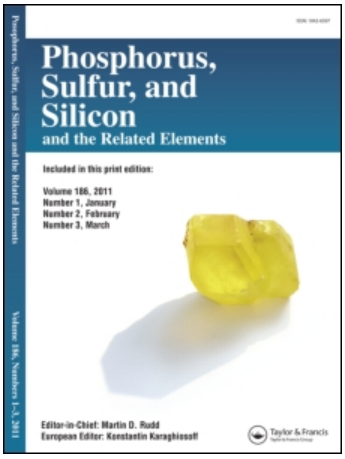

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Diastereoselective Synthesis of New Dialkylphosphorylhydrazones

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Online publication date: 28 December 2009

To cite this Article Rodrigues, Janaína Marques , Sant'Anna, Carlos Mauricio R. , Rumjanek, Victor Marcos and DaCosta, João Batista Neves(2010) 'Diastereoselective Synthesis of New Dialkylphosphorylhydrazones', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 1, 40 — 56
To link to this Article: DOI: 10.1080/10426500903444366
URL: http://dx.doi.org/10.1080/10426500903444366

Phosphorus, Sulfur, and Silicon, 185:40–56, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903444366

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DIASTEREOSELECTIVE SYNTHESIS OF NEW DIALKYLPHOSPHORYLHYDRAZONES

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A series of 22 dialkylphosphorylydrazones (dialkyl ester, N′-[(1E)-(R_1 phenyl)methylene]-phosphorohydrazidic acid), 20 of them new, along with three new N,N′-bis (diisobutylphosphorylthioamide)diamines (bis-[diisobutyl ester), N-thioxomethylene]-, diamine)phosphoramidic acid, were prepared and characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and mass spectrometry. The analysis of ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and NOE spectra confirmed the observation of the single diastereoisomer E in the synthesis of dialkylphosphorylydrazones. The results of a molecular modeling study performed in order to investigate the mechanism of the synthesis of dialkylphosphorylydrazones are in agreement with the experimental results, i.e., the favored formation of diastereoisomer E over Z.

Keywords *N,N′*-bis(diisobutylphosphorylthioamide) diamines; dialkylphosphorylydrazones; organophosphorus compounds

INTRODUCTION

Organophosphorus compounds and hydrazones have both attracted attention of various research groups during recent years. This growing interest may be attributed to the chemical versatility shown by these compounds.[1,2] Several organophosphorus compounds have anticholinesterase activity, hence their major use as pesticides.[3] They may act as analgesics and antiinflammatory agents,[4] anti-HIV agents,[5,6] and they can be used in the treatment of some bone diseases such as Paget's or malign hypercalcemia, osteoporosis, and metastatic and osteolytic diseases.[7–11] Organophosphorus compounds have also been reported in the use against rheumatoid arthritis[12,13] and as antiproliferative against *Trypanosoma cruzi.*[14] Finally, they are also part of normal metabolism as in AMP, ADP, and ATP[15,16] or in adrenergic receptors.[17] Furthermore, organophosphorus inhibits various enzymes such as glutamine synthase, dipeptidyl carboxypeptidase I, adenylosuccinate lyase, alanine racemase,[18] and tyrosinase.[18,19]

Received 23 October 2008; accepted 8 April 2009.
We thank the financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and Fundação Carlos Chagas Filho de Amparo a Pesquisa do Estado do Rio de Janeiro (FAPERJ).
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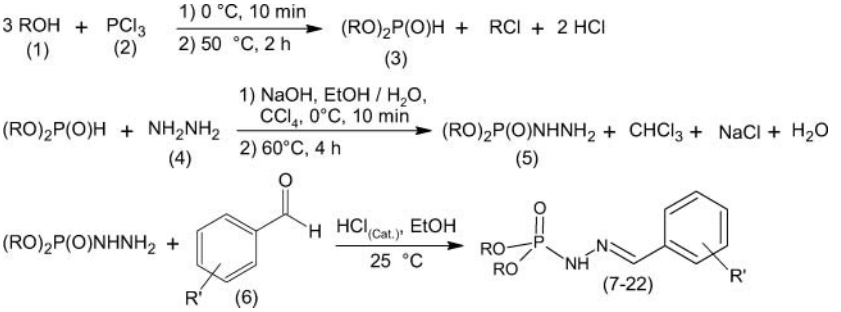
Hydrazones, on the other hand, show potential activity against cancer,[20–22] malaria,[20] bacteria,[23,24] and fungi.[24,25] These compounds are also used as DNA cleaving agents[26] and show many biological actions such as anticonvulsion,[27] analgesic, anti-inflammatory, and antithrombotic properties.[28–30]

Considering the widespread applications of both organophosphorus compounds and hydrazones, the synthesis of compounds which possess both a P atom and a hydrazone moeity may lead to new molecules with potential biological activity. Thus, in continuity of our research work on the synthesis and evaluation of the applications of organophosphorus compounds,[31–33] we have synthesized and characterized a series of aromatic dialkylphosphorylhydrazones. In order to determine the applicability and limitations of these reactions, we investigated the effect of substituents on the outcome of the reaction together with molecular modeling.

RESULTS AND DISCUSSION

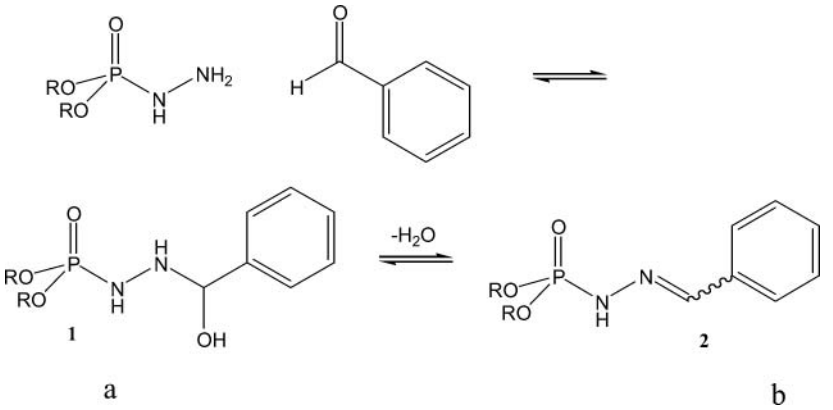
The synthesis of the dialkylphosphorylhydrazones was carried out in three steps, according to Scheme 1. The first step involves the reaction of an aliphatic alcohol (**1**) with PCl_3 (**2**) to form the corresponding dialkylphosphonate (**3**). The second step is the biphasic reaction between the hydrazine and the dialkylphosphonate (**3**) in CCl_4 and a hydroalcoholic solution of sodium hydroxide to form the different dialkylphosphorylhydrazides (**5**). The last step involves an acid-catalyzed condensation reaction between different substituted aromatic aldehydes (**6**) and the dialkylphosphorylhydrazides to yield the dialkylphosphorylhydrazones diastereoselectively with configuration *E*.



Scheme 1 Synthesis of phosphorylhydrazones.

The formation of the dialkylphosphorylhydrazones occurs by the nucleophilic attack of the hydrazidic N atom on the carbonyl C atom so that the reaction is favored by electron-attracting groups on the aromatic ring of the aldehyde. Thus, for these groups, the reactions afforded the desired compounds in good yields in about 2 h, whereas for electron-donating groups, satisfactory yields were only obtained with times of around 6 h (Table I).

Generally, the reaction of hydrazides with aldehydes occurs with ready precipitation of the hydrazone. Formation of the reaction product from dialkylphosphorylhydrazine and aromatic aldehydes probably involves the reaction intermediate a (Scheme 2).



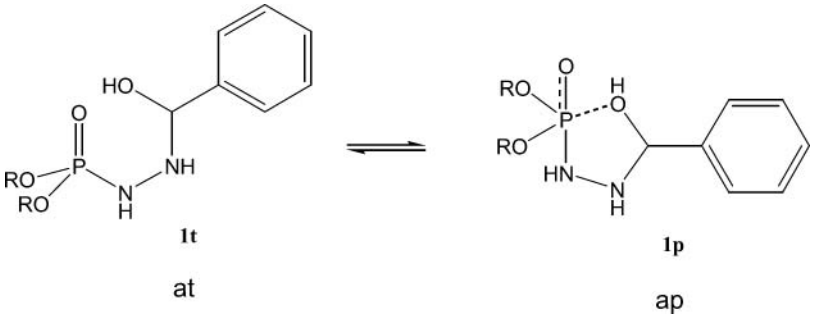
Scheme 2

Because of the possibility of occurrence of intramolecular coordination at P,[34] we propose that intermediate (a) can exist as two isomers, one with a tetracoordinated P atom (at), and the other with a pentacoordinated P atom (ap) (Scheme 3).

Assuming an E2 mechanism for the dehydration step, an antiperiplanar conformation between the N atom lone pair and the hydroxyl group attached to the chiral C atom would

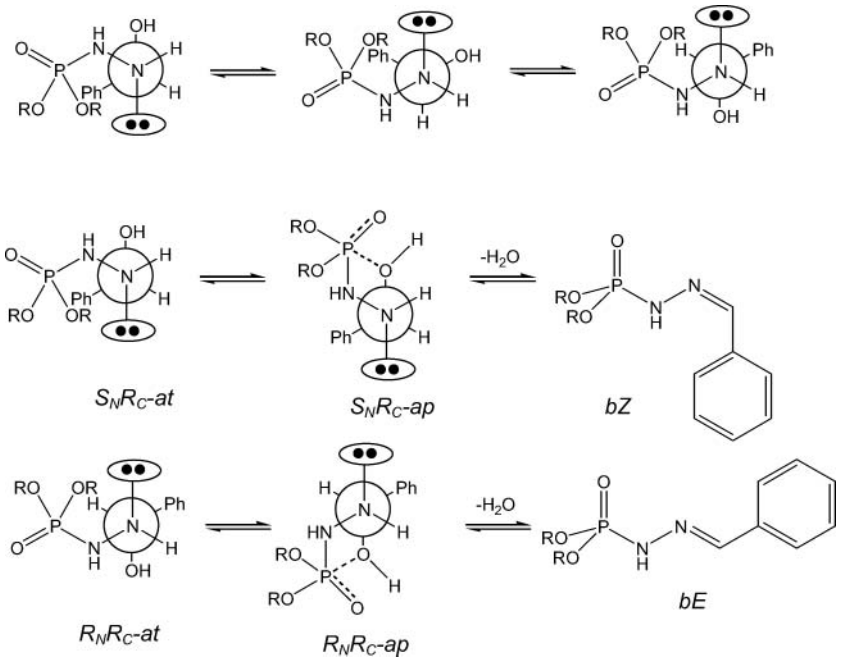
Table I Yields obtained in the syntheses of dialkylphosphorylhydrazones

Compound	R	R′	Yield (%)	Melting Point (°C)	Color	Reaction time
7	Propyl	*o*-NO_2	82	55–57	Yellow	2 h
8	Propyl	*m*-NO_2	82	100–102	Yellow	2 h
9	Propyl	*p*-NO_2	74	73–75	Yellow	2 h
10	Propyl	*p*-CN	61	65–67	Yellow	2 h
11	Propyl	*p*-COOH	76	167–169	White	2 h
12	Propyl	OCH_2O	68	85–87	Cream	6 h
13	Isopropyl	*o*-NO_2	80	102–104	Yellow	2 h
14	Isopropyl	*m*-NO_2	94	151–152	Yellow	2 h
15	Isopropyl	*p*-NO_2	84	150–152	Yellow	2 h
16	Isopropyl	*p*-CN	87	107–109	Yellow	2 h
17	Isopropyl	*p*-COOH	57	192–194	White	2 h
18	Isopropyl	OCH_2O	95	112–114	Cream	6 h
19	Isopropyl	*m*-OCH_3	22	84–85	White	2 h
			67	—	White	6 h
20	Isopropyl	*p*-OCH_3	39	79–80	White	2 h
			71	—	White	6 h
21	Isopropyl	*p*-$N(CH_3)_2$	14	127–129	Orange	2 h
			49	—	Orange	6 h
22	Isopropyl	H	84	76–78	White	2 h
23	Isopropyl	*m*-OH	61	170–172	Cream	6 h
24	Isopropyl	*p*-OH	70	156–158	Yellow	6 h
25	Isopropyl	*m*-OH e *p*-OCH_3	79	155–157	Yellow	6 h
26	Isopropyl	*p*-OH e *m*-OCH_2CH_3	60	186–188	Cream	6 h
27	Propyl	*m*-OH e *p*-OCH_3	56	154–156	Cream	6 h
28	Propyl	*p*-OH e *m*-OCH_2CH_3	77	167–169	Yellow	6 h



Scheme 3

favor the reaction. At room temperature, the pyramidal inversion of the N atoms should occur rapidly, and the antiperiplanar conformation can be obtained for both configurations of the second unsymmetrically substituted N atom by a simple rotation of the C-N bond, as can be seen in Scheme 4 for the R configuration of the C chiral center, for example. These different conformations will produce two diasteromeric products after the dehydration step.



Scheme 4

In order to rationalize the experimental results, we performed a molecular modeling study on both reactions. After a previous full optimization at the AM1 semiempirical level with the PC Spartan Pro program (Wavefunction, Inc.), the structures were fully optimized at the HF/3–21G* level followed by a single point HF/6 – 31 + G* calculation on the optimized geometries. The composition of an equilibrium mixture of the observable

Table II Data from the molecular modeling study

Structure	ΔE (3–21G*/6–31+G*)[a]	Nii/Ni[b]
SNRC-at	0.0	–
RNRC-at	–0.0042359	89.1
SNRC-ap	0.0	–
RNRC-ap	–0.0051457	234
Z-b	0.0	–
E-b	–0.0054888	336

[a]In Hartree.

[b]Number of molecules of the present mixture component relative to the previous one, at 298 K.

structures is determined by the free energy difference between them. Although ΔG depends on both entropy and enthalpy, there are many reactions for which the entropy contribution is small and can be neglected. Thus, if this is the case, the composition of the reaction mixture can be estimated directly from the energy difference between the mixture components calculated in the present work (Table II).

As can be observed in Table II, the isomerization of the tetracoordinated form of intermediate (a) to the pentacoordinated form would favor the formation of the *E* isomer. After the isomerization, the relative concentration of the pentacoordinated intermediate that will conduct to the *E* isomer (R_NR_C-ap, Scheme 3), is predicted to be enhanced 2.6 times in the equilibrium mixture in comparison with the tetracoordinated form (S_NR_C-at). This result is probably a consequence of enhanced crowding in the cyclized structures of (ap). The energy relation indicates that the difference of concentration should be even greater for the reaction product (b), where the concentration of the more stable isomer is 1.4 times enhanced in comparison with the pentacoordinated isomer (ap). Both results suggest that the *E* diastereomer should be the predominant isomeric form of the product obtained in the reaction, in accordance with the experimental results.

The structural determination of the diakylphosphorylhydrazones **7–28** involved IR; ^{1}H, ^{13}C, and ^{31}P NMR; and GC-MS spectroscopy. The characteristic IR absorption bands are 3100–3200 cm^{-1} (NH), 1250 cm^{-1} (P=O), 1100 cm^{-1} (P—O and C—O), and 1520–1630 cm^{-1} (N=C). Table III shows IR data for compounds **7–28**.

Characteristic ^{1}H NMR signals include δ = 7.7–9.3 ppm for the iminic hydrogen (—N=C—H) and δ = 7.0–10.0 ppm for the phosphoramidic hydrogen (P-N-H) with doublet multiplicity (J = 26–30 Hz) due to coupling with the P atom. Tables IV and Table V show ^{1}H NMR data for the dipropylphosphorylhydrazones and diisopropylphosphorylhydrazones synthesized, respectively.

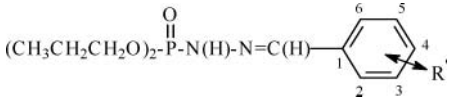
The ^{13}C NMR spectra show signals in the 140–144 ppm range, assigned to the imine carbon. This atom couples with the P atom affording a doublet with J = 18–21 Hz. Tables VI and Table VII show, respectively, ^{13}C NMR data for the dipropylphosphorylhydrazones and the diisopropylphosphorylhydrazones synthesized. Finally, the ^{31}P NMR spectra show only a singlet for the different dialkylphosphorylhydrazones (Table VIII).

Generally, the synthesis of hydrazones from substituted aldehydes leads to the formation of two diastereoisomers (*E* and *Z*), which may interconvert as shown in Scheme 2. The 22 dialkylphosphorylhydrazones synthesized show only the *E* configuration, confirmed by ^{1}H NMR, NOE, and ^{31}P NMR and also by the fragmentation pattern in their mass

Table III IR absorption bands of the phosphorylhydrazones synthesized

Comp.	P=O	P−O−C	C=N	N−H	Substituent R'
7	1237.7 (st)	1014.9 (st)	1585.6 (st)	3116.5(st)	NO_2 (st as) → 1521.4 NO_2 (st si) → 1345.9
8	1232.4 (st)	1020.5 (st)	1602.1 (st)	3117.0 (st)	NO_2 (st as) → 1530.8 NO_2 (st si) → 1350.5
9	1246.8 (st)	1021.5 (st)	1578.4 (st)	3096.2 (st)	NO_2 (st as) → 1518.0 NO_2 (st si) → 1343
10	1231.4 (st)	1013.9 (st)	1596.9 (st)	3137.2 (st)	C≡N (st) → 2224.1
11	1231.0 (st)	1022.9 (st)	1600.5 (st)	3105.4 (st)	OH (st) → 3423.1 C=O (st) → 1690.5
12	1233.8 (st)	1015.4 (st)	1624.3 (st)	3146.8 (st)	O−CH_2−O (st) → 938.4 CH (st) → 2967.6
13	1237.5 (st)	1000.3 (st)	1526.0 (st)	3143.6 (st)	NO_2 (st as) → 1526.0 NO_2 (st si) → 1350.6
14	1244.5 (st)	1023.4 (st)	1566.7 (st)	3099.9 (st)	NO_2 (st as) → 1530.4 NO_2 (st si) → 1350.5
15	1247.4 (st)	1024.5 (st)	1578.1 (st)	3097.8 (st)	NO_2 (st as) → 1515.0 NO_2 (st si) → 1342.1
16	1245.4 (st)	1006.8 (st)	1597.1 (st)	3144.0 (st)	C≡N (st) → 2226.7
17	1274.2 (st)	1011.0 (st)	1603.8 (st)	3196.3 (st)	OH (st) → 3446.3 C=O (st) → 1684.3
18	1244.2 (st)	1008.3 (st)	1624.8 (st)	3112.9 (st)	O−CH_2−O (st) → 928.8 CH (st) → 2980.7 e 2930.2
19	1238.1 (st)	1004.1 (st)	1609.8 (st)	3177.0 (st)	—
20	1238.0 (st)	1010.7 (st)	1606.9 (st)	3119.6 (st)	OCH_3 (C−O−C st as) → 1266.7 OCH_3 (C−O−C st si) → 1084.4
21	1234.8 (st)	1008.1 (st)	1609.8 (st)	3114.4 (st)	OCH_3 (st) → 2836.4 OCH_3 (C−O−C st si) → 1083.0
22	1228.2 (st)	991.2 (st)	1609.0 (st)	3194.3 (st)	C−N (st) → 1076.2
23	1225.2 (st)	1009.0 (st)	1613.9 (st)	3321.6 (st)	OH (st) → 3183.6 COH (C−O st) → 1198.5
24	1220.4 (st)	974.2 (st)	1607.0 (st)	3297.7 (st)	OH (st) → 3180.6 COH (C−O st) → 1164.8
25	1278.8 (st)	1004.4 (st)	1613.9 (st)	3178.9 (st)	OH (st) → 3180.6 COH (C−O st) → 1197.2 OCH_3 (st) → 2839.5 OCH_3 (C−O−C st as) → 1253.2 OCH_3 (C−O−C st si) → 1025.0
26	1279.8 (st)	1007.8 (st)	1604.8 (st)	3178.4 (st)	OH (st) → 3285.6 COH (C−O st) → 1184.5 OCH_2 (C−O−C st as) → 1221.8 OCH_2 (C−O−C st si) → 1036.4
27	1276.9 (st)	1015.8 (st)	1615.8 (st)	3168.0 (st)	OH (st) → 3285.6 COH (C−O st) → 1213.2 OCH_3 (st) → 2841.4 OCH_3 (C−O−C st as) → 1243.8 OCH_3 (C−O−C st si) → 1060.2
28	1280.8 (st)	1015.9 (st)	1605.2 (st)	3169.3 (st)	OH (st) → 3285.6 COH (C−O st) → 1180.5 OCH_2 (st) → 2898.6 OCH_2 (C−O−C st as) → 1226.1 OCH_2 (C−O−C st si) → 1060.7

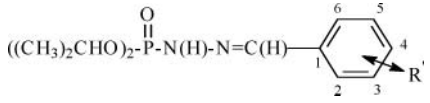
Table IV ^{1}H NMR data of dipropylphosphorylhydrazones



^{1}H NMR

	δ in ppm (multiplicity)—J in Hz										
Comp.	C**H**$_3$	C**H**$_2$CH$_2$O	CH$_2$**O**	N**H**	N=C**H**	**H2**	**H3**	**H4**	**H5**	**H6**	R'
7	0.95 (t)/6H $J_{HH} = 7.0$	1.74 (sex)/4H $J_{HH} = 7.0$	4.09 (m)/4H	8.48 (d)/1H $J_{HP} = 28.0$	8.35 (s)/1H	—	8.04 (d) $J_{HH} = 8.0$	7.46 (dd) $J_{HH} = 8.0$ $J_{HH} = 8.0$	7.59 (dd) $J_{HH} = 8.0$ $J_{HH} = 8.0$	7.97 (d) $J_{HH} = 8.0$	—
8	0.96 (t)/6H $J_{HH} = 7.0$	1.74 (sex)/4H $J_{HH} = 7.0$	4.09 (m)/4H	8.96 (d)/1H $J_{HP} = 28.0$	7.92 (s)/1H	8.42 (s)	—	8.16 (d) $J_{HH} = 8.0$	7.52 (dd) $J_{HH} = 8.0$ $J_{HH} = 8.0$	7.90 (d) $J_{HH} = 8.0$	—
9	0.95 (t)/6H $J_{HH} = 7.0$	1.73 (sex)/4H $J_{HH} = 7.0$	4.08 (m)/4H	9.06 (d)/1H $J_{HP} = 28.0$	7.90 (s)/1H	7.73 (d) $J_{HH} = 8.0$	8.20 (d) $J_{HH} = 8.0$	—	8.20 (d) $J_{HH} = 8.0$	7.73 (d) $J_{HH} = 8.0$	—
10	0.94 (t)/6H $J_{HH} = 7.0$	1.72 (sex)/4H $J_{HH} = 7.0$	4.06 (m)/4H	9.11 (d)/1H $J_{HP} = 30.0$	7.86 (s)/1H	7.61 (d) $J_{HH} = 10.0$	7.68 (d) $J_{HH} = 10.0$	—	7.68 (d) $J_{HH} = 10.0$	7.61 (d) $J_{HH} = 10.0$	—
11	0.97 (t)/6H $J_{HH} = 8.0$	1.75 (sex)/4H $J_{HH} = 8.0$	4.12 (m)/4H	8.78 (d)/1H $J_{HP} = 28.0$	7.91 (s)/1H	7.70 (d) $J_{HH} = 8.0$	8.10 (d) $J_{HH} = 8.0$	—	8.10 (d) $J_{HH} = 8.0$	7.70 (d) $J_{HH} = 8.0$	COOH 8.38 (s)
12	0.94 (t)/6H $J_{HH} = 8.0$	1.72 (sex)/4H $J_{HH} = 8.0$	4.06 (m)/4H	8.09 (d)/1H $J_{HP} = 26.0$	7.71 (s)/1H	6.76 (d) $J_{HH} = 8.0$	6.93 (d) $J_{HH} = 8.0$	—	—	7.22 (s)	O—CH$_2$-O 5.96 (s)
27	0.87 (t)/6H $J_{HH} = 7.0$	1.61 (sex)/4H $J_{HH} = 7.0$	3.91 (m)/4H	9.30 (d)/1H $J_{HP} = 28.0$	9.19 (s)/1H	7.07 (s)	—	—	6.88 (s)	6.88 (s)	O—CH$_3$ 3.75 (s) OH 7.76 (s)
28	0.88 (t)/6H $J_{HH} = 7.0$	1.61 (sex)/4H $J_{HH} = 7.0$	3.95 (m)/4H	9.28 (d)/1H $J_{HP} = 28.0$	9.29 (s)/1H	7.10 (s)	—	—	6.77 (d) $J_{HH} = 8.0$	6.92 (d) $J_{HH} = 8.0$	O—CH$_2$ 3.95 (m) O—CH$_2$C**H**$_3$ 1.31 (t) OH 7.77 (s)

Table V ^{1}H NMR data of diisopropylphosphorylhydrazones

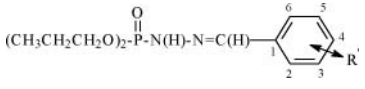


^{1}H NMR

	δ in ppm (multiplicity)—J in Hz									
Comp.	C**H**$_3$	C**H**O	N**H**	N=C**H**	**H2**	**H3**	**H4**	**H5**	**H6**	R'
13	1.33 (d)/6H $J_{HH} = 6.0$ 1.39 (d)/6H $J_{HH} = 6.0$	4.73 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	8.34 (d)/1H $J_{HP} = 30.0$	8.34 (s)/1H	—	8.06 (d) $J_{HH} = 8.0$	7.45 (t) $J_{HH} = 8.0$	7.59 (t) $J_{HH} = 8.0$	7.97 (d) $J_{HH} = 8.0$	—
14	1.33 (d)/6H $J_{HH} = 6.0$ 1.39 (d)/6H $J_{HH} = 6.0$	4.73 (sex)/2H $J_{HH} = 6.0$	8.63 (d)/1H $J_{HP} = 28.0$	7.89 (s)/1H	8.41 (s)	—	8.15 (d) $J_{HH} = 8.0$	7.52 (t) $J_{HH} = 8.0$	7.92 (d) $J_{HH} = 8.0$	—
15	1.23 (d)/6H $J_{HH} = 8.0$ 1.27 (d)/6H $J_{HH} = 8.0$	4.55 (sex)/2H $J_{HH} = 8.0$	9.91 (d)/1H $J_{HP} = 28.0$	8.01 (s)/1H	7.80 (d) $J_{HH} = 8.0$	8.24 (d) $J_{HH} = 8.0$	—	8.24 (d) $J_{HH} = 8.0$	7.80 (d) $J_{HH} = 8.0$	—
16	1.22 (d)/6H $J_{HH} = 6.0$ 1.26 (d)/6H $J_{HH} = 6.0$	4.55 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	9.82 (d)/1H $J_{HP} = 30.0$	7.94 (s)/1H	7.71 (d) $J_{HH} = 9.0$	7.83 (d) $J_{HH} = 9.0$	—	7.83 (d) $J_{HH} = 9.0$	7.71 (d) $J_{HH} = 9.0$	—
17	1.22 (d)/6H $J_{HH} = 7.0$ 1.25 (d)/6H $J_{HH} = 7.0$	4.54 (sex)/2H $J_{HH} = 7.0$	9.68 (d)/1H $J_{HP} = 28.0$	7.96 (s)/1H	7.64 (d) $J_{HH} = 8.0$	7.94 (d) $J_{HH} = 8.0$	—	7.94 (d) $J_{HH} = 8.0$	7.64 (d) $J_{HH} = 8.0$	COOH 13.02 (s)
18	1.78 (d)/6H $J_{HH} = 6.0$ 1.84 (d)/6H $J_{HH} = 6.0$	5.17 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	8.63 (d)/1H $J_{HP} = 28.0$	8.19 (s)/1H	7.40(d) $J_{HH} = 8.0$	7.71 (d) $J_{HH} = 8.0$	—	—	7.21(s)	O—CH_2—O 6.43 (s)
19	1.23 (d)/6H $J_{HH} = 6.0$ 1.26 (d)/6H $J_{HH} = 6.0$	4.54 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	9.46 (d)/1H $J_{HP} = 28.0$	7.90 (s)/1H	7.37 (m)	7.54 (m)	7.37 (m)	7.54 (m)	7.37 (m)	—

20	1.23 (d)/6H $J_{HH} = 6.0$ 1.26 (d)/6H $J_{HH} = 6.0$	4.53 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	9.49 (d)/1H $J_{HP} = 28.0$	7.86 (s)/1H	7.09 (s)	—	7.11 (m)	7.30 (m)	6.92 (m)	O−CH_3 3.75 (s)
21	1.31 (d)/6H $J_{HH} = 6.0$ 1.37 (d)/6H $J_{HH} = 6.0$	4.71 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	7.89 (d)/1H $J_{HP} = 28.0$	7.75 (s)/1H	7.53 (d) $J_{HH} = 9.0$	6.87 (d) $J_{HH} = 9.0$	—	6.87 (d) $J_{HH} = 9.0$	7.53 (d) $J_{HH} = 9.0$	O−CH_3 3.80 (s)
22	1.22 (d)/6H $J_{HH} = 6.0$ 1.25 (d)/6H $J_{HH} = 6.0$	4.52 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	9.09 (d)/1H $J_{HP} = 28.0$	7.77 (s)/1H	7.35 (d) $J_{HH} = 8.0$	6.69 (d) $J_{HH} = 8.0$	—	6.69 (d) $J_{HH} = 8.0$	7.35 (d) $J_{HH} = 8.0$	N−CH_3 2.91 (s)/6H
23	1.21 (d)/6H $J_{HH} = 6.0$ 1.24 (d)/6H $J_{HH} = 6.0$	4.52 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	9.39 (d)/1H $J_{HP} = 28.0$	7.82 (s)/1H	7.01 (s)	—	6.91 (d) $J_{HH} = 8.0$	7.16 (t) $J_{HH} = 8.0$	6.73 (d) $J_{HH} = 8.0$	—
24	1.21 (d)/6H $J_{HH} = 6.0$ 1.25 (d)/6H $J_{HH} = 6.0$	4.53 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	9.20 (d)/1H $J_{HP} = 26.0$	7.80 (s)/1H	7.36 (d) $J_{HH} = 8.0$	6.76 (d) $J_{HH} = 8.0$	—	6.76 (d) $J_{HH} = 8.0$	7.36 (d) $J_{HH} = 8.0$	OH 9.74 (s)
25	1.31 (d)/6H $J_{HH} = 6.0$ 1.37 (d)/6H $J_{HH} = 6.0$	4.72 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	7.46 (d)/1H $J_{HP} = 28.0$	7.65 (s)/1H	7.26 (d) $J_{HH} = 2.0$	—	—	6.81 (d) $J_{HH} = 8.0$	7.02 (dd) $J_{HH} = 8.0$ $J_{HH} = 2.0$	O−CH_3 3.89 (s) OH 5.79 (s)
26	1.31 (d)/6H $J_{HH} = 6.0$ 1.37 (d)/6H $J_{HH} = 6.0$	4.69 (hd)/2H $J_{HH} = 6.0$ $J_{HP} = 8.0$	8.11 (d)/1H $J_{HP} = 28.0$	7.72 (s)/1H	7.20 (d) $J_{HH} = 2.0$	—	—	6.87 (d) $J_{HH} = 8.0$	6.98 (dd) $J_{HH} = 8.0$ $J_{HH} = 2.0$	O−CH_2 4.10 (q) $J_{HH} = 8.0$ O−CH_2CH_3 1.42 (t)/3H $J_{HH} = 8.0$ OH / 6.10 (s)

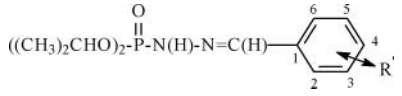
Table VI ^{13}C NMR data for dipropylhydrazones



^{13}C NMR

	δ in ppm (multiplicity)—J in Hz										
Comp.	**C**H$_3$	**C**H$_2$CH$_2$O	**C**H$_2$O	N=**C**−H	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	R'
7	9.95	23.51 (d) $J_{CP} = 6.0$	68.90 (d) $J_{CP} = 6.0$	140.03 (d) $J_{CP} = 20.0$	129.40	147.6 6	128.22	129.28	133.01	124.46	—
8	10.04	23.56 (d) $J_{CP} = 7.5$	69.09 (d) $J_{CP} = 6.5$	142.01 (d) $J_{CP} = 19.5$	136.53	121.09	148.54	123.46	129.49	132.04	—
9	9.98	23.51 (d) $J_{CP} = 6.0$	09 (d) 69. $J_{CP} = 6.5$	142.07 (d) $J_{CP} = 19.5$	140.77	126.92	123.85	147.69	123.85	126.92	—
10	9.98	23.49 (d) $J_{CP} = 8.0$	69.06 (d) $J_{CP} = 6.5$	142.52 (d) $J_{CP} = 20.0$	138.89	126.79	132.28	112.12	132.28	126.79	C≡N 118.64
11	10.01	23.53 (d) $J_{CP} = 7.5$	69.30 (d) $J_{CP} = 6.0$	143.92 (d) $J_{CP} = 19.5$	130.31	126.46	130.40	139.08	130.40	126.46	COOH 170.16
12	9.98	23.51 (d) $J_{CP} = 6.0$	68.75 (d) $J_{CP} = 6.0$	144.34 (d) $J_{CP} = 19.5$	129.22	122.28	105.17	148.02	148.57	107.96	O−CH$_2$−O 101.17
27	10.07	23.23 (d) $J_{CP} = 6.5$	67.69 (d) $J_{CP} = 5.5$	143.93 (d) $J_{CP} = 19.5$	127.76	111.66	146.77	148.94	111.84	118.95	O−CH$_3$ 55.55
28	10.05	23.21 (d) $J_{CP} = 6.5$	67.71 (d) $J_{CP} = 6.0$	144.11 (d) $J_{CP} = 19.0$	126.31	110.07	148.22	146.98	115.53	120.28	O−CH$_2$**C**H$_3$ 14.70 O−**C**H$_2$CH$_3$ 63.74

Table VII ^{13}C NMR data of diisopropylphosphorylhydrazones



^{13}C NMR

Comp.	$\underline{C}H_3$	$\underline{C}HO$	δ in ppm (multiplicity)—J in Hz N=$\underline{C}$−H	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**R'**
13	23.57 (d); $J_{CP} = 6.0$ 23.80 (d); $J_{CP} = 4.5$	72.29 (d) $J_{CP} = 4.5$	139.55 (d); $J_{CP} = 19.5$	129.52	147.63	128.19	129.25	133.13	124.55	—
14	23.53 (d); $J_{CP} = 4.5$ 23.74 (d); $J_{CP} = 4.5$	72.36 (d) $J_{CP} = 5.0$	141.61 (d); $J_{CP} = 20.0$	136.65	121.00	148.48	123.34	129.49	131.89	—
15	23.56 (d); $J_{CP} = 4.5$ 23.77 (d); $J_{CP} = 4.5$	72.47 (d) $J_{CP} = 4.5$	141.58 (d); $J_{CP} = 20.0$	140.90	126.86	123.94	147.72	123.94	126.86	—
16	23.50 (d); $J_{CP} = 4.5$ 23.71 (d); $J_{CP} = 4.5$	72.33 (d) $J_{CP} = 6.0$	142.07 (d); $J_{CP} = 19.5$	139.08	126.70	132.28	111.97	132.28	126.70	C≡N 118.64
17	23.42 (d); $J_{CP} = 4.5$ 23.63 (d); $J_{CP} = 4.5$	70.86 (d) $J_{CP} = 6.0$	142.05 (d); $J_{CP} = 19.5$ 142.59 (d); $J_{CP} = 20.0$	129.75	126.05	130.78	138.94	130.78	126.05	COOH 166.99
18	23.56 (d); $J_{CP} = 4.5$ 23.80 (d); $J_{CP} = 4.5$	71.92 (d) $J_{CP} = 5.0$	143.86 (d); $J_{CP} = 19.5$	129.37	122.25	105.14	148.08	148.57	108.02	O−CH_2−O 101.20
19	23.42 (d); $J_{CP} = 4.75$ 23.64 (d); $J_{CP} = 3.50$	70.79 (d) $J_{CP} = 5.15$	143.22 (d); $J_{CP} = 20.15$ 143.63 (d); $J_{CP} = 20.40$	134.92	126.06	128.76	129.01	128.76	126.06	—
20	23.39 (d); $J_{CP} = 4.5$ 23.60 (d); $J_{CP} = 4.5$	70.74 (d) $J_{CP} = 6.5$	142.91 (d); $J_{CP} = 21.0$ 143.38 (d); $J_{CP} = 20.0$	136.36	110.73	159.50	118.71	129.84	114.80	O−CH_3 55.03
21	23.53 (d); $J_{CP} = 4.5$ 23.80 (d); $J_{CP} = 4.5$	71.80 (d) $J_{CP} = 4.5$	143.92 (d); $J_{CP} = 19.5$	127.58	127.89	113.91	160.33	113.91	127.89	O−CH_3 55.23
22	23.40 (d); $J_{CP} = 6.0$ 23.63 (d); $J_{CP} = 4.5$	70.39 (d) $J_{CP} = 4.5$	143.88 (d); $J_{CP} = 18.0$ 144.25 (d); $J_{CP} = 18.5$	122.71	127.17	112.01	150.76	112.01	127.17	N−CH_3 39.86
23	23.51 (d); $J_{CP} = 4.5$ 23.72(d); $J_{CP} = 4.5$	70.89 (d) $J_{CP} = 6.0$	143.52 (d); $J_{CP} = 18.5$ 143.93 (d); $J_{CP} = 22.5$	136.27	111.92	157.74	117.89	129.87	116.50	—
24	23.48 (d); $J_{CP} = 4.5$ 23.69 (d); $J_{CP} = 4.5$	70.74 (d) $J_{CP} = 6.5$	143.70 (d); $J_{CP} = 21.0$ 144.11 (d); $J_{CP} = 19.5$	126.08	127.72	115.68	158.62	115.68	127.72	—
25	23.51 (d); $J_{CP} = 4.5$ 23.72(d); $J_{CP} = 4.5$	70.71 (d) $J_{CP} = 6.5$	143.52 (d); $J_{CP} = 21.5$ 143.93 (d); $J_{CP} = 19.5$	127.99	111.70	146.88	149.01	111.98	119.01	O−CH_3 55.63
26	23.48 (d); $J_{CP} = 4.5$ 23.72(d); $J_{CP} = 4.5$	70.83 (d) $J_{CP} = 6.0$	143.84 (d); $J_{CP} = 19.5$ 144.23 (d); $J_{CP} = 20.0$	126.59	110.34	148.34	147.09	115.71	120.29	O−CH_2**C**H_3 14.75 O−**C**$H_2$$CH_3$ 63.88

Table VIII ^{31}P NMR data of dialkylphosphorylhydrazones

Compound	δ in ppm (multiplicity)—J in Hz
7	2.46
8	2.82
9	2.53
10	2.59
11	2.90
12	3.40
13	0.47
14	0.86
15	0.53
16	0.62
17	0.93
18	1.49
19	1.32
20	1.21
21	1.69
22	2.14
23	0.35 (dt) $J_{HP} = 8.0$ Hz $J_{HP} = 27.2$
24	0.79 (dt) $J_{HP} = 8.0$ $J_{HP} = 27.2$
25	0.72 (dt) $J_{HP} = 7.2$ $J_{HP} = 26.4$
26	0.75 (dt) $J_{HP} = 8.0$ $J_{HP} = 26.4$
27	2.67 (dt) $J_{HP} = 8.1$ $J_{HP} = 27.5$
28	2.62 (dt) $J_{HP} = 7.29$ $J_{HP} = 28.4$

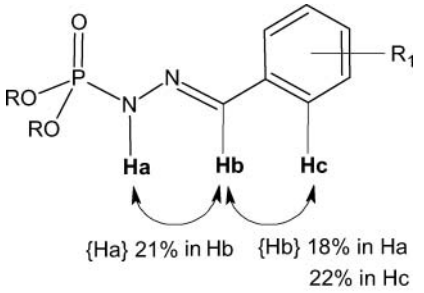


Figure 1 NOE enhancements for dialkylphosphorylhydrazones.

spectra. The ^{1}H NMR spectra show only one iminic hydrogen singlet at $\delta = 7.7$–9.3 ppm corresponding to the presence of a single diastereoisomer. This stereoselectivity is also confirmed by the presence of a single signal for all P atoms of the different dialkylphosphorylhydrazones. The use of NOE difference experiments[35] afforded the enhancements shown in Figure 1, further confirming the *E* configuration.

Further evidence for the *E* configuration comes from the fragmentation pattern in the mass spectra where, for all compounds, there is a peak at m/z+1 = 98, which is obtained from a pseudo McLafferty rearrangement,[36] only possible for the *E* isomer (Scheme 3).

CONCLUSION

The syntheses described in this work provide an efficient and easy access to dialkylphosphorylhydrazones substituted in the aromatic ring, making use of readily available starting materials. These new dialkylphosphorylhydrazones may serve as intermediates in the synthesis of new compounds with potential use in agriculture or medicinal chemistry.

EXPERIMENTAL

Synthesis of Dialkylphosphites[37]: General Procedure

In a two-necked 125 mL round flask equipped with an addition funnel and a reflux condenser fitted with a bubbler, the alcohol was added. Through the funnel, freshly distilled PCl_3 was added dropwise with magnetic stirring so the temperature was kept around 0 °C. After all the chloride was added, the mixture was kept under stirring at 50 °C for 2 h. The mixture was then kept under vacuum to remove residual HCl, and finally the phosphonate was removed with a rotary evaporator.

Dipropylphosphonate. 51.4 mL (41.2 g, 0.68 mmol) of propyl alcohol were allowed to react with 20.5 mL (32.3 g, 0.23 mmol) of PCl_3, affording 35.0 g (93%) of the desired phosphonate as a colorless liquid.

Diisopropylphosphonate. 54.0 mL (42.12 g, 0.70 mmol) of isopropyl alcohol were allowed to react with 20.5 mL (32.3 g, 0.23 mmol) of PCl_3, affording 36.6 g (94%) of a colorless liquid.

Synthesis of the Dialkylphosphorylhydrazides[38]: General Procedure

In a two-necked 125 mL round flask equipped with an addition funnel and reflux condenser fitted with a bubbler, hydrazine hydrate and a solution of NaOH in equal volumes of water and ethyl alcohol were added. A solution of the dialkylphosphonate and carbon tetrachloride was then added dropwise with magnetic stirring maintaining the temperature around 0 °C until all phosphonate was added. The reaction mixture was then kept at reflux at 60 °C for 4 h. After this time, all the contents of the flask were transferred to a separation funnel, and the organic phase was washed with CH_2Cl_2 (5 × 10 mL) and dried with sodium sulfate. Then the solvents were removed under vacuum, and a yellow oil was obtained.

Dipropylphosphorylhydrazide. Dipropylphosphonate (8.8 g, 52.9 mmol), 2.64 g (2.56 mL, 52.9 mmol) of hydrazine hydrate, 11.4 g (7.15 mL, 74 mmol) of carbon tetrachloride, and 2.12 g (52.9 mmol) of sodium hydroxide were dissolved in 10 mL of distilled water and 10 mL of ethyl alcohol. The hydrazide was obtained in 47% yield (4.84 g) as a yellow oil.

Diisopropylhydrazide. Diisopropylphosphonate (11.57 g, 69.7 mmol), 3.48 g (3.38 mL, 69.7 mmol) of hydrazine hydrate, 15 g (9.4 mL, 97 mmol) of carbon tetrachloride, and 2.80 g (70 mmol) of sodium hydroxide were dissolved in 10 mL of distilled water and 10 mL of ethyl alcohol. The corresponding hydrazide was obtained in 39% yield (5.34 g) as a yellow oil.

Synthesis of the Dialkylphosphorylhydrazones[39]: General Procedure

In a one-neck 50 mL round flask, 2.70 mmol of dialkylphosphorylhydrazide, 8 mL of ethyl alcohol, 2.55 mmol of the corresponding aldehyde, and three drops of 37.5% HCl were added. This mixture was kept under magnetic stirring at room temperature for the times described in Table I. After those times, six drops of sodium bicarbonate 10% were added, and the mixture was poured into 10 mL of cold distilled water and kept in an ice bath for 30 min. The resulting solid was filtered and dried under vacuum. For benzoic aldehyde, no bicarbonate was added.

***N*-[(1*E*)-(*o*-Nitrophenylmethanol)phosphorohydrazidic acid dipropyl ester (7).** Dipropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.38 g (0.00252 mol) of *o*-nitrobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The product was obtained in 82% yield (0.69 g).

***N*′-[(1*E*)-(*m*-Nitrophenyl)methylene]phosphorohydrazidic acid dipropyl ester (8).** Dipropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.38 g (0.00252 mol) of *m*-nitrobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The product was obtained in 82% yield (0.69 g).

***N*′-[(1*E*)-(*p*-Nitrophenyl)methylene]-phosphorohydrazidic acid dipropyl ester (9).** Dipropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.38 g (0.00252 mol) of *m*-nitrobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The product was obtained in 74% yield (0.62 g).

***N*′-[(1*E*)-(*p*-Cyanophenyl)methylene]-phosphorohydrazidic acid dipropyl ester (10).** Dipropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.33 g (0.00252 mol) of *p*-cyanobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The product was obtained in 61% yield (0.48 g).

***N*′-[(1*E*)-(*p*-Carboxyphenyl), mehylene]-phosphorohydrazidic acid dipropyl ester (11).** Dipropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.38 g (0.00253 mol) of *p*-carboxybenzaldehyde, ethanol (8 mL) and hydrochloric acid (3 drops, 37%) for 2 h. The product was obtained in 76% yield (0.64 g).

***N*′-[(1*E*)-(1,3-Benzodioxol-5-ylmethylene)]-phosphorohydrazidic acid dipropyl ester (12).** Dipropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.54 g (0.00360 mol) of piperonal, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 68% yield (0.79 g).

***N*′-[(1*E*)-(*o*-Nitrophenyl)methylene]-phosphorohydrazidic acid diisopropyl ester (13).** Diisopropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.38 g (0.00252 mol) of *o*-nitrobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The desired product was obtained in 80% yield (0.67 g).

***N*′-[(1*E*)-(*m*-Nitrophenyl)methylene]phosphorohydrazidic acid diisopropyl ester (14).** Diisopropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.38 g (0.00252 mol) of *m*-nitrobenzaldehyde, ethanol (8 mL), and

hydrochloric acid (3 drops, 37%) for 2 h. The desired product was obtained in 94% yield (0.79 g).

***N′*-[(1*E*)-(*p*-Nitrophenyl)methylene]-phosphorohydrazidic acid diisopropyl ester (15).** Diisopropylphosphorylhydrazine (0.32 g, 0.00163 mol) was allowed to react with 0.23 g (0.00152 mol) of *p*-nitrobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The desired product was obtained in 84% yield (0.42 g).

***N′*-[(1*E*)-(*p*-Cyanophenyl)methylene]-phosphorohydrazidic acid diisopropyl ester (16).** Diisopropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.33 g (0.00252 mol) of *p*-cyanobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The desired product was obtained in 87% yield (0.69 g).

***N′*-[(1*E*)-(*p*-Carboxyphenyl),mehylene]-phosphorohydrazidic acid diisopropyl ester (17).** Diisopropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.38 g (0.00253 mol) of *p*-carboxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The product was obtained in 57% yield (0.48 g).

***N′*-[(1*E*)-(1,3-Benzodioxol-5-ylmehylene)]-phosphorohydrazidic acid diisopropyl ester (18).** Diisopropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with piperonal (0.33 g, 0.00252 mol), ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 95% yield (0.75 g).

***N′*-[(1*E*)-(phenyl)methylene]-phosphorohydrazidic acid diisopropyl ester (19).** Diisopropylphosphorylhydrazine (0.74 g, 0.00378 mol) was allowed to react with 0.38 g (0.00358 mol) of benzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 2 h. The product was obtained in 84% yield (0.85 g).

***N′*-[(1*E*)-(*m*-Methoxyphenyl) mehylene]-phosphorohydrazidic acid diisopropyl ester (20).** Diisopropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.35 g (0.00257 mol) of *m*-methoxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) under two different conditions: (i) reaction time: 2 h affording a yield of 22% (0.18 g); (ii) reaction time: 6 h affording a yield of 67% (0.54 g).

***N′*-[(1*E*)-(*p*-Methoxyphenyl) mehylene]-phosphorohydrazidic acid diisopropyl ester (21).** Diisopropylphosphorylhydrazine (0.53 g, 0.00270 mol) was allowed to react with 0.35 g (0.00257 mol) of *m*-methoxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) under two different conditions: (i) reaction time: 2 h affording a yield of 40% (0.32 g); (ii) reaction time: 6 h affording a yield of 71% (0.57 g).

***N′*-[(1*E*)-[4-(N,N′-Dimehylamino) phenyl]mehylene]-phosphorohydrazidic acid diisopropyl ester (22).** Diisopropylphosphorylhydrazine (0.57 g, 0.00291 mol) was allowed to react with 0.41 g (0.00257 mol) of 4-N,N′-dimethylaminobenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) under two different conditions: (i) reaction time: 2 h affording a yield of 14% (0.13 g); (ii) reaction time: 6 h affording a yield of 49% (0.44 g).

***N′*-[(1*E*)-(*m*-Hydroxyphenyl) methylene]-phosphorohydrazidic acid diisopropyl ester (23).** Diisopropylphosphorylhydrazine (0.30 g, 0.00153 mol) was allowed to react with 0.19 g (0.00156 mol) of *m*-hydroxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 61% yield (0.28 g).

***N′*-[(1*E*)-(*p*-Hydroxyphenyl) methylene]-phosphorohydrazidic acid diisopropyl ester (24).** Diisopropylphosphorylhydrazine (0.30 g, 0.00153 mol) was allowed to react with 0.19 g (0.00156 mol) of *p*-hydroxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 70% yield (0.32 g).

***N′*-[(1*E*)-(*m*-Hydroxy-*p*-methoxyphenyl)methylene]-phosphorohydrazidic acid diisopropyl ester (25).** Diisopropylphosphorylhydrazine (0.39 g, 0.00199 mol) was allowed to react with 0.30 g (0.00197 mol) of *m*-hydroxy-*p*-methoxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 79% yield (0.51 g).

***N′*-[(1*E*)-(*m*-Ethoxy-*p*-hydroxyphenyl)methylene]-phosphorohydrazidic acid diisopropyl ester (26).** Diisopropylphosphorylhydrazine (0.42 g, 0.00214 mol) was allowed to react with 0.36 g (0.00217 mol) of *m*-ethoxy-*p*-hydroxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 60% yield (0.45 g).

***N′*-[(1*E*)-(*m*-Hydroxy-*p*-methoxyphenyl)methylene]-phosphorohydrazidic acid diisopropyl ester (27).** Diisopropylphosphorylhydrazine (0.51 g, 0.00260 mol) was allowed to react with 0.40 g (0.00263 mol) of *m*-hydroxy-*p*-methoxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 56% yield (0.49 g).

***N′*-[(1*E*)-(*m*-Ethoxy-*p*-hydroxyphenyl) methylene]-phosphorohydrazidic acid dipropyl ester (28).** Dipropylphosphorylhydrazine (0.47 g, 0.00240 mol) was allowed to react with 0.40 g (0.00241mol) of *m*-ethoxy-*p*-hydroxybenzaldehyde, ethanol (8 mL), and hydrochloric acid (3 drops, 37%) for 6 h. The product was obtained in 77% yield (0.64 g).

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