Heteroatom Chemistry
Volume 20, Number 5, 2009

An Efficient Synthesis of α-Amino Phosphonates Using Silica Sulfuric Acid As a Heterogeneous Catalyst

Malek Taher Maghsoodlou, Sayyed Mostafa Habibi Khorassani, Nourollah Hazeri, Mohsen Rostamizadeh, Seyed Sajad Sajadikhah, Zahra Shahkarami, and Nariman Maleki

Department of Chemistry, University of Sistan and Baluchestan, P.O. Box 98135-674, Zahedan, Iran

Received 29 April 2009; revised 10 June 2009

ABSTRACT: *α-Amino phosphonates were obtained in a one-pot, simple, and efficient method from the reaction between aldehyde, aniline, trialkyl phosphite, and silica sulfuric acid as a catalyst in acetonitrile at room temperature.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:316–318, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20543

INTRODUCTION

α-Amino phosphonates are an important class of compounds in pharmaceutical chemistry. The potential of α-amino phosphonates has been proved as compounds that have biological effects and medicinal importance (enzyme inhibitors [1], HIV protease [2], antibiotics [3], herbicides, fungicides, insecticides [4], plant growth regulators [5], antithrombotic agents [6], as well as peptidases and proteases) [7]). Thus a variety of synthetic approaches are desirable to synthesize of α-amino phosphonate. Among the available methods, the nucleophilic addition of phosphite to imines is the most convenient and is usually activated by an Lewis acids including lanthanide triflate [8], samarium diiodide [9], $InCl_3$ [10], $TaCl_5$–SiO_2 [11], (bromodimethyl)sulfonium bromide [12], $LiClO_4$ [13], montmorillonite KSF [14], $ZrCl_4$ [15], alumina-supported reagents as catalysts [16], Amberite-IR 120 [17], $H_3PW_{12}O_{40}$ [18], oxalic acid [19], TiO_2 [20], and dialkyl or trialkylphosphite as phosphorous reagents. However, these catalysts have various drawbacks: reactions usually give uncharacterizable products. In addition, some of these catalysts are expensive or are difficult to prepare. It is well known that heterogeneous catalysts have gained interesting attraction in recent years due to economic and environmental considerations. These catalysts are generally inexpensive and easily available. They can conveniently be handled and removed from the reaction mixture, thus making the experimental procedure simple and eco-friendly.

RESULTS AND DISCUSSION

Herein, we describe a mild and efficient protocol for the synthesis of α-amino phosphonates catalyzed by silica sulfuric acid [21] (Fig. 1). Initially, benzaldehyde was reacted with aniline and triethyl phosphite in the presence of silica sulfuric acid in acetonitrile as solvent at room temperature to give the corresponding α-amino phosphonate in 87% yield.

Several aldehydes were subjected to this procedure to give the corresponding α-amino phosphonates in high to excellent yields. The results are

Correspondence to: Malek Taher Maghsoodlou; e-mail address: MT_maghsoodlou@yahoo.com.
Contract grant sponsor: University of Sistan and Baluchestan, Zahedan, Iran.

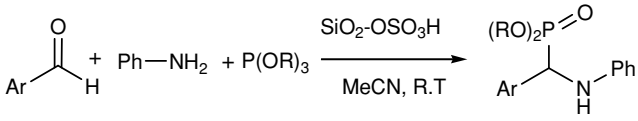

FIGURE 1 Synthesis of α-amino phosphonates.

summarized in Table 1. The structures of α-amino phosphonates were deduced from the IR and NMR spectra.

The presence of electron-donating groups on the aldehyde resulted the corresponding products in low yields, and the reaction was sluggish, in comparison with aldehydes possessing electron-withdrawing groups. In summary, we have prepared α-amino phosphonates via a one-pot reaction between trialkyl phosphite, various aldehydes, and aniline in acetonitrile using silica sulfuric acid as catalyst at room temperature.

EXPERIMENTAL

Melting points and IR spectra of all compounds were measured on an Electro thermal 9100 apparatus and a Shimadzu IR-460 spectrometer, respectively. ^{1}H, ^{13}C, and ^{31}P NMR NMR and were measured on a Bruker DRX–300 and Bruker DRX–400 AVANCE spectrometer instrument with $CDCl_3$ as solvent. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-rapid analyzer.

Synthesis of α-Amino Phosphonates

General Procedure. A mixture of aldehyde (1 mmol), aniline (1 mmol), trialkyl phosphite (1 mmol), and silica sulfuric acid (0.035 g, 10 mol%) in acetonitrile (5 mL) was stirred at room temperature for appropriate time. After completion of the reaction (as indicated by TLC), acetonitrile was removed under reduced pressure. Water was added to the residue, and the mixture was extracted with EtOAc. The organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuum, and purified by chromatography on silica gel to afford pure α-amino phosphonates.

Compound **1**: Colorless crystals, mp 87–89°C. IR (KBr) ν_{max} (cm^{-1}): 3310 (NH); ^{1}H NMR (400 MHz; $CDCl_3$): δ 1.11, 1.28 (6H, 2t, $J = 7.0$ Hz, $2CH_3$), 3.62–3.72 (1H, m, OCH_2), 3.89–3.98 (1H, m, OCH_2), 4.04–4.17 (2H, m, OCH_2), 4.77 (1H, d, $J = 24.3$ Hz, CHP), 4.90 (1H, br, NH), 6.59–6.71 (3H, m), 7.08–7.12 (2H, m), 7.26–7.49 (5H, m).

Compound **2**: Colorless crystals, mp 95–97°C. IR (KBr) ν_{max} (cm^{-1}): 3324 (NH); ^{1}H NMR (300 MHz; $CDCl_3$): δ 1.19, 1.31 (6H, 2t, $J = 7.0$ Hz), 3.89–4.24 (4H, m, $2OCH_2$), 4.34 (1H, br, NH), 4.88 (1H, d, $J = 24.7$, CHP), 6.58 (2H, d, $J = 7.6$ Hz), 7.13 (2H, dt, $J = 1.8$, 7.5 Hz), 7.53 (1H, t, $J = 8.0$ Hz), 7.84 (1H, d, $J = 7.5$ Hz), 8.14 (1H, d, $J = 7.5$), 8.36 (1H, d, $J = 2.0$ Hz).

Compound **3**: Colorless crystals, mp 88–90°C. IR (KBr) ν_{max} (cm^{-1}): 3296 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.17, 1.31 (6H, 2t, $J = 7.3$ Hz), 3.75–4.23 (4H, m, $2OCH_2$), 4.35 (1H, br, NH), 4.74 (1H, d, $J = 24.5$ Hz, CHP), 6.59 (2H, d, $J = 7.8$ Hz), 6.74 (1H, d, $J = 7.3$ Hz), 7.14 (2H, t, $J = 7.9$Hz), 7.27 (2H, t, $J = 2.9$ Hz), 7.36–7.40 (1H, m), 7.48 (1H, d, J = 1.5)

Compound **4**: Colorless crystals, mp 87–89°C. IR (KBr) ν_{max} (cm^{-1}): 3299 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.08, 1.35 (6H, 2t, $J = 7.1$ Hz), 3.59–4.28 (4H, m, $2OCH_2$), 4.41 (1H, br, NH), 5.39 (1H, d, $J = 24.7$ Hz, CHP), 6.61 (2H, d, $J = 8.0$ Hz), 6.71 (1H, t, $J = 7.3$ Hz), 7.12 (2H, t, $J = 8.1$ Hz), 7.21–7.25 (2H, m), 7.39–7.41 (1H, m), 7.57–7.61 (1H, m).

Compound **5**: Colorless crystals, mp 125–126°C. IR (KBr) ν_{max} (cm^{-1}): 3288 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.19, 1.30 (6H, 2t, $J = 7.1$ Hz), 3.84–4.17 (4H, m, $2OCH_2$), 4.80 (1H, br, NH), 4.85 (1H, d,

TABLE 1 Preparation of α-Amino Phosphonates

Entry	*Ar*	*R*	*Time (h)*	*Yield[a] (%)*	*M.P (°C)*	*Reference[b]*
1	Phenyl	Et	5	87	87–89	[17]
2	3-Nitro phenyl	Et	4	95	95–97	[17]
3	3-Chloro phenyl	Et	4	90	88–90	[20]
4	2-Chloro phenyl	Et	4	95	87–89	[20]
5	4-Nitro phenyl	Et	4	92	125–126	[17]
6	4-Chloro phenyl	Et	4	95	57–59	[20]
7	4-Metyl phenyl	Et	8	80	63–65	[17]
8	2-Chloro phenyl	Me	3	90	134–136	[19]
9	2,4-Dichloro phenyl	Me	3	94	109–111	–
10	2-Chloro-6-fluoro phenyl	Et	4	90	76–78	–
11	2,4-Dimetoxy phenyl	Et	8	80	97–98	–

[a]Yield refers to the pure isolated products.
[b]References refer to known products as mentioned in the literature.

$J = 25.1$ Hz, CHP), 6.53 (2H, d, $J = 7.7$ Hz), 6.74 (1H, t, $J = 7.4$ Hz), 7.11 (2H, t, $J = 7.3$ Hz), 7.67 (2H, dd, $J = 2.2$, J = 8.8 Hz), 8.19 (2H, d, $J = 8.2$ Hz).

Compound **6**: Colorless crystals, mp 57–59°C. IR (KBr) ν_{max} (cm^{-1}): 3305 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.18, 1.30 (6H, 2t, $J = 7.1$ Hz), 3.75–3.84 (1H, m), 3.96–4.22 (3H, m), 4.60 (1H, br, NH), 4.74 (1H, d, $J = 24.4$ Hz, CHP), 6.56 (2H, d, $J = 8.4$ Hz), 6.73 (1H, t, $J = 7.3$ Hz), 7.12 (2H, t, $J = 7.4$ Hz), 7.31 (2H, d, $J = 8.5$ Hz), 7.42 (2H, dd, $J = 2.3$, 8.6 Hz).

Compound **7**: Colorless crystal, mp 63–65°C. IR (KBr) ν_{max} (cm^{-1}): 3325 (NH); ^{1}H NMR (400 MHz; $CDCl_3$) δ: 1.13, 1.28 (6H, 2t, $J = 7.0$ Hz, $2CH_3$), 2.31 (3H, s, CH_3), 3.64–3.73 (1H, m, OCH_2), 3.89–3.99 (1H, m, OCH_2), 4.05–4.16 (2H, m, $2OCH_2$), 4.73 (1H, d, $J = 24.1$ Hz, CHP), 5.10 (1H, br, NH), 6.57–6.70 (3H, m), 7.07–7.14 (4H, m), 7.34 (2H, dd, $J = 2.2$, 8.2 Hz).

Compound **8**: Colorless crystals, mp 134–136°C. IR (KBr) ν_{max} (cm^{-1}): 3305 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 3.44, 3.86 (6H, 2d, $J = 10.8$ Hz, $2OCH_3$), 4.62 (1H, br, NH), 5.42 (1H, d, $J = 24.8$, CHP), 6.58 (2H, d, $J = 8.6$ Hz), 6.71 (1H, t, $J = 7.4$ Hz), 7.09–7.15 (2H, m), 7.21–7.28 (2H, m), 7.39–7.42 (1H, m), 7.57–7.61 (1H, m).

Compound **9**: Colorless crystals, mp 109–111°C. IR (KBr) ν_{max} (cm^{-1}): 3310 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 3.52, 3.86 (6H, 2d, $J = 10.6$ Hz, $2OCH_3$), 4.65 (1H, br, NH), 5.35 (1H, d, $J = 24.7$, CHP), 6.57 (2H, d, $J = 8.7$ Hz), 6.73 (1H, t, $J = 8.6$), 7.13 (2H, t, $J = 8.6$), 7.21–7.26 (1H, dd, $J = 1.8$, 8.4 Hz), 7.43 (1H, s), 7.51–7.55 (1H, dd, $J = 2.5$, 8.4 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ: 51.19 (d, $^1J = 153.1$ Hz, CHP), 53.86 (d, $^2J = 6.9$ Hz, OCH_3), 53.96 (d, $^2J = 6.9$ Hz, OCH_3), 113.58, 118.70, 127.46 (d, $J = 3.0$ Hz), 128.93 (d, $J = 4.2$ Hz), 129.25, 129.30, 129.57 (d, $^3J = 2.3$ Hz), 133.70, 133.98 (d, $^3J = 7.27$ Hz), 145.47 (d, $^2J = 14.6$ Hz); ^{31}P NMR (121 MHz; $CDCl_3$) δ: 24.06. Anal. Calcd for $C_{15}H_{16}Cl_2NO_3P$: C, 50.02; H, 4.48; N, 3.89. Found: C, 50.23; H, 4.56; N, 3.66.

Compound **10**: Colorless crystals, mp 76–78°C. IR (KBr) ν_{max} (cm^{-1}): 3310 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.15, 1.33 (6H, 2t, $J = 6.8$ Hz, $2CH_3$), 3.90–4.11 (2H, m), 4.19–4.29 (2H, m), 4.61 (1H, br, NH), 5.53 (1H, d, $J = 26.9$ Hz, CHP), 6.68–6.75 (3H, m), 6.92–6.98 (1H, m), 7.11–7.18 (4H, m); ^{13}C NMR (75 MHz; $CDCl_3$) δ: 16.15 (d, $^3J = 6.5$ Hz, OCH_3), 16.45 (d, $^3J = 6.5$ Hz, CH_3), 53.20 (d, $^1J = 152.2$ Hz, CHP), 63.14 (d, $^2J = 7.5$ Hz, OCH_2), 63.64 (d, $^2J = 7.5$ Hz, OCH_2), 113.69 (CH), 115.59 (CH), 118.87 (CH), 122.54 (CH), 125.43 (CH), 129.30 (CH), 129.60 (d, $J = 2.6$ Hz), 129.73 (d, $J = 2.7$ Hz), 136, 145.95 (d, $J = 14.48$ Hz); ^{31}P NMR (121 MHz; $CDCl_3$) δ: 20.92. Anal. Calcd for $C_17H_{20}ClFNO_3P$: C, 54.92; H, 5.42; N, 3.77. Found: C, 55.09; H, 5.56; N, 3.65.

Compound **11**: Colorless crystals, mp 97–98°C. IR (KBr) ν_{max} (cm^{-1}): 3305 (NH); ^{1}H NMR (300 MHz; $CDCl_3$) δ: 1.09, 1.32 (6H, 2t, $J = 7.10$ Hz, 2CH3), 3.77, 3.91 (6H, 2s, $2OCH_3$), 3.61–3.72 (1H, m), 3.86–3.90 (1H, m), 4.14–4.23 (2H, m), 4.61 (1H, br, NH), 5.29 (1H, d, $J = 24.2$ Hz, CHP), 6.45 (2H, d, $J = 6.8$ Hz), 6.61–6.70 (3H, m), 7.11 (2H, t, $J = 7.7$), 7.38 (1H, dd, $J = 2.5$, 8.7 Hz); ^{13}C NMR (75 MHz; $CDCl_3$) δ: 16.21 (d, $J = 5.9$ Hz, CH_3), 16.45 (d, $J = 5.9$ Hz, CH_3), 47.50 (d, $J = 155.2$ Hz), 55.31 (s, OCH_3), 55.72 (s, OCH_3), 63.00 (d, $J = 6.9$ Hz, OCH_2), 63.10 (d, $J = 6.9$ Hz, OCH_2), 98.39 (d, $J = 2.3$ Hz) 104.77, 113.61, 116.69, 118.09, 128.91 (d, $J = 4.3$ Hz), 129.08, 146.28 (d, $J = 14.8$ Hz), 158.22 (d, $J = 13.5$ Hz), 160.45 (d, $J = 2.8$ Hz); ^{31}P NMR (121 MHz; $CDCl_3$) δ: 23.92. Anal. Calcd for $C_{19}H_{26}NO_5P$: C, 60.15; H, 6.91; N, 3.69. Found: C, 60.32; H, 7.14; N, 3.59.

REFERENCES

[1] Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. J Med Chem 1989, 32, 1652.
[2] Peyman, A.; Stahl, W.; Wagner, K.; Ruppert, D.; Budt, K.-H. Bioorg Med Chem Lett 1994, 4, 2601.
[3] Atherton, F. R.; Hassal, C. H.; Lambert, R. W. J Med Chem 1986, 29, 29.
[4] Maier, L.; Spoerri, H. Phosphorus, Sulfur, Silicon Relat Elem 1991, 61, 69.
[5] Emsley, J.; Hall, D. In: The Chemistry of Phosphorous; Harper & Row: London, 1976; p. 494.
[6] Meyer, J. H.; Barlett, P. A. J Am Chem Soc 1998, 120, 4600.
[7] Miller, D. J.; Hammond, S. M.; Anderluzzi, D.; Bugg, T. D. H. J Chem Soc, Perkin Trans 1998, 1, 131.
[8] Manabe, K.; Kobayashi, S. Chem Commun 2000, 669.
[9] Xu, F.; Luo, Y.; Deng, M.; Shen, Q. Eur J Org Chem 2003, 4728.
[10] Ranu, B. C.; Hajra, A.; Jana, J. Org Lett 1999, 1, 1141.
[11] Chandrasekhar, S.; Jaya Prakash, S.; Jagadeshwar, V.; Narsihmula, Ch. Tetrahedron Lett 2001, 42, 5561.
[12] Kudrimoti, S.; Bommena, Rao V. Tetrahedron Lett 2005, 46, 1209.
[13] Heydari, A.; Zarei, M.; Alijanianzadeh, R.; Tavakol, H. Tetrahedron Lett 2001, 42, 3629.
[14] Yadav, J. S.; Reddy, B. V. S.; Madan, C. Synlett 2001, 1131.
[15] Yadav, J. S.; Reddy, B. V. S.; Raj, S.; Reddy, K. B.; Prasad, A. R.; Synthesis 2001, 2277.
[16] Kaboudin, B.; Nazari, R. Tetrahedron Lett 2001, 42, 8211.
[17] Bhattacharya, A. K.; Rana, K. C. Tetrahedron Lett 2008, 49, 2598.
[18] Heydari, A.; Hamedi, H.; Pourayoubi, M. Catal Commun. 2007, 8, 1224.
[19] Vahdat, S. M.; Baharfar, R.; Tajbakhsh, M.; Heydari, A.; Baghbanian, S. M.; Khaksar, S. Tetrahedron Lett 2008, 49, 6501.
[20] Hosseini-Sarvari, M. Tetrahedron 2008, 64, 5459.
[21] Zolfigol, M. A. Tetrahedron 2001, 57, 9509.