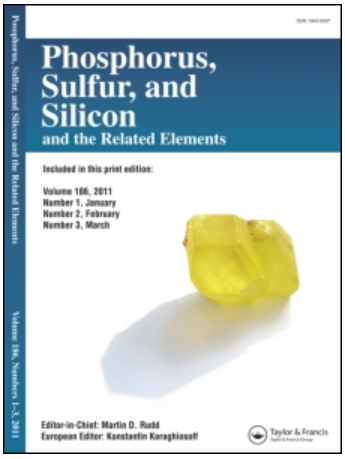

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One Pot Synthesis of Biodynamic Bisamidothiophosphonates Incorporating Asymmetric Phosphorus Atom

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One Pot Synthesis of Biodynamic Bisamidothiophosphonates Incorporating Asymmetric Phosphorus Atom

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N-alkyl-2-pyridinylidenamido(phenyl)chlorothiophosphonates have been generated in situ by oxidative phosphorylation of N-alkyl-2-aminopyridinium halides through the intermediacy of functionalized halophosphines. As evident from the proton NMR spectroscopy, the generated chiral system had induced diastereotopicity in the geminal protons attached to a prochiral carbon atom. Due to the presence of an active chlorine atom, they have been used as precursors for the synthesis of novel bisamidothiophosphonates. The bioactive nature of these compounds has been established after bioassay against the fungi Alternaria alternata*,* Aspergillus flavus, Aspergillus niger, *and* Fusarium oxysporum *and the insect* Holotrichea Consanguinea*.*

Keywords Bioassay; diastereotopicity; halophosphine; prochirality; thiophosphonate

INTRODUCTION

A novel chiral system incorporating tetracoordinated phosphorus has been developed in this study, which induced long-range diastereotopicity in the N-methylene protons attached to a prochiral carbon of the molecules. Such magnetic nonequivalence due to molecular asymmetry has been reported for a variety of compounds by a number of authors.

Siddall and Prohaska[1] observed nonequivalence of the alkoxy group of a variety of phosphorus esters. Similar findings have been reported by Rowsell[2] and Finegold[3] in the review of Jennings,[4] who compiled the chemical shift nonequivalence in prochiral groups. Moen

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and Mueller,[5] even reported the nonequivalence of a proton separated from a chiral carbon by a distance of six bonds. Pedrosa et al.[6] and Afarinkia and Jones[7,8] have achieved diastereoselective alkylated products by replacing one of such nonequivalent protons and thus, this has opened the possibility for stereoselective asymmetric synthesis.

In our previous publications, achiral bioactive amidothiophosphates from 2-aminocycloiminium salts incorporating different N-heterocycles have been reported.[9–11] The synthesis of analogous achiral thiophosphinates have been reported by Boedeker et al.[12]

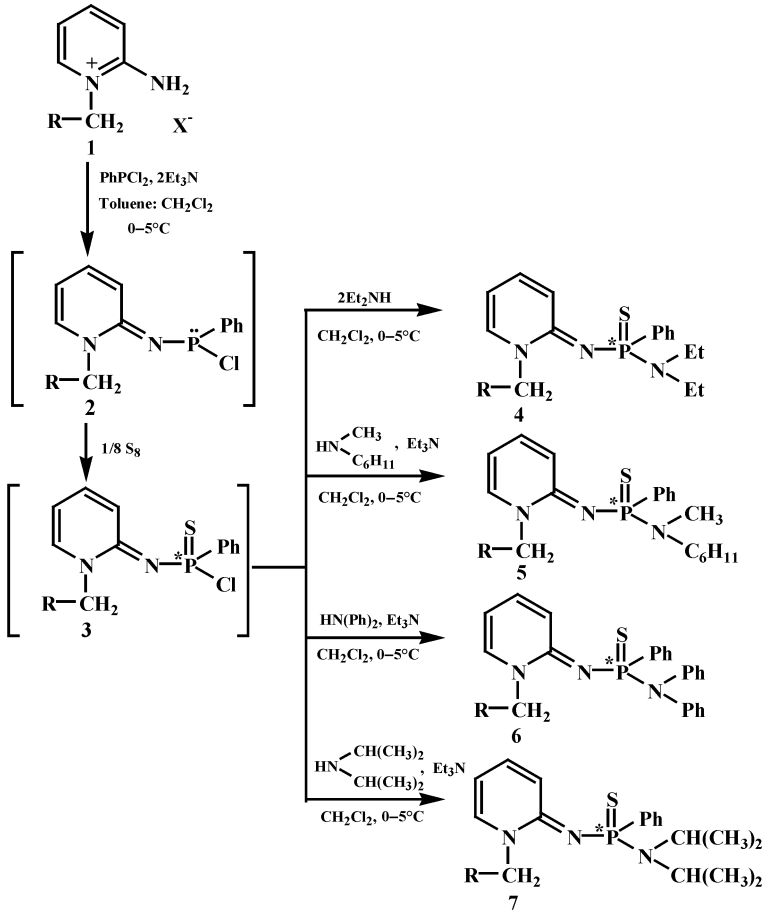
In the present work, using phenyldichlorophosphine as a phosphorylating agent, bisamidothiophosphonates have been synthesized in a one pot synthesis through the intermediacy of chlorothiophosphonates. Products incorporated a chiral phosphorus unit attached to an important heterocyclic nucleus-pyridine. As chirality is related with bioactivity,[13–16] on bioscreening, these molecules, which have been obtained as racemic products, have exhibited strong antifungal and insecticidal activities.

This study thus provided a novel class of bioactive amidothiophosphonates with the diastereotopic methylene group, thus opening further prospects for asymmetric synthesis.

RESULTS AND DISCUSSION

N-alkyl-2-aminopyridinium halides **1** have been phosphorylaed by $PhPCl_2$ (1 equivalent) and Et_3N (2 equivalents) in a 2:1 mixture of toluene and methylene chloride at 0–5°C followed by oxidation with elemental sulfur under dry nitrogen, on work-up halothiophosphonates **3** were isolated in pure state. This synthetic part of the work was already communicated.[17] In the proposed work, **3**, in situ, were converted to a new series of bisamidothiophosphonates **4–7** in a one pot synthetic procedure. By subjecting **3** to nucleophilic substitution through a different series of secondary amines in the presence of the weak base triethylamine (except in **4** where two equivalents of diethylamine have been used, which has served as a nucleophile as well as a base for the abstraction of hydrochloric acid) have achieved different series of (alkyl, alicyclic, and phenyl) asymmetrical amidothiophosphonates **4–7** (Scheme 1).

All of the products, **4–7** were obtained as stable white-to-cream and light-yellow solids and on recrystallization from methylene chloride furnished crystalline pure products, which were characterized by elemental analysis; ^{31}P, ^{1}H, ^{13}C, and 2D NMR, and mass spectroscopic techniques.



1–7	a	b	c	d	e
R	COOMe	COOEt	H	C_6H_5	$COOCH_2C_6H_5$
X	Br	Br	I	Br	Br

SCHEME 1 Scheme 1

^{31}P NMR

Reaction progress has been monitored through ^{31}P NMR spectroscopy of the reaction mixture. On such monitoring, the ^{31}P signal of the reagent $PhPCl_2$ at δ161 ppm first changed to tricoordinated halophosphines at δ 107–123 ppm, which, on the addition of sulfur, converted to tetarcoordinated halothiophosphonates with signals at δ 60.1–65.2 ppm. On

further addition of nucleophile secondary amines, an upfield shift of the order $\Delta\delta = 3.9$–7.4 ppm was been observed by the amido moiety due to a replacement of the electronegative chlorine atom, and a signal of the reaction mixture was obtained at δ 56.2–58.8 ppm, thus confirming the generation of the amidothiophosphonates. This value is in accordance with tetracoordinated pentavalent phosphorus.[18,19] Similar signals of ^{31}P NMR of the isolated products confirmed their synthesis.

^{1}H NMR

During phosphorylation, one stereogenic phosphorus was generated, which showed interesting induction of diastereotopicity. Anisochronous geminal NCH_2protons of **4a**, **4b**, **4d**, **4e**, **5a**, **5b**, **5d**, **6a**, and **7a** that were attached to a pyridine ring five bonds apart from the chiral phosphorus gave two sets of doublets at δ 4.59–5.29 ppm and 4.72–5.49 ppm with coupling constant J of the order of 14.6–21.2 Hz displaying a typical AB pattern,[4,20,21] whereas NCH_3 protons of **4c** and **5c** were assigned as a singlet at δ 3.64 and 3.71 ppm.

Another interesting induced diastereotopicity was also observed in the amido moiety of **4**, where the prochiral moiety was a nitrogen atom, such anisochronous behavior in aminophosphorus compounds has been reported in the literature both in ^{1}H NMR[22] and ^{13}C NMR[23] spectroscopy. Methylene protons of the ethylamido group gave two sets of a doublet of a doublet of a quartet in the range δ 3.03–3.14 ppm and δ 3.21–3.25 ppm due to three-bond coupling with phosphorus $^{3}J_{PH} = 7.0$–11.7 Hz in addition to geminal coupling and vicinal coupling with coupling constant $^{2}J_{HH} = 18.4$–19.1 Hz and $^{3}J_{HH} = 7.0$–7.1 Hz, respectively.

Alicyclic ring protons of **5** of N-methylcyclohexylamido moiety were observed as a complicated multiplet in the most upfield region δ 0.07–1.68 ppm showing again the nonequivalent nature of the methylene protons of a configurationally locked cyclohexyl ring forming the AB part of an ABX system.[20] Equatorial protons were found to be approximately δ 0.4 ppm more deshielded than the axial protons of the cyclohexyl ring. The coupling constant for geminal coupling was about $J_{AB} = 10.9$–12.6 Hz, and vicinal coupling J_{ax-ax} and J_{eq-ax} were 4.2–4.8 Hz and 2.4–3.5 Hz, respectively.

Aromatic protons of the pyridine and phenyl ring were observed in the expected aromatic region (Table I).

^{13}C NMR

Further support of the structure of the molecule was given by ^{13}C and 2D NMR of **4** and **5**. Carbon phosphorus coupling could be observed with

TABLE I Physical and NMR Data of Compounds

Compound.	Molecular Formula (Mol. Weight)	Color	M.P. (°C)	Yield (%)	^{31}P NMR ($CDCl_3$)	^{1}H NMR at 300 MHz ($CDCl_3$, δ ppm) J (Hz)	Elemental Analysis Calcd. Found	C%	H%	N%
4a	$C_{18}H_{24}N_3O_2PS$ (377.5)	Light yellow	95–97	69	57.2	0.98 (t, 6H, $^3J_{HH}$ = 7.0 Hz, $PNCH_2CH_3$); 3.25 (ddq, 2H, $^3J_{PH}$ = 7.0 Hz, $^3J_{HH}$ = 7.0 Hz $^2J_{HH}$ = 19.0 Hz, Ha of $PNCH_2CH_3$); 3.14 (ddq, 2H, $^3J_{PH}$ = 7.0 Hz, $^3J_{HH}$ = 7.0 Hz, , $^2J_{HH}$ = 19.0 Hz, Hb of $PNCH_2CH_3$); 3.72 (s, 3H, OCH_3); 4.70 (d, 1H, $^2J_{HH}$ = 16.2 Hz, Ha of NCH_2); 4.78 (d, 1H, $^2J_{HH}$ = 16.2 Hz, Hb of NCH_2); 6.31 (t, 1H, $^3J_{HH}$ = 6.7 Hz, H-5); 7.27–7.39 (unresolved m, 5H, PC_6H_5); 7.53 (d, 1H, $^3J_{HH}$ = 9.1 Hz, H-3); 7.86 (dd, 1H, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 2.2 Hz, H-4); 7.91 (dd, 1H, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 2.5 Hz, H-6).		57.27 57.18	6.42 6.35	11.13 11.02
4b	$C_{19}H_{26}N_3O_2PS$ (391.5)	Light yellow	88–89	70	58.4	0.98 (t, 6H, $^3J_{HH}$ = 7.0 Hz, $PNCH_2CH_3$); 1.25 (t, 3H, $^3J_{HH}$ = 7.0 Hz, OCH_2CH_3); 3.14 (ddq, 2H, $^3J_{PH}$ = 7.0 Hz, $^3J_{HH}$ = 7.0 Hz, $^2J_{HH}$ = 19.0 Hz, Hb of $PNCH_2CH_3$); 3.24 (ddq, 2H, $^3J_{PH}$ = 7.0 Hz, $^3J_{HH}$ = 7.0 Hz, , $^2J_{HH}$ = 19.0 Hz, Ha of $PNCH_2CH_3$); 4.19 (q, 2H, $^3J_{HH}$ = 7.0 Hz, OCH_2CH_3); 4.68 (d, 1H, $^2J_{HH}$ = 16.1 Hz, Ha of NCH_2); 4.78 (d, 1H, $^2J_{HH}$ = 16.1 Hz, Hb of NCH_2); 6.31 (t, 1H, $^3J_{HH}$ = 6.7 Hz, H-5); 7.27–7.37 (unresolved m, 5H, PC_6H_5); 7.54 (d, 1H, $^3J_{HH}$ = 9.1 Hz, H-3); 7.89 (dd, 1H, $^3J_{HH}$ = 5.8 Hz, $^4J_{HH}$ = 2.1 Hz, H-4); 7.91 (dd, 1H, $^3J_{HH}$ = 5.9 Hz, $^4J_{HH}$ = 2.4 Hz, H-6).		58.29 58.21	6.70 6.59	10.74 10.60

(Continued on next page)

TABLE I Physical and NMR Data of Compounds *(Continued)*

Compound.	Molecular Formula (Mol. Weight)	Color	M.P. (°C)	Yield (%)	^{31}P NMR ($CDCl_3$)	^{1}H NMR at 300 MHz ($CDCl_3$, δ ppm) J (Hz)	Elemental Analysis			
							Calcd. Found	C%	H%	N%
4c	$C_{16}H_{22}N_3PS$ (319.4)	White	98–100	56	56.2	0.95 (t, 6H, $^3J_{HH}$ = 7.0 Hz, $PNCH_2CH_3$); 3.13 (ddq, 2H, $^3J_{HH}$ = 7.1 Hz, $^3J_{PH}$ = 11.5 Hz, $^2J_{HH}$ = 18.5 Hz, Ha of $PNCH_2CH_3$); 3.25 (ddq, 2H, $^3J_{HH}$ = 7.1 Hz, $^3J_{PH}$ = 11.5 Hz, $^2J_{HH}$ = 18.5 Hz, Hb of $PNCH_2CH_3$); 3.64 (s, 3H, NCH_3); 6.21 (dt, 1H, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 1.5 Hz, H-5); 7.22–7.31 (unresolved m, 5H, PC_6H_5); 7.36 (d, 1H, $^3J_{HH}$ = 6.2 Hz, H-3); 7.91 (dd, 1H, $^3J_{HH}$ = 6.0 Hz, $^4J_{HH}$ = 2.5 Hz, H-4); 7.95 (dd, 1H, $^3J_{HH}$ = 6.2 Hz, $^2J_{HH}$ = 2.5 Hz, H-6).		60.16 60.09	6.66 6.84	13.16 13.08
4d	$C_{22}H_{26}N_3PS$ (395.5)	White	114–117	65	58.1	0.87 (t, 6H, $^3J_{HH}$ = 7.1 Hz, $PNCH_2CH_3$); 3.03 (ddq, 2H, $^3J_{HH}$ = 7.1 Hz, $^3J_{PH}$ = 11.7 Hz, $^2J_{HH}$ = 18.7 Hz, Ha of $PNCH_2CH_3$); 3.22 (ddq, 2H, $^3J_{HH}$ = 7.1 Hz, $^3J_{PH}$ = 11.7 Hz, $^2J_{HH}$ = 18.7 Hz, Hb of $PNCH_2CH_3$); 5.29 (dd, 1H, $^2J_{HH}$ = 15.02 Hz, Ha of NCH_2); 5.39 (dd, 1H, $^2J_{HH}$ = 15.02 Hz, Hb of NCH_2); 6.25 (dt, 1H, $^3J_{HH}$ = 6.8 Hz, $^4J_{HH}$ = 1.4 Hz, H-5); 7.27 (unresolved m, 10H, $NCH_2C_6H_5$, PC_6H_5); 7.16–7.27 (dd, 1H, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, H-3); 7.75 (dd, 1H, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, H-4); 7.82 (dd, 1H, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.2 Hz, H-6).		66.81 66.71	6.64 6.56	10.62 10.65

4e	$C_{24}H_{28}N_3PS$ (421.5)	Light yellow	96–97	40	58.6	0.91 (t, 6H, $^3J_{HH} = 7.0$ Hz, $PNCH_2CH_3$); 3.06 (ddq, 2H, $^3J_{HH} = 7.0$ Hz, $^3J_{PH} = 11.3$ Hz, $^2J_{HH} = 18.4$ Hz, Ha of $PNCH_2CH_3$); 3.21 (ddq, 2H, $^3J_{HH} = 7.0$ Hz, $^3J_{PH} = 11.3$ Hz, $^2J_{HH} = 18.4$ Hz, Hb of $PNCH_2CH_3$); 4.70 (d, 1H, $^2J_{HH} = 15.0$ Hz, Ha of NCH_2); 4.80 (d, 1H, $^2J_{HH} = 15.0$ Hz, Hb of NCH_2); 5.11 (s, 2H, $OCH_2C_6H_5$); 6.28 (dt, 1H, $^3J_{HH} = 6.8$ Hz, $^4J_{HH} = 1.5$ Hz, H-5); 7.21–7.32 (unresolved m, 10H, PC_6H_5, $OCH_2C_6H_5$); 7.52 (d, 1H, $^3J_{HH} = 7.2$ Hz, H-3); 7.81 (dd, 1H, $^3J_{HH} = 6.4$ Hz, $^4J_{HH} = 1.5$ Hz, H-4); 7.86 (dd, 1H, $^3J_{HH} = 6.9$ Hz, $^4J_{HH} = 1.6$ Hz, H-6).	68.38 68.41	6.71 6.50	9.97 9.98
5a	$C_{21}H_{28}N_3O_2PS$ (417.5)	Light brown	102–103	48	58.8	0.88–1.63 (m, 11H, $^2J_{AB} = 12.6$ Hz, $^3J_{ax-ax} = 4.8$ Hz, $^3J_{eq-ax} = 2.4$ Hz, $PNCH_3C_6H_{11}$); 2.49 (d, 3H, $^3J_{PH} = 11.7$ Hz, $PNCH_3C_6H_{11}$); 3.69 (s, 3H, OCH_3); 4.60 (d, 1H, $^2J_{HH} = 16.2$ Hz, Ha of NCH_2); 4.72 (d, 1H, $^2J_{HH} = 16.2$ Hz, Hb of NCH_2); 6.24 (dt, 1H, $^3J_{HH} = 6.6$ Hz, $^4J_{HH} = 1.2$ Hz, H-5); 7.19–7.39 (unresolved m, 5H, PC_6H_5); 7.49 (d, 1H, $^3J_{HH} = 7.5$ Hz, H-3); 7.78 (dd, 1H, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 1.5$ Hz, H-4); 7.83 (dd, 1H, $^3J_{HH} = 7.2$ Hz, $^4J_{HH} = 1.5$ Hz, H-6)	60.41 60.35	6.77 6.66	10.07 10.01

(Continued on next page)

TABLE I Physical and NMR Data of Compounds *(Continued)*

Compound.	Molecular Formula (Mol. Weight)	Color	M.P. (°C)	Yield (%)	^{31}P NMR ($CDCl_3$)	^{1}H NMR at 300 MHz ($CDCl_3$, δ ppm) J (Hz)	Elemental Analysis Calcd. Found	C%	H%	N%
5b	$C_{22}H_{30}N_3O_2PS$ (431.5)	White	142–143	52	58.3	0.08–1.67 (m, 11H, $PNCH_3C_6H_{11}$); 1.21 (t, 3H, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3); 4.15 (q, 2H, $^3J_{HH}$ = 7.1 Hz, OCH_2CH_3); 2.49 (d, 3H, J_{HH} = 11.7 Hz, $PNCH_3C_6H_{11}$); 4.58 (d, 1H, $^2J_{HH}$ = 16.2 Hz, Ha of NCH_2); 4.78 (d, 1H, $^2J_{PH}$ = 16.2 Hz, Hb of NCH_2); 6.26 (dt, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.2 Hz, H-5); 7.19–7.30 (unresolved m, 5H, PC_6H_5); 7.49 (t, 1H, $^3J_{HH}$ = 8.2 Hz, H-3); 7.83 (dd, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 3.3 Hz, H-4); 7.88 (dd, 1H, $^3J_{HH}$ = 7.2Hz, $^4J_{HH}$ = 3.3Hz, H-6).		61.23 61.30	7.02 7.00	9.74 9.69
5c	$C_{19}H_{26}N_3PS$ (359.5)	White	160–161	56	56.2	0.97–1.68 (m, 11H, $PNCH_3C_6H_{11}$); 2.61 (d, 3H, $^3J_{PH}$ = 11.9 Hz, $PNCH_3C_6H_{11}$); 3.71 (s, 3H, NCH_3); 6.28 (dt, 1H, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 1.3 Hz, H-5); 7.31-7.47 (unresolved m, 5H, PC_6H_5); 7.48 (d, 1H, $^3J_{HH}$ = 6.6 Hz, H-3); 7.98 (dd, 1H, $^3J_{HH}$ = 6.6 Hz, $^4J_{HH}$ = 2.6 Hz, H-4); 8.03 (dd, 1H, $^3J_{HH}$ = 6.4 Hz, $^4J_{HH}$ = 2.6 Hz, H-6).		63.47 63.39	7.30 7.20	11.69 11.57

5d	$C_{25}H_{30}N_3PS$ (435.6)	White shiny crystal	120–121	45	56.7	0.95–1.60 (m, 11H, $^2J_{AB}$ = 10.9 Hz, $^3J_{ax-ax}$ = 4.2 Hz, $^3J_{eq-ax}$ = 3.5 Hz, $PNCH_3C_6H_{11}$); 2.51 (d, $^3J_{PH}$ = 13.0 Hz, $PNCH_3C_6H_{11}$); 5.29 (d, 1H, $^2J_{HH}$ = 14.6 Hz, Ha of $NCH_2C_6H_5$); 5.49 (d, 1H, $^2J_{HH}$ = 14.6 Hz, Hb of NCH_2 C_6H_5); 6.30 (dt, 1H, $^3J_{HH}$ = 7.4 Hz, $^4J_{HH}$ = 1.3 Hz, H-5); 7.26–7.40 (unresolved m, 10H, $NCH_2C_6H_5$, PC_6H_5); 7.60 (d, 1H, $^3J_{HH}$ = 8.7 Hz, H-3); 7.81 (dd, 1H, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.5 Hz, H-4); 7.85 (dd, 1H, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.5 Hz, H-6).	68.93 68.88	6.96 6.84	9.65 9.60
6a	$C_{26}H_{24}N_3PS$ (473.5)	White	56–58	45	65.0	2.51 (s, 3H, OCH_3); 3.36 (d, 1H, $^2J_{HH}$ = 21.2 Hz, Ha of NCH_2); 3.63 (d, 1H, $^2J_{HH}$ = 21.2 Hz, Hb of NCH_2); 6.64 (t, 1H, $^3J_{HH}$ = 6.8 Hz, H-5); 7.03–7.95 (unresolved m, 18H, PC_6H_5, $PN(C_6H_5)_2$, H-3, H-4, H-6).	65.95 65.90	5.11 5.07	8.88 8.80
7a	$C_{20}H_{28}N_3PS$ (373.5)	White	88–89	56	63.9	1.13 (d, 12H, $^3J_{HH}$ = 6.9 Hz, CH_3); 3.37–3.58 (m, 2H, CH); 3.67 (s, 3H, OCH_3); 4.59 (d, 1H, $^2J_{HH}$ = 15.9 Hz, Ha of NCH_2); 4.83 (d, 1H, $^2J_{HH}$ = 15.9 Hz, Hb of NCH_2); 6.59 (dt, 1H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ = 1.6 Hz, H-5); 7.42–7.47 (m, 5H, PC_6H_5); 7.97 (d, 1H, $^3J_{HH}$ = 7.1 Hz, H-3); 8.09 (dd, 1H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ = 1.6 Hz, H-4); 8.12 (dd, 1H, $^3J_{HH}$ = 7.1 Hz, $^4J_{HH}$ = 1.6 Hz, H-6).	64.31 63.75	7.57 7.00	11.25 11.01

TABLE II ^{13}C NMR of 4b, 5b, and 5c

Compound	δ (ppm) J(Hz)
4b	14.2 ($PNCH_2CH_3$); 53.9 ($PNCH_2CH_3$); 39.7 (OCH_2CH_3); 61.8 (OCH_2CH_3); 108.1 (NCH_2); 120.4 (d, $^2J_{CP}$ = 11.4, C_{ortho}); 127.8 (d, $^3J_{CP}$ =13.6, C_{meta}); 130.6(C_{para}); 139.7 (d, $^1J_{CP}$ = 129.5, C_{ipso}); 127.8(C-5); 130.7 (C-3); 138.5 (C-4); 139.1 (C-6); 156.6 (d, $^2J_{PC}$ = 10.6, C-2); 167.4 (C=O)
5b	14.0 (OCH_2CH_3); 24.3–30.8 ($C_{\beta,\beta'}$, $C\gamma,\gamma'$, $C_{\alpha'}$ of $NCH_3C_6H_{11}$); 54.5 ($NCH_3C_6H_{11}$); 61.8(C_α of $NCH_3C_6H_{11}$); 61.4 (OCH_2CH_3); 107.9 (NCH_2); 120.5 (d, $^2J_{CP}$ = 9.8, C_{ortho}); 130.5(d, $^3J_{CP}$ = 10.6, C_{meta}); 130.6 (C_{para}); 138.9 (d, $^1J_{CP}$ = 129.1, C_{ipso}); 129.8 (C-5); 130.7 (C-3); 138.5 (C-4); 140.2 (C-6) ; 156.5 (d, $^2J_{CP}$ =10.9, C-2); 167.4 (C=O)
5c	27.8–30.8 ($C_{\beta,\beta'}$, $C\gamma,\gamma'$, $C_{\alpha'}$ of $NCH_3C_6H_{11}$); 54.5 ($NCH_3C_6H_{11}$); 60.8(C_α of $NCH_3C_6H_{11}$); 107.9 (NCH_3); 120.2 (d, $^2J_{CP}$ =9.8, C_{ortho}); 127.7(d, $^3J_{CP}$ = 10.6, C_{meta}); 130.7 (C_{para}); 139.6 (d, $^1J_{CP}$ = 129.1, C_{ipso}); 129.8 (C-5); 130.8 (C-3); 137.9 (C-4); 138.0 (C-6); 207.6 (d, $^2J_{CP}$ = 10.9, C-2)

few carbon atoms of the molecule. In this discussion, special mention of the *ipso*-carbon of the phenyl moiety directly attached to the phosphorus atom should be of interest, it showed doublet at δ 138.9–139.7 ppm with minimum intensity due to the quaternary nature with coupling constant $^1J_{CP}$ = 129.5 Hz. The *ipso*-carbon of the synthons **3** was also observed as a doublet but with a higher coupling constant of the order $^1J_{CP}$ = 213.7 Hz (Table II). The difference of the coupling constant in amidothiophosphonates and chlorothiophosphonates **3** (ΔJ = 84.2 Hz) was due to the replacement of the electronegative chlorine of **3** by the amido moiety; this is in accordance with the values reported in the literature.[24]

MASS SPECTRUM

In the mass spectrum of **4a**, the molecular ion peak together with an (M+1) peak with 36% and 50% intensity has been observed at m/z

TABLE III Mass Spectrum Data of 4a and 5b (Relative Abundances Have Been Given in Parentheses)

Compound	m/z (%)
4a	377 (M^+, 36); 378 (M+1, 50); 346 (5); 345 (10); 305 (18); 273 (20); 269 (5); 149 (100).
5b	431 (M^+, 17%); 432 (M+1, 50); 399 (10); 319 (22); 320 (50); 287 (30); 181 (5); 165 (5); 163 (100); 136 (14); 135 (76); 107 (38).

377 and 378, respectively. A radical ion at m/z 149 with 100% abundance represented a base peak and other fragmented peaks listed in Table III. The molecular ion peak in **5b** was found at m/z 431 (20%) together with (M+1) peak m/z 432 (50%) in the spectrum because of the possible acceptance of one proton by iminium nitrogen. The other peaks have been recorded at m/z 399, 319, 320, 287, 181, 165, 136, 135, and 107 with a base peak at m/z 163 with 100% abundance.

BIOACTIVITY

Strong antifungial activity was exhibited by these molecules against *Alternaria alternata, Aspergillus flavus, Aspergillus niger,* and *Fusarium oxysporum*, which we have already reported in our previous communication.[25] The present insecticidal screening was aimed to test the bioefficacy of few of the synthesized thiophosphonates on *Holotrichea consanguinea* Blanch. A dose of 50 ppm v/v was selected for inoculation. Observations on the mortality of the insect have been recorded for two, four, seven, and ten days of their introduction to the toxic soil. The results have been analyzed statistically, and results have been presented in Table IV and Figure 1.

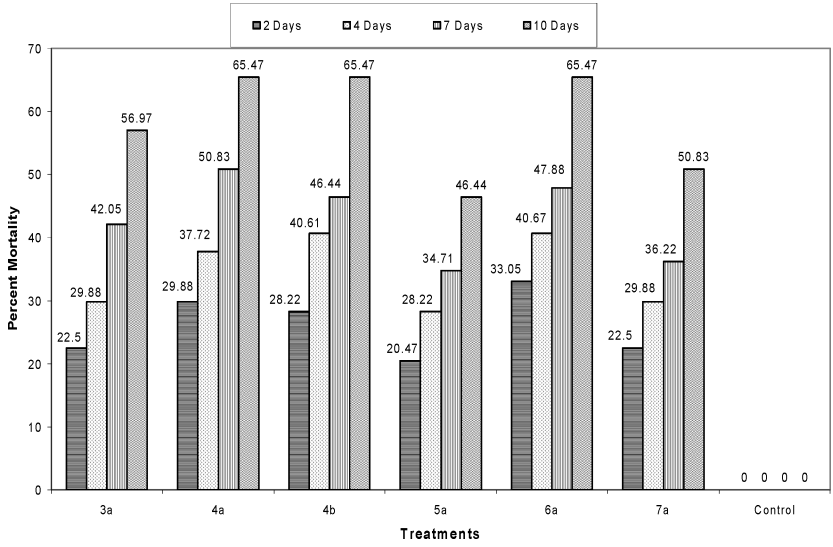


FIGURE 1 Percent mortality of *Holotrichea consanguinea* at 2, 4, 7, and 10 days after the treatment.

TABLE IV Percent Mortality of First Instar *Holotrichea consanguinea* Grubs, 2, 4, 7, and 10 Days After the Treatment by the Soil Drenching Method

S. No.	Treatments	Percent Mortality Days After Treatment			
		2 Days	4 Days	7 Days	10 Days
3a	N-(2-Methoxy-2-oxoethyl)-2-pyridinyliden-amido(phenyl)chlorothiophosphonates	15 (22.50)	25 (29.88)	45 (42.05)	70 (56.97)
4a	N-(2-Methoxy-2-oxoethyl)-2-pyridinyliden-amido(diethylamido)(phenyl)thiophosphonates	25 (29.88)	37.50 (37.72)	62.50 (50.83)	82.50 (65.47)
4b	N-(2-Ethoxy-2-oxoethyl)-2-pyridinyliden-amido(diethylamido)(phenyl)thiophosphonates	22.50 (28.22)	42.50 (40.61)	52.50 (46.44)	82.50 (65.47)
5a	N-(2-Methoxy-2-oxoethyl)-2-pyridinyliden-amido(N-methylcyclohexylamido)(phenyl) thiophosphonate	12.50 (20.47)	22.50 (28.22)	32.50 (34.71)	52.50 (46.44)
6a	N-(2-Methoxy-2-oxoethyl)-2-pyridinyliden-amido(diphenylamido)(phenyl)thiophospho-nates	30 (33.05)	42.50 (40.67)	55 (47.88)	82.50 (65.47)
7a	N-(2-Methoxy-2-oxoethyl)-2-pyridinyliden-amido(diisopropylamido)(phenyl)thiophospho-nates	15 (22.50)	25 (29.88)	35 (36.22)	60 (50.83)
	Control	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	S.Em.	2.01	1.79	2.26	2.67
	C.D. at 5%	5.91	5.26	6.64	7.84

*Figures in parentheses are angular transformed values.

S. Em. = Standard error mean, C.D. at 5% Critical difference at 5%.

CONCLUSION

In the present study a chiral thiophosphonates system was developed successfully with interesting diastereotopicities. The products exhibited substantial bioactivity against white grub, the most harmful pest insect of India. The best result with 65.47% mortality was recorded in **4a**, **4b**, and **6a** after final observations. These three compounds structurally incorporate electron-withdrawing (phenyl and ester groups) and bulky (diethylamido/diphenylamido) substituents, which fulfill the basic requirement for insecticidal activity.[26,27] There was no grub mortality in the untreated control. Test compound **4a** with effective insecticidal property was screened in a pot experiment and showed a substantial 70% mortality in the first star grubs of *H. consanguinea* Blanch in 21 days.

EXPERIMENTAL SECTION

All the commercial reagents and solvents were distilled and dried under a nitrogen atmosphere before use. Reactions were carried out in dry equipments using Schlenk techinques. The melting points were determined on an electric tempo instrument by the capillary method. NMR spectra were recorded on Jeol AL 300 at 121.50 MHz (^{31}P NMR) and 300.40 MHz (^{1}H NMR), or Jeol FX 90Q at 36.23 MHz (^{31}P NMR), 89.50 MHz (^{1}H NMR), and 75.45 MHz (^{13}C NMR). Elemental analyses were carried out on a Heraeus Carlo Erba 1108 analyzer. Fast atomic bombardment (FAB) mass spectrum was recorded on a Jeol SX 102/DA–6000 mass spectrometer/data system using Argon/Xenon (6 KV, 10 mA) as the FAB gas.

General Procedure for the N-Alkyl-2-pyridinylidenamido-(diethylamido)(phenyl)thiophosphonates (4a–f)

Triethylamine (4.5 mL, 32 mmoles) was added to a well-stirred suspension of N-alkyl-2-aminopyridinium halides (4 g, 16 mmoles) in toluene (10 mL) at 0–5°C. Simultaneously, a solution of dichlorophenylphosphine (2.2 mL, 16 mmoles) in a 2:1 mixture of toluene and methylene chloride (30:15 mL) was added dropwise with constant stirring. Sulfur (0.5 gm, 16 mmoles) was added to the reaction mixture, and stirring was continued for 2–3 days at room temperature. To this a solution of diethylamine (3.4 mL, 32 mmoles) in methylene chloride (5 mL) was added dropwise at 0–5°C. Here two equivalents of diethylamine have been used as a nucleophile as well as a base. The resulting mixture was brought to room temperature and left for stirring for 2 days. The

reaction was filtered, and solvent was removed under reduced pressure; residue was extracted with diethyl ether (2 × 50 mL). The combined ethereal extract was concentrated to one-fourth of its volume and left in a refrigerator, whereupon a white-to-light-yellow crystalline solid was deposited. The compound was filtered, recrystallized with methylene chloride, and dried.

General Procedure for the N-Alkyl-2-pyridinylidenamido-(N-methylcyclohexylamido)(phenyl)thiophosphonates (5a–d)

To a suspension of N-alkyl-2-aminopyridinium halides (4 g, 16 mmoles) in toluene (10 mL) was added triethylamine (4.5 mL, 32 mmoles) at 0–5°C. A solution of dichlorophenylphosphine (2.2 mL, 16 mmoles) in a 2:1 mixture of toluene and methylene chloride (30:15 mL) was added dropwise with constant stirring. Stirring of the mixture was continued for 2 h. To this was added sulfur powder (0.5 g, 16 mmoles). On the third day, one equivalent amount of triethylamine (2.3 mL, 16 mmoles) followed by a dropwise addition of N-methylcyclohexylamine (2.1 mL, 16 mmoles) in methylene chloride (5 mL) was done, while maintaining the temperature at 0–5°C, and the resulting mixture was stirred for 2 days. The reaction was filtered, solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (2 × 50 mL). The combined ethereal extract was concentrated and left in a refrigerator, whereupon a white-to-light-brown solid was separated, which was filtered, recrystallized with methylene chloride, and dried.

General Procedure for the N-Alkyl-2-pyridinylidenamido-(diphenylamido)(phenyl)thiophosphonates (6a)

An analogous procedure was carried out for the synthesis of **6a** by a dropwise addition of diphenylamine (2.7 g, 16 mmoles) in methylene chloride (5 mL) in the presence of a base triethylamine (2.3 mL, 16 mmoles) while maintaining the temperature at 0–5°C, and the resulting mixture was stirred for 2 days. The reaction was filtered, solvent was removed under reduced pressure, and residue was extracted with diethyl ether (2 × 50 mL). The combined ethereal extract was concentrated and left in a refrigerator, whereupon a white solid was separated, which was filtered, recrystallized with methylene chloride, and dried.

General Procedure for the N-Alkyl-2-pyridinylidenamido-(diisopropylamido)(phenyl) thiophosphonates (7a)

A procedure similar to that for **4** was followed using triethylamine (2.3 mL, 16 mmoles) and a solution of diisopropylamine (2.1 mL, 16 mmoles)

in methylene chloride (5 mL) in place of diethylamine, and the resulting mixture was stirred for 2 days. The reaction was filtered, solvent was removed, and the residue was extracted with diethyl ether (2 × 50 mL). The combined ethereal extract was concentrated and left in a refrigerator, whereupon a white solid separated, which was filtered, recrystallized with methylene chloride, and dried.

Bioactivity

A dose of 5 kg/hectare was computed for soil bioassay. 50 cc (∼ 60 g) of air-dried soil was taken in each plastic container (length = 8 cm and diameter = 5 cm) with 12 mL of stock solution (75 mg of compound dissolved in a little quantity of acetone and diluted with 180 mL of water). In these containers, one test grubs was introduced with some millet roots. For control (soil, water, and acetone mixture) grub and millet root were taken. Ten such replicates were prepared for each compound; percent mortality of the insect in each replicate was calculated. The percentage figures were then converted to the angular transformed values, which were subjected to the statistical analysis of Completely Randomized Design technique.

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