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Thiamine hydrochloride (VB1): An efficient catalyst for one-pot synthesis of α-aminophosphonates under ultrasonic irradiation

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Abstract

An efficient synthesis of novel α-aminophosphonates by the reaction of aldehydes and amines with triethyl phosphite in the presence of the easily available, inexpensive, and nontoxic catalyst thiamine hydrochloride (VB1). This method affords the α-aminophosphonates under the influence of ultrasound irradiation in aqueous medium, in short reaction times (4–6 min), high yields (85–95%), with improved purity. The process is green, mild, inexpensive and excellent yields are the main compensation of this procedure.

Keywords: Thiamine hydrochloride (VB1); α-Aminophosphonates; Triethyl phosphate; Water; Ultrasonication; Green synthesis

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Organophosphorus compounds have been found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates [1–5]. As a kind of natural amino acid analogues, α-aminophosphonates constitute an important class of compounds with diverse biological activities. The activity of α-aminophosphonates as peptidomimetics [6], enzyme inhibitors [7], pharmacogenic agents [8], haptens of catalytic antibodies [9], herbicidals [10], inhibitors of serine hydrolases [11], inhibitors of UDP-galactopyranose mutase [12] and antitumor agents [13] is reported in the literature.

A number of synthetic methods for the preparation of α-aminophosphonates have been carried out under various conditions. However, one-pot synthesis of α-aminophosphonates remains a favor due to its versatile route and high yielding reactions. Recently, three-component synthesis starting from aldehydes, amines and diethylphosphite or triethylphosphite have been reported using Lewis and Brønsted acid catalysts such as $LiClO_4$ [14], $InCl_3$ [15], lanthanide triflates/magnesium sulfate [16], $TaCl_5$–SiO_2 [17], amberlyst-15 [18], Al_2O_3-MW [19], sulfamic acid [20], scandium (tris-dodecyl sulfate) [21], $BF_3{\cdot}Et_2O$ [22], $M(OTf)_n$ [23] and $M(ClO_4)_n$ [24]. Though, many of these methods suffer from some drawbacks such as long reaction times, low yields of the products, requiring stoichiometric amounts of catalysts, costly and moisture sensitive catalysts and use of highly toxic catalysts. More recently, $ZrOCl_2{\cdot}8H_2O$ [25] or $ZrO(ClO_4)_2{\cdot}6H_2O$ [26] and TiO_2 [27] are reported to be effective catalysts for the formation of α-aminophosphonates using a three component system composing of aldehydes/ketones, amines and triethylphosphite under neat conditions.

In view of the conservation of the environment combining with economic aspects, literature demands the application of metal ion free, environmentally safe and convenient reagents in the reactions [28]. And so, we report an eco-friendly,

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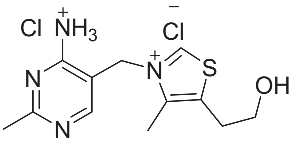


Fig. 1. Structure of thiamine hydrochloride (VB1).

facile and efficient methodology for the synthesis of α-hydroxyphosphonates using VB1. It is well known that VB1 is a cheap and non-toxic reagent. The structure of VB1 contains a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). The use of VB1 analogs as powerful catalysts for various organic transformations has been reported [29]. Compared with those methods above mentioned our reactions displayed their advantages: (i) green synthesis without organic solvents involved; (ii) shortened time and improved yields; (iii) mild conditions and ready operations.

1. Experimental

Melting points were determined on a Veego apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in $CDCl_3$/DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (J) are expressed in Hertz (Hz). Mass spectra were taken on a Macro mass spectrometer (Waters) by electrospray method (ES). Bandelin Sonorex (with a frequency of 40 kHz and a nominal power 100 W) ultrasonic bath was used for ultrasonic irradiation. The reaction vessel placed in side the ultrasonic bath containing water.

1.1. General procedure of synthesis of substituted α-aminophosphonates

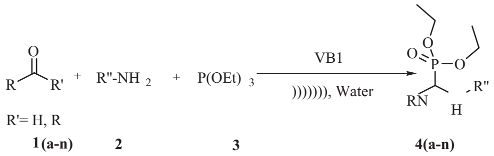
A mixture of substituted aldehydes/ketone (1 mmol), amine (1 mmol) and triethyl phosphite (1.2 mmol) were placed in a round bottom flask. Further vitamin B1 (VB1) (5 mol%) was added, to this mixture, and the mixture was irradiated under ultrasonic irradiation at ambient temperature under aqueous condition for the precise time. After the completion of reaction as monitored by TLC; 20 mL ice cold water was added to the reaction mixture and product was extracted by ethylacetate (2× 25 mL). The organic layer washed by brine (2× 20 mL) and dried over anhydrous sodium sulphate. The solvent was distilled out on Rota-evaporator under reduced pressure to afford the pure products. The products 4(a–n) were confirmed by their spectral data after comparisons with authentic samples, IR, ^{1}H NMR, mass spectra and melting point.

4a: IR (KBr, cm^{-1}): 3295 (–NH), 1233 (P–O), 1103–997 (P–O–Et); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.12 (t, 3H), 1.29 (t, 3H), 3.68 (ddq, 1H, J = 7.1, 11.2, 8.1 Hz), 3.95 (ddq, 1H, J = 7.1, 8.1, 11.2 Hz), 4.14 (m, 2H), 4.75 (br, 1H, –NH), 4.78 (d, 1H, J = 17.9 Hz), 6.61 (d, 2H, J = 8.5 Hz), 6.70 (t, 1H, J = 7.4), 7.11 (t, 2H, J = 7.4), 7.27 (1H, m), 7.34 (t, 2H, J = 7.4 Hz), 7.49 (m, 2H); MS (ESI) *m/z* 320 (M+).

4d: IR (KBr, cm^{-1}): 3296(–NH), 1236(–P=O), 1021(–O–P–C); ^{1}H NMR (400 MHz, $CDCl_3$ and DMSO-d_6): δ 1.13 (t, 3H); 1.23 (t, 3H); 3.66 (ddq, 1H, J = 7.1, 11.2, 8.1 Hz); 3.97 (ddq, 1H, J = 7.1, 8.1, 11.2 Hz); 4.13 (m, 2H); 4.75 (br, 1H, –NH); 4.78 (d, 1H, J = 17.9 Hz); 6.61 (d, 2H, J = 8.5 Hz); 6.70 (t, 1H, J = 7.4); 7.11 (t, 2H, J = 7.4); 7.26 (m, 1H); 7.34 (t, 2H, J = 7.4 Hz); 7.49 (m, 2H); MS (ESI) *m/z* 229 (M+1).

2. Result and discussion

As a continuation of our research work devoted to the development of useful synthetic methodologies [30], herein, we report an efficient and practical method for the synthesis of α-aminophosphonates using VB1, as a catalyst under ultrasound irradiation in aqueous medium. Consequently several aryl and heteroaryl aldehydes/ketones, aniline with different substituent on the aromatic ring were subjected to the addition reaction. In all the yields were excellent. We



Scheme 1. Synthesis of various α-aminophosphonates using VB1 as a catalyst.

Table 1
Optimization of solvent effect on the model reaction.[a]

Entry	Solvent	Time (min)	Yield[b] (%)
1	Solvent-free	10	20
2	Toluene	10	45
3	Acetonitrile	10	52
4	Dichloromethane	10	58
5	Ethanol	10	71
6	Methanol	10	73
7	Water	10	95

[a] Reaction of benzaldehyde, aniline and triethyl phosphite catalyzed by VB1 (5 mol %) under ultrasonic waves for 10 min.
[b] Isolated yield.

have used VB1 for the sonochemical synthesis of α-aminophosphonates. The products were isolated in high yields (Scheme 1). The structures of the products were determined from their spectral (IR, ^{1}H NMR, and MS) data.

In the current study, the commercially available catalyst VB1 is used as a catalyst but its scope has not been fully explored. VB1 can be used as buffer, neutralizing agent, sequestrate, yeast food and is also emerged as an efficient heterogeneous acid catalyst [31]. VB1 facilitates the formation of the α-aminophosphonates under ultrasonic irradiation. The use of VB1 catalyst under ultrasonic irradiation plays an important role in the synthesis and hence the reaction rate was improved and the reaction time was reduced.

To study the reaction in water, we tested reaction of triethyl phosphate, benzaldehyde, aniline and VB1 as a simple model substrate in different solvents, namely toluene, acetonitrile, DCM, methanol, ethanol and water. It was found that water (entry 7) was a solvent of choice for the reaction, and the desired product was obtained in excellent yields (95%). Not only water but methanol and ethanol also displayed moderate result. But in case of other solvents like DCM, toluene and acetonitrile reaction gave very poor yield of product. Whereas in case of solvent free condition reaction did not proceeded at all even after prolonged reaction time. All the obtained results are summarized in Table 1. We have also tried this reaction with different concentration of catalyst but we have got the best results at 5 mol % of VB1 and in the absence of the catalyst, reaction did not proceed even after prolonged reaction time. Further, we have also studied the sonochemical effect on model reaction using diverse solvents. In all cases, the experimental results show that the reaction times are reduced and the yields of the products are higher under sonication. Based on the results of this study, it seems that the ultrasonic irradiation improves the reaction times and yields. The obtained results are summarized in Table 2.

Table 2
Sonochemical effect on the synthesis of α-aminophosphonates.

Compound	Aldehyde/ketone	Aniline	With US[a]		Without US[b]	
			Time (min)	Yield[c,d] (%)	Time (min)	Yield[c,d] (%)
4a	Benzaldehyde	Aniline	5	95	60	77
4b	Benzaldehyde	4-Toludine	9	91	60	70
4c	Benzaldehyde	4-Chloroaniline	7	89	60	71
4d	Benzaldehyde	4-Anisidine	8	88	60	73
4e	2-Methylbenzaldehyde	Aniline	3	93	60	70
4f	4-Anisisaldehyde	Aniline	4	95	60	76
4g	4-Nitrobenzaldehyde	Aniline	5	91	60	72
4h	2-Chlorobenzaldehyde	Aniline	8	88	60	68
4i	2,6-Dichlorobenzaldehyde	Aniline	7	86	60	65
4j	4-Hydroxybenzaldehyde	Aniline	5	85	60	61
4k	Furan-2-carbaldehyde	Aniline	19	69	60	60
4l	Thiophene-2-carbaldehyde	Aniline	21	65	60	62
4m	Cyclohexanone	Aniline	30	41	60	31
4n	Acetophenone	Aniline	40	38	60	37

[a] Reaction of aldehyde/ketone, amine, triethylphosphite in the presence of VB1 (5 mol%) under ultrasonic waves in aqueous medium.
[b] Reaction of aldehyde/ketone, amine, triethylphosphite in the presence of VB1 (5 mol%) under stirring at ambient temperature.
[c] Isolated yield.
[d] Compounds were characterized by ^{1}H NMR, MS spectral data and were compared with the reference compounds.

After optimizing the conditions, the generality of this method was examined by the reaction of several substituted aldehydes/ketones, aniline with triethylphosphate and VB1. The results are shown in Table 2 (entry **4k**–**4n**). The newly synthesized compounds were compared (mp, MS and NMR) with compounds that were prepared using the literature method (Scheme 1). This comparison revealed that the compounds synthesized by this newly developed method were exactly similar in all aspects to the reference compounds. We also studied the reaction on heterocyclic aldehydes or ketones it gave the corresponding products, but the yields were low even after prolonged reaction time (Table 2, entry **4k**–**4n**). The reaction on ketones does not show any conversion even after prolonged reaction time, even on increasing the catalyst concentration, frequency and temperature of the ultrasonic bath the product formation was not observed. This result revealed that the reaction undergoes only on the aldehydes and rarely on ketones (Table 2, entry **4k**–**4n**).

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References

[1] R. Engel, Chem. Rev. 77 (1977) 349.
[2] J. Hiratake, J. Oda, Biosci. Biotechnol. Biochem. 61 (1997) 211.
[3] K.A. Schug, W. Lindner, Chem. Rev. 105 (2005) 67.
[4] K. Moonen, I. Lauryn, C.V. Stevens, Chem. Rev. 104 (2004) 6177.
[5] F. Palacios, C. Alonso, J.M. de los Santos, Curr. Org. Chem. 8 (2004) 1481.
[6] P. Kafarski, B. Lejczak, Phosphorus Sulfur Silicon Relat. Elem. 63 (1991) 193.
[7] M.C. Allen, W. Fuher, B. Tuck, et al. J. Med. Chem. 32 (1989) 1652.
[8] E.K. Baylis, C.D. Campbell, J.G. Dingwall, J. Chem. Soc. Perkin Trans. 1 (1984) 2845.
[9] S.J. Benkovic, R. Hirschmann, Tetrahedron Lett. 35 (1994) 6853.
[10] C.H. Hassall, E.F. Hahn, Antibiotics (Springer, Berlin) VI (1983) 1.
[11] G.F. Makhaeva, V.V. Malygin, A.Y. Aksinenko, et al. Dockl. Biochem. Biophys. 400 (2005) 92.
[12] W. Pan, C. Ansiaux, S.P. Vincent, Tetrahedron Lett. 48 (2007) 4353.
[13] X. Rao, Z. Song, L. He, Heteroat. Chem. 19 (2008) 512.
[14] (a) M.R. Saidi, N. Azizi, Synlett (2002) 1347;
(b) N. Azizi, F. Rajabi, M.R. Saidi, Tetrahedron Lett. 45 (2004) 9233;
(c) N. Azizi, M.R. Saidi, Tetrahedron 59 (2003) 5329;
(d) N. Azizi, M.R. Saidi, Eur. J. Org. Chem. 23 (2003) 4630.
[15] B.C. Ranu, A. Hajra, U. Jana, Org. Lett. 1 (1999) 1141.
[16] C. Qian, T. Huang, J. Org. Chem. 63 (1998) 4125.
[17] S. Chandrasekhar, S.J. Prakash, V. Jagadeshwar, et al. Tetrahedron Lett. 42 (2001) 5561.
[18] M. Tajbakhsh, A. Heydari, H. Alinezhad, et al. Synthesis (2008) 352.
[19] B. Kaboudin, R. Nazari, Tetrahedron Lett. 42 (2001) 8211.
[20] S.D. Mitragotri, D.M. Pore, U.V. Desai, et al. Catal. Commun. (2008) 1822.
[21] K.K. Manabe, S. obayashi, Chem. Commun. (2000) 669.
[22] H.J. Ha, Nam, Synth. Commun. 22 (1992) 1143.
[23] H. Firouzabadi, N. Iranpoor, S. Sobhani, Synthesis (2004) 2692.
[24] S. Bhagat, A.K. Chakraborti, J. Org. Chem. 72 (2007) 1263.
[25] H. Firouzabadi, M. Jafarpour, J. Iran. Chem. Soc. 5 (2008) 159.
[26] S. Bhagat, A.K. Chakraborti, J. Org. Chem. 73 (2008) 6029.
[27] M. Hosseini-Sarvari, Tetrahedron 61 (2008) 5459.
[28] (a) C. Noonan, L. Baragwanath, S.J. Connon, Tetrahedron Lett. 49 (2008) 4003;
(b) P.D. Dünkelmann, K. Jung, A. Nitsche, et al. J. Am. Chem. Soc. 124 (2002) 12084;
(c) S. Orlandi, M. Caporale, M. Benaglia, R. Annunziata, Tetrahedron: Asymmetry 14 (2003) 3827.
[29] (a) P.G. Mandhane, R.S. Joshi, D.R. Nagargoje, et al. Tetrahedron Lett. 51 (2010) 3138;
(b) R.S. Joshi, P.G. Mandhane, S.D. Diwakar, et al. Ultrason. Sonochem. 17 (2009) 298;
(c) P.G. Mandhane, R.S. Joshi, A.R. Ghawalkar, et al. Bull. Korean Chem. Soc. 30 (2009) 2969.
[30] E.H. Hu, D.R. Sidler, U.H. Dolling, J. Org. Chem. 63 (1998) 3454.
[31] A. Shaabani, A. Bazgir, F. Teimouri, Tetrahedron Lett. 44 (2003) 857.