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Synthesis and Characterization of Novel Phosphonate Derivatives of Imidazo[1,2-*a*]Pyridine

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ABSTRACT

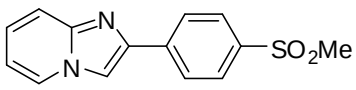
Synthesis of phosphonate derivatives of Imidazo[1,2-a]Pyridine were investigated. These compounds were synthesized by using cyanoalkyl malonates, dialkyl phosphites, and triethlyl amine as base.

Keywords: Imidazo[1,2-a]Pyridine, dialkyl phosphites, Michael addition, triethlyl amine.

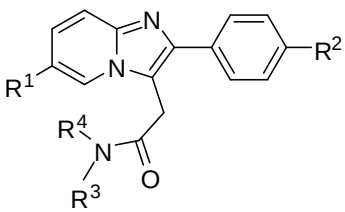
INTRODUCTION

The interest in the synthesis of Imidazo[1,2-a]Pyridine derivatives is growing because of their wide range of pharmaceutical, biological and medicinal applications. This scaffold is present in large number of compounds showing variety of therapeutic properties such as agonist of benzodiazepine receptor [1], melatonin receptor ligands [2], GABA [3], β-amyloid formation inhibitor [4], ligand for detecting β-amyloid [5] and also constitutes orally active non-peptide bradykinin B2 receptor antagonists [6]. In addition these derivatives were found to posses' antibacterial [7], antiviral [8], anti-inflammatory [9], antiulcer [10], antifungal [11] activities. Moreover it is also a core structure of several drugs such as zolimidine (1) (antiulcer), alpidem (2) (anxiolytic), and zolpidem (3) (hypnotic) [**Fig-1**] which are currently available on the market.

Fig-1



1



2 $R^1=R^2=Cl$, $R^3=R^4=C_3H_7$
3 $R^1=R^2=R^3=R^4=CH_3$

In the early 20th centuary the first work on the C-P bond formation was carried out by Arbusov which is well known as Michaelis-Arbusov reaction [12]. Later the interest in the C-P bond formation was increased because of the discovery of naturally occurring aminophosphonic acids [13] and new biologically active phosphonates [14].

Phosphonoacetic acid [15] has been shown active against cytomegalo virus and herpes virus. β-phosphonomalonic acid[16] derivatives were used as an inhibitor of ras farnesyl protein transferase in studies directed to the development of new antitumor agents. Phosphonoformate [17] has shown activity in cell cultures against HTLV-III (the virus implicated in AIDS). Very few methods are available for the synthesis of these type of compounds [18].
In continuation with our research on imidazo[1,2-*a*]pyridine analogues and phosphonates, because of the biological importance of these moiets we want to synthesize phosphonate derivatives of Imidazo[1,2-a] pyridine.

MATERIALS AND METHODS

All the chemicals used in this investigation 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] or 500 MHz NMR spectrometer [field strengths: 500, 125, and 202 MHz respectively] in $CDCl_3$ solution unless specified otherwise with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$) and ext. 85% H_3PO_4 (^{31}P: $\delta = 0$) 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 were uncorrected.

General Procedure for the synthesis of 2-phenyl imidazo[1,2-*a*]pyridine(5)
To the solution of 2-amino pyridine (5 mmol) in ethanol (30 mL), 2- bromo acetphenone(5 mmol) was added at room temperature and the mixture was refluxed for 3h.The resulting white solid was filtered off, dried and used without further purification[19].

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 6.77 (t, ^{3}J(H-H) = 6.8 Hz,, 1H, Ar-*H)*, 7.15-7.98 (m, 5H, Ar-*H)*, 7.98 (s, 1H, Ar-*H)*, 8.11 (d, ^{3}J(H-H) = 6.8 Hz, 1H, Ar-*H)*, 8.16 (s, ^{3}J(H-H) = 4.8 Hz, 1H, Ar-*H)*. ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 108.2, 112.4, 117.5, 124.7, 125.6, 126.1.128.0, 128.7, 129.2, 129.5, 129.7, 133.7, 145.7, 145.8, 158.3.

General Procedure for the synthesis of 2-phenyl imidazo[1,2-*a*]pyridine-3-carbaldehye (6)
To the solution of 2-phenyl imidazo[1,2-a]pyridine(0.005 mmol) in DMF (0.04 mmol), $POCl_3$ (0.015 mmol) was added dropwise and the mixture was stirred for one hour at room temperature. After the reaction was completed, the reaction mixture was washed with water and basified with KOH solution. The obtained white solid was filtered off, dried and used without further purification [20].

^{1}H NMR (500 MHz, $CDCl_3$): δ_H 7.15-7.18 (m, 1H, Ar-*H)*, 7.56-7.64 (m, 4H, Ar-*H)*, 7.85-7.87 (m, 3H, Ar-*H)*, 9.69-9.71 (m, 1H, Ar-*H)*, 10.10 (s, 1H, Ar-C*HO)*. ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 115.4, 117.5, 120.8, $128.9_{(5)}$, $128.9_{(2)}$,.$129.8_{(6)}$, $129.8_{(8)}$, 130.5, 132.3, 147.7, 158.3. 179.2.

General Procedure for the synthesis of phosphonate derivatives 2-phenyl imidazo[1,2-*a*]pyridine (8a-j)
Compound 8a To a solution of 2-phenyl imidazo[1,2-a]pyridine-3-carbaldehye (1.0 mmol) in dry methanol-THF(5mL), triethylamine(1.0 mmol) and cyanoethylacetate (1.0 mmol) was added. After 30 min triethyl amine (1.0 mmol) and dimethyl phosphite(1.5 mmol) were added drop wise and stirred at room temperature for 1h 30 min under nitrogen atmosphere. 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 chromatographed over silica gel column to afford the product.

Compound 8a. (isomer ratio 6:4). Colorless solid, Yield 87%, 0.37 g, Mp 150-152 ºC; IR (ν_{max}, cm^{-1}): 2932, 1743, 1523, 1249, 1047, 762, 701. ^{1}H NMR (500 MHz, $CDCl_3$): (for major isomer): δ_H 0.76 (t, ^{3}J(H-H) = 7.0 Hz, 3H, CH_3), 3.46 (d, ^{3}J(P-H) = 11.0 Hz, 3H, OCH_3), 3.71-3.73 (m, 1H, C*H)*, 3.82-3.86 (m, 1H, C*H)*, 3.96 (d, ^{3}J(P-H) = 11.0 Hz, 3H, OCH_3), 4.40-4.44 (m, 2H, CH_2*)*, 6.95-6.99 (m, 1H, Ar-*H)*, 7.30-7.34 (m, 1H, Ar-*H)*, 7.45-7.54 (m, 2H,

Ar-*H)*, 7.67-7.72 (m, 4H, Ar-*H)*, 8.77 (s, 1H, Ar-*H)*. (for minor isomer): δ_H 1.22 (t, ^3J(H-H) = 7.0 Hz, 3H, CH_3), 3.45 (d, ^3J(P-H) = 11.0 Hz, 3H, OCH_3), 3.77 (d, ^3J(P-H) = 11.0 Hz, 3H, OCH_3), 4.10-4.16 (m, 1H, C*H)*, 4.20-4.31 (m, 1H, C*H)*, 4.69-4.76 (m, 2H, CH_2*)*, remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.1, 13.7, 35.8, 36.0, 37.2, 53.4 (d, ^2J(P-C) = 7.5 Hz P-OCH_3), 53.6 (d, ^2J(P-C) = 7.5 Hz P-OCH_3), 53.9, 54.0, 63.3, 63.7, 110.4, 112.8, 113.0, 113.4, 113.8, 114.5, 117.9, 118.1, 125.6, 126.1, 128.5, 128.7, 128.9$_{(0)}$, 128.9$_{(1)}$, 128.9$_{(2)}$, 133.4,133.6, 146.1, 147.5, 150.4, 163.2, 163.3. ^{31}P NMR (202 MHz, $CDCl_3$): δ_P 22.6 (major) and 22.9 (minor). LC/MS, *m/z* 428 $[M+1]^+$; Anal. Calcd. for $C_{21}H_{22}N_3O_5P$: C,59.02; H, 5.19; N,9.83%. Found: C, 59.03; H, 5.15; N, 9.82%.

Compound 8b. (isomer ratio 6:4). Colorless solid, Yield 81%, 0.37 g, Mp 144-146 ºC; IR (ν_{max}, cm^{-1}): 2942, 1748, 1493, 1253, 1047, 768. ^{1}H NMR (400 MHz, $CDCl_3$): (for major isomer): δ_H 0.71 (t, ^3J(P-H) = 7.2 Hz, 3H, CH_3), 0.93 (t, ^3J(H-H) = 7.0 Hz, 3H, CH_3), 1.40 (t, ^3J(P-H) = 7.1 Hz, 3H, CH_3), 3.58-3.70 (m, 2H, CH_2*)*,4.04-4,12 (m, 2H, CH_2), 4.23-4.34 (m, 2H, CH_2*)*, 4.38-4.44 (m, 1H, C*H)*, 4.61-4.70 (m, 1H, C*H)*, 6.88-6.92 (m, 1H, Ar-*H)*, 7.23-7.28 (m, 1H, Ar-*H)*, 7.40-7.51 (m, 3H, Ar-*H)*, 7.61-7.71 (m, 3H, Ar-*H)*, 8.75 (d, ^3J(H-H) = 8.0 Hz 1H, Ar-*H)*. (for minor isomer): δ_H 1.00 (t, ^3J(P-H) = 7.2 Hz, 3H, CH_3), 1.16 (t, ^3J(P-H) = 7.1 Hz, 3H, CH_3), 1.26 (t, ^3J(H-H) = 8.0 Hz, 3H, CH_3), remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.1, 13.6, 16.0$_{(0)}$ (d, ^3J(P-C) = 6.0 Hz P-O-C-*C*H_3), 16.0$_{(1)}$ (d, ^3J(P-C) = 6.0 Hz P-O-C-*C*H_3), 16.2 (d, ^3J(P-C) = 6.0 Hz P-O-C-*C*H_3), 16.3 (d, ^3J(P-C) = 5.0 Hz P-O-C-*C*H_3), 34.6, 35.8, 36.1, 36,7, 63.2$_{(7),}$ 63.2$_{(2),}$ 63.5, 63.6, 63.9$_{(0)}$ (d, ^2J(P-C) = 7.0 Hz), 63.9$_{(1)}$ (d, ^2J(P-C) = 7.0 Hz), 110.7, 110.8, 111.0, 111.1, 112.6, 112.8, 113.9, 114.1, 114.6, 117.7, 117.9, 125.5, 126.4, 128.4, 128.6, 128.7, 128.9, 129.1, 133.4,133.7, 146.0, 146.2, 147.2, 147.3, 163.4, 163.6, 163.8. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 20.0 (major) and 20.5 (minor). LC/MS, *m/z* 456 $[M+1]^+$; Anal. Calcd. for $C_{23}H_{26}N_3O_5P$: C,60.65; H, 5.75; N,9.23%. Found: C, 60.75; H, 5.65; N, 9.20%.

Compound 8c. (isomer ratio 6:4). Colorless solid, Yield 86%, 0.44 g, Mp 110-112 ºC; IR (ν_{max}, cm^{-1}): 2975, 1742, 1512, 1260, 1232, 1106, 986. ^{1}H NMR (400 MHz, $CDCl_3$): (for major isomer): δ_H 0.59 (d, ^3J(H-H) = 6.4 Hz, 3H, CH_3), 0.75 (t, ^3J(H-H) = 7.2 Hz, 3H, CH_3), 1.17 (d, ^3J(H-H) = 6.0 Hz, 3H, CH_3), 1.22 (d, ^3J(H-H) = 6.0 Hz, 3H, CH_3), 1.26 (d, ^3J(H-H) = 6.4 Hz, 3H, CH_3), 3.66-3.73 (m, 1H, C*H)*, 3.79-3.84 (m, 1H, C*H)*, 4.41-4.47 (m, 2H, CH_2*)*, 4.62-4.70 (m, 1H, C*H)*, 4.88-4.93 (m, 1H, C*H)*, 6.91-6.99 (m, 1H, Ar*H)*, 7.45-7.54 (m, 4H, Ar-*H)*, 7.64-7.76 (m, 3H, Ar-*H)*, 8.82 (d, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H)*. (for minor isomer): δ_H 0.82 (d, ^3J(H-H) = 5.6 Hz, 3H, CH_3), 1.24 (t, ^3J(H-H) = 7.0 Hz, 3H, CH_3), 1.33 (d, ^3J(H-H) = 6.0 Hz, 3H, CH_3)remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.1, 13.6, 22.5,.22.6, 23.0, 23.6, 23.8$_{(0)}$, 23.8$_{(3)}$, 23.9$_{(0)}$, 23.9$_{(4)}$, 24.1, 24.4$_{(5)}$, 24.4$_{(8)}$, 36.1, 36.4, 37.0, 37.9, 63.3, 63.6, 72.5$_{(0)}$, 72.5$_{(3)}$, 73.0, 73.1, 111.3, 111.4, 112.4, 112.7, 114.7, 117.7, 117.8, 125.4, 126.5, 127.0, 128.3, 128.5, 128.7, 128.8, 128.9, 129.2, 133.5, 145.8, 147.2, 163.6, 163.7. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 18.5 (major) and 18.9 (minor). LC/MS, *m/z* 512 $[M+1]^+$; Anal. Calcd. for $C_{27}H_{34}N_3O_5P$: C, 63.39; H, 6.70; N,8.21%. Found: C, 63.32; H, 6.75; N, 8.20%.

Compound 8d. (isomer ratio 6:4). Colorless solid, Yield 84%, 0.46 g, Mp 118-120 ºC; IR (ν_{max}, cm^{-1}): 2920, 1748, 1589, 1484, 1282, 1035, 947. ^{1}H NMR (500 MHz, $CDCl_3$): (for major isomer): δ_H 0.76 (t, ^3J(H-H) = 7.0 Hz, 3H, CH_3), 3.71-3.74 (m, 1H, C*H)*, 3.83-3.89 (m, 1H, C*H)*, 4.55-4.76 (m, 2H, CH_2*)*, 6.61-6.63 (m, 1H, Ar-*H)*, 6.75-6.78 (m, 1H, Ar-*H)*, 6.92-7.05 (m, 3H, Ar-*H)*, 7.16-7.43 (m, 9H, Ar-*H)*, 7.47-7.64 (m, 4H, Ar-*H)*, 8.58 (d, ^3J(H-H) = 5.0 Hz, 1H, Ar-*H)*. (for minor isomer): δ_H 1.20 (t, ^3J(H-H) = 5.0 Hz, 3H, CH_3). remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 13.1, 13.7, 35.9, 36.3, 36.6, 37.1, 63.5, 64.0, 109.2, 109.5, 112.9, 114.4, 117.7, 118.0, 119.4$_{(4),}$ 119.4$_{(8)}$, 119.5, 120.4$_{(6)}$, 120.4$_{(0)}$, 120.8$_{(5)}$, 120.8$_{(8)}$, 125.3, 125.5, 126.0$_{(9)}$, 126.0$_{(0)}$, 128.7, 128.9, 129.0, 129.2, 129.5, 130.0$_{(9)}$, 130.0$_{(0)}$, 133.2, 135.8, 146.0, 149.6, 149.7, 163.0, 163.1. ^{31}P NMR (202 MHz, $CDCl_3$): δ_P 12.2 (major) and 12.9 (minor). LC/MS, *m/z* 552 $[M+1]^+$; Anal. Calcd. for $C_{31}H_{26}N_3O_5P$: C, 67.51; H, 4.75; N, 7.62%. Found: C, 67.43; H, 4.72; N, 7.62%.

Compound 8e. (isomer ratio 6:4). Colorless solid, Yield 81%, 0.38 g, Mp 158-160 ºC; IR (ν_{max}, cm^{-1}): 2915, 1737, 1453, 1249, 1057, 1003, 821. ^{1}H NMR (400 MHz, $CDCl_3$): (for major isomer): δ_H 0.58 (t, ^3J(H-H) = 7.0 Hz, 3H, CH_3), 0.71 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 3.17-3.20 (m, 1H, C*H)*, 3.27-3.31 (m, 1H, C*H)*, 3.61-3.77 (m, 2H, CH_2*)*,3.80-3.90, (m, 2H, CH_2), 4.40-4.55(m, 2H, CH_2*)*, 6.95 (t, ^3J(H-H) = 10.0 Hz, 1H, Ar-*H)*, 7.28-7.34 (m, 2H, Ar-*H)*, 7.46-7.59 (m, 5H, Ar-*H)*,8.74 (d, ^3J(H-H) = 10.0 Hz 1H, Ar-*H)*. (for minor isomer): δ_H 0.68 (t, ^3J(H-H) = 7.2 Hz, 3H, CH_3), 0.99 and 1.41 (2s, 6H, CH_3), remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.1, 13.8, 20.4, 20.7, 21.2, 21.4, 32.2, 34.4, 35.3, 36.2, 63.4, 64.1, 79.9, 81.4, 110.3, 112.9, 113.1, 113.5, 114.7, 117.7, 118.1, 125.7, 125.8, 126.7, 128.6, 128.7, 128.8, 128.9, 129.0, 129.2, 133.7, 146.3, 147.0, 147.4,

148.2, 163.8, 164.0, 164.3. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 14.0 (major) and 13.5 (minor). LC/MS, *m/z* 468 $[M+1]^+$; Anal. Calcd. for $C_{24}H_{26}N_3O_5P$: C, 61.67; H, 5.61; N, 8.99%. Found: C, 61.75; H, 5.65; N, 8.97%.

Compound 8f. (isomer ratio 6:4). Colorless solid, Yield 80%, 0.40 g, Mp 158-160 ºC; IR (ν_{max}, cm^{-1}): 2940, 1747, 1482, 1249, 1047, 811. ^{1}H NMR (400 MHz, $CDCl_3$): (for major isomer): δ_H 0.62 (t, ^3J(H-H) = 7.0 Hz, 3H, C*H*$_3$), 0.71 (t, ^3J(H-H) = 7.0 Hz, 3H, C*H*$_3$), 1.25 (t, ^3J(H-H) = 7.1 Hz, 3H, C*H*$_3$), 1.30-1.39 (m, 2H, CH_2), 1.42-1.59 (m, 2H, CH_2), 3.18-3.20 (m, 1H, C*H)*, 3.22-3.29 (m, 1H, C*H)*, 3.52-3.67(m, 2H, C*H*$_2$*)*, 3.81-3.90, (m, 2H, CH_2), 4.44-4.56 (m, 2H, C*H*$_2$*)*, 6.86 (t, ^3J(H-H) = 10.0 Hz, 1H, Ar-*H)*, 7.21-7.32 (m, 3H, Ar-*H)*, 7.42-7.73 (m, 4H, Ar-*H)*,8.77 (d, ^3J(H-H) = 10.0 Hz 1H, Ar-*H)*. (for minor isomer): δ_H 0.66 (t, ^3J(H-H) = 7.1 Hz, 3H, C*H*$_3$), 0.91 (t, ^3J(H-H) = 7.1 Hz, 3H, C*H*$_3$), 1.40 (t, ^3J(H-H) = 8.0 Hz, 3H, C*H*$_3$), remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 13.1, 13.8, 20.3, 20.7, 21.0, 21.2, 22.6, 22.9, 31.2, 34.2, 35.0, 36.1, 62.4, 64.1, 85.5, 86.0, 110.2, 111.9, 113.2, 113.6, 115.0, 117.7, 118.0, 124.9, 125.6, 126.5, 128.6, 128.7, 128.8, 128.9, 129.1, 129.23 133.7, 145.9, 147.1, 147.2, 148.4, 163.9, 164.0, 164.3. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 14.5 (major) and 13.9 (minor). LC/MS, *m/z* 496 $[M+1]^+$; Anal. Calcd. for $C_{26}H_{30}N_3O_5P$: C, 63.02; H, 6.10; N, 8.48%. Found: C, 63.10; H, 6.12; N, 8.50%.

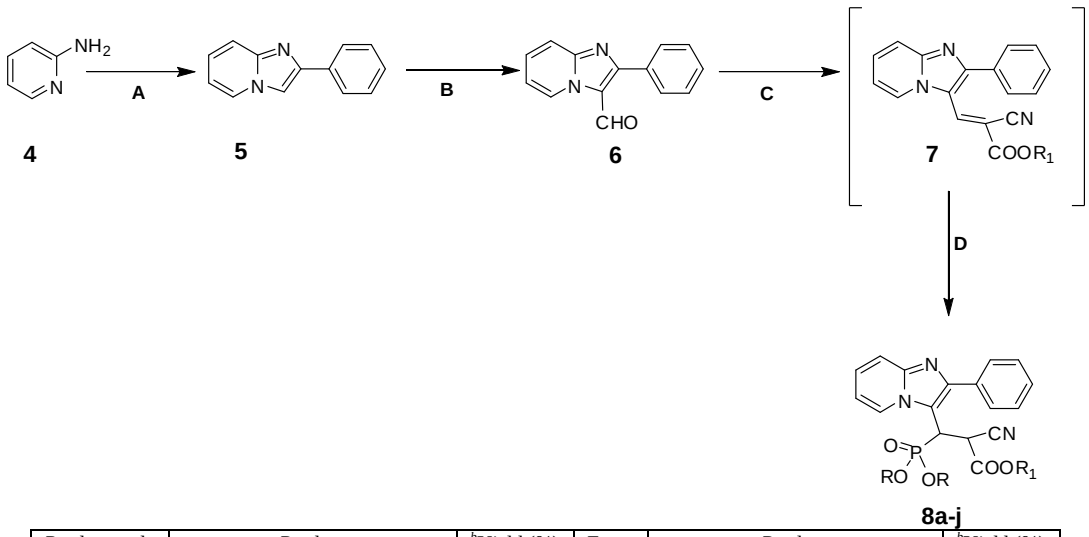
Compound 8g. (isomer ratio 6:4). Colorless solid, Yield 82%, 0.34 g, Mp 152-154 ºC; IR (ν_{max}, cm^{-1}): 2940, 1724, 1522, 1269, 1057, 703. ^{1}H NMR (500 MHz, $CDCl_3$): (for major isomer): δ_H 3.56 (d, ^3J(P-H) = 11.0 Hz, 3H, OC*H*$_3$), 3.67 (s, 3H, C*H*$_3$), 3.76-3.79 (m, 1H, C*H)*, 3.82-3.88 (m, 1H, C*H)*, 3.96 (d, ^3J(P-H) = 11.0 Hz, 3H, OC*H*$_3$), 6.95-7.01 (m, 1H, Ar-*H)*, 7.29-7.34 (m, 1H, Ar-*H)*, 7.45-7.54 (m, 2H, Ar-*H)*, 7.66-7.72 (m, 4H, Ar-*H),* 8.77 (d, ^3J(H-H) = 8.0 Hz 1H, Ar-*H)*.. (for minor isomer): δ_H 3.59 (d, ^3J(P-H) = 11.0 Hz, 3H, OC*H*$_3$), 3.69 (d, ^3J(P-H) = 11.0 Hz, 3H, OC*H*$_3$), 3.70 (s, 3H, C*H*$_3$), 4.11-4.16 (m, 1H, C*H)*, 4.20-4.31 (m, 1H, C*H)*, remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 34.6, 35.6, 36.1, 37.2, 51.4, 51.6, 53.4 (d, ^2J(P-C) = 7.5 Hz P-O*C*H$_3$), 53.7 (d, ^2J(P-C) = 7.5 Hz P-O*C*H$_3$), 53.7, 54.2, 110.4, 112.5, 113.1, 113.4, 113.5, 114.5, 117.9, 118.0, 124.9, 126.1, 128.6, 128.7, 128.9, 129.0, 129.1, 133.5,133.6, 145.1, 147.3, 150.4, 163.1, 163.3. ^{31}P NMR (202 MHz, $CDCl_3$): δ_P 22.1 (major) and 22.4 (minor). LC/MS, *m/z* 414 $[M+1]^+$; Anal. Calcd. for $C_{20}H_{20}N_3O_5P$: C, 58.11; H, 4.88; N,10.17%. Found: C, 58.03; H, 4.85; N, 10.16%.

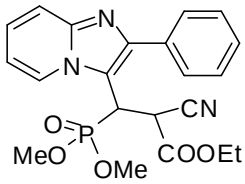
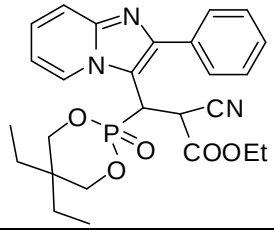
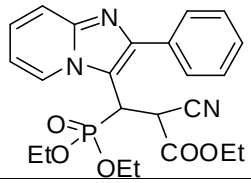
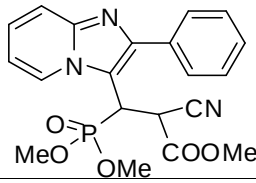
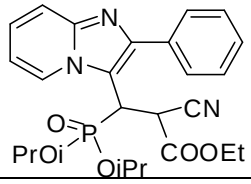
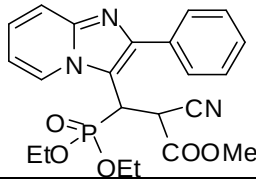
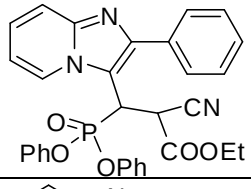
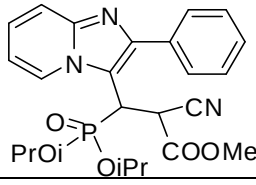
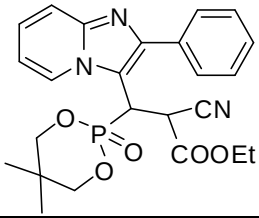
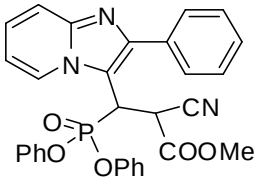
Compound 8h. (isomer ratio 6:4). Colorless solid, Yield 79%, 0.35 g, Mp 148-150 ºC; IR (ν_{max}, cm^{-1}): 2950, 1738, 1503, 1251, 1047, 748. ^{1}H NMR (400 MHz, $CDCl_3$): (for major isomer): δ_H 0.94 (t, ^3J(P-H) = 7.0 Hz, 3H, C*H*$_3$), 1.20 (t, ^3J(P-H) = 7.0 Hz, 3H, C*H*$_3$), 3.68 (s, 3H, C*H*$_3$), 4.07-4,12 (m, 2H, CH_2), 4.23-4.32 (m, 2H, C*H*$_2$*)*, 4.38-4.46 (m, 1H, C*H)*, 4.61-4.71 (m, 1H, C*H)*, 6.80-6.88 (m, 1H, Ar-*H)*, 7.22-7.28 (m, 1H, Ar-*H)*, 7.41-7.51 (m, 2H, Ar-*H)*, 7.60-7.71 (m, 4H, Ar-*H)*, 8.72 (S, 1H, Ar-*H)*. (for minor isomer): δ_H 1.03 (t, ^3J(P-H) = 7.2 Hz, 3H, C*H*$_3$), 1.16 (t, ^3J(P-H) = 7.2 Hz, 3H, C*H*$_3$), 3.73 (s, 3H, C*H*$_3$), remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 16.0 (d, ^3J(P-C) = 6.0 Hz P-O-C-*C*H$_3$), 16.1 (d, ^3J(P-C) = 6.0 Hz P-O-C-*C*H$_3$), 16.2 (d, ^3J(P-C) = 6.0 Hz P-O-C-*C*H$_3$), 16.3 (d, ^3J(P-C) = 5.0 Hz P-O-C-*C*H$_3$), 34.0, 35.6, 36.2, 36,7, 63.4, 63.6, 63.9$_{(0)}$ (d, ^2J(P-C) = 7.2 Hz), 63.9$_{(1)}$ (d, ^2J(P-C) = 7.2 Hz), 110.5, 110.7, 111.0, 111.2, 112.4, 112.8, 114.0, 114.1, 114.4, 116.9, 117.7, 125.4, 126.4, 128.0, 128.4, 128.7, 128.8, 129.3, 133.2,133.7, 146.2, 146.4, 147.3, 147.4, 163.4, 163.5, 163.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 20.3 (major) and 20.8 (minor). LC/MS, *m/z* 442 $[M+1]^+$; Anal. Calcd. for $C_{22}H_{24}N_3O_5P$: C,59.86; H, 5.48; N,9.52%. Found: C, 59.75; H, 5.45; N, 9.50%.

Compound 8i. (isomer ratio 6:4). Colorless solid, Yield 80%, 0.40 g, Mp 114-116 ºC; IR (ν_{max}, cm^{-1}): 2972, 1740, 1532, 1232, 1036, 988. ^{1}H NMR (400 MHz, $CDCl_3$): (for major isomer): δ_H 0.62 (d, ^3J(H-H) = 6.4 Hz, 3H, C*H*$_3$), 1.16 (d, ^3J(H-H) = 6.0 Hz, 3H, C*H*$_3$), 1.20 (d, ^3J(H-H) = 6.0 Hz, 3H, C*H*$_3$), 1.26 (d, ^3J(H-H) = 6.0 Hz, 3H, C*H*$_3$), 3.54 (s, 3H, C*H*$_3$), 3.70-3.76 (m, 1H, C*H)*, 3.78-3.84 (m, 1H, C*H)*, 4.52-4.63 (m, 1H, C*H)*, 4.81-4.93 (m, 1H, C*H)*, 6.90-7.03 (m, 2H, Ar-*H)*, 7.43-7.54 (m, 3H, Ar-*H)*, 7.70-7.79 (m, 3H, Ar-*H)*, 8.79 (d, ^3J(H-H) = 8.0 Hz, 1H, Ar-*H)*. (for minor isomer): δ_H 0.82 (d, ^3J(H-H) = 5.6 Hz, 3H, C*H*$_3$), 1.22 (t, ^3J(H-H) = 7.0 Hz, 3H, C*H*$_3$), 1.31 (d, ^3J(H-H) = 6.0 Hz, 3H, C*H*$_3$), 3.52 (s, 3H, C*H*$_3$), remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 22.0,.22.4, 23.1, 23.6, 23.7, 23.8, 23.9$_{(2)}$, 23.9$_{(4)}$, 24.3, 24.2, 24.4, 36.1, 36.3, 36.9, 37.8, 71.5, 72.2, 73.0, 73.1, 110.3, 111.1, 112.3, 112.6, 114.5, 117.7, 117.9, 125.4, 126.4, 127.0, 128.2, 128.3, 128.7, 128.9$_{(0)}$, 128.9$_{(4)}$, 129.2, 132.5, 145.9, 147.1, 162.6, 163.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ_P 18.1 (major) and 18.8 (minor). LC/MS, *m/z* 498 $[M+1]^+$; Anal. Calcd. for $C_{26}H_{32}N_3O_5P$: C, 62.77; H, 6.48; N,8.45%. Found: C, 62.72; H, 6.45; N, 8.40%.

Table 1. Scheme of the synthesis of phosphonate derivatives of 2-phenyl imidazo[1,2-*a*]pyridines 8a-j

Scheme 1



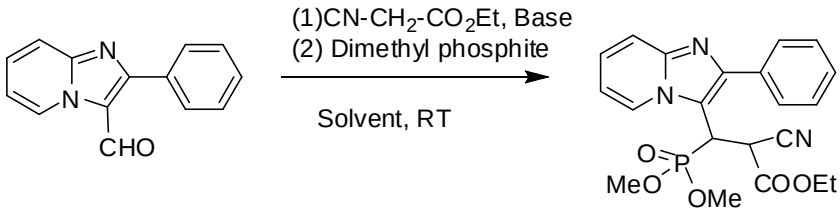
Product code	Product	[b]Yield (%)	Entry	Product	[b]Yield (%)
8a		87	8f		80
8b		81	8g		82
8c		86	8h		79
8d		84	8i		80
8e		81	8j		75

[a]*Reaction conditions: (A) Br-CH_2-CO-C_6H_5, EtOH, reflux. (B) DMF, $POCl_3$ RT. (C) CN-CH_2-COOR, MeOH-THF, and Tri ethyl amine at RT for 30 min. (D) Tri ethyl amine and di alkyl phosphite at RT for 1h 30 min (C & D are in situ reactions).*

Compound 8j. (isomer ratio 6:4). Colorless solid, Yield 75%, 0.40 g, Mp 122-124 ºC; IR (ν_{max}, cm^{-1}): 2926, 1734, 1569, 1482, 1282, 1049, 937. ^{1}H NMR (500 MHz, $CDCl_3$): (for major isomer): δ_H 3.58 (s, 3H, C*H*$_3$), 3.70-3.74 (m, 1H, C*H)*, 3.81-3.87 (m, 1H, C*H)*, 6.60-6.63 (m, 1H, Ar-*H)*, 6.71-6.76 (m, 3H, Ar-*H)*, 6.92-7.10 (m, 2H, Ar-*H)*, 7.12-7.45 (m, 8H, Ar-*H)*, 7.40-7.64 (m, 4H, Ar-*H)*, 8.55 (d, ^3J(H-H) = 5.0 Hz, 1H, Ar-*H)*. (for minor isomer): δ_H 3.68 (s, 3H, C*H*$_3$), 3.76-3.79 (m, 1H, C*H)*, remaining peaks were merged with major isomer peaks**.** ^{13}C NMR (125 MHz, $CDCl_3$): δ_C, 35.6, 36.1, 36.6, 37.0, 51.5, 54.7, 109.1, 109.5, 112.7, 114.5, 116.9, 118.0, 119.3$_{(6),}$ 119.3$_{(8)}$, 119.6, 120.4, 120.6, 120.8, 121.6, 125.3, 125.4, 126.1, 126.3, 128.6, 128.9, 129.1, 129.2, 129.4, 131.0$_{(7)}$, 131.0$_{(0)}$, 132.2, 135.9, 146.5, 149.0, 149.7, 163.0, 163.1. ^{31}P NMR (202 MHz, $CDCl_3$): δ_P 12.1 (major) and 12.9 (minor). LC/MS, *m/z* 537 $[M+1]^+$; Anal. Calcd. for $C_{30}H_{24}N_3O_5P$: C, 67.04; H, 4.50; N, 7.82%. Found: C, 67.14; H, 4.52; N, 7.80%.

For optimization of the reaction conditions, we chose the coupling between 2-phenyl imidazo[1,2-*a*]pyridine-3-carbaldehye (5), cyanoethyl acetate and dimethyl phosphite . We check the feasibility of the reaction with different bases, and solvents. The results are shown in table 2.

Scheme 2



6 **8a**

Table 2. Optimization of the synthesis of compound(8a)

Entry	Base	Solvent	[b] Yield (%)
1	K_2CO_3	THF	-
2	K_2CO_3	Methanol-THF	-
3	DBU	THF	42
4	DBU	Methanol-THF	50
5	Triethylamine	THF	67
6	Triethylamine	Methanol-THF	87
7	L-Proline	DMSO	80
8	L-Proline	THF	68
9	L-Proline	Methanol-THF	81
10	L-Asparagine	THF	71
11	L-Asparagine	Methanol-THF	80

[a]Unless otherwise noted, all reactions were carried out using 0.5 mmol of 2-phenyl imidazo[1,2-a]pyridine-3-carbaldehye, 1.0 equiv cyano ethyl acetate, 2.0 equiv of base, 1.5 equiv of di methyl phosphite, 2 ml of solvent, for 2 h at RT. [b] Yields are isolated(mixture of isomers).

RESULTS AND DISCUSSION

Herein, we report the synthesis of phosphonate derivatives of 2-phenyl imidazo[1,2-*a*]pyridines **8a-j** by reacting 2-phenyl imidazo[1,2-a]pyridine-3-carbaldehye with alkyl cyano acetate and dialkyl hydrogen phosphite in dry methanol-THF in the presence of tri ethyl amine at room temperature. The 3-substituted 2-phenyl imidazo[1,2-*a*]pyridines **8a-j** (Scheme 1, Table 1) were obtained in good yield. The reactions were carried out under nitrogen atmosphere.

Initially we synthesized compound **5** by reacting 2-amino pyridine with 2-bromo acetophenone[19], which on vilsmeyer-haack formylation gave aldehyde **6**[20]. To accomplish the phosphonate derivatives of 2-phenyl imidazo[1,2-*a*]pyridines we started with 2-phenyl imidazo[1,2-a]pyridine-3-carbaldehye(**6**), ethyl cyano acetate and dimethyl hydrogen phosphate in presence of different bases and solvent systems.

The optimization of this reaction with various bases was shown in Table 2. Primarily we started with K_2CO_3, in THF and Methanol-THF system but we did not get the product. When DBU was used we got the mixture of isomers in moderate yields. Later the reaction was performed with triethylamine in THF we obtained the mixture of isomers in 67%. Of the product **8a** when Methanol-THF solvent was used the combined yield of the isomers was increased to

87%. Afterward we checked the feasibility of the reaction with chiral catalyst L-Proline and L-Asparagine in different solvent systems. But these bases also yielded the equivalent percentage of the mixture of isomers as other bases produced. Hence these results indicated that the triethylamine was suitable base in Methanol-THF solvent system for the formation of phosphonate **8a** (isomer ratio 6:4). The isomers could not be separated by column chromatography, as the retention time of both the isomers were same in TLC.

By adopting the above successful route, we synthesized the compounds 8**a-j** All the compounds were characterized by IR, NMR, mass spectroscopy and elemental analysis. In the IR spectra, the characteristic peak corresponding to P=O group was observed at 1249-1282 cm^{-1} and 1035-1106 cm^{-1} for P-O-$C_{aliphatic}$ stretching[18] The ^{1}H and ^{13}C NMR spectra of all the compounds were complicated due to the peaks for both the isomers and also coupling of phosphorus with proton and carbon. Finally the structure of one of the isomer compound **8a** is proven by X-ray crystallography (Fig 2) [21]

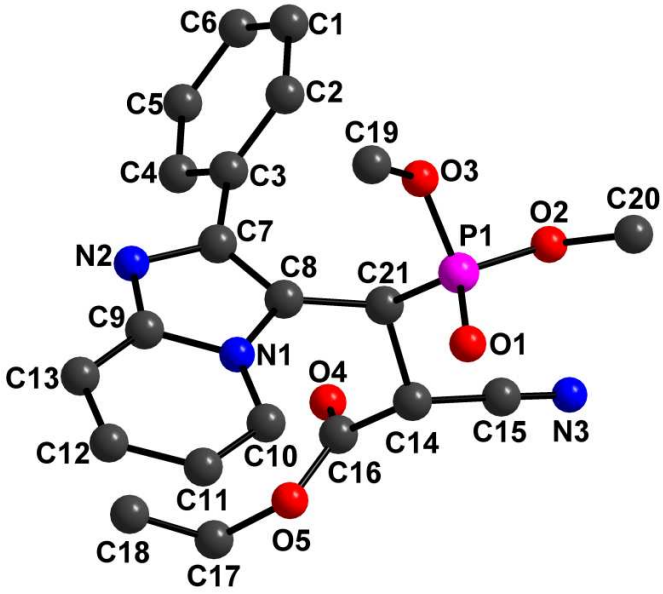


Figure 2: Molecular structure of compound 8a (Hydrogens are omitted for clarity).

CONCLUSION

In summary, we have synthesized some of novel phosphonate derivatives of Imidazo[1,2-a]Pyridine.

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