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A facile catalyst-free and efficient one-pot, three-component reaction (Kabachinik-Fields Reaction) for the synthesis of novel α-aminophosphonates

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ABSTRACT

*A facile and an efficient method has been developed for the synthesis of novel α-aminophosphonates **(4a-j)** by the one-pot, three-component reaction of equimolar quantities of 2-Amino-6-Nitrobenzothiazole **(1)**, dimethyl phosphite **(2)** and various aldehydes **(3a-j)** in dry toluene at reflux conditions via Kabachinik-Fields reaction in high yields (70-80%) without any catalyst. Their chemical structures were established by IR, ^{1}H, ^{13}C, ^{31}P-NMR, mass spectral studies and elemental analyses.*

Keywords: α-aminophosphonates, Kabachinik-Fields reaction, dimethyl phosphite, cataylst-free reaction.

INTRODUCTION

The α-aminophosphonate moiety is a versatile and novel pharmacaphore due to broad spectrum of biological activity exhibited by compounds bearing this structural unit. Thus, the development of new synthetic methodologies for α-aminophosphonates has attracted the attention of medical/organic chemists. α-aminophosphonates are the important class of compounds, since they are considered to be structural analogs of the corresponding α-amino acids, as well as heterocyclic phosphonates [1] and the ω-aminophosphonates [2], with several biological activities. Their applications are significant in agriculture as plant regulators, herbicides [3], pesticides and in medicine as anti-cancer agents [4], enzyme inhibitors [5], peptide mimics [6], antibiotics and pharmacological agents [7]. A great variety of synthetic methods have been developed for the synthesis of α-aminophosphonates. Of them, Kabachinik-Fields [8] reaction is one of the most versatile pathways for the formation of carbon-phosphorus bonds. These synthetic methods are generally carried out in the presence of various bases such as potassium fluoride on alumina [9], lithium diisopropylamine (LDA) [10], 1, 8-diazabicycloundec-7-ene (DBU) [11] magnesium oxide (MgO) [12]. A few Lewis acids such as zirconium tetrachloride ($ZrCl_4$), indium trichloride ($InCl_3$), tantalum pentachloride ($TaCl_5$), ferric chloride ($FeCl_3$) and Lanthanide-triflates were also used as catalysts.

Based on the importance of α-aminophosphonates, we herein report the synthesis of novel α-aminophosphonates using 2-Amino-6-Nitrobenzothiazole **(1)** as an amine, dimethyl phosphite **(2)**, various aldehydes (**3a-j)** without any catalyst.

MATERIALS AND METHODS

Sigma-Aldrich, Merck and Lancaster Chemicals were used as such. Solvents used for spectroscopic and other physical studies were reagent grade and were further purified by standard procedures and techniques. The IR spectra (KBr pellets) were recorded on a Perkin-Elmer FT-IR 1000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Burker ACF NMR spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) with TMS as an internal standard. ^{31}P NMR spectra were measured using 85% H_3PO_4 as external reference. Mass spectra were recorded on LCMS-2010A, SHIMADZU spectrometer. Melting points were determined in an open capillary tube on Mel-temp apparatus, Tempo instruments, India and were uncorrected.

General procedure for the synthesis of α-aminophosphonates (4a-j):
Synthesis of dimethyl {[(6-nitro-1, 3-benzothiazol-2-yl) amino](3-nitrophenyl)methyl}phosphonate (4a):
To a stirred solution of 2-Amino-6-Nitrobenzothiazole **(1)** (0.001 mole), 3-Nitro benzaldehyde **3a** (0.001 mole) in anhydrous toluene (20 mL) was added drop wise and stirring continued at room temperature (RT) for 1 hour. Then dimethyl phosphite (0.001 mole) in dry toluene (20 mL) was added drop wise. Stirring was continued at room temperature (RT) for half-an-hour, and then the mixture was heated at gentle for 5-6 hours. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, as indicated by TLC (silica gel) using hexane and ethyl acetate (3:1) as a mobile phase, the solvent was removed in a rota-evaporator and the crude product obtained was purified by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate (3:1) as an eluent to afford the analytically pure **4a**. Similarly, the compounds **4b** to **4j** were prepared by adopting the above procedure.

Analytical data
Dimethyl {[(6-nitro-1, 3-benzothiazol-2-yl) amino](3-nitrophenyl)methyl}phosphonate
4a:
Yield: 74 %, M.P:190-192 ^{o}C. FT-IR (KBr): 3314 (N-H), 1242 (P=O), 750 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.2-7.9 (m, 7H), 5.47(dd, 1H), 4.41(t, 1H), 3.35 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 155.2, 148.2, 147.4, 145.7, 133.1, 129.1, 125.4, 122.7, 120.2, 119.1. ^{31}P NMR ($CDCl_3$): δ 19.78. LC-MS (*m/z*): 439 $(M+H)^{+}$. *Anal*. Calcd for $C_{16}H_{15}N_4O_7PS$: C, 43.84; H, 3.45; N, 12.78. Found: C, 43.96; H, 3.38; N, 12.69.

Dimethyl {(3-cyanophenyl)[(6-nitro-1,3-benzothiazol-2-yl)amino]methyl}phosphonate
4b:
Yield: 71 %, M.P:171-173 ^{o}C. FT-IR (KBr): 3446 (N-H), 1213 (P=O), 752 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.5-8.3 (m, 7H), 5.23 (dd, 1H), 4.52(t, 1H), 3.40 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 154.2, 146.2, 145.4, 144.7, 132.1, 128.1, 124.4, 121.7, 119.2, 118.1. ^{31}P NMR ($CDCl_3$): δ 20.86. LC-MS (*m/z*): 419 $(M+H)^{+}$. *Anal*. Calcd for $C_{17}H_{15}N_4O_5PS$: C, 48.80; H, 3.61; N, 13.39. Found: C, 48.67; H, 3.68; N, 13.51.

Dimethyl {[(6-nitro-1,3-benzothiazol-2-yl)amino](4-nitrophenyl)methyl}phosphonate
4c:
Yield: 79 %, M.P:183-185^{o}C. FT-IR (KBr): 3319 (N-H), 1235 (P=O), 743 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.4-8.3 (m, 7H), 5.72 (dd, 1H), 4.51(t, 1H), 3.20 (s, 1H). ^{31}P NMR ($CDCl_3$): δ 26.86.

Dimethyl {(3-methoxyphenyl) [(6-nitro-1,3-benzothiazol-2-yl)amino]methyl}phosphonate
4d:
Yield: 75 %, M.P:190-192 ^{o}C. FT-IR (KBr): 3317 (N-H), 1233 (P=O), 734 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.6-8.3 (m, 7H), 5.57(dd, 1H), 4.51(t, 1H), 3.31 (s, 1H).^{31}P NMR ($CDCl_3$): δ 23.15.

Dimethyl {[(6-nitro-1, 3-benzothiazol-2-yl) amino][3-(2,2,2- trifluoroethyl)phenyl]methyl}phosphonate
4e:
Yield: 73 %, M.P:200-202 ^{o}C. FT-IR (KBr): 3443 (N-H), 1236 (P=O), 753 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.7-8.5 (m, 7H), 5.47(dd, 1H), 5.41(t, 1H), 3.35 (s, 1H).^{31}P NMR ($CDCl_3$): δ 24.55.

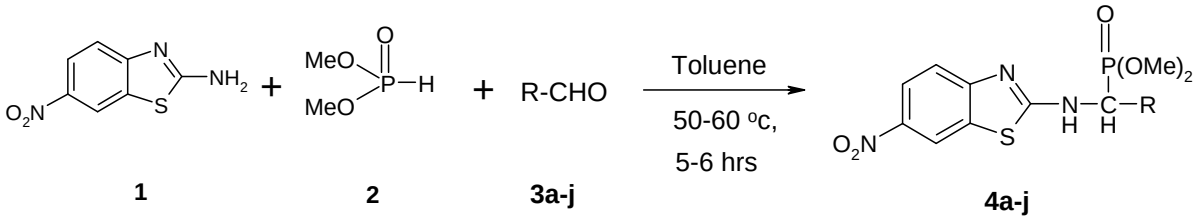
Dimethyl {(3-chlorophenyl)[(6-nitro-1,3-benzothiazol-2-yl)amino]methyl}phosphonate
4f:
Yield: 77 %, M.P:183-185 ^{o}C. FT-IR (KBr): 3444 (N-H), 1242 (P=O), 757 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.3-7.9 (m, 7H), 5.65 (dd, 1H), 4.41(t, 1H), 3.35 (s, 1H).^{31}P NMR ($CDCl_3$): δ 26.16.

Dimethyl {(4-chlorophenyl)[(6-nitro-1,3-benzothiazol-2-yl)amino]methyl}phosphonate
4g:
Yield: 74 %, M.P:188-190 ^{o}C. FT-IR (KBr): 3443 (N-H), 1222 (P=O), 754 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.5-8.4 (m, 7H), 5.47(dd, 1H), 4.56(t, 1H), 3.37 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 152.2, 149.2, 146.4, 145.7, 130.1, 127.1, 124.4, 123.7, 120.2, 118.1. ^{31}P NMR ($CDCl_3$): δ 19.23. LC-MS (*m/z*): 429 (M+2) $^{+}$. *Anal*. Calcd for $C_{16}H_{15}ClN_3O_5PS$: C, 44.92; H, 3.53; N, 9.82. Found: C, 44.84; H, 3.49; N, 9.76.

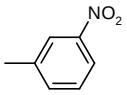
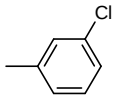
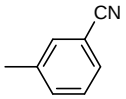
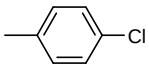
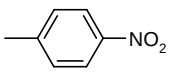
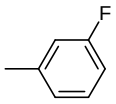
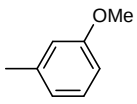
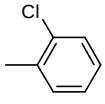
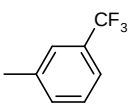
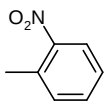
Dimethyl {(3-Fluorophenyl)[(6-nitro-1,3-benzothiazol-2-yl)amino]methyl}phosphonate
4h:
Yield: 72 %, M.P:173-175 ^{o}C. FT-IR (KBr): 3445 (N-H), 1232 (P=O), 761 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.4-7.9 (m, 7H), 5.67(dd, 1H), 4.51(t, 1H), 3.34 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 151.2, 147.2, 146.4, 140.7, 133.1, 127.1, 123.4, 120.7, 119.2, 117.1. ^{31}P NMR ($CDCl_3$): δ 27.85. LC-MS (*m/z*): 412 (M+H) $^{+}$. *Anal*. Calcd for $C_{16}H_{15}FN_3O_5PS$: C, 46.72; H, 3.68; N, 10.22. Found: C, 46.63; H, 3.62; N, 10.18.

Dimethyl {(2-chlorophenyl)[(6-nitro-1,3-benzothiazol-2-yl)amino]methyl}phosphonate
4i:
Yield: 78 %, M.P:193-195 ^{o}C. FT-IR (KBr): 3440 (N-H), 1226 (P=O), 743 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.5-8.3 (m, 7H), 5.65(dd, 1H), 5.51(t, 1H), 3.37 (s, 1H).^{31}P NMR ($CDCl_3$): δ 21.55.

Dimethyl {[(6-nitro-1,3-benzothiazol-2-yl)amino](2-nitrophenyl)methyl}phosphonate
4j:
Yield: 71 %, M.P:200-202 ^{o}C. FT-IR (KBr): 3319 (N-H), 1221 (P=O), 758 (P-$C_{aliphatic}$).^{1}H NMR ($CDCl_3$): δ 7.6-8.2 (m, 7H), 5.71(dd, 1H), 5.41(t, 1H), 3.35 (s, 1H).^{31}P NMR ($CDCl_3$): δ 24.83.



1 **2** **3a-j** **4a-j**

Compound	R	Compound	R
4a		**4f**	
4b		**4g**	
4c		**4h**	
4d		**4i**	
4e		**4j**	

Scheme 1. Synthesis of of α-aminophosphonates 4a-j.

RESULTS AND DISCUSSION

α-Aminophosphonates **4a-j** were synthesized by one-pot, three-component reaction of equimolar quantities of 2-Amino-6-Nitrobenzothiazole **(1)**, dimethyl phosphite **(2)** and various aldehydes **(3a-j)** in dry toluene at reflux conditions for 5-6 hours in 76-85% yields.The progress of the reaction was monitored by thin layer chromatography (TLC) analysis and the products were purified by column chromatography using hexane: ethyl acetate (3:1) as eluent. We found that the reaction proceeds smoothly without catalyst.

The structures of the title compounds **4a-j** were established by their spectroscopical data. All the compounds **4a-j** exhibited infrared absorption bands for P=O, P-C $_{(aliphatic)}$ and N-H in the regions 1249-1202, 769-745 and 3446–3343 cm^{-1} respectively [13]. Chemical shifts for aromatic protons of the title compounds **4a-j** appeared as a complex multiplet in the region 6.34-8.44 ppm [14]. The proton of methyne (P-C-H) chemical shift appeared as a doublet of doublet [14] at δ 5.20-5.85 and 5.67-5.82 due to its coupling with phosphorus and the neighbouring N-H proton. The N-H proton exhibited a triplet [14] at δ 4.30-5.44 indicating its coupling with neighbouring proton and phosphorus. The ^{13}C NMR spectral data of **4a-n** showed characteristic chemical shifts for aromatic carbons. The carbon chemical shifts of P-O-CH_2 and P-CH-N appeared as a doublet at δ 66.9-69.4 (d, $^{2}J_{P\text{-}O\text{-}C}$ = 6.5 Hz) and singlet at δ 56.1-62.9 respectively [15]. The ^{31}P NMR chemical shifts appeared as singlets in the region δ 18.59-35.01 for all the compounds [16] **4a-n.** The LC mass spectra of **4a-n** agreed with the proposed structures.

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CONCLUSION

A facile one-pot, three-component reaction of amines **1**, dimethyl phosphite **2**, various aldehydes **3a-j** for the synthesis of novel α-aminophosphonates **4a-j** was accomplished by Kabachinik-Fields reaction in higher yields. The highlight was that the reaction proceeds smoothly without any catalyst.

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