An Efficient One-Pot Synthesis of α-Amino Phosphonates Catalyzed by Bismuth Nitrate Pentahydrate

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Received 30 December 2006

Respectfully dedicated to my PhD supervisor and mentor, Dr. Ram P. Sharma, FASc on the occasion of his 68th birthday

Abstract: A simple, efficient, and environmentally benign method has been developed for the synthesis of α-amino phosphonates through a one-pot reaction of aldehydes with amines and diethyl phosphite in the presence of bismuth nitrate pentahydrate as a catalyst. Some of the major advantages of this protocol are: good yields, the involvement of a less-expensive and non-toxic catalyst, mild and solvent-free reaction conditions and also tolerance towards other functional groups present in the substrates. Eighteen examples are described, highlighting the substrate scope of the reaction.

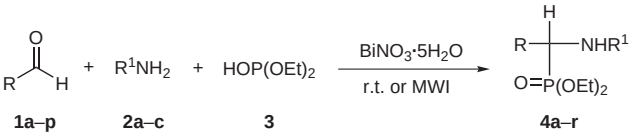
Key words: α-amino phosphonates, aldehydes, amines, alkyl phosphite, bismuth nitrate pentahydrate, synthetic methods

The synthesis of α-amino phosphonates has attracted the attention of organic chemists and medicinal chemists worldwide as they are considered to be structural analogues of the corresponding α-amino acids and transition-state mimics of peptide hydrolysis. The utilities of α-amino phosphonates as enzyme inhibitors,[1] peptide mimics,[2] antibiotics and pharmacological agents,[3] herbicidal[4] and haptens of catalytic antibodies[5] have been reported. Several synthetic approaches have been reported but the nucleophilic addition reaction of phosphites with imines is one of the most preferred methods, which is usually catalyzed by an alkali-metal alkoxide, e.g. NaOEt or Lewis acids[6] such as $BF_3{\cdot}OEt_2$, $SnCl_2$, $SnCl_4$, $ZnCl_2$ and $MgBr_2$.[7,8] However, these reactions can not proceed in one pot from a carbonyl compound, an amine and a phosphite because the water that is generated during the course of reaction can decompose or deactivate Lewis acids.[9] This drawback has been overcome by some recent methods using lanthanide triflates/$MgSO_4$,[10] $InCl_3$,[11] $ZrCl_4$[12] and $TaCl_5$–SiO_2.[13] However, many of these methods involve stoichiometric amount of catalysts, expensive reagents,[10] longer reaction times,[13] low yields of products in case of aliphatic aldehydes and amines and in addition, use of harmful organic solvents[10–12] such as CH_2Cl_2, THF or MeCN are undesirable from the viewpoint of today's environmental consciousness. Hence, there is a need to develop an efficient, practically potential and environmentally benign method for the synthesis of α-amino phosphonates.

SYNLETT 2007, No. 5, pp 0745–0748
Advanced online publication: 08.03.2007
DOI: 10.1055/s-2007-970762; Art ID: G37306ST

Recently, bismuth nitrate has emerged as an efficient Lewis acid[14–16] due to its relatively low toxicity, readily availability at a low cost and tolerance to trace amounts of water. Hence, we considered $BiNO_3{\cdot}5H_2O$ to be an ideal Lewis acid to address some of the limitations posed by known methods. Herein, we disclose $BiNO_3{\cdot}5H_2O$-catalyzed one-pot synthesis of structurally diverse α-amino phosphonates from aldehydes, amines and diethyl phosphite.

The reaction of aldehydes with amines results in situ generation of imine intermediate which subsequently reacts with diethylphosphite and affords the α-amino phosphonates in one pot. The reaction of benzaldehyde with aniline and diethylphosphite was carried out in the presence of $BiNO_3{\cdot}5H_2O$ (10 mol%) under neat conditions or microwave (Scheme 1). The bismuth atom coordinates with the imine nitrogen to facilitate the nucleophilic attack of diethylphosphite to increase the yield of the product.



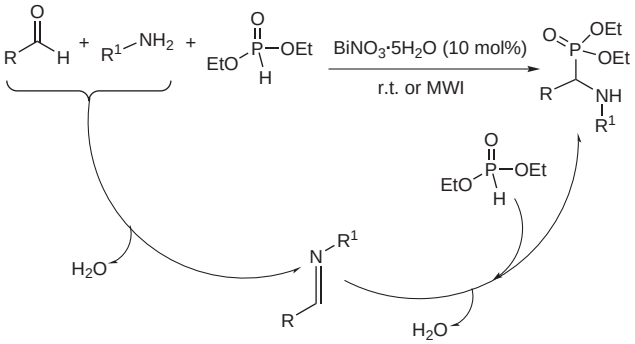
Scheme 1

A wide variety of structurally diverse aldehydes were subjected to this novel procedure in the presence of a catalytic amount (10 mol%) of $BiNO_3{\cdot}5H_2O$ and converted into the corresponding α-amino phosphonates in high to excellent yields (see Table 1).

In all cases, the three-component reaction proceeded smoothly to furnish the corresponding α-amino phosphonates. Excellent yields of the products were obtained in case of aromatic aldehydes due to their higher reactivity. However, in case of conjugated aldehydes, products were obtained in low yields. Tolerance towards various functional groups in the substrates was evident from the substrates bearing methylenedioxy, methoxy, ethers, halides, olefinic and hydroxy groups. The presence of electron-withdrawing groups at the *para* position in the aldehyde ring resulted in higher yields while at the *meta* position in lower yields. Also, the presence of electron-donating groups in the amine ring resulted in higher yields. A plausible mechanism of formation of α-amino phosphonates

in one pot catalyzed by $BiNO_3{\cdot}5H_2O$ is depicted in Scheme 2.

In conclusion, $BiNO_3{\cdot}5H_2O$ was found to be an efficient catalyst in one-pot reaction of aldehydes, amines, and diethyl phosphite to afford α-amino phosphonates. The main advantages of this method are: mild, clean and solvent-free reaction conditions, good to excellent yields, and environmentally benign reagent. In addition, our methodology might be useful for substrates containing a wide variety of other functional groups. Furthermore, this method is also expected to have much better application in organic synthesis because of the very low cost and nontoxic nature of the reagent. This reaction system not only provides a novel method for the synthesis of biologically important α-amino phosphonates but is also an environmentally friendly chemical process.



Scheme 2 Plausible mechanism of formation of α-amino phosphonates catalyzed by $BiNO_3{\cdot}5H_2O$

Table 1 One-Pot Synthesis of α-Amino Phosphonates Catalyzed by $BiNO_3{\cdot}5H_2O$[17]

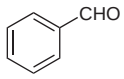
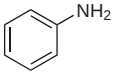
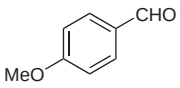
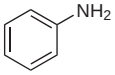
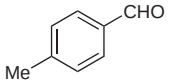
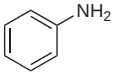
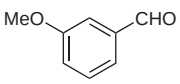
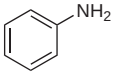
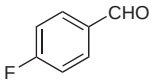
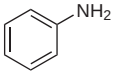
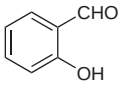
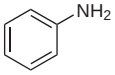
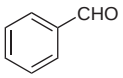
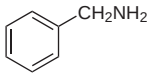
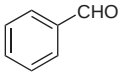
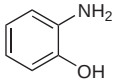
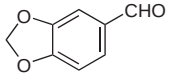
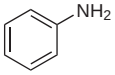
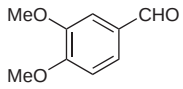
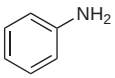
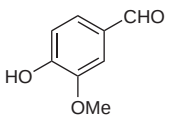
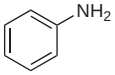
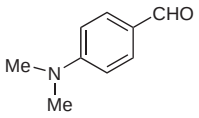
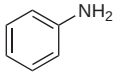
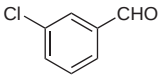
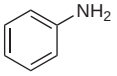
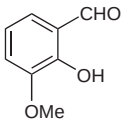
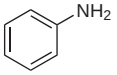
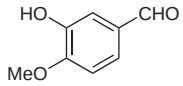
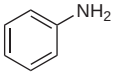
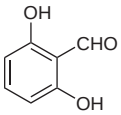
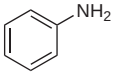
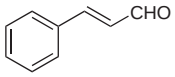
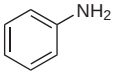
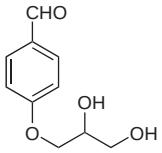
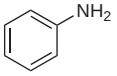
						Method A[a]		Method B[b]	
Entry	RCHO		R^1NH_2		Product	Time (h)	Yield (%)[c]	Time (min)	Yield (%)[c]
1		1a		2a	**4a**	10	93	4	96
2		1b		2a	**4b**	10	93	2	95
3		1c		2a	**4c**	10	94	2	96
4		1d		2a	**4d**	8	91	3	95
5		1e		2a	**4e**	8	90	4	92
6		1f		2a	**4f**	8	92	2	94
7		1a		2b	**4g**	10	91	4	95
8		1a		2c	**4h**	8	89	2	91
9		1g		2a	**4i**	5	95	2	98
10		1h		2a	**4j**	5	93	2	96
11		1i		2a	**4k**	5	95	1	98

Table 1 One-Pot Synthesis of α-Amino Phosphonates Catalyzed by $BiNO_3 \cdot 5H_2O$[17] (continued)

Entry	RCHO		R^1NH_2		Product	Method A[a] Time (h)	Method A[a] Yield (%)[c]	Method B[b] Time (min)	Method B[b] Yield (%)[c]
12		1j		2a	**4l**	7	80	1	88
13		1k		2a	**4m**	10	89	3	92
14		1l		2a	**4n**	8	93	3	95
15		1m		2a	**4o**	8	94	2	97
16		1n		2a	**4p**	8	88	2	92
17		1o		2a	**4q**	5	85	2	90
18		1p		2a	**4r**	7	92	2	96

[a] Method A: reaction mixtures stirred at r.t.
[b] Method B: reactions carried out under microwave.
[c] Yields refer to those of pure isolated products fully characterized by spectral data.

Acknowledgment

A.K.B. is grateful to the Director, NCL, Pune for financial support (MLP008626), to Dr. Mukund K. Gurjar, Head, Division of Organic Chemistry and Prof. Krishna N. Ganesh, J. C. Bose Fellow and Director, IISER, Pune for constant encouragement and support. T.K. is grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi for a research fellowship.

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(17) **Method A**: To a mixture of aldehyde (1 mmol) and amine (1 mmol), $BiNO_3 \cdot 5H_2O$ (10 mol%) was added and stirred at r.t. for 5 min, then diethylphosphite (1 mmol) was added dropwise. The stirring of the reaction mixture was continued for the appropriate time (see Table 1) till the completion (TLC) of reaction. The reaction mixture was diluted with H_2O and extracted with EtOAc (3 × 20 mL). The combined EtOAc extract was washed with brine, dried (anhyd Na_2SO_4), and evaporated to furnish crude product, which was purified by column chromatography (hexane–EtOAc, 7:3) over silica gel to provide pure α-amino phosphonates. All the products were characterized by spectral data.
Method B: To a mixture of aldehyde (1 mmol), amine (1 mmol), and diethylphosphite (1 mmol), $BiNO_3 \cdot 5H_2O$ (10 mol%) was added and the reaction mixture was irradiated with microwave (Kenstar Model No. OM-9918C; 2450 MHz, 2350 W) for the specified period of time in an open vessel. Work-up of the reaction was carried out as described above.

Diethyl {[(2-Hydroxyphenyl)amino](phenyl)methyl}phosphonate (4h)
Yield 0.304 g, 91%, colorless syrupy liquid. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 7.46–6.46 (m, 9 H), 4.89 (d, $^1J_{PH}$ = 26.0 Hz, 1 H), 3.61–4.33 (m, 4 H), 1.13 (t, *J* = 7.2 Hz, 3 H), 1.10 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 145.29 (s, Ph), 135.73 (s, Ph), 134.88 (s, Ph), 128.56 (s, Ph), 128.51 (s, Ph), 128.18 (s, Ph), 128.07 (s, Ph), 127.85 (s, Ph), 119.88 (s, Ph), 118.25 (s, Ph), 114.38 (s, Ph), 111.94 (s, Ph), 64.31 (d, $^2J_{PC}$ = 7.3 Hz, -O*C*H$_2$CH$_3$), 63.70 (d, $^2J_{PC}$ = 7.0 Hz, -O*C*H$_2$CH$_3$), 55.99 (d, $^1J_{PC}$ = 153.0 Hz, -*C*HP), 16.49 (d, $^3J_{PC}$ = 5.5 Hz, -OCH$_2$*C*H$_3$), 16.19 (d, $^3J_{PC}$ = 5.9 Hz, -OCH$_2$*C*H$_3$). Anal. Calcd for $C_{17}H_{22}NO_4P$ (335.33): C, 60.89; H, 6.61; N, 4.18. Found: C, 60.72; H, 6.58; N, 4.10.

Diethyl [1,3-Benzodioxol-5-yl(phenylamino)methyl]phosphonate (4i)
Yield 0.355 g, 98%, white solid; mp 112–13 °C. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 7.16–6.57 (m, 8 H), 5.94 (s, 2 H), 4.72 (d, $^1J_{PH}$ = 23.1 Hz, 1 H), 4.17 (m, 4 H), 1.30 (t, *J* = 6.1 Hz, 3 H), 1.17 (t, *J* = 6.5 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 145.29 (s, Ph), 144.80 (s, Ph), 144.51 (s, Ph), 143.92 (s, Ph), 143.85 (s, Ph), 127.35 (s, Ph), 125.49 (s, Ph), 125.44 (s, Ph), 119.21 (s, Ph), 116.59 (s, Ph), 112.12 (s, Ph), 108.67 (s, Ph), 108.58 (s, Ph), 61.64 (d, $^2J_{PC}$ = 7.0 Hz, -O*C*H$_2$CH$_3$), 61.58 (d, $^2J_{PC}$ = 7.1 Hz, -O*C*H$_2$CH$_3$), 54.12 (s, -O*C*H$_3$), 53.91 (d, $^1J_{PC}$ = 152.1 Hz, -*C*HP), 14.65 (d, $^3J_{PC}$ = 5.8 Hz, -OCH$_2$*C*H$_3$), 14.47 (d, $^3J_{PC}$ = 6.0 Hz, -OCH$_2$*C*H$_3$). Anal. Calcd for $C_{18}H_{22}NO_5P$ (363.34): C, 59.50; H, 6.10; N, 3.85. Found: C, 59.32; H, 6.05; N, 3.78.

Diethyl [(4-Hydroxy-3-methoxyphenyl)(phenylamino)methyl]phosphonate (4k)
Yield 0.357 g, 98%, colorless syrupy liquid. ^{1}H NMR (200 MHz, $CDCl_3$, TMS,): δ = 7.14–6.60 (m, 8 H), 4.77 (d, $^1J_{PH}$ = 24.4 Hz, 1 H), 4.16–3.67 (m, 4 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 1.28 (t, *J* = 7.43 Hz, 3 H), 1.10 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS,): δ = 145.34 (s, Ph), 145.29 (s, Ph), 144.80 (s, Ph), 143.85 (s, Ph), 127.35 (s, Ph), 125.44 (s, Ph), 119.21 (s, Ph), 116.59 (s, Ph), 112.84 (s, Ph), 112.12 (s, Ph), 108.67 (s, Ph), 108.58 (s, Ph), 63.44 (d, $^2J_{PC}$ = 7.0 Hz, -O*C*H$_2$CH$_3$), 63.39 (d, $^2J_{PC}$ = 7.3 Hz, -O*C*H$_2$CH$_3$), 54.12 (s, -O*C*H$_3$), 53.91 (d, $^1J_{PC}$ = 152.0 Hz, -*C*HP), 16.48 (d, $^3J_{PC}$ = 6.4 Hz, -OCH$_2$*C*H$_3$), 16.30 (d, $^3J_{PC}$ = 6.0 Hz, -OCH$_2$*C*H$_3$). Anal. Calcd for $C_{18}H_{24}NO_5P$ (365.36): C, 59.17; H, 6.62; N, 3.83. Found: C, 59.05; H, 6.45; N, 3.78.

Diethyl [(2-hydroxy-6-methoxyphenyl)(phenylamino)methyl]phosphonate (4n)
Yield 0.346 g, 95%, white solid; mp 116–18 °C. ^{1}H NMR (200 MHz, $CDCl_3$, TMS,): δ = 7.13–6.64 (m, 8 H), 5.25 (d, $^1J_{PH}$ = 24.2 Hz, 1 H), 4.21–3.86 (m, 4 H), 4.13 (s, 3 H), 1.29 (t, *J* = 7.0 Hz, 3 H), 1.10 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 147.03 (s, Ph), 146.51 (s, Ph), 146.22 (s, Ph), 144.15 (s, Ph), 129.22 (s, Ph), 122.12 (s, Ph), 120.56 (s, Ph), 120.19 (s, Ph), 118.52 (s, Ph), 113.88 (s, Ph), 110.36 (s, Ph), 63.50 (d, $^2J_{PC}$ = 7.2 Hz, -O*C*H$_2$CH$_3$), 56.07 (s, -O*C*H$_3$), 49.58 (d, $^1J_{PC}$ = 155.6 Hz, -*C*HP), 16.50 (d, $^3J_{PC}$ = 6.1 Hz, -OCH$_2$*C*H$_3$), 16.23 (d, $^3J_{PC}$ = 5.9 Hz, -OCH$_2$*C*H$_3$). Anal. Calcd for $C_{18}H_{24}NO_5P$ (365.36): C, 59.17; H, 6.62; N, 3.83. Found: C, 59.02; H, 6.42; N, 3.75.

Diethyl [(3-Hydroxy-4-methoxyphenyl)(phenylamino)methyl]phosphonate (4o)
Yield 0.354 g, 97%, colorless syrupy liquid. ^{1}H NMR (200 MHz, $CDCl_3$, TMS,): δ = 7.12–6.57 (m, 8 H), 4.73 (d, $^1J_{PH}$ = 24.0 Hz, 1 H), 4.15–3.68 (m, 4 H), 3.80 (s, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.12 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS,): δ = 147.02 (s, Ph), 147.00 (s, Ph), 146.37 (s, Ph), 129.19 (s, Ph), 128.59 (s, Ph), 119.60 (s, Ph), 118.37 (s, Ph), 118.18 (s, Ph), 114.67 (s, Ph), 114.01 (s, Ph), 63.55 (d, $^2J_{PC}$ = 7.0 Hz, -O*C*H$_2$CH$_3$), 55.93 (s, -O*C*H$_3$), 55.51 (d, $^1J_{PC}$ = 153.8 Hz, -*C*HP), 16.47 (d, $^3J_{PC}$ = 5.5 Hz, -OCH$_2$*C*H$_3$), 16.30 (d, $^3J_{PC}$ = 5.8 Hz, -OCH$_2$*C*H$_3$). Anal. Calcd for $C_{18}H_{24}NO_5P$ (365.35): C, 59.17; H, 6.62; N, 3.83. Found: C, 59.12; H, 6.48; N, 3.78.

Diethyl {[4-(2,3-dihydroxypropoxy)phenyl](phenylamino)methyl}phosphonate (4r)
Yield 0.392 g, 96%, colorless syrupy liquid. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 7.39–6.57 (m, 9 H), 4.77 (d, $^1J_{PH}$ = 25.6 Hz, 1 H), 4.14–3.65 (m, 4 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.13 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): δ = 158.33 (s, Ph), 158.28 (s, Ph), 146.43 (s, Ph), 146.14 (s, Ph), 129.18 (s, Ph), 129.01 (s, Ph), 128.06 (s, Ph), 120.19 (s, Ph), 118.46 (s, Ph), 114.73 (s, Ph), 114.68 (s, Ph), 113.98 (s, Ph), 70.43 (s, -*C*HOH), 69.08 (s, -*C*H$_2$OH), 63.49 (d, $^2J_{PC}$ = 7.3 Hz, -O*C*H$_2$CH$_3$), 63.43 (d, $^2J_{PC}$ = 7.3 Hz, -O*C*H$_2$CH$_3$), 55.26 (d, $^1J_{PC}$ = 151.0 Hz, -*C*HP), 16.42 (d, $^3J_{PC}$ = 5.5 Hz, -OCH$_2$*C*H$_3$), 16.25 (d, $^3J_{PC}$ = 5.5 Hz, -OCH$_2$*C*H$_3$). Anal. Calcd for $C_{20}H_{28}NO_6P$ (409.41): C, 58.67; H, 6.89; N, 3.42. Found: C, 58.50; H, 6.78; N, 3.36.