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Novel Phosphono-Substituted Pyrimidines: Synthesis and Characterization

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Fourteen novel organothiophosphonates incorporating pyrimidine heterocycles have been synthesized through an economical synthetic strategy. The products were well characterized through different spectral techniques. The ^1H NMR spectra have shown interesting diastereotopic properties thus, showing chirality in the molecule. The chlorothiophosphonates were the first step products which were further substituted to several other products through nucleophilic substitution reaction. This study has shown unique prospects for synthesis of chiral molecules.

Keywords Chlorothiophosphonates; diastereotopic properties; nucleophilic substitution; organothiophosphonates

INTRODUCTION

Phosphorus, a nonmetallic element (Group XV, period III), plays very crucial and important roles in the living system and also in synthetic chemistry, hence, in our day-to-day life. Its role in the biochemistry of cells and tissues is worth mentioning here. Among the synthetic phosphorus compounds, the organophosphorus derivatives are undeniably the most versatile and useful ones.[1–10]

In our research group, we have developed a novel synthetic route for the synthesis of organophosphorus derivatives in which phosphorus has existed in different coordination states,[11–16] where we used the N-cycloiminium salts as the starting material. In the present work, we have used another phosphorylating agent, the dichlorophenylphosphine, in place of phosphorus trichloride, which has been still utilized

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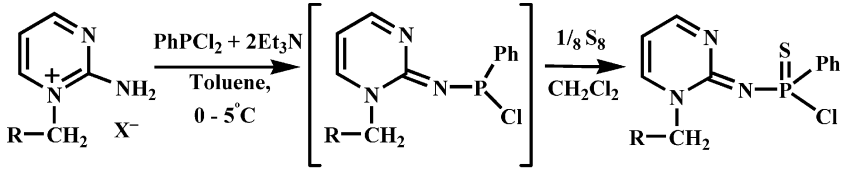
in our projects. Through the dichlorophenylphosphine, a variety of new organothiophosphonates with interesting diastereotopicity have been synthesized. In connection with our work of thiophosphonates of pyridine heterocycles, we are reporting herein a new series of compounds involving pyrimidine heterocycles.

Owing to the vital importance of pyrimidine nucleus, we have selected this heterocycle for our proposed research work. The importance of such type of compounds can be judged from their abounding literature that provides several synthetic strategies along with their chemical properties. The reason behind opting for the pyrimidine nucleus is its remarkably important nature.

RESULTS AND DISCUSSION

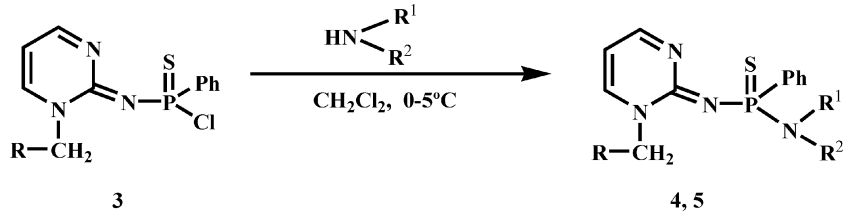
2-Aminopyrimidine, on stirring with equimolar amount of substituted methylhalides**,** in tetrahydrofuran at room temperature, afforded N-alkyl-2-aminopyrimidinium halides **(1)** in quantitative yields. These salts **(1)** were treated with equimolar amount of dichlorophenylphosphine and two equivalents of triethylamine in a mixture of toluene and methylene chloride, at 0–5°C. After 4–5 h of stirring at ambient temperature, the N-alkyl-2-pyrimidinylidenamido(chloro)(phenyl)phosphines **(2)** were in situ oxidized with elemental sulfur to access the N-alkyl-2-pyrimidinylidenamido(chloro)(phenyl)thiophosphonates **(3)** (Scheme 1).



1/3	R = a: H	b: CH_3	c: C_6H_5	d: $COOCH_3$	e: $COOC_2H_5$

SCHEME 1

For the substituted thiophosphonates, the N-alkyl-2-pyrimi dinylidenamido(chloro)(phenyl)thiophosphonates **(3)** were subsequently subjected to nucleophilic substitution with different secondary amines viz. diethylamine, and N-methylcyclohexylamine to achieve the substituted thiophosphonates (**4**, **5**) (Scheme 2).



	R				
	a	b	c	d	e
3/4,5	H	CH_3	C_6H_5	$COOCH_3$	$COOC_2H_5$

	R^1	R^2
4	C_2H_5	C_2H_5
5	CH_3	C_6H_{11}

SCHEME 2

All the newly synthesized products were cream to yellow colored, sharp melting solids, which are soluble in slightly polar solvents. The physical parameters of these products have been summarized in Table I.

Characterization

These compounds were characterized through elemental analysis and ^1H, ^{31}P and ^{13}C NMR techniques. The results have been represented in Table II. Taking into consideration the different chemical shift values for different protons, as a result of shielding, deshielding and anisotropic effects, assignments for different protons of these compounds have been made.

^{31}P NMR Spectra

The ^{31}P NMR chemical shift values for these were found to be between δ 55.0-73.4 ppm and displayed a sharp signal. This observation is suggestive of tetra-coordination around the phosphorous atom in the above derivatives.

^1H NMR Spectra

In the most upfield region, a triplet was observed at δ 1.00–1.08 ppm for methyl protons of $1PNCH_2CH_3$ moiety of **4**, with coupling constant $^3J_{HH}$ = 6.9–7.0 Hz. The methylene protons of the same moiety resonated as a set of doublet of doublet of quartet at δ 3.06–3.26 and

TABLE I Analytical Data of Synthesized Compounds

Compound	Mol. formula (M W)	Yield (%)	M. P. (°C)	Color	Elemental analysis (%) C	H	N
5a	$C_{11}H_{11}N_3PSCl$ (283.721)	58	115–17	White	46.56 (46.51)	3.90 (3.87)	14.81 (14.90)
5b	$C_{12}H_{13}N_3PSCl$ (297.748)	48	120–122	White	48.41 (48.40)	4.40 (4.37)	14.11 (14.15)
5c	$C_{17}H_{15}N_3PSCl$ (359.819)	62	110–112	White	56.75 (56.71)	4.20 (4.23)	11.68 (11.69)
5d	$C_{12}H_{13}N_3O_2SCl$ (341.758)	57	110–112	White	45.69 (45.63)	3.84 (3.83)	12.29 (12.25)
5e	$C_{14}H_{15}N_3O_2PSCl$ (355.785)	53	114–116	White	47.26 (47.23)	4.25 (4.23)	11.81 (11.84)
6a	$C_{15}H_{21}N_4PS$ (320.4)	70	102–105	Yellow	56.23 (56.25)	6.60 (6.61)	17.48 (17.43)
6b	$C_{16}H_{23}N_4PS$ (334.4)	68	106–107	Yellow	57.75 (57.72)	6.93 (6.95)	16.75 (16.77)
6c	$C_{21}H_{25}N_4PS$ (396.4)	73	96–99	Yellow	63.61 (63.60)	6.36 (6.33)	14.13 (14.10)
6d	$C_{17}H_{23}N_4PS$ (346.4)	63	110–112	Yellow	58.94 (58.92)	6.92 (6.90)	16.17 (16.19)
6e	$C_{18}H_{25}N_4O_2PS$ (392.4)	78	118–120	Yellow	55.08 (55.03)	6.42 (6.40)	14.27 (14.24)
7a	$C_{18}H_{25}N_4PS$ (360.5)	62	110–112	Yellow	59.98 (59.95)	6.99 (6.97)	15.54 (15.52)
7b	$C_{19}H_{27}N_4PS$ (374.5)	60	115–117	Yellow	60.94 (60.92)	7.27 (7.25)	14.96 (14.94)
7c	$C_{24}H_{29}N_4PS$ (436.6)	65	107–110	Yellow	66.03 (66.01)	6.69 (6.65)	12.83 (12.82)
7d	$C_{21}H_{29}N_4O_2PS$ (432.5)	70	120–122	Yellow	58.32 (58.31)	6.77 (6.75)	12.95 (12.92)

δ 3.29–3.47 ppm, respectively, due to geminal and vicinal couplings along with three-bond coupling with phosphorus atom. The coupling constants observed for these peaks were $^2J_{HH} = 11.4$–15.0 Hz, $^3J_{PH} = 3.0$–4.2 Hz, $^3J_{HH} = 6.0$–7.2 Hz, respectively.

All the eleven protons of the cyclohexyl moiety of **5** resonated as a complex multiplet at δ 0.78–1.51 ppm. Since these protons experience slightly different magnetic fields, they absorbed at different positions. The equatorial protons, however, resonated slightly downfield in comparison to the axial protons with a difference of about δ 0.12–0.70 ppm. The CH_3 protons of the same moiety resonated as a doublet in the range δ 1.41–2.56 ppm, due to three-bond coupling with the phosphorus nucleus ($^3J_{PH} = 8.0$–12.0 Hz). Among the pyrimidine ring protons, the H-5

TABLE II Spectral (^{1}H, ^{13}C, & ^{31}P NMR) Data of Compounds (in δ ppm)

Compound	^{31}P NMR	^{1}H NMR (JHz)	^{13}C NMR
5a	73.4	2.20 (s, 3H, NCH_3); 4.20 (unresolved dd, 1H, H-5); 7.38-7.47 (m, 5H, PC_6H_5); 7.50-7.59 (merged dd, 2H, $^3J_{HH} = 6.2$, $^4J_{HH} = 3.0$, H-4 and H-6)	—
5b	65.8	1.23 (t, 3H, $^3J_{HH} = 7.2$, $NCH_2\mathbf{CH}_3$); 5.01(q, $^3J_{HH} = 6.9$, $N\mathbf{CH}_2CH_3$); 6.20 (dd, 1H, $^3J_{HH} = 6.1$, 6.0, H-5); 7.30-7.42 (m, 5H, PC_6H_5); 7.48 (dd, 1H, $^3J_{HH} = 6.0$, $^4J_{HH} = 2.7$, H-6); 7.52 (dd, 1H, $^3J_{HH} = 6.0$, $^4J_{HH} = 2.5$, H-4)	—
5c	65.8	4.15 (d, 1H, $^2J_{HH} = 18.0$, Ha of $N\mathbf{CH}_2C_6H_5$); 4.18 (d, 1H, $^2J_{HH} = 18.2$, Hb of $N\mathbf{CH}_2C_6H_5$); 6.25 (dd, 1H, $^3J_{HH} = 6.0$, 6.0, H-5) 7.26-7.37 (m, 10H, PC_6H_5 and $PNCH_2\mathbf{C}_6\mathbf{H}_5$); 7.44 (dd, 1H, $^3J_{HH} = 6.0$, H-6); 7.82 (dd, 1H, $^3J_{HH} = 6.0$, H-4)	—
5d	65.5	2.22 (s, 3H, OCH_3); 4.63 (d, 1H, $^2J_{HH} = 15.0$, Ha of NCH_2); 4.85 (dd, 1H, $J_{HH} = 15.0$, Hb of NCH_2); 6.67 (dd, 1H, $^3J_{HH} = 6.0$, 6.0, H-5); 7.49-7.52 (m, 5H, C_6H_5); 8.12 (dd, 1H, $^3J_{HH} = 6.0$, $^4J_{HH} = 3.0$, H-6); 8.16 (dd, 1H, $^3J_{HH} = 6.0$, $^4J_{HH} = 3.0$, H-4)	—
5e	65.0	1.23 (t, 3H, $^3J_{HH} = 6.0$, $OCH_2\mathbf{CH}_3$); 4.27 (q, 2H, $^3J_{HH} = 6.0$, $O\mathbf{CH}_2CH_3$); 4.60 (d, 1H, $^2J_{HH} = 18.0$, Ha of NCH_2); 4.84 (d, 1H, $^2J_{HH} = 18.0$, Hb of NCH_2); 6.67 (dd, 1H, $^3J_{HH} = 6.0$,6.0, H-5); 7.48-7.52 (m, 5H, C_6H_5); 8.11-8.19 (merged dd, 2H, $^3J_{HH} = 9.0$ $^2J_{HH} = 3.0$, H-4 and H-6)	—
6a	85.1	1.08 (t, 6H, $^3J_{HH} = 6.9$, $PNCH_2\mathbf{CH}_3$); 3.12 (ddq, 2H, $^3J_{HH} = 11.4$, $^3J_{PH} = 7.2$, $^2J_{HH} = 4.2$, Ha of $PN\mathbf{CH}_2CH_3$); 3.32 (ddq, 2H, $^2J_{HH} = 13.0$, $^3J_{PH} = 7.5$ $^3J_{HH} = 4.6$, Hb of $PN\mathbf{CH}_2CH_3$); 3.68 (s, 3H, NCH_3); 6.27 (dd, 1H $^3J_{HH} = 6.2$, 6.0, H-5); 7.38 (m, 5H, PC_6H_5); 7.64 (dd, $^3J_{HH} = 6.0$, $^3J_{HH} = 3.5$, H-6); 8.02 (dd, $^3J_{HH} = 6.1$, $^3J_{HH} = 2.6$, H-4)	—

(Continued on next page)

TABLE II Spectral (^{1}H, ^{13}C, & ^{31}P NMR) Data of Compounds (in δ ppm) *(Continued)*

Compound	^{31}P NMR	^{1}H NMR (JHz)	^{13}C NMR
6b	60.5	1.05 (t, 6H, $^3J_{HH}$ = 6.9, PNCH$_2$**CH**$_3$); 1.45 (t, 3H, $^3J_{HH}$ = 7.2, NCH$_2$**CH**$_3$); 3.13 (ddq, 2H, $^3J_{HH}$ = 13.9, $^3J_{PH}$ = 7.2 $^3J_{HH}$ = 5.3, Ha of PN**CH**$_2$CH$_3$); 3.18 (ddq, 2H, $^2J_{HH}$ = 14.0, $^3J_{PH}$ = 7.2 $^3J_{PH}$ = 4.2, Hb of PN**CH**$_2$CH$_3$); 4.11 (m, 2H, $^3J_{HH}$ = 7.2, N**CH**$_2$CH$_3$); 6.28 (dd, 1H, $^3J_{HH}$ = 7.1, H-5); 7.62-7.66 (m, 5H, PC$_6$H$_5$); 7.99 (dd, 1H, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 3.0, H-6); 8.02 (dd, 1H, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0, H-4)	14.4 (NCH$_2$**CH**$_3$); 14.5 (PNCH$_2$**CH**$_3$); 40.3 ((PN**CH**$_2$CH$_3$); 48.9 (N**CH**$_2$CH$_3$); 104.8 (C-5); 127.6 & 127.7 (d, $^3J_{CP}$ = 13.6, C$_m$); 129.7 C$_p$); 131.0 & 131.2 (d,$^2J_{CP}$ = 7.5, C$_o$); 141.2 & 142.0 (d, $^1J_{CP}$ = 131.0, C$_i$); 146.8 (C-6); 153.12 (C-2); 162.8 (C-4)
6c	53.8	1.04 (t, 6H, $^3J_{HH}$ = 7.2, PNCH$_2$**CH**$_3$); 3.26 (ddq, 2H, $^2J_{HH}$ = 13.9, $^3J_{PH}$ = 7.2, $^3J_{HH}$ = 6.4 Ha of PN**CH**$_2$CH$_3$); 3.47 (ddq, 2H, $^2J_{HH}$ = 14.0 $^3J_{PH}$ = 7.2, $^3J_{HH}$ = 4.8 Hb of PN**CH**$_2$CH$_3$); 5.23 (d, 1H, $^2J_{HH}$ = 14.2**,** Ha of NCH$_2$); 5.32 (d, 1H, $^2J_{HH}$ = 14.8, Hb of NCH$_2$); 6.26 (dd, 1H, $^3J_{HH}$ = 7.0, H-5); 7.27-7.36 (unresolved m, 10 H, PC$_6$H$_5$ and NCH$_2$**C**$_6$**H**$_5$); 8.05 (unresolved d, 1H, H-6); 8.48 (dd, 1H, $^3J_{HH}$ = 8.2, $^4J_{HH}$ = 4.6, H-4)	—
6d	61.0	1.01 (t, 6H, $^3J_{HH}$ = 6.9, PNCH$_2$**CH**$_3$); 3.15 (ddq, 2H, $^3J_{HH}$ = 6.9, PN**CH**$_2$CH$_3$); 3.22 (ddq, 2H, $^3J_{HH}$ = 6.9, Hb of PN**CH**$_2$CH$_3$); 4.21 (r, 3H, OCH$_3$); 5.61 (s, 2H, NCH$_2$); 6.21 (dd, 1H, $^3J_{HH}$ = 7.2, 6.0, H-5); 7.42-7.50 (m, 5H, PC$_6$H$_5$); 7.52 (dd, 1H, $^3J_{HH}$ = 7.1, $^4J_{HH}$ = 1.2, H-6); 7.54 (dd, 1H, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 1.2, H-4)	—
6e	60.5	0.99 (t, 6H, $^3J_{HH}$ = 6.9, PNCH$_2$**CH**$_3$); 1.28 (t, 3H, $^3J_{HH}$ = 6.9, OCH$_2$**CH**$_3$); 3.07 (ddq, 2H, $^2J_{HH}$ = 15.0, $^3J_{PH}$ = 7.1 $^3J_{HH}$ = 6.0, Ha of PN**CH**$_2$CH$_3$); 3.29 (ddq, 2H, $^2J_{HH}$ = 12.0, $^3J_{HH}$ = 7.1 $^3J_{HH}$ = 6.0, Hb of PN**CH**$_2$CH$_3$); 4.25 (q, 2H, $^3J_{HH}$ = 6.0,	14.1 (NCH$_2$**CH**$_3$); 39.9 (PN**CH**$_2$CH$_3$); 54.4 (O**CH**$_2$CH$_3$); 62.2 (N**CH**$_2$); 104.7 (C-5); 127.5 & 127.7 (d, $^2J_{CP}$ = 12.8, C$_m$); 129.8 C$_p$); 130.7 & 130.9 (d,$^2J_{CP}$ = 9.8, C$_o$); 138.3 & 140.1 (d, $^1J_{CP}$ = 134.3, C$_i$); 148.2 (C-6); 153.8 (C-2); 163.8 (C-4); 166.84 (CO)

		$O\mathbf{CH}_2CH_3$); 4.63 (d, 1H, $^2J_{HH}$ = 15.0, Ha of NCH_2); (d, 1H, $^2J_{HH}$ = 15.0, Hb of NCH_2); 6.33 (dd, 1H, $^3J_{HH}$ = 6.0, 6.0, H-5); 7.36 (m, 5H, PC_6H_5); 7.91 (dd, 1H, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0, H-6); 7.94 (dd, 1H, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0, H-4)	
7a	61.0	0.78–1.50 (m, 11H, $PN(CH_3)\mathbf{C_6H}_{11}$); 1.71 (d, 3H, $^3J_{PH}$ = 12.0, $PN(\mathbf{CH}_3)C_6H_{11}$);4.25 (s, 3H, NCH_3); 6.25 (dd, 1H, $^3J_{HH}$ = 6.0, 6.0, H-5); 7.57-7.61 (m, 5H, PC_6H_5); 7.86 (dd, 1H, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0, H-6); 8.47 (dd, 1H, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0, H-4)	—
7b	59.8	1.18 (t, 3H, $^3J_{HH}$ = 6.9, $NCH_2\mathbf{CH}_3$); 1.41–1.59 (m, 11H, $PN(\mathbf{CH}_3)C_6H_{11}$); 2.62 (d, 3H, $^3J_{PH}$ = 12.5, $PN(\mathbf{CH}_3)C_6H_{11}$); 4.18 (m, 2H, $^3J_{HH}$ = 6.9, $N\mathbf{CH}_2CH_3$); 6.38 (dd, 1H, $^4J_{HH}$ = 6.0, 6.0, H-5); 7.35–7.37 (m, 5H, PC_6H_5); 7.86 (dd, 1H, $^3J_{HH}$ = 6.2, $^3J_{HH}$ = 2.8, H-6); 7.92 (dd, 1H, $^3J_{HH}$ = 6.2, $^4J_{HH}$ = 3.0, H-4)	—
7c	55.0	0.91–1.59 (m, 11H, PNC_6H_{11}); 2.56 (d, 3H, $^3J_{HH}$ = 12.3, $PNCH_3$); 5.23 (d, 1H, $^2J_{HH}$ = 13.9, Ha of NCH_2); 5.37 (d, 1H, $^2J_{HH}$ = 14.0, Hb of NCH_2); 6.26 (dd, 1H, $^3J_{HH}$ = 6.6, H-5); 7.34 (s, 5H, $NCH_2C_6H_5$); 7.36–7.55 (m, 5H, PC_6H_5); 7.57 (dd, 1H, $^3J_{HH}$ = 6.8, $^4J_{HH}$ = 4.2, H-6); 7.91 (dd, 1H, $^3J_{HH}$ = 7.0, $^4J_{HH}$ = 4.0, H-4)	—
7d	59.8	0.88–1.51 (m, 14H, PNC_6H_{11} and $OCH_2\mathbf{CH}_3$); 2.52 (d, 3H, $^3J_{PH}$ = 12.0, $PNCH_3$); 4.16 (q, 2H, $^3J_{HH}$ = 6.0, $O\mathbf{CH}_2CH_3$); 4.54 (d, 1H, $^2J_{HH}$ = 18.0, Ha of NCH_2); 4.73 (d, 1H, $^2J_{HH}$ = 15.0, Hb of NCH_2); 6.27 (dd, 1H, $^3J_{HH}$ = 6.0, 6.0; H-5); 7.58-7.61 (m, 5H, PC_6H_5); 7.86 (dd, 1H, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0, H-6); 7.88 (dd, 1H, $^3J_{HH}$ = 6.0, $^4J_{HH}$ = 3.0, H-4)	—

proton was shifted to the higher field and was observed in the region δ 6.26–6.33 ppm, since it experienced shielding. The doublet of doublet, which was observed for H-5 proton, was due to three-bond coupling with both H-4 and H-6 protons, with coupling constants, $^3J_{HH} = 6.0$ Hz and $^3J_{HH} = 6.0$ Hz, respectively. The H-4 and H-6 protons also showed doublet of doublets at δ 7.94 ppm and δ 7.91 ppm, respectively, due to three- and four-bond couplings. Since these protons have nearly the same chemical environment, they resonated as a merged signal, in few cases. The NCH_2 of **5c-e** showed a set of doublet in the range δ 4.54–5.23 ppm and δ 4.73–5.36 ppm, respectively due to diastereotopic nature of these protons which has caused geminal coupling ($^2J_{HH} = 14.0$–18.2 Hz). It was interesting to note that the NCH_2 protons of **5b** showed an unresolved quartet at δ 3.47 ppm ($^3J_{HH} = 6.0$ Hz).

The phenyl protons of PC_6H_5 moiety appeared as a multiplet or split singlets at δ 7.36–7.44 ppm. The splitting of the signal is most probably due to slightly different magnetic environments of the ring protons.

^{13}C NMR Spectra

The ^{13}C NMR data were also found helpful in the characterization of the compounds.

The methyl and methylene carbons of $PNCH_2CH_3$ moiety resonated at δ 14.1 and 39.9 ppm, respectively. The CH_2 and CH_3 carbon resonances of the OCH_2CH_3 moiety were observed at δ 52.7 ppm and δ 54.4 ppm, respectively. The presence of a signal at δ 62.2 ppm was due to NCH_2 carbon.

The pyrimidine ring carbons, C-2, C-4, C-5, and C-6, resonated at δ 153.8, 163.9, 104.7, and δ 148.2 ppm, respectively.

The carbons of the phenyl ring have shown different shifts in ^{13}C spectrum: C_o at δ 130.7 and δ 130.8 ppm ($^2J_{CP} = 9.8$ Hz), C_P at δ 129.8 ppm and C_m at δ127.6 and 127.7 ppm ($^3J_{CP} = 12.8$ Hz). The *ipso* carbon signal of the phenyl ring appeared as a doublet at δ 138.3 and 140.1 ppm ($^1J_{CP} = 135.8$ Hz).

The CO carbon resonated at δ 166.8 ppm, due to its being the most deshielded one. The peaks for C_i, C-2 and CO were of minimum intensity due to their quaternary nature (no NOE available).

EXPERIMENTAL

All the 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 high vacuum. Melting points were measured by 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 external standard and ^{1}H spectra were recorded on Jeol AL 300 at 300.4 MHz (Obset 130 KHz) using TMS as internal standard. Elemental analyses were carried out on Heraeus Carlo Erba 1108 analyzer.

Synthesis of N-Alkyl-2-pyrimidinylidenamido(chloro)(phenyl)thiophosphonates (3)

To a well-stirred suspension of 2-aminopyrimidinium halide (2.37 g, 0.01 mol) in toluene (10 ml), was added a mixture of dichlorophenylphosphine (1.37 ml, 0.01 mol) in toluene (20 ml), through a dropping funnel, along with the addition of two equivalents of triethylamine (2.78 ml; 0.02 mol), at 0–5°C. The addition was completed in one- half h, after which the mixture was slowly brought to ambient temperature. After 4-5 h stirring at ambient temperature, an equimolar amount of sulfur powder (0.32 g, 0.01 mol) was added, followed by the addition of methylene chloride (30 ml). The reaction mixture was then filtered off, after 2 days, and the solvent was removed in vacuo. The crude product so obtained was properly dried and then extracted with diethylether (3×50 ml). The combined ethereal extract was concentrated to one-fourth of its initial volume and kept in a refrigerator, whereupon a white colored solid was obtained. It was separated and dried under reduced pressure.

Synthesis of N-Alkyl-2-pyrimidinylidenamido(diethylamido)(phenyl)thiophosphonates (4)

N-Alkyl-2-aminopyrimidinium halide (3.0 g, 0.01 mol) was suspended in toluene (10 ml) under nitrogen atmosphere. To this suspension was then added triethylamine (2.78 ml, 0.02 mol), along with the dropwise addition of dichlorophenylphosphine (1.34 ml, 0.01 mol) also mixed in toluene (20 ml), while maintaining the temperature of the reaction mixture at 0–5°C. The addition was completed in 1 h, after which the reaction mixture was slowly brought to ambient temperature. After 3–4 hr. of stirring, sulfur powder (0.32 g, 0.01 mol) was added to it, along with methylene chloride (30 ml). Two equivalents of diethylamine (2.09 ml, 0.01 mol) mixed in methylene chloride were also added dropwise to the reaction mixture. Afterwards it was stirred for 24 h, while maintaining the temperature at 0–5°C. The reaction mixture was then filtered off after stirring for next 2–3 days at ambient temperature, and the solvent of the filtrate was trapped out under reduced pressure. The crude product so obtained was extracted with diethylether (3×50 ml), and the

combined ethereal extract was concentrated to one-fourth of its original volume and kept in a refrigerator. After 4–8 h, a yellow colored solid compound was deposited, which was separated, washed with hexane, and dried under reduced pressure.

Synthesis N-Alkyl-2-pyrimidinylidenamido (N-methylcyclohexylamido)(phenyl)thiophosphonates (5)

To a well-stirred suspension of N-alkyl-2-aminopyrimidinium halides (3.0 g, 0.01 mol) in toluene (10 ml), was added triethylamine (2.78 ml, 0.02 mol), along with dropwise addition of dichlorophenylphosphine (1.34 ml, 0.01 mol) in toluene (20 ml), while maintaining the temperature of the reaction mixture at 0-5°C, with continuous stirring. In 1 h, the addition was completed and the reaction mixture was then slowly brought to room temperature. Afterwards, sulfur powder (0.32 g, 0.01 mol) was added to this mixture over 3-4 h, along with the addition of methylene chloride (20 ml). A mixture of N-methylcyclohexylamine (1.32 ml, 0.01 mol) in methylene chloride (20 ml) was also added dropwise, along with triethylamine (1.39 ml, 0.01 mol). During the addition, the temperature of the reaction was maintained at 0-5°C. The stirring was continued for another 24-30 h at room temperature. The reaction mixture was filtered off and the solvent of the filtrate was trapped out in vacuo. The crude obtained thereon was extracted with diethylether (3×50 ml), and the combined ethereal extract was concentrated to one-fourth of its original volume and then kept in a refrigerator, whereupon a while-yellow solid product was obtained. It was separated, washed with hexane ,and dried under reduced pressure.

CONCLUSION

An economical synthetic route has been developed for the synthesis of organothiophosphonates including a pyrimidine nucleus. These molecules are expected to be highly bioactive, hence we will perform further research work on bioscreening of these molecules.

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