

Novel synthesis of 3-chloromethylidene-2-ethoxy-1,2λ⁵-oxaphospholan-2-ones catalysed by palladium(II)

Chunlin Ma,^{*a} Xiyun Lu^b and Yongxiang Ma^c

^a Department of Chemistry, Liaocheng Teachers College, Liaocheng 252059, PR China

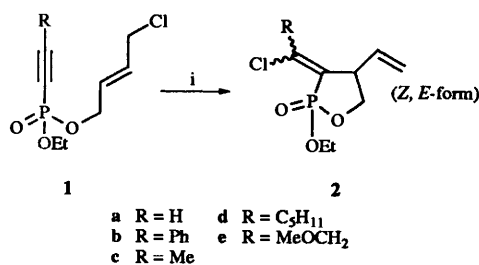
^b Shanghai Institute of Organic Chemistry, Academia Sinica, PR China

^c Department of Chemistry, Lanzhou University, Lanzhou 730000, PR China

2-Ethoxy-3-methylidene-1,2λ⁵-oxaphospholan-2-one rings have been constructed by Pd(OAc)₂-LiCl catalysed cyclization of 4-chlorobut-2-enyl ethyl alkynylphosphonate. A mechanism involving *trans* or *cis* halogenopalladation, followed by intramolecular insertion of a carbon-carbon double bond into a carbon-palladium bond and subsequent dehalogenopalladation, is briefly discussed.

Because of their numerous biological activities,¹ α-methylidene-γ-butyrolactones have been the focus of a number of studies, especially of synthetic ones. Replacement of a carbon by a phosphorus has often resulted in the discovery of new compounds with valuable properties. Preliminary biological results (experimental induction of ACD in guinea pigs and cytotoxicity in hepatoma tissue cultures) have shown that the biological activity of 2-ethoxy-3-methylidene-1,2λ⁵-oxaphospholan-2-ones is very different from that of the corresponding α-methylidene-γ-butyrolactones.²

Among the numerous syntheses of α-methylidene-γ-butyrolactones and the few syntheses of 2-ethoxy-3-methylidene-1,2λ⁵-oxaphospholan-2-ones,³ an attractive method for the construction of α-methylidene-γ-butyrolactone rings by a Pd(OAc)₂-LiX catalysed cyclization reaction of halogenoallylic alk-2-ynoates has recently been reported.⁴ We thought that we could use the same approach for the synthesis of 2-ethoxy-3-methylidene-1,2λ⁵-oxaphospholan-2-ones by replacing the halogenoallylic alk-2-ynoate with 4-chlorobut-2-enyl ethyl alkynylphosphonate. Therefore, we attempted a Pd(OAc)₂-LiCl catalysed cyclization of 4-chlorobut-2-enyl ethyl alkynylphosphonate, which can be easily synthesized from ethyl hydrogen alkynylphosphonate and 1,4-dichlorobut-2-ene. 3-(Chloromethylidene)-2-ethoxy-4-vinyl-1,2λ⁵-oxaphospholan-2-ones **2a-e** were obtained in high yield, Scheme 1, Table 1.



Scheme 1 Reagents and conditions: i, 5% Pd(OAc)₂-6 equiv. LiCl, HOAc, room temp.

This reaction did not proceed well in MeCN, C₆H₆, EtOH, THF and MeNO₂; HOAc was the most suitable solvent. Several palladium complexes such as PdCl₂, Pd(PhCN)₂Cl₂ and Pd(OAc)₂ can catalyse the cyclization, but palladium dichloride catalysed the reaction slowly, probably due to its low solubility in acetic acid.

The ratios of *Z*:*E* isomers (Table 1) shows that the cyclization occurs with low stereoselectivity. This is probably because coordination of palladium with the carbon-carbon multiple

Table 1 Cyclization of 4-chlorobut-2-enyl ethyl alkynylphosphonates **1a-e** catalysed by Pd(OAc)₂-LiCl in acetic acid^a

Entry	Substrate	<i>t</i> /h	Product	Yield of 2 (%) ^b
1	1a	24	2a	89 (50:50)
2	1b	26	2b	78 (60:40)
3	1c	27	2c	77 (62:38)
4	1d	24	2d	82 (54:47)
5	1e	24	2e	80 (63:37)

^a All products gave satisfactory IR, mass, ¹H NMR and ³¹P NMR spectroscopic data and elemental analyses. ^b The numbers in parentheses are ratios of *Z* to *E* isomers of the *exo* double bonds, the configurations of which were assigned on the basis of the ¹H NMR and ³¹P NMR resonance.^{4,5}

bonds in substrate **1** did not form a palladium-ene complex before chloropalladation of the triple bond had occurred, whereas this coordination had occurred in cyclization of 4-halogenobut-2-enyl alk-2-ynoates.⁴ A possible mechanism is shown in Scheme 2.

The present reaction could occur through a mechanism similar to that for the cyclization of 4-halogenobut-2-enyl alk-2-ynoate,⁴ *via cis*- and *trans*-halogenopalladation of the triple bond,⁶ followed by insertion of the double bond in phosphonate **1** into the newly formed carbon-palladium bond to form intermediates **5** and **6**, and finally dehalopalladation to form a new double bond and regenerate the Pd(OAc)₂ catalyst.

Experimental

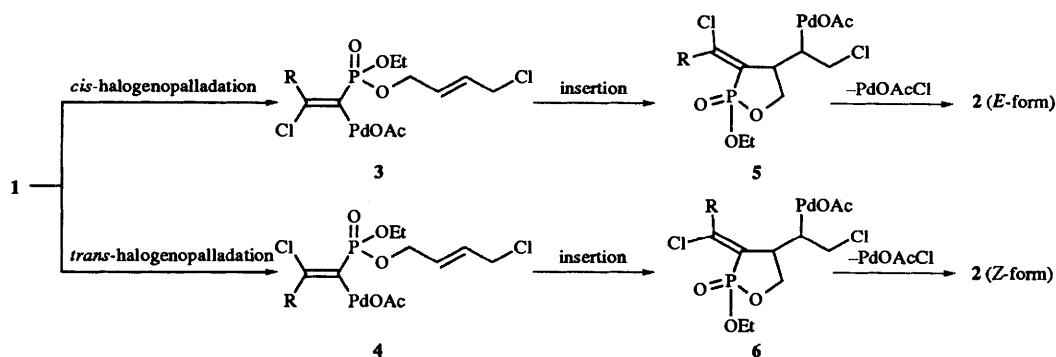
Typical procedures for the preparation of compounds **2**.

Compound **2a**

To a solution of **1a** (113 mg, 0.50 mmol) in HOAc (2.5 cm³) was added palladium(II) acetate (6 mg, 0.025 mmol) and lithium chloride (128 mg, 3 mmol) with stirring. The reaction mixture was stirred at room temperature for 24 h and the reaction was monitored by TLC. Diethyl ether (30 cm³) was then added and the mixture was washed with water (3 × 5 cm³), saturated aqueous NaHCO₃ (3 × 5 cm³) and saturated aqueous NaCl (5 cm³) and then dried (MgSO₄). Preparative TLC on silica gel (eluent: light petroleum-ethyl acetate, 5:1) afforded the product **2a** in pure form.

Compounds **2b-e** were prepared similarly.

3-(Chloromethylidene)-2-ethoxy-4-vinyl-1,2λ⁵-oxaphospholan-2-one 2a. ν_{max} (neat)/cm⁻¹ 3000, 1620, 1270, 1000, 930, 840 and 740; δ_{H} (200 MHz; CDCl₃) 6.52 (*Z* isomer, 1 H, dd,



Scheme 2

J 3, 36), 6.49 (*E* isomer, 1 H, dd, J 3, 35.5), 5.5 (1 H, m), 5.20 (2 H, m), 4.23 (2 H, m), 3.9 (1 H, dt, J 5, 8), 3.7 (2 H, m) and 1.3 (3 H, d, J 8); δ_{P} (90 MHz; CDCl_3) 25.26 (*Z* isomer) and 25.41 (*E* isomer); m/z (EI) 225 (35%, $\text{MCl}^{37} + 1$), 223 (100, $\text{MCl}^{35} + 1$), 195 (38), 159 (23) and 113 (16) [Found (CI): 222.020. Calc. for $\text{C}_8\text{H}_{12}^{35}\text{ClO}_3\text{P}$: 222.021].

3-[Chloro(phenyl)methylidene]-2-ethoxy-4-vinyl-1,2 λ^5 -oxaphospholan-2-one 2b. ν_{max} (neat)/ cm^{-1} 3000, 1640, 1270, 970, 840 and 760; δ_{H} (200 MHz; CDCl_3) 7.75 (*Z* isomer, 2 H, m), 7.65 (*E* isomer, 2 H, m), 7.45 (3 H, m), 6.0 (1 H, m), 5.40 (2 H, m), 4.20 (2 H, m), 4.0 (2 H, m), 3.8 (1 H, m) and 1.2 (3 H, t, J 7.5); δ_{P} (90 MHz; CDCl_3) 26.82 (*Z* isomer) and 27.68 (*E* isomer); m/z (CI) 301 (35%, $\text{MCl}^{37} + 1$), 299 (100, $\text{MCl}^{35} + 1$), 263 (26), 155 (33), 128 (10), 115 (35) and 77 (16) [Found (CI): 298.050. Calc. for $\text{C}_{14}\text{H}_{16}^{35}\text{ClO}_3\text{P}$: 298.052].

3-(1-Chloroethylidene)-2-ethoxy-4-vinyl-1,2 λ^5 -oxaphospholan-2-one 2c. ν_{max} (neat)/ cm^{-1} 3000, 1650, 1260, 960, 840 and 760; δ_{H} (200 MHz; CDCl_3) 5.9 (1 H, m), 5.2 (2 H, m), 4.3 (4 H, m), 3.75 (1 H, m), 2.24 (3 H, s) and 1.2 (3 H, t, 7); δ_{P} (90 MHz; CDCl_3) 25.51 (*Z* isomer), 25.92 (*E* isomer); m/z (EI) 239 (36%, $\text{MCl}^{37} + 1$), 237 (100, $\text{MCl}^{35} + 1$), 209 (22), 155 (13) and 78 (14) [Found (CI): 236.035. Calc. for $\text{C}_9\text{H}_{14}^{35}\text{ClO}_3\text{P}$: 236.037].

3-(1-Chlorohexylidene)-2-ethoxy-4-vinyl-1,2 λ^5 -oxaphospholan-2-one 2d. ν_{max} (neat)/ cm^{-1} 3000, 1650, 1270, 980, 840 and 720; δ_{H} (200 MHz; CDCl_3) 5.8 (1 H, m), 5.20 (2 H, m), 4.20 (2 H, m), 3.9 (2 H, m), 3.6 (1 H, m), 2.4 (2 H, m), 1.45 (2 H, m), 1.3 (7 H, m) and 0.9 (3 H, t, J 7); δ_{P} (90 MHz; CDCl_3) 26.82 (*Z* isomer) and 27.48 (*E* isomer); m/z (EI) 295 (35%, $\text{MCl}^{37} + 1$), 293 (100, MCl^{35}), 265 (15), 147 (10) and 42 (12) [Found (CI): 292.097. Calc. for $\text{C}_{13}\text{H}_{22}^{35}\text{ClO}_3\text{P}$: 292.099].

3-(1-Chloro-2-methoxyethylidene)-2-ethoxy-4-vinyl-1,2 λ^5 -oxaphospholan-2-one 2e. ν_{max} (neat)/ cm^{-1} 3000, 1650, 1270, 1040,

960, 840 and 740; δ_{H} (200 MHz; CDCl_3) 5.9 (1 H, m), 5.2 (2 H, m), 4.3 (2 H, m), 4.1 (4 H, m), 3.8 (1 H, m), 3.3 (3 H, s) and 1.3 (3 H, t, J 7); δ_{P} (90 MHz; CDCl_3) 26.21 (*Z* isomer) and 26.84 (*E* isomer); m/z (EI) 269 (34%, $\text{MCl}^{37} + 1$), 267 (100, $\text{MCl}^{35} + 1$), 239 (40), 207 (35), 171 (40) and 153 (20) [Found (CI): 266.045. Calc. for $\text{C}_{10}\text{H}_{16}^{35}\text{ClO}_4\text{P}$: 266.047].

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