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Note

A facile preparation of *N*-methylpentan-1-amine: A key intermediate for ibandronate sodium

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A facile preparation of *N*-methylpentan-1-amine, which is a key intermediate for the synthesis ibandronate sodium, an anti-osteoclast agent is described. This route is cost effective over the previous methods. Part of this work could be an easy access for the preparation of various *N*,*N*-alkyl or aryl amine derivatives.

Keywords: *N*-Methylpentan-1-amine, ibandronate sodium, anti-osteoclast agent, cost effective

Phosphonate functionality containing molecules exhibit important pharmacological properties and are widely used in the treatment of various diseases[1,2]. Majority of phosphonates (mono and bisphosphonates) are useful in the treatment of osteoporosis (such as sodium alendronate) and hypercalcemia, for calcium regulation (such as disodium clodronate, etidronic acid), and inhibition of bone resorption (such as sodium ibandronate, sodium risedronate, disodium tiludronate)[3-10]. Osteoporosis is a wide-spread disease in the elder population and effects up to 50% of females and 15% of males[11]. The fragility of the bones leads to a high risk of fractures and the quality of life decreases significantly. Bisphosphonates are the most widely used prescription medicines for the treatment and prevention of postmenopausal osteoporosis. The nitrogen containing bisphosphonates such as alendronate and risedronate have demonstrated antifracture efficacy when administered orally.

Ibandronate sodium, nitrogen containing bisphosphonate, is a highly potent anti-osteoclast agent[12]. In comparison with other bisphosphonates, it has high anti-resorptive potency[13]. The combination of its anti-resorptive potency and the excellent safety profile provides the basis for ibandronate sodium to be administered with increased doses and extended dosing intervals without compromising tolerability[14].

The innovator, Boehringer Mannheim, has reported the synthesis of ibandronate sodium (**Figure 1**) *via* an intermediate *N*-methylpentan-1-amine. The synthesis describes the reaction of benzaldehyde with *N*-pentylamine to get corresponding benzylidene derivative followed by the reduction of double bond and alkylation with formaldehyde/formic acid giving *N*-benzyl-*N*-methylpentan-1-amine. The reductive debenzylation of the obtained tertiary amine resulted in *N*-methylpentan-1-amine **5,** which was followed by three steps to yield ibandronate sodium[15].

In another approach, *N*-methylpentan-1-amine was prepared by methylation of *N*-benzylidenepentan-1-amine with dimethyl sulfate at 90-100°C. The obtained by-product benzaldehyde was removed by steam distillation[16]. In another report, *N*-benzylmethanamine was condensed with 1-bromopentane in the presence of a base to obtain *N*-benzyl-*N*-methylpentan-1-amine. Hydrogenolysis of this tertiary amine in Pd/C yielded the *N*-methylpentan-1-amine[17]. A major difficulty encountered in the synthesis of ibandronate sodium is the preparation of its intermediate *N*-methylpentan-1-amine. Another publication[18] reports the synthesis of *N*-methylpentan-1-amine by condensing valeryl chloride with methanamine hydrochloride to form amide followed by reduction with $LiAlH_4$ (LAH).

The troublesomeness of all the earlier syntheses of ibandronate sodium including innovator's process is the formation of dimer at the reduction stage and all the above processes utilize the pyrophoric reagents such as Pd/C, LAH, *etc*. Additional efforts to remove organic impurities and residual metals make these processes industrially unviable.

Results and Discussion

In continuation of the research on process development of pharmaceutically important moieties[19], it is attempted to improve the synthesis of ibandronate sodium by modifying the preparation of *N*-methylpentan-1-amine.

In this communication is described the synthesis of *N*-methylpentan-1-amine from readily available benzoyl chloride (**Scheme I**). Benzoyl chloride was treated with methanamine at 0-5°C to yield *N*-methyl benzamide. The alkyation of amidic -NH of compound **3** by using 1-bromopentane gave *N*-methyl-*N*-pentylbenzamide **4**. Various conditions were attempted for this alkylation such as K_2CO_3/DMF, K_2CO_3/toluene, K_2CO_3/DMSO, NaOH/DMF, KOH/DMSO, KOH/DMF and KOH/H_2O to reach the target. As a result of this exercise, KOH/DMSO combination gave fairly good purity but only 70% yield. To improve the yield, a phase transfer catalyst (PTC) was planned to be introduced into the reaction system. Various PTCs such as tetrabutylammonium chloride (TBAC), tetrabutylammonium bromide (TBAB), tetrabutyl-ammonium iodide (TBAI) and 18-crown-6 were tried. The reaction containing TBAB or 18-crown-6 gave good results with respect to both yield and purity. Being cost effective for the preparation of key intermediate **5**, TBAB was chosen for further studies.

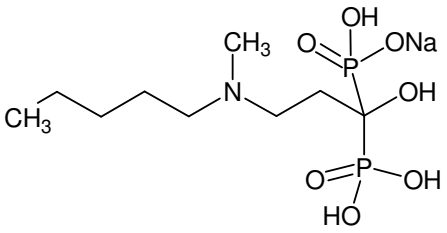


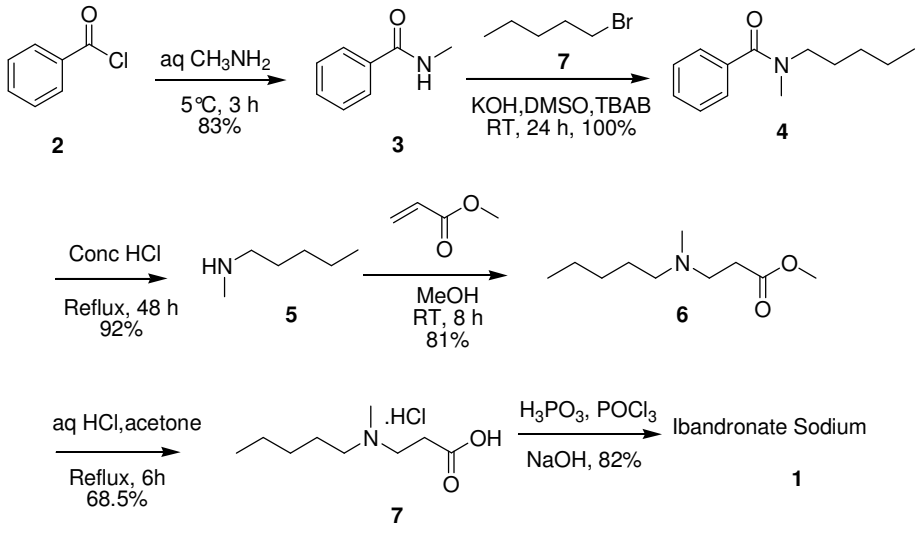
Figure 1

Since reaction volume is one of the key parameters at industrial scale of synthesis, efforts were extended to reduce the reaction volume by decreasing DMSO quantity in the reaction. After various changes, 0.5 volume (0.5 mL/g) of DMSO was finalized.

The amide functionality of compound **4** was removed by refluxing with HCl for 48 hr followed by simple acid-base work-up to give crude **5**, which was further purified by fractional distillation giving *N*-methylpentan-1-amine **5** with high purity and yield. Purity of the product was confirmed as 98% by GC and overall yield starting from benzoyl chloride was ~75%. Usage of in-expensive raw materials, high yield and purity of the product makes this approach attractive.

N-Methylpentan-1-amine **5** was further treated with methyl acrylate to yield compound **6**. The methyl ester of compound **6** was hydrolysed under neutral conditions by refluxing in water followed by salt formation with aq. HCl, to obtain 3-(*N*-methyl-*N*-pentylamino)propanoic acid hydrochloride **7**. Compound **7** was treated with H_3PO_4/$POCl_3$ followed by adjustment of *p*H to 4.5-5.0 using aq. NaOH to give the title moiety ibandranoate sodium **1** in high yield (82%). The overall yield starting from benzoyl chloride was ~35%.

In conclusion, a simpler process to prepare *N*-methylpentan-1-amine followed by synthesis of ibandronate sodium is described. This process is easier to adopt on industrial scale and higher yield of the title compound was obtained using this strategy. Further, synthesis of various secondary and tertiary amines using this methodology is under progress.



Scheme I

Experimental Section

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 and $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over anhydrous sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out over silica gel (230-400 mesh) unless otherwise stated.

Preparation of *N*-methyl benzamide, 3. To monomethylamine (40% aq., 918 mL), benzoyl chloride **2** (250.0 g, 1.778 mole) was slowly added over a period of 30-45 min at 0-5°C. The reaction-mixture was maintained for 3 hr at 5°C. The solution was extracted with toluene (3 × 500 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulphate and the solvent was evaporated under vacuum. The obtained residue was purified by recrystallization from *n*-hexane to give *N*-methyl benzamide, **3** as a colourless solid. Yield: 210.0 g (83.0%); m.p. 79.5-80.5°C; (lit.[20] 80°C); IR (KBr): 1641, 1556, 3327 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.9 (s, 3H), 7.4-7.65 (m, 3H), 7.8-7.9 (d, 2H), 8.4-8.5 (bs, 1H,-NH (D_2O exchangeable); MS: *m/z* (M^++1) 136.07.

Preparation of *N*-methyl-*N*-pentylbenzamide, 4. To a stirred solution of 90 mL DMSO and *N*-methyl benzamide **3** (180.0 g, 1.331 mole), was added potassium hydroxide (149.4 g, 2.625 mole) and tetrabutylammonium bromide (6.0 g, 0.0186 mole) at RT. The reaction-mixture was stirred at RT for 24 hr. After the starting material disappeared on TLC, 300 mL of water was added to reaction-mixture. The aqueous layer was extracted with toluene (2 × 360.0 mL) and the combined organic layer washed with brine and dried over anhydrous sodium sulphate. The solvent was distilled under vacuum to give *N*-methyl-*n*-pentylbenzamide **4** as a pale yellow liquid. Yield: 100%; ^{1}H NMR ($CDCl_3$): δ 0.9-1.0 (m, 3H), 1.0-1.2 (m, 2H), 1.2-1.4 (m, 2H), 1.4-1.8 (m, 2H), 2.8-3.0 (t, 1H), 3.0-3.2 (t, 2H), 3.2-3.4 (m, 1H), 3.4-3.6 (m, 1H), 7.2-7.45 (m, 5H); MS: *m/z* (M^++1) 206.45.

Preparation of *N*-methylpentan-1-amine, 5. A solution of *N*-methyl-*N*-pentylbenzamide **4** (195.0 g, 0.9498 mole) and Conc. hydrochloric acid (975 mL) was heated to reflux for 48 hr. On completion, the reaction-mixture was cooled to 0-5°C and benzoic acid was filtered off. The aqueous layer was extracted with toluene (2 × 585 mL). The *p*H of the aqueous layer was adjusted to 10-12 with 50% NaOH solution to separate the insoluble organic layer. The organic layer was fractionally distilled to get pure compound *N*-methyl-*n*-pentylamine **5** as oil. Yield: 138.0 g (92.0%); b.p. 46-8°C (lit[21] 45-47°C (60 mm)); IR (KBr): 1470, 2957, 3392 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.9 (t, 3H), 1.2-1.4 (m,4H), 1.5 (m, 2H), 2.4 (s, 3H), 2.5-2.6 (m, 2H), 4.8 (bs, 1H); ^{13}C NMR ($CDCl_3$): δ 13.5,20.1,22.1,29.1,35.9,51.7; MS: *m/z* (M^++1) 102.98.

Preparation of methyl 3-(*N*-methyl-*N*-pentyl-amino)propanoate, 6. To a solution of *N*-methyl-pentan-1-amine **5** (90.0 g, 0.889 mole) in 250 mL methanol, methyl acrylate (102.5 g, 1.191 mole) was added dropwise at 0-5°C. The reaction-mixture was warmed to RT over a period of 2 hr and stirred for 8 hr at RT. Then methanol was concentrated under reduced pressure. After complete removal of methanol, traces of methyl acrylate was removed under high vacuum to get 3-(*N*-methyl-*n*-pentyl-amino)-*n*-propanoate **6** as liquid. Yield: 135.0 g (81%); IR (KBr): 1467, 1728, 2870, 2959, 3399 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.8-0.9 (m, 3H), 1.2-1.4 (m, 4H), 1.4-1.5 (m, 2H), 2.2 (s, 3H), 2.3-2.35 (t, 2H), 2.4-2.45 (t, 2H), 2.65 (t, 2H), 3.7 (s, 3H); MS: *m/z* (M^++1) 188.1.

Preparation of 3-(*N*-methyl-*N*-pentylamino)-propanoic acid hydrochloride, 7. A solution of methyl 3-(*N*-methyl-*N*-pentylamino)propanoate **6** (60.0 g, 0.320 mole) and water (120.0 mL) was refluxed for 6 hr. Then water (60 mL) was concentrated under reduced pressure. To the reaction-mixture was added 19% aq. HCl (72 mL). The reaction-mixture was further stirred at RT for 30 min. Then water was distilled off completely under reduced pressure. The residue was purified by recrystallization from acetone to get 3-(*N*,*N*,*N*-methyl-*n*-pentylamino)-*n*-propionic acid hydrochloride **7** as white solid. Yield: 46.1 g (68.5%); m.p. 97.0-98.5°C;

IR (KBr): 1182, 1726, 2705, 2958, 3416 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.9 (t, 3H), 1.2-1.4 (m, 4H), 1.6-1.8 (m, -2H), 2.6 (s, 3H), 2.8-2.9 (t, 2H), 3.0 (t, 2H), 3.2 (t, 2H), 10.4-10.8 (broad, 1H); ^{13}C NMR ($CDCl_3$): δ 13.5, 21.7, 23.2, 28.2, 28.8, 39.8, 51.1, 56.3, 171.1; MS: *m/z* (M^++1) 174.

Preparation of ibandronate sodium, 1. A mixture of 3-(*N*-methyl-*N*-pentylamino)propanoic acid hydrochloride **7** (10.0 g, 0.047 mole) and phosphorrous acid (9.8 g, 0.119 mole) was heated to 75°C. Then phosphorous trichloride (26.4 g, 0.192 mole) was added slowly over a period of 3 hr while maintaining the same temperature. The reaction-mixture was stirred for further 5 hr at the same temperature. Thereafter the reaction-mixture was cooled to 30°C. Water (40 mL) was added to the reaction-mixture and the mass refluxed for 8 hr. The *p*H of the reaction mass was adjusted to 4.5-5.0 with aqueous NaOH, diluted with methanol, and was stirred for 2.0 hr. The obtained solid was filtered and washed with methanol to produce **1** as white crystalline solid. Yield: 14.0 g (82%); ^1H NMR (D_2O): δ 0.8 (t, 3H), 1.2-1.3(m broad, 4H), 1.3-1.5 (m, broad, 2H), 2.2-2.4 (t, broad, 2H), 2.8 (s, -3H), 2.9-3.0 (m, 1H), 3.05-3.3 (m, 2H), 3.4-3.5 (m, 1H); MS: *m/z* (M^++1) 318.

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