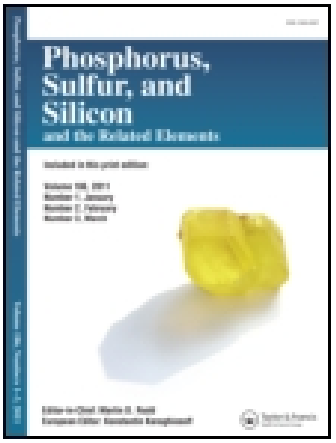

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Microwave-Assisted Synthesis of N,N-Dialkyl-P-Alkylphosphonamidic Anhydrides

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MICROWAVE-ASSISTED SYNTHESIS OF *N,N*-DIALKYL-*P*-ALKYLPHOSPHONAMIDIC ANHYDRIDES

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A new rapid, efficient, solvent-free, microwave-assisted, and high-yielding method for the synthesis of N,N-dialkyl-P-alkylphosphonamidic anhydrides has been developed. The method involves the use of 4-dimethylaminopyridine and water under microwave irradiation. The reaction of N,N-dialkylaminoalkyl/phenyl phosphonochloridates 2a–h with 4-dimethylaminopyridine (DMAP) gave pyridinium salts, which were converted into N,N-dialkyl-P-alkylphosphonamidic anhydrides 4a–h.

Keywords *N,N*-Dialkylaminoalkyl/phenylphosphonochloridates; *N,N*-dialkyl-*P*-alkylphosphonamidic anhydrides; 4-dimethylaminopyridine (DMAP); microwave irradiation

INTRODUCTION

The chemistry of organophosphorus (OP) compounds is a rapidly developing area of research because of their importance in industrial, agricultural, biochemical, and medicinal applications.[1] It is interesting to note that the variation in their physical, chemical, and biological properties is governed by the selection of the group attached to phosphorus atom. Phosphorous compounds containing the P–C bond are not particularly abundant in nature; nevertheless they have diverse biological activity, and as a consequence they have attracted the attention of synthetic as well as medicinal chemists. Similarly, other OP compounds containing the P–N–C linkage have also been reported as insecticides, fungicides, herbicides, fire retardants, and lubricants.[2] In particular, anhydrides of organophosphorus compounds (pyrophosphates) having the P–O–P linkage are known to have a rich history both in terms of their synthetic utility as well as their biological importance.[3] Recently, these anhydrides have been reported to serve as potent inhibitors and activators of enzymes.[4–6] There are several methods for the synthesis of pyrophosphates[7–10] and phosphonamidic anhydrides.[11] However, anhydrides of the *N,N*-dialkyl-*P*-alkylphosphonamidic acids have not been fully explored. The biological activity of pyrophosphates has prompted us to develop the rapid and efficient synthetic procedure for the synthesis of *N,N*-dialkyl-*P*-alkylphosphonamidic

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anhydrides. Perusal of the literature revealed that reported methods for the synthesis pyrophosphates are associated with several drawbacks, such as longer reaction times, use of carcinogenic solvents, harsh reaction conditions, and tedious workup, and chromatographic techniques are often used to afford the compounds of desired purity.[7–11] Recently, there has been considerable interest in the microwave (MW)-assisted synthesis of a variety of organic compounds due to the selective absorption of microwave energy by polar molecules.[12] Microwave-assisted organic synthesis is known for the spectacular accelerations produced in many reactions as a consequence of the heating rate, a phenomenon that can not be easily reproduced by classical heating. As a result, higher yields, mild conditions, and shorter reaction times can often be achieved.[13]

RESULTS AND DISCUSSION

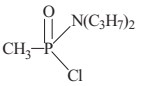
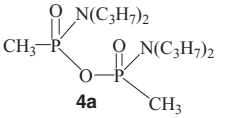
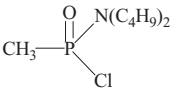
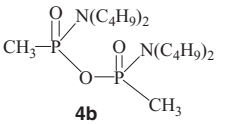
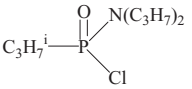
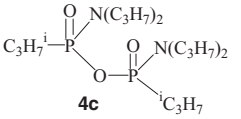
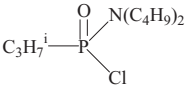
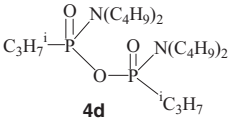
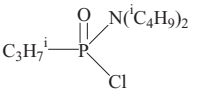
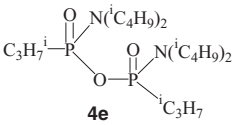
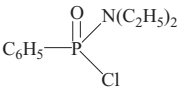
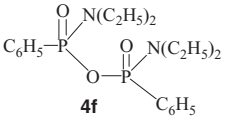
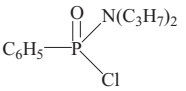
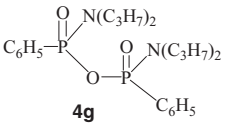
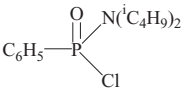
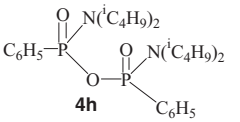
Inspired by the concept of microwave heating, we thought that *N,N-dialkyl-P*-alkylphosphonamidic anhydrides could be prepared from *N,N*-dialkylamino alkyl/phenylphosphonic chlorides **2a–h**.[14] In this regard, initially, we prepared alkyl/phenyl phosphonic dichloride **1** by a reported method by Kinnear and Parren.[15] After obtaining the *N, N*-dialkylamino alkyl/phenylphosphonic chlorides **2a–h**, we optimized the reaction conditions for the overall two-step process. In this regard, each of *N,N*-dialkylamino alkyl/phenylphosphonic chlorides **2a–h** were treated with various organic bases [dimethyl aminopyridine (DMAP), pyridine, triethylamine, diethyl aniline, N-methyl imidazole, and diisopropyl ethylamine] in presence of microwave irradiations under identical conditions. The yield of product **4a–h** was compared. However, the better yield was obtained when DMAP was used to produce the pyridinium salts **3a–h**. Best overall yields of *N,N*-dialkyl-*P*-alkylphosphonamidic anhydrides **4a–h** were obtained when *N,N*-dialkylamino alkyl/phenylphosphonic chlorides were first treated with DMAP followed by water in the molar ratio of 1:1:0.5 (Table I) at 180 W. The yields of products **4a–h** were excellent ranging from 85–93%. The purity of the compounds was checked on silica TLC plate using a benzene:acetone mixture (8:2). The compounds **4a–h** were characterized by IR, NMR, GC-MS, and elemental analysis. The IR showed strong and broad bands in the range of 975–969 cm^{-1}, due to antisymmetric stretching of the P—O—P linkage.[16] The other frequencies assigned for P—N—C, P—C, and P═O linkage were found to be comparable to those reported in the literature.[17] It was observed that compounds **4a–h** showed two signals in ^{31}P NMR due to the presences of two diastereotropic phosphorus atoms. The results of other analyses of **4a–h** are compiled in the Experimental section.

The results in Table I showed the novelty of the method, as compounds **4a–h** can be prepared in less than 10 min for each case with out isolating pyridinium salts **3a–h**. A further interesting aspect of this method is that the reactions are carried out in the absence of an organic solvent, hence making a more environmentally attractive process.

CONCLUSION

In conclusion, we have developed a rapid and efficient method for the synthesis of *N,N*-dialkyl-*P* -alkylphosphonamidic anhydrides **4a–h** with excellent yields. The main advantage of this method is that reactions were clean and had operational simplicity. Since column chromatography was not required to get pure products, this reaction is more attractive for organic chemists.

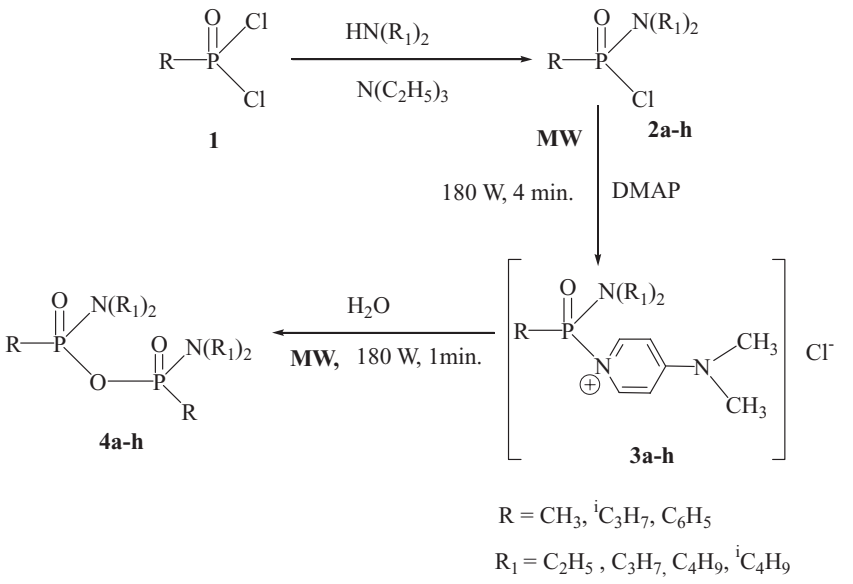
Table I Synthesis of *N,N*-dialkyl-*P*-alkylphosphonamidic anhydrides **4a–h** using microwave irradiations

Substrate	Product	Reaction time (min.)	Yield (%)[a]	Mp (°C)	^{31}P NMR (δ ppm)[b]
	 **4a**	5	85	oil	27.14, 26.25
	 **4b**	5	90	oil	27.00, 26.16
	 **4c**	6	91	38	33.95, 33.34
	 **4d**	6	88	39	33.48, 32.84
	 **4e**	6	87	40	32.98, 32.56
	 **4f**	7	90	42	16.53, 16.23
	 **4g**	7	89	47	16.74, 16.50
	 **4h**	7	93	50	18.24, 17.99

[a]Product yields.
[b]^{31}P NMR spectra were recorded in $CDCl_3$ at 162 MHz.

EXPERIMENTAL

Melting points were determined on a hot stage microscope and are uncorrected. IR spectra were recorded on Bruker FT-IR spectrometer model Tensor 27 on KBr disk, and solid compounds were analyzed by making KBr pellets. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ on a Bruker DPX Avance FT-NMR at 400, 100, and 162 MHz, respectively, using tetramethylsilane as an internal standard for ^{1}H, ^{13}C, and 85% H_3PO_4 as



Scheme 1

an external standard for ^{31}P NMR. A Chemito GC model 1000 instrument was used with a flame ionization detector (FID). A capillary column (30 m × 0.25 mm LD-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 that began at 50°C and ramped up to 280°C at 25°C/min. Nitrogen was used as carrier gas (at a flow rate of 30 mL/min). Air for FID was supplied at 300 mL/min and hydrogen at 30 mL/min. In all analyses, 0.1 μl sample was injected and peaks were recorded on Iris32 data acquisition station. The GC-MS analyses were performed in EI (70 eV) in full scan mode with an Agilent 6890 GC equipped with a model 5973 mass selective detector (Agilent Technologies, USA). An SGE BPX5 capillary column with 30 m length × 0.32 mm internal diameter × 0.25 μm film thickness was used at temperature program of 80°C (2 min)–20°C/min–280°C (3 min). Helium was used as the carrier gas at a constant flow rate of 1.2 mL/min. The samples were analyzed in split less mode at injection temperature. For these studies, a microwave oven (Samsung CE 2977N operating at 2450 MHz with an oven cavity of 336 × 241 × 349 mm and 28 L volume) at a power level of 180 W, equipped with inverter technology was used. The purity of compounds was checked on TLC plate (silica gel coated on aluminium plate) using benzene/acetone mixture (8:2), and the Rf value for each final product was found at 0.6–0.77.

General Procedure for the Preparation of *N,N*-Dipropyl-*P*-methylphosphonamidic Anhydride (4a–h)

To 4-dimethylaminopyridine (1.22 g, 0.01 M) in a conical flask was added *N,N*-dipropyl methylphosphonochloridate (1.97 g, 0.01 M) and the resulting mixture was mixed well. Following this, the mixture was irradiated with microwaves of 180 W energy for 4 min, resulting in salt production. Water (900 μL, 0.005 M) was added to the resultant

salt, and the reaction mixture was shaken until dissolution occurred. The mixture was further irradiated at 180 W for 1 min. The progress of the reaction was monitored by ^{31}P NMR until the signal of *N, N*-dipropyl methylphosphonochloridate disappeared. The reaction mass was washed and extracted with n-pentane (4 × 25 mL), and the solvent was evaporated to afford *N,N*-dipropyl-*P*-methylphosphonamidic anhydride. The product was triturated with pentane to get analytical purity.

***N,N*-Dipropyl-*P*-methylphosphonamidic anhydride (4a).** Anal. Calcd. $C_{14}H_{34}N_2O_3P_2$: C, 49.40; H, 10.07; N, 8.23. Found: C, 49.43; H, 10.05; N, 8.25. IR (KBr): 694(P—C), 971 (P—O—P), 1089, 1152 (P—N—C), 1237 (P═O), 1434 (C—N), 2885 (C—H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.88 (t, $J = 7.3$ Hz, 12H, CH_3), 1.53 (m, $J = 7.3$ Hz, 8H, CH_2), 1.67 (d, $J_{P-H} = 18.6$ Hz, 6H, CH_3), 2.98 (m, $^3J_{P-H} = 11.4$ Hz, 8H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.53 (CH_3), 18.90 (CH_2), 21.06 ($J_{P-C} = 150.5$ Hz, CH_3), 46.50 ($^3J_{P-C} = 5.5$ Hz, CH_2); GCMS (EI); m/z (%): 340 (4.46), 240 (78.57), 226 (20.53), 162 (41.07), 168 (22.32), 100 (100), 43 (19.64).

***N,N*-Dibutyl-*P*-methylphosphonamidic anhydride (4b).** Anal. Calcd. $C_{18}H_{42}N_2O_3P_2$: C, 54.53; H, 10.68; N, 7.07. Found : C, 54.50; H, 10.65; N, 7.08. IR (KBr): 698(P—C), 970 (P—O—P), 1080, 1150 (P—N—C), 1235 (P═O), 1435 (C—N), 2889 (C—H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.93 (t, $J = 7.2$ Hz, 12H, CH_3), 1.27 (m, $J = 7.2$ Hz, 8H, CH_2), 1.33 (m, $J = 7.0$ Hz, 8H, CH_2), 1.63 (d, $J_{P-H} = 18.6$ Hz, 6H, CH_3), 3.01 (m, $^3J_{P-H} = 11.4$ Hz, 8H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.35 (CH_3),15.73 (CH_2), 18.95 (CH_2), 20.09 ($J_{P-C} = 150.5$ Hz, CH_3), 44.67 ($^3J_{P-C} = 5.5$ Hz,CH_2); GCMS (EI); m/z (%): 396 (4.46), 318 (6.25), 275 (100), 190 (74.10), 148 (38.28), 128 (74.10), 106 (22.32), 92 (31.25), 41 (24.10).

***N,N*-Dipropyl-*P*-isopropylphosphonamidic anhydride (4c).** Anal. Calcd. $C_{18}H_{42}N_2O_3P_2$: C, 54.53; H,10.68; N, 7.07. Found : C, 54.50; H,10.65; N 7.09. IR (KBr): 696 (P—C), 975 (P—O—P), 1088, 1153 (P—N—C), 1237 (P═O), 1437 (C—N), 2888 (C—H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.82 (t, $J = 6.3$ Hz, 12H, CH_3), 1.10 (dd, $^3J_{P-H} = 21.4$ Hz, 12H, CH_3), 1.54 (m, $J = 6.3$ Hz, 8H, CH_2), 2.05 (m, $J_{P-H} = 19.9$ Hz, 2H, CH), 3.0 (m, $^3J_{P-H} = 11.3$ Hz, 8H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.23 (CH_3), 15.97 ($^3J_{P-C} = 10.0$ Hz, CH_3), 18.45 (CH_2), 21.05 ($J_{P-C} = 144.3$ Hz, CH), 44.56 ($^3J_{P-C} = 5.6$ Hz, CH_2); GCMS (EI); m/z (%): 396 (3.6), 353 (5.45), 296 (24.54), 254 (50), 224 (12.72), 190 (18.18),148 (25.45), 100 (100), 43 (23.63).

***N,N*-Dibutyl-*P*-isopropylphosphonamidic anhydride (4d).** Anal. Calcd. $C_{22}H_{50}N_2O_3P_2$: C, 58.38; H,11.14; N, 6.19. Found: C, 58.35; H,11.15; N 6.20. IR (KBr): 705(P—C), 978 (P—O—P), 1090, 1155 (P—N—C), 1235 (P═O), 1435 (C—N), 2887(C—H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.75 (t, $J = 6.4$ Hz, 12H, CH_3), 1.05 (dd, $^3J_{P-H} = 21.4$ Hz, 12H, CH_3), 1.10 (m, $J = 6.4$ Hz, 8H, CH_2), 1.52 (m, $J = 6.5$ Hz, 8H, CH_2), 2.05 (m, $J_{P-H} = 19.9$ Hz, 2H, CH), 3.02 (m, $^3J_{P-H} = 11.3$ Hz, 8H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.98 (CH_3), 14.36 ($^3J_{P-C} = 10.0$ Hz,CH_3), 18.36 (CH_2), 21.05 ($J_{P-C} = 144.2$ Hz, CH), 23.06 (CH_2), 46.50 ($^3J_{P-C} = 5.5$ Hz, CH_2); GCMS (EI); m/z (%): 452 (4.5), 409 (3.6), 324 (18.18), 282 (12.72), 176 (20.90), 141 (18.18),128 (100), 41 (10.35).

***N,N*-Diisobutyl-*P*-isopropylphosphonamidic anhydride (4e).** Anal. Calcd. $C_{22}H_{50}N_2O_3P_2$: C, 58.38; H,11.14; N, 6.19. Found: C, 58.35; H,11.15; N 6.20. IR (KBr): 698 (P—C), 980 (P—O—P), 1090, 1150 (P—N—C), 1240 (P═O), 1436 (C—N), 2885 (C—H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0.80 (d, $J = 6.5$ Hz, 12H, CH_3), 1.05 (dd, $^3J_{P-H} = 21.4$ Hz, 12H, CH_3), 1.52 (m, $J = 6.1$Hz, 4H, CH), 2.05 (m, $J_{P-H} = 19.9$ Hz, 2H, CH), 3.02 (m, $^3J_{P-H} = 11.3$ Hz, 8H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.98 (CH_3), 14.36 ($^3J_{P-C} = 10.0$ Hz,CH_3), 19.56 (CH), 21.05 ($J_{P-C} = 144.2$ Hz, CH), 46.47 ($^3J_{P-C} = 5.5$ Hz,

CH_2); GCMS (EI); m/z (%): 452 (7.23), 409 (4.56), 324 (24.28), 282 (14.24), 176 (20.90), 141 (18.18),128 (100), 41 (10.35).

***N,N*-Diethyl-*P*-phenylphosphonamidic anhydride (4f).** Anal. Calcd. $C_{20}H_{30}N_2O_3P_2$: C, 58.82; H, 7.40; N, 6.86. Found: C, 58.80; H, 7.39; N, 6.87. IR (KBr): 698 (P—C), 975 (P—O—P), 1089, 1150 (P—N—C), 1240 (P=O), 1437 (C—N), 2888 (C—H), 2995 (C_6H_5), cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 1.02(t, $J = 6.5$ Hz, 12H, CH_3), 2.99 (m, $^3J_{P-H} = 11.3$ Hz, 8H, CH_2), 7.44–8.23(m, $J_{P-H} = 20.1$ Hz, 10H, Ar—H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.32 (CH_3), 47.15 ($^3J_{P-C} = 5.5$ Hz, CH_2), 128–135 ($J_{P-C} = 147.2$ Hz,Ar—C); GCMS (EI); m/z (%): 408 (8.89), 336 (18.15), 260 (9.34), 196 (28.10), 124 (9.72), 72 (100), 43 (10.56).

***N,N*-Dipropyl-*P*-phenylphosphonamidic anhydride (4g).** Anal. Calcd. $C_{24}H_{38}N_2O_3P_2$: C, 62.06; H, 8.25; N, 6.03. Found : C, 62.07; H, 8.24; N 6.05. IR (KBr): 698 (P—C), 974 (P—O—P), 1085, 1150 (P—N—C), 1240 (P=O), 1441(C—N), 2890 (C—H), 2975 (C_6H_5) $cm^{-1;}$ ^1H NMR (400 MHz, $CDCl_3$) : δ 0. 76 (t, $J = 6.5$ Hz, 12H, CH_3), 1.65 (m, $J = 6.7$ Hz, 8H, CH_2), 3.05 (m, $^3J_{P\text{-}H} = 11.3$ Hz, 8H, CH_2), 7.35–7.95 (m, $J_{P\text{-}H} = 20.1$Hz,10H, Ar—H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.32 (CH_3), 18.25 (CH_2), 46.45 ($^3J_{P-C} = 5.6$ Hz, CH_2), 128–135 ($J_{P-C} = 147.4$ Hz, Ar—C); GCMS (EI); m/z (%): 464 (3.55), 364 (24.27), 292 (7.76), 224 (24.27), 150 (14.50), 140 (14.72), 100 (100), 43 (14.56).

***N,N*-Diisobutyl-*P*-phenylphosphonamidic anhydride (4h).** Anal. Calcd. $C_{28}H_{46}N_2O_3P_2$: C, 64.60; H, 8.91; N, 5.38. Found: C, 64.62; H, 8.90; N, 5.40. IR (KBr): 690 (P-C), 969 (P-O-P), 1085, 1150 (P-N-C), 1238 (P = O), 1437 (C-N), 2889 (C-H), 2988 (C_6H_5) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) : δ 0. 75 (d, $J = 6.5$ Hz, 12H, CH_3), 1.92 (m, $J = 6.6$ Hz, 4H, CH), 2.95 (m, $^3J_{P\text{-}H} = 11.3$ Hz, 8H, CH_2), 7.35–7.85 (m, $J_{P\text{-}H} = 20.1$Hz, 10H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.35 (CH_3), 18.25 (CH), 44.46 ($^3J_{P\text{-}C} = 5.7$ Hz, CH_2), 128–135 ($J_{P\text{-}C} = 147.4$ Hz, Ar-C); GCMS (EI); m/z (%): 520 (4.43), 392 (100), 338 (9.70), 252 (14.56), 217 (4.58), 196 (14.56), 152 (19.40), 128 (68.93), 57 (16.47), 41 (18.44).

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