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A New Convenient Way to Synthesize 1-Hydroxyphosphonates From Heterocyclic Aldehydes and Ketones Under Microwave Irradiation

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ABSTRACT: *A simple and efficient method has been developed for the synthesis of 1-hydroxyphosphonates from heterocyclic aldehydes and ketones under solvent-free conditions using microwave irradiation. Various phosphites have been used to find the influence of steric exclusion on the reaction. The products are readily obtained in satisfactory yields, on the solid support of MgO. The reactions are also induced by oil-heat, and we find that the condition of microwave is better than oil-heat with respect to reaction times and product yields.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:347–353, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20304

INTRODUCTION

1-Hydroxyphosphonates are particularly attractive not only by their biological activities [1–5], but also because they are attractive precursors to other 1-functionalized phosphonates [6–11], which are also commonly applied in the Horner–Wadsworth–Emmons (HWE) olefination reaction to produce 1-functionalized olefins and acetylenes [12,13]. Surface-mediated solid-phase reactions are of growing interest [14–16] because of their ease of setup and workup, mild reaction conditions, high yields, lack of solvent, and the low cost of the reactions in comparison with their homogeneous counterparts. And the application of microwave (MW) technology in organic synthesis [17–20], particularly in the solid state, is increasing rapidly because of its simplicity, less pollution, and minimum reaction time.

Although there are many attractive routes for the synthesis of 1-hydroxyphosphonates [21–31], the aldehyde substrates are often limited to alkyl and aryl aldehydes. On the other hand, many heterocyclic phosphonates have been proven to be biologically active [32–34]. In continuation of our study on the synthesis of heterocyclic phosphonate derivatives [36,37] with bioactivities, we report a new convenient way to synthesize 1-hydroxyphosphonates from heterocyclic aldehydes and ketones, on the solid support of MgO, using MW irradiation.

RESULTS AND DISCUSSION

Synthesis of the Products

First, 4-methyl-5-formylthiazole and diethyl phosphite are treated with 2 equiv. and 4 equiv. of MgO, respectively, under MW irradiation (Scheme 1). We find that the yields are increased when 4 equiv. of MgO rather than 2 equiv of MgO is used (Entry 23, Table 1). So, the reaction between 1 equiv. of heterocyclic aldehyde or ketone, 1 equiv. of diethyl

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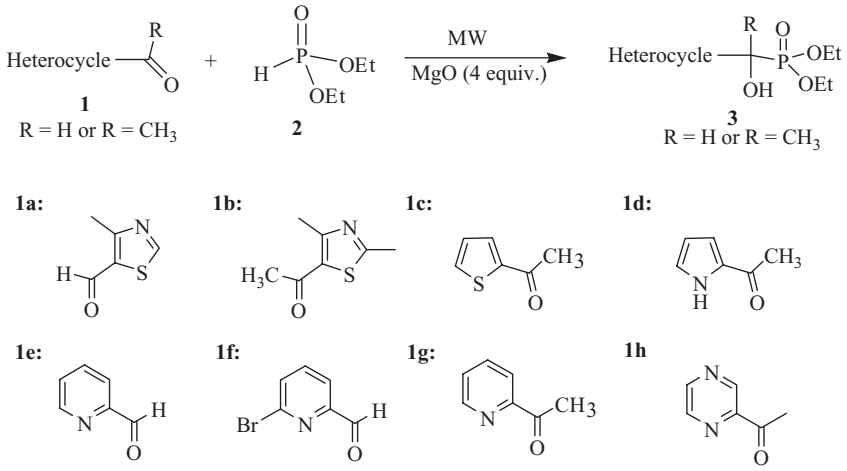


SCHEME 1

phosphite, and 4 equiv. of MgO is manipulated in an open container, in a domestic MW (Scheme 1). At the end of the reaction, the internal temperature was registered. The intermittent heating is important to obtain cleaner products and better yields.

The results (Entries 1–8, Table 1) show that the reactions smoothly advance when the substrates are heterocyclic aldehydes or six-membered heterocyclic ketones. But, when the substrates are five-membered heterocyclic ketones, the reaction does not occur. This result can be explained by the higher electron density and the lower electropositive center of five-membered heterocyclic ketones compared to six-membered heterocyclic ketones.

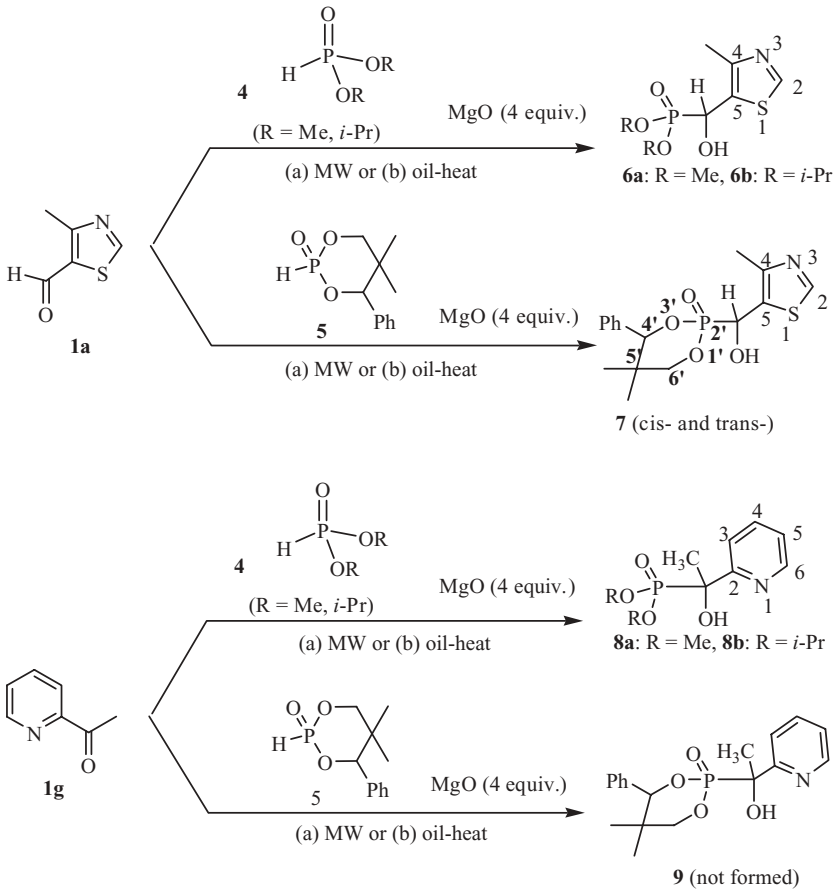
The reaction between 1 equiv. of 4-methyl-5-formylthiazole (**1a**) or 2-acetylpyridine (**1g**), 1 equiv. of phosphites with different steric exclusion, and 4 equiv. of MgO is also manipulated under MW irradiation (Scheme 2), to find the influence of steric exclusion. Lesser the steric exclusion, the better the yield. When the reactant of phosphite is the cyclic 4-phenyl-5,5-dimethyl-1,3,2-dioxaphosphinane-2-oxide with bulky steric exclusion, the yield is lower than other chained phosphites that have less steric exclusion (Entry 11, Table 1). When treating 2-acetylpyridine with 4-phenyl-5,5-dimethyl-1,3,2-dioxaphosphinane-2-oxide, the anticipated 1-hydroxyphosphonate is not formed and only the starting materials are recovered, owing to the bulky steric exclusion of 2-acetylpyridine than that of 4-methyl-5-formylthiazole (Entry 14, Table 1).

To aascertain the effect of MW on the reaction, comparative studies were carried out by manipulating the reaction in an oil-bath without changing other conditions (Entries 15–22, Table 1). The results show that MW heating has advantages over the oil-heat method in terms of reaction times (6–10 min to 2–4 h) and product yields. To evaluate the influence of MgO, 4-methyl-5-formylthiazole was treated with diethyl phosphite without MgO under MW irradiation (Entry 24). No new compounds were found.

TABLE 1 Results of Reactions Under MW Irradiation and Oil-heat

Entry	*Compound*	*Condition*	*Time*	*Yield* (%)*
1	**3a**	MW (700 W)†	3 × 2 min	83
2	**3b**	MW (700 W)‡	5 × 2 min	0
3	**3c**	MW (700 W)‡	5 × 2 min	0
4	**3d**	MW (700 W)‡	5 × 2 min	0
5	**3e**	MW (700 W)†	2 × 2 min	87
6	**3f**	MW (700 W)†	2 × 2 min	84
7	**3g**	MW (700 W)†	3 × 2 min	80
8	**3h**	MW (700 W)†	3 × 2 min	80
9	**6a**	MW (700 W)†	3 × 2 min	74
10	**6b**	MW (700 W)†	3 × 2 min	72
11	**7**	MW (700 W)†	5 × 2 min	57
12	**8a**	MW (700 W)†	3 × 2 min	76
13	**8b**	MW (700 W)†	3 × 2 min	61
14	**9**	MW (700 W)‡	5 × 2 min	0
15	**6a**	Heat (60–70°C)	2 h	65
16	**3a**	Heat (60–70°C)	2 h	71
17	**6b**	Heat (60–70°C)	2 h	63
18	**7**	Heat (80–90°C)	4 h	46
19	**8a**	Heat (60–70°C)	4 h	63
20	**3g**	Heat (60–70°C)	4 h	66
21	**8b**	Heat (60–70°C)	4 h	45
22	**9**	Heat (80–90°C)	8 h	0
23	**3a**	MW (700 W)†	3 × 2 min	67§
24	**3a**	MW (700 W)†	3 × 2 min	0‖
25	**3a**	MW (700 W)†	3 × 2 min	0¶

*Isolated yield.
†At the end of the reaction, the internal temperature is 60–70°C.
‡At the end of the reaction, the internal temperature is 80–90°C.
§With 2 equiv. of MgO.
‖Without MgO.
¶ With 4 equiv. of SiO_2.



SCHEME 2

We also tried to induce the reactions by SiO_2. The mixture of 1 equiv. of 4-methyl-5-formylthiazole, 1 equiv. of diethyl phosphite, and 4 equiv. of SiO_2 are exposed to MW irradiation for 8 min and no reaction was found when monitored with TLC (Entry 25). This shows that basic MgO plays an important role.

In summary, we describe a very simple and efficient procedure for the preparation of 1-hydroxyphosphonates from heterocyclic aldehydes and ketones under solvent-free conditions using MW irradiation. This study allowed us to obtain entitled compounds in good yields within a short time. The bioactivity of these compounds are under study.

Structures of the Products

The structures of all the 1-hydroxyphosphonates were confirmed by elemental analyses, ^{1}H NMR, ^{31}P NMR, and ^{13}C NMR. Their physical constants are listed in Table 2, and data of ^{1}H NMR, ^{31}P NMR, and ^{13}C NMR spectra are listed in Table 3.

TABLE 2 The Physical Constants and Elemental Analysis of Synthesized Compounds

			Found (Calcd)		
Compound	*State*	*mp (°)*	*C*	*H*	*N*
3a	Light yellow solid	28–29	35.20 (35.44)	5.31 (5.10)	6.09 (5.90)
3e	White solid	51	48.88 (48.98)	6.65 (6.58)	5.67 (5.71)
3f	White solid	88–89	36.89 (37.06)	4.97 (4.66)	4.21 (4.32)
3g	White solid	50	50.99 (50.96)	6.97 (7.00)	5.55 (5.40)
3h	White solid	80–81	46.11 (46.15)	6.61 (6.58)	10.69 (10.76)
6a	White solid	63	40.55 (40.75)	5.79 (6.08)	5.53 (5.28)
6b	White solid	61–62	44.69 (45.04)	7.07 (6.87)	4.41 (4.78)
7	White solid	165–166	53.98 (54.38)	5.47 (5.70)	4.28 (3.96)
8a	White solid	89	46.71 (46.76)	6.09 (6.10)	5.87 (6.06)
8b	White thick liquid	. . .	54.26 (54.35)	7.58 (7.72)	4.63 (4.88)

TABLE 3 ^{1}H, ^{13}C and ^{31}P Chemical Shifts (ppm) of Compounds **3, 6, 7**, and **8** (TMS, $CDCl_3$) and Coupling Constants *J* (Hz)

Compound	*^{1}H NMR and ^{13}C NMR δ (ppm)*	*^{31}P NMR δ (ppm)*
3a	8.66 (s, 1H, C_2—H), 5.31 (d, 1H, OH—CH, $J_{PH} = 10.4$), 4.15–4.02 (m, 4H, 2-OCH_2CH_3), 2.38 (d, 3H, C_4—CH_3, $J_{PH} = 2.4$), 1.27–1.23 (m, 6H, 2-OCH_2CH_3).* 152.41 (C_2), 150.33 (d, C_4, $J_{PC} = 41.6$), 128.96 (C_5), 64.87 (d, OH—CH, $J_{PC} = 681.2$), 64.14 (d, —OCH_2CH_3, $J_{PC} = 25.2$), 63.37 (d, —OCH_2CH_3, $J_{PC} = 31.2$), 16.67, 16.62 (2-OCH_2CH_3), 15.76 (—C_4—CH_3).*	20.96*
3e	8.58 (d, 1H, H_6, $J_{H_6H_5} = 2.7$), 7.76–7.71 (m, 1H, H_4), 7.57 (d, 1H, H_3, $J_{H_3H_4} = 7.5$), 7.32–7.28 (m, 1H, H_5), 5.12 (d, 1H, OH—CH, $J_{PH} = 11.1$), 4.24–4.16 (m, 2H, 2-OCH_2CH_3), 4.07–3.97 (m, 2H, 2-OCH_2CH_3), 1.35 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 6.9$), 1.19 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 7.2$).† 153.99, 147.96, 136.72, 123.07, 122.34 (—C_5H_4N), 70.01 (d, OH—C, $J_{PC} = 639.6$), 63.38 (d, —OCH_2CH_3, $J_{PC} = 27.6$), 62.98 (d, —OCH_2CH_3, $J_{PC} = 28.2$), 16.39 (d, —OCH_2CH_3, $J_{PC} = 26.1$), 16.31 (d, —OCH_2CH_3, $J_{PC} = 24.9$)†	19.66†
3f	7.62–7.44 (m, 3H, H_3, H_4, H_5), 5.11 (d, 1H, OH—CH, $J_{PH} = 12.3$), 4.26–4.18 (m, 2H, 2-OCH_2CH_3), 4.12–4.03 (m, 2H, 2-OCH_2CH_3), 1.35 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 7.2$), 1.25 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 7.2$).† 156.95, 140.63, 138.96, 127.20, 120.95 (—C_5H_4N), 70.41 (d, OH—C, $J_{PC} = 631.8$), 63.48 (d, —OCH_2CH_3, $J_{PC} = 28.2$), 63.38 (d, —OCH_2CH_3, $J_{PC} = 31.2$), 16.31 (s, 2-OCH_2CH_3).†	19.74*
3g	8.51 (d, 1H, H_6, $J_{H_6H_5} = 4.4$), 7.73–7.70 (m, 1H, H_4), 7.60 (d, 1H, H_3, $J_{H_3H_4} = 8.0$), 7.25–7.22 (m, 1H, H_5), 6.13 (br, 1H, —OH), 4.19–4.12 (m, 2H, 2-OCH_2CH_3), 3.96–3.83 (m, 2H, 2-OCH_2CH_3), 1.75 (d, 3H, —CH_3, $J_{PH} = 15.6$), 1.30 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 6.8$), 1.10 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 6.8$).* 158.27, 147.29, 137.27, 122.99, 121.82 (—C_5H_4N), 73.59 (d, OH—C, $J_{PC} = 655.2$), 63.59 (d, —OCH_2CH_3, $J_{PC} = 24.4$), 63.44 (d, —OCH_2CH_3, $J_{PC} = 24.4$), 24.56 (—CH_3), 16.71 (d, —OCH_2CH_3, $J_{PC} = 21.6$), 16.51 (s, —OCH_2CH_3).*	23.18*
3h	8.97 (s, 1H, H_3), 8.58–8.56 (m, 2H, H_5, H_6), 5.50 (br, 1H, —OH), 4.22–4.08 (m, 4H, 2-OCH_2CH_3), 1.87 (d, 3H, —CH_3, $J_{PH} = 15.6$), 1.32 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 7.2$), 1.26 (t, 3H, 2-OCH_2CH_3, $J_{HH} = 7.2$).† 154.98, 143.73, 143.26, 141.97 (—$C_4H_3N_2$), 73.07 (d, OH—C, $J_{PC} = 654.3$), 63.51 (d, —OCH_2CH_3, $J_{PC} = 28.8$), 63.41 (d, —OCH_2CH_3, $J_{PC} = 30.0$), 23.66 (—CH_3), 16.35 (d, —OCH_2CH_3, $J_{PC} = 18.6$), 16.29 (d, —OCH_2CH_3, $J_{PC} = 18.0$).†	21.95*
6a	8.70 (s, 1H, C_2—H), 5.34 (d, 1H, OH—CH, $J_{PH} = 11.1$), 3.78 (d, 3H, O—CH_3, $J_{PH} = 1.8$), 3.75 (d, 3H, O—CH_3, $J_{PH} = 1.8$), 2.40 (d, 3H, —C_4—CH_3, $J_{PH} = 2.7$).† 152.70 (C_2), 150.38 (d, C_4, $J_{PC} = 37.2$), 128.90 (C_5), 64.53 (d, OH—CH, $J_{PC} = 685.2$), 54.43 (d, —OCH_3, $J_{PC} = 29.6$), 53.92 (d, —OCH_3, $J_{PC} = 24.0$), 15.56 (—C_4—CH_3).*	22.26†
6b	8.69 (s, 1H, C_2—H), 5.23 (d, 1H, OH—CH, $J_{PH} = 10.0$), 4.75–4.67 (m, 2H, 2 O—CH), 2.42 (s, 3H, C_4—CH_3), 1.31–1.21 (m, 12H, 4-CH—CH_3).* 152.23 (C_2), 149.87 (C_4), 129.58 (C_5), 72.38 (d, 2-O—CH, $J_{PC} = 292.8$), 64.71 (d, OH—CH, $J_{PC} = 699.2$), 24.39, 24.09, 23.84 (4-CH—CH_3), 15.73 (—C_4—CH_3).*	19.34*
7	8.54 and 8.42 (s, 1H, *trans*- and *cis*-C_2—H), 7.32–7.25(m, 5H, *trans*- and *cis*-CH of benzene), 5.62 and 5.57 (s, 1H, *trans*- and *cis*-$H_{4'}$), 5.44–5.38 (m, 1H, *trans*- and *cis*-OH—CH), 4.66 and 4.58 (d, 1H, *trans*- and *cis*-ax-$H_{6'}$, $J = 10.4$), 4.00–3.93 (m, 1H, *trans*- and *cis*-eq-$H_{6'}$), 2.32(s, 3H, C_4—CH_3), 1.04 (s, 3H, $C_{5'}$—CH_3), 0.73 (d, 3H, $C_{5'}$—CH_3, $J_{PH} = 10.8$).* 152.18 (C_2), 149.72 (C_4), 136.22, 136.02, 130.23, 128.65, 128.06, 127.58, 127.47 (*trans*- and *cis*-C_5 and —C_6H_5), 90.33 and 89.68 (*trans*- and *cis*-$C_{4'}$), 81.12 and 80.62 (*trans*- and *cis*-$C_{6'}$), 67.06 (d, OH—CH, $^{1}J_{PC} = 674.8$), 36.75 ($C_{5'}$), 21.24 ($C_{5'}$—CH_3), 17.51 ($C_{5'}$—CH_3), 15.50 (—CH_3).*	*cis*-6: 13.05* *trans*-6: 12.95*
8a	8.55 (d, 1H, H_6, $J_{H_6H_5} = 4.00$), 7.77–7.74 (m, 1H, H_4), 7.62 (d, 1H, H_3, $J_{H_3H_4} = 7.20$), 7.29–7.26 (m, 1H, H_5), 6.13 (br, 1H, —OH), 3.84 (d, 3H, 2-OCH_3, $J_{PH} = 12.0$), 3.59 (d, 3H, 2-OCH_3, $J_{PH} = 10.4$), 1.78 (d, 3H, —CH_3, $J_{PH} = 15.6$).* 157.96, 147.38, 137.36, 123.07, 121.64 (—C_5H_4N), 73.81 (d, OH—C, $J_{PC} = 655.20$), 54.31–54.11 (m, 2-OCH_3), 24.54 (—CH_3).*	25.42*
8b	8.46 (d, 1H, H_6, $J_{H_6H_5} = 3.60$), 7.68–7.64 (m, 1H, H_4), 7.56 (d, 1H, H_3, $J_{H_3H_4} = 8.0$), 7.20–7.17 (m, 1H, H_5), 6.07 (br, 1H, —OH), 4.73–4.69 (m, 1H, O—CH), 4.44–4.39 (m, 1H, O—CH), 1.69 (d, $J_{PH} = 15.6$, 3H, —CH_3), 1.28–0.95 (m, 12H, 4-CH—CH_3).* 158.54, 147.12, 137.03, 122.84, 121.87 (—C_5H_4N), 73.40 (d, OH—C, $J_{PC} = 666.8$), 72.05 (d, —OCH, $J_{PC} = 27.2$), 71.79 (d, —OCH, $J_{PC} = 35.6$), 24.56 (—CH_3), 24.36 (—$OCHCH_3$), 24.24 (—$OCHCH_3$), 24.07 (d, —$OCHCH_3$, $J_{PC} = 23.2$), 23.55 (d, —$OCHCH_3$, $J_{PC} = 23.2$).*	21.48*

*Measured on a Varian Mercury Plus 400 instrument.
†Measured on a Brucker AVANCE-300 NMR instrument.

TABLE 4 Crystallographic Data for Compound **1g**

Empirical formula	$C_{11}H_{18}NO_4P$
CCDC deposit No.	293781
Color	Colorless
Crystal size (mm)	$0.26 \times 0.24 \times 0.22$
Crystal system	Monoclinic
Space group	$P2(1)/c$
Unit-cell dimensions (Å)	
a (Å)	12.488(4)
b (Å)	8.654(3)
c (Å)	12.428(4)
α (deg)	90
β (deg)	97.138(5)
γ (deg)	90
Volume (Å^3)	1332.6(8)
Z	4
Formula weight	259.23
Density (calcd.) (mg/m^3)	1.292
Absorption coefficient (mm^{-1})	0.209
F(000)	552
Diffractometer scan wavelength (Å)	SMART CCD 1000
Temperature (K)	0.71073
θ range for data collection (deg)	294(2)
Index ranges	1.64–26.36
No. of data collected	$-15 \le h \le 15$, $-10 \le k \le 6$, $-15 \le l \le 15$
No. of unique data	7184
No. of refined parameters	2701
Absorption correction	158
Refinement method	Semiempirical from equivalents Full-matrix least-square on F^2
Data/restraints/parameters	2701/0/158
Goodness of fit on F^2	1.027
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0383$, $wR_2 = 0.0977$
R indices (all data)	$R_1 = 0.0635$, $wR_2 = 0.1125$
Largest diff. peak and hole (e Å^3)	0.337/−0.268

Single crystals of diethyl 1-hydroxy-1-(pyridin-2-yl)ethylphosphonate (**1g**) were obtained by slow evaporation of a $CDCl_3$ solution. The crystal data, data collection, and refinement parameters for the compound **1g** are listed in Table 4. Data were collected with a SMART CCD 1000 area detector, graphite monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å). The structures were determined by direct methods using the SHELXS-97 package and refined on F^2 from the collected data ($I > 2\sigma(I)$) using the full-matrix least-squares procedures using the SHELXL-97 package.

The crystal structure of **1g** is shown in Figure 1. It is a perspective view of the compound showing the atomic numbering scheme. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference maps and then added geometrically, refined isotropically with a riding model. The fractional coordinates of non-hydrogen atoms and equivalent isotropic thermal parameters are given in Table 5, and selected bond lengths and angles are listed in Table 6. The bond length of P(1)—O(2) [1.4703(15) Å] is shorter than that of a normal P—O bond (1.60 Å) [38], which is close to that of the P(1)—O(3) and P(1)—O(4) bonds. So, the bond between P(1) and O(2) is a double bond and that between P(1)—O(3) and P(1)—O(4) are single bonds. The bond length of P(1)—C(6) [1.842(2) Å] reveals that it is a P—C single bond (1.80–1.85 Å) [38]. And the angle of O(1)—C(6)—P(1) is 104.72(13)°.

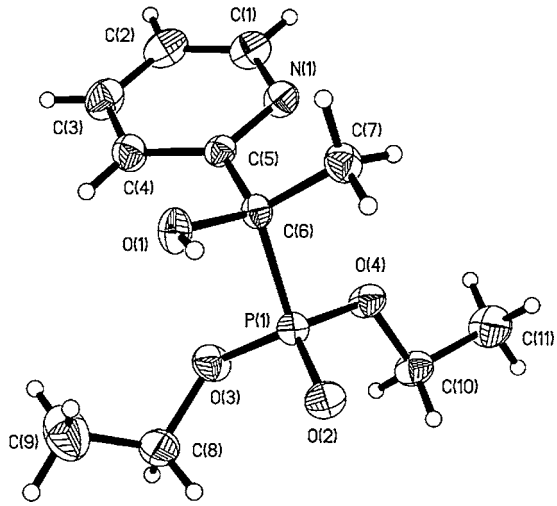


FIGURE 1 Molecular structure of compound **1g** showing the atomic numbering.

TABLE 5 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients (10^3 Å^2) for Compound **1g**

Atom	*x*	*y*	*z*	*U (eq)*
P(1)	8307(1)	1288(1)	3977(1)	35(1)
O(1)	8811(1)	−1635(2)	4067(1)	46(1)
O(2)	9377(1)	1830(2)	4454(1)	47(1)
O(3)	8149(1)	1290(2)	2703(1)	52(1)
O(4)	7335(1)	2273(2)	4293(1)	47(1)
N(1)	6036(1)	−975(2)	4336(2)	47(1)
C(1)	5091(2)	−1516(3)	3858(2)	58(1)
C(2)	4973(2)	−2326(3)	2896(2)	63(1)
C(3)	5868(2)	−2571(3)	2384(2)	62(1)
C(4)	6855(2)	−2024(3)	2860(2)	51(1)
C(5)	6909(2)	−1246(2)	3839(2)	36(1)
C(6)	7986(2)	−674(2)	4415(2)	34(1)
C(7)	8016(2)	−697(3)	5646(2)	48(1)
C(8)	9012(2)	1575(3)	2042(2)	66(1)
C(9)	9436(3)	158(4)	1623(3)	92(1)
C(10)	7308(2)	3951(2)	4149(2)	53(1)
C(11)	6504(2)	4595(3)	4818(3)	73(1)

TABLE 6 Selected Bond Lengths and Bond Angles for Compound **1g**

Atoms	Bond Lengths (Å)	Atoms	Bond Angles (deg)
P(1)—O(2)	1.4703(15)	O(2)—P(1)—O(3)	113.59(9)
P(1)—O(3)	1.5704(16)	O(2)—P(1)—O(4)	114.62(9)
P(1)—O(4)	1.5725(14)	O(3)—P(1)—O(4)	104.35(9)
P(1)—C(6)	1.842(2)	O(2)—P(1)—C(6)	113.26(9)
O(1)—C(6)	1.433(2)	O(3)—P(1)—C(6)	107.14(9)
O(3)—C(8)	1.455(3)	O(4)—P(1)—C(6)	102.88(8)
O(4)—C(10)	1.463(2)	C(8)—O(3)—P(1)	124.09(15)
N(1)—C(1)	1.338(3)	C(10)—O(4)—P(1)	121.00(13)
N(1)—C(5)	1.339(3)	C(1)—N(1)—C(5)	117.2(2)
C(1)—C(2)	1.378(4)	N(1)—C(1)—C(2)	123.9(2)
C(2)—C(3)	1.370(4)	C(3)—C(2)—C(1)	118.4(2)
C(3)—C(4)	1.383(3)	C(2)—C(3)—C(4)	118.9(2)
C(4)—C(5)	1.385(3)	C(3)—C(4)—C(5)	119.0(2)
C(5)—C(6)	1.526(3)	N(1)—C(5)—C(4)	122.54(19)
C(6)—C(7)	1.525(3)	N(1)—C(5)—C(6)	116.53(17)
C(8)—C(9)	1.457(4)	C(4)—C(5)—C(6)	120.92(18)
C(10)—C(11)	1.488(3)	O(1)—C(6)—C(7)	111.48(16)
		O(1)—C(6)—C(5)	107.16(15)
		C(7)—C(6)—C(5)	112.16(16)
		O(1)—C(6)—P(1)	104.72(13)
		C(7)—C(6)—P(1)	109.25(14)
		C(5)—C(6)—P(1)	111.82(13)
		O(3)—C(8)—C(9)	112.7(2)
		O(4)—C(10)—C(11)	108.08(18)

In the ^{1}H NMR spectra of the 1-hydroxyphosphonates, all the hydrogen atom signals on the carbon that is connected to the hydroxy group show a doublet peak between 5.11 and 5.34 ppm (except for compound **7**, which is a mixture of isomers), because of the coupling of the P atom. Besides, the ^{1}H atom of the hydroxy group in **3g, 3h, 8a**, and **8b** prepared from heterocyclic ketones show a broad peak. However, the ^{1}H atom of the hydroxy group in **3a, 3e, 3f, 6a, 6b**, and **7** is replaced by ^{2}H in $CDCl_3$. So no signal can be found in those prepared from heterocyclic aldehydes. We can see the big steric exclusion of heterocyclic ketones block the replacement of ^{1}H. From the ^{31}P NMR spectra of compounds **6a, 3a, 6b**, and **7**, we can see that the singlet of ^{31}P move to high field with the enlargement of the fraction of phosphonate. In ^{13}C NMR, the $^1J_{PC}$ constants between the P and the C atoms connected with the hydroxy group are extremely large (631.8–699.2 Hz).

EXPERIMENTAL

Melting points are determined using a Yanaco MP-500 apparatus and are uncorrected. Nuclear magnetic resonance spectra are recorded on Varian Mercury Plus 400 NMR and Bruker AVANCE-300 NMR instruments in $CDCl_3$. Tetramethylsilane (TMS) is used as an internal standard for ^{1}H NMR and ^{13}C NMR, and 85% H_3PO_4 is used as an external standard for ^{31}P NMR spectroscopy. Elemental analyses are carried out on a Yana MT-3 instrument.

The 4-phenyl-5,5-dimethyl-1,3,2-dioxaphosphinane-2-oxide [39], 4-methyl-5-formylthiazole [40], and 6-bromo-picolinaldehyde [41] were synthesized. Other heterocyclic aldehydes and ketones that were used are commercially available.

*General Procedure for the Synthesis of Diethyl Hydroxy(4-methylthiazol-5-yl)methylphosphonate (**1a**)*

Method A (Using MW). 4-Methyl-5-formylthiazole (0.381 g, 3 mmol), diethyl phosphite (0.414 g, 3 mmol), and 4 equiv. of MgO (0.484 g, 12 mmol) were sufficiently mixed and exposed to MW irradiation. The heating was intermittent (every 2 min), and the reaction mixtures were stirred. By monitoring with TLC, the reaction was stopped at 6 min. Then 2×10 mL chloroform was poured into the container and MgO was eliminated by filtration. The solvent was evaporated at reduced pressure and the residue was recrystallized (ethylacetate-light petroleum) to afford the pure product as a white solid (yield = 83%). (Product **8b** was purified by preparative TLC on silica gel using ethyl acetate as the eluent.)

Method B (Using Oil-heat). 4-Methyl-5-formylthiazole (0.381 g, 3 mmol), diethyl phosphite (0.414 g, 3 mmol) and 4 equiv. of MgO (0.484 g, 12 mmol) were sufficiently mixed and heated in an oil-bath (60–70°C). By monitoring with TLC, the reaction was stopped at 2 h and the product was purified as in method A (yield = 71%).

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