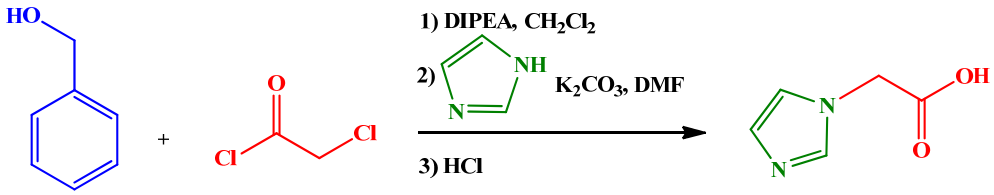
# A very efficient and convenient route for synthesis of imidazol-1-yl-acetic acid: the most important precursor for the synthesis of zoledronic acid

Javad Mokhtari Aliabad*[a], Mehry Hosseini[a], Issa Yavari[a], Morteza Rouhani[a]

[a] Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran

j.mokhtari@srbiau.ac.ir

**Graphical Abstract:**




**Abstract:**

A convenient synthesis of imidazol-1-yl-acetic acid is described. Condensation reaction of a benzyl alcohol and a chloroacetyl chloride in the presence of *N*,*N*-diisopropylethylamine gave a benzyl 2-chloroacetate, which on treatment with an imidazole and then a hydrochloric acid afforded the imidazol-1-yl-acetic acid in good yield.

**Keywords:** Imidazol-1-yl-acetic acid, zoledronic acid, biphosphonic acids, hypercalcemia, drug precursors.

## Introduction:

Bisphosphonic acids are beneficial antihypercalcemic medicines and could be utilized as remedial factors for the therapy of illnesses which are specified by unusual calcium metabolism.[1] They have showed efficiency in detention bone decline and restituing normocalcemia in patients with metastatic bone disease, hypercalcemia of malignancy, osteoporosis and Paget's disease and they have the potential for other medical usages as well.[2] Bisphosphonates, particularly, bisphosphonates of 3-amino-1-hydroxy- 3-(methylpentylamino)propylidene bisphosphonic acid (ibandronate, **1a**) and 4-amino-1-hydroxybutylidene-1,1- bisphosphonic acid (alendronate, **1b**) and are used for the treatment of Paget's disease of bone and osteoporosis (Fig. 1).[3]

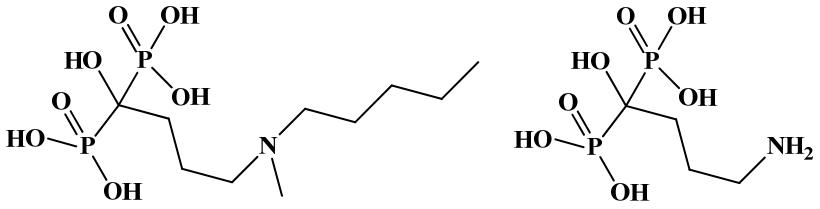



**Figure 1:** Structure of ibandronate (**1a)** and alendronate (**1b).**

Zoledronic acid is a third-generation bisphosphonate derivative specified by a side chain that containes an imidazole ring (Fig. 2). It prevents osteoclast activity and bone resorption and is utilized to remedy tumor induced hypercalcemia like an illness situation determined by the

increased amounts of calcium in the blood (normal range 9–10.5 mg/dL or 2.2–2.6 mmol/L) generally created by some types of cancer.

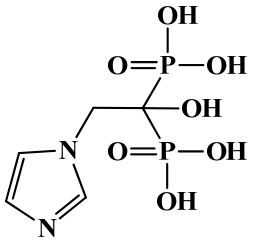



**Figure 2:** Structure of Zoledronic acid.

Zoledronic acid is also applied along with the cancer chemotherapy to remedy bone harm evinced by multiple myeloma. Multiple myeloma is a kind of cancer of plasma cells that are section of the immune system cells in bone marrow and generate antibodies. It is also used for chemotherapy treatment of other type of cancers that started in another part of the body but have developed to the bones. The usage of zoledronic acid can not repress cancer developing, however, it can be applied to remedy bone illness in patients who are suffering from cancer. It acts by decreasing bone breakdown and reducing the quantity of calcium left from the bones into the blood. Zometa™ is a commercially existing medicine, which is offered as a sterile powder or solution in vials suitable for intravenous infusion. Following the available methods for synthesis of Zoledronic acid in quantity have several difficulties while the most important is isolation of imidazol-1-yl-acetic acid as a key intermediate. As part of our ongoing program for the novel drug detection project, we decided to develop a very eficient, practical, simple approach to generate imidazol-1-yl-acetic, which is very suitable for its scale-up. Herein we report our detailed research on the synthesis of imidazol-1-yl-acetic via a much modified approach.[4-10]

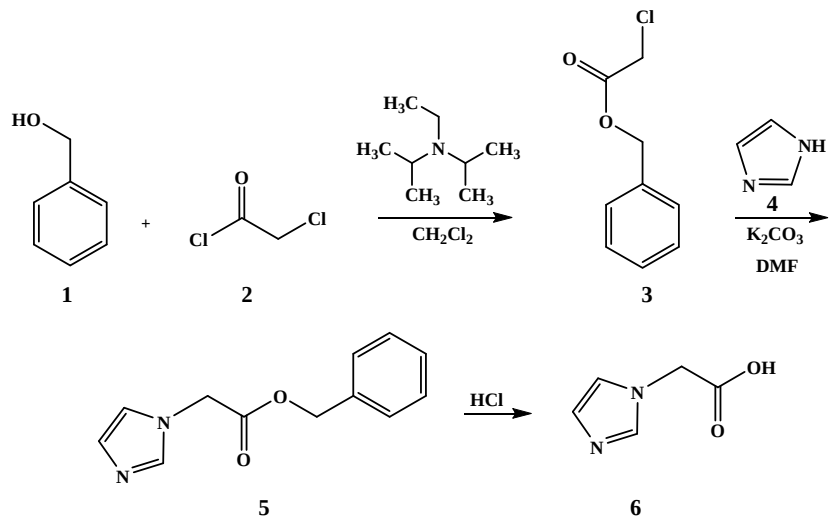
Herein, we wish to report for the first time, a novel and economic synthesis approach of imidazol-1-yl-acetic.

## Results and discussion

According to our suggested protocol, a mixture of benzyl alcohol **1** and chloroacetyl chloride **2** underwent 1:1 condensation in the presence of *N*,*N*-diisopropylethylamine (DIPEA) as a basic catalyst in dichloromethane to afford the corresponding benzyl 2-chloroacetate **3** in total 66% yield (Scheme 1). The reaction was carried out by reaction between 2-chloroacetate 3 and an imidazole **4** in dimethylformamide (DMF) containing $K_2CO_3$ at room temprature for 24 hours. After nearly complete conversion into the corresponding benzyl 2-(1*H*-imidazol-1-yl)acetate **5**, as was indicated by TLC monitoring, an equivalent amount of HCl 10% was added to the mixture and stirring was continued for further 24 hours at 65 °C. The reaction went to completion within 24 hours. TLC and NMR analysis of the reaction mixture clearly indicated the formation of the corresponding imidazol-1-yl-acetic aicd **6** good yield (Scheme 1).

There is a one-pot method for the production of biphosphonic acids in literature.[11] However, this approach uses from hydrolysis of nitriles via the aqueous methansulfonic acid which requires multi-step process for synthesis of starting materials. Here, we suggest the novel and very economic method for the production of 2-(1*H*-imidazol-1-yl)acetate 5 which is the most important key intermediate in the synthesis of Zoledronic acid.

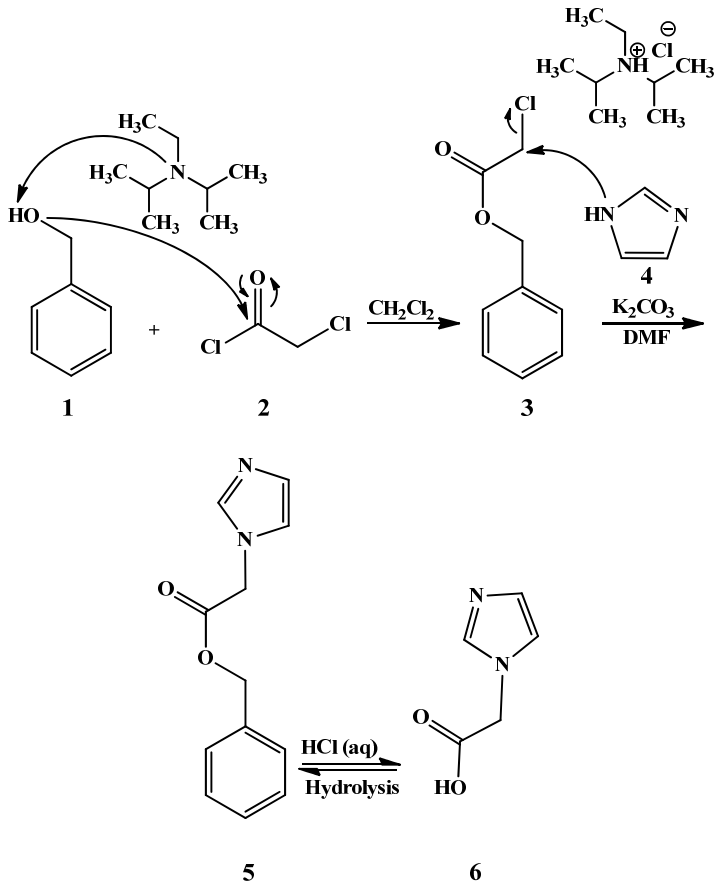
Using simple and cost-effective synthetic route, reasonable final yield, mild reaction condition and etc. makes our synthetic approach a suitable candidate for industrial synthesis of Zoledronic acid and its derivatives.




**Scheme 1:** Synthesis of imidazol-1-yl-acetic **6.**

The structures of the isolated products were concluded on the basis of their $^{1}$H NMR and $^{13}$C NMR spectroscopy. $^{1}$H NMR (500 MHz, DMSO) δ 4.76 (s, 2H, $CH_2$), 7.34 (s, 2H, 2CH), 8.59 (s, 1H, NCHN); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 52.10, 119.70, 123.28, 135.75, 172.86.

A mechanistic explanation for this reaction is demonstrated in Scheme 2. At first, benzyl alcohol **1** condenses with chloroacetyl chloride **2** to produce the benzyl 2-chloroacetate **3**. Diisopropylethylamine facilitates the reaction via deprotonation of of benzyl alcohol. The next step followed by $S_N2$ attack of imidazole **4** to the benzyl 2-chloroacetate **3** in the presence of $K_2CO_3$ to give benzyl 2-(1*H*-imidazol-1-yl)acetate **5**. Then, **5** may undergo acidic hydrolysis under reaction conditions by HCl (aq) to afford imidazol-1-yl-acetic acid **6**. It seems that nucleophilic attacks (addition of **1** on **2** and of **4** on **3**) can be accelerated by the added base. These roles are in agreement with the proposed mechanism.




**Scheme 2:** Proposed mechanism for the formation of imidazol-1-yl-acetic acid **6.**

## Conclusion:

In conclusion, we have studied an effevtive approach for the synthesis of imidazol-1-yl-acetic acid from a three-steps reaction between benzyl alcohol, chloroacetyl chloride, imidazole and hydrochloric acid. Considering the efficient and simple procedure, the availability of the starting materials, high yields of product and easy workup, this synthetic approach provides an economic and efficient route to synthesis of this important precursor. This synthesized key intermediate in the current study may find beneficial applications in synthetic medicinal chemistry.

## Experimental:

All chemicals were obtained from Merck (Germany) and Fluka (Switzerland). $^{1}H$ and $^{13}C$ NMR spectra were measured ($D_2O$ solution) with a Bruker DRX-500 Avance spectrometer at 500.13 and 125.75 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Merck silica gel, 230–240 mesh. Mass spectra were obtained using a Finnigan-Mat 8430 spectrometer operating at an ionization potential of 70 eV.

To optimize the reaction conditions, the reaction of benzyl alcohol **1** and chloroacetyl chloride **2** was used as a model for synthesis of benzyl 2-chloroacetate **3**. To find out the optimum solvent and base, the model reaction was carried out at different reaction conditions (Table 1). According to the obtained data, using dichloromethane as a solvent and diisopropylethylamine as a base for the benzyl 2-chloroacetate formation represents the best reaction conditions.

**Table 1:** Reaction between benzyl alcohol **1** and chloroacetyl chloride **2** in different solvent and base conditions.

| Entry | Base | Solvent | Yield (%) |
|---|---|---|---|
| **1** | --- | $CH_3CN$ | 25 |
| **2** | Pyridine | $CH_2Cl_2$ | 75 |
| **3** | Triethylamine | THF | 45 |
| **4** | Triethylamine | $PhCH_3$ | 20 |
| **5** | --- | $PhCH_3$ | 10 |
| **6** | Triethylamine | $CH_2Cl_2$ | 70 |
| **7** | Diisopropylethylamine | $CH_2Cl_2$ | 85 |

The second step of the reaction was also examined under various solvent and base conditions (Table 2). Table 2 clearly demonstrates that DMF and $K_2CO_3$ were the most suitable solvent and

base respectively, for the production of benzyl 2-(1*H*-imidazol-1-yl)acetate **5** from the reaction of 2-chloroacetate **3** and an imidazole **4**.

**Table 2:** Reaction between 2-chloroacetate **3** and imidazole **4** in different solvent and base conditions.

| Entry | Base | Solvent | Yield (%) |
|---|---|---|---|
| **1** | --- | DMF | - |
| **2** | --- | $CH_3CN$ | - |
| **3** | $K_2CO_3$ | DMF | 88 |

**Synthesis of benzyl 2-chloroacetate 3**

A mixture of benzyl alcohol (0.20 g, 1 mmol), chloroacetyl chloride (0.281 $cm^3$, 3 mmol) and disopropylethylamine (0.242 cm3, 1 mmol) was stirred at room temperature for 24 h. After nearly complete conversion into the corresponding benzyl 2-chloroacetate, as was indicated by TLC monitoring, the HCl 10% aqueous solution (5 ml) was added to the mixture and stirring was continued for further 10 min at room temperature. Next, the product was transformed into the organic phase by water (5 ml) and $CH_2Cl_2$ (5ml). After separation of the organic phase, it was dried with anhydrous sodium sulfate. Then, the solvent evaporated by rotary evaporator and hence benzyl 2-chloroacetate was precipitated.

**Synthesis of benzyl 2-(1H-imidazol-1-yl)acetate 5**

Imidazole (0.254 $cm^3$, 4 mmol) and benzyl 2-chloroacetate (0.85 g, 4 mmol) and $K_2CO_3$ were added and the mixture was allowed to stir for 24 h at room temperature. After completion of the reaction as was indicated by TLC monitoring, the ethyl acetate (10 ml) and water (10 ml) were added to the reaction mixture. The organic phase was separated and

was dried with anhydrous sodium sulfate. The resulting product **5** was precipitated by solvent evaporation with a rotary evaporator.

**Synthesis of imidazol-1-yl-acetic acid 6**

The imidazol-1-yl-acetic acid 6 and HCl 10% (aq) (2 ml) were stirred at 65 °C for 24h. Then toluene (2 ml) was added to the mixture and add stirring was continued for further 10 min at ambient temperature. After the separation of aqueous phase from organic phase, the water was evaporated by a rotary evaporator and the imidazol-1-yl-acetic acid 6 was precipitated.

**Acknowledgment**

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**Supporting Information**

NO (this text will be deleted prior to publication)

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