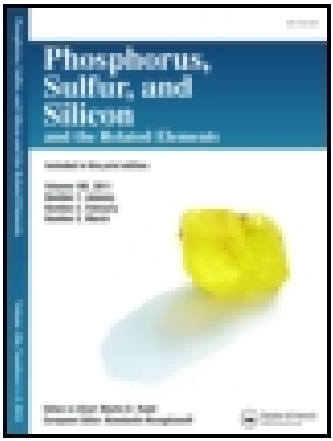

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Synthesis and Biological Activity of α -Oxo-2-Pyridyl Methyl Phosphinates

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Synthesis and Biological Activity of α-Oxo-2-Pyridyl Methyl Phosphinates

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In an attempt to discover novel compounds with high activity and low toxicity, a series of new O,O-dimethyl-α-(substituted phenoxyacetoxy)-2-pyridyl methyl phosphinates, ***5a–5h****, have been designed and synthesized by the reaction of substituted phenoxyacetic chloride with 1-hydroxy-2-pyridyl methyl phosphinate, The structures of all new compounds were characterized by elementary analysis, IR,* ^{1}*H NMR, and MS spectroscopies. The results of preliminary bioassay indicate that most of the target compounds have excellent inhibitory activities on barnyard grass and rape.*

Keywords α-Oxo-2-pyridyl methyl phosphinates; herbicidal activities; synthesis

INTRODUCTION

Pyruvate dehydrogenase complex (PDHc) is already known to be a site of pesticide action, because it plays a pivotal role in cellular metabolism catalyzing the oxidative decarboxylation of pyruvate and the subsequent acetylation of coenzyme A (CoA) to acety-CoA.[1–4] An attempt to design inhibitors of PDHC as herbicides using biochemical reasoning was reported by Baillie et al.[5] Series of acetylphosphinates and acetylphosphonates have been prepared as mechanism- based inhibitors of PDHc because their lowest homologues are regarded as bioisosters of pyruvate (acetyl formate).[6] A. C. Baillie et al.[5] reported

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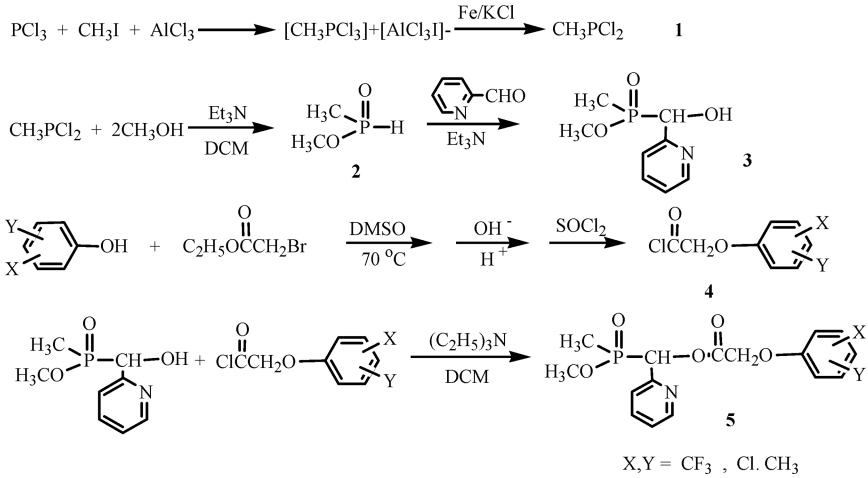
that some acetylphosphinates and acetyl phosphonates showed modest herbicidal activity due to their inhibition against PDHc. However, the activity of them was not sufficiently high for full development as herbicides. In the course of our research for new phosphinate derivatives with good biological activities, it has been shown that certain substituted phenoxy acetoxy alkyl phosphinates possess good herbicide activities. In order to find new phosphinates with better pesticide activity, the pyridine structural unit is introduced into their molecules, so *O*,*O*-Dimethyl-(substituted phenoxyacetoxy)-2-pyridyl methyl phosphonates were synthesized by the reaction of substituted phenoxyacetic chloride **4** with 1-hydroxy-2-pyridyl methyl phosphinate **3** under mild conditions. The synthetic route is shown in Scheme 1.



SCHEME 1

RESULTS AND DISCUSSION

Preparation of Compounds 3 and 5

The reaction of dialkyl phosphates with aldehydes is a convenient method used to synthesize α-hydroxyphosphonates. There are some reports on the synthesis of α-hydroxyphosphinates. However, there are few reports on the reaction of dimethylphosphinate **2** with 2-pyridinecarbox-aldehyde. Herein, we report the reaction of **2** with 2-pyridinecarbox-aldehyde to produce α-hydroxyphosphinate **3**. The reaction under mild conditions (room temperature) resulted in high yields of the products **5a–5h** (Table I) as shown in Scheme 1. However, the addition of a base (triethylamine) was essential to the addition

TABLE I Preparation of α-Oxophosphinates

Compd.	X Y	Formula	Color	n_{20}^{D}	r.t. (h)	Yield (%)
5a	2-Cl, 4-Cl	$C_{16}H_{16}Cl_2NO_5P$	Light yellow	1.5412	4	73
5b	2-F, H	$C_{16}H_{17}FNO_5P$	Light yellow	1.5216	4	68
5c	3-CF_3, H	$C_{17}H_{17}F_3NO_5P$	Light yellow	1.5248	4	62
5d	4-Cl, H	$C_{16}H_{17}ClNO_5P$	Light yellow	1.5198	4	76
5e	2-Cl, 5-CH_3	$C_{17}H_{19}ClNO_5P$	Light yellow	1.5131	4	70
5f	4-Cl, 5-CH_3	$C_{17}H_{19}ClNO_5P$	Light yellow	1.5275	4	70
5g	2-Cl, 6-Cl	$C_{16}H_{16}Cl_2NO_5P$	Light yellow	1.5026	4	64
5h	2-Cl, 3-Cl	$C_{16}H_{16}Cl_2NO_5P$	Light yellow	1.5162	4	61

reaction. Without the use of the triethylamine as a catalyst, the reaction was greatly slowed and the yields were very low too. We try to synthesize compound **3** by the addition reaction of **2** with 2-pyridinecarboxaldehyde in the presence of KF/Al_2O_3, but only corresponding α-hydroxyphosphonates were found. The compounds **5** were prepared from the compound **3** and substituted phenoxyacetic chlorides **4** in the presence of triethylamine.

The Structures of the Title Compounds 5

The molecular structures of all new compounds **5** obtained were confirmed by ^{1}H NMR, IR spectra, MS and elemental analyses. In the ^{1}H NMR spectra of **5**: both the proton in the P-OCH_3 and the P-CH_3 moiety displayed a doublet of doublets, which was due to couplings to the phosphorus. The proton in the OCH_2CO moiety exhibited doublets, while the proton in the P-CH moiety displayed doublet of doublets, which was due to couplings to the phosphorus. Also, **5** showed other Ar-H at 6.86–8.64 ppm as multiple absorptions. For ^{31}P NMR spectra, the phosphorus atom of **5a** showed double peaks, giving chemical shifts at 47.1–48.4 ppm. The IR spectra of all compounds showed normal stretching absorption bands indicating the existence of the Ph-H ($\sim$2950 cm^{-1}), C=O ($\sim$1760 cm^{-1}), C=C ($\sim$1620, $\sim$1450 cm^{-1}), P=O ($\sim$1250 cm^{-1}), P-O-C ($\sim$1050 cm^{-1}) and P-C ($\sim$750 cm^{-1}). The EI mass spectra of compound **5** gave the anticipated molecular ion peaks. All the fragmentation ions of **5** were consistent with the structure and can be assigned clearly.

Herbicidal Activities

The data for the bioassays are listed in Table II. The preliminary biological tests showed that some of the compounds **5a–h**, such as **5a**,

TABLE II The Inhibition Percentage of Compounds 5 to Barnyard Grass and Rape[a]

		Barnyard grass				Rape			
		Stalk		Root		Stalk		Root	
Compd.	X Y	10	100 (ppm)	10	100 (ppm)	10	100 (ppm)	10	100 (ppm)
5a	2-Cl, 4-Cl	55.5	66.6	94.8	97.4	91.6	94.4	98.8	98.8
5b	2-F, H	33.3	40.7	46.1	7.70	2.80	0.00	20.0	50.0
5c	3-CF_3, H	37.0	46.3	94.8	94.8	83.3	94.4	90.0	97.7
5d	4-Cl, H	40.7	51.8	92.3	97.4	91.6	94.4	96.6	98.8
5e	2-Cl,5-CH_3	35.1	27.8	48.7	79.5	66.6	88.8	95.5	96.6
5f	4-Cl,5-CH_3	60.7	78.6	97.8	97.8	94.8	94.8	97.6	98.8
5g	2-Cl, 6-Cl	57.1	57.1	42.2	82.2	20.5	71.8	46.5	89.5
5h	2-Cl, 3-Cl	67.8	67.8	62.2	91.1	5.1	84.6	29.1	94.2

[a]Negative inhibition percentage shows promotive action for plant growth.

5c, **5d**, **5e**, **5f**, etc., have excellent herbicidal activities for the root of barnyard grass and rape. It is found that most of the target compounds **5a–h**, such as **5a**, **5c**, **5d**, **5f,** etc., have excellent inhibitory activities against stalk of rape. The property of substituting groups (X, Y) on benzene ring has a great effect on the herbicidal activity of the compounds **5a–h**. Especially, compounds **5a**, **5d**, and **5f** showed 96.6–98.8% inhibitory effect on the root of rape at a dose of 10 ppm. According to the results of herbicidal assays, there is a need for testing further the herbicidal activity of compounds **5a**, **5d,** and **5f** at lower concentrations.

CONCLUSION

In summary, we have synthesized a series of new *O*,*O*-dimethyl-α-(substituted phenoxyacetoxy)-2-pyridyl methyl phosphinates under mild reaction conditions. This method has the potential in the synthesis of many biologically active phosphinates. The results of preliminary bioassay indicate that most of the target compounds **5a–h** have excellent inhibitory activities on barnyard grass and rape.

EXPERIMENTAL

General Remarks

Melting points are uncorrected. MS were measured with a Finnigan Trace MS spectrometer. IR were recorded with a PE-983 infrared spectrometer as KBr pellets. NMR were recorded in $CDCl_3$ with a Varian Mercury 400 spectrometer and resonances relative to TMS. Elementary

TABLE III ^{1}H NMR Chemical Shifts (TMS, $CDCl_3$) of 5 and Coupling Constants *J* (Hz)

Compd.	δ/ppm, TMS, 400 MHz
5a	1.51–1.61 (dd, 3H, P-CH_3, J = 14.4 Hz), 3.69–3.73 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.90–4.92 (d, 2H, -OCH_2CO-, J = 10.0 Hz), 6.21–6.31 (dd, 1H, -OCHP, J = 1 0.4 Hz), 6.81–8.62 (m, 7H, -C_5H_4N, -C_6H_3), ^{31}P NMR, 47.1–48.4, J = 518 Hz.
5b	1.50–1.59 (dd, 3H, P-CH_3, J = 14.8Hz), 3.68–3.72 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.91–4.93 (d, 2H, -OCH_2CO-, J = 9.6 Hz), 6.22–6.34 (dd, 1H, -OCHP, J = 12.4 Hz), 6.94–8.63 (m, 8H, -C_5H_4N, -C_6H_4).
5c	1.51∼1.59 (dd, 3H, P-CH_3, J = 14.8 Hz), 3.68–3.73 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.89–4.92 (d, 2H, -OCH_2CO-, J = 11.6 Hz), 6.22–6.34 (dd, 1H, -OCHP, J = 12.8 Hz), 7.11–8.64 (m, 8H, -C_5H_4N, -C_6H_4).
5d	1.50∼1.60 (dd, 3H, P-CH_3, J = 14.8Hz), 3.68∼3.73 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.82∼4.84 (d, 2H, -OCH_2CO-, J = 10.4 Hz), 6.21∼6.32 (dd, 1H, -OCHP, J = 12.4 Hz), 6.84∼8.63 (m, 8H, -C_5H_4N, -C_6H_4).
5e	1.50–1.58 (dd, 3H, P-CH_3, J = 13.7 Hz), 2.28 (s, 3H, $PhCH_3$), 3.69–3.73 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.90–4.92 (d, 2H, -OCH_2CO-, J = 9.6 Hz), 6.23–6.35 (dd, 1H, -OCHP, J = 12.4 Hz), 6.67–8.63 (m, 7H, -C_5H_4N, -C_6H_3).
5f	1.50–1.60 (dd, 3H, P-CH_3, J = 14.8 Hz), 2.27 (s, 3H, $PhCH_3$), 3.68–3.72 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.83–4.86 (d, 2H, -OCH_2CO-, J = 10.4 Hz), 6.21–6.32 (dd, 1H, -OCHP, J = 12.4 Hz), 6.62–8.63 (m, 7H, -C_5H_4N, -C_6H_3).
5g	1.58–1.66 (dd, 3H, P-CH_3, J = 14.8 Hz), 3.72–3.79 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.83–4.86 (d, 2H, -OCH_2CO-, J = 10.4 Hz), 6.30∼6.42 (dd, 1H, -OCHP, J = 12.4 Hz), 7.04–8.63 (m, 7H, -C_5H_4N, -C_6H_3).
5h	1.50–1.61 (dd, 3H, P-CH_3, J = 14.4 Hz), 3.69–3.73 (dd, 3H, P-OCH_3, J = 12.4 Hz), 4.93–4.95 (d, 2H, -OCH_2CO-, J = 10.0 Hz), 6.22–6.32 (dd, 1H, -OCHP, J = 12.4 Hz), 6.79–8.62 (m, 7H, -C_5H_4N, -C_6H_3).

analyses were taken with a Vario EL III elementary analysis instrument. The reagents solvents were available commercially and purified according to conventional methods before use.

Dichloromethylphosphine **1** was prepared according to the literature procedure, [7∼12]**1:** b p 80–82°C, n_D^{20} 1.4952, Yield, 40–45%.

General Procedure for Preparation of 2[13]

To a solution of dichloromethylphosphine **1** (5.85 g, 50.0 mmol) in dry benzene (40 mL) was added dropwise with stirring to a cooled solution of methanol (3.84 g, 120 mmol) and triethylamine (5.05 g, 50.0 mmol) under nitrogen at 0∼5°C. After the reaction mixture was standing for 1 h and then filtered, the filtrate was condensed to give dimethylphosphinate **2**, which was used directly without further purification.

TABLE IV IR Data of Compounds 5

Compd.	υ ph-H	υ C-H	υ C=O	υ Ph	υ P=O	υ C-O-C	υ P-O-C	υ P-C
6a	3070	2955, 2851	1770	1590,1487,1436	1229	1167	1040,900	756
6b	3070	2955, 2852	1771	1590,1506,1436	1236	1175	1040,900	753
6c	3076	2932, 2857	1784	1593,1495,1457	1175	1127	1040,894	762
6d	3070	2955, 2851	1770	1593,1492,1437	1218	1142	1042,901	749
6e	3057	2954, 2852	1771	1590,1491,1436	1225	1169	1041,900	749
6f	3217	2956, 2857	1761	1592,1492,1436	1218	1183	1043,895	750
6g	3068	2954, 2851	1774	1590,1456,1437	1232	1178	1043,900	786
6h	3076	2955, 2851	1769	1578,1457,1436	1224	1147	1041,894	771

General Procedure for Preparation of 3[14–20]

To a solution of **2** (1.88 g, 20.0 mmol) prepared above in dry benzene (20 mL) was added with stirring to a solution of 2-pyridine- carboxaldehyde (2.57 g, 24.0 mmol) and catalyst triethylamine (1.01 g, 10.0 mmol) under nitrogen at 0–5°C. After the reaction mixture was stirred for 6–8 h at 50–60°C, the solvent was removed under reduced pressure. The residue was chromatographed on silica with 20% acetone in petroleum ether as eluent to give the compound **3**.

White crystal, Yield: 86.6%. m.p. 89–90°C. IR (KBr)υ: 3258(s, OH), 3055 (w, Ph-H), 2921, 2822 (m, C-H), 1221 (s, P=O), 1132(s, C-OH), 1032, 891 (s, P-O-C), 792 (s, P-C) cm^{-1}; ^1H NMR ($CHCl_3$,300Hz)δ: 1.40–1.64 (dd, 3H, -CH_3, J = 15.2 Hz), 3.48–3.68(dd, 3H, -OCH_3, J = 12.4 Hz), 4.48(s, br, 1H,OH), 4.76–4.94 (d, 1H, -OCHP, J = 10.4 Hz), 6.76–7.22 (m, 4H, -C_5H_4N). MS(70ev) m/z(%):201(M^+), 94 (84.83), 79 (100); Anal. calcd. (%) for $C_8H_{12}NO_3P$: C, 47.77; H, 6.01; N, 6.96. Found (%): C, 47.64; H, 6.26; N, 7.08.

General Procedure for Preparation of Substituted Phenoxyacetyl Chlorides 4

Substituted phenoxyacetic acids were prepared according to the literature procedure, [21] substituted phenoxyacetic acids**:** X,Y = 2-Cl, 4-Cl, m.p. 137–139°C, Yield, 89.8%; X,Y = 2-F, H, m.p. 140–140.5°C, Yield, 90.5%; X,Y = 3-CF_3, H, m.p. 97.0–98.0°C, Yield, 72.6%; X,Y = 4-Cl, H, m.p. 159–61°C, Yield, 87.7%; X,Y = 2-Cl,5-CH_3, m.p. 136–138°C, Yield, 78.5%; X,Y = 4-Cl,5-CH_3, m.p. 181–183°C, Yield, 86.0%; X,Y = 2-Cl, 6-Cl, m.p. 138–139°C, Yield, 70.5%; X,Y = 2-Cl, 3-Cl, m.p. 171–173°C, Yield, 87.2%.

TABLE V Elemental Analysis and MS Data of Compound 5

Compd.	Calcd.(found) C	H	N	MS
5a	47.55 (47.33)	3.99 (3.95)	3.47 (3.09)	403 (M^++1 41.51), 339 (30.70), 292 (12.06), 242 (48.69), 228 (61.41), 200 (40.40), 185 (44.19), 175 (50.37), 162 (12.87), 145 (42.49), 133 (26.31), 108 (71.68), 93 (100), 78 (51.42), 63 (46.56).
5b	54.40 (54.56)	4.85 (4.69)	3.96 (3.65)	353 (M^++1 42.72), 242 (29.96), 228 (62.18), 200 (33.88), 185 (46.72), 125 (74.42), 108 (75.93), 93 (100), 78 (66.08), 63 (53.09).
5c	50.63 (51.11)	4.25 (4.44)	3.47 (3.25)	403 (M^++1 45.23), 242 (32.62), 228 (48.81), 200 (41.62), 185 (36.89), 175 (54.40), 162 (10.91), 145 (75.99), 133 (17.27), 108 (78.95), 93 (97.45), 78 (100), 63 (53.85).
5d	51.98 (51.71)	4.63 (4.56)	3.79 (3.33)	369 (M^++1 39.42), 242 (31.92), 228 (69.56), 200 (23.30), 185 (60.50), 141 (60.49), 108 (80.49), 93 (100), 78 (42.15), 63 (56.42).
5e	53.21 (53.37)	4.99 (4.87)	3.65 (3.31)	383 (M^++1 100), 242 (43.94), 228 (39.91), 200 (36.94), 185 (37.75), 155 (61.33), 125 (56.81), 108 (80.44), 93 (94.97), 78 (39.86), 63 (64.36).
5f	53.21 (52.72)	4.99 (5.20)	3.65 (3.14)	383 (M^++1 51.34), 242 (4.88), 228 (3.48), 200 (37.99), 185 (85.44), 155 (52.57), 125 (63.07), 108 (82.23), 93 (100), 78 (44.82), 63 (66.76).
5g	47.55 (47.08)	3.99 (3.95)	3.47 (2.98)	403 (M^++1 28.68), 242 (31.28), 228 (26.85), 200 (20.37), 185 (8.62), 175 (34.59), 162 (4.30), 145 (27.69), 133 (22.93), 108 (46.35), 93 (100), 78 (33.72), 63 (69.37).
5h	47.55 (47.64)	3.99 (3.98)	3.47 (3.07)	403 (M^++1 39.30), 242 (27.75), 228 (61.34), 200 (35.64), 185 (32.11), 175 (47.92), 162 (4.44), 145 (48.23), 133 (24.37), 108 (65.98), 93 (100), 78 (41.92), 63 (67.27).

A mixture of substituted phenoxyacetic acid (50.0 mmol) and thionyl chloride (25 mL) was stirred and refluxed for 4 h. The thionyl chloride was removed under reduced pressure to give substituted phenoxyacetyl chlorides **4**, which were used directly without further purification.

General Procedure for Synthesis of *O,O*-Dimethyl-α-(Substituted Phenoxyacetoxy)-2-Pyridyl Methyl Phosphinates 5

A solution of substituted phenoxyacetyl chloride **4** (22.0 mmols) in DCM (10 mL) was added to stirred mixture of 1-hydroxyalkyl phosphinate **3** (4.02 g, 20.0 mmols) and triethylamine (2.22 g, 22.0 mmols) in DCM (25 mL) at 20°∼25°C. The mixture was stirred at ambient temperature for 4 hours, and then at 40°C for 1 hour, washed with 0.1 M hydrochloric acid, saturated sodium hydrogen carbonate solution, and brine respectively. The resultant mixture was dried and evaporated. The residue was chromatographed on silica with 20% acetone in petroleum ether as eluent to give the title compounds **5**. Yield: 61%∼76%. All results are listed in Tables III, IV, and V.

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