Arabian Journal of Chemistry (2014) 7, 833–838

King Saud University

Arabian Journal of Chemistry

www.ksu.edu.sa
www.sciencedirect.com

ORIGINAL ARTICLE

Neat synthesis and antioxidant activity of α-aminophosphonates

Guna Subba Reddy [a], Kunda Uma Maheswara Rao [a], Chereddy Syama Sundar [a], Sarva Santhi Sudha [a], Buchammagari Haritha [a], Sirasanagandla Swapna [b], Cirandur Suresh Reddy [a,*]

[a] *Dept. of Chemistry, S.V University, Tirupati 517502, AP, India*
[b] *Dept. of Bio-Chemistry, S.V University, Tirupati 517502, AP, India*

Received 2 November 2011; accepted 15 January 2013
Available online 4 February 2013

KEYWORDS

Multi-component reaction;
Amberlyst-15;
Microwave Irradiation;
Antioxidant activity

Abstract A simple, efficient, and environmentally benign method for a three-component reaction of an amine, an aldehyde and diethyl phosphite catalyzed by Amberlyst-15 has been developed to afford α-amino phosphonates in high yields and short reaction times under solvent-free reaction conditions using microwave irradiation. The major advantages of the present method are inexpensive, ecofriendly and reusable catalyst and also studied their antioxidant activity of synthesized compounds.

1. Introduction

α-Aminophosphonates are probably the most important substitutes for the corresponding amino acids in biological systems. (Giannousi and Bartlett, 1987) Indeed, a number of potent antibiotics, (Atherton et al., 1986) enzyme inhibitors, (Allen et al., 1989) and pharmacological agents (Kaboudin and Moradi, 2005) are α-aminophosphonates as well as their derivatives, notably peptides. α-Aminophosphonates are also found as constituents of natural products. These important compounds have been synthesized by various routes. Among the literature methods, (Abhimanyu and P., 2006; Heydari et al., 2009; Hou et al., 2011; Banik et al., 2010; Rao et al., 2008; Mitragotri et al., 2008) the Kabachnik–Fields reaction is one of the most convenient approaches to α-aminophosphonates. It is a one-pot, three-component reaction of carbonyl compound, amine, and dialkyl phosphite. The reaction usually needs Lewis acids such as $SnCl_4$, (Laschat and Kunz) $BF_3.OEt_2$ (Ha and Nam, 1992) and $ZrCl_4$. (Yadav and S., 2001) However, these reactions could not be carried out in a one-pot single step operation with a carbonyl compound, an amine and a dialkyl phosphite because the amine and water formed during imine formation decompose or deactivate the Lewis acid. (Atherton et al., 1986) This drawback has been partly overcome in some recent methods using lanthanide triflates/$MgSO_4$, (Li et al., 1999) $InCl_3$, (Ranu et al., 1999) $TaCl_5$–SiO_2, (Chandrasekhar et al., 2001) bismuth nitrate pentahydrate, (Bhattacharya and K., 2007) $Mg(ClO_4)_2$, Bhagat and Chakraborti, 2007 TiO_2, (Sarvari, 2008) Amberlite-IR120, (Bhattacharya and Rana, 2008) sulfamic

* Corresponding author. Tel.: +91 9849694958; fax: +91 877 2289555.
E-mail address: csrsvu@gmail.com (C. Suresh Reddy).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.arabjc.2013.01.004

acid, (Mitragotri et al., 2008) $H_3PW_{12}O_{40}$, (Heydari et al., 2007) trimethylanilinium chloride, (Heydari and Arefi, 2007) lithium perchlorate (Heydari et al., 1998) and Amberlyst-15. (Tajbakhsh et al., 2011) However, these catalysts have various other setbacks such as less accessibility of reagents, and require a long reaction time. Further, when the starting materials contain aliphatic amines, the reactions involving them usually give uncharacterizable products. In addition, some of these catalysts are expensive or are difficult to prepare. Hence the search continues for the development of a better and green synthetic protocol for them that is simple, efficient and cost effective and this remains an ever-challenging objective. In continuation of our program on the development of novel organic synthetic methodologies, (Rao et al., 2011) we have investigated the synthesis of α-aminophosphonate derivatives in the presence of amberlyst-15 using microwave irradiation.

The use of solid acidic catalysts has gained importance in organic synthesis due to several advantages such as, operational simplicity, nontoxicity, reusability, low cost and ease of isolation after completion of the reaction. Amberyst-15 resin has emerged as an efficient heterogeneous catalyst for various chemical transformations. (Yadav et al., 2005) Owing to the numerous advantages associated with this cheap and non-hazardous catalyst, we considered Amberyst-15 resin to be an ideal heterogeneous acid catalyst for the synthesis of α-amino phosphonates. Application of microwave irradiation to this reaction increases the efficiency, which otherwise requires long reaction time. Moreover, microwave-assisted reactions are believed to satisfy the demands of 'green chemistry' allowing for solvent-free conditions to be employed. Herein, we report a novel one-pot synthesis of a-amino phosphonates catalyzed by Amberyst-15 resin under solvent-free reaction conditions using microwave irradiation and also studied the anti oxidant activity of synthesized compounds.

2. Experimental

2.1. Synthesis of diethyl(3,5-dichloro-4-hydroxyphenylamino)(3-nitrophenyl) methyl phosphonate 4(d)

3,5-dichloro-4-hydroxy phenylamine (1 mmol), 3-nitro benzaldehyde (1 mmol), diethylphosphite (1 mmol) and Amberlyst-15 (100 mg) were added into a 25 mL three-necked flask and exposed to microwave irradiation (CATA-4R—Scientific Microwave oven, 490 W) for 4 min. After completion of the reaction (TLC), the reaction mixture was cooled and DCM (25 mL) was added. The catalyst was filtered from the reaction mixture and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography (100–200 mesh) eluting with petroleum ether–ethyl acetate (4:1) to afford the corresponding pure α-amino phosphonate. The same procedure is successfully applied to remaining compounds. All the products were characterized from their spectral data.

2.2. Spectral data

2.2.1. Diethyl(3, 5-dichloro-4-hydroxyphenylamino)(1H-indol-3-yl)methylphosphonate 4(a)

Yield: 84 % IR (KBr) (ν_{max} cm^{-1}): 3300 (NH), 1260 (P═O), 750 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (3H, t, J = 8.0 Hz, P-$OCH_2C\underline{H}_3$), 1.25 (3H, t, J = 8.0 Hz, P-$OCH_2C\underline{H}_3$), 3.64–3.72 (1H, m, P-$OC\underline{H}_2CH_3$), 3.81–3.90 (1H, m, P-$OC\underline{H}_2CH_3$), 3.99–4.10 (2H, m, P-$OC\underline{H}_2CH_3$), 5.20 (1H, d, J = 20.0 Hz, P-CH), 5.32 (1H, s, Ar–OH), 6.06 (1H, s, NH), 6.60–7.83 (7H, m, Ar–H), 11.10 (1H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 16.4 (d, J = 5.9 Hz, P-$OCH_2\underline{C}H_3$), 16.6 (d, J = 5.6 Hz, P-$OCH_2\underline{C}H_3$), 52.7 (d, J = 152.0 Hz, P-CH), 54.2 (d, J = 7.2 Hz, P-$O\underline{C}H_2CH_3$), 62.9 (d, J = 7.0 Hz, P-$O\underline{C}H_2CH_3$), 110.9 (C-1^1), 111.7 (C-5^1), 117.4 (C-8^1), 118.6 (C-2 & C-6), 120.5 (C-7^1), 121.0 (C-2^1), 123.0 (C-6^1), 127.3 (C-3 & C-5), 130.5 (C-9^1), 132.5 (C-4^1), 140.0 (C-4), 142.9 (C-1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 23.48. EI-MS (m/z, %): 444 (M + 2, 60), 443 (M + 1, 60), 442 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{19}H_{21}Cl_2N_2O_4P$: C, 51.48; H, 4.78; N, 6.32. Found: C, 51.40; H, 4.71; N, 6.23.

2.2.2. Diethyl(3,5-dichloro-4-hydroxyphenylamino)(4-(dimethylamino)phenyl) methylphosphonate 4(b)

Yield: 86 %. IR (KBr) (ν_{max} cm^{-1}): 3333 (NH), 1263 (P═O), 748 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.07 (3H, t, J = 8.4 Hz, P-$OCH_2C\underline{H}_3$), 1.21 (3H, t, J = 8.4 Hz, P-$OCH_2C\underline{H}_3$), 3.09 (3H, s, –NCH_3), 3.18 (3H, s, –NCH_3), 3.78–3.92 (1H, m, P- $OC\underline{H}_2CH_3$), 3.94–3.97 (1H, m, P-$OC\underline{H}_2CH_3$), 3.99–4.18 (2H, m, P-$OC\underline{H}_2CH_3$), 5.28 (1H, s, Ar–OH), 5.40 (1H, d, J = 24.0 Hz, P-CH), 6.55 (1H, s, NH), 6.60–8.42 (6H, m, Ar–H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 16.9 (d, J = 6.2 Hz, P-$OCH_2\underline{C}H_3$), 17.2 (d, J = 5.9 Hz, P-$OCH_2\underline{C}H_3$), 41.8 (NC^{11} & NC^{11}), 52.9 (d, J = 154.2 Hz, P-CH), 62.6 (d, J = 7.6 Hz, P-$O\underline{C}H_2CH_3$), 62.9 (d, J = 7.0 Hz, P-$O\underline{C}H_2CH_3$), 111.7 (C-3^1 & C-5^1), 114.7 (C-2 & C-6), 125.9 (C-1^1), 126.7 (C-2^1 & C-6^1), 129.7 (C-3 & C-5), 141.4 (C-4), 143.7 (C-1), 150.5 (C-4^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 22.20. EI-MS (m/z, %): 448 (M + 2, 60), 447 (M + 1, 60), 446 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{19}H_{25}Cl_2N_2O_4P$: C, 51.02; H, 5.63; N, 6.26. Found: C, 59.02; H, 5.60; N, 6.16.

2.2.3. Diethyl(3,5-dichloro-4-hydroxyphenylamino)(2-hydroxyphenyl)methylphosphonate 4(c)

Yield: 89 %. IR (KBr) (ν_{max} cm^{-1}): 3328 (NH), 1268 (P═O), 744 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.09 (3H, t, J = 8.2 Hz, P-$OCH_2C\underline{H}_3$), 1.18 (3H, t, J = 8.0 Hz, P-$OCH_2C\underline{H}_3$), 3.72–3.88 (1H, m, P-$OC\underline{H}_2CH_3$), 3.95–4.08 (1H, m, P-$OC\underline{H}_2CH_3$), 4.14–4.28 (2H, m, P-$OC\underline{H}_2CH_3$), 5.28 (1H, s, Ar–OH), 5.92 (1H, d, J = 22.0 Hz, P-CH), 6.14 (1H, s, NH), 6.54–8.70 (6H, m, Ar–H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 16.2 (d, J = 6.8 Hz, P-$OCH_2\underline{C}H_3$), 16.8 (d, J = 6.0 Hz, P-$OCH_2\underline{C}H_3$), 52.0 (d, J = 152.2 Hz, P-CH), 62.0 (d, J = 7.2 Hz, P-$O\underline{C}H_2CH_3$), 62.6 (d, J = 7.2 Hz, P-$O\underline{C}H_2CH_3$), 111.5 (C-2 & C-6), 114.7 (C-3^1), 119.8 (C-5^1), 125.9 (C-1^1), 127.7 (C-3 & C-5), 128.2 (C-6^1), 128.5 (C-4^1), 140.4 (C-4), 144.5 (C-1), 156.7 (C-2^1). ^{31}P NMR (202.4, MHz, $CDCl_3$) δ: 21.82. EI-MS (m/z, %): 420 (M + 2, 18), 421 (M + 1, 55), 420 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{17}H_{20}Cl_2NO_5P$: C, 48.59; H, 4.80; N, 3.33. Found: C, 48.50; H, 4.72; N, 3.28.

2.2.4. Diethyl (3,5-dichloro-4-hydroxyphenylamino)(3-nitrophenyl)methylphosphonate 4(d)

Yield: 92 %. IR (KBr) (ν_{max} cm^{-1}): 3319 (NH), 1260 (P═O), 752 (P-$C_{aliphatic}$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (3H, t,

J = 7.8 Hz, P-OCH$_2$C$\underline{H}_3$), 1.19 (3H, t, J = 7.6 Hz, P-OCH$_2$ C$\underline{H}_3$), 3.64–3.72 (1H, m, P-OC$\underline{H}_2$CH$_3$), 3.78–3.94 (1H, m, P-OC$\underline{H}_2$CH$_3$), 4.02–4.20 (2H, m, P-OC$\underline{H}_2$CH$_3$), 5.34 (1H, s, –OH), 5.42 (1H, s, Ar–OH), 5.48 (1H, d, J = 20.0 Hz, P-CH), 6.08 (1H, s, NH), 6.17–8.48 (6H, m, Ar–H). ^{13}C NMR (125.7 MHz, CDCl$_3$) δ: 16.2 (d, J = 6.8 Hz, P-OCH$_2$C$\underline{H}_3$), 16.8 (d, J = 6.0 Hz, P-OCH$_2$C$\underline{H}_3$), 52.0 (d, J = 152.2 Hz, P-CH), 62.0 (d, J = 7.2 Hz, P-O$\underline{C}$H$_2$CH$_3$), 62.6 (d, J = 7.2 Hz, P-O$\underline{C}$H$_2$CH$_3$), 111.5 (C-2 & C-6), 125.9 (C-1^1), 125.7 (C-3 & C-5), 126.7 (C-2^1), 128.2 (C-6^1), 131.5 (C-4^1), 133.8 (C-5^1), 140.4 (C-4), 142.5 (C-1), 147.7 (C-3^1). ^{31}P NMR (202.4, MHz, CDCl$_3$) δ: 22.64. EI-MS (m/z, %): 450 (M + 2, 60), 448 (M$^{+\bullet}$, 100). Anal. Calcd for $C_{17}H_{19}Cl_2N_2O_6P$: C, 45.45; H, 4.26; N, 6.24. Found: C, 45.34; H, 4.21; N, 6.19.

2.2.5. Diethyl(2-(benzyloxy)phenyl)(3,5-dichloro-4-hydroxyphenylamino) methylphosphonate 4(e)

Yield: 83%. IR (KBr) (ν_{max} cm^{-1}): 3320 (NH), 1268 (P═O), 745 (P-C$_{aliphatic}$). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 1.09 (3H, t, J = 8.6 Hz, P-OCH$_2$C$\underline{H}_3$), 1.18 (3H, t, J = 8.4 Hz, P-OCH$_2$C$\underline{H}_3$), 3.24–3.36 (1H, m, P-OC$\underline{H}_2$CH$_3$), 3.42–3.64 (1H, m, P-OC$\underline{H}_2$CH$_3$), 3.86–4.18 (2H, m, P-OC$\underline{H}_2$CH$_3$), 5.12 (1H, s, –OCH$_2$), 5.40 (1H, s, Ar–OH), 5.32 (1H, d, J = 24.0 Hz, P-CH), 6.28 (1H, s, NH), 6.14–8.62 (11H, m, Ar–H). ^{31}P NMR (202.4, MHz, CDCl$_3$) δ: 24.12. EI-MS (m/z, %): 511 (M + 2, 60), 510 (M + 2, 20), 509 (M$^{+\bullet}$, 100). Anal. Calcd for $C_{24}H_{26}Cl_2NO_5P$: C, 56.48; H, 5.14; N, 2.74. Found: C, 56.40; H, 5.10; N, 2.66.

2.2.6. Dimethyl(3,5-dichloro-4-hydroxyphenylamino)(1H-indol-3-yl) methylphosphonate 4(f)

Yield: 89%. IR (KBr) (ν_{max} cm^{-1}): 3331 (NH), 1257 (P═O), 741 (P-C$_{aliphatic}$). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.12 (3H, s, P-OCH$_3$), 3.28 (3H, s, P-OCH$_3$), 5.22 (1H, d, J = 20.0 Hz, P-CH), 5.32 (1H, s, Ar–OH), 6.06 (1H, s, NH), 6.56–7.98 (7H, m, Ar–H), 10.10 (1H, s, NH). ^{13}C NMR (125.7 MHz, CDCl$_3$) δ: 52.7 (d, J = 152.0 Hz, P-CH), 55.4 (d, J = 5.9 Hz, P-OCH$_3$), 55.9 (d, J = 5.6 Hz, P-OCH$_3$), 110 .9 (C-1^1), 112.2 (C-5^1), 116.4 (C-7^1), 117.9 (C-2 & C-6), 118.7 (C-8^1), 121.8 (C-6^1), 122.7 (C-2^1), 127.8 (C-3 & C-5), 128.9 (C-9^1), 134.4 (C-4^1), 137.7 (C-4), 140.7 (C-1). ^{31}P NMR (202.4, MHz, CDCl$_3$) δ: 22.52. EI-MS (m/z, %): 416 (M + 2, 60), 415 (M + 1, 18), 414 (M$^{+\bullet}$, 100). Anal. Calcd for $C_{17}H_{17}Cl_2N_2O_4P$: C, 49.18; H, 4.13; N, 6.75. Found: C, 49.08; H, 4.05; N, 6.64.

2.2.7. Dimethyl(3,5-dichloro-4-hydroxyphenylamino)(4-(dimethylamino)phenyl) methylphosphonate 4(g)

Yield: 90 %. IR (KBr) (ν_{max} cm^{-1}): 3320 (NH), 1268 (P═O), 753 (P-C$_{aliphatic}$). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.10 (3H, s, –NCH$_3$), 3.20 (3H, s, –NCH$_3$), 3.72 (3H, s, P-OCH$_3$), 3.94 (3H, s, P-OCH$_3$), 5.32 (1H, s, Ar–OH), 5.46 (1H, d, J = 24.0 Hz, P-CH), 6.55 (1H, s, NH), 6.63–8.52 (6H, m, Ar–H). ^{13}C NMR (125.7 MHz, CDCl$_3$) δ: 42.7 (NC^{11} & NC^{11}), 52.0 (d, J = 153.8 Hz, P-CH), 52.9 (d, J = 6.2 Hz, P-OCH$_3$), 53.8 (d, J = 5.9 Hz, P-OCH$_3$), 110.8 (C-3^1 & C-5^1), 113.9 (C-2 & C-6), 124.7 (C-2^1 & C-6^1), 128.8 (C-1^1), 130.8 (C-3 & C-5), 139.8 (C-4), 142.8 (C-1), 151.8 (C-4^1), ^{31}P NMR (202.4, MHz, CDCl$_3$) δ: 22.80. EI-MS (m/z, %): 420 (M + 2, 60), 419 (M + 1, 15), 418 (M$^{+\bullet}$, 100). Anal. Calcd for $C_{17}H_{21}Cl_2N_2O_4P$: C, 48.70; H, 5.05; N, 6.68. Found: C, 48.70; H, 5.05; N, 6.68.

2.2.8. Dimethyl(3,5-dichloro-4-hydroxyphenylamino)(2-hydroxyphenyl) methylphosphonate 4(h)

Yield: 83 %. IR (KBr) (ν_{max} cm^{-1}): 3327 (NH), 1264 (P═O), 750 (P-C$_{aliphatic}$). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.48 (3H, s, P-OCH$_3$), 3.62 (3H, s, P-OCH$_3$), 5.34 (1H, s, Ar–OH), 5.84 (1H, d, J = 22.8 Hz, P-CH), 6.20 (1H, s, NH), 6.45–8.72 (6H, m, Ar–H). ^{13}C NMR (125.7 MHz, CDCl$_3$) δ: 52.8 (d, J = 152.0 Hz, P-CH), 54.2 (d, J = 6.8 Hz, P-OCH$_3$), 54.8 (d, J = 6.0 Hz, P-OCH$_3$), 111.9 (C-2 & C-6), 115.5 (C-3^1), 120.5 (C-5^1), 125.9 (C-3 & C-5), 126.5 (C-1^1), 127.2 (C-4^1), 127.6 (C-6^1), 140.0 (C-4), 144.7 (C-1), 155.5 (C-2^1), ^{31}P NMR (202.4, MHz, CDCl$_3$) δ: 21.82. EI-MS (m/z, %): 420 (M + 2, 60), 419 (M + 1, 15), 418 (M$^{+\bullet}$, 100). Anal. Calcd for $C_{17}H_{21}Cl_2N_2O_4P$: C, 48.70; H, 5.05; N, 6.68. Found: C, 48.60; H, 4.98; N, 6.57.

2.2.9. Dimethyl(3,5-dichloro-4-hydroxyphenylamino)(3-nitrophenyl) methylphosphonate 4(i)

Yield: 88 %. IR (KBr) (ν_{max} cm^{-1}): 3319 (NH), 1260 (P═O), 752 (P-C$_{aliphatic}$). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.42 (3H, s, P-OCH$_3$), 3.64 (3H, s, P-OCH$_3$), 5.30 (1H, s, –OH), 5.38 (1H, s, Ar–OH), 5.52 (1H, d, J = 22.2 Hz, P-CH), 6.12 (1H, s, NH), 6.20–8.32 (6H, m, Ar–H). ^{13}C NMR (125.7 MHz, CDCl$_3$) δ: 16.2 (d, J = 6.8 Hz, P-OCH$_3$), 16.8 (d, J = 6.0 Hz, P-OCH$_3$), 52.0 (d, J = 152.2 Hz, P-CH), 110.6 (C-2 & C-6), 124.7 (C-1^1), 125.5 (C-3 & C-5), 127.7 (C-2^1), 128.9 (C-6^1), 133.5 (C-4^1), 135.7 (C-5^1), 141.7 (C-4), 143.8 (C-1), 148.8 (C-3^1). ^{31}P NMR (202.4, MHz, CDCl$_3$) δ: 21.52. EI-MS (m/z, %): 422 (M + 2, 60), 420 (M$^{+\bullet}$, 100). Anal. Calcd for $C_{15}H_{15}Cl_2N_2O_6P$: C, 42.78; H, 3.59; N, 6.65. Found: C, 42.68; H, 3.50; N, 6.58.

2.2.10. Dimethyl(2-(benzyloxy)phenyl)(3,5-dichloro-4-hydroxyphenylamino) methylphosphonate 4(j)

Yield: 85 %. IR (KBr) (ν_{max} cm^{-1}): 3320 (NH), 1268 (P═O), 745 (P-C$_{aliphatic}$). ^{1}H NMR (400 MHz, CDCl$_3$) δ: 3.34 (3H, s, P-OCH$_3$), 3.56 (3H, s, P-OCH$_3$), 5.08 (1H, s, –OCH$_2$), 5.42 (1H, s, Ar–OH), 5.60 (1H, d, J = 20.8 Hz, P-CH), 6.12 (1H, s, NH), 6.15–8.50 (11H, m, Ar–H). ^{31}P NMR (202.4, MHz, CDCl$_3$) δ: 21.12. EI-MS (m/z, %): 511 (M + 2, 60), 510 (M + 1, 20), 509 (M$^{+\bullet}$, 100). Anal. Calcd for $C_{22}H_{22}Cl_2NO_5P$: C, 54.79; H, 4.60; N, 2.90. Found: C, 54.71; H, 4.54; N, 2.81.

2.3. Antioxidant activity

The antioxidant activity of 4a–j was performed according to three methods. All the synthesized compounds show good activity against DPPH, NO and reducing power scavenging. Among the synthesized compounds 4 h, exhibited high activity when compared with other compounds.

2.3.1. DPPH Radical Scavenging Activity

The scavenging activity of α-aminophosphonates against DPPH radical was performed in accordance with Choi et al. Choi et al. (2002) 85 μM of DPPH was added to a medium containing different α-aminophosphonates. The medium was

incubated for 30 min at room temperature. The decrease in absorbance was measured at 518 nm. Ascorbic acid was used as standard reference to record maximal decrease in DPPH radical absorbance. The values are expressed in percentage of inhibition of DPPH radical absorbance with those of the standard control values without the title compounds (ascorbic acid maximal inhibition was considered 100% of inhibition).

$$\text{DPPH Scavenged}(\%) = \frac{(A_{cont} - A_{test})}{A_{cont}} \times 100$$

where A_{cont} is the absorbance of the control reaction and A_{test} is the absorbance in the presence of the sample.

In the case of α-aminophosphonates 4**a–j** (Fig. 1) derivatives, **4h** showed the highest DPPH radical scavenging activity with IC_{50} at 49.35 μg/mL when compared with other compounds. The remaining compounds exhibited DPPH radical scavenging activity in the following order: **4e** (IC_{50} 52.7 μg/mL), **4b** (IC_{50} 59.8 μg/mL), **4j** (IC_{50} 60.16 μg/mL), **4i** (IC_{50} 62.1 μg/mL), **4c** (IC_{50} 62.2 μg/mL), **4f** (IC_{50} 63.4 μg/mL), **4g** (IC_{50} 66.5 μg/mL), **4a** (IC_{50} 68.2 μg/mL), **4d** (IC_{50} 70.8 μg/mL) and when compared with ascorbic acid (IC_{50} 50.06 μg/mL).

2.3.2. Nitric Oxide (NO) scavenging activity

The scavenging activity of α-aminophosphonates against nitric oxide radical was performed in accordance with A Shirwaiker et al. Shirwaiker et al. (2004) Sodium nitropruside (5 μM) in phosphate buffer pH 7.4 was incubated with 100 μM concentration of test compounds dissolved in a suitable solvent (dioxane/methanol) and tubes were incubated at 25 °C for 120 min. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 ml of incubation solution was taken and diluted with 0.5 ml of griess reagent (1% Sulfanilamide, 0.1% *N*-naphthylethylenediamine dihydrochloride and 2% *o*-phosphoric acid dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthylethylenediamine dihydrochloride was read at λ 546 nm. The experiment was repeated in triplicate.

In the case of α-aminophosphonates **4a–j** (Fig. 2) derivatives, **4e** showed the highest NO scavenging with IC_{50} of 53.09 μg/mL when compared with other compounds. The remaining compounds exhibited reducing power activity in the following order: **4h** (IC_{50} 53.7 μg/mL), **4g** (IC_{50} 56.2 μg/mL), **4f** (IC_{50} 59.46 μg/mL), **4j** (IC_{50} 65.8 μg/mL), **4b** (IC_{50} 65.9 μg/mL), **4i** (IC_{50} 67.7 μg/mL), **4d** (IC_{50} 74.8 μg/mL), **4c** (IC_{50} 76.5 μg/mL), **4a** (IC_{50} 81.9 μg/mL) and when compared with ascorbic acid (IC_{50} 64.9 μg/mL).

2.3.3. Reducing power assay

The reducing power of synthesized compounds **4a–j** was determined according to the method of Oyaizu et.al. Saha et al. (2008) The compounds having 50–100 μM were mixed with 2.5 mL of phosphate buffer (0.2 M, pH 6.6) and 2.5 mL of 1% potassium ferricyanide and incubated at 50 °C for 20 min. To this mixture 2.5 mL of 10% trichloroacetic acid (TCA) was added and the mixture was centrifuged at 3000 rpm for 20 min. The upper layer (2.5 mL) was mixed with 2.5 mL of deionized water and 0.5 mL of 0.1% ferric chloride and the UV absorbance was measured at 700 nm using a spectrophotometer. Increase of absorbance of the reaction mixture indicates higher reducing power. Mean values from three independent samples were calculated for each compound and standard deviations were less than 5 %.

In the case of α-aminophosphonates **4a–j** (Fig. 3) derivatives, **4h** showed the highest reducing power with IC_{50} of 1.75 μg/mL when compared with other compounds. The remaining compounds exhibited reducing power activity in the following order: **4e** (IC_{50} 1.86 μg/mL), **4j** (IC_{50} 2.09 μg/mL), **4f** (IC_{50} 2.21 μg/mL), **4g** (IC_{50} 2.35 μg/mL), **4i** (IC_{50} 2.63 μg/mL), **4b** (IC_{50} 2.81 μg/mL), **4d** (IC_{50} 3.03 μg/mL), **4a** (IC_{50} 3.12 μg/mL), **4c** (IC_{50} 3.38 μg/mL) and when compared with ascorbic acid (IC_{50} 2.42 μg/mL).

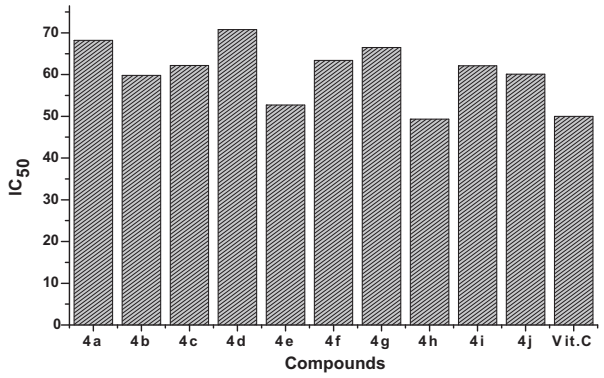


Figure 1 DPPH radical scavenging activity.

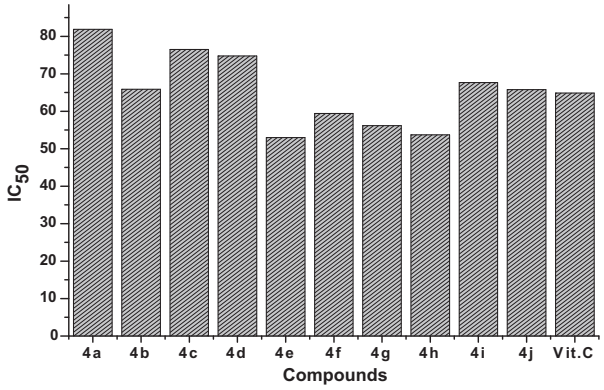


Figure 2 Nitric oxide (NO) scavenging activity.

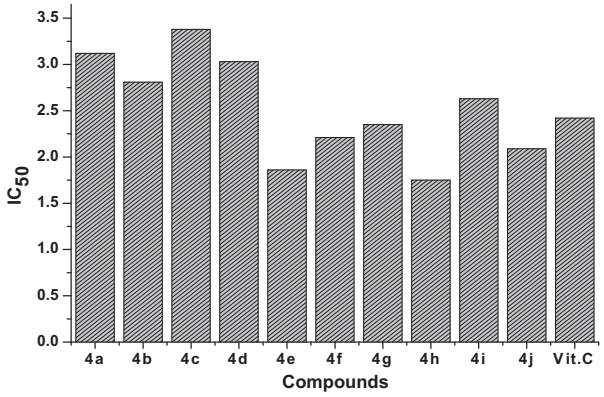
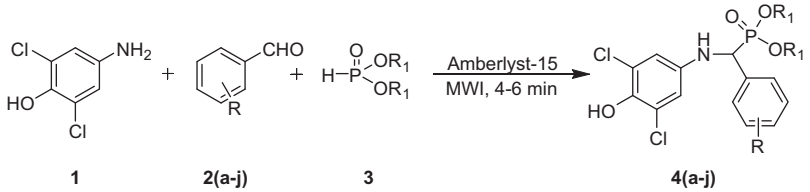


Figure 3 Reducing power assay.



Scheme 1 One pot synthesis of α-aminophosphonates using Amberlyst-15 under MWI.

Table 1 Influence of temperature on the synthesis of 4d.

S.No	Temp(°C)	Time (min)	Yield[a] (%)
1	RT	60	81
2	50	50	72
3	70	50	69
4	90	50	70
5	120	35	68
6	MWI	4	92

[a] Isolated yield.

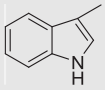
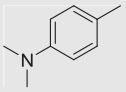
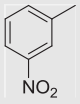
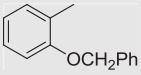
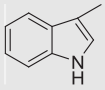
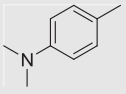
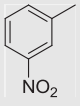
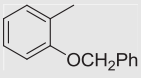
3. Results and discussion

The conventional method for this three component one pot reaction requires high temperatures and long reaction times to afford the corresponding phosphonates. A new method is developed for the preparation of α-aminophosphonates from a mixture of amine, aldehydes and diethyl phosphite in the presence of amberlyst-15 as catalyst under solvent free conditions by microwave irradiation. (see Scheme 1.)

To optimize the reaction conditions, the reaction of 3,5-dichloro-4-hydroxy phenyl amine (1 mmol), 3-nitro benzaldehyde (1 mmol), and diethylphosphite (1 mmol) was selected as a model. This reaction has been performed in different organic solvents such as toluene, methanol, dioxane, tetrahydrofuran, acrylonitrile, chloroform, dichloromethane, diethyl ether in the presence of Amberlyst-15 at room temperature and a low yield (< 75%) of the α-aminophosphonates was obtained in all these experiments. Use of a higher amount of catalyst also did not lead to a significant change in the reaction yields. The best result was obtained (91 %) when the same reaction was done under solvent free conditions with a small amount of (0.1 g) catalyst in one hour at room temperature. To increase the rate of reaction the same experiment was done at different temperatures (Table 1) in the presence of amberlyst-15 as catalyst. In all the cases the reaction time was decreased but the low yield of product was obtained. When the same experiment was done by microwave irradiation in the presence of amberlyst-15 as catalyst, surprisingly the reaction was completed in 4 min with 92 % yield.

Based on the optimized reaction conditions, a group of α-aminophosphonates were synthesized by the reaction of aromatic amine, aromatic/heterocyclic aldehydes and diethyl phosphite. In all the cases the reaction was completed within 4 min in good to excellent yields. In these experiments, the catalyst was isolated by filtration and could be reloaded with fresh reagents for further runs, thus, recyclization of the catalyst is possible without significant loss of activity (Table 2, **entry**

Table 2 Synthesis of α-aminophosphonates (4a–j).

Entry	R	R_1	Time (Min)	Yield (%)
4a		Et	4	84
4b		Et	4	86
4c		Et	6	89
4d		Et	5	92(91,90,90,89)[a]
4e		Et	6	83
4f		Me	5	89
4 g		Me	6	90
4 h		Me	5	83
4i		Me	4	88
4j		Me	6	85

[a] Isolated yields after recycling of catalyst.

4d). The products were obtained as solids and purified by column chromatography using silica gel as adsorbent and petroleum ether-ethyl acetate (3:1) as eluent. The chemical structures of **4a–j** were confirmed by elemental analysis, IR, ^{1}H–, ^{13}C–, ^{31}P– NMR and mass spectral data.

4. Conclusion

A simple, efficient, and environmentally benign method for the synthesis of α-aminophosphonates was developed and also studied their antioxidant activity.

Acknowledgments

The authors thank Prof. C.D. Reddy, Dept. of Chemistry, S.V. University, Tirupati for helpful discussions and for CSIR [01(2347)/09/EMR-II] New Delhi for providing financial assistance.

References

Abhimanyu, S.P., Arumugam, S., 2006. A novel $Cu(OTf)_2$ mediated three component high yield synthesis of α-aminophosphonates. Arkivoc. (x), 183–189.

Allen, M.C., Fuhrer, W., Tuck, B., Wade, R., Wood, J.M., 1989. Renin inhibitors. Synthesis of transition-state analogue inhibitors containing phosphorus acid derivatives at the scissile bond. J. Med. Chem. 32, 1652–1661.

Atherton, F.R., Hassal, C.H., Lambert, R.W., 1986. Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (1-aminoethyl)phosphonic acid and (aminomethyl)phosphonic acid. J. Med. Chem. 29, 29–40.

Atherton, F.R., Hassal, C.H., Lambert, R.W., 1986. Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (l-aminoethyl) phosphonic acid and (aminomethy1)phosphonic acid. J. Med. Chem. 29, 29–40.

Banik, A., Batta, S., Bandyopadhyay, D., Banik, B.K., 2010. A highly efficient Bismuth Salts-catalyzed route for the synthesis of α-aminophosphonates. Molecules 15, 8205–8213.

Bhagat, S., Chakraborti, A.K., 2007. An extremely efficient three-component reaction of aldehydes/ketones, amines, and phosphites for the synthesis of α-aminophosphonates catalyzed by magnesium perchlorate. J. Org. Chem. 72, 1263–1270.

Bhattacharya, A.K., Tanpreet Kaur, T., 2007. An efficient one-pot synthesis of α-amino phosphonates catalyzed by bismuth nitrate pentahydrate. Synlett. 745–748.

Bhattacharya, A.K., Rana, K.C., 2008. Amberlite-IR 120 catalyzed three-component synthesis of α-amino phosphonates in one-pot. Tetrahedron Lett. 49, 2598–2601.

Chandrasekhar, S., Prakash, S.J., Jagadeshwar, V., Narsihmulu, C., 2001. Three component coupling catalyzed by $TaCl_5$–SiO2: synthesis of α-aminophosphonates. Tetrahedron Lett. 42, 5561–5563.

Choi, C.W., Kim, S.C., Hwang, S.S., Choi, B.K., Ahn, H.J., Lee, M.Y., Park, S.H., Kim, S.K., 2002. Antioxidant activity and free radical scavenging capacity between Korean medicinal plants and flavonoids by assay-guided comparison. Plant Sci. 153, 1161–1168.

Giannousi, P.P., Bartlett, P.A., 1987. Phosphorus amino acid analogues as inhibitors of leucine aminopeptidase. J. Med. Chem. 30, 1603–1609.

Ha, H.J., Nam, G.S., 1992. An efficient synthesis of anilinobenzylphosphonates. Synth. Commun. 22, 1143–1148.

Heydari, A., Arefi, A., 2007. One-pot three-component synthesis of α-aminophosphonate derivatives 8, 1023–1026.

Heydari, A., Karimian, A., Ipaktschi, J., 1998. Lithium perchlorate/diethylether catalyzed aminophosphonation of aldehydes. Tetrahedron Lett. 39, 6729–6732.

Heydari, A., Hamadi, H., Pourayoubi, M., 2007. A new one-pot synthesis of α-amino phosphonates catalyzed by $H_3PW_{12}O_{40}$. Catal. Commun. 8, 1224–1226.

Heydari, A., Khaksar, S., Tajbakhsh, M., 2009. Trifluoroethanol as a metal-free, homogeneous and recyclable medium for the efficient one-pot synthesis of α-amino nitriles and α-amino phosphonates. Tetrahedron Lett. 50, 77–80.

Hou, J.T., Gao, J.W., Zhang, Z.H., 2011. $NbCl_5$: an efficient catalyst for one-pot synthesis of α-aminophosphonates under solvent-free conditions. Appl. Organomet. Chem. 25, 47–53.

Kaboudin, B., Moradi, K., 2005. A simple and convenient procedure for the synthesis of 1-aminophosphonates from aromatic aldehydes. Tetrahedron Lett. 46, 2989–2991.

Laschat, S., Kunz, H., 1992. Carbohydrates as chiral templates: stereoselective synthesis of (R) - and (S)-α-aminophosphonic acid derivatives. Synthesis, 90–95.

Li, G., Wei, H.X., Hook, J.D., 1999. Ytterbium (III) triflate-catalyzed asymmetric nucleophilic addition of functionalized lithium (α-carbalkoxyvinyl)cuprates to chiral p-toluenesulfinimines (thiooxime S-oxides). Tetrahedron Lett. 40, 4611–4614.

Mitragotri, S.D., Pore, D.M., Desai, U.V., Wadgaonkar, P.P., 2008. Sulfamic acid: an efficient and cost-effective solid acid catalyst for the synthesis of α-aminophosphonates at ambient temperature. Catal. Commun. 9, 1822–1826.

Mitragotri, S.D., Pore, D.M., Desai, U.V., Wadgaonkar, P.P., 2008. Sulfamic acid: an efficient and cost-effective solid acid catalyst for the synthesis of α-aminophosphonates at ambient temperature. Catal. Commun. 9, 1822–1826.

Ranu, B.C., Hajra, A., Jana, U., 1999. General procedure for the synthesis of α-amino phosphonates from aldehydes and ketones using Indium(III) chloride as a catalyst. Org. Lett. 1, 1141–1143.

Rao, X., Song, Z., He, L., 2008. Synthesis and antitumor activity of novel α-aminophosphonates from diterpenic dehydroabietylamine. Heteroat. Chem. 19, 512–516.

Uma Maheswara Rao, K., Syama Sundar, Ch., Siva Prasad, S., Nayak, S.K., Suresh Reddy, C., 2011. Neat synthesis and antioxidant activity of α-hydroxyphosphonates. Bull. Korean Chem. Soc. 32, 3343–3347.

Saha, M.R., Hasan, S.M.R., Akter, R., Hossain, M.M., Alam, M.S., Alam, M.A., Mazumder, M.E.H., 2008. In vitro free radical scavenging activity of methanol extract of the leaves of *mimusops elengi linn*. Bangl. J. Vet. Med. 6, 197–202.

Sarvari, M.H., 2008. TiO_2 as a new and reusable catalyst for one-pot three-component syntheses of α-aminophosphonates in solvent-free conditions. Tetrahedron 64, 5459–5466.

Shirwaiker, A., Rajendran, K., Dinesh kumar, C., 2004. In vitro antioxidant studies of *Annona squamosa* Linn Leaves. Indian J. Expl. Biol. 42, 803–807.

Tajbakhsh, M., Heydari, A., Alinezhad, H., Ghanei, M., Khaksar, S., 2011. Coupling of aldehydes, amines and trimethyl phosphite promoted by Amberlyst-15: highly efficient synthesis of α-amino phosphonates. Synthesis, 352–354.

Yadav, J.S., Reddy, B.V.S., Raj, S., Reddy, K.B., Prasad, A.R., 2001. Zr4 + -Catalyzed efficient synthesis of α-aminophosphonates. Synthesis, 2277–2280.

Yadav, J.S., Subbareddy, B.V., Vishnumurthy, P., 2005. Amberlyst-15 as a novel and recyclable solid acid for the coupling of aromatic aldehydes with homopropargyl alcohol. Tetrahedron Lett. 46, 1311–1313.