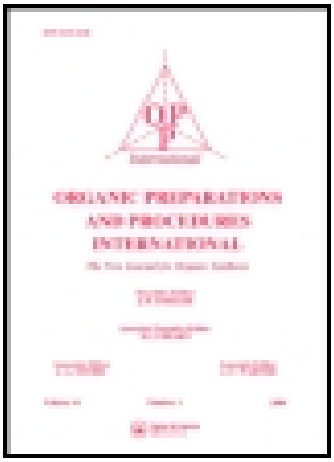

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AN EFFICIENT SYNTHESIS OF THE POTENTIAL MARINE TOXIN PTYCHODISCUS BREVIS [PB-1] AND ITS ANALOGUES

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OPPI BRIEFS

AN EFFICIENT SYNTHESIS OF THE POTENTIAL MARINE TOXIN *PTYCHODISCUS BREVIS* [PB-1] AND ITS ANALOGUES

Submitted by (10/24/06) Arvind K. Gupta, D. K. Dubey, Mamta Sharma and M. P. Kaushik*

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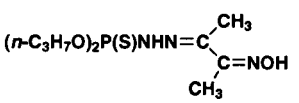
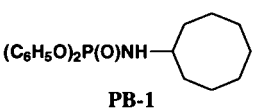
Marine derived *dinoflagellates* have become a rich source of structurally novel and pharmacologically active secondary metabolites. Some of the species of *dinoflagellates* also produce toxic compounds and are responsible for seafood poisoning. This class of marine toxin has attracted the attention of organic chemists due to their involvement in human intoxication and socioeconomic impact brought about by toxic effect of these toxins. *Ptychodiscus brevis* (*Gymnodinium breve*, PB-1) is a marine *dinoflagellate* which is the cause of massive fish kills, mollusk poisoning and human food poisoning along the Florida coast and in the Gulf of Mexico.[1]

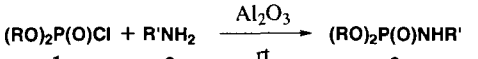




PB-1

Several attempts have been made to isolate the toxins from the cultured cells;[2] however, discrepancies exist in the reported physical properties,[1,3-5] the main reason being presumably the difficulty associated with the separation and purification of the toxin mixture. Elucidation of the chemical structure is imperative not only for the understanding of the molecular basis of mechanism of action, but also for the design of proper countermeasures such as detection, determination of structure and therapeutic methods.[6] Over the past decade, *Gymnodinium breve* toxin such as O,O-di-(*n*-propyl) (*E*)-2-[1-methyl-2-oxopropylidene]phosphorohydrazidothiolate (*E*) oxime[7] and O,O-diphenyl cyclooctylphosphoramidate (PB-1, **3a**) were isolated from the *dinoflagellate*[8] and their structures were established by X-ray crystallography and spectroscopic techniques. Thus, synthesis and chemical modification followed by structure–function relationship studies provide attractive targets for chemists.

Various methods are known for the synthesis of phosphoramidates (**3**).[8-11] Prominent among them is the reaction of dialkyl chlorophosphate with alkyl/cycloalkylamines under argon atmosphere in the presence of inert solvent. Although the reaction is straightforward, it suffers from several drawbacks, such as tedious work up, long reaction times, poor atom economy (requires extra equivalents of base as acid scavenger), and use of organic solvents. The other reaction[12] is performed at high temperature 240°C resulting in tar formation, which reduces the yields of the desired products. In spite of availability of large number of synthetic methods, no attempt has been made to synthesize these compounds using readily available solid supports. Surface mediated solid-phase reactions are of growing interest[13-14] because of the ease of set up and work-up, mild reaction conditions, and rate of reactions, selectivity, high yields, absence of solvent and low cost of the reaction. As a part of our efforts to explore the utility of the surface-mediated reactions for the synthesis of organophosphorus compounds,[15-18] we report herein a new method for the synthesis of *Ptychodiscus brevis* (PB-1) and its analogues in the presence of a mixture of dialkyl/arylchlorophosphate, primary amine (except entry-I where secondary amine has been used) and neutral alumina under solvent-free condition, producing high yields of phosphoramidates (**3**)



1 **2** **3**

a) R = C_6H_5, R' = cyclooctyl (PB-1); b) R = C_6H_5, R' = cycloheptyl; c) R = C_6H_5, R' = cyclohexyl; d) R = C_6H_5, R' = cyclopentyl; e) R = C_6H_5, R' = cyclododecyl; f) R = C_6H_5, R' = *n*-octyl; g) R = C_6H_5, R' = *n*-hexyl; h) R = C_6H_5, R' = *n*-decyl; i) R = C_6H_5, R' = dicyclohexyl; j) R = C_6H_5, R' = β-naphthyl; k) R = 4-nitrophenyl, R' = cyclooctyl; l) R = 4-CN-phenyl, R' = cyclooctyl; m) R = CH_3, R' = cyclooctyl; n) R = CH_3, R' = cycloheptyl; o) R = CH_3, R' = cyclohexyl; p) R = CH_3, R' = cyclopentyl; q) R = C_2H_5, R' = cyclooctyl; r) R = C_2H_5, R' = cycloheptyl; s) R = C_2H_5, R' = cyclohexyl; t) R = C_2H_5, R' = cyclopentyl; u) R = *n*-C_3H_7, R' = cyclooctyl; v) R = *n*-C_3H_7, R' = cycloheptyl; w) R = *n*-C_3H_7, R' = cyclohexyl; x) R = *n*-C_3H_7, R' = cyclopentyl; y) R = *i*-C_3H_7, R' = cyclooctyl; z) R = *i*-C_3H_7, R' = cycloheptyl; zi) R = *i*-C_3H_7, R' = cyclohexyl; zii) R = *i*-C_3H_7, R' = cyclopentyl

Scheme 1

Reaction of diphenyl chlorophosphate with cyclooctylamine was performed as model reaction in the presence of alumina under various reaction conditions, monitored by ^{31}P NMR to determine the consumption of diphenyl chlorophosphate and formation of the corresponding product. Dicyclohexylamine reacted very rapidly and the reaction was complete just after addition. Reaction of β-naphthylamine took a somewhat longer time (20 minutes) to complete. The effect of the nature of the solid support on the reaction rate was also studied. Various supports such as Al_2O_3 (neutral), Al_2O_3 (basic), symctone clay, montmorillonite KSF clay, kieselgel, SiO_2, active charcoal and active carbon were used; Al_2O_3 (neutral) was found to be superior to others in terms of conversion and reaction time. All the reactions on alumina reached completion within 20 minutes under neat condition and at ambient temperature while, without alumina, even extended reaction times (up to 3 h) showed no significant enhancement in the yields (35%). It was also observed that by increasing the reaction time on alumina, there was no significant

change in the yield of products. A series of compounds were prepared by this procedure in excellent yields (80-98%) at 0°C and their structure was confirmed by GC-MS. The data of analysis are summarized in *Tables 1 and 2*.

Table 1. Yields, mps (bps) and ^{1}H NMR Data of Compounds **3**[a]

Cmpd	Yield (%)	mp/bp (°C) (mm Hg)	*lit*[11] (°C)	^{1}H NMR (δ)
3a	98	111-112	112-113	7.20 (m, 10-H, Ar), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.60 (m, 14-H for 7 CH_2);
3b	96	105-106	106-107	7.12 (m, 10-H, Ar), 3.74 (dd, NH, 1-H exchangeable), 3.46 (m, 1-H), 1.75 (m, 12-H for 6 CH_2);
3c	98	102-103	102.5-105	7.25 (m, 10-H, Ar), 3.72 (dd, NH, 1-H exchangeable), 3.50 (m, 1-H), 1.54 (m, 10-H for 5 CH_2);
3d	88	98-99	97-98	7.21 (m, 10-H, Ar), 3.77 (dd, NH, 1-H exchangeable), 3.43 (m, 1-H), 1.55 (m, 8-H for 4 CH_2);
3e	89	138-139	----[b]	7.22 (m, 10-H, Ar), 3.72 (dd, NH , 1-H exchangeable), 3.40 (m, 1-H), 1.60 (m, 24-H for 11 CH_2);
3f	90	133-134	130 -132	7.27 (m, 10-H, Ar), 3.73 (dd, NH, 1-H exchangeable), 3.5 (m, 2-H, CH_2), 1.76 (m, 12-H for 6 CH_2), 1.21 (t, 3-H, CH_3);
3g	95	129-130	131-133	7.30 (m, 10-H, Ar), 3.72 (dd, NH, 1-H exchangeable), 3.48 (m, 2-H, CH_2), 1.75 (m, 8-H for 4 CH_2), 1.30 (t, 3-H, CH_3);
3h	83	148-149	147-148	7.23 (m, 10-H, Ar), 3.73 (dd, NH, 1-H exchangeable), 3.48 (m, 2-H, CH_2), 1.76 (m, 16-H for 8 CH_2), 1.28 (t, 3-H, CH_3);
3i	84	168-170	169-170	7.23 (m, 10-H, Ar), 3.52 (m, 2-H), 1.51 (m, 20-H for 10 CH_2);
3j	80	147-148	----[c]	7.63 (m, 17-H, Ar), 3.70 (dd, NH, 1-H exchangeable);
3k	80	166-168	----[d]	7.21 (m, 8-H, Ar), 3.71 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.62 (m, 14-H for 7 CH_2 groups);
3l	82	138-139	----[e]	7.24 (m, 8-H, Ar), 3.71 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.62 (m, 14-H for 7 CH_2 groups);
3m	95	145-147/0.5	138-140/0.1	3.80 (dd, 1-H exchangeable), 3.72 (d, 6-H, J_{H-P} = 12.0Hz), 3.45 (m, 1-H), 1.62 (m, 14-H 7 CH_2)
3n	90	130-132/1	131-132/1	3.76 (d, 6-H , J_{H-P} = 12.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.46 (m, 1-H);
3o	88	134-136/1	129-130/0.5	3.78 (d, 6-H, J_{H-H} = 12.0Hz), 3.73 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.61 (m, 10-H for 5 CH_2), 1.55 (m, 12-H for 6 CH_2)
3p	88	130-132/1.5	130-131/1.0	3.80 (d, 6-H, J_{H-H} = 12.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.62 (m, 8-H for 4 CH_2);
3q	90	160-162/1	160-162/1.2	4.25 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.65 (m, 14-H for 7 CH_2), 1.33 (t, 6-H, J_{H-H} = 7.0 Hz)
3r	85	158-159/1	156-158/1	4.3 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.55 (m, 12-H for 6 CH_2 Protons) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz)
3s	92	149-150/0.8	150-151/1.0	4.34 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.71 (dd, NH, 1-H exchangeable), 3.46 (m, 1-H), 1.50 (m, 10-H for 5 CH_2 Protons) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz);

Table 1. Continued...

Cmpd	Yield (%)	mp/bp (°C) (mm Hg)	*lit*[11] (°C)	^{1}H NMR (δ)
3t	82	144-145/1	138-139/0.5	4.35 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable) 3.45 (m, 1-H), 1.60 (m, 8-H for 4 CH_2 Protons) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz)
3u	88	173-175/1	164-166/0.5	4.05 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.74 (m, 4-H, 2 CH_2), 1.65 (m, 14-H for 7 CH_2 Protons) 0.97 (t, 6-H, J_{H-H} = 7.0 Hz);
3v	80	170-171/0.8	160-162/0.1	4.03 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.46 (m, 1-H), 1.72 (m, 4H, 2 CH_2, J = 7.04 Hz), 1.58 (m, 12-H for 6 CH_2 Protons) 0.96 (t, 6-H, J_{H-H} = 7.48 Hz);
3w	81	168-169/1	174-176/1.5	4.06 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.71 (dd, NH, 1-H exchangeable), 3.44 (m, 1-H), 1.72 (m, 4-H, 2 CH_2, J = 7.04 Hz), 1.51 (m, 10-H for 5 CH_2 Protons), 0.99 (t, 6-H, J_{H-H} = 7.0 Hz);
3x	89	159-160/1	156-158/1.0	4.05 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0Hz), 3.72 (dd, NH, 1-H exchangeable) 3.45 (m, 1-H), 1.74 (m, 4-H, 2 CH_2, J = 7.04 Hz), 1.61 (m, 8-H for 4 CH_2 Protons) 0.98 (t, 6-H, J_{H-H} = 7.0 Hz)
3y	82	160-162/1	162-163/1.2	4.55 (sept, 2-H, J_{H-H} = 6.0 J_{H-P} = 6.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.65 (m, 14-H for 7 CH_2 Protons) 1.25 (d, 12-H, J_{H-H} = 6.0 Hz);
3z	85	156-157/1	156-158/0.5	4.53 (sept, 2-H, J_{H-H} = 6.0 J_{H-P} = 6.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.55 (m, 12-H for 6 CH_2 Protons) 1.26 (d, 12-H, J_{H-H} = 7.0 Hz);
3z i	87	147-148/1	146-149/1.0	4.34 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.71 (dd, NH, 1-H exchangeable), 3.46 (m, 1-H), 1.50 (m, 10-H for 5 CH_2 Protons) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz);
3z ii	88	140-141/1	141-142/1.2	4.35 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable) 3.45 (m, 1-H), 1.61 (m, 8-H for 4 CH_2 Protons) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz);

a) Reactions were carried out at ambient temperature and monitored by TLC and GC. All the reactions were complete within 10-20 minutes. Compounds **3m** and onwards are low melting hence purified by vacuum distillation. ^{1}H NMR of compound **3e**, **3f** were recorded in DMSO-d_6 b) Calcd for $C_{24}H_{34}NO_3P$: C, 69.39; H, 8.35; N, 3.37. Found: C, 69.43; H, 8.42; N 3.58. (c) Calcd for $C_{22}H_{18}NO_3P$: C, 70.40; H, 4.80; N 3.73. Found: C, 70.53; H, 4.93; N, 3.69. (d) Calcd for $C_{20}H_{24}N_3O_7P$: C, 53.45; H, 5.38; N 9.35. Found: C, 53.78; H, 5.12; N 9.47. (e) Calcd for $C_{22}H_{24}N_3O_3P$: C, 64.55; H, 5.87; N 10.27. Found: C, 64.52; H, 5.83; N, 10.49.

Table 2. IR, and ^{31}P NMR of Compounds **3**

Cmpd	IR (cm^{-1})	^{31}PNMR (δ)
3a	3219 (NH), 2950, 2890 (CH), 1410 (C-N), 1250 (P=O), 980-965 (P-O-Aryl)cm^{-1}	-1.79
3b	3222 (NH), 2955, 2880 (CH), 1415 (C-N), 1260 (P=O), 990-975 (P-O-Aryl)cm^{-1}	-1.76
3c	3220 (NH), 2960, 2870 (CH), 1420 (C-N), 1255 (P=O), 980-965 (P-O-Aryl)cm^{-1}	-1.64
3d	3219 (NH), 2950, 2890 (CH), 1410 (C-N), 1250 (P=O), 980-965 (P-O-Aryl)cm^{-1}	-1.47
3e	3225 (NH), 2965, 2870 (CH), 1425 (C-N), 1260 (P=O), 980-965 (P-O-Aryl)cm^{-1}	0.38
3f	3220 (NH), 2970, 2880 (CH), 1415 (C-N), 1260 (P=O), 980-965 (P-O-Aryl)cm^{-1}	0.63
3g	3220 (NH), 2970, 2880 (CH), 1425 (C-N), 1265 (P=O), 988-970 (P-O-Aryl)cm^{-1}	0.56
3h	3225 (NH), 2975, 2885 (CH), 1415 (C-N), 1260 (P=O), 980-965 (P-O-Aryl)cm^{-1}	0.57
3i	2970, 2880 (CH), 1410 (C-N), 1260 (P=O), 980-960 (P-O-Aryl)cm^{-1}	-12.97
3j	3220 (NH), 2900, 2860 (CH), 1410 (C-N), 1250 (P=O), 980-965 (P-O-Aryl)cm^{-1}	-11.34
3k	3270 (NH), 3000, 2950 (CH), 1500 and 1340 (NO_2), 1290 (P=O), 1200-1210 (P-O-Aryl), 1180-1175 (P-O-Aryl) cm^{-1}	-12.97
3l	3255 (NH), 2990, 2950 (CH), 2250 (C-N), 1430 (C-N)1260 (P=O), 1160-1150 (P-O-Aryl) cm^{-1}	-12.02
3m	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	10.63
3n	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	10.73
3o	3230 (NH), 2945, 2877 (C-H), 1260, (P=O), 1080, 1040 (P-O-C) cm^{-1}	10.88
3p	3225 (NH), 2955, 2880 (C-H), 1255, (P=O), 1090, 1050 (P-O-C) cm^{-1}	10.76
3q	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	9.28
3r	3230 (NH), 2960, 2880 (C-H), 1265, (P=O), 1080, 1045 (P-O-C) cm^{-1}	9.09
3s	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	8.89
3t	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	8.78
3u	3230 (NH), 2966, 2890 (C-H), 1250, (P=O), 1090, 1045 (P-O-C) cm^{-1}	8.15
3v	3230 (NH), 2960, 2895 (C-H), 1265, (P=O), 1090, 1050 (P-O-C) cm^{-1}	8.21
3w	3235 (NH), 2965, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	8.27
3x	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	8.38
3y	3225 (NH), 2965, 2890 (C-H), 1260, (P=O), 1090, 1050 (P-O-C) cm^{-1}	6.09
3z	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	6.20
3z i	3230 (NH), 2945, 2877 (C-H), 1260, (P=O), 1080, 1040 (P-O-C) cm^{-1}	6.29
3z ii	3220 (NH), 2950, 2890 (C-H), 1250, (P=O), 1090, 1050 (P-O-C) cm^{-1}	6.37

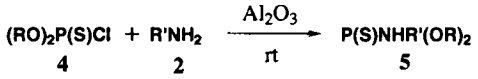
All the products had satisfactory IR, NMR and MS data and were compared with authentic samples.[19]

Table 3. Yields, mps and ^{1}H NMR and ^{31}P NMR Data of **5** [a]

Cmpd	Yield (%)	mp (°C)	*lit*[11] (°C)	^{31}P NMR (δ)	^{1}H NMR (δ)
5a	87	68-69	70-71	74.33	3.80 (d, d 1-H exchangeable), 3.72 (d, 6-H, J_{H-P} = 12.0 Hz), 3.45 (m, 1-H), 1.62 (m, 14-H for 7 CH_2)
5b	82	61-62	62-63	74.39	3.76 (d, 6-H , J_{H-P} = 12.0Hz), 3.72 (dd, NH, 1-Hexchangeable), 3.46 (m, 1-H);
5c	85	58-60	59-60	74.42	3.78 (d, 6-H, J_{H-H} = 12.0 Hz), 3.73 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.61 (m, 10-H for 5 CH_2) 1.55 (m, 12-H for 6 CH_2)
5d	83	52-53	51-53	74.52	3.80 (d, 6-H, J_{H-H} = 12.0Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.62 (m, 8-H for 4 CH_2);
5e	87	77-78	75-77	70.68	4.25 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.65 (m, 14-H for 7 CH_2) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz)
5f	81	70-71	70-72	70.89	4.31 (m, 4-H, J_{H-H} = 7.0J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.55 (m, 12-H for 6 CH_2) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz)
5g	83	68-69	69-70	70.94	4.34 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.71 (dd, NH, 1-H exchangeable), 3.46 (m, 1-H), 1.5 (m, 10-H for 5 CH_2) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz);
5h	84	61-62	62-64	70.99	4.35 (m, 4-H, J_{H-H} = 7.0 J_{H-P} = 8.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.60 (m, 8-H for 4 CH_2) 1.33 (t, 6-H, J_{H-H} = 7.0 Hz)
5i	96	127-128	129-130	74.02	7.20 (m, 10-H), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.61 (m, 14H for 7 CH_2);
5j	97	110-111	112-113	74.21	7.12 (m, 10-H), 3.74 (dd, NH , 1-H exchangeable), 3.46 (m, 1-H), .75 (m, 12-H for 6 CH_2);
5k	97	101-102	102-104	74.32	7.25 (m, 10-H), 3.72 (dd, NH, 1-H exchangeable), 3.50 (m, 1-H), .54 (m, 10-H for 5 CH_2);
5l	94	82-83	84-85	74.46	7.21 (m, 10-H), 3.77 (dd, NH, 1-H exchangeable), 3.43 (m, 1-H), 1.55 (m, 8-H for 4 CH_2);
5m	95	146-147	147-149	74.01	7.21 (m, 10-H), 3.72 (dd, NH , 1-H exchangeable), 3.40 (m, 1-H), 1.61 (m, 24-H for 11 CH_2);
5n	88	71-72	73-75	70.89	4.53 (sept, 2-H, J_{H-H} = 6.0 J_{H-P} = 6.0 Hz), 3.72 (dd, NH, 1-H exchangeable), 3.45 (m, 1-H), 1.55 (m, 12-H for 6 CH_2) 1.26 (d, 12-H, J_{H-H} = 7.0 Hz);

a) Reactions were carried out at ambient temperature and monitored by TLC and GC. All the reactions were complete within 10-15 minutes and all the products had satisfactory IR, NMR and MS data and were compared with authentic samples.[19]

The reactions were clean with no tar formation. Various thiophosphoramidates were also prepared by the same method and the results are summarized in *Table 3*



a) R = CH_3, R' = cyclooctyl; b) R = CH_3, R' = cycloheptyl; c) R = CH_3, R' = cyclohexyl; d) R = CH_3, R' = cyclopentyl; e) R = C_2H_5, R' = cyclooctyl; f) R = C_2H_5, R' = cycloheptyl; g) R = C_2H_5, R' = cyclohexyl; h) R = C_2H_5, R' = cyclopentyl; i) R = C_6H_5, R' = cyclooctyl; j) R = C_6H_5, R' = cycloheptyl; k) R = C_6H_5, R' = cyclohexyl; l) R = C_6H_5, R' = cyclopentyl; m) R = C_6H_5, R' = cyclododecyl; n) R = C_2H_5, R' = cycloheptyl

Scheme 2

The products were isolated by simple washing with diethyl ether or ethyl alcohol. The pure products were obtained by either crystallization and/or by vacuum distillation. No by-products such as phosphoramidic acids and polymerized products, which are generally obtained by use of other classical methods. The recovered alumina can be recycled five times without loss of activity after thorough washing with acetone and activation at 150°C.

In summary, a simple work-up, low consumption of solvent, rapid reaction rate, relatively clean reaction with no tar formation makes this method an attractive and a useful contribution to present methodologies.

EXPERIMENTAL SECTION

Melting points were determined on a hot stage microscope and are uncorrected. IR spectra were recorded on Nicolet FT-IR spectrometer model impact 410 neat or as KBr disks. ^1H and ^{31}P NMR spectra were recorded on Bruker DPX Avance 400 MHz FT- NMR in $CDCl_3$ using tetramethylsilane as an internal standard for ^1H and 85% H_3PO_4 as an external standard for ^{31}P NMR. A Nucon GC model 5765 instrument was used with flame ionization detector (FID). A capillary column (30 m x 0.25 mm I.D-BP5) packed with 5% phenyl and 95% dimethyl polysiloxane (SGE) coated on fused silica was employed. The injection port and detector block were maintained at 280°C and 260°C respectively and the column oven was at programmed temperature profile started at 50°C, ramped up to 280°C at 25°C/min. Nitrogen was used as a carrier gas (at a flow rate of 30ml/min). Air for FID was supplied at 300ml/min and hydrogen at 30 mL/min. In all analysis, 1ml sample were injected and peaks recorded on computerized data acquisition station.GC- MS data were recorded on Varian 3400 GC coupled to a TSQ 7000 mass spectrometer (Finnigan Mat). In order to operate GC the injector temperature 250°C, Transfer line temperature 280°C, Column temperature programming 50°C (2 min.) @ 10°C/min to 280°C (5 min.), carrier gas helium at pressure of 10 psi conditions were used. To obtain EI mass spectra Ion source pressure 1.5 x 10^{-6} torr, source temperature 150°C, electron energy 70eV and emission current 400mA were used as the operating conditions. To perform chemical ionization (CI) technique, the ion source pressure with methane as the reagent gas 1.5 x 10^{-3} torr, source temperature 150°C, electron energy 100 eV and emission current 300mA were maintained to operate the mass spectrometer. Elemental analysis was performed on elemental analyzer Carlo Erba Instrumantazione Model NOD1106 by using benzanilide as a reference compound.

General Procedure (3 and 6).- In a typical experimental procedure, neutral alumina (0.306 g, 3.0 mmol) activated by heating in oven at 150°C for 1 h was added to a round bottom round bottom flask. It was sealed by a rubber septum and cooled to 0°C. The amine (2.2 mmol) was added through a syringe followed by the dialkyl chlorophosphate or dialkyl chlorothiophosphate

(2.0 mmol) and the heterogeneous reaction mixture was shaken (a vortex shaker) at 0°C. The progress of reaction was monitored by TLC and GC by withdrawing a few milligrams of mixture and suspending it in 1 mL of acetonitrile or diethyl ether. When the reaction was complete, the mixture was extracted with dichloromethane (3 x 5 mL) and the alumina was filtered off by suction. The solvent was removed from the filtrate and residue was recrystallized from chloroform or ethanol and/or distilled to afford the pure products.

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2,6-DIISOPROPYL-4-METHYLPYRYLIUM HEXAFLUOROPHOSPHATE

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Although the acylation of alkenes has been studied for more than a century, the diacylation to give pyrylium salts was discovered only around 1960 because the diacylation products (the pyrylium salts) being soluble in water, were being unintentionally discarded, despite the fact that sometimes they can be the main reaction product.[1] Although this method (the Balaban-Nenitzescu-Praill synthesis of pyrylium salts) has been known for nearly half a century and many substituted pyrylium salts with identical substituents at positions 2 and 6 have been prepared in