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An Efficient One Pot Synthesis of Carbazole-Based *α*-Aminophosphonates under Solvent- Free and Catalyst-Free Conditions

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ABSTRACT

Synthesis of carbazole-based α-aminophosphonates has been carried out using Kabachnik-Fields reactions under solvent and catalyst free conditions at room temperature with high yield and low reaction time. Compounds are characterized using IR, multinuclear NMR, mass spectral and elemental data analyses. The structure for one of these compounds has been confirmed by X-ray crystallography.

Keywords: *α*-aminophosphonates, Kabachnik-Fields reaction, one-pot synthesis, carbazole

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INTRODUCTION

The α-aminophosphonates, phosphorus analogues of α-amino acids, are found to exhibit potential antibacterial, anticancer, antimicrobial and antithrombotic activities [1]. They have also been widely used as fungicides, herbicides and insecticides [2]. A number of biological screening results reveal that α-aminophosphonates can also be possible to use as cytotoxic (anti cancer) compounds, antiviral agents, enzyme inhibitors (including HIV protease), peptide mimics and antibiotics [3]. Owing to these versatile applications, various new synthetic methodologies for α-aminophosphonates have been developed [4]. Synthesis of α-aminophosphonates using Pudovik reaction [phosphites and imines] has a number of limitations as imines are generally hygroscopic, unstable at high temperature and light, and difficult to isolate in pure form. In this aspect, a multicomponent [phosphites, carbonyls and amines] Kabachnik-Fields reaction is very efficient to synthesize α-aminophosphonates. Kabachnik-Fields reactions were carried out in the presence of several Lewis acid catalysts such as Zr(IV) [5a] compounds; $Mg(ClO_4)_2$ [5b] and lanthanide triflates in different solvents [6] including in water [6d] as well as solvent free conditions [6e]. Several organic acids (as an e.g. camphor sulphonic acids) [7] and bases [tetramethylguanidine (TMG) [8], *N*,*N*-dimethylpiperizene [9] etc. were also used as catalysts to synthesize α-aminophosphonates. Effective synthesis in a short time under solvent and catalyst free conditions make the methodology more interesting particularly keeping in view the environmentally benign and low cost processes. Even though carbazole-based α-aminophosphonates [8] are known to possess considerable microbial and antioxidant behavior, the synthesis was carried *via* Pudovik reaction using corresponding imines, solvents like toluene and TMG as a catalyst that fall under margins mentioned above. With the interest on organophosphonates [10] and carbazole being a biologically active scaffold [11], we report an efficient method for the synthesis of carbazole based *α*-aminophosphonates under solvent

and catalyst free conditions with very high yield and less reaction time *via* three component coupling reaction of 3-amino-9-ethylcarbazole, aryl aldehydes and dialkyl/ diarylphosphites. We have also characterized one of these analogues using X-ray crystallography.

MATERIALS AND METHODS

All the chemicals used were purchased from Aldrich Chemical Co and were used without further purification. Freshly distilled solvents were used. For TLC, aluminum plates coated with silica gel containing F254 indicator were used and the spots were visualized by UV light and/or by exposing to iodine. Column chromatography was performed on silica gel 100-200 mesh, using EtOAc and hexanes mixture as eluent. The ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded using 5 mm tubes on a Bruker 400 MHz NMR spectrometer [field strengths: 400, 100, and 162 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: δ = 0) and ext. 85% H_3PO_4 (^{31}P: δ = 0) respectively. All *J* values were in Hz. IR spectra were recorded on a JASCO FT/IR 5300 spectrometer. Elemental (C, H, N) analysis were done using Perkin-Elmer 240C CHN FLASH EA analyzer. Melting points were determined by using a SUPERFIT hot-stage melting point apparatus and are uncorrected.

General procedure for the synthesis of α-aminophosphonates:
To a 10 mL round-bottomed-flask 3-amino-9-ethylcarbazole (0.21gm, 1.0 mmol), aldehyde (0.117gm, 112µl, 1.1 mmol) and diphenyl phosphite (0.703gm, 0.56 mL, 3.0 mmol) were taken under nitrogen and the flask was closed with a stopper. The contents were stirred at room temperature for 5 minutes. After completion of the reaction (monitored by TLC), water (5 mL) was added to the reaction mixture and extracted with ethyl acetate (3 x 10 mL). The organic layer (EtOAc) was washed with brine (2 x 5 mL) solution, dried over anhydrous sodium sulphate, concentrated under reduced pressure and the crude product was purified by column chromatography (hexane/ EtOAc; 7:3) to afford the *α*-aminophosphonate **4a** in 98% yield. Compounds **4b-4o** were prepared in a manner similar to **4a** by using the corresponding starting materials with similar molar quantities. Unless otherwise specified all the reaction were carried out with 1.0 mmole of 3-amino-9-ethylcarbazole (**1**) and the crude products were purified by (hexane/ EtOAc; 7:3) mixture as the eluent.

Diphenyl (9-ethyl-9H-carbazol-3-ylamino) (phenyl) methylphosphonate (4a). white solid, Yield 98%, 0.522 g, Mp 150-152 ºC; IR (ν_{max}, cm^{-1}): 3382, 2978, 1487, 1265, 1184, 947. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.39 (t, ^{3}J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 4.30 (q, ^{3}J(H-H) = 7.2 Hz, 2H, C*H*$_2$), 5.28 (d, ^{2}J(P-H) = 24.4 Hz, 1H, PC*H*), 6.92-6.95 (m, 3H, Ar-*H*), 7.14-7.43 (m, 16H, Ar-*H*), 7.65 (s, 1H, Ar-*H*), 7.67 (d, ^{3}J(H-H) = 2.0 Hz, 1H, Ar-*H*), 7.96 (d, ^{3}J(H-H) = 7.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.9, 37.5, 57.6 (d, ^{1}J(P-C) = 154.0 Hz), 105.4, 108.4, 109.2, 115.2, 118.1, 120.4, 120.5 (d, *J*(P-C) = 5.0 Hz), 120.8 (d, *J*(P-C) = 4.0 Hz), 122.4, 123.5, 125.2, 125.3, 125.5, 128.3 (d, *J*(P-C) = 5.0 Hz), 128.8 (d, *J*(P-C) = 3.0 Hz), 129.7 (d, *J*(P-C) = 8.0 Hz), 129.9, 134.7, 135.2, 139.0, 139.2, 140.3, 150.3 (d, *J*(P-C) = 10.0 Hz), 150.4,(d, *J*(P-C) = 10.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 15.8. LC/MS, *m/z* 533 $[M+H]^+$; Anal. Calcd. for $C_{33}H_{29}N_3O_3P$: C,74.42; H, 5.49; N,5.26%. Found: C, 74.32; H, 5.45; N, 5.28%.

Dimethyl (9-ethyl-9H-carbazol-3-ylamino)(phenyl)methylphosphonate (4b). white solid, Yield 96%, 0.392 g, Mp 170-172 ºC; IR (ν_{max}, cm^{-1}): 3382, 2953, 1472, 1256, 1022, 795 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.37 (t, ^{3}J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 3.55 (d, ^{3}J(P-H) = 10.4 Hz, 3H , POC*H*$_3$), 3.83 (d, ^{3}J(P-H) = 10.8 Hz, 3H, POC*H*$_3$), 4.27 (q, ^{3}J(H-H) = 7.2 Hz, 2H, C*H*$_2$), 4.95 (d, ^{2}J(P-H) = 23.6 Hz, 1H, PC*H*), 6.91 (d, ^{3}J(H-H) = 7.6 Hz, 1H, Ar-*H*), 7.14 (t, ^{3}J(H-H) = 7.6 Hz, 1H, Ar-*H*), 7.20 (d, ^{3}J(H-H) = 8.4 Hz, 1H, Ar-*H*), 7.27-7.58 (m, 8H, Ar-*H*), 7.94 (d, ^{3}J(H-H) = 7.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.5, 53.8 (d, ^{2}J(P-C) = 7.0 Hz, PO*C*H$_3$), 54.0 (d, ^{2}J(P-C) = 7.0 Hz, PO*C*H$_3$), 57.3 (d, ^{1}J(P-C) = 152.0 Hz), 105.2, 108.3, 109.1, 115.1, 118.0, 120.3, 122.4, 123.4, 125.5, 128.0 (d, *J*(P-C) = 5.0 Hz), 128.1 (d, *J*(P-C) = 3.0 Hz), 128.8 (d, *J*(P-C) = 2.0 Hz), 129.0, 134.5, 135.9, 140.3. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 25.4. LC/MS, *m/z* 409 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{25}N_2O_3P$: C, 67.64; H, 6.17; N, 6.86%. Found: C, 67.60; H, 6.10; N, 6.82%.

Diethyl (9-ethyl-9H-carbazol-3-ylamino)(phenyl)methylphosphonate (4c). white solid, Yield 96%, 0.419 g, Mp 122-124 ºC; IR (ν_{max}, cm^{-1}): 3301, 2980, 1491, 1235, 1019, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.16 (t, ^{3}J(H-H) = 6.8 Hz, 3H, C*H*$_3$), 1.32 (t, ^{3}J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 1.37 (t, ^{3}J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 3.73-3.79 (m, 2H, POC*H*$_2$), 3.97-4.04 (m, 2H, POC*H*$_2$), 4.27 (q, ^{3}J(H-H) = 7.2 Hz, 2H, C*H*$_2$), 4.91 (d, ^{2}J(P-H) = 23.6 Hz, 1H, PC*H*), 6.93 (d, ^{3}J(H-H) = 8.0 Hz, 1H, Ar-*H*), 7.14 (t, ^{3}J(H-H) = 7.2 Hz, 1H, Ar-*H*), 7.20 (d, ^{3}J(H-H) = 8.4 Hz, 1H, Ar-*H*), 7.26-7.59 (m, 8H, Ar-*H*), 7.94 (d, ^{3}J(H-H) = 7.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 16.2 (d, ^{3}J(P-

C) = 6.0 Hz, $POCH_2CH_3$), 16.5 (d, ^3J(P-C) = 6.0 Hz, $POCH_2CH_3$), 37.5, 57.8 (d, ^1J(P-C) = 147.0 Hz), 63.3 (d, ^2J(P-C) = 7.0 Hz, $POCH_2$), 63.5 (d, ^2J(P-C) = 7.0 Hz, $POCH_2$), 105.5, 108.3, 109.0, 115.3, 118.0, 120.3, 122.4, 123.4, 125.4, 128.0 (d, *J*(P-C) = 3.0 Hz), 128.1 (d, *J*(P-C) = 5.0 Hz), 128 6 (d, *J*(P-C) = 3.0 Hz), 128.9, 134.6, 135.9, 140.3. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 22.8. LC/MS, *m/z* 437 $[M+H]^+$. Anal. Calcd. for $C_{25}H_{29}N_2O_3P$: C, 68.79; H, 6.70; N, 6.42%. Found: C, 68.89; H, 6.68; N, 6.45%.

Diphenyl (2-chlorophenyl)(9-ethyl-9H-carbazol-3-ylamino)methylphosphonate (4d). white solid, Yield 85%, 0.482 g, Mp 188-190 ºC; IR (ν_{max}, cm^{-1}): 3304, 2982, 1489, 1262, 1184, 938, 762. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.37 (t, ^3J(H-H) = 6.8 Hz, 3H, CH_3), 4.13 (q, ^3J(H-H) = 7.2 Hz, 2H, CH_2), 5.94 (d, ^2J(P-H) = 25.2 Hz, 1H, PC*H*), 6.92 (d, ^3J(H-H) = 7.6 Hz, 3H, Ar-*H*), 7.08-7.43 (m, 16H, Ar-*H*), 7.73 (d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*), 7.97 (d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.5, 52.7 (d, ^1J(P-C) = 158.0 Hz), 104.8, 108.3, 109.2, 114.8, 118.1, 120.0 (d, *J*(P-C) = 4.0 Hz), 120.3, 120.5 (d, *J*(P-C) = 5.0 Hz), 120.8 (d, *J*(P-C) = 4.0 Hz), 122.4, 123.5, 125.0, 125.5 (d, *J*(P-C) = 6.0 Hz), 125.8, 127.5 (d, *J*(P-C) = 3.0 Hz), 129.2 (d, *J*(P-C) = 4.0 Hz), 129.5, 129.6, 129.7, 130.0, 133.4, 134.5, 134.6, 140.3, 150.3 (d, *J*(P-C) = 10.0 Hz), 150.4 (d, *J*(P-C) = 10.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 14.9. LC/MS, *m/z* 568 $[M+H]^+$; Anal. Calcd. for $C_{33}H_{28}ClN_2O_3P$: C, 69.90; H, 4.98; N, 4.94%. Found: C, 69.85; 5.05; N, 4.86%.

Diphenyl (4-chlorophenyl)(9-ethyl-9H-carbazol-3-ylamino)methylphosphonate (4e). White solid, Yield 92%, 0.522 g, Mp 148-150 ºC; IR (ν_{max}, cm^{-1}): 3374, 2972, 1491, 1271, 1204, 930, 764. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (t, ^3J(H-H) = 6.8 Hz, 3H, CH_3), 4.31 (q, ^3J(H-H) = 7.2 Hz, 2H, CH_2), 5.26 (d, ^2J(P-H) = 24.4 Hz, 1H, PC*H*), 6.91 (dd, ^3J(H-H) = 8.8 Hz, ^3J(H-H) = 2.0 Hz, 1H, Ar-*H*), 6.99-7.37 (m, 16H, Ar-*H)*, 7.44 (m, 1H, Ar-*H*), 7.59-7.61 (m, 2H, Ar-*H*), 7.96 (d, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.9, 37.5, 57.1 (d, ^1J(P-C) = 153.0 Hz), 105.4, 108.4, 109.2, 115.1, 118.2, 120.4 (d, *J*(P-C) = 5.0 Hz), 120.7 (d, *J*(P-C) = 4.0 Hz), 122.3, 123.5, 125.4, 125.5, 125.6, 129.0 (d, *J*(P-C) = 2.0 Hz), 129.6 (d, *J*(P-C) = 6.0 Hz), 129.8 (d, *J*(P-C) = 3.0 Hz), 133.9, 134.2 (d, *J*(P-C) = 4.0 Hz), 134.8, 138.7, 138.8, 140.4, 150.2 (d, *J*(P-C) = 9.0 Hz), 150.4 (d, *J*(P-C) = 10.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 15.1. LC/MS, *m/z* 568 $[M+H]^+$. Anal. Calcd. for $C_{33}H_{28}ClN_2O_3P$: C, 69.90; H, 4.98; N, 4.94%. Found: C, 69.85; H, 4.91; N, 5.07%.

Diphenyl (9-ethyl-9H-carbazol-3-ylamino)(2-nitrophenyl)methylphosphonate (4f). Orange yellow colored solid, Yield 88%, 0.508 g, Mp 168-170 ºC; IR (ν_{max}, cm^{-1}): 3303, 2970, 1487, 1260, 1186, 939, 764. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.38 (t, ^3J(H-H) = 6.8 Hz, 3H, CH_3), 4.28 (q, ^3J(H-H) = 7.2 Hz, 2H, CH_2), 5.23 (dd→t, ^3J(P-H) = ^3J(H-H) = 9.2 Hz, 1H, N*H*), 6.72 (dd, ^2J(P-H) = 27.2 Hz, ^3J(H-H) = 9.6 Hz, 1H, PC*H*), 6.97 (dd, ^3J(H-H) = 8.8 Hz, ^3J(H-H) = 2.0 Hz, 1H, Ar-*H*), 7.03 (d, ^3J(H-H) = 7.6 Hz, 2H, Ar-*H*), 7.13-7.55 (m, 15H, Ar-*H*), 7.98 (d, ^3J(H-H) = 4.4 Hz, 2H, Ar-*H*), 8.03 (d, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.4, 50.8 (d, ^1J(P-C) = 155.0 Hz), 104.7, 108.3, 109.3, 114.4, 118.1, 119.9 (d, *J*(P-C) = 4.0 Hz), 120.4, 120.7 (d, *J*(P-C) = 3.0 Hz), 122.2, 123.5, 125.3, 125.5, 128.9, 129.3, 129.7, 131.3, 133.6, 134.6, 137.9, 138.1, 140.2, 149.7 (d, *J*(P-C) = 6.0 Hz), 150.0 (d, *J*(P-C) = 10.0 Hz), 150.3 (d, *J*(P-C) = 9.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 14.0. LC/MS, *m/z* 578 $[M+H]^+$. Anal. Calcd. for $C_{33}H_{28}N_3O_5P$: C, 68.62; H, 4.89, N, 7.28%. Found: C, 68.75; H, 4.82; N, 7.21%.

Diphenyl (9-ethyl-9H-carbazol-3-ylamino)(3-nitrophenyl)methylphosphonate (4g). Orange yellow colored solid, Yield 94%, 0.542 g, Mp 154-156 ºC; IR (ν_{max}, cm^{-1}): 3310, 2973, 1489, 1261, 1211, 943, 766 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.39 (t, ^3J(H-H) = 7.2 Hz, 3H, CH_3), 4.29 (q, ^3J(H-H) = 7.2 Hz, 2H, CH_2), 4.91 (dd→t, ^3J(P-H) = ^3J(H-H) ≈ 9.0 Hz, 1H, N*H*), 5.37 (dd, ^{2}(P-H) = 25.2 Hz, ^3J(H-H) = 8.0 Hz, 1H, PC*H*), 6.90 (dd, ^3J(H-H) = 8.8 Hz, 2.4 Hz, 1H, Ar-*H*), 7.03-7.44 (m, 15H, Ar-*H*), 7.54 (t, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H*), 7.92 (d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*), 8.01 (d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*), 8.15 (d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*), 8.52 (d, ^3J(H-H) = 1.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.5, 57.0 (d, ^1J(P-C) = 151.0 Hz), 105.3, 108.5, 109.4, 115.0, 118.2, 120.2 (d, *J*(P-C) = 4.0 Hz), 120.3, 120.5, 122.2, 123.3, 123.5, 125.5, 125.7 (d, *J*(P-C) = 7.0 Hz), 129.9, 134.2, 134.9, 138.1, 138.3, 140.4, 148.5, 150.1 (d, *J*(P-C) = 9.0 Hz), 150.3, (d, *J*(P-C) = 10.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 13.9. LC/MS, *m/z* 578 $[M+H]^+$. Anal. Calcd. for $C_{33}H_{28}N_3O_5P$: C, 68.62; H, 4.89; N, 7.28%. Found: C, 68.59; H, 4.93; N, 7.33%.

Diphenyl (9-ethyl-9H-carbazol-3-ylamino)(4-nitrophenyl)methylphosphonate (4h). Orange yellow colored solid, Yield 96%, 0.553 g, Mp 144-146 ºC; IR (ν_{max}, cm^{-1}): 3304, 2974, 1489, 1344, 1261, 1211, 941, 764 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (t, ^3J(H-H) = 7.2 Hz, 3H, CH_3), 4.31 (q, ^3J(H-H) = 7.2 Hz, 2H, CH_2), 5.41 (d, ^2J(P-H) = 25.2 Hz, 1H, PC*H*), 6.91 (dd, ^3J(H-H) = 8.4 Hz, ^3J(H-H) = 2.0 Hz, 1H, Ar-*H*), 7.05-7.45 (m, 15H, Ar-*H*), 7.87 (dd, ^3J(H-H) = 8.8 Hz, 2.4 Hz, 2H, Ar-*H*), 7.94 (d, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H*), 8.23 (d, ^3J(H-H) = 8.4 Hz, 2H,

Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.5, 57.3 (d, ^1J(P-C) = 150.0 Hz), 105.3, 108.4, 109.3, 114.9, 118.2, 120.2$_{(8)}$, 120.2$_{(4)}$ (d, J(P-C) = 3.0 Hz), 120.5 (d, J(P-C) = 5.0 Hz), 122.2, 123.5, 123.9 (d, J(P-C) = 2.0 Hz), 125.6$_{(6)}$, 125.6$_{(4)}$, 125,7, 129.1 (d, J(P-C) = 6.0 Hz), 129.8, 134.8, 138.2, 138.3, 140.3, 143.3, 147.8 (d, J (P-C) = 4.0 Hz), 149.9 (d, J(P-C) = 10.0 Hz), 150.2 (d, J(P-C) = 9.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 13.9. LC/MS, *m/z* 578 $[M+H]^+$. Anal. Calcd. for $C_{33}H_{28}N_3O_5P$: C, 68.62; H, 4.89; N, 7.28%. Found: C, 68.49; H, 4.86; N, 7.36%.

Diphenyl (4-cyanophenyl)(9-ethyl-9H-carbazol-3-ylamino)methylphosphonate (4i). Pale yellow colored solid, Yield 92%, 0.513 g, Mp 160-162 ºC; IR (ν_{max}, cm^{-1}): 3304, 3055, 2228, 1489, 1261, 1211, 937. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.39 (t, ^3J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 4.30 (q, ^3J(H-H) = 7.2 Hz, 2H, C*H*$_2$), 5.31 (d, ^2J(P-H) = 25.2 Hz, 1H, PC*H*), 6.86-6.88 (m, 1H, Ar-*H*), 6.99 (d, ^3J(H-H) = 8.0 Hz, 2H, Ar-*H*), 7.12-7.45 (m, 13H, Ar-*H*), 7.65 (d, ^3J(H-H) = 8.0 Hz, 2H, Ar-*H*), 7.78 (d, ^3J(H-H) = 7.6 Hz, 2H, Ar-*H*), 7.92 (d, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.5, 57.5 (d, ^1J(P-C) = 151.0 Hz), 105.3, 108.5, 109.3, 112.1 (d, J(P-C) = 4.0 Hz), 114.9, 118.2, 118.5, 120.2, 120.3 (d, J(P-C) = 3.0 Hz), 120.5, 120.6, 122.2, 123.5, 125.6 (d, J(P-C) = 8.0 Hz), 125.7, 128.9, 129.0, 129.8, 132.5 (d, J(P-C) = 3.0 Hz), 134.8, 138.2, 138.4, 140.4, 141.2 (d, J(P-C) = 1.0 Hz), 150.0 (d, J(P-C) = 10.0 Hz), 150.2 (d, J(P-C) = 10.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 14.1. LC/MS, *m/z* 558 $[M+H]^+$. Anal. Calcd. for $C_{34}H_{28}N_3O_3P$: C, 73.24; H, 5.06; N, 7.54%. Found: C, 73.12; H, 5.11; N, 7.45%.

Diphenyl (9-ethyl-9H-carbazol-3-ylamino)(4-fluorophenyl)methylphosphonate (4j). Pale yellow colored solid, Yield 95%, 0.522 g, Mp 142-144 ºC; IR (ν_{max}, cm^{-1}): 3304, 2982, 1489, 1264, 1210, 934, 766. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (t, ^3J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 4.31 (q, ^3J(H-H) = 6.8 Hz, 2H, C*H*$_2$), 5.29 (d, ^2J(P-H) = 24.4 Hz, 1H, PC*H*), 6.94 (dd, ^3J(H-H) = 8.8 Hz, 2.4 Hz, 1H, Ar-*H*), 6.99 (d, ^3J(H-H) = 0.8 Hz, 1H, Ar-*H*), 7.02 (s, 1H, Ar-*H)*, 7.09 (t, ^3J(H-H) = 8.4 Hz, 2H, Ar-*H*), 7.16-7.48 (m, 13H, Ar-*H)*, 7.64-7.68 (m, 2H, Ar-*H)*, 7.98 (d, ^3J(H-H) = 7.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.4, 56.8 (d, ^1J(P-C) = 154.0 Hz), 105.3, 108.4, 109.1, 115.1, 115.6 (d, J = 2.0 Hz), 115.9 (d, J = 3.0 Hz), 118.1, 120.3 (d, J = 4.0 Hz), 120.7 (d, J = 4.0 Hz), 122.3, 123.4, 125.3 (d, J = 11.0 Hz), 125.5, 129.7 (d, J = 5.0 Hz), 129.8, 129.9 (d, J = 2.0 Hz), 130.0, 131.0, 134.7, 138.7, 138.9, 140.3, 150.2 (d, J(P-C) = 10.0 Hz), 150.4 (d, J(P-C) = 9.0 Hz), 161.4 (d, J = 3.0 Hz), 163.8 (d, J = 4.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 15.5, (d, ^6J(P-F) = 4.9 Hz). LC/MS, 551 $[M+H]^+$. Anal. Calcd. for $C_{33}H_{28}FN_2O_3P$: C, 71.99; H, 5.13; N, 5.09%. Found: C, 71.89; H, 5.08; N, 5.15%.

Diphenyl (9-ethyl-9H-carbazol-3-ylamino)(p-tolyl)methylphosphonate (4k). Colorless solid, Yield 90%, 0.491 g, Mp 146 ºC; IR (ν_{max}, cm^{-1}): 3308, 3057, 1487, 1264, 1186, 937. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.40 (t, ^3J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 2.34, (s, 3H, C_6H_4C*H*$_3$), 4.30 (q, ^3J(H-H) = 7.2 Hz, 2H, C*H*$_2$), 5.27 (d, ^2J(P-H) = 24.0 Hz, 1H, PC*H*), 6.94-6.99 (m, 3H, Ar-*H*), 7.13-7.56 (m, 17H, Ar-*H*), 7.97 (d, ^3J(H-H) = 8.0 Hz, 1H, A-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.9, 21.2, 37.5, 57.3 (d, ^1J(P-C) = 155.0 Hz), 105.5, 108.4, 109.2, 115.3, 118.1, 120.4, 120.5 (d, J(P-C) = 4.0 Hz), 120.8 (d, J(P-C) = 4.0 Hz), 122.5, 123.5, 125.2, 125.3, 125.5, 128.2, (d, J(P-C) = 6.0 Hz), 129.6 (d, J (P-C) = 3.0 Hz), 129.7 (d, J(P-C) = 9.0 Hz), 132.1, 134.7, 138.1 (d, J(P-C) = 3.0 Hz), 139.1, 139.3, 140.3, 150.4 (d, J(P-C) = 9.0 Hz), 150.6 (d, J(P-C) = 10.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 16.9. LC/MS, *m/z* 547 $[M+H]^+$. Anal. Calcd. for $C_{34}H_{31}N_2O_3P$: C, 74.71; H, 5.72; N, 5.13%. Found: C ,74.65; H, 5.78; N, 5.20%.

4-((diphenoxyphosphoryl)(9-ethyl-9H-carbazol-3-ylamino)methyl)benzoic acid (4l). The crude reaction mixture was directly subjected to column chromatography and was purified by hexane/ EtOAc (2:8) mixture as the eluent. Colorless solid, Yield 86%, 0.495 g, Mp 136-138 ºC; IR (ν_{max}, cm^{-1}): 3573, 3246, 1694, 1489, 1258, 1180, 945. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.28 (t, ^3J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 4.26 (q, ^3J(H-H) = 7.2 Hz, 2H, C*H*$_2$), 5.63 (d, ^2J(P-H) = 25.2 Hz, 1H, PC*H*), 6.97 (d, ^3J(H-H) = 0.8 Hz, 1H, Ar-*H*), 6.99 (t, ^3J(H-H) = 1.2 Hz, 1H, Ar-*H*), 7.05-7.36 (m, 13H, Ar-*H*), 7.51 (d, ^3J(H-H) = 2.0 Hz, 1H, Ar-*H*), 7.83 (dd, ^3J(H-H) = 8.4 Hz, ^3J(H-H) = 2.0 Hz, 2H, Ar-*H*), 7.94 (d, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H*), 8.04 (d, ^3J(H-H) = 7.6 Hz, 2H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 12.7, 36.8, 56.9 (d, ^1J (P-C) = 154.0 Hz), 105.0, 108.1, 108.9, 115.1, 117.7, 119.8, 120.2 (d, J(P-C) = 4.0 Hz), 120.5 (d, J(P-C) = 4.0 Hz), 122.4, 123.4, 125.1, 125.2 (d, J(P-C) = 3.0 Hz), 128.6 (d, J(P-C) = 6.0 Hz), 129.5 (d, J(P-C) = 3.0 Hz), 129.6 (d, J(P-C) = 2.0 Hz), 130.5 (d, J(P-C) = 3.0 Hz), 134.6, 139.2, 140.3, 140.9, 150.1 (d, J(P-C) = 10.0 Hz), 150.4 (d, J(P-C) = 10.0 Hz), 168.1. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 15.9. LC/MS, *m/z* 577 $[M+H]^+$. Anal. Calcd. for $C_{34}H_{29}N_2O_5P$: C, 70.83; H, 5.07; N, 4.86%. Found: C, 70.91; H, 5.11; N, 4.82%.

Diphenyl (2,3-dimethoxyphenyl)(9-ethyl-9H-carbazol-3-ylamino)methylphosphonate (4m). This compound was purified by hexane/ EtOAc (3:2) mixture as the eluent. Pale yellow colored solid, Yield 93%, 0.551 g, Mp 144-146 ºC; IR (ν_{max}, cm^{-1}): 3308, 2984, 1590, 1491, 1265, 1188, 939, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.37 (t, ^3J(H-H) = 6.8 Hz, 3H, C*H*$_3$), 3.84 (s, 3H, OC*H*$_3$), 3.99 (s, 3H, OC*H*$_3$), 4.27 (q, ^3J(H-H) = 6.8 Hz, 2H, C*H*$_2$), 5.92 (d,

^{2}J(P-H) = 24.8 Hz, 1H, PC*H*), 6.83 (d, ^{3}J(H-H) = 8.0 Hz, 1H, Ar-*H*), 6.93-7.46 (m, 18H, Ar-*H)*, 7.98 (d, ^{3}J(H-H) = 7.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.8, 37.4, 50.3 (d, ^{1}J(P-C) = 160.0 Hz), 55.7, 61.1, 105.4, 108.3, 109.1, 112.5, 115.3, 118.0, 120.1 (d, *J*(P-C) = 4.0 Hz), 120.4, 120.5 (d, *J*(P-C) = 4.0 Hz), 120.9 (d, *J*(P-C) = 4.0 Hz), 122.5, 123.5, 124.3, 125.0, 125.2, 125.4, 129.2, 129.5, 129.6, 134.7, 139.1 (d, *J*(P-C) = 16.0 Hz), 140.3, 147.6 (d, *J*(P-C) = 8.0 Hz), 150.4 (d, *J*(P-C) = 10.0 Hz), 150.6 (d, *J*(P-C) = 10.0 Hz), 152.4. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 16.8. LC/MS, *m/z* 593 $[M+H]^+$. Anal. Calcd. for $C_{35}H_{33}N_2O_5P$: C, 70.93; H, 5.61; N, 4.73%. Found: C, 70.83; H, 5.48; N, 4.65%.

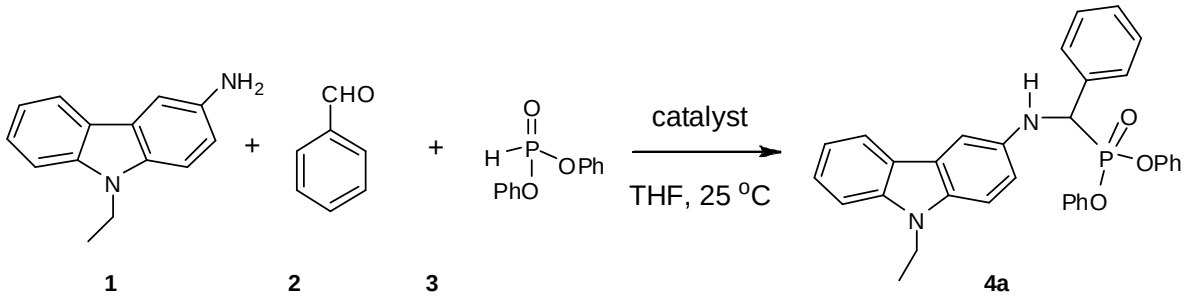
Diphenyl (9-ethyl-9H-carbazol-3-ylamino)(2,3,4-trimethoxyphenyl)methylphosphonate (4n). This compound was purified by hexane/ EtOAc (3:2) mixture as the eluent. Pale yellow colored solid, Yield 95%, 0.591 g, Mp 152-154 ºC; IR (ν_{max}, cm^{-1}): 3310, 2939, 1590, 1489, 1260, 1215, 945, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.38 (t, ^{3}J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 4.05 (s, 3H, OC*H*$_3$), 4.28 (q, ^{3}J(H-H) = 6.8 Hz, 2H, C*H*$_2$), 5.80 (d, ^{2}J(P-H) = 24.8 Hz, 1H, PC*H*), 6.64 (d, ^{3}J(H-H) = 8.8 Hz, 1H, Ar-*H*), 6.93-7.45 (m, 17H, Ar-*H*), 7.97 (d, ^{3}J(H-H) = 7.6 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.9, 37.5, 50.0 (d, ^{1}J(P-C) = 161.0 Hz), 56.0, 60.7, 61.4, 105.2, 107.7 (d, *J*(P-C) = 3.0 Hz), 108.4, 109.1, 115.4, 118.1, 120.3, 120.4 (d, *J*(P-C) = 4.0 Hz), 121.0 (d, *J*(P-C) = 5.0 Hz), 121.2, 122.6, 123.1 (d, *J*(P-C) = 5.0 Hz), 123.5, 125.0, 125.3, 125.4, 129.6 (d, *J*(P-C) = 8.0 Hz), 134.7, 139.0, 139.2, 140.3, 141.8, 150.4, 150.6 (d, *J*(P-C) = 10.0 Hz), 150.7 (d, *J*(P-C) = 9.0 Hz), 152.3 (d, *J*(P-C) = 7.0 Hz), 153.8 (d, *J*(P-C) = 3.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 16.8. LC/MS, *m/z* 623 $[M+H]^+$. Anal. Calcd. for $C_{36}H_{35}N_2O_6P$: C, 69.44; H, 5.67; N, 4.50%. Found: C, 69.31; H, 5.59; N, 4.55%.

Diphenyl(4-(benzyloxy)-3-methoxyphenyl)(9-ethyl-9H-carbazol-3- ylamino)methylphosphonate (4o). Colorless solid, Yield 89%, 0.595 g, Mp 140-142 ºC; IR (ν_{max}, cm^{-1}): 3331, 3057, 2972, 1590, 1470, 1264, 1192, 934. ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 1.41 (t, ^{3}J(H-H) = 7.2 Hz, 3H, C*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 4.31 (q, ^{3}J(H-H) = 7.2 Hz, 2H, C*H*$_2$), 5.14 (s, 2H, PhC*H*$_2$O), 5.20 (d, ^{2}J(P-H) = 23.6 Hz, 1H, PC*H*), 6.88 (d, ^{3}J(H-H) = 8.4 Hz, 1H, Ar-*H*), 6.93 (s, 1H, Ar-*H*), 6.95 (d, ^{3}J(H-H) = 1.6 Hz, 2H, Ar-*H*), 7.11-7.44 (m, 20H, Ar-*H)*, 7.96 (d, ^{3}J(H-H) = 8.0 Hz, 1H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C.13.9, 37.5, 56.1, 57.5 (d, ^{1}J(P-C) = 154.0 Hz), 71.0, 105.5, 108.4, 109.1, 111.7 (d, *J*(P-C) = 5.0 Hz), 114.0, 115.3, 118.1, 120.4 (d, *J*(P-C) = 4.0 Hz), 120.6 (d, *J*(P-C) = 5.0 Hz), 120.8 (d, *J*(P-C) = 5.0 Hz), 122.4, 123.5, 125.2, 125.3, 125.5, 127.3, 127.9, 128.0, 128.6, 129.6, 129.7, 130.1, 134.7, 137.0, 139.2, 139.3, 140.3, 148.2 (d, *J*(P-C) = 4.0 Hz), 149.9, 150.4 (d, *J*(P-C) = 10.0 Hz), 150.5 (d, *J*(P-C) = 10.0 Hz). ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 15.9. LC/MS, *m/z* 670 $[M+H]^+$. Anal. Calcd. for $C_{41}H_{37}N_2O_5P$: C, 73.64; H, 5.58; N, 4.19%. Found: C, 73.55; H, 5.62; N, 4.23%.

RESULTS AND DISCUSSION

As several triflate salts are very well known to catalyze the Kabachnik-Fields reaction [6], we treated 3-amino-9-ethyl carbazole (**1,** 0.5 mmol**)** with benzaldehyde (**2,** 0.55 mmol**)** and diphenylphosphite (**3,** 1.0 mmol) in the presence of several triflate salts as catalysts (10 mol %) using tetrahydrofuran (THF) as solvent at 25 ^{o}C for **5** minutes. These reactions afforded α-aminophosphonate **4a** (scheme 1) with high yield (89-92 %).

Scheme 1



1 **2** **3** **4a**

Interestingly, same experiment without any catalyst (as a control experiment) proceeded smoothly and gave the product **4a** with the yield of 89%. This indicates that the catalyst doesn't have any role in this particular reaction. We also performed this type of reaction in various polar aprotic as well as polar protic solvents to study the effect of

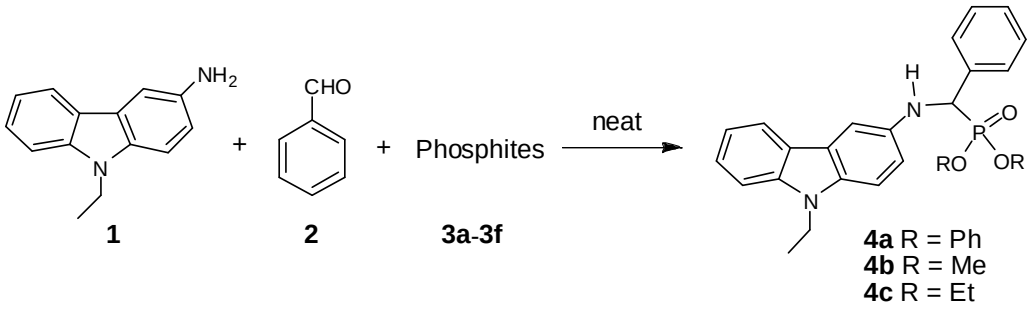
solvents without any catalysts. The results are summarized in Table 1. Except water, other solvents mentioned in the table worked very well. Reaction in water may have an effect on the formation of complex between amine and phosphites that is expected to involve in the reaction mechanism [12]. Finally, the reaction without any solvents and catalysts came up with a complete conversion of the starting material to the desired product **4a**.

Table 1. Effect of solvent on one-pot reaction

Entry	Solvents	Yield(%)[a]
1	CH_3CN	83
2	CH_2Cl_2	77
3	C_2H_5OH	92
4	CH_3OH	88
5	H_2O	62
6	Neat	98

*Other parameters: benzaldehyde **2** (0.5 mmol), diethylphosphite (1.0 mmol), solvent (0.25M), 5 minutes. [a]Yield refers to pure and isolated products*

We also explored the reactions using different trialkylphosphites and dialkylphosphites under solvent and catalyst free conditions (Table 2). Reaction times and yields are very much favorable in case of dialkyl (aryl) phosphites compared to trialkyl (aryl) phosphites.



Scheme 2. Reactivity of different phosphites under neat reaction conditions

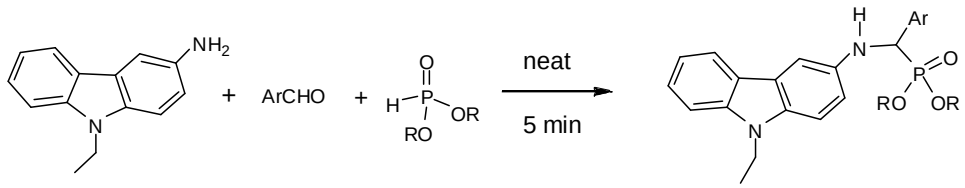
Table 2. Reactivity of dialkyl and trialkyl phosphites in one-pot reaction

Entry	Phosphites	Time (min)	Product	Yield (%)[a]
1	$P(OPh)_3$ **3a**	20	**4a**	85
2	$HP(O)(OPh)_2$ **3b**	5		98
3	$P(OMe)_3$ **3c**	20	**4b**	90
4	$HP(O)(OMe)_2$ **3d**	5		96
5	$P(OEt)_3$ **3e**	20	**4c**	92
6	$HP(O)(OEt)_2$ **3f**	5		95

*Other parameters: 3-amino-9-ethylcarbazole **1** (0.5 mmol), benzaldehyde **2** (0.5 mmol), di alkyl/arylphosphite (1.0 mmol) or trialkyl/arylphosphite (1.0 mmol), [a]yield refers to pure and isolated products.*

In a similar fashion, we performed the reaction with diverse aromatic aldehydes and diphenyl/dialkyl phosphites. Aldehydes with different substitutions undergo this reaction smoothly and provide α-aminophosphonates **4a** to **4o** with very good yield (85-98%). The results are summarized in Table 3.

Table 3. One-pot synthesis of *α*-aminophosphonates 4a-4o under neat reaction conditions



1 **4a-4o**

Compound	Ar	R	^{31}P NMR (δ)	Yield (%)[a]
4a	C_6H_5	Ph	15.8	98
4b	C_6H_5	Me	22.8	96
4c	C_6H_5	Et	25.4	96
4d	2-ClC_6H_4	Ph	14.9	85
4e	4-ClC_6H_4	Ph	15.1	92
4f	2-$NO_2C_6H_4$	Ph	14.0	88
4g	3-$NO_2C_6H_4$	Ph	13.9	94
4h	4-$NO_2C_6H_4$	Ph	13.9	96
4i	4-CNC_6H_4	Ph	14.1	92
4j	4-FC_6H_4	Ph	15.5	95
4k	4-MeC_6H_4	Ph	16.9	90
4l	4-(COOH)C_6H_4	Ph	15.9	86
4m	2,3-$(MeO)_2C_6H_3$	Ph	16.8	93
4n	2,3,4-$(MeO)_3C_6H_2$	Ph	16.8	95
4o	2-(BnO)-3-(MeO)C_6H_3	Ph	15.9	89

*Reaction conditions: 3-amino-9-ethylcarbazole **1** (1.0 mmol), arylaldehyde (1.1 mmol), dialkyl/ arylphosphite (3.0 mmol). [a]yield refers to pure and isolated products.*

All the compounds **4a-4o** are characterized by IR, NMR, mass spectroscopy and elemental analysis. In the IR spectra, the characteristic peak corresponding to group stretching of the *α*-aminophosphonates was observed at 3301-3382 cm^{-1} (for N-H) and 1235-1271 cm^{-1} (for P=O) [8]. In the ^{1}H-NMR spectra the PC*H* protons appears as a doublet in the region δ 4.91-6.72 with ^2J(P-H) = 23.6-35.2 Hz for all the compounds due to phosphorous and proton coupling but in the case of **4f** and **4g**, the PC*H* proton is observed as doublet of doublet at δ ≈ 6.02 [^2J (P-H) ≈ 26.6 Hz , ^3J(H-H) ≈ 10.0 Hz] while the N-H proton appears as a triplet at δ ≈ 5.07 [^2J (P-H) = ^3J(H-H) ≈ 9.1 Hz]. The N-H proton was not appeared for all compounds that might be due to rapid proton exchange with each other. In case of 2- and 3-nitro, the NH protons might have involved in intramolecular hydrogen bonding [13]. The methoxy protons of the dimethyl phosphite moiety of the compound **4b** observed as two distinct doublets at δ 3.55 [^3J (P-H) = 10.4 Hz] and 3.83 [^3J (P-H) = 10.8 Hz], and indicates that they are not equivalent. The ^{13}C NMR spectra are also quite useful for further analysis. The carbon attached to phosphorus (P*C*H) exhibits a doublet in the region δ 50.0-57.8 (d, ^1J(P-C) = 147.0-160.0 Hz) for all the compounds. The large value of the coupling constant is consistent with the α-carbon being connected to phosphorus as depicted [14]. In the ^{31}P-NMR spectra, all these products show a single peak in the region δ 14.0-26.0 except for **4j** that gives a doublet which might be due to the coupling of phosphorous with fluorine [d, ^6J(P-F) = 4.9 Hz]. Finally the structure of one of these compounds **4m** is established by X-ray crystallography (Figure 1) [15].

CONCLUSION

In summary, we developed an efficient and environmentally benign route to synthesize *α*-aminophosphonates attached to carbazole scaffold in good to excellent yield. The reaction is also advantageous due to the absence of catalyst under mild conditions and short period of time. The structure for one of these compounds has been confirmed by X-ray crystallography.

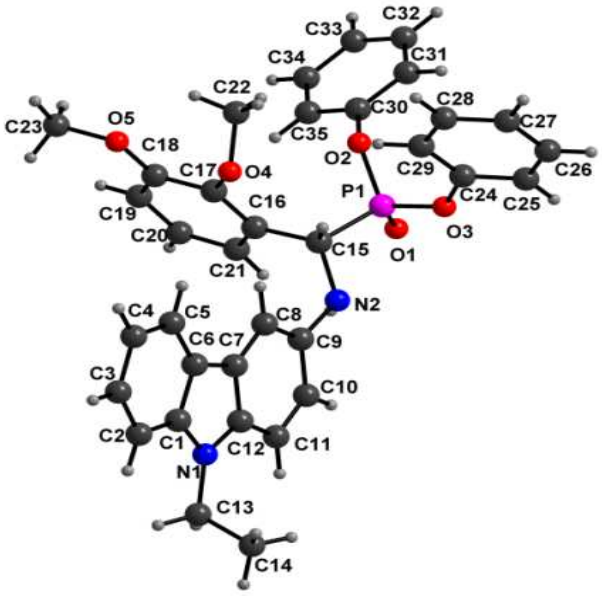


Figure 1: Molecular structure of compound 4m

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[15] X-ray data was collected on a OXFORD diffractometer using Mo-K_α (λ = 0.71073 Å) radiation. The structure was solved and refined by standard methods. ***Crystal data for* 4m**: $C_{35}H_{33}N_2O_5P$, M = 592.63, Triclinic, Space group $P\bar{1}$, a = 9.1566(6), b = 13.8156(12), c = 14.0424(10) Å, α = 61.164(8), β = 77.897(6)^o, γ = 84.685(6), V = 1521.5(2) Å^3, Z = 2, μ = 0.136 mm^{-1}, data/restraints/parameters: 4374/0/398, R indices ($I > 2\sigma(I)$): R1 = 0.0419, *wR*2 (all data) = 0.0815. CCDC no. 848039.