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ORIGINAL ARTICLE

Triton X-100 catalyzed synthesis of α-aminophosphonates

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Abstract Synthesis of α-aminophosphonates by a three-component condensation of an aldehyde, amines and dialkyl phosphites in the presence of a non-ionic surfactant Triton X-100 catalyst at 70 °C in aqueous medium is accomplished. The advantages are high yield, mild reaction conditions, simple work-up and eco-friendliness. All the newly-synthesized compounds (**4a–j**) exhibited moderate *in vitro* antibacterial and antifungal activities.

1. Introduction

The synthesis of α-amino phosphonates has attracted much attention recently due to their structural analogy to α-amino acids (Naydenova et al., 2010) and significant biological activities. They act as peptide mimics (Fields, 1999), enzyme inhibitors (Allen et al., 1989; Giannousis and Bartlett, 1987), antibiotics and pharmacological agents (Atherton et al., 1986). As a result different methods have been developed for the synthesis of α-amino phosphonates (Romanenko and Kukhar, 2006; Ordonez et al., 2009; Thirumurugan et al., 2010). Among them, the Kabachnik–Fields reaction appears to be still one of the simplest and most direct approaches (Tillu et al., 2011; Chandrasekhar et al., 2001). This reaction proceeds *via* an imine formed by the reaction of carbonyl compounds and amines, where it is converted to the corresponding aminophosphonates by phosphite addition. This one-pot reaction can be promoted by acid or base catalysts, microwave irradiation or by heating (Ranu and Hajra, 2002). Several acid catalysts, such as Lewis acids, examples are $BiCl_3$ (Zhan and Li, 2005), $FeCl_3$ (Rezaei et al., 2009), $YbCl_3$ (Xu et al., 2006), $Al(OTf_3)$ (Sobhani and Tashrifi, 2009), CAN (Kasthuraiah et al., 2007), $SbCl_3/Al_2O_3$ (Ambica et al., 2008) and Brønsted acids, examples are sulfamic acid (Mitragotri et al., 2008), oxalic acid (Vahdat et al., 2008), heteropoly acids (Heydari et al., 2007), solid acids montmorillonite KSF (Yadav et al., 2001), silica sulfuric acid (Yang et al., 2009), and Amberlite-IR 120 (Bhattacharya and Rana, 2008) and base catalysts, such as $CaCl_2$ (Kaboudin and Zahedi, 2008) and PPh_3 (Tian et al., 2009), as well as other catalysts, such as ZnO (Kassaee et al., 2009), TiO_2 (Hosseini-Sarvari, 2008), tosylchloride (Kaboudin and Jafari, 2008), phenyltrimethylammoniumchlo-

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ride (Heydari and Arefi, 2007), (bromodimethyl) sulfoniumbro mide (Kudrimoti and Rao Bommena, 2005), tetramethyl-tetra-3,4-pyridinoporphyrazinato copper(II) methyl sulfate [Cu(3,4-tmtppa)($MeSO_4$)$_4$] (Sobhani et al., 2008), tetra-*tert*-butylphthalo cyanine (Matveeva et al., 2003), β-cyclodextrine (β-CD) (Kabou din and Sorbiun, 2007) and NBS (Wu et al., 2006), have been used to promote this reaction. However, all the reported methods have drawbacks, such as the long reaction time, unsatisfactory yields, difficult operations and environmental pollution caused by toxic reagents and organic solvents. Owing to the importance of α-aminophosphonates from pharmaceutical, industrial and synthetic points of view, there is a great demand for the development of more convenient, practical and efficient method for their synthesis.

In continuation of our work on the synthesis of various biologically important compounds, we report here a highly efficient procedure for the preparation of α-aminophosphonate and its derivatives via one-pot three component Kabachnik–Fields reaction using non-ionic surfactant catalyst Triton X-100 (5 mol%) in aqueous media. Even though Lewis and Bronsted acid surfactant catalyzed reactions are reported for them, there are very few reports involving non-ionic surfactants as catalyst (Bhattacharya et al., 2003). The non-ionic surfactant Triton X-100 (TR) is one of the most commonly used detergents in biochemistry as solubilizer with a wide range of applications to biological systems (Jones, 1999). Solubilization of lipid membranes triggered by Triton X-100 is a well-described phenomenon. It is also used as an emulsifier, and complexing agent in both aqueous and non-aqueous media.

In this communication, we report three component condensation of piperanal, amine/substituted amines and diethylphosphite/dimethylphosphite in water in the presence of Triton X-100 (5 mol%). This reaction led to the formation of diethyl/dimethyl benzo[*d*][1,3]dioxol-5-yl (phenylamino)methylphosphonate derivatives in good yields (Scheme 1).

2. Experimental

2.1. General

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 683 spectrophotometer using KBr optics. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker avance 500 MHz NMR spectrometer operating at 500 MHz for ^{1}H NMR, 125 MHz for ^{13}C and 202 MHz for ^{31}P NMR. NMR data recorded in $CDCl_3$ were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectra were recorded on a JEOL GCMATE II GC–MS spectrometer at SAIF, IIT, Chennai. Elemental analyses were performed using a Perkin–Elmer 2400 instrument at the Central Drug Research Institute (CDRI), Lucknow, India. All chemicals were purchased from Sigma–Aldrich and were used with out further purification. Double distilled water was used as solvent.

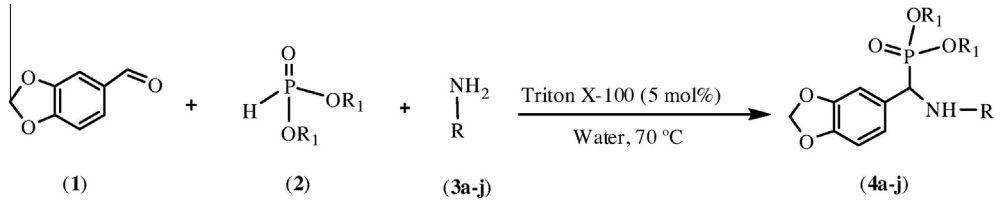
2.2. Chemistry

2.2.1. General procedure for the synthesis of diethyl/dimethyl benzo[d][1,3]dioxol-5-yl(phenylamino) methylphosphonate derivatives (**4a–j**)

In a typical experiment piperanal (1.0 mmol), the respective aniline (1.0 mmol) and the respective phosphite (1.0 mmol) were taken in a mixture of Triton X-100 (5 mol%) and water (2 mL) in a round bottomed flask. The resulting mixture was vigorously stirred at 70 °C until completion of the reaction as monitored by thin-layer chromatography (TLC). After completion of reaction the mixture was extracted with ethyl acetate, the aqueous phase was back extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered. The filtrate was evaporated under reduced pressure. The resulting product was purified by column chromatography on silica gel (60–120 mesh, ethylacetate/hexane, 1:2) to afford pure products. Structures of the all the products were confirmed by analytical and spectral data.

*2.2.1.1. Diethyl benzo[d][1,3]dioxol-5-yl(phenylamino)methylphosphonate (**4a**).* Solid, yield 82%, mp 128–129 °C; IR(KBr): ν_{max} = 3230 (N–H), 1232 (P═O), 1015 (P–O–C), 750 (P–C) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–6.50 (m, 8Ar-H), 6.92 (s, 1H, NH), 5.80 (s, 2H, OCH_2O), 4.59 (d, J = 25.0 Hz, 1H, P–CH), 4.15–3.92 (m, 4H, 2 × P(O)CH_2), 1.31–1.26 (t, J = 7 Hz, 6H, 2 × P(O)CH_2CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): 148.2 (C-5), 147.2 (C-1^1), 145.2 (C-9), 129.3 (C-3), 126.5 (C-3^1 & C-5^1), 114.6 (C-2^1 & C-6^1), 126.5 (C-3^1 & C-5^1), 124.2 (C-4^1), 121.3 (C-11), 115.5 (C-10), 110.2 (C-4), 101.2 (C-7), 63.4 (d, J = 7.0 Hz, P(O)*C*H_2), 63.3 (d, J = 6.6 Hz, P(O)*C*H_2), 55.7 (d, J = 152.4 Hz, C-2), 16.4 (d, J = 5.9 Hz, P(O)CH_2*C*H_3), 16.2 (d, J = 5.5 Hz, P(O)CH_2*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.20; GC–MS m/z (%): 363 (M·, 100). Anal. Calc. for $C_{18}H_{22}NO_5P$: C,59.50; H, 6.10; N, 3.85. Found: C, 59.51; H, 6.09; N, 3.83.

*2.2.1.2. Diethylbenzo[d][1,3]dioxol-5-yl(4-chlorophenylamino) methylphosphonate (**4b**).* Solid, yield 84%, mp 115–116 °C; IR(KBr): ν_{max} = 3292 (N–H), 1234 (P═O), 1015 (P–O–C), 752 (P–C) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05–6.50 (m, 7Ar-H), 6.76 (s, 1H, NH), 5.83 (s, 2H, OCH_2O), 4.59 (d, J = 25.0 Hz, 1H, P–CH), 4.17–3.94 (m, 4H, 2 × P(O)CH_2), 1.31–1.28 (t, J = 7 Hz, 6H, 2 × P(O)CH_2CH_3); ^{13}C NMR(125 MHz, $CDCl_3$): δ = 148.0 (C-5), 145.3 (C-9), 145.2



Scheme 1 Synthesis of α-aminophosphonates catalyzed by Triton X-100.

(C-1[1]), 131.8 (C-2[1] & C-6[1]), 129.1 (C-3), 126.5 (C-3[1] & C-5[1]), 124.2 (C-4[1]), 121.3 (C-11), 115.5 (C-10), 110.2 (C-4), 101.2 (C-7), 63.4 (d, J = 7.0 Hz, P(O)*C*H_2), 63.3 (d, J = 7.0 Hz, P(O)*C*H_2), 55.8 (d, J = 152.4 Hz, C-2), 16.4 (d, J = 5.6 Hz, P(O)CH_2*C*H_3), 16.2 (d, J = 5.7 Hz, P(O)CH_2*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.35; GC–MS m/z (%): 397 (M•, 100). Anal. Calc. for $C_{18}H_{21}ClNO_5P$: C, 54.35; H, 5.32; N, 3.52. Found: C, 54.32; H, 5.30; N, 3.50.

*2.2.1.3. Diethyl benzo[d][1,3]dioxol-5-yl(4-bromophenylamino) methylphosphonate (**4c**).* Solid, yield 83%, mp 135–136 °C; IR(KBr): ν_{max} = 3296 (N–H), 1235 (P═O), 1017 (P–O–C), 751 (P–C) cm^{-1}; ^{1}H NMR(500 MHz, $CDCl_3$): δ = 7.19–6.46 (m, 7Ar-H), 6.12 (s, 1H, NH), 5.93 (s, 2H, OCH_2O), 4.59 (d, J = 24.0 Hz, 1H, P–CH), 4.16–3.94 (m, 4H, 2 × P(O)CH_2), 1.31–1.15 (t, J = 7 Hz, 6H, 2 × P(O)CH_2CH_3); ^{13}C NMR(125 MHz, $CDCl_3$): δ = 148.2 (C-1[1]), 148.0 (C-5), 147.4 (C-9), 144.7 (C-3[1] & C-5[1]), 129.2 (C-3), 123.1 (C-2[1] & C-6[1]), 121.3 (C-10), 121.2 (C-11), 115.3 (C-4), 115.0 (C-4[1]), 101.2 (C-7), 63.4 (d, J = 6.9 Hz, P(O)*C*H_2), 63.2 (d, J = 7.0 Hz, P(O)*C*H_2), 56.4 (d, J = 150.0 Hz, C-2), 16.3 (d, J = 5.7 Hz, P(O)CH_2*C*H_3), 16.2 (d, J = 5.4 Hz, P(O)CH_2*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.25; GC–MS m/z (%): 442 (M•, 100). Anal. Calc. for $C_{18}H_{21}BrNO_5P$: C, 48.89; H, 4.79; N, 3.17. Found: C, 48.85; H, 4.76; N, 3.15.

*2.2.1.4. Diethylbenzo[d][1,3]dioxol-5-yl(3-chloro-4-fluorophenylamino) methylphosphonate (**4d**).* Solid, yield 79%, mp 130–132 °C; IR(KBr): ν_{max} = 3319 (N–H), 1232 (P═O), 1023 (P–O–C), 754 (P–C)cm^{-1}; ^{1}H NMR(500 MHz, $CDCl_3$): δ = 7.20–6.95 (m, 6Ar-H), 6.56 (s, 1H, NH), 5.82 (s, 2H, OCH_2O), 4.60 (d, J = 25.0 Hz, 1H, P–CH), 4.16–3.89 (m, 4H, 2 × P(O)CH_2), 1.31–1.19 (t, J = 7 Hz, 6H, 2 × P(O)CH_2CH_3); ^{13}C NMR(125 MHz, $CDCl_3$): 147.5 (C-5), 145.6 (C-1[1]), 144.9 (C-9), 128.3 (C-3), 124.2 (C-4[1]), 120.4 (C-11), 119.8 (C-3[1]), 116.0 (C-6[1]), 114.9 (C-2[1]), 113.9 (C-5[1]), 112.8 (C-10), 112.6 (C-4), 101.5 (C-7), 63.2 (d, J = 6.8 Hz, P(O)*C*H_2), 63.1 (d, J = 7.0 Hz, P(O)*C*H_2), 60.5 (d, J = 151.2 Hz, C-2), 16.4 (d, J = 5.5 Hz, P(O)CH_2*C*H_3), 16.2 (d, J = 5.7 Hz, P(O)CH_2*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.32; GC–MS m/z (%): 415 (M•, 100). Anal. Calc. for $C_{18}H_{21}ClFNO_5P$: C, 52.00; H, 4.85; N, 3.37. Found: C, 51.09; H, 4.84; N, 3.35.

*2.2.1.5. Diethyl benzo[d][1,3]dioxol-5-yl(4-methoxyphenylamino)methylphosphonate (**4e**).* Solid, yield 86%, mp 126–127 °C; IR(KBr): ν_{max} = 3320 (N–H), 1238 (P═O), 1017 (P–O–C), 753 (P–C) cm^{-1}; ^{1}H NMR(500 MHz, CDCl3): δ = 7.20–6.58 (m, 7Ar-H), 6.64 (s, 1H, NH), 5.80 (s, 2H, OCH_2O), 4.58 (d, J = 25.2 Hz, 1H, P–CH), 4.15–3.84 (m, 4H, 2 × P(O)CH_2), 2.54 (s, 3H, OCH_3), 1.30–1.26 (t, J = 7 Hz, 6H, 2 × P(O)CH_2CH_3); ^{13}C NMR(125 MHz, $CDCl_3$): 150.6 (C-4[1]), 148.9 (C-5), 146.8 (C-9), 140.1 (C-1[1]),129.7 (C-3), 120.5 (C-11), 117.2 (C-3[1] & C-5[1]), 115.6 (C-2[1] & C-6[1]), 112.8 (C-10), 112.5 (C-4), 101.4 (C-7), 64.5 (d, J = 7.0 Hz, P(O)*C*H_2), 64.3 (d, J = 7.0 Hz, P(O)*C*H_2), 60.5 (d, J = 152.0 Hz, C-2), 56.8 (Ar-OCH_3), 16.3 (d, J = 5.5 Hz, P(O)CH_2*C*H_3), 16.2 (d, J = 5.4 Hz, P(O)CH_2*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.30; GC–MS m/z (%): 381 (M•, 100). Anal. Calc. for $C_{19}H_{24}NO_6P$: C, 58.01; H, 6.15; N, 3.56. Found: C, 58.00; H, 6.13; N, 3.5.

*2.2.1.6. Dimethyl benzo[d][1,3]dioxol-5-yl(phenylamino)methylphosphonate (**4f**).* Solid, yield 82%, mp 142–143 °C; IR(KBr): ν_{max} = 3290 (N–H), 1236 (P═O), 1067 (P–O–C), 750 (P–C) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.19–6.50 (m, 8Ar-H), 6.54 (s, 1H, NH), 5.82 (s, 2H, OCH_2O), 4.59 (d, J = 24.9 Hz, 1H, P–CH), 4.15 (d, J = 9.2 Hz, 3H, P(O)CH_3), 4.12 (d, J = 9.0 Hz, 3H, P(O)CH_3); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.5 (C-5), 146.9 (C-1[1]), 145.1 (C-9), 129.2 (C-3), 128.4 (C-3[1] & C-5[1]), 120.5 (C-4[1]), 120.0 (C-11), 112.8 (C-10), 112.4 (C-2[1] & C-6[1]), 112.2 (C-4), 102.3 (C-7), 64.3 (d, J = 152.4 Hz,C-2), 53.3 (d, J = 5.6 Hz, P(O)*C*H_3), 53.2 (d, J = 5.5 Hz, P(O)*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.24; GC–MS m/z (%): 335 (M•, 100). Anal. Calc. for $C_{16}H_{18}NO_5P$: C, 57.31; H, 5.41; N, 4.18. Found: C, 57.29; H, 5.40; N, 4.17.

*2.2.1.7. Dimethyl benzo[d][1,3]dioxol-5-yl(4-chlorophenylamino)methylphosphonate (**4g**).* Solid, yield 78%, mp 126–127 °C; IR(KBR): ν_{max} = 3340 (N–H), 1234 (P═O), 1020 (P–O–C), 754 (P–C) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.61–6.40 (m, 7Ar-H), 6.42 (s, 1H, NH), 5.79 (s, 2H, OCH_2O), 4.54 (d, J = 24.8 Hz, 1H, P–CH), 4.05 (d, J = 9.8 Hz, 3H, P(O)CH_3), 3.08 (d, J = 9.2 Hz, 3H, P(O)CH_3), ^{13}C NMR(125 MHz, $CDCl_3$): δ = 148.2 (C-5), 145.9 (C-1[1]), 145.5 (C-9), 128.5 (C-3), 128.9 (C-3[1] & C-5[1]), 124.5 (C-4[1]), 120.5 (C-11), 112.6 (C-10), 115.5 (C-2[1] & C-6[1]), 110.2 (C-4), 101.2 (C-7), 65.5 (d, J = 152.2 Hz, C-2), 52.4 (d, J = 6.8 Hz, P(O)*C*H_3), 52.3 (d, J = 6.2 Hz, P(O)*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.22; GC–MS m/z (%): 369 (M•, 100). Anal. Calc. for $C_{16}H_{17}ClNO_5P$: C, 51.98; H, 4.63; N, 3.79. Found: C, 51.96; H, 4.61; N, 3.78.

*2.2.1.8. Dimethyl benzo[d][1,3]dioxol-5-yl(4-bromophenylamino)methylphosphonate (**4h**).* Solid, yield 76%, mp 132–133 °C; IR(KBr): ν_{max} = 3294 (N–H), 1236 (P═O), 1024 (P–O–C), 758 (P–C) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57–6.39 (m, 7Ar-H), 5.80 (s, 2H, OCH_2O), 4.50 (d, J = 25.8 Hz, 1H, P–CH), 4.20 (d, J = 10.2 Hz, 3H, P(O)CH_3), 4.10 (d, J = 9.8 Hz, 3H, P(O)CH_3); ^{13}C NMR(125 MHz, $CDCl_3$): δ = 148.4 (C-5), 145.8 (C-9), 145.5 (C-1[1]), 132.2 (C-3[1] & C-5[1]), 128.4 (C-3), 120.5 (C-11), 114.9 (C-4[1]), 113.8 (C-2[1] & C-6[1]), 113.0 (C-4), 111.9 (C-10), 102.4 (C-7), 65.3 (d, J = 150.8 Hz, C-2), 53.4 (d, J = 7.2 Hz, P(O)*C*H_3), 53.2 (d, J = 6.8 Hz, P(O)*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.29; GC–MS m/z (%): 414 (M^+, 100). Anal. Calc. for $C_{16}H_{17}BrNO_5P$: C, 46.40; H, 4.14; N, 3.38. Found: C, 46.39; H, 4.12; N, 3.36.

*2.2.1.9. Dimethylbenzo[d][1,3]dioxol-5-yl(3-chloro-4-fluorophenylamino) methylphosphonate (**4i**).* Solid, yield 76%, mp 122–123 °C; IR(KBr): ν_{max} = 3324 (N–H), 1240 (P═O), 1020 (P–O–C), 758 (P–C) cm^{-1}; ^{1}H NMR(500 MHz, $CDCl_3$): δ = 7.81–6.20 (m, 6Ar-H), 6.18 (s, 1H, NH), 5.84 (s, 2H, OCH_2O), 4.58 (d, J = 25.5 Hz, 1H, P–CH), 4.15 (d, J = 9.2 Hz, 3H, P(O)CH_3), 4.10 (d, J = 9.0 Hz, 3H, P(O)CH_3); ^{13}C NMR(125 MHz, $CDCl_3$): δ = 148.3 (C-5), 145.9 (C-9), 145.2 (C-4[1]), 143.9 (C-1[1]), 130.1 (C-3), 121.2 (C-3[1]), 120.3 (C-11), 115.0 (C-6[1]), 114.5 (C-2[1]), 113.9 (C-5[1]), 112.5 (C-10), 111.9 (C-4), 101.3 (C-7), 68.2 (d, J = 152.0 Hz, C-2), 54.3 (d, J = 6.0 Hz, P(O)*C*H_3), 54.2 (d, J = 6.4 Hz, P(O)*C*H_3); ^{31}P NMR($CDCl_3$): δ = 22.19; GC–MS m/z (%):

Table 1 Antibacterial activity of compounds (**4a–j**).

Product	Zone of inhibition (%)					
	Escherichia coli			*Staphylococcus aureus*		
	100 ppm	50 ppm	25 ppm	100 ppm	50 ppm	25 ppm
4a	08	05	02	09	05	01
4b	07	05	03	07	04	02
4c	08	04	–	08	04	–
4d	05	03	01	07	04	–
4e	07	04	–	06	05	–
4f	08	05	03	10	06	02
4g	08	04	–	09	04	01
4h	07	05	–	08	05	02
4i	06	03	–	09	05	–
4j	05	02	–	07	03	–
Penicillin[a]	12	07	–	11	08	–

[a] Reference compound.

387 (M•, 100). Anal. Calc. for $C_{16}H_{16}ClFNO_5P$: C, 49.56; H, 4.16; N, 3.61. Found: C, 49.54; H, 4.14; N, 3.60.

*2.2.1.10. Dimethylbenzo[d][1,3]dioxol-5-yl(4-methoxyphenylamino)methylphosphonate (**4j**).* Solid, yield 80%, mp 138–139 °C; IR(KBr): ν_{max} = 3321 (N–H), 1248 (P═O), 1028 (P–O–C), 753 (P–C)cm^{-1}; ^1H NMR(500 MHz, $CDCl_3$): δ = 7.56–6.38 (m, 7Ar-H), 6.14 (s, 1H, NH), 5.80 (s, 2H, OCH_2O), 4.60 (d, J = 25.5 Hz, 1H, P–CH), 4.06 (d, J = 10.3 Hz, 3H, $P(O)CH_3$), 3.93 (d, J = 9.1 Hz, 3H, $P(O)CH_3$), 2.46 (s, 1H, OCH_3); ^{13}C NMR(125 MHz, $CDCl_3$): δ = 150.5 (C-4[1]), 148.2 (C-5), 145.9 (C-9), 135.5 (C-1[1]), 128.5 (C-3), 120.1 (C-11), 115.0 (C-3[1] & C-5[1]), 114.9 (C-2[1] & C-6[1]), 112.9 (C-4), 112.0 (C-10), 101.8 (C-7), 68.5 (d, J = 150.8 Hz, C-2), 55.4 (Ar-OCH_3) 53.4 (d, J = 6.2 Hz, P(O)CH_3), 53.2 (d, J = 6.0 Hz, P(O)CH_3); ^{31}P NMR($CDCl_3$): δ = 22.28; GC–MS m/z (%): 365 (M•, 100). Anal. Calc. for $C_{17}H_{20}NO_6P$: C, 55.89; H, 5.52; N, 3.83. Found: C, 55.86; H, 5.50; N, 3.81.

2.3. Biological evaluation

2.3.1. Antibacterial activity assay

Antibacterial activity of (**4a–j**) was assayed against the growth of *Staphylococcus aureus* and *Escherichia coli* following the disc-diffusion assay at three concentrations (100, 50, 25 ppm). The inhibition zone was measured from the border of the disc to the edge of the clear zone. The majority of the compounds exhibited moderate to good activity against both the bacteria (Table 1).

2.3.2. Antifungal activity assay

The compounds (**4a–j**) were screened for their antifungal activity against *Aspergillus niger* and *Helminthosporium oryzae* species along with the standard fungicide Griseofulvin by the disc diffusion method (Benson et al., 1990) at three different concentrations (100, 50, 25 ppm). The majority of the compounds exhibited moderate activity against both the bacteria (Table 2).

3. Results and discussion

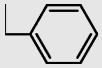
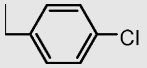
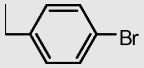
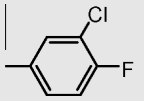
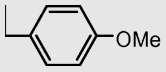
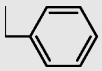
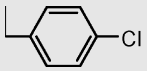
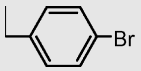
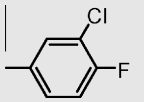
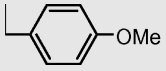
In our study, the simplest and most typical starting materials were used in different combinations. In most of the cases, piperanal (**1**), primary amines (**3a–j**) such as aniline and its derivatives, *para*-chloroaniline, *para*-bromoaniline, 4-floro3-choroaniline, *para*-methoxyaniline and diethyl phosphite/ dimethyl phosphite (**2**) were used.

Table 2 Antifungal activity of compounds (**4a–j**).

Product	Zone of inhibition (%)					
	Aspergillus niger			*Helmenthosphorium oryzae*		
	100 ppm	50 ppm	25 ppm	100 ppm	50 ppm	25 ppm
4a	07	05	03	09	06	03
4b	08	05	03	08	05	02
4c	08	06	02	09	05	03
4d	05	03	01	07	04	–
4e	09	04	–	06	04	–
4f	08	06	03	09	06	02
4g	08	04	–	09	04	01
4h	08	04	–	08	04	–
4i	09	05	02	09	05	01
4j	07	03	–	08	04	01
Griseofulvin[a]	11	08	06	13	08	06

[a] Reference compound.

Table 3 Triton X-100 catalyzed one-pot synthesis of α-aminophosphonates.

Product	R_1	R	Time (min)	Yield (%)[a]
4a	C_2H_5		50	82
4b	C_2H_5		40	84
4c	C_2H_5		40	83
4d	C_2H_5		50	79
4e	C_2H_5		30	86
4f	CH_3		60	82
4g	CH_3		40	78
4h	CH_3		50	76
4i	CH_3		50	76
4j	CH_3		40	80

[a] Isolated yields.

Table 4 Effect of catalyst concentration on Scheme 1.

Entry	Catalyst (mol%)	Yield (%)
1	5	86
2	10	50
3	15	40
4	20	30

The three components (**1, 2, 3a–j**) were measured in equimolar quantities and the mixtures were allowed to react vigorously in aqueous media at 70 °C for 30–60 min with stirring to afford the corresponding α-aminophosphonates. Several structurally diverse aniline/substituted anilines, diethyl phosphite and dimethyl phosphite were subjected to this novel procedure to give the corresponding α-amino phosphonates in high to excellent yields. The results are summarized in Table 3.

The presence of electron donating groups on aniline gave the corresponding products in good yields. The wide applicability of the present method is evident from the fact that it is tolerant toward various functional groups including alkoxy and halo compounds. Further we studied the role of catalyst concentration on the model reaction **4e**. We have varied the catalyst concentration to 5, 10, 15, 20 mol%. The result revealed that, when the reaction was carried out in the presence of 10, 15, 20 mol% of catalyst it gave lower yield of product even after prolonged reaction time. At the same time when the concentration of catalyst was 5 mol% we got excellent yields of product in a short span. Even after increasing the catalyst concentration above 5 mol% the yields of the products did not improve. So it is established that the 5 mol% of catalyst is sufficient to catalyze and bring it to completion. The results are listed in Table 4.

All the products were purified by column chromatography and were characterized by elemental analysis, ^{1}H NMR, IR, ^{13}C NMR, ^{31}P NMR and mass spectral data.

4. Conclusion

In conclusion, Triton X-100 was found to be an efficient catalyst for the one-pot reaction of aldehyde, amines and diethylphosphite/dimethylphosphite to afford the corresponding α-aminophosphonates in moderate to good yields. The main advantages of the present synthetic protocol are mild reaction, solvent-free conditions, ecofriendly catalyst and easy work-up procedure. The derivatives are characterized by physicochemical and spectral analysis such as ^{1}H NMR, IR, ^{13}C NMR, ^{31}P NMR and mass spectral data. The spectral data obtained were in full agreement with the proposed structures. The majority of the compounds exhibited moderate activity against both bacteria.

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