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Unsaturated Cyclic α-Hydroxyphosphonates

De-Qing Shi, Zi-Liang Sheng, Xiao-Peng Liu, and Hong Wu

Department of Chemistry, Central China Normal University, Wuhan 430079, People's Republic of China

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ABSTRACT: *In an attempt to find novel plant growth regulators, a series of unsaturated cyclic α-hydroxyphosphonates were synthesized by the addition reactions of 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxides with 5-aryl-2E,4E-pentadienaldehydes. The cis and trans isomers of the products were isolated. The structures of all products were confirmed by elemental analyses and by NMR and IR spectroscopy or MS. The results of preliminary bioassay indicate that the title compounds possess potential inhibitory activity on the elongation of wheat coleoptile.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 14:266–268, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10139

INTRODUCTION

We have reported the synthesis of several unsaturated phosphonates, some of which exhibit plant growth regulating activity [1,2]. Organic heterocyclic phosphorus compounds play an important role in pesticide chemistry. 1,3,2-Dioxaphosphinane compounds are important for their wide biological activities and their stereochemistry [3–5]. We introduced the 1,3,2-dioxaphosphinane ring into unsaturated α-hydroxyphosphonates, and designed the cyclic phosphonates **6**. The synthetic route involves the addition reactions of 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxides with 5-aryl-2*E*,4*E*-pentadienaldehydes as shown in Scheme 1.

Correspondence to: De-Qing Shi; e-mail: shidq@public.wh.hb.cn.

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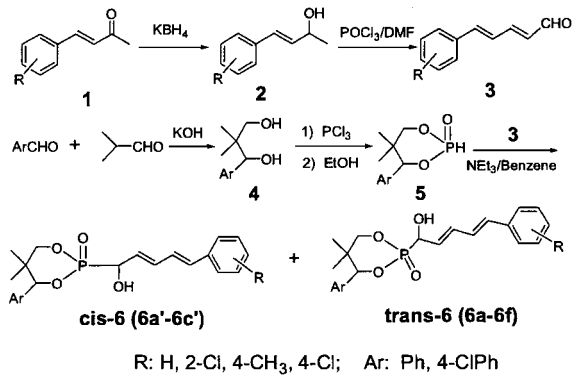
RESULTS AND DISCUSSION

Synthesis and Structure

The title compounds **6** were synthesized by the multistep route outlined in Scheme 1. Reduction of 4-aryl-3-buten-2-ones **1** with potassium borohydride afforded the corresponding 4-aryl-3-buten-2-ols **2**, which by Vilsmeier–Haack reaction with $POCl_3$/DMF gave the key intermediates 5-aryl-2*E*,4*E*-pentadienaldehydes **3** in moderate yields. Treatment of **3**, in the presence of triethylamine or sodium hydride, with 4-aryl-5,5-dimethyl-1,3,2-dioxaphosphinane 2-oxide **5** afforded the target unsaturated cyclic α-hydroxyphosphonates **6**.

The reaction of dialkyl phosphites with aldehydes is a convenient method used to synthesize α-hydroxyphosphonates. The steric hindrance of compound **5** affected the conversion of **3** to **6**, thus, the yields of the products were moderate (Table 1) even in the presence of strong base sodium hydride. The addition of a base was essential to the addition reaction. Without triethylamine or sodium hydride as a catalyst, the reaction slowed greatly and the yields were very low. The addition reactions showed good regioselectivity; the phosphorus atom of compound **5** attacked only the carbon atom in the carbonyl group of dienals, and no conjugated addition products were found.

All the products **6** were purified by flash column chromatography on silica gel; for Ar=Ph, cis and trans isomers were obtained in a ratio between 0.8 and 1.5. However, when aryl was 4-chlorophenyl, only trans isomers were obtained. The structures of



SCHEME 1

compounds **6** were confirmed by ^{1}H NMR, ^{31}P NMR, IR spectra, MS, and elemental analyses.

In the ^{1}H NMR spectra of **6**, the hydroxy proton displays a broad singlet, while the proton in the P—C moiety exhibits a doublet of doublets. In the trans isomers, the difference in the chemical shifts for the protons of the two methyl groups in the heterocycle is larger than that in cis isomers (0.32–0.36 ppm and 0.12–0.16 ppm, respectively). In the cis isomers, P=O and the proton geminal to the aryl group both lie in axial positions; so the proton is deshielded and absorbs downfield relative to the proton in the trans isomer, consistent with the literature [6]. In the ^{31}P NMR spectra, the chemical shifts reflect electronic and steric effects [7]. As the O—P—O bond angle in the cis isomer is smaller, its signal is downfield relative to that of the trans isomer.

The IR spectra of all compounds showed normal stretching absorption bands indicating the existence of the OH (~3300 cm^{-1}), P=O (~1260 cm^{-1}), C=C (~1650 cm^{-1}), and P—O—C (~1050, ~950 cm^{-1}). The EI mass spectra of compound **6a** gave the anticipated molecular ion peaks. All the fragmentation ions were consistent with the structure and can be clearly assigned.

Biological Activities

The results of preliminary tests for the plant growth regulating activities indicated that some of the title compounds inhibit the elongation of wheat coleoptile and cucumber root. For example, the relative ratios of the inhibition of wheat coleoptile elongation by compounds **6c′** and **6f** were, respectively, 16.94 and 13.55% at the concentration of 1.0×10^{-4} while the relative inhibition ratios of cucumber root by compounds **6d, 6e**, and **6f** were 100% at the same concentration.

EXPERIMENTAL

Instruments

^{1}H NMR and ^{31}P NMR spectra were recorded with JEOL FX-90Q and a BRUKER AC-P200 spectrometer with TMS and 85% H_3PO_4 as the internal and external reference, respectively, and $CDCl_3$ as the solvent, while mass spectra were obtained with a Hewlett-Packard 5988 and Finnigan TRACE MS spectrometer, using the EI method. IR spectra were measured by a SHIMADZU-435 instrument. Elemental analyses was performed with a Yanaco CHN CORDER MT-3 elementary analyzer. Melting points were determined with a Thomas–Hoover apparatus and the thermometer was uncorrected.

The reagents and solvents used were available commercially and were purified according to conventional methods before use. 4-Aryl-3-butenones-2 (**1**) were synthesized by aldol condensation of substituted benzaldehydes with acetone according to Ref. [8]. 4-Aryl-2-methyl-3-butenols-2 (**2**) and 1-aryl-2,2-dimethyl-1,3- propanediols (**4**) were prepared according to literature [9,10]; yield: 86–95%. Compounds **3** were obtained by Vilsmeier–Haack reaction of **2** with $POCl_3$ and DMF [9]; yield: 43–65%.

TABLE 1 Data of Phosphonates **6**

								Found (Calcd)	
	Ar	*R*	*Formula*	*Color*	*m.p. (°C)*	*Yield (%)*	*r.t. (h)*	*C*	*H*
6a′	Ph	4-Cl	$C_{22}H_{24}ClO_4P$	Yellow	181–183			63.55 (63.08)	6.01 (5.73)
6a	Ph	4-Cl	$C_{22}H_{24}ClO_4P$	Yellow	183–184	52	24	63.33 (63.08)	5.67 (5.73)
6b′	Ph	4-CH_3	$C_{23}H_{27}O_4P$	Yellow	184–185			69.61 (69.35)	6.92 (6.78)
6b	Ph	4-CH_3	$C_{23}H_{27}O_4P$	Yellow	187–188	72	48	69.08 (69.35)	6.85 (6.78)
6c′	Ph	H	$C_{22}H_{25}O_4P$	Yellow	176–178	70	48	68.69 (68.75)	6.25 (6.51)
6c	Ph	H	$C_{22}H_{25}O_4P$	Yellow	187–189			68.47 (68.75)	6.40 (6.51)
6d	4-ClPh	4-Cl	$C_{22}H_{23}Cl_2O_4P$	White	176–178	65	36	57.95 (58.28)	5.12 (5.08)
6e	4-ClPh	H	$C_{22}H_{24}ClO_4P$	Yellow	210–211	61	48	63.44 (63.08)	5.55 (5.73)
6f	4-ClPh	4-CH_3	$C_{23}H_{26}ClO_4P$	White	171–172	56	24	63.76 (63.82)	6.19 (6.01)

TABLE 2 ^{1}H and ^{31}P Chemical Shifts of **6a–f** (TMS, $CDCl_3$) and Coupling Constants J (Hz)

6a′	0.78 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 3.30 (sb, 1H, OH), 3.91 (dd, 1H, $^{2}J_{P-H} = 20.6$, $^{3}J_{H-H} = 11.2$, CH–P), 4.12–4.58 (m, 2H,CH_2), 5.76 (d, 1H, $^{3}J_{P-H} = 10.6$, CH–Ar), 5.76–5.98 (m, 1H, =CH–C–P), 6.20–6.57 (m, 3H, =CH–CH=CH–Ar), 7.17–7.25 (m, 9H , Ar–H)
6a	0.69 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 3.34 (sb, 1H, OH), 3.90 (dd, 1H, $^{2}J_{P-H} = 19.8$, $^{3}J_{H-H} = 10.8$, CH–P), 4.16–4.42 (m, 2H, CH_2), 5.66 (d, 1H, $^{3}J_{P-H} = 10.2$, CH–Ar), 5.72–6.00 (m, 1H, =CH–C–P), 6.29–6.66 (m, 3H, =CH–CH=CH–Ar), 7.20–7.30 (m, 9H , Ar–H)
6b′	0.75 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 3.25 (sb, 1H, OH), 3.91 (dd, 1H, $^{2}J_{P-H} = 20.2$, $^{3}J_{H-H} = 9.4$, CH–P), 4.20–4.62 (m, 2H, CH_2), 5.80 (d, 1H,$^{3}J_{P-H} = 9.9$, CH–Ar), 5.76–5.98 (m, 1H, =CH–C–P), 6.20–6.57 (m, 3H, =CH–CH=CH–Ar), 7.06–7.26 (m, 9H, Ar–H). δ ^{31}P: 14.83
6b	0.70 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 3.10 (sb, 1H, OH), 3.92 (dd, 1H, $^{2}J_{P-H} = 18.6$, $^{3}J_{H-H} = 10.0$, CH–P), 4.26–4.70 (m, 2H, CH_2), 5.65 (d, 1H, $^{3}J_{P-H} = 10.4$, CH–Ar), 5.72–6.00 (m, 1H, =CH–C–P), 6.29–6.66 (m, 3H, =CH–CH=CH–Ar), 7.08–7.39 (m, 9H , Ar–H). δ ^{31}P: 13.26
6c′	0.76 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 2.90 (sb, 1H, OH), 3.89 (dd, 1H, $^{2}J_{P-H} = 23.4$, $^{3}J_{H-H} = 10.8$, CH–P), 4.28–4.46 (m, 2H, CH_2), 5.72 (d, 1H, $^{3}J_{P-H} = 10.4$, CH–Ar), 5.78–5.98 (m, 1H, =CH–C–P), 6.20–6.57 (m, 3H, =CH–CH=CH–Ar), 7.00–7.36 (m, 9H , Ar–H)
6c	0.72 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 3.28 (sb, 1H, OH), 3.99 (dd, 1H, $^{2}J_{P-H} = 19.8$, $^{3}J_{H-H} = 10.8$, CH–P), 4.20–4.52 (m, 2H, CH_2), 5.64 (d, 1H, $^{3}J_{P-H} = 10.3$, CH–Ar), 5.72–6.12 (m, 1H, =CH–C–P), 6.24–6.76 (m, 3H, =CH–CH=CH–Ar), 7.08–7.40 (m, 9H , Ar–H)
6d	0.76 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 3.08 (sb, 1H, OH), 3.89 (dd, 1H, $^{2}J_{P-H} = 19.2$, $^{3}J_{H-H} = 11.7$, CH–P), 4.18–4.56 (m, 2H, CH_2), 5.80 (d, 1H, $^{3}J_{P-H} = 10.4$, CH–Ar), 5.89–6.02 (m, 1H, =CH–C–P), 6.40–6.78 (m, 3H, =CH–CH=CH–Ar), 7.15–7.27 (m, 9H , Ar–H)
6e	0.75 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 3.22 (sb, 1H, OH), 3.82 (dd, 1H, $^{2}J_{P-H} = 18.6$, $^{3}J_{H-H} = 11.0$, CH–P), 4.21–4.67 (m, 2H, CH_2), 5.55 (d, 1H, $^{3}J_{P-H} = 11.0$, CH–Ar), 5.82–5.92 (m, 1H, =CH–C–P), 6.58–6.90 (m, 3H, =CH–CH=CH–Ar), 7.10–7.45 (m, 9H , Ar–H)
6f	0.72 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 3.38 (sb, 1H, OH), 3.86 (dd, 1H, $^{2}J_{P-H} = 19.4$, $^{3}J_{H-H} = 10.6$, CH–P), 4.14–4.42 (m, 2H, CH_2), 5.60 (d, 1H, $^{3}J_{P-H} = 10.4$, CH–Ar), 5.78–5.96 (m, 1H, =CH–C–P), 6.50–6.71 (m, 3H, =CH–CH=CH–Ar), 7.11–7.36 (m, 9H , Ar–H)

*General Procedure for the Synthesis of 4-Aryl-5,5-dimethyl-1,3,2-dioxaphosphinane 2-Oxides (**5**)*

Compound **4** (0.1 mol) and 1,2-dichloroethane (30 ml) were added into a 100-ml reaction flask, the solution of 0.1 mol of PCl_3 in 20 ml of 1,2-dichloroethane was added dropwise with cooling in ice. The mixture was then stirred at 5–10°C for 2 h, 0.1 mol of anhydrous ethanol in 10 ml of 1,2-dichloroethane was added dropwise at room temperature, and the mixture was refluxed for 1–1.5 h and evaporated at reduced pressure. The residual solid was recrystallized from toluene to afford the pure product as white crystal. **5a**: Ar: Ph, yield: 83%, m.p. 182–183°C. **5b**: Ar: 4-ClPh, yield: 91%, m.p. 179–180°C.

General Procedure for the Synthesis of **6**

Compounds **3** (2 mmol), **5** (2–3 mmol), and triethylamine (4 mmol) in 10 ml anhydrous benzene were added. The mixture was then stirred at room temperature for 24–48 h and evaporated at reduced pressure. The residual solid was purified by column chromatography on silica gel, using petroleum ether–ethyl acetate (1:2–4, v/v) as the eluent. First, the trans isomers were received first and then the cis isomers (Tables 1 and 2).

IR and MS of **6a**. IR (KBr, cm^{-1}): 3336 (sb, OH), 2947, 1677 (s), 1489 (s), 1261 (s, P=O), 1104, 1050, 949 (s, P–O–C) EI-MS (*m/e*): 418 (22.3%), 420 (M^+, 3:1), 401 (69.8%), 403 (23.3%), 273 (49.1%), 275, 256, 245 (82.4%), 227, 193 (84.3%), 171 (94.7%), 145 (96.3%), 125 (100%), 107, 91, 77, 63, 56.

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