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Facile synthesis, characterization and antimicrobial activities of diphenylphosphoryl derivatives of substituted aryl and nitrogen heterocycles

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Abstract: Diphenylphosphoryl derivatives of substituted aryl and nitrogen heterocycles were prepared by a one-pot process involving sequential reaction of diphenylphosphine chloride with dry methyl alcohol/ethyl alcohol and then with different halides of substituted nitrogen heterocycles/aryl halides. The title compounds (5a-j) structures were established by analytical, IR, NMR (^{1}H, ^{13}C and ^{31}P) and mass spectra, and they have been screened for their antimicrobial activity. They exhibited significant antibacterial and antifungal activity.

Keywords: Diphenylphosphoryl derivatives; nitrogen heterocycles; antibacterial activity; antifungal activity.

1. Introduction

Generally nitrogen heterocycles having phosphorus functional groups are useful compounds in textile, pharmaceutical, agricultural industry.[1] The organophosphorus derivatives having pyridine has focused because the compounds having phosphorus and nitrogen are particularly interesting from the view point of their biological activity.[2,3] Pyridine analogues of these compounds were found to be excellent ligands after deprotonation through the coordination via the lone pairs of the oxygen to the metal.[4] The compounds are less flexible due to their central rigid part and the neighbouring sterically demanding phenyl groups. These compounds possess a number of characteristics such as use as drug components for chemotherapeutic applications, antifungal and antibacterial activity due to their maximum interactions with microorganisms.[5] Here we synthesized diphenylphosphoryl derivatives of pyridine with different halides of substituted nitrogen heterocycles/aryl halides**.**

2. Results and discussion

The synthesis of novel diphenylphosphoryl derivatives (**5a-j**) is accomplished in a two-step process. The synthetic route involves the reaction of diphenylchlorophosphine (**1**) with CH_3OH/C_2H_5OH (**2**) in dry THF in presence of triethylamine in N_2 atmosphere at 0-20 ^{o}C to afford the corresponding alkoxy intermediate (**3**). In the second step the intermediate (**3**) was reacted with

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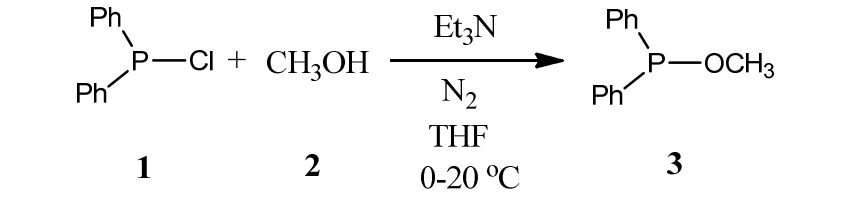
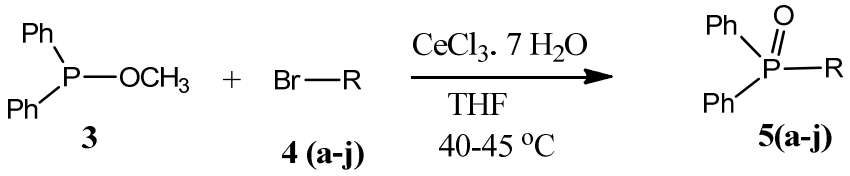
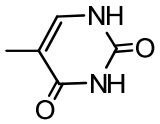
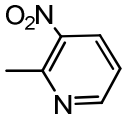
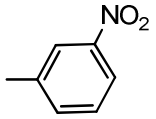
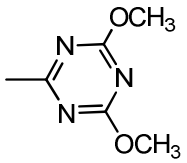
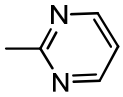
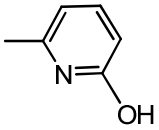
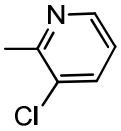
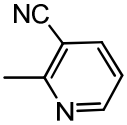
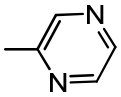
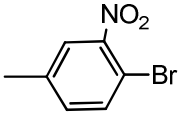
various aromatic halides (4a-j) in dry THF in presence of $CeCl_3.7H_2O$ as catalyst to afford the title compounds (**5a-j**) in good yields (**scheme 1**).





Compound	R	Compound	R
5a		5f	
5b		5g	
5c		5h	
5d		5i	
5e		5j	

Scheme 1. Synthesis of diphenylphosphoryl derivatives of substituted aryl and nitrogen heterocycles

The second step of the reaction was completed at 40-45°C with stirring for 3-5 hours. The progress of the reaction was monitored by TLC analysis at different time intervals and the crude products obtained after removing the solvent were purified by column chromatography on silica gel using ethyl acetate and hexane (4:6) as step grade mixtures as eluents. The synthetic and analytical data of title compounds (**5a-j**) are given in the experimental part. All the compounds (**5a-j**) exhibited absorption bands for P=O, NO_2, -NH, C=O, -OH and CN in the regions 1221-1299, 1550-1591, 3350-3396, 1655-1700, 3420 and CN cm^{-1} respectively.[6] The ^1H NMR spectra (400 MHz) of **5a-j** resonated the aromatic protons as multiplet at δ 6.66-7.99. The –NH proton signal was observed at δ 7.10, 9.14 as a singlet. The ^{13}C NMR spectral data for 5a, 5c, 5d and 5h were recorded and the data given in the experimental

part. The C=O carbon gave signal at δ 165.5. The remaining carbon signals are observed in the expected regions.[7] Compounds **5a-j** exhibited phosphorus-31 resonance signals in the range of 25.25 to 29.65 ppm.[8] The LC-MS of a few of the compounds were recorded and the presence of M^+ ions in their mass spectra and the data presented are in the experimental section.

2.1.Antimicrobial activity

Antimicrobial activity of 5a-j was tested against the growth of *Staphylococcus aureus* (ATCC 25923) (gram +ve) and *Escherichia coli* (ATCC 25922) (gram –ve) by disc diffusion method at various concentrations (100, 50 µg/mL) **Table 1**. All the compounds showed moderate activity against both the bacteria. The highlight is that the five compounds 5g, 5h and 5j were more effective than even the standard penicillin.

They were also screened for antifungal activity against *Aspergillus niger* (ATCC 16404) and *Helminthosporium oryzae* (ATCC 11000) species along with the standard fungicide Griseofulvin **Table 2** by the disc diffusion method at two different concentrations (100, 50 µg/mL). It is gratifying to observe that majority of the compounds **(3a-l)** exhibited higher antifungal activity when compared with that of Griseofulvin. Significant result is that **5d**, **5f**, **5g**, **5h** and **5j** exhibited higher activity than the standard Griseofulvin against both the fungi. Thus new group of compounds with very high antimicrobial/fungicidal activity than the presently used commercial bactericides/fungicides have been discovered.

Table 1. Antibacterial activity of compounds 5a-j (µg/mL)

Compound	Zone of inhibition (mm)			
	Escherichia coli		*Staphylococcus aureus*	
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
5a	7	8	7	7
5b	6	9	6	8
5c	8	10	7	7
5d	7	8	5	8
5e	7	9	6	8
5f	6	10	5	7
5g	8	11	7	9
5h	8	12	6	9
5i	6	10	6	8
5j	8	11	7	10
Penicillin[a]	8	12	7	10

[a]Reference Compound

Table 2. Antifungal activity of compounds 3a-j (µg/mL)

Compound	Zone of inhibition (mm)			
	Aspergillus niger		*Helminthosporium oryzae*	
	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL
5a	7	7	7	8
5b	6	8	8	7
5c	7	8	5	9
5d	7	9	7	7
5e	6	9	6	8
5f	8	11	10	12
5g	7	12	9	11
5h	6	8	7	7
5i	6	9	6	9
5j	8	11	8	11
Griseofulvin[a]	7	12	9	12

[a]Reference Compound

3. Conclusion

In conclusion, we reported an efficient easy process to synthesis biologically active diphenyl-phosphoryl derivatives and all are showing significant antimicrobial activity.

4. Experimental

All the chemicals were purchased from Aldrich and used without further purification. TLC was performed on precoated plates with silica gel 60F254 (Merk). Column chromatography was performed on silica gel (0.040-0.063 mm, Macherey Nagel). IR Spectra were recorded on JASCO Japan FT/IR -5300 Spectrophotometer at University of Hyderabad, Hyderabad using KBr optics. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Bruker A VIII 400 MHz NMR spectrometer at IIT-Chennai operating at 400 MHz for 1H, 100 MHz for ^{13}C and 161.6 MHz for ^{31}P NMR data were recorded in DMSO-*d6* and were referenced to TMS (^{1}H and ^{13}C) and 85% H_3PO_4 (^{31}P). Mass spectra were recorded on LCMS-2010A Shimadzu, Japan, spectrometer at University of Hyderabad, Hyderabad. Elementary analyses were performed using EA 1112 Thermo Finnigan, France, instrument at University of Hyderabad, Hyderabad, India.

Preparation of Intermediate; ethyl [(dichlorophosphoryl) amino] (phenyl) acetate: A solution of $P(Ph)_2Cl$ **(1)** (0.84 mL, 0.003 mol) in 20 mL of dry THF was added drop wise over a period of 20 min to a stirred solution of MeOH **(2)** (0.003 mol) and triethyl amine (0.9 mL, 0.003 mol) in 25 mL of THF at -20 ºC. After stirring for 3h at 0 ºC, formation of the intermediate, methoxydiphenylphosphine **(3a)** was ascertained by TLC analysis run in a 3:7 mixture of ethyl acetate and hexane and the average of Rf value observed was 0.75. Triethylamine hydrochloride was removed by filtration. The filtrate was used for the next reaction step without further purification.

Typical procedure for the Synthesis of 5a-j: To a stirred solution of the intermediate **(3a)** in dry THF, a solution of 5-bromouracil **(4)** (0.57g, 0.003 mole) was added drop wise at 0 ºC. After the completion of the addition, the temperature of the reaction was raised to 40-45 ºC and the reaction mixture was stirred for 3-5 h. After the completion of the reaction, as indicated by TLC conducted in 3:7 mixtures of ethyl acetate and hexane, an average Rf value of 0.60 was observed. The solvent was evaporated under reduced pressure to get the crude product. It was purified by column chromatography on silica gel (100-200 mesh) ethyl acetate: hexane, 1:9) to afford the pure compound. The compounds thus obtained were characterized by ^{1}H, ^{13}C, ^{31}P NMR and mass spectral data.

(Diphenylphosphoryl)pyrimidine-2,4(1H,3H)-dione (5a)[9]: Yield 70% ; m.p: 174-176 °C; IR ($CHCl_3$) cm^{-1}: 1221 (P=O), 1700-1655 (C=O), 3350-3396 (NH); ^{1}H-NMR (400 MHz, DMSO-*d6*) (δ/ppm): 7.24-7.78 (m,11 H, Ar-H), 6.18 (brs, 1H, NH-), 9.82 (brs, 1H, NH-); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 109.37 (C-5), 127.8 (2xC-3' and 2xC-5'), 130.5 (2xC-2'and 2xC-6'), 133.7 (2xC-1'), 135.1 (2xC-4'), 150.2 (C-2), 154.4 (C-6), 167.5 (C-6); ^{31}P-NMR (60.92 MHz, DMSO-d_6) (δ/ppm): 27.10; LCMS m/z: 313.5 (M+H); Anal. Calcd. for $C_{16}H_{13}N_2O_3P$: C, 61.52; H, 4.21; N, 8. 89. Found: C, 61.13; H, 4.18; N, 8.87.

(3-Nitropheny(diphenyl)phosphane oxide (5)[10]: Yield 65%; m.p: 145-147 °C; IR ($CHCl_3$) cm^{-1}:1550 (NO_2), 1235 (P=O); ^{1}H-NMR (400 MHz, DMSO-d_6) (δ/ppm): 7.40-7.89 (m,14H, Ar-H); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 125.6 (C-2, 3-nitrophenyl), 127.1 (C-4, 3-nitrophenyl), 128.4 (2xC-3 and 2xC-5, phenyl), 129.4 (C-5, 3-nitrophenyl), 132.7 (2xC-2 and 2xC-6, phenyl), 134.0 (C-1, 3-nitrophenyl), 134.8 (2xC-1, phenyl), 135.1 (2xC-4, phenyl), 138.6(C-6, 3-nitrophenyl), 148.8 (C-3, 3-nitrophenyl); ^{31}P-NMR (60.92 MHz, DMSO-d_6) (δ/ppm): 28.82; LCMS m/z : 324.5 (M+H); Anal. Calcd. for $C_{18}H_{14}NO_3P$: C, 66.82; H, 4.37; N, 4.29. Found: C, 66.91; H, 4.39; N, 4.31.

2-(Diphenylphosphoryl)pyrimidine (5c)[11]: Yield 67%; m.p: 187-189 °C; IR (KBr) cm^{-1}: 1271 (P=O); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 7.39-7.99 (m,13H, Ar-H); ^{13}C-NMR (125.77 MHz, DMSO-

d6) (δ/ppm): 127.0 (C-4), 129.4 (2xC-3' and 2xC-5'), 132.8 (2xC-2' and 2xC-6'), 134.5 (2xC-4'), 134.8 (2xC-1'), 158.6 (C-3 & C-5), 165.5 (C-1); ^{31}P-NMR (60.92 MHz, DMSO-d_6) (δ/ppm): 25.54; LCMS m/z:281.1 (M+H); Anal. Calcd. for $C_{16}H_{13}N_2OP$: C, 68.88; H, 4.70; N, 10.50. Found: C, 68.73; H, 4.71; N, 10.56.

3-Chloro-2-(diphenylphosphoryl)pyridine (5d): Yield 63%; m.p: 141-143 °C; IR (KBr) cm^{-1}: 1263 (P=O); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 7.36-7.59 (m, 13H, Ar-H); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 126.8 (C-4), 129.1 (2xC-3' and 2xC-5'), 132.0 (2xC-2' and 2xC-6'), 133.4(C-6), 134.2 (2xC-4'), 134.7 (2xC-1'), 135.5 (C-5), 150.3 (C-3), 156.9 (C-1); ^{31}P-NMR (60.92 MHz, DMSO-d_6) (δ/ppm): 26.50; LCMS m/z: 315.1 (M+H); Anal. Calcd. for $C_{17}H_{13}NOP$: C, 65.00; H, 4.20; N, 4.50. Found: C, 65.13; H, 4.18; N, 4.46.

2-(Diphenylphosphoryl)pyrazine (5e): Yield 60%; m.p: 129-131 °C; IR (KBr) cm^{-1}: 1292 (P=O); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 7.26-7.41 (m, 13H, Ar-H),); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 129.3 (2xC-3' and 2xC-5'), 132.8 (2xC-2' and 2xC-6'), 134.1 (2xC-1'), 134.3 (2xC-4'), 143.3 (C-3), 146.3 (C-6), 147.8 (C-4), 151.9 (C-1); ^{31}P-NMR (60.92 MHz, DMSO-d_6) (δ/ppm): 29.65 ; LCMS m/z: 281.3 (M+H); Anal. Calcd. for $C_{16}H_{31}N_2OP$: C, 68.58; H, 4.64; N, 10.18. Found: C, 68.55; H, 4.595; N, 10.16.

2-(Diphenylphosphoryl)-3-nitropyridine (5f): Yield 69 %; m.p: 139-141 °C; IR (KBr) cm^{-1}: 1590 (NO_2), 1275 (P=O); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 7.84-7.88 (m,13H, Ar-H); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 127.1 (C-4), 129.5 (2xC-3' and 2xC-5'), 132.5 (2xC-2' and 2xC-6'), 133.0 (C-5), 134.7 (2xC-4'), 135.4 (2xC-1'), 145.8 (C-6), 151.8 (C-1), 156.9 (C-3); ^{31}P-NMR (60.92 MHz, DMSO-d_6) (δ/ppm): 28.20; LCMS m/z: 325 ($M^{+\cdot}$); Anal Calcd. for $C_{17}H_{13}N_2O_3P$: C, 62.08; H, 4.07; N, 8.68. Found: C, 62.38; H, 4.05; N, 8.36.

2-(Diphenylphosphoryl)-4,6-dimethoxy-1,3,5-triazine (5g): Yield 65 %; m.p: 188-190 °C; IR (KBr) cm^{-1}: 1280 (P=O); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 7.22-7.37 (m, 10H, Ar-H), 3.50 (s, 3H, 2xOCH_3), ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 55.5 (2xOCH_3); 134.5 (2xC-1'), 128.5 (2xC-3' and 2xC-5'), 132.9 (2xC-2' and 2xC-6'), 135.5 (2xC-4'), 168.8 (C-1), 175.5 (C-3 & C-5); ^{31}P-NMR (60.92 MHz, DMSO-d_6) (δ/ppm): 27.20; LCMS m/z : 342 (M+H); Anal. Calcd. for $C_{17}H_{16}N_3O_3P$: C, 59.90; H, 4.72; N, 12.39. Found: C, 59.85; H, 4.75; N, 12.36.

(6-Hydroxypyridin-2-yl)diphenylphosphine oxide (5h)[12,13]: Yield 65 %; m.p: 155-157 °C; IR (KBr) cm^{-1}: 3420 (-OH),1265 (P=O); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 6.50 (s, 1H, Ar-OH), 7.65-7.98 (m,13H, Ar-H); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 109.1 (C-6), 118.7 (C-4), 127.9 (2xC-3' and 2xC-5'), 132.8 (2xC-2' and 2xC-6'), 133.5 (2xC-1'), 135.1 (2xC-4'), 135.5 (C-5), 150.8 (C-1), 156.1 (C-3); LCMS m/z: 296.5 (M+H); Anal. Calcd. for $C_{17}H_{14}NO_2P$: C, 69.26, H, 4.76, N, 4.78. Found: C, 69.50; H, 4.75; N, 4.73.

2-(Diphenylphosphoryl)nicotinonitrile (5i): Yield 58 %; m.p: 174-176 °C; IR (KBr) cm^{-1}: 1291 (P=O), 2250 (CN); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 6.66-7.29 (13H, m, Ar-H); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 110.1 (C-6), 117.2 (Ar-CN), 128.9 (2xC-3' and 2xC-5'), 131.2 (2xC-2' and 2xC-6'), 134.1 (2xC-1'), 136.1 (C-4), 137.2 (2xC-4'), 138.7 (C-5), 155.5 (C-3), 158.8 (C-1); LCMS m/z: 305 (M+H); Anal. Calcd. For $C_{18}H_{13}N_2OP$: C, 71.25, H, 4.32, N, 9.48. Found: C, 71.50; H, 4.30; N, 9.53.

(4-bromo-3-nitrophenyl)(diphenyl)phosphane oxide (5j): Yield 66 %; m.p: 167-169 °C; IR (KBr) cm^{-1}: 1591 (NO_2), 1299 (P=O); ^{1}H-NMR (400 MHz DMSO-d_6) (δ/ppm): 7.61-7.98 (m, 13H, Ar-H); ^{13}C-NMR (125.77 MHz, DMSO-d_6) (δ/ppm): 113.2 (2xC-4'), 118.7 (C-4), 127.8 (C-2), 129.3 (2xC-3' and 2xC-5'), 130.1 (2xC-2' and 2xC-6'), 132.1 (C-5), 134.1 (C-1), 135.1 (2xC-1'), 140.5 (C-6), 151.4 (C-3); LCMS m/z: 403 (M+H); Anal. Calcd. for $C_{18}H_{13}NO_3P$: C, 53.74, H, 3.27, N, 3.47. Found: C, 53.89; H, 3.29; N, 3.49.

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