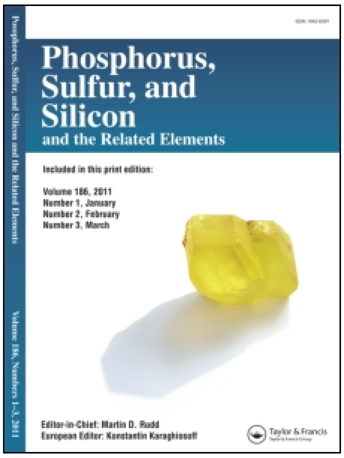

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Synthesis of Functionalized Chiral Phosphines and Chlorothiophosphonates

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Synthesis of Functionalized Chiral Phosphines and Chlorothiophosphonates

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N-alkyl-2/4-aminocycloiminium salts of pyridine on reaction with dichlorophenylphosphine in the presence of triethylamine generated a novel series of tricoordinated chiral halophosphines, which, through its asymmetric phosphorus atom, induced diastereotopicity in the geminal N-methylene group. Halophosphines have been synthesized as a key precursor, which, in situ converted to stable tetracoordinated phosphorus by oxidation with elemental sulfur to obtain a new series of synthon compounds with an active chlorine atom. Chlorothiophosphonates have also exhibited a similar chemical-shift nonequivalence of geminal protons of NCH_2. These compounds have been used for generation of variety of chiral bisamidothiophosphonates and investigated for insecticidal activity against Holotrichia consanguinea (whitegrub), which is an active pest of the crops of North India.

Keywords Prochirality; diastereotopicity; chlorophophines; chlorothiophosphonates

INTRODUCTION

The rich biological[1,2] and synthetic[3] profile of phosphorus-containing chiral compounds has prompted the development of a new strategy for their synthesis.[4–7] Usually halophosphines incorporating a configurationally stable tetrahedral center on the NMR time scale[8] served as a precursor for a catalyst in asymmetric synthesis and biologically active molecules. In this study, we report a general synthetic route for a novel series of functionalized halophosphines and chlorothiophosphonates with chiral phosphorus.

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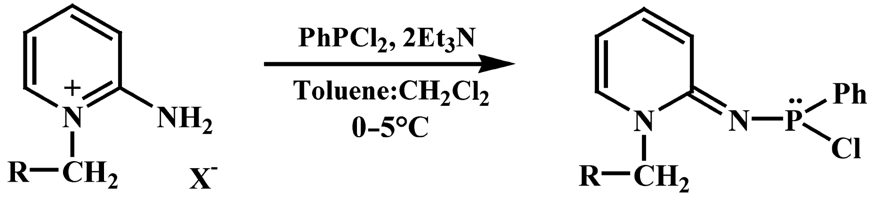


1 **2**

1/2	a	b	c	d
R	COOMe	COOEt	H	C_6H_5
X	Br	Br	I	Br

SCHEME 1

RESULTS AND DISCUSSION

N-Alkyl-2-aminopyridinium halides **1**, when reacted with dichloro phenylphosphines (1 equivalent) and Et_3N (1 equivalent) in a 2:1 mixture of toluene and methylene chloride, produced N-alkyl-2-pyridinylidenamino(phenyl) chlorophosphines **2** (Scheme 1).

The products were moisture sensitive and stable only under a dry nitrogen atmosphere, characterized by ^{31}P and ^{1}H NMR spectroscopy (Table I). The reaction was monitored through ^{31}P spectroscopy of the reaction mixture where a signal of the reagents ($PhPCl_2$) at δ 161 ppm progressively disappeared with the appearance of the signal of products **2** in the range δ 107–123 ppm. This range is in well accordance with tri-coordinated aminohalophosphines.[9,10] These chiral synthons can serve as good precursors for varities of asymmetric organophosphorus compounds by simple substitution of chlorine by various nucleophiles.

In ^{1}H spectroscopy, interesting nonequivalence of geminal methylene protons was observed. Each proton appeared as a doublet at δ 4.25–4.63 and 4.35–4.75 ppm due to geminal coupling ($^{2}J_{HH}$= 15.0–17.0 Hz). This unique phenomenon has been observed by different workers also in chiral phosphorus derivatives.[11,13] This anisochronous behavior of methylene protons was due to a generated chiral phosphorus center during phosphorylation, which was five bonds apart from the prochiral carbon atom.

Halophosphines **2**, on reaction with elemental sulfur in methylene chloride, furnished another series of asymmetric active chlorine-containing chlorothiophosphonates **3** (Scheme 2), which were stable white to light-yellow colored crystalline solids and were characterized

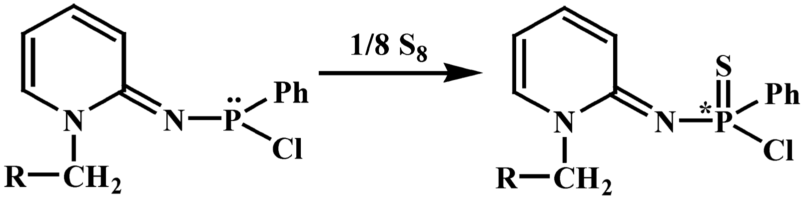
TABLE I Physical and NMR Data of Chlorophosphines 2 and Chlorothiophosphonates 3 and 5

Compound	Molecular Formula (Mol. Weight)	Color	M.P. (°C)	Yield (%)	^{31}P NMR ($CDCl_3$)	^{1}H NMR Hz ($CDCl_3$, δ ppm) J (Hz)	Element Analysis		
							C%	H%	N%
2a	$C_{14}H_{14}N_2O_2PCl$ (308.7)	White	85	50	123	3.68 (s, 3H, OCH_3); 4.63 (d, 1H, $^2J_{HH} = 17.0$ Hz, Ha of NCH_2); 4.75 (d, 1H, $^2J_{HH} = 17.0$ Hz, Hb of NCH_2); 6.68 (t, 1H, $^3J_{HH} = 7.0$ Hz, H-5); 7.40–7.61 (unresolved m, 6H, PC_6H_5, H-3); 8.05 (dd, 1H, $^3J_{HH} = 7.0$ Hz, $^4J_{HH} = 2.8$ Hz, H-4); 8.24 (d, 1H, $^3J_{HH} = 7.0$ Hz, H-6)	54.47 54.48	4.57 4.48	9.07 9.09
2c	$C_{12}H_{12}N_2PCl$ (250.6)	White	80	42	107	3.05 (s, 3H, NCH_3); 6.20 (t, 1H, $^3J_{HH} = 6.2$ Hz, H-5); 7.23–7.42(unresolved m, 6H, PC_6H_5, H-3); 7.92 (dd, 2H, $^3J_{HH} = 6.2$ Hz, $^4J_{HH} = 2.4$ Hz, H-4,); 8.06 (d, 1H, $^3J_{HH} = 6.2$ Hz, H-6)	57.49 57.43	4.83 4.61	11.17 11.12
2d	$C_{18}H_{16}N_2PCl$ (326.7)	White	89	40	115	4.25 (d, 1H, $^2J_{HH} = 15.0$ Hz, Ha of NCH_2); 4.35 (d, 1H, $^2J_{HH} = 15.0$ Hz, Hb of NCH_2); 6.01 (t, 1H, $^3J_{HH} = 7.0$ Hz, H-5); 7.01–7.18 (unresolved m, 11H, PC_6H_5, $NCH_2C_6H_5$, H-3); 7.80 (d, 2H, $^3J_{HH} = 7.0$ Hz, H-4, H-6)	66.16 66.00	4.94 4.72	8.57 8.32
3a	$C_{14}H_{14}N_2O_2SPCl$ (340.7)	White	118	68	63.8	3.77 (s, 3H, OCH_3); 4.65 (d, 1H, $^2J_{HH} = 17.0$ Hz, Ha of NCH_2); 4.97 (d, 1H, $^2J_{HH} = 17.0$ Hz, Hb of NCH_2); 6.72 (dt, 1H, $^3J_{HH} = 7.1$ Hz, $^4J_{HH} = 1.4$ Hz, H-5); 7.45–7.56 (unresolved m, 5H, PC_6H_5); 7.79 (dd, 1H, $^3J_{HH} = 7.1$ Hz, $^4J_{HH} = 1.4$ Hz, H-3); 8.11 (dd, 1H, $^3J_{HH} = 7.1$ Hz, $^4J_{HH} = 2.8$ Hz, H-4); 8.36 (dd, 1H, $^3J_{HH} = 7.1$ Hz, $^4J_{HH} = 2.8$ Hz, H-6)	49.34 49.20	4.14 4.01	8.22 8.12

(Continued on next page)

TABLE I Physical and NMR Data of Chlorophosphines 2 and Chlorothiophosphonates 3 and 5 *(Continued)*

Compound	Molecular Formula (Mol. Weight)	Color	M.P. (°C)	Yield (%)	^{31}P NMR ($CDCl_3$)	^1H NMR Hz ($CDCl_3$, δ ppm) J (Hz)	Element Analysis		
							C%	H%	N%
3b	$C_{15}H_{16}N_2O_2SPCl$ (354.7)	White	95	75	65.2	1.20 (t, 3H, $^3J_{HH} = 7.1$ Hz, OCH_2CH_3); 4.21 (q, 2H, $^3J_{HH} = 7.1$ Hz, OCH_2CH_3); 4.65 (d, 1H, $^2J_{HH} = 16.1$ Hz, Ha of NCH_2); 4.91 (d, 1H, $^2J_{HH} = 16.1$ Hz, Hb of NCH_2); 6.7 (dt, 1H, $^3J_{HH} = 6.7$ Hz, $^4J_{HH} = 1.4$ Hz, H-5); 7.44–7.57 (unresolved m, 5H, PC_6H_5); 7.70 (dd, 1H, $^3J_{HH} = 6.7$ Hz, $^4J_{HH} = 1.4$ Hz, H-3); 8.19 (dd, 1H, $^3J_{HH} = 7.5$ Hz, $^4J_{HH} = 1.6$ Hz, H-4); 8.22 (dd, 1H, $^3J_{HH} = 7.8$ Hz, $^4J_{HH} = 1.6$ Hz, H-6)	50.78 50.72	4.54 4.44	7.89 7.79
3c	$C_{12}H_{12}N_2PSCl$ (282.7)	Light yellow	89	52	63.3	3.74 (s, 3H, NCH_3); 6.52 (dt, 1H, $^3J_{HH} = 6.0$ Hz, $^4J_{HH} = 1.2$ Hz, H-5); 7.15–7.32 (unresolved, 5H, PC_6H_5); 7.39 (dd, 1H, $^3J_{HH} = 6.0$ Hz, $^4J_{HH} = 1.2$ Hz, H-3); 7.96 (dd, 1H, $^3J_{HH} = 6.0$ Hz, $^4J_{HH} = 2.2$ Hz, H-4); 8.01 (dd, 1H, $^3J_{HH} = 6.0$ Hz, $^4J_{HH} = 2.2$ Hz, H-6)	50.98 50.99	4.28 4.10	9.91 9.80
3d	$C_{18}H_{16}N_2PSCl$ (358.8)	White	90	45	61.0	4.72 (d, 1H, $^2J_{HH} = 15.0$ Hz, Ha of NCH_2); 5.02 (d, 1H, $^2J_{HH} = 15.0$ Hz, Hb of NCH_2); 6.28 (dt, 1H, $^3J_{HH} = 6.9$ Hz, $^4J_{HH} = 1.2$ Hz, H-5); 7.15–7.30 (unresolved m, 11H, PC_6H_5, $NCH_2C_6H_5$); 7.38 (dd, 1H, $^3J_{HH} = 6.9$ Hz, $^4J_{HH} = 1.2$ Hz, H-3); 7.89 (d, 1H, $^3J_{HH} = 6.9$ Hz, H-4); 8.10 (d, 1H, $^3J_{HH} = 6.9$ Hz, H-6)	60.25 60.30	4.49 4.41	7.81 7.85
5a	$C_{14}H_{14}N_2O_2SPCl$ (340.7)	Yellow	96	58	66.2	2.37 (s, 3H, OCH_3); 3.55 (s, 2H, NCH_2); 7.50-7.60 (unresolved m, 5H, PC_6H_5); 8.05 (dd, 2H $^3J_{HH} = 8.5$ Hz, $^4J_{HH} = 2.8$ Hz, H-3, H-5); 8.33 (dd, 2H, $^3J_{HH} = 8.5$ Hz, $^4J_{HH} = 2.8$ Hz, H-4, H-6)	49.34 49.21	4.14 4.05	8.22 8.25



2 **3**

2/3	a	b	c	d
R	COOMe	COOEt	H	C_6H_5

SCHEME 2

by elemental analysis, ^{31}P, ^{1}H, (Table I) and ^{13}C NMR; and mass spectroscopy. Here, the phenomenon of diastereotopicity can also be observed for NCH_2 protons in ^{1}H spectrum, which gave two doublets due to geminal coupling in the range δ 4.65–4.72 and 4.91–5.02 ppm with coupling constant ($^{2}J_{HH}$= 15.0–17.0 Hz).

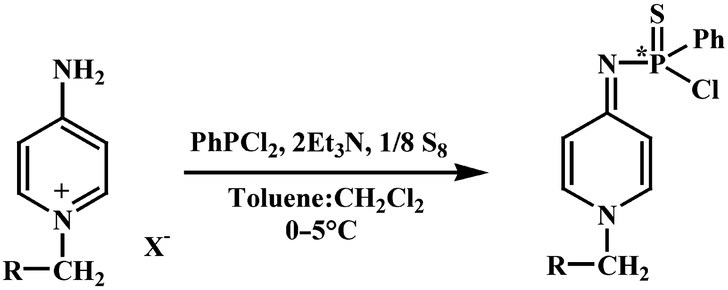
These stable active chlorine-containing chiral synthons obtained as the racemic mixture also can act as precursors for various chiral thiophosphonates via substitution through different nucleophiles.

Further confirmation of **3b** has been done by ^{13}C NMR. The *ipso*-carbon of the phenyl group attached to phosphorus showed a doublet with a high coupling constant in the range ($^{1}J_{CP}$= 213.7 Hz) due to a nearby electronegative chlorine atom[14] (Table II).

TABLE II Mass Spectrum and ^{13}C NMR data of 3b

Compound	m/z (%)	δ (ppm) J (Hz)
3b	354 (M^+, 22); 356 (M+2, 7); 320 (6); 321 (10); 181 (100); 165 (10); 163 (73); 136 (56); 135 (53); 107 (22)	14.5 (OCH_2CH_3); 53.0 (NCH_2); 62.3 (OCH_2CH_3); 110.2 (C-5); 120.0 (d, $^{2}J_{CP}$ = 12.1 Hz, C-3); 128.0 (d, $^{3}J_{CP}$ = 16.2 Hz, C_{meta}); 130.0 (C_{para});130.5 (d, $^{2}J_{CP}$ = 12.4 Hz, C_{ortho}); 139.6 (C-4); 140.6 (C-6); 140.7 (d, $^{1}J_{CP}$ = 213.7 Hz, C_{ipso},); 157.5 (d, $^{2}J_{CP}$ = 11.3 Hz, C-2); 160 (C=O)

Relative abundances have been given in parentheses.



4 **5**

R = COOCH$_3$, X = Br
SCHEME 3

Mass spectrum of N-(2-ethoxy-2-oxoethyl)-2-pyridinylidenamido (phenyl)chloro thiophosphonate **3b** has been shown in Table II. The molecular ion peak appeared at m/z 354 with 22% abundance together with an M+2 peak at m/z 356 approximately one-third of the intensity of the molecular ion peak (7%) because of the presence of ^{37}Cl isotope, which further splitted in a different ion peak at m/z 320, 321, 181, 136, 135, 107, 165, and 163. A base peak was found at m/z 181 with 100% abundance.

Similarly, N-alkyl-4-aminopyridinium halides **4** yielded the corresponding N-alkyl-4-pyridinylidenamido(phenyl) chlorothiophosphonate **5** (Scheme 3). As expected, in this compound geminal protons of N-methylene groups were equivalent because the stereogenic phosphorus centre is very far away (Table I); hence, we observed a singlet for N-methylene protons in the region δ 2.37 ppm.

INSECTICIDAL ACTIVITY

As reported by Hartly,[15] chirality enchances the bioactivity of the compounds; asymmetrical chlorothiophosphonates **3a–d** were also found to be active against whitegrubs *Holotrichia consanguinea* (Coleoptera: Scarabacidae) when subjected to insecticidal activity by the soil drenching method.[16] The first instar stage of whitegrub at 50-ppm v/v dose has been selected for this study. Percent mortality of the insect in each replicate was calculated by counting the number of dead insects. The percentage figures then converted to the angular transformed values,

TABLE III Percent Mortality of First Instar *Holotrichia consanguinea* Grubs 2, 6, and 10 Days After the Treatment by the Soil Drenching Method

S. No	Treatments	Percent Mortality Days After Treatment		
		2 Days	6 Days	10 Days
3a	N-(2-Methoxy-2--oxoethyl)-2-pyridinylidenamido(phenyl)chlorothiophosphonates	32.50 (34.71)	45 (42.05)	70 (56.97)
3b	N-(2-Ethoxy-2-oxoethyl)-2-pyridinylidenamido(phenyl)chlorothiophosphonates	30 (33.05)	37.50 (37.72)	62.50 (52.27)
3c	N-Methyl-2-pyridinylidenamido(phenyl) chlorothiophosphonates	15 (22.50)	25 (29.88)	42.50 (40.67)
3d	N-Benzyl-2-pyridinylidenamido(phenyl) chlorothiophosphonates	25 (32.38)	32.50 (34.71)	55 (47.88)
	Control	0.00	0.00	0.00
	Standard Error Mean ±.	4.32	2.12	5.60
	Critical Difference at 5 %	13.00	6.36	7.13

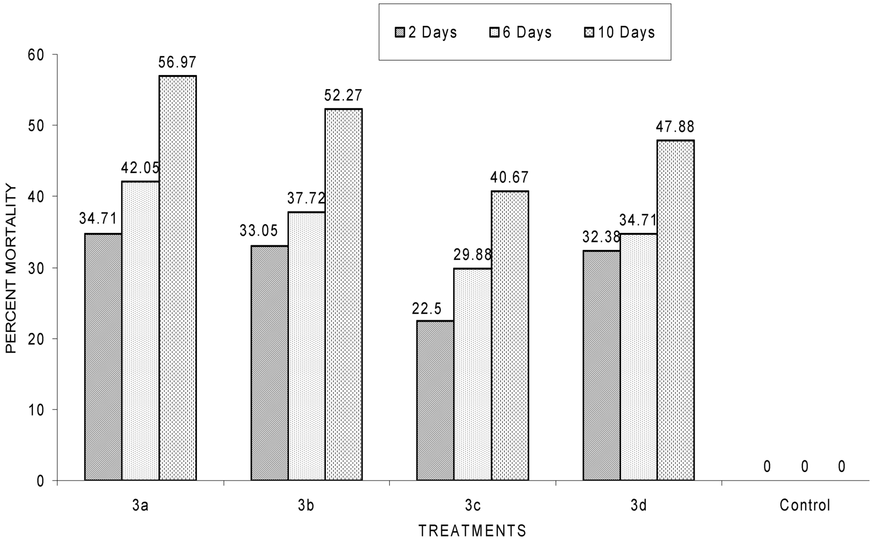


FIGURE 4 Percent mortality of first instar *Holotrichia consanguinea* grubs 2, 6, and 10 days after the treatment.

which have been subjected to a complete randomized technique[17] (Table III and Figure 1).

CONCLUSION

The present work evolved an economical synthetic strategy for few chiral molecules. Furthermore, insecticidal analysis showed that compounds **3a** and **3b**, having electron-withdrawing (phenyl and ester) groups in the vicinity of a phosphorus atom, were found to be best with 56.97% and 52.27% grub mortality. Compound **3d** was observed with 47.88% mortality. **3c** with 40.67% was found to be inferior to the other three compounds. In the control, there was no grub mortality. These results confirmed the previous reported[18] finding that bulky and electron-withdrawing substituent enhance the bioactivity, and hence **3a**, **3b**, and **3d** were found to be superior in insecticidal activity.

EXPERIMENTAL

All experiments were performed in an atmosphere of dry nitrogen using schlenk technique. Solvents were distilled and dried by common methods before use. The melting points were determined on an electric tempo instrument by the capillary method. All the glasswares were dried in an electric oven at a high temperature for 2–3 h. ^{31}P NMR spectra were recorded on an FT NMR spectrometer Jeol AL 300 at 121.50 MHz (obset 156 KHz), ^{1}H NMR were recorded on Jeol AL 300 at 300.40 MHz (obset 130 KHz), and ^{13}C NMR spectra were recorded on Jeol FT NMR system AL 300 at 75.45 MHz (obset 124 KHz). Elemental analyses were carried out on a Heraeus Carlo Erba 1108 analyzer. 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.

N-Alkyl-2-pyridinylidenamino(phenyl)chlorophosphines (2a–c): General procedure

To a well-stirred suspension of N-alkyl-2-aminopyridinium halides (3.81 g, 15 mmoles) in toluene (10 mL) was added triethylamine (4.29 mL, 30 mmoles) with stirring at 0–5°C. A solution of dichlorophenylphosphines (2.12 mL, 15 mmoles) in a mixture 2:1 of toluene and methylene chloride (30:15 mL) was added dropwise with constant stirring. After stirring for 2–3 days at r.t., the reaction mixture was filtered, and the solvent was removed from the filterate under reduced pressure. The residue thus obtained was extracted with diethyl ether (2 × 50 mL). Combined ethereal extracts were concentrated up to 30% and left in a refrigerator, whereupon a white solid deposited, which was filtered, dried, and recrystallized from methylene chloride.

N-Alkyl-2/4-pyridinylidenamido(phenyl)chlorothio phosphonates (3a–d and 5a) General procedure

N-alkyl-2/4-aminocycloiminium halides (3.81 g, 15 mmoles) was suspended in toluene (10 mL), and triethylamine (4.29 mL, 30 mmoles) was added slowly with stirring at 0–5^{o}C , followed by a solution of dichlorophenylphosphines (2.12 mL, 15 mmoles) in a mixture 2:1 of toluene and Methylene chloride (30:15 mL), which was added dropwise with constant stirring. After 2 h. of stirring, the reaction mixture was brought to r.t., and sulfur powder (0.49 g, 15 mmoles) was added to it. The resulting mixture was left for 2–3 days and then was filtered, and solvent was removed from the filterate in vacuo. The residue thus obtained was extracted with diethyl ether (2 × 50 mL). Combined ethereal extracts were concentrated up to 30% and left in a refrigerator, whereupon a white to light-yellow solid deposited, which was filtered, dried, and recrystallized from methylene chloride.

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 little quantity of acetone and diluted with 120 mL of water). In these containers one test grub was introduced with some millet roots. For control, (soil, water, and acetone mixture) grub and millet root have been taken. Ten such replicates were prepared for each compound, and 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 (CRD) technique.[17]

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