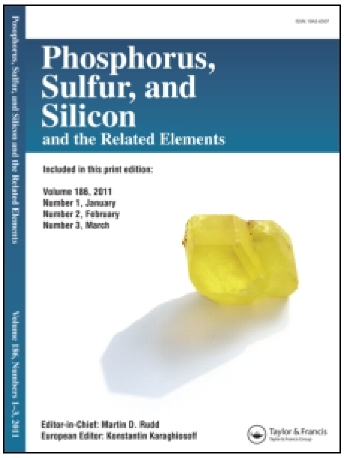

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A Synthetic Strategy for Novel Organothiophosphates Incorporating a Pyridine Ring

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A Synthetic Strategy for Novel Organothiophosphates Incorporating a Pyridine Ring

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Eight novel amidothiophosphates have been successfully achieved using cycloiminium salts of pyridine as the starting material. Phosphorylation was done using phosphorus trichloride, and the resulting functionalized iminohalophosphines in situ were further oxidized and substituted through sulfur and a suitable secondary amine (alkyl, alicyclic, and aryl). The reactions were carried out in a dry nitrogen atmosphere. The synthesized products were characterized using different spectroscopic techniques (^{1}H and ^{31}P NMR). The pyridine nucleus incorporating a phosphoryl group is highly bioactive. Hence, the synthesized organothiophosphates should be potential pesticidal molecules.

Keywords Amidothiophosphate; cycloiminium salts; iminohalophosphines

INTRODUCTION

The importance of the phosphoryl group has been reported in the literature, as it regulates important biological functions of both plants and animals.[1–3] It is conceivable that its attachment to a pyridine nucleus, which itself exhibits a wide spectrum of biological activity,[4–8] will enhance the biological activity of the synthesized product.

In the literature, several synthetic routes for these derivatives have been reported by different workers.[9–12] In our research group, we have evolved an economical synthetic route where thiazole, benzothiazole, and pyrimidine nuclei have been incorporated with a thiophosphate moiety. In this novel synthetic strategy, corresponding cycloiminium

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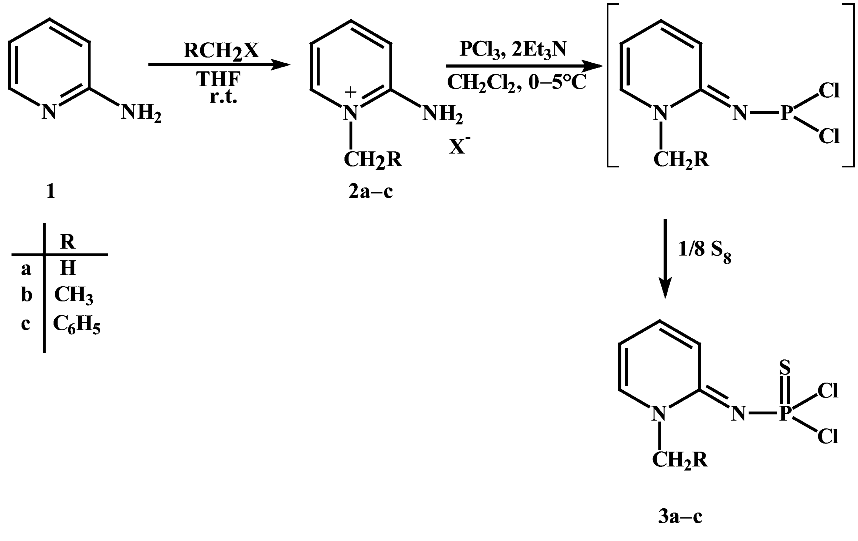
salts of these heterocyclic nuclei were phosphorylated with phosphorus trichloride in the presence of a weak base.[13–16] Viewing the importance of the pyridine nucleus in the proposed work, the similar synthetic strategy was extended on the cycloiminium salts of pyridine nucleus, which on phosphorylation achieved the desired title compounds.

RESULTS AND DISCUSSION

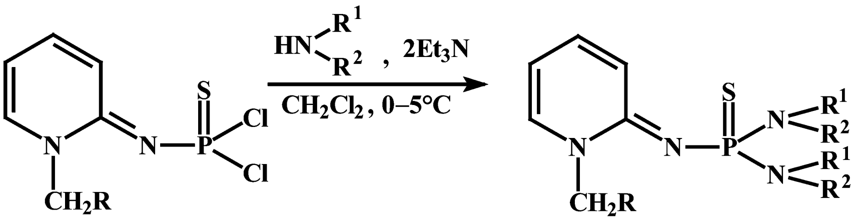
Under nitrogen, the N-alkyl-2-aminopyridinium halides (2) have been reacted with an equimolar amount of phosphorus trichloride and two equivalents of triethylamine at 0–5°C in methylene chloride to generate corresponding iminodichlorophosphines. These intermediates have been oxidized in situ with elemental sulfur (1/8 equivalents) at an ambient temperature generating cycloiminylidenamidothiophosphoric dichlorides (3) in a good yield. These were stable, cream-to-yellow, sharp melting crystalline solids (Scheme 1).



	R
a	H
b	CH_3
c	C_6H_5

SCHEME 1

3a–c were subsequently subjected to nucleophilic substitution with different secondary amines viz. diethylamine, diphenylamine, and N-methylcyclohexylamine (Scheme 2). Thus, through this synthetic strategy, 8 novel representatives of 2 series of alkylidenamidothiophosphoric esters, namely cycloiminylidenamidothiophosphoric dichlorides (3a–c) and cycloiminyldenamidobis(dialkyl/diaryl/alkylali-



3a–c **4a–c, 5a, 6c**

	R^1	R^2	R
4a–c	C_2H_5	C_2H_5	$H/CH_3/C_6H_5$
5a	C_6H_5	C_6H_5	H
6c	CH_3	C_6H_{11}	C_6H_5

SCHEME 2

cyclicamido)thiophosphates (4a–c, 5a, and 6c), have been obtained in a good yield.

All products were crystalline, sharp melting solids; stable under a nitrogen atmosphere; and were characterized through elemental analysis and ^1H and ^{31}P NMR techniques. The results have been represented in Table I.

The N—CH_2 protons of 3a&c and 4a&c appear as a singlet in the range δ3.50 to δ5.32 ppm, whereas N—CH_2 protons of 3b and 4b show a quartet ($^3J = 7.1$ Hz) at δ4.09–.δ4.27 ppm. The deshielding of the H-6 proton of the pyridine ring is highest as an amino nitrogen is situated nearby to it. Thus, the H-6 proton appears as an unresolved triplet or multiplet at δ 7.61–7.82 ppm.

The H-5 proton appears as a doublet of a triplet or a merged triplet ($^3J_{HH} = 6.0–8.0$, $^4J_{HH} = 1.8$ Hz) at δ6.60–6.82 ppm showing vicinal coupling with both the H-4 and H-6 and *m*-coupling with H-3 protons. A doublet of doublet is observed for the H-3 proton showing vicinal coupling with H-4 and *m*-coupling with H-5. The N—CH_2 protons of the $PNCH_2CH_3$ (4a–c) moieties exhibit diastereotopicity; in the ^1H NMR spectra a doublet of a doublet of a quartet has been observed in 4a–c due to geminal coupling, coupling with phosphorus, and vicinal coupling with adjacent methyl protons. Furthermore, ^1H NMR spectra of compound 6c exhibited interesting behavior due to the presence of a cyclohexyl ring at a nitrogen of an amido moiety, which, as expected, has

TABLE I Physical and Spectral Data of Compounds

Compound	Mol. Formula (mol.wt.)	Yield (%)	M.P. (°C)	Elemental Analysis (%) Calc./Found			^{31}P NMR	^{1}H NMR δ ppm (JHz)
				C	H	N		
3a	$C_6H_7N_2PSCl_2$ (241.079)	68	90–92	29.89 29.86	2.93 2.90	11.6 11.80	50.2	3.75 (s, 3H, NCH_3); 6.67(t, 1H, $^3J_{HH} = 7.2$, H-5); 7.23–7.26 (unresolved m, 3H, H-3, H-4 and H-6)
3b	$C_7H_9N_2PSCl_2$ (255.079)	62	80–90	32.96 32.93	3.55 3.52	10.98 10.96	48.0	1.41 (t, 3H, $^3J_{HH} = 6.9$, NCH_2CH_3); 4.27 (q, $^3J_{HH} = 7.1$ NCH_2); 6.62 (dt, 1H, $^3J_{HH} = 7.5$, $^4J_{HH} = 1.5$, H-5); 7.32 (t, 1H, $^3J_{HH} = 7.9$, $^4J_{HH} = 1.5$, H-3); 7.51–7.70 (unresolved m, 2H, H-4 and H-6)
3c	$C_{12}H_{11}N_2PSCl_2$ (317.177)	70	105	45.44 45.41	3.49 3.44	8.83 8.86	44.5	5.33 (s, 2H, NCH_2); 6.67 (dt, 1H, $^3J_{HH} = 6.0$, $^4J_{HH} = 1.8$, H-5); 7.42 (m, 6H, -C_6H_5 and H-3); 7.65–7.71 (unresolved m, 2H, H-4 and H-6)
4a	$C_{14}H_{27}N_4PS$ (314.435)	71	101–103	53.48 53.45	8.65 8.63	17.82 17.80	63.6	1.01 (t, 12H, $^3J_{HH} = 6.9$, NCH_2CH_3); 3.05 (ddq, 4H, $^2J_{HH} = 11.9$, $^3J_{PH} = 6.9$, $^3J_{HH} = 4.9$, Ha of $PNCH_2CH_3$); 3.25 (ddq, 4H, $^2J_{HH} = 11.5$, $^3J_{PH} = 7.1$, $^3J_{HH} = 4.3$, Hb of $PNCH_2CH_3$); 3.51 (s, 3H, NCH_3); 6.21 (t, 1H, H-5); 7.32–7.61 (unresolved m, 3H, H-3, H-4 and H-6).
4b	$C_{15}H_{29}N_4PS$ (328.462)	67	103–105	54.85 54.80	8.89 8.86	17.06 17.08	58.7	1.09 (t, 12H, $^3J_{HH} = 7.1$, $PNCH_2CH_3$); 1.39 (t, 3H, $^3J_{HH} = 7.1$, NCH_2CH_3); 3.13 (ddq, 4H, $^2J_{HH} = 15.6$, $^3J_{PH} = 13.2$, $^3J_{HH} = 8.6$, Ha of NCH_2CH_3); 3.32 (ddq, 4H, $^2J_{HH} = 15.6$, $^3J_{PH} = 13.2$, $^3J_{HH} = 8.6$, Hb of NCH_2CH_3); 4.09 (q, 2H, $^3J_{HH} = 7.1$, NCH_2CH_3); 6.27 (dt, 1H, $^3J_{HH} = 6.7$, $^4J_{HH} = 1.4$, H-5), 7.30–7.32 (unresolved m, 2H, H-3 and H-4); 7.43 (unresolved t, 1H, H-6)

4c	$C_{20}H_{31}N_4PS$ (390.533)	76	92–95	61.51 61.53	8.00 8.02	14.35 14.37	63.9	1.02 (t, 12H, ${}^3J_{HH} = 6.8$, $PNCH_2CH_3$); 3.15 (ddq, 4H, ${}^2J_{HH} = 16.8$, ${}^3J_{PH} = 11.9$, ${}^3J_{HH} = 7.1$, Ha of $PNCH_2CH_3$); 3.25 (ddq, 4H, ${}^2J_{HH} = 16.8$, ${}^3J_{PH} = 11.9$, ${}^3J_{HH} = 7.1$, Hb of $PNCH_2CH_3$); 3.50 (s, 2H, NCH_2), 6.25 (unresolved t, 1H, H-5); 7.32–7.52 (unresolved m, 2H, H-3 and H-4); 7.60 (unresolved d, 1H, H-6).
5a	$C_{30}H_{27}N_4PS$ (506.701)	60	103–105	71.09	5.33	11.02	40.7	5.80 (s, 3H, NCH_3); 6.61 (t, 1H, H-5); 7.20 (s, 20H, NPh_2); 7.42 (unresolved d, 1H, H-3); 7.51 (unresolved d, 1H, H-4); 7.52 (d, 1H, H-6)
6c	$C_{26}H_{39}PS$ (470.663)	63	108–110	66.32	8.32	11.88	61.9	0.80–0.91 (dddd, 4H, ${}^3J_{HH} = 11.35$, ${}^3J_{Hax\text{-}Hax} = 9.14$, ${}^3J_{Heq\text{-}Hax} = 3.0$, H-6 and H-7); 1.10–1.31 (dddd, 4H, ${}^2J_{HH} = 11.8$, ${}^3J_{Hax\text{-}Hax} = 8.2$, ${}^3J_{Heq\text{-}Hax} = 2.7$, H-5 and H-9); 1.32–1.48 (dddd, 8H, ${}^2J_{HH} = 12.28$, ${}^3J_{Hax\text{-}Hax} = 7.3$, ${}^3J_{Heq\text{-}Hax} = 2.5$, H-3, H-4, H-8 and H-10); 1.50–1.71 (dddd, 4H, ${}^2J_{HH} = 12.3$, ${}^3J_{Hax\text{-}Hax} = 7.1$, ${}^3J_{Heq\text{-}Hax} = 2.0$, H-2 and H-11); 1.72–1.80 (tt, 2H, ${}^3J_{HH} = 14.3$, ${}^3J_{Hax\text{-}Hax} = 7.0$, ${}^3J_{Heq\text{-}Hax} = 2.0$, H-1); 2.51 (d, 3H, ${}^3J_{PH} = 12.0$, NCH_3); 5.25 (s, 2H, NCH_2); 6.32 (unresolved t, 1H and H-5); 7.20–7.41 (merged dd, 2H, H-3 and H-4); 7.52 (merged dd, 1H, H-6)

acquired the chair conformation. As reported in the literature[17] here also, the equatorial and axial protons on the same carbon of a locked 6-membered ring forms the AB part of the ABX system. The H_A (equatorial) protons are relatively deshielded than the H_B (axial) protons by about 0.10 to 0.91 ppm. Five bunches of protons appear as a multiplet due to geminal ($^2J_{HH} = 10–14$ Hz) and vicinal ($a_X - a_X$, $^3J_{HH} = 7.0–9.2$) ($a_x - e_x$, $^3J_{HH} = 2–3$ Hz) couplings, respectively.

All physical and spectral details of synthesized products have been presented in Table I.

EXPERIMENTAL

All solvents and commercial reagents were purified prior to use. The glasswares, syringes, and needles used in these moisture-sensitive reactions were oven dried at 140°C. Upon work, solvents were evaporated under reduced pressure, using a high vacuum. Melting points were measured by the capillary method on an electric tempo m.p. apparatus and are uncorrected. ^{31}P spectra were recorded on Jeol AL 300 at 121.50 MHz (Obset 156 KHz) using 85% H_3PO_4 as an external standard, and ^1H spectra were recorded on Jeol AL 300 at 300.4 MHz (Obset 130 KHz) using TMS as an internal standard. Elemental analyses were carried out on Heraeus Carlo Erba 1108 analyzer.

N-Alkyl-2-pyridinylidenamidothiophosphoric dichlorides (3a–c): General Procedure

To a well-stirred suspension of N-alkyl-2-aminopyridinium halides (3.0 g, 12.7 mmoles) in methylene chloride (20 mL) at 0–5°C was added phosphorus trichloride (1.4 mL, 12.6 mmoles) followed by a dropwise addition of a solution of triethylamine (3.5 mL, 25.4 mmoles) in methylene chloride (30 ml) under a N_2 atmosphere. After 5–6 h of stirring at r.t. sulfur powder (4.4 g, 12.7 mmoles) was added to it. The resulting mixture was left for stirring for 24–30 h after which the solvent was removed under vacuo and the residue was extracted with ether (2 × 30 mL). The combined extract was concentrated to 30 mL and kept in the refrigerator (0°C), whereupon cream to pale yellow solids separated, which were filtered and dried.

N-Alkyl-2-pyridinylidenamidobis(diethylamido)-thiophosphates (4a–c): General Procedure

A similar procedure that was used for 3a–c was followed, and after 24–30 h of stirring, a solution of diethylamine (4.7 g, 50.8 mmoles) in methylene chloride was added dropwise at 0–5°C, and the resulting mixture was further stirred for 24–30 h. The solvent was removed under vacuo, and the residue was extracted with ether (2 × 30 mL). The combined etheral extract was concentrated and kept in a refrigerator. Cream-to-yellow crystals separated out, which were filtered and dried. In the present procedure, two excess equivalents of diethylamine acted as base.

N-Alkyl-2-pyridinylidenamido bis(diphenylamido)-thiophosphates (5a): General Procedure

The previously stated procedure was followed using diphenylamine (2.2 g, 12.7 mmoles) in place of diethylamine, alongwith the dropwise addition of a solution of two equivalents of triethylamine (3.5 mL, 25.4 mmoles) in methylene chloride (20 mL) (which was serving as base). On keeping the concentrated ether extract in refrigerator (0°C), white flakes were obtained, which were filtered and dried.

N-Alkyl-2-pyridinylidenamidobis(N-methyl cyclohexylamido) thiophosphates (6c): General Procedure

The previously stated procedure was followed using N-methyl cyclohexylamine (3.0 mL, 22.6 mmoles) in place of earlier stated amines with the dropwise addition of a solution of two equivalents of triethylamine (3.5 mL 25.4 mmoles) in methylene chloride (20 mL) (which was serving as a base). On keeping the concentrated ether extract in a refrigerator (0°C), yellow crystals were obtained, which were filtered and dried.

CONCLUSION

An economical synthetic route has been developed for the synthesis of organothiophosphates including a pyridine nucleus. These molecules are expected to be highly bioactive, and, hence, in our further research work, bioscreening of these molecules will be done.

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