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A Novel and Efficient Synthesis of *N,N*-Dialkylaminoisopropyl- and *O*-alkylisopropyl-2-(1-alkyl-2-oxopropylidene)phosphono-hydrazido Oximes - Potential Marine Fish Toxin Analogues. Part 1

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Abstract: A novel and efficient method for the synthesis of *N,N*-dialkylaminoisopropyl- and *O*-alkylisopropyl-2-(1-alkyl-2-oxopropylidene)phosphonohydrazido oximes (**4**) using activated silica as dehydrating agent has been developed. The reaction involves the condensation of substituted diacetyl monoxime and *N,N*-dialkylaminoisopropyl-phosphono hydrazide or O-alkylisopropylphosphono hydrazides and gave the corresponding analogues of a naturally occurring fish toxin in excellent yields under mild conditions.

Keywords: Hydrazides, diacetyl monoxime, marine fish toxin, phosphonohydrazido oxime

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Introduction

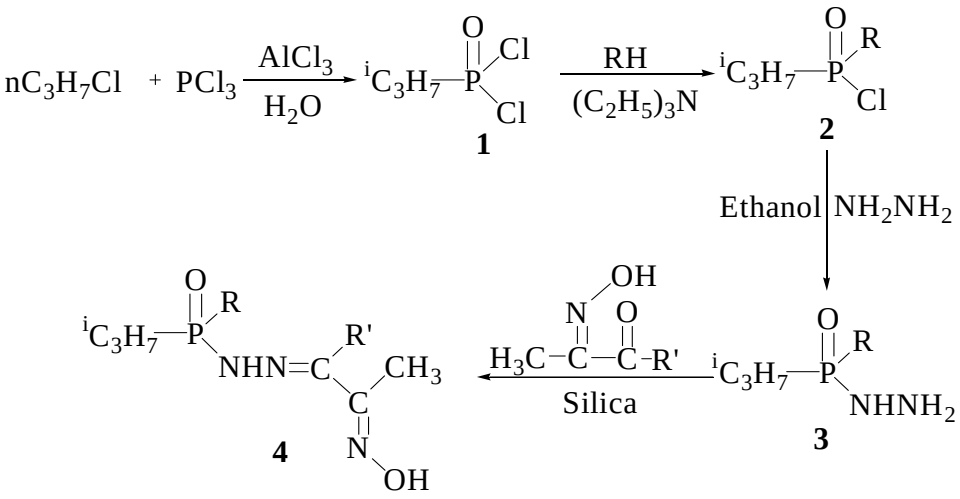
The toxins associated with ‘blooms’, or explosive growth of certain marine dinoflagellates, have caused massive fish kills off the coasts of the United States, Canada, and Japan, and have been the subject of intense studies in the last fifty years [1-2]. Although most of the 400 species of

dinoflagellates are nontoxic, but there are notable exceptions, i.e., the *Gonyaulax* species, which give rises to anaxitoxins/gonyautoxins [1-2] and *Ptychodiscus brevis* that produces brevetoxins [3-4]. The dinofiagellate *Ptychodiscus brevis* has been implicated in production of toxin red tide also along the gulf coast of Florida [5-6]. Marine derived *dinoflagellates* have also become a rich source of structurally novel and pharmacologically active secondary metabolites [1]. Toxins produced by *Ptychodiscus brevis* are lipoidal in nature and their structures were established as *O,O*-dipropyl-(E)-2-(1-methyl-2-oxopropylidene)phosphorohydrazidothiolate-(*E*)-oxime [7] and *O,O*-diphenylcyclooctyl phosphoramidate (PB-1) on the basis of X-ray crystallography [8]. These marine toxins have attracted the attention of organic chemists due to their involvement in human intoxication and the socio-economic impact brought about by those incidents [9-11]. It is interesting to note that this naturally occurring fish toxin [7] is the only organophosphorus (OP) compound which contains thiophosphoryl moiety like other insecticides [12] and does not possess any good leaving groups. Another unique feature of this compound is the presence of a free oximino function, which is not found in any of the earlier reported toxic OP compounds. The non availability of P=O analogues of naturally occurring fish toxin [7] from the natural sources has prompted us to develop the general synthetic method for the preparation of P=O and its analogues for complete toxicological and pharmacological studies. Moreover, P=O compounds have been reported to be more toxic than P=S derivatives; for example paraoxon is more toxic than parathion [10, 12]. To explore its chemical and biological properties, it was decided to develop a convenient method for the synthesis of P=O analogues of naturally occurring fish toxin by doing structural modifications. To the best of our knowledge there is no report in the literature for the synthesis of *N,N*-dialkylaminoisopropyl- and *O*-alkylisopropyl-2-(1-alkyl-2-oxopropylidene)phosphonohydrazido oximes **4**.

Result and Discussion

Retrosynthetic analysis of the compounds indicated that they can be synthesized from the corresponding phosphonohydrazides and α-ketooximes. We have followed this procedure to obtain the *N,N*-dialkylaminoisopropyl- and *O*-alkyl isopropyl-2-(1-alkyl-2-oxopropylidene) phosphonohydrazido oximes **4** in excellent yields (Scheme 1).

Scheme 1.



In order to synthesize the target compounds, the intermediates **1, 2, 3** were prepared by following literature procedures [13-15]. Various *N,N*-dialkylaminoisopropylphosphono hydrazides and *O*-alkyl-isopropylphosphono hydrazides were condensed with substituted diacetyl monoxime in the presence of activated silica in benzene at 80- 90 °C, to obtain both *N,N*-dialkylaminoisopropyl-and *O*-alkyl isopropyl-2-(1-alkyl-2-oxopropylidene) phosphonohydrazido oximes **4** in excellent yield (Table 1).

Table1 . Physical data of the newly synthesized compounds **4**[a].

Entry	R	R^1	Reaction time(h)	^{31}P-NMR[c]	m. p. (^{0}C)	Yield[b] (%)
4a	$N(C_2H_5)_2$	CH_3	3.5	38.99	162	75
4b	$N(C_3H_7)_2$	CH_3	3.8	38.16	185	81
4c	$N(C_3H_7)_2$	C_6H_5	4.0	37.97	187	78
4d	$N(C_4H_9)_2$	CH_3	3.5	39.02	142	84
4e	$N(C_4H_9)_2$	C_6H_5	4.0	38.76	193	92
4f	OC_3H_7	CH_3	3.0	36.18	168	87
4g	$O^iC_3H_7$	CH_3	3.5	35.74	181	83
4h	OC_4H_9	CH_3	3.0	36.08	138	74
4i	$O^iC_4H_9$	CH_3	3.5	35.69	147	69

a) All the reactions were performed in benzene under refluxed conditions; b) isolated yield; c) ^{31}P-NMR data were recorded at 162 MHz using either $CDCl_3$ or DMSOd-$_6$ as a solvent

The reactions of *N,N*-dialkylaminoisopropylphosphono hydrazides and *O*-alkylisopropyl-phosphono hydrazides with substituted diacetyl monoxime shown in Scheme 1 appear simple, but they require a selective coupling of butane-2,3-dione monoxime (diacetyl monoxime) and the corresponding phosphono hydrazides to afford the desired compounds. A variety of reagents are capable to converting a C=O into a C=N bond. The traditional synthesis involves the condensation of a carbonyl group with NH_2-Y (Y=OH, NH, $NHCONH_2$, etc) through an addition-elimination reaction. Initially, the more basic nitrogen of the hydrazides adds to the carbonyl moiety to furnish a tetrahedral intermediate, which transforms the C=O into a C=N compound after elimination of water, but removal of water is a reversible process, thus it needs to be removed by azeotropic distillation or by use of various dehydrating agents. However, the transformation of the C=O is particularly challenging in the synthesis of *N,N*-dialkylaminoisopropyl- and *O*-alkylisopropyl-2-(1-alkyl-2-oxopropylidene)-phosphonohydrazido oximes, due to the presence of reactive free oxime (N=OH) and hydrazimino (-NH-N=) functionalities, which can undergo Beckmann rearrangements and/or cyclization reactions. This is probably the reason why no attempts to synthesize **4** have been made previously. Initially the reaction of diethylaminoisopropylphosphono hydrazide with butane-2,3-dione monoxime was performed as a model reaction in the presence of various dehydrating reagents and by varying the reaction temperature. The efficiency of various dehydrating reagents such as Al_2O_3 (neutral, acidic,

basic), SiO_2, $ZnCl_2$, H_3PO_4, H_3PO_3, KF-SiO_2, $POCl_3$, PTSA, $BiCl_3$, DCC, $MgSO_4$, V_2O_5-SiO_2 were studied in different mole ratios (10-120 mole %). Amongst all these, anhydrous SiO_2 gave the best result. The effect of solvents on the synthesis of the target molecules was also studied by carrying out the reaction in various solvents like THF, dioxane, hexane, ethanol, diethyl ether, benzene, DCM, chloroform, CCl_4 and it was observed that benzene afforded the best results.

Conclusions

In summary, we have developed a more convenient and selective method for the synthesis of *N,N*-dialkylaminoisopropyl- and *O*-alkylisopropyl-2-(1-alkyl-2-oxopropylidene)phosphonohydrazido oximes **4**. It was found that SiO_2 promoted the reaction in high yields. The simplicity of the reaction conditions with short reaction times and without requiring the use of column chromatography to obtain the pure products in high yields should make this method attractive for organic chemists.

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Experimental

General

^{1}H-, ^{31}P- and ^{13}C-NMR spectra were recorded in $CDCl_3$/DMSO-d_6 solutions on a Bruker AVANCE 400 NMR spectrometer operating at 400 MHz. LCMS analysis (EI, 70V) were performed on a Hewlett-Packard HP 5971 instrument.

General procedure for the preparation of N,N-diethylaminoisopropyl-2-(1-methyl-2-oxopropylidene)-phosphonohydrazido oxime (**4a**)

A mixture of butane-2,3-dione monoxime (1 g, 0.01 mol) and activated silica gel (2 g) was placed in a two-necked round bottom flask containing benzene (20 mL). *N,N*-diethylaminoisopropyl-phosphono hydrazide (1.93 g, 0.01 mol) diluted in benzene (20 mL) was slowly added at room temperature with efficient stirring and the mixture was refluxed for 3 h. The reaction progress was monitored by ^{31}P-NMR till the signal of phosphono hydrazide starting material disappeared. The reaction mixture was filtered through a Buchner funnel and washed with benzene (2x10 mL). The filtrate and washes were combined and the solvent was removed by distillation. Finally, the crude desired product was triturated with dry ether gave a white crystalline powder which was crystallized from ethanol-ether (7:3); m. p. = 162, yield 75%; ^{1}H-NMR δ: 1.03 (t, J = 12.07 Hz, 6H, CH_3), 1.10 (dd, J = 8.45 Hz, 6H, CH_3), 1.25 (dd, J = 8.45 Hz, 6H, CH_3), 1.86 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.45 (m, 1H, J^{P-H} = 27.56, CH), 3.18 (m, J = 12.23 Hz, 4H, CH_2), 6.45 (d, J^{P-H} = 28.58, 1H, NH), 8.01 (s, 1H, OH); ^{13}C-NMR δ: 9.58 (CH_3), 15.55 (CH_3), 16.45 (CH_3), 23.16 (CH_3), 24.34 (CH_3), 38.45

(CH), 145.39 (C=N-NH), 156.09 (C=N-OH); MS (m/z): 277 ($M+H^+$), 299 ($M+Na^+$); Calcd. for $C_{11}H_{25}N_4O_2P$ (%): C 47.81, H 9.12, N 20.28; Found (%): C 47.83, H 9.11, N 20.25.

N,N-Dipropylaminoisopropyl-2-(1-methyl-2-oxopropylidene)phosphonohydrazido oxime (**4b**). ^{1}H-NMR δ: 0.75 (t , J = 9.70 Hz,6H ,CH_3), 1.10 (dd, J = 8.29 Hz, 6H, CH_3), 1.25 (dd, J = 8.29 Hz, 6H, CH_3), 1.55 (m, J = 10.35 Hz, 4H, CH_2), 1.80 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.40 (m, J^{P-H} = 27.86 Hz, 1H, CH), 2.95 (m, J = 11.85 Hz, 4H, CH_2), 6.35 (d, J^{P-H} = 25.68, 1H , NH), 7.85 (s, 1H, OH); ^{13}C-NMR δ: 9.36 (CH_3), 15.30 (CH_3), 16.45 (CH_3), 19.97 (CH_2), 20.86 (CH_3), 24.68 (CH_3), 31.45 (CH), 42.20 (CH_2), 147.87 (C=N-NH), 156.93 (C=N-OH); MS (m/z): 305 ($M+H^+$), 328 ($M+Na^+$); Calcd. for $C_{13}H_{29}N_4O_2P$ (%): C 51.30, H 9.60, N 18.41; Found (%): C 51.27, H 9.58, N 18.39.

N,N-Dipropylaminoisopropyl-2-(1-phenyl-2-oxopropylidene)phosphonohydrazido oxime (**4c**). ^{1}H-NMR δ: 0.85 (t, J = 10.23 Hz, 6H, CH_3), 1.10 (dd, J = 8.56 Hz,6H, CH_3), 1.15 (dd, J = 8.56 Hz, 6H, CH_3), 1.45 (m, J = 9.36 Hz, 4H,CH_2), 2.10 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.30 (m, J^{P-H} = 31.52 Hz, 1H, CH), 2.95 (m, J = 10.54 Hz, 4H, CH_2), 6.50 (d, J^{P-H} = 27.59 Hz, 1H, NH), 7.1-7.5 (m, J = 7.93 Hz, 5H, C_6H_5), 7.85 (s, 1H, OH); ^{13}C-NMR δ: 9.58 (CH_3), 15.45 (CH_3), 16.13 (CH_3), 21.97 (CH_2), 23.72 (CH_3), 31.45 (CH), 46.63 (CH_2), 128-130 (Ar-C), 147.64 (C=N-NH), 157.14 (C=N-OH); MS (m/z): 389 ($M+H^+$), 328 ($M+ Na^+$); Calcd. for $C_{18}H_{31}N_4O_2P$ (%): C 59.00, H 8.53, N 15.29; Found (%) : C 58.98, H 8.50, N 15.26.

N,N-Dibutylaminoisopropyl-2-(1-methyl-2-oxopropylidene)phosphonohydrazido oxime (**4d**). ^{1}H-NMR δ: 0.83(t, J = 12.77 Hz, 6H, CH_3), 1.05 (dd, J = 8.51 Hz, 6H, CH_3), 1.10 (dd, J = 8.51 Hz, 6H, CH_3), 1.25 (m, J = 10.32 Hz, 4H, CH_2), 1.45 (m, J = 10.32 Hz, 4H,CH_2), 1.78 (s, 3H, CH_3), 2.10 (s ,3H, CH_3), 2.40 (m, J^{P-H} = 25.59 Hz,1H, CH),3.05 (m, J = 9.56 Hz, 4H ,CH_2), 6.42 (d, J^{P-H} = 20.65 Hz, 1H ,NH), 7.50 (s,1H, OH); ^{13}C- NMR δ: 9.58 (CH_3), 15.48 (CH_3), 16.05 (CH_3),20.36 (CH_2), 23.32 (CH_3), 24.50 (CH_3), 31.03 (CH), 44.72 (CH_2), 145.36 (C=N-NH), 155.92 (C=N-OH); MS (m/z): 333 ($M+H^+$) , 355 ($M+ Na^+$) ; Calcd. For $C_{15}H_{33}N_4O_2P$ (%): C 54.20, H 10.01, N 16.85; Found (%): C 54.18, H 9.98, N 16.85.

N,N-Dibutylaminoisopropyl-2-(1-phenyl-2-oxopropylidene)phosphonohydrazido oxime (**4e**). ^{1}H-NMR δ: 0.75 (t, J = 11.78 Hz, 6H, CH_3), 1.05 (dd, J = 9.37 Hz, 6H, CH_3), 1.20 (dd, J = 9.37 Hz, 6H, CH_3), 1.45 (m, J = 10.52 Hz, 4H, CH_2), 2.05 (s, 3H, CH_3), 2.35 (m, J^{P-H} = 26.93 Hz, 1H, CH), 3.05 (m, J = 10.85 Hz, 4H, CH_2), 6.15 (d, J^{P-H} = 27.38 Hz, 1H, NH), 7.2-7.5 (m, J = 8.75 Hz, 5H, C_6H_5), 7.86 (s, 1H, OH); ^{13}C-NMR δ: 9.58 (CH_3), 15.70 (CH_3), 16.05 (CH_3), 20.36 (CH_2), 23.62 (CH_3), 31.32 (CH), 44.74 (CH_2), 128-130 (Ar-C), 145.36 (C=N-NH), 155.60 (C=N-OH); MS (m/z): 395 ($M+H^+$); Calcd. for $C_{20}H_{35}N_4O_2P$ (%): C 60.89, H 8.94, N 14.20; Found (%): C 60.90, H 8.93 N 14.17.

O-propylisopropyl-2-(1-methyl-2-oxopropylidene)phosphonohydrazido oxime (**4f**). ^{1}H-NMR δ: 0.85 (t, J = 9.33 Hz, 3H, CH_3), 0.95 (dd, J = 7.37 Hz, 3H, CH_3), 1.20 (dd, J = 7.23 Hz, 3H, CH_3), 1.65 (m, J = 8.95 Hz, 2H, CH_2), 2.20 (m, J^{P-H} = 29.56, 1H, CH), 1.95 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.90 and 4.05 (m, J = 9.36 Hz, 2H, CH_2), 6.55 (d, J^{P-H} = 26.67 Hz ,1H ,NH), 7.58 (s, 1H, OH); ^{13}C-NMR δ: 9.63 (CH_3), 15.87 (CH_3), 16.05 (CH_3), 19.20 (CH_2), 23.74 (CH_3), 24.46 (CH_3), 26.53 (CH), 65.49

(CH_2), 145.86 (C=N-NH), 157.44 (C=N-OH); MS (m/z): 264 ($M+H^+$); Calcd. for $C_{10}H_{22}N_3O_3P$ (%): C 45.63, H 8.36, N 15.96; Found (%): C 45.65, H 8.38, N 14.95.

O-isopropylisopropyl-2-(1-methyl-2-oxopropylidene) phosphonohydrazid ooxime (**4g**). ^{1}H-NMR δ: 0.95 (dd, *J* = 8.89 Hz, 3H, CH_3), 1.10 (dd, *J* = 8.89 Hz, 3H, CH_3), 1.15 (d, *J* = 10.67 Hz, 3H, CH_3), 1.20 (d, *J* = 8.02 Hz, 3H, CH_3), 1.85 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.10 (m, J^{P-H} = 29.56, 1H, CH), 3.95 and 4.05 (m, *J* = 8.33 Hz,1H, CH), 8.50 (d, J^{P-H} = 27.69 Hz, 1H, NH), 11.35 (s, 1H, OH); ^{13}C-NMR δ: 9.63 (CH_3), 15.87 (CH_3), 16.05 (CH_3), 23.74 (CH_3), 24.46 (CH_3), 26.53 (CH), 69.49 (CH), 146.36 (C=N-NH), 156.44 (C=N-OH); MS (m/z): 264 ($M+H^+$); Calcd. for $C_{10}H_{22}N_3O_3P$ (%): C 45.63, H 8.36, N 15.96; Found (%):C 45.65, H 8.39, N 14.95.

O-butylisopropyl-2-(1-methyl-2-oxopropylidene) phosphonohydrazido oxime (**4h**). ^{1}H-NMR δ: 0 .85 (t, *J*= 6.83Hz, 3H, CH_3), 0.95 (dd, *J*= 7.42 Hz, 3H, CH_3), 1.20 (dd, *J*= 7.04 Hz, 3H, CH_3), 1.40 (m, *J*= 7.23 Hz, 2H, CH_2), 1.75 (m, *J*= 7.23 Hz, 2H, CH_2), 1.95 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.10 (m, J^{P-H} = 31.69 Hz, 1H, CH), 3.90 and 4.05 (m, *J*= 7.43 Hz, 2H, CH_2), 6.55 (d, J^{P-H} = 20.35 Hz, 1H, NH), 7.58 (s, 1H, OH); ^{13}C-NMR δ: 9.63 (CH_3), 15.87 (CH_3), 16.05 (CH_3), 17.80 (CH_2), 19.20 (CH_2), 23.74 (CH_3), 24.46 (CH_3), 26.53 (CH), 69.49 (CH_2), 145.86 (C=N-NH), 157.44 (C=N-OH); MS (m/z): 278 ($M+H^+$); Calcd. for $C_{11}H_{24}N_3O_3P$ (%): C 47.65, H 8.66, N 15.16; Found (%): C 45.68 H 8.64, N 15.15.

O-isobutylisopropyl-2-(1-methyl-2-oxopropylidene)phosphonohydrazido oxime (**4i**). ^{1}H-NMR δ: 0.85 (d, *J* = 10.03 Hz, 3H, CH_3), 0.95 (dd, *J* = 8.33 Hz, 3H, CH_3), 1.10 (dd, *J* = 8.33 Hz, 3H, CH_3), 1.15 (d, *J* = 10.03 Hz, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 2.10 (m, J^{P-H} = 29.50 Hz, 1H, CH), 3.60 (m, *J* = 9.63 Hz, 1H, CH), 3.90 and 4.05 (m, *J* = 9.63 Hz, 2H, CH_2), 6.55 (d, J^{P-H} = 31.58 Hz, 1H, NH), 7.58 (s, 1H, OH); ^{13}C-NMR δ: 9.63 (CH_3), 15.87 (CH_3), 16.05 (CH_3), 23.74 (CH_3), 24.46 (CH_3), 26.53 (CH), 46.30 (CH), 69.40 (CH_2), 145.86 (C=N-NH), 157.44 (C=N-OH); MS (m/z): 278($M+H^+$); Calcd. for $C_{11}H_{24}N_3O_3P$ (%): C 47.65, H 8.66, N 15.16; Found (%): C 45.63 H 8.67, N 15.13.

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Sample Availability: Contact authors.