Synthesis of 4-Oxo-2-alkenylphosphonates via Nitrile Oxide Cycloaddition: γ-Acylation of Allylic Phosphonates

Shi Yong Lee, Bum Sung Lee, Chi-Wan Lee, and Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1, Kusong-dong, Yusong-gu, Taejon, 305-701, Korea

Received August 9, 1999

A long polyethylenic chain is frequently exhibited in the structure of natural compounds such as retinoids and carotenoids.[1] Accordingly, considerable interest has been devoted to the construction of long conjugated chains, and many of the attempted methods have employed functionalized phosphonates under Wadsworth−Emmons olefination conditions. γ-Phosphonocrotonates[2] and protected phosphonoaldehydes[3] have been mainly used as building blocks, whereas the preparations and the applications of 4-oxo-2-alkenylphosphonates are less known.[4] A few literature references for 4-oxo-2-alkenylphosphonates furnish synthetic approaches to them that involve Wittig reaction of 2-oxoalkylphosphonium ylides with α-phosphonoaldehydes[5] and the oxidation of the corresponding alcohols within the limits of aromatic derivatives.[6] We herein present the synthesis of 4-oxo-2-alkenylphosphonates from allylic phosphonates using 2-isoxazolines as intermediates. Nitrile oxide cycloaddition chemistry has been well developed as a tool for the introduction of various functionalities,[7] but no one has used it yet to prepare 4-oxo-2-alkenylphosphonates.

Nitrile oxides, generated via a Mukaiyama procedure,[8] were cycloadded to allylic phosphonates (**1**) that were available from an Arbuzov reaction[9] and α-alkylation[10] of the resultant allylphosphonate (Scheme 1). A cycloaddition reaction under the condition of anhydrous THF, room temperature, and 15 h afforded the phosphonate-containing 2-isoxazolines (**2**) in good yields (Table 1). As expected for the terminal olefins as dipolarophiles,[7,11] the substituents bearing the phosphonate moiety occupied the 5-position of the 2-isoxazoline rings uniformly, and no regio-inverted products were observed. When internal olefins such as crotyl- and 2-cyclohexenylphosphonate were employed, regio-confused mixtures whose two components are not separable from each other were obtained in poor yields.

Scheme 1

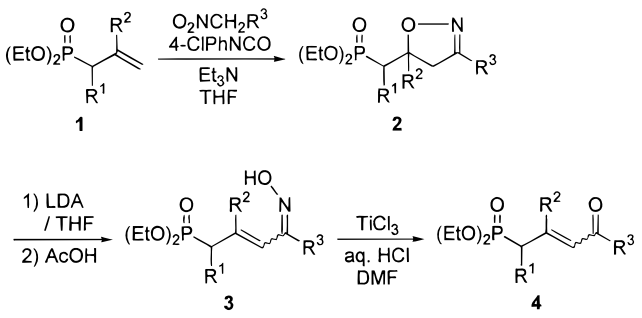
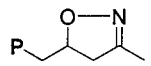
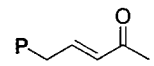
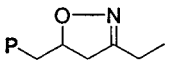
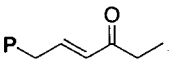
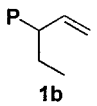
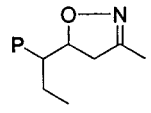
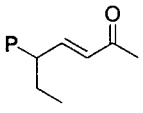
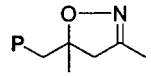
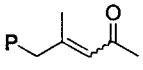
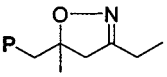
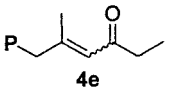


Table 1. Cycloaddition of Nitrile Oxides to Allylic Phosphonates and Eliminative Ring Opening of Phosphonoalkyl-2-isoxazolines

starting material **1**[a]	intermediate **2**[a]	yield (%)[b]	product **4**[a]	yield (%)[b]
 **1a**	 **2a**	88	 **4a**	64
1a	 **2b**	83	 **4b**	78
 **1b**	 **2c**	80	 **4c**	75
 **1c**	 **2d**	67	 **4d**	73[c]
1c	 **2e**	71	 **4e**	76[c]

[a] **P** = P(O)(OEt)$_2$. [b] Yield of isolated product. [c] Purified product was a 1:1.7 mixture of *E* and *Z* isomers.

The phosphonoalkyl-2-isoxazolines **2** underwent eliminative ring fission on treatment with LDA in anyhdrous THF at −78 °C followed by addition of AcOH to give γ-phosphono-α,β-unsaturated oximes (**3**) (Scheme 1).[12] After general workup without additional purification, the oximes **3** were treated with an aqueous HCl solution of titanium(III) chloride in DMF, and the mixture was stirred for about 7 h at room temperature to afford the hydrolyzed 4-oxo-2-alkenylphosphonates (**4**).

* Phone: 82-42-869-2819. Fax: 82-42-869-2810. E-mail: dyoh@sorak.kaist.ac.kr.

(1) For reviews, see: (a) Liu, R. S. H.; Asato, A. E. *Tetrahedron* **1984**, *40*, 1931. (b) Sporn, M. B.; Roberts, A. B.; Goodman D. S. *The retinoids: Biology, Chemistry and Medicine*, 2nd ed.; Raven Press: New York, 1994; pp 319−387.

(2) (a) Van den Tempel, P. J.; Huisman, H. O. *Tetrahedron* **1966**, *22*, 293. (b) Gedye, R. N.; Westaway, K. C.; Arora, P.; Bisson, R.; Khalil, A. H. *Can. J. Chem.* **1977**, *55*, 1218. (c) Liu, R. S. H.; Asato, A. E. *Methods Enzymol.* **1982**, *88*, 506.

(3) Duhamel, L.; Guillemont, J.; Le Gallic, Y.; Ple, G.; Poirier, J.-M.; Ramondenc, Y.; Chabardes, P. *Tetrahedron Lett.* **1990**, *31*, 3129.

(4) Font, J.; De March, P. *Tetrahedron* **1981**, *37*, 2391.

(5) (a) Ohler, E.; Kang, H.-S.; Zbiral, E. *Chem. Ber.* **1988**, *121*, 299. (b) Ohler, E.; Kang, H.-S.; Zbiral, E. *Synthesis* **1988**, 623.

(6) Muller, E. L.; Modro, A. M.; Modro, T. A. *Org. Prep. Proced. Int.* **1999**, *31*, 216.

(7) For reviews, see: Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988.

(8) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(9) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.

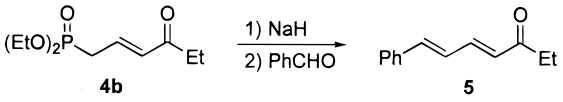
(10) (a) Yuan, C.; Zhang, R.; Yao, J. *Chem. Abstr.* **1987**, *107*, 39948t. (b) Phillips, A. M. M. M.; Modro, T. A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *55*, 41.

(11) Caramella, P.; Grunanger, P. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 291−392.

(12) Jager, V.; Grund, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 50.

10.1021/jo991261y CCC: $19.00
Published on Web 12/15/1999

Scheme 2



4b **5**

The results are summarized in Table 1. The products bearing no substituent at the 2-position (**4a**−**c**) were typically in only *E* configuration, whereas for **4d** and **4e** the (*Z*)-olefins were obtained as the major products along with the (*E*)-olefins in the ratio of 1.7:1.[13] These results are attributed to a steric interaction of the 2-methyl group, which is from the starting allylic phosphonate **1c**.

Comparing starting materials with products, the overall procedure represents the regioselective acylation of allylic phosphonates at the γ-position. In general, lithiated derivatives of allylic phosphonates show both α- and γ-orientation or exclusive α-orientation in their nucleophilic reactions toward acyl chlorides, esters, or other appropriate carbonyl electrophiles.[14] For the exclusive γ-carbonylation of allylic phosphonates, Collignon and coworkers recently tried the transient introduction of a bulky trimethylsilyl group at the α-position for blocking.[15]

For the purpose of practical application of our products **4** as building blocks for synthesis of polyethylene-structured natural compounds such as retinoids, their olefinating ability under Wadsworth−Emmons conditions must be examined. Actually, our attempt to olefinate an aldehyde directly with **4** proved to be successful. As shown in Scheme 2, the reaction of benzaldehyde with the sodium anion of diethyl 4-oxo-2-hexenylphosphonate (**4b**) gave the corresponding dienone **5** with the *E* configuration in a good yield of 86%. There is a literature example that 4-oxo-2-alkenylphosphonate was applied to the synthesis of retinoids as an important building block. Font et al. prepared the ethylene ketal of dimethyl 4-oxo-2-pentenylphosphonate by Arbuzov reaction of trimethyl phosphite with the ethylene ketal of 5-bromo-3-penten-2-one, which was rather difficult to obtain.[16] Condensation of this phosphonate with β-ionone using NaH as a base yielded β-C_{18}-tetraenone, which is an important precursor to retinol derivatives,[1] after acidic hydrolysis.

In conclusion, we have provided a novel synthetic route to 4-oxo-2-alkenylphosphonates, which can serve as useful building blocks for synthesis of natural products containing a polyethylenic chain by four-carbon chain elongation. The synthetic procedure to 4-oxo-2-alkenylphosphonates from allylic phosphonates via 2-isoxazolines, generated through cycloaddition of nitrile oxides, presents a new method for regioselective γ-acylation of allylic phosphonates.

Experimental Section

General. All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. THF was dried over and distilled from sodium metal with benzophenone as the indicator. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using either TMS, residual $CHCl_3$, or solvent as an internal standard. The starting materials were synthesized as described in the literature with minor modification.

General Procedure for the Cycloaddition of Nitrile Oxides to Allylic Phosphonates. To a stirred solution of allylic phosphonate **1** (2.0 mmol), nitroalkane (2.4 mmol), and 4-chlorophenyl isocyanate (0.627 g, 4.0 mmol) in anhydrous THF (6 mL) under N_2 at room temperature was added 10 drops of triethylamine. After being stirred for 15 h, the mixture was diluted with diethyl ether, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (EtOAc/acetone, 80/20) to give phosphonoalkyl-2-isoxazoline **2** as a colorless oil.

5-Diethylphosphonomethyl-3-methyl-2-isoxazoline (2a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 5.0 Hz, 6H), 1.91−2.05 (m, 1H), 1.94 (s, 3H), 2.17−2.30 (m, 1H), 2.79−2.87 (m, 1H), 2.99−3.09 (m, 1H), 4.00−4.11 (m, 4H), 4.72−4.82 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 16.3 (d, J = 6.1 Hz), 31.7 (d, J = 136.7 Hz), 44.3 (d, J = 4.1 Hz), 61.8 (d, J = 6.5 Hz), 75.0, 155.6; MS *m*/*z* (relative intensity) 236 ($M^+ + H^+$, 0.84), 235 (M^+, 0.46), 125 (100).

General Procedure for the Synthesis of 4-Oxo-2-alkenylphosphonates (4) from Phosphonoalkyl-2-isoxazolines (2). To a stirred solution of phosphonoalkyl-2-isoxazoline **2** (1.0 mmol) in anhydrous THF (6 mL) under N_2 at −78 °C was added LDA (0.50 mL of a 2.0 M solution in heptane/THF/ethylbenzene, 1.0 mmol) dropwise by syringe, and the mixture was stirred for 1 h. The cooling bath was removed, and the mixture was allowed to reach room temperature. After 30 min, glacial acetic acid (0.12 mL, 2.0 mmol) and brine solution (2 mL) were added in turn, and then the mixture was extracted with dichloromethane. The combined organic extracts were washed once with water and filtered through a short column packed with $MgSO_4$. Removal of the solvent left a crude oil, which then was dissolved in DMF (4 mL), treated with titanium(III) chloride (6.2 mL of an 8.6% solution in 28% hydrochloric acid), and stirred for ca. 7 h at room temperature. After addition of water (10 mL) the reaction mixture was extracted with diethyl ether. The combined extracts were washed with water and saturated $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo. The residue was subjected to silica gel chromatography (EtOAc/EtOH, 95/5) to give **4** as a colorless oil.

Diethyl (*E*)-4-oxo-2-pentenylphosphonate (4a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 6H), 2.18 (s, 3H), 2.68 (ddd, J = 23.1, 7.9, 1.0 Hz, 2H), 3.98−4.09 (m, 4H), 6.10 (dd, J = 16.0, 4.7 Hz, 1H), 6.57−6.70 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.2 (d, J = 5.9 Hz), 26.8, 30.7 (d, J = 137.6 Hz), 62.2 (d, J = 6.7 Hz), 134.9 (d, J = 13.1 Hz), 136.4 (d, J = 11.1 Hz), 197.4 (d, J = 2.9 Hz); HRMS *m*/*z* (M^+) calcd for $C_9H_{17}O_4P$ 220.0864, found 220.0873.

7-Phenyl-4,6-heptadien-3-one (5). To a suspension of sodium hydride (0.020 g, 60%, 0.50 mmol) in anhydrous THF (2 mL) at room temperature was added diethyl 4-oxo-2-hexenylphosphonate (**4b**; 0.110 g, 0.47 mmol) in anhydrous THF (3 mL) slowly. The mixture was stirred until hydrogen evolution had ceased and the solution was homogeneous (ca. 1 h), and then benzaldehyde (0.057 mL, 0.56 mmol) was added. After the mixture stirred for ca. 1 h, the reaction was quenched with an aqueous NH_4Cl solution, and the resulting solution was extracted with dichloromethane. The organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the crude product. Purification by flash silica gel chromatography (EtOAc/hexane, 10/90) furnished the dienone **5** as a colorless oil (0.075 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, J = 7.4 Hz, 3H), 2.61 (q, J = 7.4 Hz, 2H), 6.27 (d, J = 15.4 Hz, 1H), 6.81−6.94 (several peaks, 2H), 7.27−7.37 (several peaks m, 4H), 7.44−7.47 (several peaks, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3, 33.9, 126.7, 127.2, 128.8, 129.1, 129.4, 136.1, 141.0, 142.2, 201.0.

Acknowledgment. This research was supported by a grant from the Korea Advanced Institute of Science and Technology.

Supporting Information Available: Spectral data of compounds **2**, **4**, and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO991261Y

(13) The configurations and the ratios of (*E*)- and (*Z*)-olefins were determined by NOE experiment and ^{1}H NMR analysis.

(14) (a) Yuan, C.; Chaozhong, L. *Heteroat. Chem.* **1992**, *3*, 637. (b) Gerber, K. P.; Modro, T. A.; Muller, E. L.; Phillips, A. M. M. M. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *75*, 19. (c) Al-Badri, H.; About-Jaudet, E.; Combret, J.-C.; Collignon, N. *Synthesis* **1995**, 1401.

(15) Al-Badri, H.; About-Jaudet, E.; Collignon, N. *Tetrahedron Lett.* **1995**, *36*, 393.

(16) Camps, J.; Font, J.; De March, P. *Tetrahedron* **1981**, *37*, 2493.