Hydrophosphorylation of Imines Catalyzed by Tosyl Chloride for the Synthesis of α-Aminophosphonates

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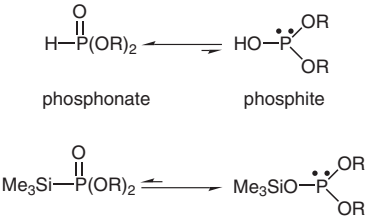
Abstract: A simple, efficient, and general method has been developed for the synthesis of α-aminophosphonic esters using TsCl as an efficient catalyst. α-Aminophosphonic acids were obtained in good to high yields (65–85%) and purity under mild conditions by the reaction of diethyl phosphite with imines in the presence of TsCl.

Key words: α-aminophosphonates, imines, alkyl phosphite, *p*-tosyl chloride, addition reaction

Phosphorus–carbon bond formation reactions have attracted growing attention because of their novel application in organic synthesis and bioorganic chemistry. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[1–4] Among the α-functional phosphonic acids, 1-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. The 1-aminophosphonic acids are important substitutes for the corresponding α-amino acids in biological systems.[5] Indeed a number of potent antibiotics,[6] enzyme inhibitors,[7] and pharmacological agents[8] are 1-aminophosphonic acids or peptide analogues. Aminophosphonic acids are also found as constituents of natural products.[9] Many effective methods for the preparation of 1-aminoalkylphosphonic acids have been developed. Of these methods, the Kabachnik–Fields[10] synthesis of 1-aminoalkyl phosphonates via hydrophosphorylation of a Schiff base catalyzed by a base or an acid is the most convenient. The addition of a *H*-phosphonic acid diester to structurally diverse imines appears to be a general method for the preparation of N-substituted 1-aminoalkanephosphinic acids.[11] The diesters of *H*-phosphonic acids are important reagents in organophosphorus chemistry for the synthesis of a variety of bioactive products including aminophosphonates, aminophosphonic acids, P–C phosphonates, etc.[12] These important reagents have tautomeric forms in the form of phosphite–phosphonate in equilibrium with each other (Scheme 1) which is shifted mainly toward phosphonate. In fact the chemical reactivity of dialkyl phosphonates refers to nucleophilic properties of the phosphite form in equilibrium (Scheme 1).[13] The silylation of the diesters of *H*-phosphonic acid shifts this equilibrium to a P(III) form, thus liberating an electron pair on phosphorus which makes it easier to carry out many reactions at the phosphorus centre (Scheme 1).[14] However, use of this reagent brings problems, including inconvenient reaction conditions, anaerobic and anhydrous conditions, and also some severe side reactions.



Scheme 1

In recent years, the development of more economical and environmentally friendly conversion processes has gained interest. In continuation of our interest in developing novel methodologies for the synthesis of organophosphorous compounds,[15] herein we report an efficient, practical, environmentally benign and high yielding method for the synthesis of 1-aminophosphonates via hydrophosphorylation of imines using TsCl as catalyst.[16]

First, benzylideneaniline (**1a**) was treated with diethyl phosphite in the presence of 10 mol% of TsCl in dichloromethane at room temperature. The reaction proceeded smoothly to afford the corresponding α-aminophosphonate **2a** in excellent yield (83%). The reaction failed after 48 hours without any catalyst. The reactions of several imines were examined in the presence of catalytic amount (10 mol%) of TsCl in dichloromethane at room temperature, and the results are summarized in Table 1. It has been suggested that TsCl has two main roles in this reaction: shift of the tautomeric equilibrium to the phosphite form and imine activation by in situ protonation of the imine (Scheme 2).

As shown in Table 1, a mixture of imine **1** with diethyl phosphite in the presence of TsCl as catalyst, afforded the desired product **2** in 65–85% yields.

To our knowledge, many imines are hygroscopic, unstable at high temperatures, and difficult to purify by distillation or column chromatography. Thus it is desirable from a synthetic point of view that imines, generated in situ from aldehydes and amines, immediately react with *H*-phosphonate to afford 1-aminophosphonate. We thus examined the addition of diethyl phosphite to a mixture of benzaldehyde and aniline in the presence of TsCl as cata-

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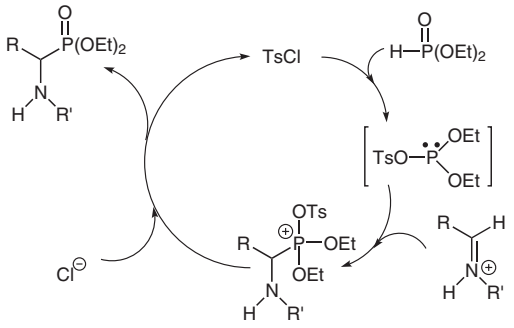
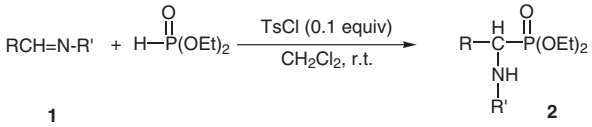


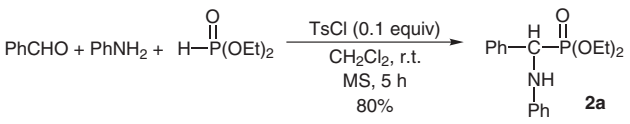
Scheme 2

Table 1 One-Pot Synthesis of 1-Aminophosphonates Using TsCl as Catalyst



Entry	R	R′	Time (h)	Yield (%)[a]	^{31}P NMR [δ (ppm)]
a	Ph	Ph	2	83	23.31
b	4-MeC_6H_4	Ph	3	85	23.49
c	4-(*i*-Pr)C_6H_4	Ph	3	80	23.58
d	4-MeOC_6H_4	Ph	3	72	23.53
e	4-$O_2NC_6H_4$	Ph	3	76	21.41
f	PhCH=CH	Ph	2	71	22.67
g	Ph	3-$O_2NC_6H_4$	2	82	22.39
h	4-MeC_6H_4	3-$O_2NC_6H_4$	3	81	21.41
i	4-(*i*-Pr)C_6H_4	3-$O_2NC_6H_4$	4	68	22.69
j	4-MeOC_6H_4	3-$O_2NC_6H_4$	3	73	22.61
k	Ph	cyclohexyl	4	65	24.59
l	PhCH=CH	cyclohexyl	3	73	24.91

[a] Yield refers to isolated yield by column chromatography.



Scheme 3

lyst. It was found that the reaction of benzaldehyde, aniline, and diethyl phosphite took place smoothly within five hours in the presence of 10 mol% of TsCl and 4 Å molecular sieves at room temperature to give the desired 1-aminophosphonate **2a** in 80% isolated yield (Scheme 3). The reaction failed using aliphatic aldehydes.

In all the reactions we have reported in this paper, cleavage of the Et–O–P bond was not detected and the conversion of the substrates to their corresponding α-aminophosphonate was clean. Workup of the reaction mixture was very easy and gave highly pure products, which did not need further purification. All NMR data could be assigned and were in accord with the proposed structures of the products.[17]

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References and Notes

(1) (a) Engel, R. *Chem Rev.* **1977**, *77*, 349. (b) Hiratake, J.; Oda, J. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 211. (c) Schug, K. A.; Lindner, W. *Chem. Rev.* **2005**, *105*, 67. (d) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177. (e) Palacios, F.; Alonso, C.; de los Santos, J. M. *Curr. Org. Chem.* **2004**, *8*, 1481.

(2) Dingwall, J. G.; Campell, C. D.; Baylis, E. K. UK Patent Appl., 1542938, **1979**; *Chem Abstr.* **1979**, *88*, 105559j.

(3) Kafarski, P.; Lejczak, B.; Tyka, R.; Koba, L.; Pliszczak, E.; Wieczorek, P. *J. Plant Growth Regulation* **1995**, *14*, 199.

(4) Ishiguri, Y.; Yamada, Y.; Kato, T.; Sasaki, M.; Mukai, K. Eur. Patent Appl., EP 82301905, **1982**; *Chem. Abstr.* **1983**, *98*, 102686u.

(5) (a) Giannousis, P. P.; Bartlett, P. A. *J. Med. Chem.* **1987**, *30*, 1603. (b) Maier, L.; Lea, P. J. *Phosphorus Sulfur* **1983**, *17*, 1. (c) Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845. (d) Hilderbrand, R. L. In *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, FL, **1982**. (e) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur* **1991**, *63*, 193.

(6) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29.

(7) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652.

(8) Hassal, C. H. In *Antibiotics*, Vol. VI; Hahn, F. E., Ed.; Springer Verlag: Berlin, **1983**, 1.

(9) (a) Kukhar, V. P.; Hudson, H. R. In *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons: Chichester, **2000**. (b) Kaboudin, B. *Phosphorus, Sulfur Silicon* **2002**, *177*, 1749.

(10) (a) Kabachnik, M. J.; Medved, T. *Izv. Akad. Nauk SSSR* **1953**, 1126. (b) Kabachnik, M. J.; Medved, T. *Izv. Akad. Nauk SSSR* **1954**, 1024. (c) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528. (d) Lewkowski, J. *J. Organomet. Chem.* **2003**, *681*, 225. (e) Lewkowski, J. *Heteroat. Chem.* **2004**, *15*, 162. (f) Azizi, N.; Saidi, M. R. *Tetrahedron* **2003**, *59*, 5329. (g) Chandrasekhar, S.; Prakash, S. J.; Jagadeshwar, V.; Narsihmulu, C. *Tetrahedron Lett.* **2001**, *42*, 5561. (h) Matveeva, E. D.; Podrugina, T. A.; Tishkovskaya, E. V.; Tomilova, L. G.; Zefirov, N. S. *Synlett* **2003**, 2321. (i) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930. (j) Kaboudin, B.; Moradi, K. *Synthesis* **2006**, 2339. (k) Kaboudin, B.; Jafari, E. *Synthesis* **2006**, 3063. (l) Kaboudin, B.; Jafari, E. *Synthesis* **2007**, 1823. (m) Kaboudin, B.; Moradi, K.; Sardarian, A. R. *ARKIVOC* **2007**, *(viii)*, 210. (n) Kaboudin, B.; Rahmani, A. *Synthesis* **2003**, 2705. (o) Kaboudin, B.; Saadati, F. *Synthesis* **2004**, 1249. (p) Kaboudin, B.; Rahmani, A. *Org. Prep. Proced. Int.* **2004**, *36*, 82. (q) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989.

(11) (a) Qian, C.; Huang, T. *J. Org. Chem.* **1998**, *63*, 4125. (b) Kabachnik, M. M.; Ternovskaya, T. N.; Zobnina, E. V.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2002**, *38*, 480. (c) Ranu, B. C.; Hajra, A.; Jana, U. *Org. Lett.* **1999**, *1*, 1141. (d) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Synthesis* **2004**, 2692.

(12) (a) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2007**, *72*, 1263. (b) Azizi, N.; Saidi, M. R. *Tetrahedron* **2003**, *59*, 5329. (c) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (d) Manabe, K.; Kobayashi, S. *Chem. Commun.* **2000**, 669. (e) Saidi, M. R.; Azizi, N. *Synlett* **2002**, 1347. (f) Lee, S.; Park, J. H.; Kang, J.; Lee, J. K. *Chem. Commun.* **2001**, 1698. (g) Ghosh, R.; Maiti, S.; Chakraborty, A.; Maiti, D. K. *J. Mol. Catal. A: Chem.* **2004**, *210*, 53. (h) Azizi, N.; Rajabi, F.; Saidi, M. R. *Tetrahedron Lett.* **2004**, *45*, 9233. (i) Sardarian, A. R.; Kaboudin, B. *Tetrahedron Lett.* **1997**, *38*, 2543. (j) Kaboudin, B. *Chem. Lett.* **2001**, 880. (k) Kaboudin, B.; Nazari, R. *J. Chem. Res., Synop.* **2002**, 291. (l) Kaboudin, B.; Nazari, R. *Synth. Commun.* **2001**, *31*, 2245. (m) Kaboudin, B.; Balakrishna, M. S. *Synth. Commun.* **2001**, *31*, 2773. (n) Kaboudin, B. *Tetrahedron Lett.* **2003**, *44*, 1051.

(13) (a) Grayson, M.; Fareley, C. F.; Strenli, C. A. *Tetrahedron* **1967**, *23*, 1065. (b) Doak, G.; Freedman, L. *Chem. Rev.* **1961**, *61*, 31. (c) Troev, K. D. In *Chemistry and Application of H-Phosphonates*; Elsevier: Amsterdam, **2006**.

(14) (a) Wozniak, L.; Chojnowski, J. *Tetrahedron* **1989**, *45*, 2465. (b) Kleeber, W. H.; Post, H. W. *J. Org. Chem.* **1956**, *21*, 509.

(15) (a) Kaboudin, B. *Tetrahedron Lett.* **2002**, *43*, 8713. (b) Kaboudin, B.; Haghighat, H. *Tetrahedron Lett.* **2005**, *46*, 7955. (c) Kaboudin, B.; Nazari, R. *Tetrahedron Lett.* **2001**, *42*, 8211. (d) Kaboudin, B.; Haghighat, H.; Yokomatsu, T. *J. Org. Chem.* **2006**, *71*, 6604. (e) Kaboudin, B.; Karimi, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5324. (f) Kaboudin, B.; Farjadian, F. *Beilstein J. Org. Chem.* **2006**, *2*, 4. (g) Yamagishi, T.; Kusano, T.; Kaboudin, B.; Yokomatsu, T.; Sakuma, C.; Shibuya, S. *Tetrahedron* **2003**, *59*, 767. (h) Kaboudin, B.; Sorbiun, M. *Tetrahedron Lett.* **2007**, *48*, 9015. (i) Kaboudin, B.; Haruki, T.; Yamaghishi, T.; Yokomatsu, T. *Tetrahedron* **2007**, *63*, 8199. (j) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Synthesis* **2007**, 3226. (k) Kaboudin, B.; Karimi, M. *ARKIVOC* **2007**, *(viii)*, 124.

(16) (a) Kazemi, F.; Massah, A. R.; Javaherian, M. *Tetrahedron* **2007**, *63*, 5083. (b) Kazemi, F.; Sharghi, H.; Nasseri, M. A. *Synthesis* **2004**, 205.

(17) TsCl (1 mmol, 0.18 g) was added to a stirred mixture of diethyl phosphite (0.012 mol) in CH_2Cl_2 (10 mL) at r.t. Imine (0.01 mol) was added to the reaction mixture and the mixture was stirred for 2–4 h at r.t. H_2O (50 mL) was added to the reaction mixture and the organic layer was extracted with EtOAc (4 × 50 mL), dried with $CaCl_2$, and the solvent was evaporated to give the crude product. Chromatography on silica gel with EtOAc–*n*-hexane (1:9 → 5:5) and evaporation of the solvent under reduced pressure gave the pure products in 65–85% yields. All the products gave satisfactory spectral data in accordance with the assigned structures and literature reports.[12a,16b]

Diethyl[phenyl(phenylamino)methyl]phosphonate (2a): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.0 Hz, 3 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 3.60–3.75 (m, 1 H), 3.85–4.01 (m, 1 H), 4.03–4.22 (m, 2 H), 4.76 (d, J_{HP} = 24.2 Hz, 1 H), 6.59 (d, *J* = 8.5 Hz, 2 H), 6.69 (t, *J* = 7.2 Hz, 1 H), 7.11 (t, *J* = 8.3 Hz, 2 H), 7.22–7.52 (m, 5 H). ^{31}P NMR (101.2 MHz, $CDCl_3$, H_3PO_4): δ = 23.31. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 16.2 (d, J_{PC} = 6.3 Hz), 16.4 (d, J_{PC} = 6.3 Hz), 56.1 (d, J_{PC} = 150.3 Hz), 63.1, 63.2, 113.8, 118.3, 127.9 (d, J_{PC} = 5.7 Hz), 128.5 (d, J_{PC} = 2.5 Hz), 129.2, 136.0 (d, J_{PC} = 2.5 Hz), 146.3 (d, J_{PC} = 14.5 Hz).