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A Simple Synthesis of 1-Aminophosphonic Acids from 1-Hydroxyiminophosphonates with NaBH$_4$ in the Presence of Transition Metal Compounds

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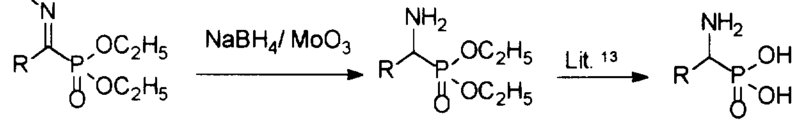
Abstract: A new procedure has been developed for the synthesis of 1-aminophosphonic acids. Diethyl phosphonates are converted to hydroxyiminophosphonates when treated with hydroxylamine hydrochloride. Reduction of hydroxyiminophosphonates with NaBH$_4$ in MeOH in the presence of MoO$_3$ or NiCl$_2$ and hydrolysis of 1- aminophosphonates gave 1-aminophosphonic acids in good yield.

1-Aminophosphonic acids are analogues of naturally occurring 1-amino acids in biological systems. They are an important class of compound with applications as potent antibiotics, enzyme inhibitors, pharmacological agents, herbicides, antiviral agents, as well as being the key building block of phosphonopeptides[1-4]. Several approaches to the synthesis of these materials are available. In the present work we describe a route for the synthesis of 1-aminophosphonic acids via reduction of 1-hydroxyiminophosphonates.

A number of methods already exist for the reduction of oximes [5]; such as catalytic hydrogenation over 5% Pd/C with trace amount of water[6]; catalytic hydrogenation over Raney nickel with methanol or liquid ammonia [7]; reduction over aluminum amalgam in ether[8]; reduction over activated zinc dust in formic acid[9], and reduction with lithiumborohydride /trimethylsilyl chloride mixture in THF[10].

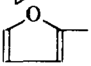
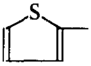
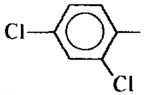
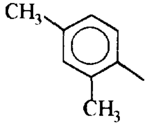


1 **2** **3**

Scheme 1

Herein we report the simple reduction of 1-hydroxyiminophosphonate **1** with NaBH$_4$ in the presence of transition metal compounds. In the literature there are various methods for the reduction of simple ketoximes using $NaBH_4$ in the presence of transition metal compounds such as Co(II), Ni(II),Cu(II), Rh(III), Pd(II) and Mo(VI)[11] . The present synthetic route begins with readily available acyl or aroyl halides and triethyl phosphite and leads to formation of diethyl acyl(aroyl)phosphonates, utilizing the classical Michaelis-Arbuzov rearrangement[12]. The reaction of phosphonates with hydroxylamine hydrochloride in pyridine and ethanol yields the crude 1-hydroxyiminophosphonates nearly quantitatively. The reduction of 1-hydroxyiminophosphonates with $NaBH_4$ in the presence of MoO_3 or $NiCl_2.6H_2O$ at ambient temperature in methanol and at normal pressure gave the corresponding *O,O*-diethyl 1-aminoalkyl(aryl)phosphonates **2** in good yield (Scheme) (Table).

Table 1 α-Aminophosphonic Acids Synthesized[14a]

		2			**3**	
	R	Yield(%) MoO_3-	 $NiCl_2$	^{31}P NMR(ppm)	Yield(%)	m.p. (^0C) ,
a	CH_3	59	51	31.12	96	271-3[3b,14c,d]
b	C_2H_5	64	61	30.02	92	262-4[14c]
c	$(CH_3)_2CH$	68	67	28.13	91	268-70[14b,e]
d	$C_6H_5CH_2$	71	73	30.26	90	268-71[3b]
e		69	52	29.12	88	216-8[14f]
f		67	61	29.71	85	220-4[14e]
g		71	66	30.14	89	248-50[14e]
h	C_6H_5	92	79	31.61	96	281-3[14c,e]
i		77	76	31.21	93	263-6[14d]
j		91	83	30.26	92	261-3[14a]

The cleavage of esters **2** can be easily achieved with propylene oxide, and this leads to 1-aminophosphonic acids **3** in high yields[13,14]. In general, using MoO_3 gave better yields than $NiCl_2.6H_2O$ and the ratio for the best yield was: substrate/ $NaBH_4$/ MoO_3 1/1.5/5 or substrate/

$NaBH_4/NiCl_2$ 1/2/5. The mechanism of the reaction is uncertain. The substrate either gives a complex with the transition metal compound, reduction occurring with the hydride donor, or the reduction occurs directly with the transition metal hydride. Some advantageous features of our procedure are: (a) Starting materials are cheap, and the experimental procedure is very simple; (b) 1-aminophosphonates can be obtained in one step; and (c) 1-aminophosphonates may be synthesized without fear of thermal decomposition of the hydroxyimino substrate. (d) This method may be applicable to large scale production of 1-aminophosphonates and hence 1-aminophosphonic acids.

General method for the preparation of *O,O*-diethyl 1-aminophosphonic acids

To a mixture of 1-hydroxyiminophosphonate (10 mmol) and MoO_3(15 mmol, 1.5 equivalent) or $NiCl_2.6H_2O$ (20 mmol, 2 equivalent) in distilled methanol (100 mL) was added carefully $NaBH_4$ (50 mmol, 5 equivalent) (exothermic reaction) at rt. The resulting dark colored mixture was stirred at ambient temperature for 6h (checked by TLC; Silica Gel, EtOAc: Hexane) and then filtered. The resultant mixture was concentrated under reduced pressure . The residue was treated with aqueous KOH (20%) and extracted several times with dichloromethane. The aqueous layer was saturated with NaCl and extracted again with dichloromethane. The combined organic layer were washed with water and again with brine, before being dried over $MgSO_4$. After filtration and evaporation of solvent, the 1-amino derivative was obtained as an oil. Further purification, if necessary, was achieved by distillation under high vacuum. To a mixture of hot ethanol (10 ml) and *O,O*-diethyl 1-aminophosphonic acid (1 mmol) was added propylene oxide (1 ml) with stirring. After the precipitation was complete, the analytically pure aminophosphonic acids were filtered of.

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REFERENCES

1. Gancarz, R.;Chakraborty, S., *Synthesis*, **1977**, 625, (b) Giannousis, P.P.; Bartlett, P.A., *J. Med. Chem.*, **1987**, *30*, 1603. (c) Maier, L.; Lea, P.J., ***Phosphorus & Sulfur***, **1983**, *17*, 1. (d) Baylis, E.K.; Campbell, C.D.; Dingwall, J.G., *J. Chem. Soc. Perkin Trans. 1*. **1984**, 2445. (e) For a Review, see Dhawan, B.; Redmore, D., ***Phosphorus & Sulfur***, **1987**, *32*, 119. (f) Kafarski, P.; Lejczak, B., ***Phosphorus & Sulfur***, **1991**, *63*, 193. (g) Schöllkopf, U.; Schröder, R.; Stafforst, D., *Liebigs Ann. Chem.* **1974**, 44. (h) Neuzil, E; Assaigne, A., *Exp. Ann.Biochim. Med.*, **1980**, *34*, 165. (i) Hilderbrand, R.L., in ''*The Role of Phosphonates in Living systems*'', CRC Press: Boca Raton, Fl 1982.
2. (a) Hassal, C.H., in ''*Antibiotics*''; ed. F. E. Hahn, Springer Verlag, Berlin, 1983, *Vol* VI, 1-11. (b) Atherton, F.R.; Hassal, C.H.; Lambert, R.W., *J. Med. Chem.*, **1986**, *29*, 29.

3. (a) Allen, M.C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J.M., *J. Med. Chem.* **1989**, *32*, 1652. (b) Hanessian, S.; Bennani, Y.L., *Synthesis*, **1995**, 1272.

4. (a) Lukanov, L.K.; Venkov, A.P., *Synthesis*, **1992**, 263. (b) Mc Kenna, C.E.; Khawli, L.A.; Bapat, A.; Harutunian, V.; Cheng, Y-C., *Biochemical Pharmacology*, **1987**, *36*, 3103. (c) Redmore, D. In *Topics in Phosphorus Chemistry*; Griffith, E.J.; Grayson, M. Eds.; Vol. 8; Wiley: New York, 1976.

5. Hudlicky, M.; *Reduction in Organic Chemistry*, Ellis Horwood Series, Chemical Science, 1984.

6. Beaujon, J.H.R.; Cocolas, G.; Hartung, W.H., *Org. Syn. Coll. Vol.*, **1973**, *5*, 376.

7. (a) Adkins, H.; Billica, H.R., *J. Am. Chem. Soc.* **1948**, *70*, 695. (b) Adkins, H.; Billica, H.R., *Org. Syn. Coll. Vol.*, **1955**, *3*, 1976.

8. (a) Drinkwater, D.J.; Smith, P.W.G., *J. Chem. Soc. (c)*, **1971**, 1305. (b) Fieser, L.F. and Fieser, M., *Reagents in Organic Synthesis*, J. Wiley and Sons Inc., 1967, 20-22.

9. Zambito, A.; Howe, E.E., *Org. Syn. Coll. Vol.*, **1973**, *5*, 373.

10. Green, D.; Patel, G.; Elgendy, S.; Baban, J.A.; Claeson, G.; Kakkar, V.V.; Deadman, J., Tetrahedron Lett. **1993**, *34*, 6917.

11. (a) Heinzman, S.W.; Ganem, B., *J. Am. Chem. Soc.* **1982**,*104*, 6801. (b) Nose, A.; Kudo, T., *Chem Pharm. Bull.* **1981**, *29*, 1159. (c) Ipaktschi, J., *Chem. Ber.* **1984**, *117*, 856. (d) Satoh, T.; Namba, K.; Suzuki, S., *Chem. Pharm. Bull.* **1971**, *19*, 817. (e) Nishiki, M.; Miyataka, H.; Niino,Y.; Mitsuo, N.; Satoh, T., *Tetrahedron Lett.* **1982**, *23*, 193.

12. (a) Berlin, K.D.; Taylor, H.A., *J. Am. Chem. Soc.* **1964**, *86*, 3862. (b) Berlin, K.D.; Hellwege, D.M.; Nagabhsushanam, M., *J. Org. Chem.* **1965**, *30*, 1265. (c) Berlin, K.D.; Burpo, D.H., *J. Org. Chem.* **1965**, *30*, 1265.

13. Diel, P.J.; Maier, L., *Phosphorus, Sulfur, and Silicon* **1991**, *56*, 1. (b) Maier, L.; Spörri, H., *Phosphorus, Sulfur, and Silicon* **1991**, *61*, 69. (c) Hubert, C.; Oussaid, B.; Etemad-Moghadam, G.; Koenig, M.; Garrigues, B., *Synthesis*, **1994**, 51. (d) Takahashi, H.; Yoshioka, M.; İmai, N.; Onimura, K.; Kobayashi, S., *Synthesis*, **1994**, 763. (e) Kovalik, J.; Subotkowska, L.K. Mastalerz, P., *Synthesis*, **1981**, 57. (f) Maury, C.; Royer, J.; Husson, H.P., *Tetrahedron Lett.* **1992**, *33*, 6127. (g) Costisella, B.; Keitel, I.; Gross, H., *Tetrahedron* **1981**, *37*, 1227. (h) Hamilton, R.; Walker, B.; Walker, B.J., *Tetrahedron Lett.* **1995**, *36*, 4451.

14. (a) The 1-aminophosphonates **2** and 1-aminophosphonic acids **3** were fully characterized by ^{1}H NMR, IR spectroscopy (the compounds **2j**and **3j** are new, ^{31}P NMR for **3j** (D_2O, pH= 4) : δ 13.53. (b) Berlin, K.D., Roy, N.K.; Claunch, R.T.; Bude, D., *J. Am. Chem. Soc.* **1968**, *90*, 4494. (c) Soroka, M.; Jaworska, D.; Szczesny, Z., Liebigs Ann. Chem. 1990, 1153. (d) Yang, H.; Wang, J.; Zhang, Y.; *Chinese Sci. Bull.* **1989**, *34*, 1983. (e) Lukszo, J.; Kowalik, J.; Mastalerz, P., *Chem. Lett.* **1978**, 1103. (f) Wieczorek, P.; Kaczanowska, M.; Lejczak, B.; Kafarski, P., *Pestic. Sci.*, **1990**, *30*, 43.

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