六員環状エノールリン化合物の立体選択的合成(農芸化学科)

Stereoselective Synthesis of Six-membered Cyclic Enol Phosphorus Compounds**

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Summary

2-Phenyl- and 2-phenoxy-4-alkylidene-1, 3, 2-benzodioxaphosphorin 2-oxides are obtained in 48-70% yield on heating *O*, *O*-di-(2-alkylketophenyl) phenyl phosphonates and *O*-(2-alkylketophenyl) *O*, *O*-diphenyl phosphates, respectively. This facile cyclization reaction forms only the *Z*-isomer. The *Z*-isomer is probably favored because in its formation there is minimal interaction between the vinylic alkyl substituent and aromatic H-5 in the required coplanar conformation for the phenyl and enolate groups to achieve attack at phosphorus.

Introduction

As a part of a metabolic study of *O*-(2-alkylphenyl) *O*, *O*-diphenyl phosphates, the author prepared the alkylidene cyclic phosphorus compounds by reaction of PCl_3 with *o*-$HOC_6H_4COCH_2R_1$ (R_1=H, Me, Et) in the presence of an appropriate base.[4, 5] Treatment of 2-alkylketophenols with PCl_3 and Et_3N readily gave the 2-chloro-1, 3, 2-dioxaphosphorinan, and followed by an alcohol or phenol in the presence of Et_3N to give the corresponding 2-alkoxy and 2-phenoxy derivatives, which were not assigned stereochemistry[1]. The cyclic phosphites were treated with equimolar *m*-chloroperbenzoic acid in dichloromethane at -50℃ to obtain the cyclic phosphates[5]. The cyclic phosphorothionates were prepared by stirring a mixture of the phosphates and equimolar elemental sulfur in carbon disulfide for 5 hr at 50℃ and isolated the products by distillation[5]. The author found that a particularly convenient method to prepare the cyclic phosphorus involves treatment of the appropriate 2-alkylketophenyl phosphonates or phosphates with K_2CO_3 in acetonitrile at 70℃[6, 7].

This report describes the detailed synthetic method of the cyclic enol phosphates and phosphonates with high stereospecificity in the cyclization reaction to form the

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** The study was carried out at the Pesticide Chemistry and Toxicology Laboratory, University of California, Berkeley, under the direction of Professor John E. Casida

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Sci. Bull. Coll. Agric. Univ. Ryukyus **30** : 211～216 (1983)

Z-configuration.

Experimental Section

1 Chemicals, spectroscopy and chromatography

Spectral data for the new compounds are given in Tables 1 and 2. ^{1}H and ^{13}C NMR spectra were obtained with $CDCl_3$ solutions and tetramethylsilane as the internal standards (δ=0 ppm). The instruments used were: Perkin-Elmer R32B 90 MHz spectrometer for ^{1}H; Nicolet NT-180 spectrometer operated at 45.3 MHz for ^{13}C; UCB-180 spectrometer operated at 72.9 MHz for ^{31}P. Chemical ionization (CI)-mass spectra (MS) were obtained with the Finnigan 1050D mass spectrometer using isobutane as the reagent gas at a Cl source pressure of 0.5-1.0 torr. TLC utilized 0.25 mm silica gel 60 F-254 plates for analysis and 1 mm sillica gel GF plates for preparative isolation. The solvents were dichloromethane, chloroform-dichloromethane (1:1) and hexane-acetone (7:2). Products on TLC plates were detected by UV and 2, 6-dichloroquinone-4-chloroimide or vaniline-sulfuric acid spray reagents.

2 2-Alkylketophenyl phosphonates (1-3) and phosphates (4-6) (Table 1)

The 2-alkylketophenol was added to equivalent 20% NaOH with stirring, then an equal volume of acetonitrile was added to precipitate the sodium phenylate, which was dried (dessicator under reduced pressure). Phenylphosphonyl dichloride (0.01 mol) was added slowly to the phenylate salt (0.02 mol) in acetonitrile (100 ml) with stirring for 2 hr at 25°C. Filtration, solvent evaporation and TLC (dichloromethane-acetone 9:1) gave triaryl phosphonates **1-3**.

Phosphate esters **4-6** were prepared by adding diphenyl chlorophosphate (0.05mol) to equivalent 2-alkylketophenol suspended in 20% NaOH at 10°C. After stirring 2 hr at 10°C the mixture was extracted with chloroform which was back-washed two times each with 2% NaOH and distilled water and then dried (Na_2SO_4) and subjected to column chromatography (sillca gel, dichloromethane-acetone 9:1); the base wash alone did not adequately remove interfering phenol (see below) and some thermal decomposition occurred on attempted distillation.

3 2-Phenyl-4-alkylidene-1, 3, 2-benzodioxaphosphorin 2-oxides (7-9) and the analogous 2-phenoxy compounds (10-12) (Table 2)

A mixture of *O, O*-di (2-alkylketophenyl) phenylphosphonates (**1-3**) (0.01 mol) or *O*-(2-alkylketophenyl) *O, O*-diphenyl phosphates (**4-6**) (0.01 mol) and K_2CO_3 (0.01 mol) in acetonitrile (50 ml) was stirred 30 min at 70°C (the optimum time and temperature). After filtration and solvent evaporation the residue was chromatographed (TLC, silica gel, dichloromethane) to give **7-12**. Triphenyl phosphate is a by-product in preparation of **10-12** and maximum yields depend on high purity **4-6**.

4 Triphenyl phosphate from reaction of 11 with phenol

A mixture of **5** (0.01 mol), phenol (0.05 mol) and K_2CO_3 (0.05 mol) in acetonitrile (50 ml) was held 20 min at 70°C. ^{31}P NMR ($CDCl_3$) revealed alkylidene cyclic phosphate **11** (δ−21.9) and triphenyl phosphate (δ−20.1). Five different TLC solvent systems failed to provide adequate separation of triphenyl phosphate from **11** (and also **10**, **12**) as follows: dichloromethane; acetone–hexane 1:1; hexane–ethyl acetate 4:1; dichloromethane–acetone 9:1. HPLC on a Porasil analytical column (7.8 mm ID × 30 cm) eluted with hexane–ethyl acetate (4:1, flow rate of 2 ml/min) provided adsorbance detector, t_R min); 5.5%, 3.3 min; **11**, 57%, 3.2 min; triphenyl phosphate, 21%, 3.5 min; 2–hydroxypropiophenone, 12%, 1.6 min; phenol, 5%, 2.3 min. HPLC was also suitable to separate triphenyl phosphate from **10** (t_R 3.3 min) but not from **12** (t_R 2.5 min).

Results and Discussion

1 Cyclization reaction in synthesis of 4–alkylidene derivatives

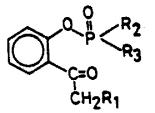
Cyclic phosphorus compounds **7**–**12** were obtained in 48–70% yields on treatment of **1**–**3** and **4**–**6** with equimolar K_2CO_3 in acetonitrile for 30 min at 70°C (Table 2). The yields are limited by the sensitivity of the products 7–12 to attack by phenols liberated on cyclization. Thus, in conversion of **1**–**3** to **7**–**9** in 50% yields, the liberated alkylketophenol can reattack the product to give essentially a reversible reaction. Higher yields (60–70%) are obtained for **10**–**12** in which case the by–product is triphenyl phosphate, formed on reattack of the phenol liberated on cyclization (or present in impure starting material). Thus, cyclization of **5** in the presence of 0.5 equivalent phenol gives a large amount of triphenyl phosphate in addition to **11**. The cyclization reactions of **1**–**3** and **4**–**6** evident on treatment with base are also prominent under the conditions of CI–MS (Table 1).

2 Stereoselectivity of cyclization reaction

Although the 4–alkylidene derivatives with R_1=Me, Et have two possible geometrical isomers, they each give a single ^{31}P NMR signal (**8**, **9**, **11**, **12**) and a single HPLC peak (**8**, **9**). ^{13}C NMR also reveals a single isomer. Proton H_a of **8**, **9**, **11**, **12** has a lower chemical shift than that of **7**, **10** due to the inductive effect of the alkyl group. Proton H_a is coupled with phosphorus in a mannar analogous to a *W*–effect.[2] These NMR findings establish that **8**, **9**, **11**, **12** exist exclusively in the *Z*–form configuration.

A high degree of stereoselectivity is rarely encountered in synthesis of acyclic enol phosphates[3]. In contrast, a stereospecific reaction appears to be involved in synthesis of cyclic phosphorus esters **8**, **9**, **11**, **12** under the basic or thermal conditions discussed above. Formation of an enolate species from **2**, **3** and **5**, **6** is a prerequisite for reaction and the planar enolate must be coplanar with the aromatic ring nucleophilic

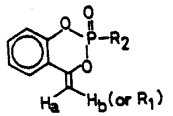
Table 1. Triary Phosphonates (**1–3**) and Phosphates (**4–6**)



Cpds.	R_1	R_2	R_3	^{1}H NMR ($CDCl_3$) δ	^{31}P NMR ($CDCl_3$) δ	CI–MS, $(M+1)^+$, m/z (rel. int.) Parent	cyclic*
1	H	Ph	(*o*–C_2H_3O)OPh	2.50 (s, 6H)	10.0	395 (0)	259 (100)
2	Me	Ph	(*o*–C_3H_5O)OPh	2.87 (q, 4H), 1.08 (t, 6H)	9.9	409 (0)	273 (100)
3	Et	Ph	(*o*–C_4H_7O)OPh	2.82 (t, 4H), 1.67 (m, 4H), 0.84 (t, 6H)	9.8	423 (0)	287 (100)
4	H	OPh	OPh	2.55 (s, 3H)	−20.6	369 (55)	275 (100)
5	Me	OPh	OPh	2.89 (q, 2H), 1.06 (t, 3H)	−20.5	383 (82)	289 (100)
6	Et	OPh	OPh	2.80 (t, 2H), 1.62 (m, 2H), 0.84 (t, 3H)	−20.6	397 (52)	303 (76)

* Cyclic product from loss of 2–alkylketophenol (**1–3**) or phenol (**4–6**). $(M+29)^+$ of cyclic product also evident with **1–3**.

Table 2. 2–Phenyl– and 2–phenoxy–4–alkylidene–1,3,2–benzodioxaphosphorin 2–oxides



Cpds.[a]	R_1	R_2	mp, °C	^{1}H NMR ($CDCl_3$) δ Ha	Hb (or R_1)	J (Hz) Ha–P	Ha–Hb (or Ha–CH)	^{13}C NMR ($CDCl_3$) δ C=C	R_1	^{31}P NMR ($CDCl_3$) δ	CI–MS m/z [b] $(M+1)^+$
7	H	Ph	oil	5.21 (dd)	4.99 (d, 1H)	3.2	2.9	96.1 (7.4)		5.2	259
8	Me	Ph	53–54	5.67 (dq)	1.82 (d, 3H)	2.3	7.0	107.7 (7.4)	10.4	5.9	273
9	Et	Ph	66–67	5.62 (dt)	2.30 (m, 2H) 1.00 (t, 3H)	2.1	7.4	114.9 (7.1)	18.3 13.7	5.9	287
10	H	OPh	oil	5.23 (dd)	4.28 (d, 1H)	5.2	3.2	96.5 (8.2)		−22.9	275
11	Me	OPh	oil	5.66 (dq)	1.76 (d, 3H)	3.8	7.1	108.2 (8.4)	10.2	−21.9	289
12	Et	OPh	oil	5.64 (dt)	2.06 (m, 2H) 1.00 (t, 3H)	3.9	7.4	115.1 (8.7)	18.2 13.5	−22.1	303

a Yields of 48–50% for phosphonates **7–9** and 60–70% for phosphates **10–12**.
b $(M+1)^+$ is always the base peak and $(M+29)^+$ is second in relative intensity (12–45%).

attack at phosphorus. Two equilibrating *E* and *Z* enolates might be envisaged, however, only the *Z*–enolate can lead to **8**, **9** and **11**, **12**. In the *E*–enolate the vinylic alkyl group (R_1) is opposite to aromatic H–5 leading to maximum repulsive interaction between the two groups, while in the *Z*–enolate the Ha– H–5 interaction is minimized. Thus, the observed selectivity can be rationalized on the basis of the *Z*–enolates as the lower energy intermediate.

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六員環状エノールリン化合物の立体選択的合成

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摘　　要

2－Phenyl 及び 2－phenoxy－4－alkylidene－1, 3, 2－benzodioxaphosphorin 2－oxide 類を *o*, *o*－di (2－alkylketophenyl) phenyl phosphonate 類及び *o*－(2－alkylketophenyl) *o*, *o*－diphenyl phosphate 類の加熱によって，それぞれ48－70%の収量で得た。この簡単な閉環反応は立体選択的に*Z*体のみを生じた。これはおそらく閉環の際に，塩基の作用によって生じるエノール基がリン原子を攻撃する時には，ビニールアルキル基とベンゼン環の5位の水素が，同じ平面構造上に存在せねばならないので，最も相互作用が少ない*Z*エノールを形成するからであると思われた。

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