

Cellulose-SO₃H catalyzed synthesis of bis(α -aminophosphonates) and their antioxidant activity

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Abstract: A simple and efficient synthesis of bis(α -aminophosphonates) has been developed by the reaction of aromatic aldehydes, 1,4-phenylenediamine and diethylphosphite in the presence of cellulose-SO₃H as catalyst under neat conditions at room temperature for 10-30 minutes. The synthesized compounds were screened for their antioxidant activity against DPPH, NO and H₂O₂ scavenging methods. All the compounds exhibited good to moderate activity.

Keywords: Bis(α -aminophosphonates); 1,4-phenylenediamine; diethylphosphite; cellulose-SO₃H; antioxidant activity. © 2017 ACG Publications. All rights reserved.

1. Introduction

Phosphorus-carbon bond formation reactions have attracted serious attention of chemistry researchers because of their application in the synthesis of α -functionalized phosphonic acids and their derivatives.¹⁻⁷ Since they are valuable intermediates for the preparation of bioactive compounds having good therapeutic values, a number of synthetic methods and routes for α -amino phosphonates have been developed.⁸⁻⁹ Kabachnik-Fields and Pudovik reactions are the most general, straightforward and widely applied methods for the construction of C-P bonds.¹⁰ Amongst them, acid/ base catalyzed nucleophilic addition reactions of phosphites to imines are well reported as it is the most convenient route. Specifically, Lewis acids such as BF₃.OEt₂, ZnCl₂ and SnCl₄ have been successfully employed in this transformation.¹¹⁻¹³ However, all these reactions were not succeed with one-pot single step reaction methodology as they are reversible due to the water liberated from the imine formation reaction will decomposes the product formed and hence deactivates the Lewis acid.¹⁴

This drawback has been limited up to certain extent by some of the recent synthetic methods for the synthesis of α -aminophosphonates by the addition of dialkyl/ diarylphosphites to schiff's bases,¹⁵ *N*- α -naphthylimines prepared from terephthalic and isophthalic aldehydes to yield corresponding *N*- α -naphthylamino-phosphonates in good yields.¹⁶ Lewkowski *et al.*,¹⁷ synthesized bis(α -aminophosphonates) *via* the phosphite addition to *N*-(*o*-substituted phenyl) terephthalic schiff's bases. Bis(α -aminophosphonates) were synthesized by Rezaei *et al.*¹⁸ using aldehydes, diethyl phosphite and diamines in the presence of FeCl₃ catalyst in moderate yields. Lewkowski *et al.*,¹⁹ synthesized bis(α -aminophosphonates) *via* the phosphite addition to imine bearing (*R,R*) 1,2 diamino cyclohexane moiety whose reactions were diastereoselective.

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In recent, the significant focus on the green and sustainable resources is motivating the scientists and technologists. In such hierarchy, the two biopolymers such as cellulose and starch are using as most common solid supporting catalysts. In latest, the derivatives of cellulose and starch are receiving the significant attention and where their catalytic applications are under exploration.²⁰⁻²² Due to significant potential biological activity of α -aminophosphonates the emphasis was focused on the development of an efficient and at the same time bio-friendly sustainable synthesis for them. In this context the search for efficient and green catalyst arose. Efforts in this direction led to the discovery of Cellulose-SO₃H that was already proved as promising solid acid catalyst for the synthesis of some important class of organic compounds,²³ like α -amino nitriles, quinolines and imidazoazines. In continuation of our efforts in accomplishing new α -aminophosphonates from the simple synthetic procedures, we are herewith describing an efficient method for the synthesis of bis(α -aminophosphonates) *via* an one-pot, three-component neat reaction of aromatic aldehydes, 1,4-phenylenediamine and diethyl phosphite in the presence of cellulose-SO₃H catalyst.

2. Experimental

All the chemicals and reagents used in the study were obtained from Sigma-Aldrich & Alfa Aesar. Melting points of the synthesized compounds were recorded on Guna Digital Melting Point apparatus and IR spectral characterization was performed on Bruker Alpha-EcoATR-FTIR interferometer with single reflection sampling module equipped with ZnSe crystal. Similarly the ¹H, ¹³C & ³¹P NMR spectral analysis was performed on Bruker AMX 500 MHz NMR spectrometer and spectral patterns were recorded at an operating frequency of 400 MHz for ¹H, 100 MHz for ¹³C and 160 MHz for ³¹P NMR in CDCl₃ solvent and referenced to TMS (¹H and ¹³C) and 85% H₃PO₄ (³¹P) and the corresponding chemical shifts were reported in δ scale. Mass spectral studies were performed on a Jeol SX 102 DA/600 mass spectrometer and elemental analysis was performed on a Thermo Finnigan Instrument.

1.1. General procedure for the preparation of bis-aminophosphonates (4a-j)

2 mmol of Benzaldehyde (**1a**), 1 mmol of 1,4-phenylenediamine (**2**) and 2.5 mmol of diethylphosphite (**3**) were taken in a round bottom flask along with 5mol% of cellulose-SO₃H catalyst and stirred the reaction mixture at room temperature under solvent-free conditions for a period of 25 min. Then the progress of the reaction was monitored by TLC analysis by using 3:1 hexane and ethyl acetate solution. After completion of the reaction crude tetraethyl ((1,4-phenylenebis(azanediyl))bis(phenylmethylene))bis (phosphonate) (**4a**) was purified by column chromatography by using 9:1 hexane and ethyl acetate as eluent and collected the desired product **4a**. The same procedure was followed for the synthesis of remaining compounds **4b-j** and all of them were characterized by spectral (IR, ¹H, ¹³C, ³¹P NMR, Mass) and elemental (C, H, N) analysis.

2.1.1. Tetraethyl ((1,4-phenylenebis(azanediyl))bis(phenylmethylene))bis(phosphonate) (4a).²⁴⁻³⁴ Yield: 83%, m.p.: 118-120°C; IR (ZnSe) cm⁻¹: ν 3310 (-NH), 3047 (C-H_{aromatic}), 2854 (C-H_{aliphatic}), 1234 (P=O), 1020 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.44-6.56 (14H, m, Ar-H), 5.08 (2H, d, J = 24 Hz, P-CH), 4.02-3.97 (4H, m, 2 \times -CH₂), 3.81-3.73 (2H, m, -CH₂CH₃), 3.70-3.61 (2H, m, -CH₂CH₃), 1.14 (6H, t, J = 6Hz, 2 \times -CH₃), 0.89 (6H, t, J = 6Hz, 2 \times -CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 137.6, 136.6, 130.4, 128.4, 127.2, 123.0, 63.4, 63.3, 56.2, 16.2, 16.1; ³¹P NMR (CDCl₃, 160 MHz): δ 20.60; LC-MS: m/z (%): 560 (M⁺). Anal. Calcd for C₂₈H₃₈N₂O₆P₂: % C, 59.99; H, 6.83; N, 5.00. Found: C, 59.91; H, 6.77; N, 4.96.

2.1.2. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-bromophenyl) methylene)) bis(phosphonate) (4b).³³⁻³⁴ Yield: 90%, m.p.: 124-126°C; IR (ZnSe) cm⁻¹: ν 3302 (-NH), 3067 (C-H_{aromatic}), 2904 (C-H_{aliphatic}), 1231 (P=O), 1025 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.43-6.54 (12H, m, Ar-H), 5.04 (2H, d, J = 24 Hz, P-CH), 3.98-3.93 (4H, m, 2 \times -CH₂), 3.80-3.73 (2H, m, -CH₂CH₃), 3.69-3.60 (2H, m, -CH₂CH₃), 1.01 (6H, t, J = 6 Hz, 2 \times -CH₃), 0.85 (6H, t, J = 6Hz, 2 \times -CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 138.4, 137.0, 129.3, 128.9, 128.6, 128.1, 65.4, 65.1, 57.5, 18.8, 18.2; ³¹P NMR (CDCl₃,

160 MHz): δ 21.65; LC-MS: m/z (%): 716 (M^{++}); Anal. Calcd for $C_{28}H_{36}Br_2N_2O_6P_2$: C, 46.82; H, 5.05; N, 3.90. Found: C, 46.79; H, 5.02; N, 3.88.

2.1.3. *Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-hydroxyphenyl) methylene)) bis(phosphonate) (4c)*:^{33,36-38} Yield: 82%, m.p.: 120-123°C; IR (ZnSe) cm^{-1} : ν 3298 (-NH), 3077 (C-H_{aromatic}), 2904 (C-H_{aliphatic}), 1218 (P=O), 1025 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.39-6.75 (12H, s, Ar-H), 5.10 (2H, d, J = 24Hz, P-CH), 4.02-3.96 (4H, m, 2 \times -CH₂), 3.82-3.74 (2H, m, -CH₂CH₃), 3.72-3.68 (2H, m, -CH₂CH₃), 1.12 (6H, t, J = 6 Hz, 2 \times CH₃), 0.91 (6H, t, J = 6 Hz, 2 \times CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 142.2, 138.8, 138.2, 131.7, 129.5, 128.2, 62.9, 62.6, 58.3, 16.3, 16.0; ³¹P NMR (CDCl₃, 160 MHz): δ 22.21; LC-MS: m/z (%): 592 (M^{++}); Anal. Calcd for $C_{28}H_{38}N_2O_8P_2$: C, 56.75; H, 6.46; N, 4.73. Found: C, 56.70; H, 6.42; N, 4.68.

2.1.4. *Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-methoxyphenyl) methylene)) bis(phosphonate) (4d)*:³³⁻³⁵ Yield: 80%, m.p.: 125-127°C; IR (ZnSe) cm^{-1} : ν 3300 (-NH), 3076 (C-H_{aromatic}), 2905 (C-H_{aliphatic}), 1226 (P=O), 1025 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.38-6.73 (12H, m, Ar-H), 5.11 (2H, d, J = 24Hz, P-CH), 4.01 (6H, s, -OCH₃), 4.06-3.94 (4H, m, 2 \times -CH₂), 3.80-3.72 (2H, m, -CH₂CH₃), 3.70-3.65 (2H, m, -CH₂CH₃), 1.02-0.97 (6H, m, 2 \times CH₃), 0.95-0.84 (6H, m, 2 \times CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 138.6, 138.2, 137.8, 130.5, 129.3, 128.0, 63.1, 62.8, 58.2, 30.5, 18.6, 18.2; ³¹P NMR (CDCl₃, 160 MHz): δ 22.12; LC-MS: m/z (%): 620 (M^{++}); Anal. Calcd for $C_{30}H_{42}N_2O_8P_2$: C, 58.06; H, 6.82; N, 4.51. Found: C, 58.00; H, 6.79; N, 4.48.

2.1.5. *Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-nitrophenyl) methylene)) bis(phosphonate) (4e)*:³⁴ Yield: 89%, m.p.: 128-130°C; IR (ZnSe) cm^{-1} : ν 3305 (-NH), 3078 (C-H_{aromatic}), 2904 (C-H_{aliphatic}), 1238 (P=O), 1022 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.35-6.72 (12H, m, Ar-H), 5.04 (2H, d, J = 24Hz, P-CH), 4.01-3.94 (4H, m, 2 \times -CH₂), 3.82-3.74 (2H, m, -CH₂CH₃), 3.72-3.68 (2H, m, -CH₂CH₃), 1.11 (6H, t, J = 6Hz, 2 \times -CH₃), 0.92 (6H, t, J = 6Hz, 2 \times -CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 145.5, 139.5, 138.2, 137.6, 131.2, 128.1, 62.7, 62.3, 58.1, 16.2, 16.0; ³¹P NMR (CDCl₃, 160 MHz): δ 22.18; LCMS: m/z (%): 650 (M^{++}); Anal. Calcd for $C_{28}H_{36}N_4O_{10}P_2$: C, 51.69; H, 5.58; N, 8.61. Found: C, 51.60; H, 5.50; N, 8.58.

2.1.6. *Tetraethyl ((1,4-phenylenebis(azanediyl))bis(p-tolylmethylene))bis(phosphonate) (4f)*:³³⁻³⁵ Yield: 85%, m.p.: 128-130°C; IR (ZnSe) cm^{-1} : ν 3304 (-NH), 3079 (C-H_{aromatic}), 2901 (C-H_{aliphatic}), 1230 (P=O), 1023 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.34-6.76 (12H, m, Ar-H), 5.12 (2H, d, J = 24 Hz, P-CH), 2.54 (6H, s, 2 \times -CH₃), 4.10-3.92 (4H, m, 2 \times -CH₂), 3.80-3.72 (2H, m, -CH₂CH₃), 3.70-3.66 (2H, m, -CH₂CH₃), 1.01-0.98 (6H, m, 2 \times -CH₃), 0.95-0.83 (6H, m, 2 \times -CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 145.4, 144.2, 133.5, 130.3, 129.5, 127.8, 63.3, 62.4, 58.3, 30.7, 18.4, 18.5; ³¹P NMR (CDCl₃, 160 MHz): δ 22.17. LC-MS: m/z (%): 588 (M^{++}); Anal. Calcd for $C_{30}H_{42}N_2O_6P_2$: C, 61.22; H, 7.19; N, 4.76. Found: C, 61.19; H, 7.14; N, 4.70.

2.1.7. *Tetraethyl ((1,4-phenylenebis(azanediyl))bis((3,4-dimethoxyphenyl) methylene)) bis(phosphonate) (4g)*: Yield: 84%, m.p.: 122-124°C; IR (ZnSe) cm^{-1} : ν 3305 (-NH), 3075 (C-H_{aromatic}), 2907 (C-H_{aliphatic}), 1231 (P=O), 1020 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.31-6.72 (10H, m, Ar-H), 5.03 (2H, d, J = 24 Hz, P-CH), 4.03 (12H, s, 4 \times -OCH₃), 4.09-3.91 (4H, m, 2 \times -CH₂), 3.79-3.72 (2H, m, -CH₂CH₃), 3.69-3.64 (2H, m, -CH₂CH₃), 1.10 (6H, t, J = 6 Hz, 2 \times CH₃), 0.89 (6H, t, J = 6 Hz, 2 \times CH₃); ¹³C NMR (CDCl₃, 100 MHz): δ 146.3, 144.7, 134.3, 130.5, 128.8, 127.5, 122.2, 119.8, 63.4, 68.7, 62.4, 57.6, 18.4; ³¹P NMR (CDCl₃, 160 MHz): δ 21.78; LC-MS: m/z (%): 680 (M^{++}); Anal. Calcd for $C_{32}H_{46}N_2O_{10}P_2$: C, 56.47; H, 6.81; N, 4.12. Found: C, 56.40; H, 6.78; N, 4.09.

2.1.8. *Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-isopropylphenyl) methylene)) bis(phosphonate) (4h)*:³⁵ Yield: 79%, m.p.: 125-127°C; IR (ZnSe) cm^{-1} : ν 3303 (-NH), 3078 (C-H_{aromatic}), 2905 (C-H_{aliphatic}), 1232 (P=O), 1023 (P-O-C_{aliphatic}); ¹H NMR (CDCl₃, 400 MHz): δ 7.30-6.70 (12H, m, Ar-H), 5.05 (2H, d, J = 24 Hz, P-CH), 4.01-3.93 (4H, m, 2 \times -CH₂), 3.80-3.74 (2H, m, -CH₂CH₃), 3.67-3.63 (2H, m, -CH₂CH₃), 2.81-2.77 (2H, m, 2 \times -CH(CH₃)₂), 1.24 (12H, d, J = 5.3 Hz, 2 \times -CH(CH₃)₂), 1.11

(6H, t, $J = 6$ Hz, $2 \times -\text{CH}_3$), 0.90 (6H, t, $J = 6$ Hz, $2 \times -\text{CH}_3$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 145.5, 135.5, 133.2, 126.7, 125.9, 118.2, 71.3, 64.7, 34.2, 25.6, 16.8; ^{31}P NMR (CDCl_3 , 160 MHz): δ 21.72; LC-MS: m/z (%): 644 (M^+); Anal. Calcd for $\text{C}_{34}\text{H}_{50}\text{N}_2\text{O}_6\text{P}_2$: C, 63.34; H, 7.82; N, 4.35. Found: C, 63.30; H, 7.79; N, 4.30.

2.1.9. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((4-(dimethylamino)phenyl) methylene))bis(phosphonate) (4i):³²⁻³⁵ Yield: 80%, m.p.: 119-122°C; IR (ZnSe) cm^{-1} : ν 3304 (-NH), 3080 ($\text{C}-\text{H}_{\text{aromatic}}$), 2902 ($\text{C}-\text{H}_{\text{aliphatic}}$), 1230 (P=O), 1020 (P-O- $\text{C}_{\text{aliphatic}}$); ^1H NMR (CDCl_3 , 400 MHz): δ 7.46-6.79 (12H, m, Ar-H), 5.15 (2H, d, $J = 24$ Hz, P-CH), 4.10-4.01 (4H, m, $2 \times -\text{CH}_2$), 3.89-3.81 (2H, m, $-\text{CH}_2\text{CH}_3$), 3.66-3.62 (2H, m, $-\text{CH}_2\text{CH}_3$), 3.10 (12H, s, $2 \times -\text{N}(\text{CH}_3)_2$), 1.10 (6H, t, $J = 6$ Hz, $2 \times -\text{CH}_3$), 0.89 (6H, t, $J = 6$ Hz, $2 \times -\text{CH}_3$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 146.4, 136.2, 127.5, 125.9, 119.6, 118.3, 72.5, 64.9, 41.5, 17.3; ^{31}P NMR (CDCl_3 , 160 MHz): δ 22.32; LC-MS: m/z (%): 646 (M^+). Anal. Calcd. for $\text{C}_{32}\text{H}_{48}\text{N}_4\text{O}_6\text{P}_2$: C, 59.43; H, 7.48; N, 8.66. Found: C, 59.40; H, 7.43; N, 8.59.

2.1.10. Tetraethyl ((1,4-phenylenebis(azanediyl))bis((1H-indol-3-yl)methylene)) bis(phosphonate) (4j): Yield: 78%, m.p.: 117-119°C; IR (ZnSe) cm^{-1} : ν 3302 (-NH), 3076 ($\text{C}-\text{H}_{\text{aromatic}}$), 2905 ($\text{C}-\text{H}_{\text{aliphatic}}$), 1227 (P=O), 1023 (P-O- $\text{C}_{\text{aliphatic}}$); ^1H NMR (CDCl_3 , 400 MHz): δ 7.45-6.78 (14H, m, Ar-H), 8.50 (2H, d, $J = 7.5$ Hz, Ar-NH), 5.14 (2H, d, $J = 24$ Hz, P-CH), 4.10-4.02 (4H, m, $2 \times -\text{CH}_2$), 3.87-3.79 (2H, m, $-\text{CH}_2\text{CH}_3$), 1.80-1.75 (2H, m, $-\text{CH}_2\text{CH}_3$), 1.11 (6H, t, $J = 6$ Hz, $2 \times -\text{CH}_3$), 0.91 (6H, t, $J = 6$ Hz, $2 \times -\text{CH}_3$); ^{13}C NMR (CDCl_3 , 100 MHz): δ 138.5, 137.2, 129.6, 123.7, 125.5, 121.6, 119.8, 119.3, 118.9, 113.7, 111.4, 71.3, 64.5, 16.7; ^{31}P NMR (CDCl_3 , 160 MHz): δ 22.35; LC-MS: m/z (%): 638 (M^+); Anal. Calcd for $\text{C}_{32}\text{H}_{40}\text{N}_4\text{O}_6\text{P}_2$: C, 60.18; H, 6.31; N, 8.77. Found: C, 60.10; H, 6.29; N, 8.70.

In such, we are successful in employing the catalytic activity of cellulose- SO_3H for the synthesis of simple α -aminophosphonates³⁹ as well as the bis- α -aminophosphonates with good yields and simple operating procedures in comparison to the other reported methods.²⁴⁻³⁸

2.3. Antioxidant activity

2.3.1. DPPH Radical Scavenging Activity

The radical scavenging activity of bis(α -aminophosphonates) against DPPH radical was performed according to the Choi *et al* method.⁴⁰ A 85 μM of DPPH solution was added to a medium containing different bis-aminophosphonic diesters. The medium was incubated for 30 min at room temperature. Then the absorbance values were recorded at 517 nm. A control sample without title compounds was also analyzed in the same procedure and the results were expressed as percentage of radical scavenging activity (%RSA), where ascorbic acid was used as standard reference. The DPPH radical scavenging activity was calculated by using the equation given below. All the experiments were conducted in triplicate and radical scavenging activity values are calculated from the absorbance values using the following formula;

$$\text{Radical Scavenging Activity (\%)} = \frac{[(A_{\text{control}} - A_{\text{sample}})]}{(A_{\text{control}})} \times 100$$

Where, A_{control} = Absorbance of the control and A_{sample} = Absorbance of the sample

In the case of bis-aminophosphonic diesters **4a-j** (Fig. 1) derivatives, **4e** showed the highest DPPH radical scavenging activity with IC_{50} at 26.8 $\mu\text{g/mL}$ in comparison to the other compounds. The order of remaining compounds exhibiting DPPH radical scavenging activity is as listed below: **4c** (IC_{50} 27.8 $\mu\text{g/mL}$), **4f** (IC_{50} 29.4 $\mu\text{g/mL}$), **4b** (IC_{50} 29.7 $\mu\text{g/mL}$), **4a** (IC_{50} 30.8 $\mu\text{g/mL}$), **4h** (IC_{50} 31.5 $\mu\text{g/mL}$), **4g** (IC_{50} 32.2 $\mu\text{g/mL}$), **4i** (IC_{50} 34.8 $\mu\text{g/mL}$), **4d** (IC_{50} 35.6 $\mu\text{g/mL}$), **4j** (IC_{50} 45.7 $\mu\text{g/mL}$), and ascorbic acid reference (IC_{50} 30.5 $\mu\text{g/mL}$).

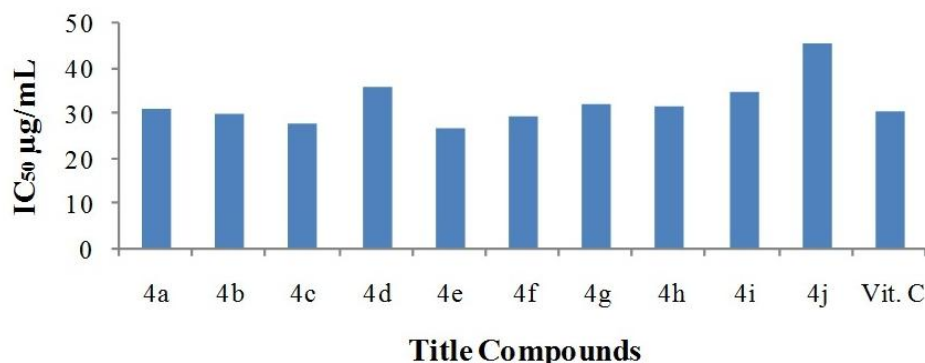


Figure 1. DPPH Radical Scavenging Activity of 4a-j

2.3.2. Nitric Oxide (NO) Scavenging Activity

The nitric oxide radical scavenging activity of bis-aminophosphonic diesters was performed according to the Shirwaiker *et al.* method.⁴¹ In this method, NO radical was generated spontaneously from the sodium nitroprusside (SNP) buffer solution. The 3mL of reaction mixture containing 2mL of 10 mM sodium nitroprusside, 0.5mL saline phosphate buffer (SPB) and 0.5mL of extract (25-100µg/mL) were incubated at 25°C for a period of 150min. After 150 min of incubation, 0.5mL of the prepared reaction mixture was mixed with 1.5mL Griess reagent [1.0% sulphanilamide + 2.5% H₃PO₄ + 0.1% *N*- (1 naphthyl) ethylenediamine dihydrochloride]. Then the absorbance was measured at 546 nm by using UV-visible spectrophotometer and the results were expressed as a percentage of nitric oxide scavenging with respect to the control sample.

In the case of bis-aminophosphonic diesters **4a-j** (Fig. 2) derivatives, **4e** showed the highest nitric oxide scavenging with IC₅₀ of 33.8 µg/mL when compared with other compounds. The remaining compounds exhibited NO scavenging activity in the following order: **4a** (IC₅₀ 34.3 µg/mL), **4b** (IC₅₀ 35.6 µg/mL), **4h** (IC₅₀ 39.8 µg/mL), **4c** (IC₅₀ 40.2 µg/mL), **4i** (IC₅₀ 41.5 µg/mL), **4d** (IC₅₀ 42.6 µg/mL), **4f** (IC₅₀ 47.7 µg/mL), **4g** (IC₅₀ 48.7 µg/mL), **4j** (IC₅₀ 50.6 µg/mL) and when compared with standard ascorbic acid reference (IC₅₀ 42.4 µg/mL).

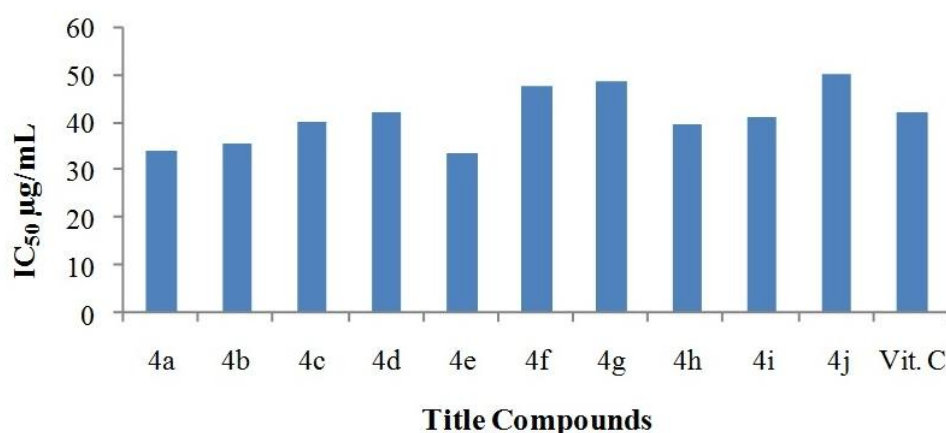


Figure 2. NO Scavenging Activity of 4a-j

2.3.3. Hydrogen Peroxide (H₂O₂) Scavenging Activity

Hydrogen peroxide scavenging activity was determined by using a Gow-Chin Yen and Hui-Yin Chen modified method.⁴² Initially a solution of hydrogen peroxide (40 mM) was prepared in

phosphate buffer (pH 7.4) and spectrophotometrically quantified at 230 nm. Then the aqueous extracts (25 - 100 µg/mL) in distilled water was added to this hydrogen peroxide solution (0.6 mL, 40 mM) and the absorbance of hydrogen peroxide at 230 nm was determined after 20 min against a blank solution. The percentages of peroxide radical scavenging capacity of title compounds were calculated.

Among all the bis-aminophosphonic diester derivatives **4a-j** (Fig 3), **4c** showed the highest H₂O₂ scavenging activity with IC₅₀ of 40.5 µg/mL when compared with other compounds. The remaining compounds exhibited H₂O₂ scavenging activity in the following order: **4e** (IC₅₀ 42.5 µg/mL), **4b** (IC₅₀ 43.5 µg/mL), **4f** (IC₅₀ 43.7 µg/mL), **4a** (IC₅₀ 44.3 µg/mL), **4d** (IC₅₀ 48.4 µg/mL), **4h** (IC₅₀ 48.9 µg/mL), **4g** (IC₅₀ 51.6 µg/mL), **4i** (IC₅₀ 55.8 µg/mL), **4j** (IC₅₀ 61.5 µg/mL), and when compared with ascorbic acid (IC₅₀ 60.2 µg/mL).

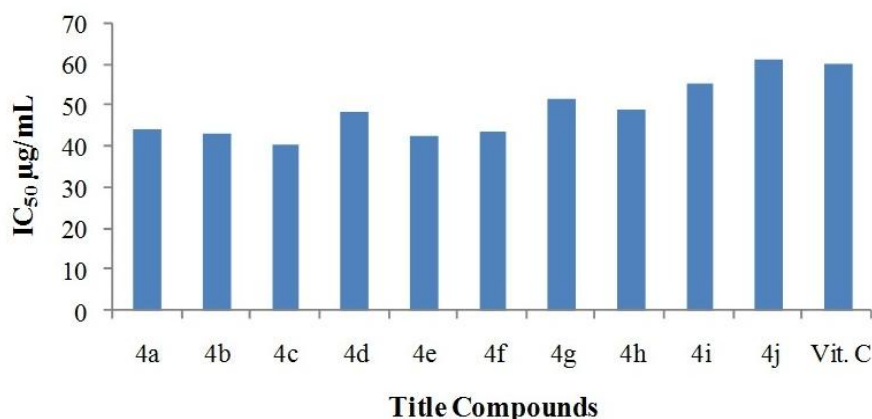
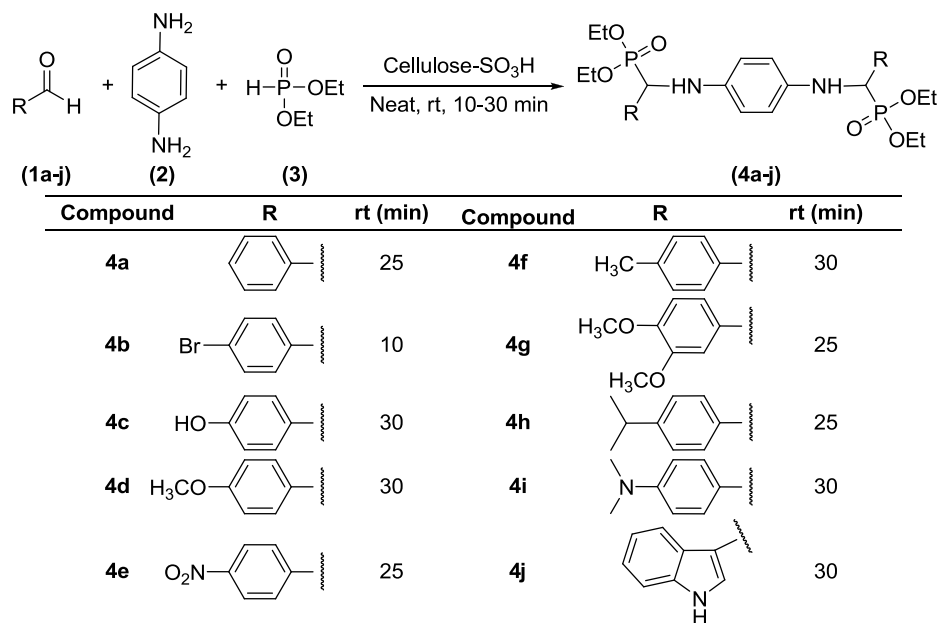


Figure 3. H₂O₂ Scavenging Activity of 4a-j

3. Results and discussion

3.1. Chemistry

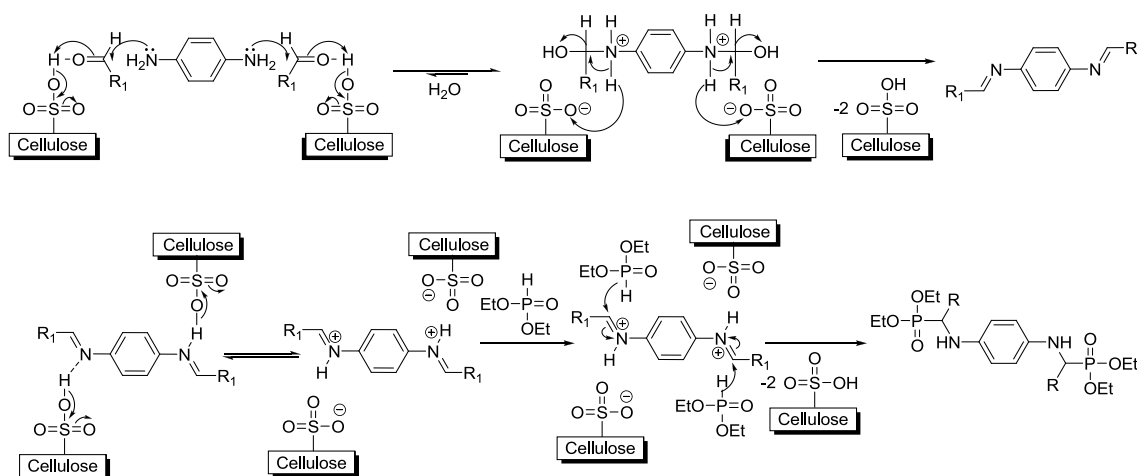
In this accomplishment, we are herewith reporting the synthesis of a series of bis(α -aminophosphonates) from the reaction of various aromatic aldehydes, 1,4-phenylenediamine and diethyl phosphite in the presence of cellulose-SO₃H catalyst in an one-pot, three-component procedure at room temperature under solvent free conditions (Scheme 1).



Scheme 1. Synthesis of bis(α -aminophosphonates)

Initially in optimizing the reaction conditions we have selected a model reaction for the synthesis of **4b** from 4-bromo benzaldehyde (**1b**), 1,4-phenylenediamine (**2**), and diethylphosphite (**3**). Initially the model reaction has been performed in different solvents such as methanol, toluene, tetrahydrofuran, dioxane, chloroform, dichloromethane, diethyl ether and acrylonitrile in the presence of cellulose-SO₃H at room temperature and obtained the compound **4b** in low yields. Use of higher catalyst concentrations and elevated temperatures has not given any significant improvement in the reaction yields. Remarkably the solvent free room temperature reaction has given 90% yield of **4b** with 5mol% of cellulose-SO₃H catalyst in 10 min and adopted these optimized conditions as valid. The reaction progress was monitored by TLC analysis by using hexane and ethyl acetate (3:1) as eluent. After successful completion of the reaction, the obtained crude product was purified by silica gel column chromatography by using hexane and ethyl acetate (9:1) as eluent and collected the desired product **4b**. By following the same reaction procedure the other products of the series (**4b-j**) were synthesized.

The interaction of 1,4-phenylenediamine and an aldehyde has been accelerated by the use of cellulose-SO₃H in the due course of the reaction, at initiation itself. This interaction helps to remove the water formed during the generation of imine intermediate. Here the key role of the cellulose-SO₃H catalyst i.e., able to form the quaternary ammonium salt of cellulose sulfate and hence arresting the backward reaction to form substrates again. The formed imine will interact again with cellulose-SO₃H catalyst and generates the iminium salt of cellulose sulfate and abstracts a proton from the diethyl phosphite and enhances the nucleophilicity on the phosphorus atom and makes it to add to the electrophilic carbon atom in imine and ultimately forms the required bis(α -aminophosphonates). In overall view, the cellulose-SO₃H catalyst successfully catalyzes the two steps of the Kabachnik-Fields reaction. The advantage of the cellulose-SO₃H catalyst is it is recoverable and reusable as it just transfers a proton and chemically remains stable. This operational simplicity may finds to use this as a choice of industrial applications for the synthesis of α -aminophosphonates and their derivatives.



Scheme 2. Mechanistic pathway for the synthesis of bis(α -aminophosphonates)

3.2. Antioxidant activity

The antioxidant activity of the title compounds **4a-j** having substituted with 4-bromo, 4-hydroxy, 4-methoxy, 4-nitro, 4-methyl, 3,4dimethoxy, 4-iso-propyl, 4-di-methylamino groups and 3-indolyl moiety has been screened against DPPH, NO and Hydrogen peroxide scavenging methods. The successful screening revealed that all the synthesized compounds have shown good activity and specifically compounds **4e** (substituted with 4-nitro group) and **4c** (substituted with 4-hydroxy group) have exhibited high antioxidant activity in comparison to the other compounds of the series. This is due to the fact that the compounds **4c** & **4e** having nitro and hydroxy groups respectively on them are able to generate free radicals easily and hence easily binds with the other free radical that are

generated in the test solutions. The antioxidant activity of the compounds was referenced to the standard ascorbic acid (Vitamin C) and hence detailed their comparative results in this study.

4. Conclusion

In conclusion, Cellulose-SO₃H was found and herewith reporting that it is an efficient catalyst for the synthesis of corresponding bis(α -aminophosphonates) and affording them in good to excellent yields. All the title compounds (**4a-j**) were tested for their antioxidant activity against the three methods *viz.*, DPPH, NO and H₂O₂ radical scavenging methods. In result, it is noticed that compounds **4e** and **4c** have exhibited high antioxidant activity and remaining compounds have showed moderate activity. The main advantages of the present method are use of eco-friendly catalyst, mild reaction conditions, simple reaction work-up procedures and good product yields.

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