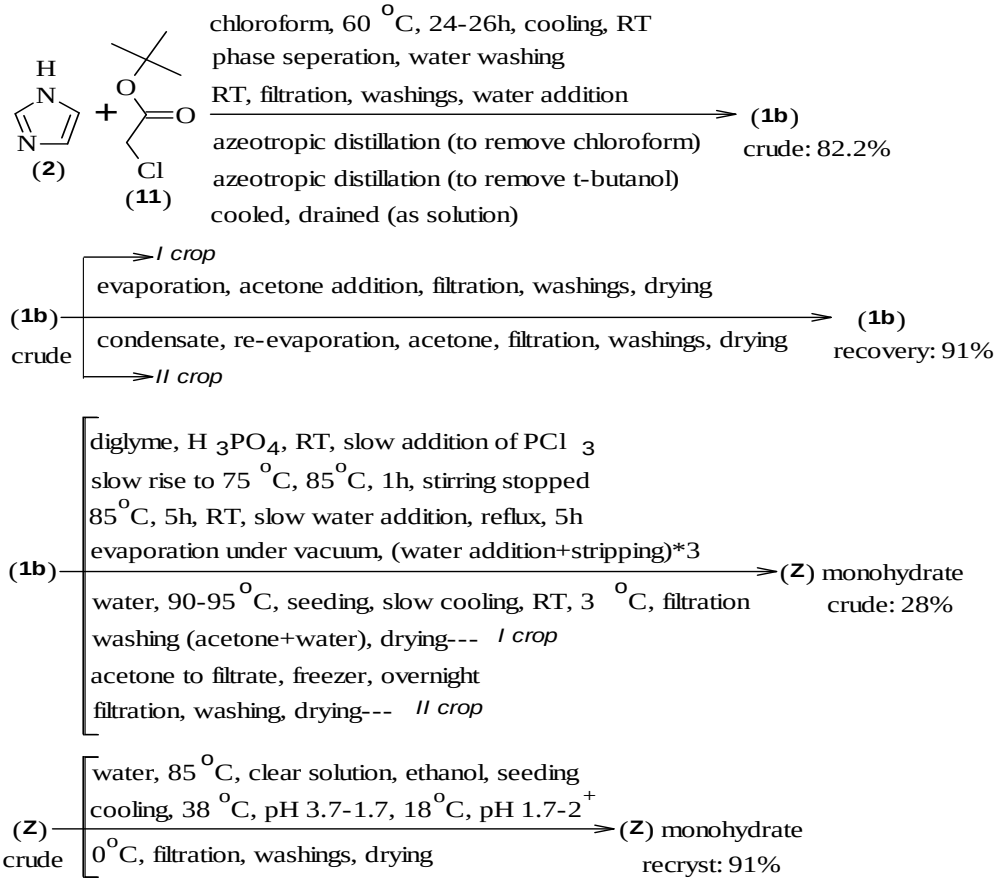

**Scheme 14. Synthesis of (Z) from (2) via condensation, hydrolysis and phosphorylation.**

A major issue associated with the synthesis of (**Z**) is in the phosphorylation, the reaction starts as a biphasic system then gradually become viscous, sticky and finally thickens into a non-stirrable mass. Hence an improved industrial process was needed to synthesize (**Z**) and

other dronic acids. With this concern, Samsel, E, G., & Wu, T, C. 2007, had illustrated scalable a process to synthesize bisphosphonic acids in a patent (**Table 20**). As per the disclosure, 6.13 Kg of (**2**), 5.48 Kg of t-butyl chloroacetate (**11**) and 54.0 Kg of chloroform were taken in big reactor provided with condenser. It was gradually heated to 60 $^{o}$C under stirring over a period of 2 h and later maintained for 24 h at 60 $^{o}$C. The reaction mixture was cooled to ambient temperature and washed four times with 7.2 Kg*4 of water. Once again 15.1 Kg of water was added and azeotropic distillation was done to remove chloroform (at 53 $^{o}$C) with a bath temperature of 60-65 $^{o}$C. In the similar way, t-butanol was removed by azeotropic distillation with a bath temperature of 115 $^{o}$C. The azeotrope of t-butanol and water distills out at 80 $^{o}$C. The liquid residue was cooled and drained to isolate crude (**1b**). Yield: 82.2%, 3.77 Kg as a liquid residue weighing 17.54 Kg. To 1.13 Kg of liquid residue was evaporated under reduced pressure to get 380.0 g of solid. To it, 234.0 g of acetone was added and stirred well. The solid formed was filtered, washed with acetone and dried under $N_2$ flow to isolate I crop of (**1b**). Initial evaporate condensate was concentrated under reduced pressure, washed with acetone and dried under $N_2$ flow to isolate II crop of (**1b**). Yield: 91.0% of recovery, 219.0 g, purity: 98.9% by NMR assay. In the next step, 100.0 g of (**1b**), 400 ml of diglyme and 55 ml of phosphoric acid were taken in a reactor provided with condenser and dropping funnel. To the reaction mixture slowly added 330.0 g of $PCl_3$through the dropping funnel. After the addition, reaction temperature was gradually raised to 70 $^{o}$C and then kept at 85 $^{o}$C. After about an hour, stirring was stopped due to lump formation but the reaction was kept at 85 $^{o}$C for 5 h. It was cooled to ambient temperature and 320 ml of water was added slowly. The lump dissolved completely, stirring was initiated again and refluxed for 5 h. Around 420.0 g of water was distilled under reduced pressure and again added 250 ml of water. Further distillation was continued to remove 316.0 g of water. Once again 150 ml of water was added and the mixture was heated to 90-95 $^{o}$C under stirring to get clear solution. It was seeded with (**Z**) monohydrate crystals, cooled to ambient temperature and then to 3 $^{o}$C. The solid formed was filtered under suction, washed with 300 ml of acetone and dried under $N_2$ flow to isolate the I$^{st}$ crop of (**Z**), 52.4 g. To the filtrate acetone was added, refrigerated overnight and filtered to isolate the II$^{nd}$ crop of (**Z**), 12.0 g. Yield: 28%, 64.4 g, purity: NMR spectrum had shown the presence of impurities like diglyme, acetone and $H_3PO_3$. A similar pathway was followed to covert 333.0 g of (**1b**) to (**Z**). But to the residue obtained (1.2 Kg) after the evaporation under reduced pressure, 1.5 L of acetone was added and the mixture was allowed to stand for 16h. The solid formed was filtered, washed with acetone and dried under $N_2$ flow to get (**Z**). Yield: 28.0%, 202.0 g. An experiment was

also illustrated by the use of PEG-400 instead of diglyme to get (**Z**) in 7.0% yield and poor product purity as well. The work extends to provide a recrystallization process to get pure (**Z**) in monohydrate form. As per it, 64.4 g of crude (**Z**) and 1.5 L of water were taken in a reactor and heated to 85 $^{o}$C under stirring to get clear solution with a pH: 1.7. To the clear solution 500 ml of ethanol was added along with seeding of (**Z**) monohydrate crystals and then cooled gradually. At 38 $^{o}$C, pH was adjusted from 3.7 to 1.7 by the addition of HCl. At 18 $^{o}$C, pH was adjusted from 1.7 to above 2.0. The slurry was cooled to 0 $^{o}$C and kept under stirring for 4 h. The solid formed was filtered, washed with 400 ml of ethanol and dried in hot air oven under $N_2$ flow to isolate (**Z**) monohydrate (**Scheme 15**). Yield: 91.0%, 58.64 g, moisture content: 6.46%, purity: 92.2% by NMR (wt%) on anhydrous basis.

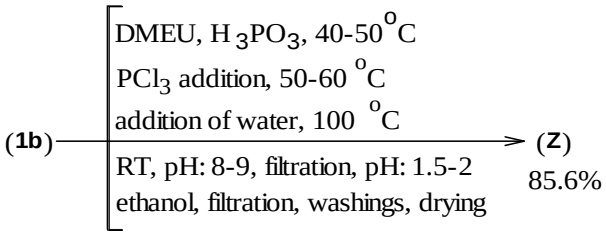
| **Table 20.** Details of the patent entitled "Process for manufacturing bisphosphonic acids" [33]. |
|---|
| **Application**: CA2646418A, 2007-03-16 |
| **Publication**: CA2646418A1, 2007-09-27 |
| **Published also as**: CN101443341A; EP1996599A2; US2009137808A1; WO2007109542A2; WO2007109542A3 |
| **Inventors**: Samsel, E, G., & Wu, T, C. |




**Scheme 15. Synthesis of (Z) from (2) in high scale and phosphorylation in diglyme/PEG-400 medium.**

Past processes to synthesize (**Z**), suffer from some setbacks, which includes the solidification of reaction mixture during phosphorylation. This would lead to several difficulties during large scale drug manufacturing and reproducibility of yield/purity. In this context, Baptista, J., & Mendes, Z. 2007, had illustrated a modified approach in a patent (**Table 21**) to synthesize bisphosphonic acids using suitable aprotic polar solvents. As per the disclosure, 25.0 g of (**1b**), 18.9 g of $H_3PO_3$ and 150 ml of N,N'-dimethylethyleneurea (DMEU) were taken a reactor provided with condenser and dropping funnel. The mixture was heated to 40-50 $^oC$ and 26 ml of $PCl_3$ was added slowly under stirring. Further the reaction mass was heated to 50-60 $^oC$ until the reaction completion (by HPLC analysis). Added water and heated to 80 $^oC$ then to 100 $^oC$ under stirring till the reaction completion. The reaction mixture was cooled to ambient temperature and adjusted the pH to 8-9 by the addition of NaOH solution. It was filtered, pH was adjusted to 1.5-2 and added ethanol to enforce the precipitation. The solid formed was filtered, washed and dried under vacuum at 40-50 $^oC$ to get (**Z**), (**Scheme 16**). Yield: 85.6%, 25.7 g, purity: 99.5% by HPLC (a%).

| **Table 21. Details of the patent entitled "Process for the preparation of biphosphonic acids and salts thereof".**[34] |
|---|
| **Application**: US51374007A, 2007-11-06 |
| **Publication**: US2009326227A1, 2009-12-31 |
| **Published also as**: AU2007319040A1; BRPI0716691A2; CA2668783A1; CN101605802A; EP2094717A1; JP2010508376A; NO20091806L; NZ577343A; PT103600A; PT103600B; RU2009121527A; RU2425049C2; WO2008056129A1; ZA200903228B |
| **Inventors**: Baptista, J., & Mendes, Z. |

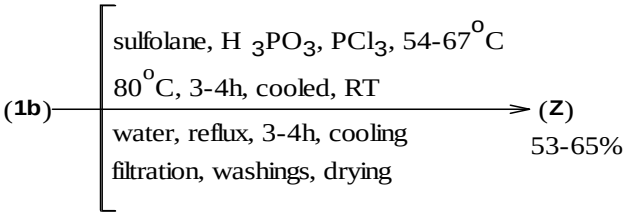



**Scheme 16. Synthesis of (Z) from (1b) by phosphorylation in DMEU medium.**

In view to perform phosphorylation with better stirrability, a least solidifying process was illustrated by Liu, Y., & Delaup, A, J. 2008, in a patent (**Table 22**) to synthesize bisphosphonic acids and in particular (**Z**). To avoid the lump formation, some critical addition methods of reagents and workup modifications were demonstrated. According to the disclosure, $H_3PO_3$ and $PCl_3$ are added to the mixture of (**1b**) in sulfolane at around 55-60 $^oC$ through separate streams (co-addition) or by alternate addition practices. $H_3PO_3$ and the $PCl_3$ are added to reaction mass in some feasible forms. For instance, at least a portion of $H_3PO_3$

can be added in solid form or in solution (in sulfolane); or all of it can be added either as a solid or in solution. Similarly, at least a portion of $PCl_3$ can be added in solid form, in liquid form, or in solution; or all of it can be added either as a solid, as a liquid, or in solution. The molar ratio of both $H_3PO_3$ and $PCl_3$ are varied from 1:1 to 1:6 as per the input of (**1b**). The reaction mixture was then quenched to water or to preheated water (75-85 $^oC$). It was then cooled, added anti-solvent and filtered to isolate (**Z**), (**Scheme 17**). Four examples are illustrated, the experimental details in brief and the results are furnished in **Table 23**.

| **Table 22. Details of the patent entitled "Processes for manufacturing bisphosphonic acids".[35]** |
|---|
| **Application**: US2008065842W, 2008-06-05 |
| **Publication**: WO2008157050A1, 2008-12-24 |
| **Published also as**: CA2689504A1 |
| **Inventors**: Liu, Y., & Delaup, A, J. |

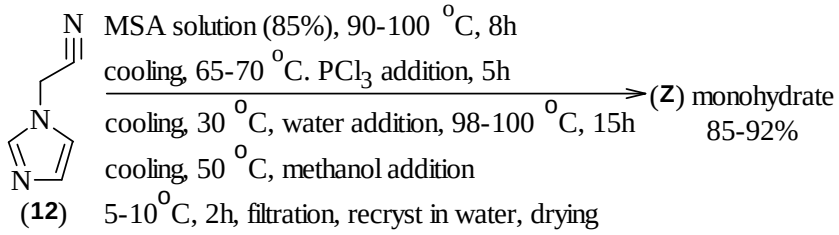



**Scheme 17. Synthesis of (Z) from (1b) by modulated addition reagents for phosphorylation in sulfolane medium.**

| **Table 23. Details experimental conditions done in sulfolane medium and results** | | | | |
|---|---|---|---|---|
| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** | **Exp. 4** |
| (**1b**) input | 15.97 g | 15.97 g | 15.9 g | 79.92 g |
| Addition $H_3PO_3$ & $PCl_3$ | alternate | alternate | co-addition | alternate |
| Addition at | 60-67 $^oC$ | 54-64 $^oC$ | 60-67 $^oC$ | 60-64 $^oC$ |
| Addition after | 80 $^oC$, 4 h | 80 $^oC$, 4 h | 80 $^oC$, 4 h | 80 $^oC$, 4 h |
| Quenching to water | 50.0 g, (RT) | - | - | - |
| Quenching to pre-heated water | - | 100.0 g, (80$^oC$) | 50.0 g, (80 $^oC$) | 250.0 g, (80 $^oC$) |
| Hydrolysis | reflux, 3 h | reflux, 4 h | reflux, 4 h | reflux, 4 h |
| Cooling to | RT, overnight | 1.2 $^oC$, 1.5 h | 48-50 $^oC$ | RT |
| Acetone | - | - | 200 ml, 1-2 $^oC$, 2 h | 1L, 1-2 $^oC$, 2 h |
| Acetone wash | 38.0 g | 20.0 g | 35.0 g | 150.0 g |
| Drying under $N_2$ | not mentioned | not mentioned | not mentioned | 1 h |
| Yield | 65.0%, 24.1 g | 53.0%, 19.1 g | 61.0%, 22.1 g | 63.56%, 109.6 g |
| Purity, by NMR (w%) | 95.3% | 98.3% | 98.6% | not mentioned |

The work demonstrated by Jaeggi, K, A., & Widler, L. 1989 [17], involves the phosphorylation of (**1a**) to get (**Z**) with an yield of 41.0%. A tedious workup and low yield made this process not suitable for large scale manufacturing. To improve the yield, Nazarenko, A, B., & Fedorov, V, E. 2009, had illustrated an improved, novel and simple method to synthesize (**Z**) in a patent (**Table 24**) using MSA. As per the disclosure, synthesis of (**Z**) monohydrate was done by the reaction of 1-*H*-imidazol-1-ylacetonitrile (**12**) with an aqueous solution of MSA at 70-100 $^{o}$C and then reacted with $PCl_3$ at 50-100 $^{o}$C. During the process intermediates are not isolated, which made the process simple and gave significantly high yield (upto 92%). Some experiments are done at a molar ratio of (**12**): MSA: $PCl_3$ (1:1.5-3.0; 1.2-3.0), details of those experiments and results are tabulated in Table **25**.

| **Table 24. Details of the patent entitled "Method of producing Zoledronic acid".[36]** |
|---|
| **Application**: RU2009134277A, 2009-09-15 |
| **Publication**: RU2415145C1, 2011-03-27 |
| **Published also as**: None |
| **Inventors**: Nazarenko, A, B., & Fedorov, V, E. |




**Scheme 18: Synthesis of (Z) from (13) under MSA mediation.**

| **Table 25. Details of experiments to synthesize (Z) monohydrate with results.** | | | | |
|---|---|---|---|---|
| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** | **Exp. 4** |
| (**13**) | 107.0 g | 107.0 g | 107.0 g | 53.5 g |
| MSA (*equiv*) | 2.5 | 2.5 | 1.25 | 3.0 |
| Reaction | 90-100 $^{o}$C, 8 h | 70-80 $^{o}$C, 8 h | 90-100 $^{o}$C, 8 h | 90-100 $^{o}$C, 8 h |
| $PCl_3$ (*equiv*) | 1.7 | 1.7 | 1.5 | 1.7 |
| Addition at & after | 65$^{o}$C, 5 h | 65$^{o}$C, 5 h | 65$^{o}$C, 5 h | 65$^{o}$C, 5 h |
| Water addition & next | 800 ml at 30 $^{o}$C, 98-100 $^{o}$C, 15 h | 800 ml at 30 $^{o}$C, 98-100 $^{o}$C, 15 h | 800 ml at 30 $^{o}$C, 98-100 $^{o}$C, 15 h | 400 ml at 30 $^{o}$C, 98-100 $^{o}$C, 15 h |
| Antisolvent | 1 L, methanol | 1 L, ethanol | 1 L, methanol | 0.5 L, methanol |
| Stirring | 5-10 $^{o}$C, 2 h | 5-10 $^{o}$C, 2 h | 5-10 $^{o}$C, 2 h | 5-10 $^{o}$C, 2 h |
| Yield (after recryst in water) | 92.0%, 266.0 g | 90.0%, 260.0 g | 85.0%, 245.5 g | 90.0%, 130.0 g |
| Mp (dec.) | 242-244 $^{o}$C | 243-244 $^{o}$C | 242-244 $^{o}$C | 240-241 $^{o}$C |
| Purity, by HPLC (a%) | 99.1% | 99.2% | Not mentioned | 99.2% |

In context to avoid the lump formation during the reaction, a new methodology was adopted by Dembkowski, L., *et al*. 2009 to synthesize (**Z**). It was illustrated in a patent (**Table 26**), wherein (**1a**) was added to $PCl_3$ under stirring at 0-5 $^oC$ in the absence of a diluent. Phosphorylation was allowed occur preferable at 80-85 $^oC$ for 2-3 h. Hydrolysis (6-7 h) was initiated after removing the excess $PCl_3$ by distillation. The reaction mixture was treated with activated charcoal and filtered to remove the insolubles. A suitable anti-solvent was used to precipitate (**Z**) as its monohydrate. Interestingly, the process avoids the use of $H_3PO_4$ or $H_3PO_3$ for phosphorylation. Instead, excess of $PCl_3$ itself acts as the solvent and reagent to covert (**1a**) to (**Z**) monohydrate (**Scheme 19**). The work demonstrates the synthesis of (**Z**) monohydrate and its recrystallization in four distinct experiments, the details of those are depicted in **Table 27**. Illustrations in the work continue to provide an efficient recrystallization process to isolate pure crystals of (**Z**) monohydrate from water. The experimental details and the corresponding results obtained for three disclosed examples are tabulated in **Table 28**.

| **Table 26. Details of the patent entitled "Process for the preparation of [1-hydroxy-2-(1H-imidazol-1-yl)-ethylidene] bisphosphonic acid" [37].** |
|---|
| **Application**: PL2009000092W, 2009-10-17 |
| **Publication**: WO2010050830A1, 2010-05-06 |
| **Published also as**: EP2350102A1; PL213599B1; PL386416A1; US2012116092A1; US8524912B2 |
| **Inventors**: Dembkowski, L., Krzyzanowski, M., Rynkiewicz, R., Szramka, R., Roznerski, Z., Zyla, D., Rachon, J., & Makowiec, S. |

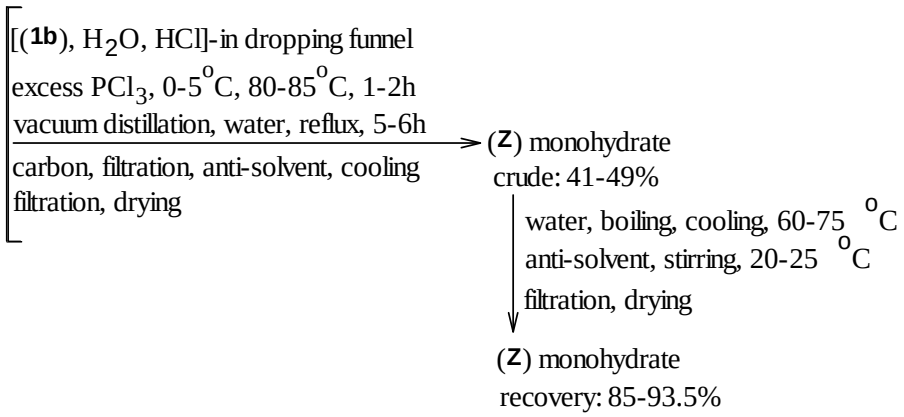
**Table 27. Details of experiments and results to isolate (Z) monohydrate using $PCl_3$ as solvent and reagent for phosphorylation.**

| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** | **Exp. 4** |
|---|---|---|---|---|
| (**1b**) | 39.0 g | 26.0 g | 13.0 g | 26.0 g |
| Water/HCl | 27 ml, 27 ml | 18 ml, 18 ml | 9 ml, 9 ml | 18 ml, 18 ml |
| $PCl_3$ | 162 ml | 108 ml | 54 ml | 108 ml |
| Addition | 0-5 $^oC$, 1-1.5 h | 0-5 $^oC$, 30 min | 0-5 $^oC$, 1 h | 0-5 $^oC$, 2 h |
| Stirring | 80-85 $^oC$, 2 h | 0-5$^oC$, 1 h<br>80-85 $^oC$, 1 h | 80-85 $^oC$, 2 h | 80-85 $^oC$, 1.5 h |
| $PCl_3$ removal | vacuum distillation | vacuum distillation | vacuum distillation | vacuum distillation |
| Water & Hydrolysis | 300 ml, reflux, 6 h | 200 ml, reflux, 6 h | 100 ml, reflux, 6 h | 200 ml, reflux, 6 h |
| Activated charcoal | 3.75 g | 1.0 g | 1.3 g | 2.6 g |
| Anti-solvent, at | methanol, 300 ml, 55-60 $^oC$ | ethanol, 150 ml, 70 $^oC$ | isopropanol, 100 ml, 65-55 $^oC$ | acetone, 200 ml, 55-45 $^oC$ |
| Cooling | 20-25 $^oC$, 5 h | 20-25 $^oC$, 4 h | 20-25 $^oC$, 18 h | 20-25 $^oC$, 4 h |
| Drying | 55 $^oC$, 6 h | 50 $^oC$,- | 50 $^oC$, 5 h | 55 $^oC$, 4 h |

| | | | | |
|---|---|---|---|---|
| Yield | 41.0%, 36.68 g | 49.0%, 29.3 g | 41.0%, 12.1 g | 45.0%, 26.7 g |
| Purity, by HPLC (a%) | 99.98% | 100.0% | 100.0% | 99.91% |
| TGA | 6.18% | 6.3% | 6.02% | 6.19% |

**Table 28. Details of recrystallization attempts**

| **Input/operation** | **Recryst. 1** | **Recryst. 2** | **Recryst. 3** |
|---|---|---|---|
| Crude | 12.0 g | 15.0 g | 10.0 g |
| Water | 240 ml | 300 ml | 200 ml |
| Heating | to boiling | to boiling | to boiling |
| Anti-solvent, at | methanol, 240 ml, 60 $^{o}$C | ethanol, 300 ml, 70 $^{o}$C | isopropanol, 200 ml, 75 $^{o}$C |
| Cooling | 20-25 $^{o}$C, 3 h | 20-25 $^{o}$C, 14 h | 20-25 $^{o}$C, 3 h |
| Drying | 55 $^{o}$C, 6 h | 55 $^{o}$C, 6 h | 55 $^{o}$C, 5 h |
| Recovery | 86.0%, 10.37 g | 85.0%, 12.78 g | 93.5%, 9.35 g |
| HPLC purity (a%) | 100.0% | 100.0% | 100.0% |
| TGA | 6.28% | 6.24% | 6.18% |

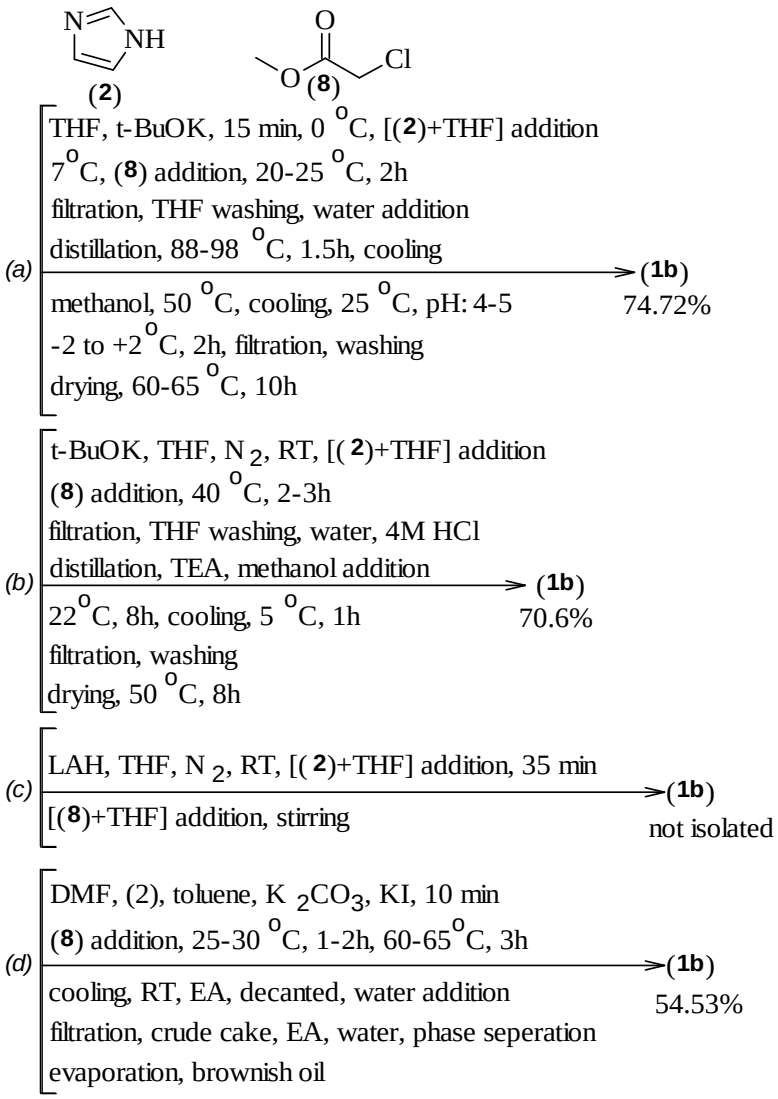



**Scheme 19. Synthesis of (Z) monohydrate by phosphorylation of (1a) in excess $PCl_3$.**

A major hindrance to synthesize (**Z**) was the formation of high viscous reaction mixture, which was not stirrable. In some other instances, the polyphasic nature of the reaction mixture having cyclic pyrophosphonate intermediates. These issues had led to poor heat transfer, high exothermicity and related work-up issues. The excess of phosphonation agents would force the formation of impurities leading to poor yield and purification issues. Hence, there was an urge to find a suitable solvent/diluent to execute phosphorylation in high yield with industrially feasible conditions. In line to address these issues, Kas, M., *et al*. 2009, had demonstrated an elaborate process to synthesize (**Z**) from (**2**) in a patent (**Table 29**). In this work, synthesis of (**1b**), (**Scheme 20**) was achieved in three methods (using t-BuOK & LAH) and a comparative method (using $K_2CO_3$, KI) was also executed as per the past disclosure [25]. Two of the illustrations [*(a)* & *(b)*] are by the use of t-BuOK in THF medium to covert (**2**) to

(**1b**). The experimental details and the corresponding results are tabulated in **Table 30**. An attempt was done *(c)* to convert 20.25 g of (**2**) using 2.58 g of LAH in 150 ml of THF. To the mixture added 26 ml of (**8**) in 45 ml of THF, analysis by HPLC had showed momoalkylation of (**2**) with 0.1% of diester. It was not hydrolyzed further to (**1b**). In the comparative example *(d)*, 50.0 g of (**2**) was taken and finally a brownish oil of (**1b**) was isolated. Yield: 54.53%, 50.5 g. This method was bit tedious to isolate (**1b**) as an oily mass, it supposed to be solid as obtained by the easier methods driven by t-BuOK.

| **Table 29. Details of the patent entitled "Process for making Zoledronic acid" [38].** |
|---|
| **Application**: US62686309A, 2009-11-27 |
| **Publication**: US2010130746A1, 2010-05-27 |
| **Published also as**: None |
| **Inventors**: Kas, M., Benes, M., & Pis, J. |




**Scheme 20. Synthesis of (1b) from (2) mediated by different bases.**

| Table 30. Details of experiment to convert (2) to (1b) using t-BuOK in THF medium. | | |
|---|---|---|
| **Input/operation** | ***(a)*** | ***(b)*** |
| Base, solvent | 333.9 g of t-BuOK, 1060 ml of THF | 34.46 g of t-BuOK, 90 ml of THF |
| Addition of (**2**) | 200.0g in 600 ml of THF, 0 $^{o}$C | 21.95 g in 75 ml of THF, RT |
| Addition of (**8**) | 302.9 g, 7 $^{o}$C | 25.6 ml, 40 $^{o}$C |
| Reaction | 20-25 $^{o}$C, 2 h | 40 $^{o}$C, 2-2.5 h |
| Workup | Filtration & washed by 450 ml of THF | Filtration & washed by 20 ml of THF |
| Water addition & next | 300 ml, distillation | 30 ml, 8 ml of 4N HCl, distillation |
| Hydrolysis | 88-98 $^{o}$C, 1.5 h | - |
| Anti-solvent | cooled, 1050 ml of methanol, 50 $^{o}$C | 150 ml of methanol |
| pH | 4-5, at 25 $^{o}$C, by 45 ml of HCl | Added 4.5 ml of TEA |
| Stirring & next | -2 to +2 $^{o}$C, 2 h, filtration | 22 $^{o}$C, 8 h & 5 $^{o}$C, 1 h, filtration |
| Washings | 500 ml of methanol | 10 ml of methanol |
| Drying | 60-65 $^{o}$C, 10 h | 50 $^{o}$C, 8 h |
| Yield | 74.72%, 276.8 g | 70.6%, 25.98 g |
| Purity by HPLC (a%) | 99.22% | 0.5% of diacid |

The work extends to provide numerous methods for the synthesis of (**Z**) and its recrystallization. Two comparative examples are provided, which are related to the previous disclosure by Kubela, R., & Tao, Y. 2008 [39]. The work involves the use of PEG-400 as the medium for the phosphorylation of (**1b**) in the presence of $H_3PO_3$, $PCl_3$ or $POCl_3$ to get (**Z**) monohydrate. The experiment details and the corresponding results are depicted in **Table 31**. The lump formation issue was observed in these batches to get (**Z**) monohydrate with yields in the range of 31-33%.

| Table 31. The experimental details and the results of phosphorylation of (1b) in PEG-400 medium to get (Z) monohydrate. | | |
|---|---|---|
| **Input/operation** | **Comparative Exp. 1** | **Comparative Exp. 2** |
| PEG-400, (**1b**) & $H_3PO_3$ | 50 ml, 6.0 g & 11.7 g | 50 ml, 6.0 g & 11.7 g |
| Heated to & then | 50 $^{o}$C, 15 min, cooled, 30 $^{o}$C | 50 $^{o}$C, 15 min, cooled, 30 $^{o}$C |
| $PCl_3$ addition | 19.6 g, 30 min, 30-50 $^{o}$C | *(not used)* |
| $POCl_3$ addition | *(not used)* | 13.1 ml, 30 min, 30-50 $^{o}$C |
| Mass nature & heated to | viscous mass, 60 $^{o}$C, 4 h | viscous mass, 95-100 $^{o}$C, 4 h |
| Water addition & hydrolysis | 80 ml at 40$^{o}$C, 80 $^{o}$C, 4 h | 80 ml at 40 $^{o}$C, 80 $^{o}$C, 4 h |
| Anti-solvent addition | 150 ml of ethanol at 20 $^{o}$C | 150 ml of ethanol at 20 $^{o}$C |
| Isolation | filtration, 20 ml ethanol wash | filtration, 20 ml ethanol wash |
| Drying | 50 $^{o}$C, 15 h | 50 $^{o}$C, 15 h |
| Yield | 31.3%, 4.32 g | 32.9%, 4.54 g |

Furthermore, the work reports a comparative example using diethyl carbonate and another process using diethyl carbonate along with PEG-400 to synthesize (**Z**) monohydrate by phosphorylation of (**1b**). The experimental details using the alkyl carbonate medium and the results are tabulated in **Table 32**. From the outcome, it was evident that, use of PEG-400 along with diethyl carbonate had significantly promoted the reaction with good yield of 84.0%. This was due to better stirrability during phosphorylation.

**Table 32. The experimental details and results of (Z) monohydrate, prepared under diethyl carbonate medium.**

| Input/operation | Comparative exp. 1 | Exp. 2 |
|---|---|---|
| Initial input & conditions | 7.44 g of $H_3PO_3$, 35 ml of diethyl carbonate at 40 $^oC$, 1 h, undissolved | 7.44 g of $H_3PO_3$, 20 ml of diethyl carbonate & 15 ml of PEG-400 at 40 $^oC$, dissolved |
| (**1b**) addition | 3.0 g at 40 $^oC$, viscous mass | 3.0 g at 40 $^oC$, non-viscous |
| $POCl_3$ addition | 8.3 ml, 80-90 $^oC$, 3 h | 8.3 ml, 80-90 $^oC$, 3 h |
| Water addition | 40 ml, reflux, 17 h | 40 ml, 85 $^oC$, 20 h |
| Anti-solvent addition | 0 $^oC$, 130 ml of ethanol | 0 $^oC$, 130 ml of ethanol |
| Isolation | filtration, washed with 20 ml of ethanol, dried at 60 $^oC$, 17 h | filtration, washed with 20 ml of ethanol, dried at 60 $^oC$, 20 h |
| Yield | 59.0%, 4.05 g | 84.0%, 5.81 g |

With a positive outcome by the use of combination of diluents to synthesize (**Z**) monohydrate, propylene carbonate (PC) was used as a diluent for the same along with PEG-400/600/1000. Three illustrations were provided to synthesize (**Z**) monohydrate under PC mediation and an example was also provided as a confirmatory batch (reduced reaction time) using diethyl carbonate (DEC) along with PEG-400. $PCl_3$ was more preferred than $POCl_3$ in these set of experiments. The details of experiment and the corresponding results are fetched in **Table 33**. A record high yield (98-99%) of (Z) monohydrate was obtained in experiments performed by the use of PEG-600 & PEG-1000 under PC medium by the addition of $PCl_3$.

**Table 33. List of experiments done in presence of diluents combination to synthesize (Z) monohydrate and the corresponding results.**

| Input/operation | Exp. 1 | Exp. 2 | Exp. 3 | Exp. 4 |
|---|---|---|---|---|
| Initial input & conditions | 7.44 g of $H_3PO_3$, 20 ml of DEC & 15 ml of PEG-400 at 40 $^oC$, dissolved | 200 ml of PEG-400, 200 ml of PC, 60.0 g of (**1b**), 117.0 g of $H_3PO_3$ & 200 ml of PC, 40-45 $^oC$ | 7.44 g of $H_3PO_3$, 20 ml of PC & 15 ml of PEG-600 at 40 $^oC$, dissolved | 7.44 g of $H_3PO_3$, 20 ml of PC & 15 ml of PEG-1000 at 50 $^oC$, dissolved |
| (**1b**) addition | 3.0 g at 40 $^oC$, non-viscous | - | 3.0 g at 40 $^oC$, non-viscous | 3.0 g at 40 $^oC$, non-viscous |
| $POCl_3$ addition | 40 $^oC$, 8.3 ml, | - | - | - |

| | | | | |
|---|---|---|---|---|
| | 70-90 $^{o}$C, 2h | | | |
| $PCl_3$ addition | | 30 $^{o}$C, 196.0 g, 56-60 $^{o}$C, 4 h | 40 $^{o}$C, 9 ml, 55-60 $^{o}$C, 4 h | 40 $^{o}$C, 9 ml, 55-60 $^{o}$C, 4 h |
| Water addition | 40 ml, 85 $^{o}$C, 17 h | 30 $^{o}$C, 350 ml, 80-85 $^{o}$C, 3 h | 40 ml, 85 $^{o}$C, 18 h | 40 ml, 85 $^{o}$C, 18 h |
| Anti-solvent addition | 0 $^{o}$C, 130 ml of ethanol | 25 $^{o}$C, 1.5 L ethanol, 8-12$^{o}$C, 2h | 0 $^{o}$C, 150 ml of ethanol | 0 $^{o}$C, 150 ml of ethanol |
| Isolation | filtration, washed with 20 ml of ethanol, dried at 50 $^{o}$C, 20 h | filtration, washed with 400 ml of ethanol, dried at 57-62 $^{o}$C,- | filtration, washed with 40 ml of ethanol, dried at 60 $^{o}$C, 10 h | filtration, washed with 40 ml of ethanol, dried at 60 $^{o}$C, 10 h |
| Yield | 75.0%, 5.21 g | 105.0 g | 99.0%, 6.85 g | 98.0%, 6.75 g |
| Purity | not mentioned | 99.6%, TGA (7.69%) | not mentioned | not mentioned |

The work extends further to provide three illustrations for the purification of (**Z**) monohydrate. In one of the example, 6.0 g of (**Z**) monohydrate and 100 ml of water are taken in a reactor provided with condenser. The mixture was heated under stirring to reflux to get clear solution. It was cooled 20 $^{o}$C and stirred at 19-23 $^{o}$C for 1.5 h. The suspended solid was filtered, washed with 10 ml of ethanol and dried at 60 $^{o}$C to get crystallized (**Z**) monohydrate. Recovery: 86.8%, 5.21 g. Other two examples proceed through pH adjustment pathway to crystallize (**Z**) monohydrate. The experimental details and the results are tabulated in **Table 34**.

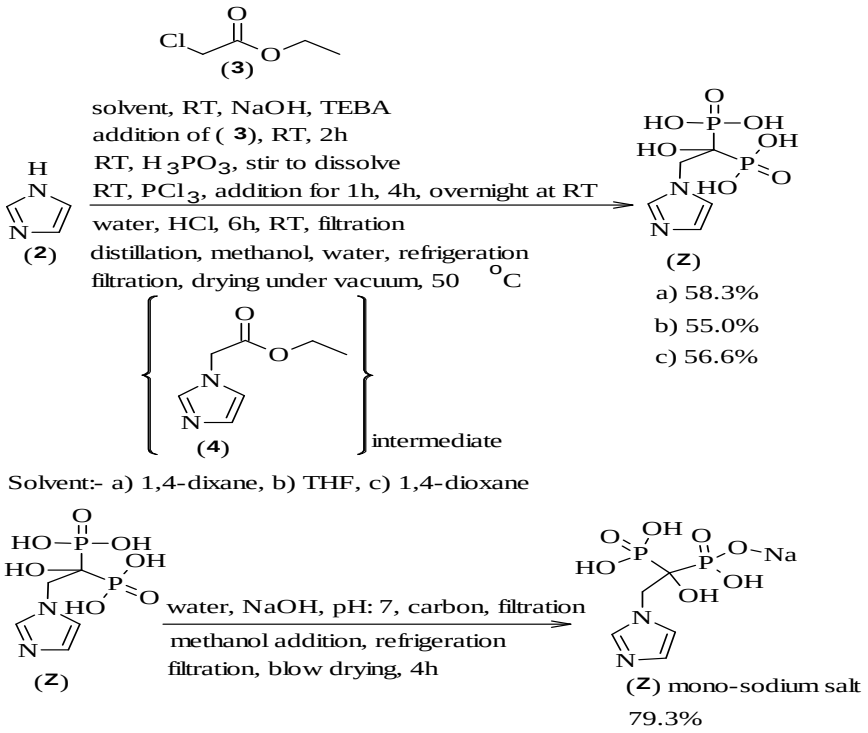
**Table 34. Recrystallization details and results of (Z) monohydrate**

| **Input/operation** | **Crystallization Exp. 1** | **Crystallization Exp. 2** |
|---|---|---|
| Initial input | 195 ml of water, 35.85 g of NaOH, stirred to get solution | 1.1 L of water, 61.0 g of NaOH |
| Crude (**Z**) monohydrate | 65.0 g | 130.86 g |
| Stirring | till clear solution | - |
| Decolourization | 3.25 g of activated charcoal & 19.5 ml of water, 15 min, filtration, washed by 45.5 ml of water | 10.0 g of activated charcoal, boiled for 5 min, filtration, washed by 100 ml of hot water |
| Acidification | 89.36 g of HCl & 276 ml of water, 45 min | 260 ml of 36% HCl, quick addition |
| Isolation | 0 $^{o}$C, 2h, filtration, washed with 65 ml of water & 130 ml of ethanol, dried at 60 $^{o}$C | 5 $^{o}$C, pH: 1 by NaOH pellets, 5 $^{o}$C, 2 h, filtration, washed with 100 ml of, dried at 50 $^{o}$C 24 h |
| Recovery | 91.7%, 59.57 g | 82.6%, 108.13 g |

Lump formation, high reaction temperature for phosphorylation and low yield are the major issues related to synthesize (**Z**). A novel work in a patent (**Table 35**) by Hu, Y., *et al*. 2010,

had demonstrated a one-step synthesis of (**Z**) from (**2**) in the presence of a phase-transfer catalyst, under the alkaline condition to get the intermediate (**4**). Further, an insitu phosphorylation of (**4**), by $H_3PO_3$, $PCl_3$ and hydrolysis under acidic condition gave (**Z**) under the anti-solvent mediation (**Scheme 21**). The adoption of phase transfer catalyst had accelerated the rate of reaction and the yield had improved up to 62%, compared to the conventional mode of (**Z**) synthesis. The details of experiments performed to isolate (**Z**) and the corresponding results are depicted in **Table 37**. The work extends to cover the varied input of TEBA to isolate (**Z**) with a yield ranging from 21.7-62.0%. Similarly, three different phase transfer catalysts were also used under identical reaction conditions. But the impact of TEBA was found better from the experimental results. The work provides a method for the conversion of (**Z**) to its mono-sodium salt. As per the disclosure, to 35.0 g of (**Z**) and 280 ml of water added 6.0 g of NaOH to dissolve it completely (pH: 7). To the clear solution, added 2.0 g of activated charcoal, filtered and slowly added 105 ml of methanol under stirring. It was then refrigerated to get the crystals. The crystals formed were filtered and blow dried for 4h to get (**Z**) mono-sodium salt. Yield: 79.3%, 30.0 g, mp: 239 $^{o}$C (dec.). The disclosed method ensures high product quality with good yield.

| **Table 35. Details of the patent entitled "Method for preparing Zoledronic acid and sodium salt thereof by utilizing phase transfer catalyst" [40].** |
|---|
| **Application**: CN201010610896A, 2010-12-23 |
| **Publication**: CN102070668B, 2013-07-24 |
| **Published also as**: CN102070668A |
| **Inventors**: Hu, Y., Zhang, Y., & Zheng, A. |




**Scheme 21. One step synthesis of (Z) from (2) and the isolation of (Z) mono-sodium salt.**

| **Table 36. The experimental details to isolate (Z) from (2) using benzyltriethylammonium chloride (TEBA).** | | | |
|---|---|---|---|
| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** |
| (**2**) | 15.0 g | 15.0 g | 15.0 g |
| Solvent | 200 ml of 1,4-dioxane | 200 ml of THF | 200 ml of 1,4-dioxane |
| NaOH addition | 10.0 g, RT | 9.7 g, RT | 10.5 g, RT |
| TEBA | 3.0 g | 2.3 g | 4.5 g |
| (**3**) addition | 40 ml | 35 ml | 45 ml |
| Reaction time | RT, 2 h | RT, 2 h | RT, 2 h |
| $H_3PO_3$ addition | 36.0 g, RT | 36.5 h, RT | 40.0 g, RT |
| $PCl_3$ addition | 38 ml, RT, drop wise for 1 h | 40 ml, RT, drop wise for 1.5 h | 38 ml, RT, drop wise for 1 h |
| Reaction time | RT, 4 h then left overnight | RT, 4 h then left overnight | RT, 4 h then left overnight |
| Water addition | 70 ml | 100 ml | 70 ml |
| Conc. HCl | 70 ml | 70 ml | 70 ml |
| Hydrolysis | RT, 6 h | RT, 6 h | RT, 6 h |
| Isolation | Filtration, evaporation under vacuum, 200 ml of methanol addition, filtration | Filtration, evaporation under vacuum, 200 ml of methanol addition, filtration | Filtration, evaporation under vacuum, 200 ml of methanol addition, filtration |
| Crystallization | 50 ml of water and 50 ml of methanol, refrigeration | 50 ml of water and 50 ml of methanol, refrigeration | 50 ml of water and 50 ml of methanol, refrigeration |
| Drying | vacuum oven at 50 °C | vacuum oven at 50 °C | vacuum oven at 50 °C |
| Yield | 58.3%, 35.0 g | 55.0%, 33.0 g | 56.6%, 34.0 g |
| mp | 239 °C (dec.) | 239 °C (dec.) | 239 °C (dec.) |

In view to synthesize (**Z**) in an eco-friendly pathway with low production cost and high efficiency, Lanxiang, S., *et al*. 2011, had demonstrated a three step process in patent (**Table 37**) starting from (**2**) by avoiding chlorobenzene. As per the disclosure, (**2**) was reacted with (**3**) in the presence of a suitable phase transfer catalyst to isolate the intermediate (**4**). It was then hydrolyzed to form (**1a**), further its phosphorylation and acid mediated hydrolysis gave crude (**Z**). Its recrystallization from water gave (**Z**) with 56-59% of yield. Two examples are given to synthesize (**Z**) from (**2**), the details are tabulated with results in **Table 38**. More importantly, during phosphorylation sticky mass was formed which slowly expanded and solidified.

| **Table 37. Details of the patent entitled "New preparation method of Zoledronic acid".[41]** |
|---|
| **Application**: CN201110122157A, 2011-05-12 |
| **Publication**: CN102775444A, 2012-11-14 |
| **Published also as**: None |
| **Inventors**: Lanxiang, S., Yanxia, H., Baohua, Z., & Xuetao, W. |

**Table 38. The details of experiment to synthesize (Z) from (2) under mild reaction conditions using dodecyl benzyl dimethyl ammonium chloride/bromide (DBDAC/DBDAB).**

| **Input/operation** | **Exp. 1** | **Exp. 2** |
|---|---|---|
| Initial input | 34.0 g of (**2**), 500 ml of ethylene dichloride, 78.0 g of $CO_2$ and 1.0 g of DBDAC | 34.0 g of (**2**), 500 ml of methylene dichloride, 78.0 g of $K_2CO_3$ and 1.0 g of DBDAB |
| Condition | under stirring in an ice bath | under stirring in an ice bath |
| (**3**) & reaction | 67.4 g, slow addition, 40-50 $^oC$, 8 h | 67.4 g, slow addition, 40-50 $^oC$, 8 h |
| Workup | filtration, washings, saturated NaCl wash, drying, distillation to remove ethylene dichloride | filtration, washings, saturated NaCl wash, drying, distillation to remove methylene dichloride |
| Isolation of (**4**) | high vacuum fractional distillation, 135-140 $^oC$ at 667Pa | high vacuum fractional distillation, 135-140 $^oC$ at 667Pa |
| Yield of (**4**) | 90.1%, 69.4 g, as yellow oily mass | 92.0%, 70.86 g, as yellow oily mass |
| Input of (**4**) for hydrolysis | 69.4 g, 300 ml of water & 300 ml of conc. HCl | 69.4 g, 300 ml of water & 300 ml of conc. HCl |
| Condition | Reflux, 8 h | Reflux, 8 h |
| Granular activated carbon (GAC) addition | 10.0 g at 40-50 $^oC$, reflux, 30 min | 10.0 g at 40-50 $^oC$, reflux, 30 min |
| Isolation | evaporation under vacuum, approx. 60-70 ml of residual volume, 5 $^oC$, 2 h, 200 ml of ethanol, filtration, washed with 100 ml of ethanol, drying at 70-80 $^oC$ | evaporation under vacuum, approx. 60-70 ml of residual volume, 5 $^oC$, 2 h, 200 ml of ethanol, filtration, washed with 100 ml of ethanol, drying at 70-80 $^oC$ |

| | | |
|---|---|---|
| Yield of (**1a**) | 91.8%, 78.6 g | 91.8%, 78.6 g |
| mp | 193-194 $^{o}$C | 193-194 $^{o}$C |
| Input of (**1a**) for phosphorylation | 78.56 g, 7.8 g of TFA & 72 ml of $H_3PO_4$, 100 $^{o}$C, to dissolve | 78.56 g, 7.8 g of sulfuric acid & 72 ml of $H_3PO_4$, 100 $^{o}$C, to dissolve |
| $PCl_3$ addition | 79.75 g, 80 $^{o}$C, slow | 79.75 g, 80 $^{o}$C, slow |
| Reaction | sticky mass, 100 $^{o}$C, 4 h | sticky mass, 100 $^{o}$C, 5 h |
| Water addition | 100 ml, hot filtration, reflux, 3 h | 100 ml, hot filtration, reflux, 3 h |
| Isolation | evaporation under vacuum, 2.4 L of ethanol, under stirring, refrigeration, filtration & recrystallization in water | evaporation under vacuum, 2.4 L of ethanol, under stirring, refrigeration, filtration & recrystallization in water |
| Yield | 58.8%, 76.8 g | 57.0%, 67.6 g |
| mp | 238.3-239.3 $^{o}$C | 238.3-239.3 $^{o}$C |

To achieve higher yield, easy phosphorylation, cost reduction and scalable process, Yinchuan, Z., *et al*. 2011, had demonstrated a process in a patent (**Table 38**) to synthesize (**Z**) monohydrate from (**1a**) or (**1b**) using liquid paraffin as the diluent. As per the disclosure, six examples are given to get (**Z**) monohydrate. Liquid paraffin, (**1a**) or (**1b**) and $H_3PO_4$ (85%) were taken in a reactor provided with condenser and dropping funnel. The mixture was heated to 50-60 $^{o}$C, added $PCl_3$ slowly under stirring. After the addition, reaction was maintained at 80 $^{o}$C for 20-23 h under stirring. Interestingly, solidification of the reaction mass was not observed. To the reaction mass, water was added and refluxed for 4-24 h. It was cooled to ambient temperature and the phase separation was done. A clear colorless aqueous phase was collected, was decolorized by adding charcoal in most instances. It was heated to 40-60 $^{o}$C under stirring and added ethanol slowly, cooled to ambient temperature and further cooled to 3 $^{o}$C. The precipitate formed was filtered, washed with ethanol and dried at 50 $^{o}$C for 24 h to isolate (**Z**) monohydrate. More details regarding the experiment and corresponding results are depicted in **Table 39**.

| **Table 38. Details of the patent entitled "Preparation method of Zoledronic acid".[42]** |
|---|
| **Application**: CN201110452920A, 2011-12-29 |
| **Publication**: CN102408443A, 2012-04-11 |
| **Published also as**: CN102408443B |
| **Inventors**: Yinchuan, Z., Qingan, W., Fuqun, Z., & Qiuhuo, Z. |

**Table 39. The details of the experiment performed to isolate (Z) monohydrate using liquid paraffin as the diluent and the corresponding results.**

| Exp. No. | (1a)/(1b) input | Water addition | Hydrolysis duration | Ethanol addition | Yield | Purity (a%) |
|---|---|---|---|---|---|---|
| **Exp.1** | 5.13 g of (**1a**) | 40 ml | 4 h | 90 ml, 60 $^{o}$C | 71.0%, 6.5 g | 96.8% |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Exp. 2** | 20.0 g of (**1b**) | 212 ml | 24 h | 477 ml, 60 $^{o}$C | 79.3%, 36.5 g | 97.7% |
| **Exp. 3** | 20.0 g of (**1b**) | 212 ml | 18 h | 477 ml, 60 $^{o}$C | 81.1%, 37.5 g | 98.7% |
| **Exp. 4** | 20.0 g of (**1b**) | 212 ml | 22 h | 500 ml, 60 $^{o}$C | 56.6%, 26.1 g | 96.3% |
| **Exp. 5** | 80.0 g of (**1b**) | 212 ml | 22 h | 2L, 40 $^{o}$C | 74.5%, 137.2 g | 97.2% |
| **Exp. 6** | 80.0 g of (**1b**) | 212 ml | 18 h | 2L, 40 $^{o}$C | 77.6%, 143.0 g | 98.2% |

To prevent the formation of secondary products and to make the process economically feasible, Keglevich, G., *et al*. 2012, had illustrated a modified process in a patent (**Table 40**) to synthesize (**Z**) from (**1b**) by using the reagents in appropriate quantities for phosphorylation. The work demonstrated that, $H_3PO_4$ or $H_3PO_3$ was not necessary for phosphorylation, instead it can be achieved by using triphosgene, mesyl chloride, $PCl_3$ etc. Three examples were provided in this regard, the experiment details and the results are tabulated in **Table 41**.

| **Table 40. Details of the patent entitled "Novel process for the preparation of dronic acids" [43].** |
|---|
| **Application**: HU2012000009W, 2012-02-08 |
| **Publication**: WO2012107787A1, 2012-08-16 |
| **Published also as**: EA027231B1; EA201300893A1; EP2673282A1; EP2673282B1; HU1100071A2; HU230718B1; HUE031236T2; LT2673282T; PL2673282T3; PT2673282T |
| **Inventors**: Keglevich, G., Gruen, A., Garadnay, S., & Neu, J. |

| **Table 41. The experimental details to synthesize (Z) from (1b) in absence of $H_3PO_4$ or $H_3PO_3$.** | | | |
|---|---|---|---|
| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** |
| (**1b**) | 6.3 g | 4.2 | 6.3 g |
| Diluent | 14 ml of MSA | 12 ml of MSA | 14 ml of MSA |
| Addition & next | after 30 min, RT, 5.9 g of triphosgene, 80 $^{o}$C, 4 h | after dissolution, RT, 3.2 g of mesyl chloride, RT, 4 h | after 30 min, 13.6 ml of $PCl_3$, 80 $^{o}$C, 3 h |
| Further addition | 9.2 ml of $PCl_3$, 80 $^{o}$C, 16 h | At 50-60 $^{o}$C, 6.4 ml of $PCl_3$, 70-75 $^{o}$C, 4-5 h | - |
| Water addition & next | RT, 36 ml of water, 105-110 $^{o}$C, 5 h | RT, 24 ml of water, 110 $^{o}$C, 5 h | RT, 36 ml of water, 105-110 $^{o}$C, 5 h |
| Decolorization by activated carbon | 0.75 g, filtration, washed by 5 ml of water | 0.5 g, filtration, washed by 4 ml of water | 0.75 g, filtration, washed by 5 ml of water |
| pH adjustment | to 1.8 by 10M NaOH solution | to 0.25 by 40% NaOH solution | to 1.8 by 10M NaOH solution |
| Isolation | RT, stirring for 24 h, | RT, stirring for 24 h, | RT, stirring for 24 |

| | | | |
|---|---|---|---|
| | filtration, washings & drying | filtration, washings & drying | h, filtration, washings & drying |
| Crude (**Z**) | 59.0%, 8.1 g, free acid: 19.5%, purity: 82% | 62.0%, 3.0 g, free acid: 25.0%, purity: 93% | 74.0%, 10. 1g, free acid: 23.0%, purity: 83% |
| Recrystallized from 5 vol of 1N HCl , (**Z**) | 41.0%, 5.5 g, free acid: 99.0%, purity: 100% | 45.0%, 2.2 g, free acid: 99.0%, purity: 100% | 46.0%, 6.3 g, free acid: 98.0%, purity: 98.0% |

In order to simplify the phosphorylation, Kai, S., *et al.* 2012, had reported a process (**Table 42**) to synthesize (**Z**) monohydrate from (**1b**) using commercially affordable aliphatic hydrocarbon along with water as the diluent for phosphorylation. Moreover, the reaction was performed by using a single phosphorus containing reagent ($PCl_3$). An industrially feasible, simple and mild reaction conditions are adopted to synthesize (**Z**) monohydrate in reasonably good yield (80-90%) without solidification issues in phosphorylation stage. The work extends to synthesize few other diphosphonic acids under similar protocol. The details of experiment and the results obtained are tabulated in **Table 43**.

| **Table 42. Details of the patent entitled "Preparation method for diphosphonic acid compound" [44].** |
|---|
| **Application**: CN201210186236A, 2012-06-07 |
| **Publication**: CN102690288A, 2012-09-26 |
| **Published also as**: CN102690288B |
| **Inventors**: Kai, S., Yan, J., Huanji, C., Zhihui, Z., Tingting, F., Xiaoyu, W., & Jie, L. |

**Table 43. The details of experiment performed to synthesize (Z) monohydrate using $PCl_3$ alone.**

| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** |
|---|---|---|---|
| Initial input | 200 ml of n-hexane & 1.1 ml of water, | 50 ml of n-decane & 3 ml of water | 2 L of n-tetradecane & 4.8 ml of water |
| $I^{st}$ lot $PCl_3$ | 2.75 g, -20 $^oC$, 30 min | 6.87 g, 0 $^oC$, 2 h, 25$^oC$ | 13.74 g, 50 $^oC$, 24 h, 100 $^oC$ |
| Addition of (**1b**) | 2.52 g, -20 $^oC$ | 2.52 g, 25 $^oC$ | 2.52 g, 100 $^oC$ |
| $2^{nd}$ lot $PCl_3$ | 4.12 g, -20 $^oC$ | 10.99 g, 0 $^oC$ | 21.98 g, 80 $^oC$ |
| Reaction duration | 8 h, 50 $^oC$ | 18 h, 70 $^oC$ | 24 h, 80 $^oC$ |
| Hydrolysis | HCl addition, 8 h, 80 $^oC$ | HCl addition, 18 h, 95 $^oC$ | HCl addition, 24 h, 100 $^oC$ |
| workup | RT, phase separation, evaporation of aqueous phase under vacuum | RT, phase separation, evaporation of aqueous phase under vacuum | RT, phase separation, evaporation of aqueous phase under vacuum |
| Isolation | 12.6 ml of acetone, -20 $^oC$, 1 h, filtration, drying, 20 $^oC$, 5 h | 60 ml of methanol, -10 $^oC$, 8 h, filtration, drying, 60 $^oC$, 5 h | 250 ml of n-butanol, 20 $^oC$, 24 h, filtration, drying, 70 $^oC$, 5 h |
| Yield | 81.0%, 4.7 g | 91.0%, 5.3 g | 83.0%, 4.82 g |
| Purity by HPLC (a%) | 99.5% | 99.8% | 99.7% |

To overcome the deficiencies in the prior art to synthesize (**Z)** and to improvise the process to suite for large scale manufacturing with better yield and high purity, Hao, E., *et al*. 2015, had demonstrated a process (**Table 44**) to synthesize sodium (**Z**) from (**2**) using ionic liquid as diluent for phosphorylation. The work also provides the detail of process optimization studies performed to achieve better yield and purity of (**Z**). As per the disclosure, 13.62 g of (**2**) and [bmim]$BF_4$ were taken in a reactor provided with condenser and dropping funnel. The mixture was heated to 60 $^oC$ under stirring and slowly added 24.51 g of (**3**) for over 2 h. The reaction mixture was then refluxed for 16 h and cooled to isolate crude (**4**). Yield: 77.8%, 24.0 g, not purified). It was taken a reactor provided with a condenser and dropping funnel. Added 34 ml of conc. HCl and gradually heated to 85 $^oC$. The reaction mixture was then heated to reflux for 10 h. After the reaction completion, water was evaporated to dryness under reduced pressure to obtain the residue. To the residue added 20 ml of ethanol, stirred for 2h , filtered and dried in oven at 80 $^oC$ to isolate (**1a**). Yield: 79.4%, 25.65 g, as white solid. In the next step, 17.26 g of (**1a**), 40 ml of [bmim]$BF_4$ and 16 ml of $H_3PO_4$ (85%) were taken in a reactor and heated to 60$^oC$ under stirring. Through the dropping funnel, slowly added 30 ml of $PCl_3$ in a span of 4h and refluxed at 60-65$^oC$ for 4h. The reaction mass was filtered and residue and filtrate were separately quenched to HCl solution and refluxed for 6 h. The combined aqueous phase was evaporated to dryness to get yellow oily mass. To it added 120 ml of acetone and 120 ml of ethanol, stirred for 15 min and filtered to isolate crude (**Z**). It was recrystallized from 30 ml of water and dried to isolate (**Z**) monohydrate. Yield: 90.1%, 35.8 g, purity: 98.5% by HPLC (a%). In the next step, 46.4 g of (**Z**) monohydrate, 450 ml of water and 5.6 g of NaOH were taken in a reactor and refluxed for 30 min to get clear solution. It was gradually cooled and filtered to isolate I crop of sodium (**Z**). The filtrate was concentrated to half of its volume by evaporation under reduced pressure. It was cooled t and filtered to isolate the II crop of sodium (**Z**). Both crops were collectively dissolved in a mixture of 410 ml of water and 60 ml of isopropanol under heating. To the clear solution, added activated charcoal, filtered, cooled and dried at 40-60 $^oC$ to get sodium (**Z**). Yield: 85%, 42.4 g, purity: 99.8% by HPLC (a%), mp: 239 $^oC$. Under the process optimization category, ionic liquid used was recovered and reused multiple times for the reaction. After five times of reuse, the yield was dropped from 90.1-87.7%. In another set of initiatives, phosphorylation was carried out at different temperatures in range from 55-80 $^oC$. The impact of reaction temperature on yield was recorded as follows, 55 $^oC$ (63.4%), 60 $^oC$ (78.5%), 65 $^oC$ (90.0%), 70 $^oC$ (87.3%) & 80 $^oC$ (62.7%). A drastic decrease in the yield was observed at 80$^oC$, but the range of 65-70 $^oC$ was found to be the ideal zone for phosphorylation. In the

similar way, $PCl_3$ addition time had also played a vital role to have an impact on the yield. The experimental results obtained in this context are as follows, 2.5 h (51.7%), 3.5 h (71.6%), 4.0 h (90.1%), 4.5 h (90.1%) & 5.5 h (88.5%). Maximum yield was obtained by the addition of $PCl_3$ to the reaction mass over a period of 4-4.5 h. A few experiments were also reported by using different ionic liquids for the reaction, a consistent yield of 90-92% was obtained with all the variants.

| **Table 44. Details of the patent entitled "Preparation method for sodium Zoledronic acid".[45]** |
|---|
| **Application**: CN201510001167A, 2015-01-05 |
| **Publication**: CN104610357A, 2015-05-13 |
| **Published also as**: None |
| **Inventors**: Hao, E., Jiang, X., Liu, Y., Zhang, Q., Wang, D., Xie, M., Wang, H., Guo, H., & Li, G. |

To overcome the shortcomings to synthesize (**Z**) from past disclosures, Wu, Y., *et al*. 2016, had illustrated a high yield and solvent free process (**Table 45**) to phosphorylate (**1b**) using $H_3PO_3$ along with $PCl_3$ or $POCl_3$. The process was demonstrated in substantial high scale, thus the process would suite for large scale manufacturing of the drug (**Z**). The work provides four examples of solvent free phosphorylation of (**1b**) and two comparative examples of the same in sulfolane and chlorobenzene. The brief details of comparative examples are provided with results in **Table 46**. The overall yield by the use of solvent (sulfolane/chlorobenzene) to synthesize (**Z**) in comparative examples was found to be 50-52%. In those experiments which are performed in the absence of solvent (**Table 47**), overall yield of (**Z**) was found to be 52-55%.

| **Table 45. Details of the patent entitled "Synthesis process of Zoledronic acid" [46].** |
|---|
| **Application**: CN201611114482A, 2016-12-07 |
| **Publication**: CN106699809A, 2017-05-24 |
| **Published also as**: None |
| **Inventors**: Wu, Y., Chen, X., Liu, K., Zhang, Y., & Zhang, K. |

| **Table 46. Details of solvent mediated phosphorylation of (1b) to synthesize (Z).** | | |
|---|---|---|
| **Input/operation** | **Comparative Exp. 1** | **Comparative Exp. 2** |
| Initial input | 400.0 g of sulfolane, 110.0 g of (**1b**), 224.0 g of $H_3PO_3$ and 375.0 g of $PCl_3$, 40-45 $^oC$, 2 h | 400.0 g of sulfolane, 110.0 g of (**1b**), 224.0 g of $H_3PO_3$ and 375.0 g of $PCl_3$, 40-45 $^oC$, 2 h |
| Hydrolysis | 1.1 L of 9N HCl solution, 90-100 $^oC$, 5h | 550 ml of 9N HCl solution, 90-100 $^oC$, 5 h |
| Workup | 11.0 g of activated carbon, 30 min, hot filtration, 200 ml water wash, | 11.0 g of activated carbon, 30 min, hot filtration, 200 ml water wash, |

| | | |
|---|---|---|
| | cool to RT, added to 320.0 g of ethanol | cool to RT, added to 320.0 g of ethanol |
| Isolation | RT, 4 h, filtration, 110.0 g of ethanol wash, drying at 60 $^{o}$C for 3 h | RT, 4h, filtration, 110.0 g of ethanol wash, drying at 60 $^{o}$C for 3 h |
| Crude (**Z**) | 78.1%, 185.3 g | 65.0%, 154.2 g |
| Purity | 95.5% | 96.8% |
| Recrystallization | 140.0 g of crude in 2.24 L of water, reflux, 7.0 g of activated carbon, hot filtration, 0-5 $^{o}$C, 2 h, drying, 60 $^{o}$C, 3 h | 140.0 g of crude in 2.24 L of water, reflux, 7.0 g of activated carbon, hot filtration, 0-5 $^{o}$C, 2 h, drying, 60 $^{o}$C, 3 h |
| Yield of (**Z**) | 80.7%, 120.5 g, as crystalline powder | 81.7%, 122.0 g, as crystalline powder |
| Purity | 99.8% | 99.8% |

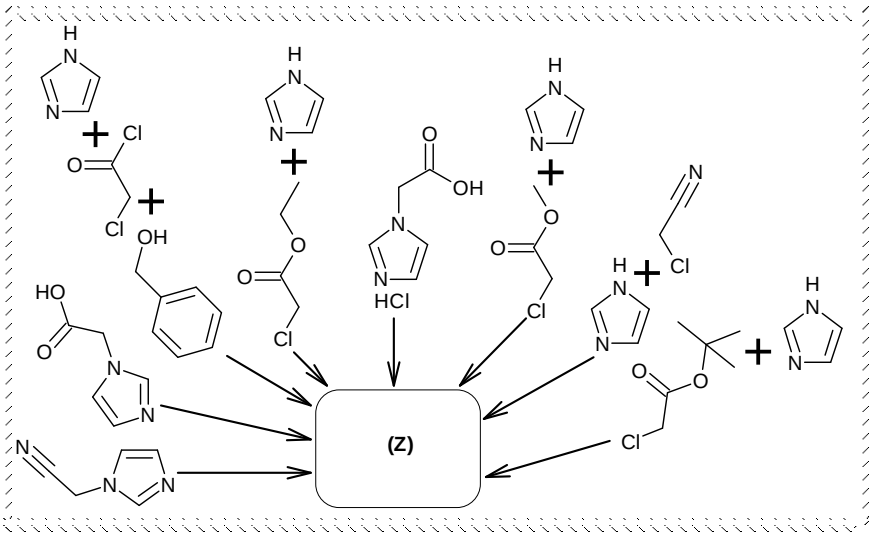
**Table 47. Details of solvent free phosphorylation of (1b) to synthesize (Z).**

| **Input/operation** | **Exp. 1** | **Exp. 2** | **Exp. 3** | **Exp. 4** |
|---|---|---|---|---|
| Initial input | 1.1 Kg of (**1b**), 2.5 Kg of $H_3PO_3$ and 4.2 Kg of $PCl_3$, 65-70 $^{o}$C, 4 h | 110.0 g of (**1b**), 180.0 g of $H_3PO_3$ and 300.0 g of $POCl_3$, 75-80 $^{o}$C, 3 h | 110.0 g of (**1b**), 286.0 g of $H_3PO_3$ and 480.0 g of $PCl_3$, 50-55 $^{o}$C, 6 h | 110.0 g of (**1b**), 215.0 g of $H_3PO_3$ and 360.0 g of $PCl_3$, 40-55 $^{o}$C, 6 h |
| Hydrolysis | 5.5 L of 9N HCl solution, 90-100 $^{o}$C, 5 h | 880 ml of water, 80-90 $^{o}$C, 6 h | 770 ml of water, 70-80 $^{o}$C, 3 h | 660 ml of 9N HCl solution, 90-100 $^{o}$C, 4 h |
| Workup | 110.0 g of activated carbon, 30 min, hot filtration, 200 ml water wash, cool to RT, added to 32 Kg of ethanol | 11.0 g of activated carbon, 30 min, hot filtration, 200 ml water wash, cool to RT, added to 270.0 g of methanol | 11.0 g of activated carbon, 30 min, hot filtration, 200 ml water wash, cool to RT, added to 320.0 g of isopropanol | 11.0 g of activated carbon, 30 min, hot filtration, 200 ml water wash, cool to RT, added to 350.0 g of ethanol |
| Isolation | RT, 4 h, filtration, 1.1 Kg of ethanol wash, drying at 60 $^{o}$C for 3 h | RT, 4 h, filtration, 110.0 g of methanol wash, drying at 60 $^{o}$C for 3 h | RT, 4 h, filtration, 110.0 g of ethanol wash, drying at 60 $^{o}$C for 3 h | RT, 4 h, filtration, 110.0 g of ethanol wash, drying at 60 $^{o}$C for 3 h |
| Crude (**Z**) | 84.4%, 2.0 Kg | 82.7%, 196.1g | 84.3%, 200.1 g | 86.4%, 205.1 g |
| Purity | 99.8% | 99.8% | 99.8% | 99.8% |
| Recrystallization | 1.4 Kg of crude in 25.2 L of water, reflux, 70.0 g of activated carbon, hot filtration, 0-5 | 140.0 g of crude in 2.24 L of water, reflux, 7.0 g of activated carbon, hot filtration, 0-5 | 140.0 g of crude in 2.24 L of water, reflux, 7.0 g of activated carbon, hot filtration, 0-5 $^{o}$C, 2 h, drying, 60$^{o}$C, 3 h | 140.0 g of crude in 2.38 L of water, reflux, 7.0 g of activated carbon, hot filtration, 0-5 |

| | °C, 2 h, drying, 60 °C, 3 h | °C, 2 h, drying, 60 °C, 3 h | | °C, 2 h, drying, 60 °C, 3 h |
|---|---|---|---|---|
| Yield of (**Z**) | 83.7%, 1.25 Kg | 83.9%, 125.3 g | 87.3%, 130.3 g | 85.9%, 128.3 g |
| Purity | 99.9% | 99.9% | 99.9% | 99.9% |

## SUMMARY

Numerous pathways were opted for the synthesis and purification of (**Z**) in patents filed by various researchers/organizations. In outline, the key starting materials used to synthesize (**Z**) can be listed as follows, 1-*H*-imidazol-1-ylacetic acid hydrochloride (**1a**), 1-*H*-imidazol-1-ylacetic acid (**1b**) 1*H*-imidazole (**2**), ethyl-chloroacetate (**3**), chloroacetyl chloride (**5**), benzyl alcohol (**6**), methyl chloroacetate (**8**), chloroacetonitrile (**9**), methyl 1-*H*-imidazol-1-ylacetate (**10**), t-butyl chloroacetate (**11**) and 1-*H*-imidazol-1-ylacetonitrile (**12**). These raw materials (**Scheme 22**) were used under specific conditions in distinct experiments to obtain (**Z**). Moreover, variety of solvents and solvent-free conditions were also employed for the synthesis, as narrated in the review work flow. Furthermore, less drastic conditions and green solvents were also ventured for the industrial suitability of the process.




**Scheme 22. An overview of key raw materials used to synthesize (Z).**

## CONCLUSION

The present in detail review work was aimed at the chronological extraction of methods disclosed in patents for the synthesis and purification of (**Z**). Moreover, the process related issues, yield improvement strategies, and recrystallization methods associated with (**Z**) were also given an equal emphasis. Every new patent venture was focused to commercialize the drug manufacturing with ease. This was achieved by using various starting materials, reagents, solvents, reaction optimizations, crystallization techniques, etc. The present

methodological review will provide the necessary information to process chemists about the past patent disclosures on the synthesis and purification of (**Z**). This venture would provide a platform for the future inventions/innovations towards the commercialization of (**Z**).

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