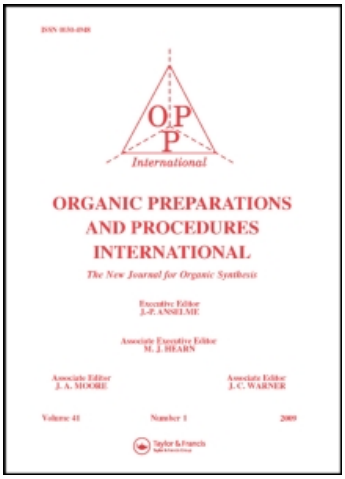

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A FACILE AND DIRECT SYNTHESIS OF ALENDRONATE FROM PYRROLIDONE

Guangyu Xu[a]; Yuyuan Xie[a]; Xihan Wu[a]
[a] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Shanghai Institutes for Biological Sciences, Shanghai, PR CHINA

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10. V. H. Abelian, T. Okubo *et al.*, *Biosci., Biotechnol. Biochem*, **57**, 481 (1993).

11. T. Yamada, Y. Naemura *et al.*, *Jpn Kokai Tokkyo Koho JP* 05,68,578, **1993**; *Chem.Abstr.*,**118,** 253413k (1993).

12. Y. Shimizu *et al.*, *Jpn Kokai Tokkyo Koho JP* 05,284,983, **1993;** *Chem. Abstr.*, **120,** 105170e (1994).

13. H. Kawagishi, K. Sugiyama. *Biosci., Biotechnol., Biochem.*, **56**, 689 (1992).

14. T. Osumi, S. Uchikuga, *et al., Jpn Kokai Tokkyo Koho JP* 11 116, 542, **1999;** *Chem. Abstr.*, **130,** 325393b (1999).

15. S. Ando, T. Kakuta *et al., Jpn Kokai Tokkyo Koho JP* 2000 26, 383, **2000;** *Chem. Abstr.*, **132,** 108292e (2000).

16. F. E. King and D. A. A. Kidd. *J. Chem. Soc.*, 3315 (**1949**).

17. J. C. Craig, H. N. Bhargav and, E. T. Everhart, *et al., J. Org. Chem.*, **53**, 1167 (1988).

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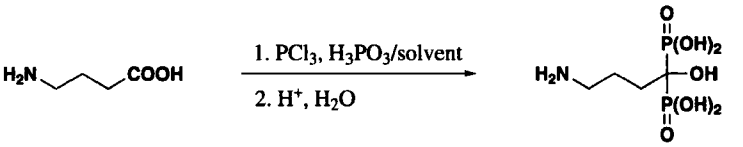
A FACILE AND DIRECT SYNTHESIS OF ALENDRONATE FROM PYRROLIDONE

Submitted by (12/26/03) Guangyu Xu* , Yuyuan Xie and Xihan Wu

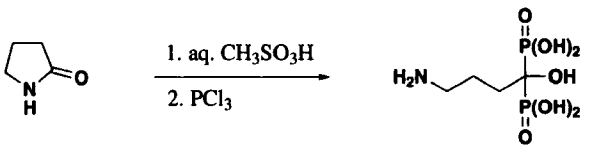
State Key Laboratory of Drug Research
Shanghai Institute of Materia Medica
Shanghai Institutes for Biological Sciences
Shanghai, 201203, P. R. CHINA
E-mail: guangyu_xu@yahoo.com

Alendronate (Fosamax), 4-amino-1-hydroxybutylidenebisphosphonic acid (alendronic acid) monosodium, is an anti-resorption agent used for the prevention and treatment of osteoporosis and for the prevention of osteoporotic fractures in postmenopausal women.[1] Various methods for the preparation of alendronic acid have been disclosed. In most of these methods, it was obtained from the reaction of γ-aminobutyric acid with phosphorous acid and phosphorous trichloride in such solvents as chlorobenzene,[2] methanesulfonic acid,[3] polyalkylene(glycol)[4] and methanesulfonic anhydride.[5] Alendronic acid can also be synthesized by 4-phthalimidobutanoyl

chloride with $P(OMe)_3$ and $HP(O)(OMe)_2$ as phosphonylation agents.[6] We now report a new procedure to synthesize alendronic acid and its sodium salt from pyrrolidone which is much cheaper than γ-aminobutyric acid as starting material.



Hydrolysis of pyrrolidone in aqueous methanesulfonic acid following by reaction with phosphorous trichloride and hydrolysis with water gave the corresponding acid or its monosodium salt after adjustment pH value in good yields. The readily available aqueous methanesulfonic acid (85%) was used both as acid catalyst and as solvent during the reaction. We found that the addition of phosphorous acid had little effect on the yield and the optimal molar ratio of phosphorous trichloride to water (from aqueous methanesulfonic acid) was 1:1.72.



In summary, a one-pot synthesis of alendronic acid and its sodium salt from pyrrolidone has been developed. The inexpensive and available material and reaction solvent make this procedure a practical and convenient protocol for the preparation of alendronic acid and its sodium salt.

EXPERIMENTAL SECTION

Melting points were determined using a Büchi 510 melting point apparatus, and were not corrected. ^1H NMR and ^{31}P NMR spectra were recorded on Bruck-400 NMR spectrometer in D_2O. Microanalyses were carried out on a Leco CHN-2000 elemental analyzer.

Preparation of Alendronic Acid Monosodium Salt.- A 250 mL three necked flask equipped with an addition funnel, a thermometer and a reflux condenser connected with a caustic scrubber was charged with pyrrolidone (8.6 g, 0.101 mol) and aqueous 85% methanesulfonic acid (49.5 mL, d 1.429). The mixture was heated to 100-105°C and maintained at this temperature for 6 h and cooled to 75°C. Phosphorus trichloride (30 mL, 0.342 mol) was then added over 20 min and the mixture was kept at 75°C for 8 h. To the clear, pale yellow solution cooled to 0-5°C, 70 mL water was added dropwise and the mixture was refluxed for 5 h. After cooling to 20°C, the pH of the solution was adjusted to 4.3 with 50% NaOH and the resulting suspension was kept at 0-5°C for 4 h. The product was collected and recrystallized from hot water (45 mL), and dried to yield 26.6 g (81% yield) of white crystalline monosodium alendronate as a trihydrate, mp. 258-261°C

(dec.), *lit.*[3] 257-262.5°C (dec.), ^{1}H NMR (D_2O): δ 2.00 (m, 4H), 3.06 (t, 2H, J = 6.8 Hz), ^{31}P NMR (H_3PO_4/D_2O): δ 18.6.

Anal. Calcd for $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$: C, 14.77; H, 5.54; N, 4.31

Found: C, 14.90; H, 5.53; N, 4.45

Preparation of Alendronic Acid.- The free acid was obtained by the above procedure except that the pH was adjusted to 1.8 instead of 4.3. Isolation and drying of the product is identical, providing 19.4g (72% yield) of alendronic acid monohydrate as a white powder, mp. 237°C (dec.), *lit.*[7] 235°C (dec.).

Anal. Calcd for $C_4H_{13}NO_7P_2 \cdot H_2O$: C, 17.97; H, 5.62; N, 5.24, Found: C, 17.82; H, 5.80; N, 5.30

REFERENCES

1. U. A. Liberman, S. R. Weiss, J. Bröll, H. W. Minne, H. Quan, N. H. Bell, J. Rodriguez-Portales, R. W. Downs, J. Dequeker, M. Favus, E. Seeman, R. R. Recker, T. Capizzi, A. C. Santora, A. Lombardi, R. V. Shah, L. J. Hirsch and D. B. Karpf, *N. Eng. J. Med.*, **333**, 1437 (1995)

2. R. Gall and E. Bosies, DE 3623397; *Chem. Abstr.*, **108**, 186991a (1988)

3. G. R. Kieczykowski, R. B. Jobson, D. G. Melillo, D. F. Reinhold, V. J. Grenda and I. Shinkai, *J. Org. Chem.*, **60**, 8310 (1995)

4. R. Kubela and Y. Tao, PCT WO 9834940; *Chem. Abstr.*, **129**, 149100x (1998)

5. J. B. i Lladó, E. P. Lista and M. del C. O. Miguel, PCT WO 0110874; *Chem. Abstr.*, **134**, 163171f (2001)

6. G. R. Kieczykowski, *US Patent 5039819; Chem. Abstr.*, **115**, 183588h (1991)

7. L. Widler, K. A. Jaeggi, M. Glatt, K. Müller, R. Bachmann, M. Bisping, A.-R. Born, R. Cortesi, G. Guiglia, H. Jeker, R. Klein, U. Ramseier, J. Schmid, G. Schreiber, Y. Seltenmeyer and J. R. Green, *J. Med. Chem.*, **45**, 3721 (2002)

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