Tetrahedron Letters 50 (2009) 6076–6078

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# One-pot synthesis of γ-hydroxy-γ-oxaphosphonates using pentacovalent oxaphosphorane chemistry

Jae-Min Hwang [a], Tasneem Islam [b,*], Kang-Yeoun Jung [a,*]

[a] Department of Environmental & Applied Chemistry, College of Engineering, Kangnung-Wonju National University, Gangneung 210-702, Republic of Korea
[b] Department of Biological, Chemical and Physical Sciences, Roosevelt University, IL 60173, USA

ARTICLE INFO

*Article history:*
Received 25 July 2009
Revised 19 August 2009
Accepted 20 August 2009
Available online 23 August 2009

*Keywords:*
Phosphonates
Oxaphospholene
Enolate
Aldol product

ABSTRACT

P(V)-2,2,2-triethoxy-2,2-dihydro-5-methoxy-1,2λ$^5$-oxaphospholene was synthesized as a new type of enolate which was hydrolyzed to give a series of phosphonates. In addition, aldol reaction of the oxaphospholene intermediate with several aldehydes as electrophiles under mild and neutral conditions produced phosphonate-containing aldol compounds through a two-step one-pot reaction.



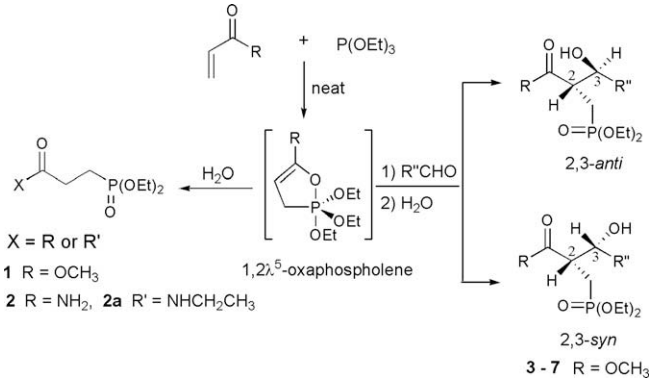
Phosphonate analogues have been extensively studied in recent years due to their applications as antibiotics and anti-viral agents as well as insecticides and herbicides.[1,2] They show much greater stability to hydrolysis and resistance to proteases than phosphates and have been used as isosteric mimics of carboxylic acids or phosphate esters. Thus, new or improved methods for phosphonate synthesis continue to attract much attention.

In our attempt to develop new methodology for the synthesis of biologically active phosphonate derivatives, we have previously reported the synthesis of carbon analogues of Ramirez's 1,3,2λ$^5$-dioxaphospholenes.[3] These oxaphospholenes were prepared from trialkylphosphite and methyl vinyl ketone and were reacted with a series of aldehydes to make phosphonate-containing aldol compounds under mild conditions. We subsequently applied this methodology to efficiently synthesize antifungal agent, (±)-*trans* and *cis*-neocnidilides.[4]

Despite our success in the development of a new methodology for the synthesis of phosphonate-containing aldol compounds and its application toward the synthesis of antifungal agent, this strategy has a major limitation. It did not allow us to manipulate the keto functional group and further extend the C–C bond. Thus, transformation of the keto group on the final aldol compounds into the corresponding carbonyl derivatives proved to be challenging to make highly functionalized phosphonate derivatives.

Herein we report our success in overcoming this aforementioned problem by synthesizing pentacovalent 2,2,2-trialkoxy-2,2-dihydro-5-methoxy-1,2λ$^5$-oxaphospholenes. Reaction of these oxaphospholenes with various aldehydes resulted in an ester group in the final aldol compounds which can be easily functionalized and more importantly allow extension of C–C bond.

Trimethyl and triethyl phosphites were reacted with methyl acrylate to give the corresponding pentacovalent 2,2,2-trimethoxy or triethoxy-2,2-dihydro-5-methoxy-1,2λ$^5$-oxaphospholenes as a new type of enolate (Scheme 1). However, both oxaphospholene intermediates started to decompose when exposed to air. Triethyl phosphite adduct proved to be more stable and resulted in higher




**Scheme 1.**

* Corresponding authors. Tel.: +82 33 640 2403; fax: +82 33 641 2410 (K.-Y.J.).
*E-mail addresses:* tislam@roosevelt.edu (T. Islam), kyjung@kangnung.ac.kr (K.-Y. Jung).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.08.059

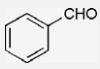
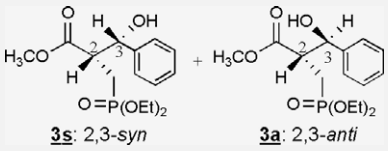
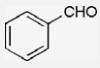
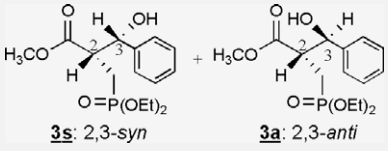
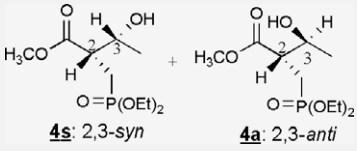
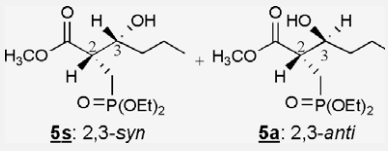
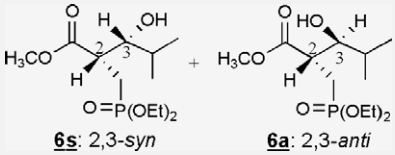
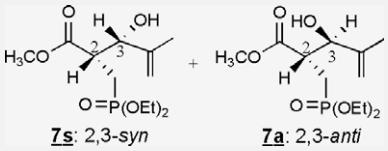
yield compared to the outcome of trimethyl phosphite reaction. Because of the instability, only the triethoxyoxaphospholene intermediate was prepared and used for further reaction without purification.[5]

A new P(V)-2,2,2-triethoxy-1,2λ$^5$-oxaphospholene was obtained from the reaction of freshly distilled triethyl phosphite with methyl acrylate at room temperature which was hydrolyzed immediately with water to give β-methylesterphosphonate **1**, in 82% yield. Triethylphosphite was also treated with acrylamide at room temperature, however, no reaction was observed. Carrying out the reaction at room temperature and slowly increasing to 80 °C gave the corresponding P(V)-1,2λ$^5$-oxaphospholene which after hydrolysis yielded a mixture of two products, amidophosphonate **2** and N-alkylated amidophosphonate **2a**, respectively. These mixtures were separated by column chromatography and the ratio was determined to be **2:2a** = 1:5 (yield 83%). We, then, attempted to control the ratio of products by changing the reaction conditions such as amount of phosphite and reaction temperature. Varying the amount of trialkylphosphites did not affect the ratio of the products. However, when we carried out the reaction at 80 °C, we observed that unalkylated product **2** was obtained as the major product, **2:2a** = 9:1.[5] The unalkylated product **2** can then be further modified to give the N-substituted phosphonates.[6]

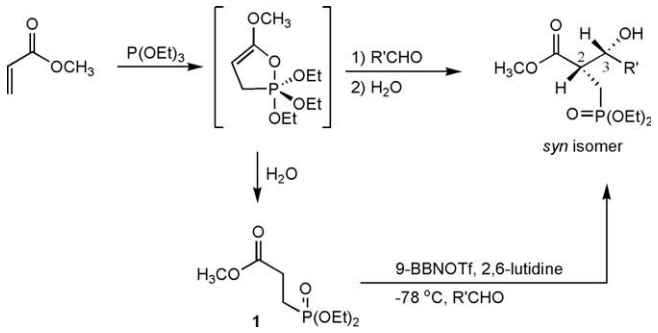
The P(V)-2,2,2-triethoxy-2,2-dihydro-5-methoxy-1,2λ$^5$-oxaphospholene intermediate synthesized was also reacted with a series of aldehydes to afford compounds **3**–**7**[7] in a two-step one-pot approach.

Our initial condensation reaction with benzaldehyde was performed neat at ambient temperature and afforded only 60% of **3s** and **3a** along with hydrolyzed product **1**, after 3 days (Table 1, entry 1). Improved result was obtained when the reaction was conducted in $CH_2Cl_2$ and refluxed at 40 °C (entry 2). However, in all other cases, optimal yields were achieved when the condensation reaction was carried out neat at 0 °C (only for entry 3) and at room temperature (entries 4–6). Condensation reaction of P(V)-2,2,2-triethoxy-2,2-dihydro-5-methoxy-1,2λ$^5$-oxaphospholene intermediate with aldehydes at various temperatures resulted in approximately 1:1 ratio of *syn* and *anti* isomers, which varied from the previously published results (approximately *syn*:*anti* = 1.3–4.9:1).[3] Previous report where triethylphosphite was reacted with methyl vinyl ketone demonstrated that the steric bulk of the ligands on the phosphorus and/or around the aldehydes influences

**Table 1**
Ratio of isomers and yields of the phosphonate-containing aldol products

| Entry | Aldehydes (R′CHO) | Solvent | Temperature | Reaction time | Phosphonate products | Yield[a] (%) | Ratio[b] (*syn*:*anti*) |
|---|---|---|---|---|---|---|---|
| 1 |  | Neat | rt | 3 days |  **3s**: 2,3-*syn* **3a**: 2,3-*anti* | 60 | 1:1.1 |
| 2 |  | $CH_2Cl_2$ | rt → 40 °C | 24–26 h |  **3s**: 2,3-*syn* **3a**: 2,3-*anti* | 81 | 1:1.2 |
| 3 | $CH_3CHO$ | Neat | 0 °C | 32–36 h |  **4s**: 2,3-*syn* **4a**: 2,3-*anti* | 75 | 1:1.1 |
| 4 |  | Neat | rt | 24–26 h |  **5s**: 2,3-*syn* **5a**: 2,3-*anti* | 77 | 1:1.1 |
| 5 |  | Neat | rt | 24–26 h |  **6s**: 2,3-*syn* **6a**: 2,3-*anti* | 77 | 1:1.1 |
| 6 |  | Neat | rt | 24–26 h |  **7s**: 2,3-*syn* **7a**: 2,3-*anti* | 78 | 1:1.1 |

[a] Isolated yields after HPLC purification.
[b] *Syn*:*anti* ratio determined by HPLC and confirmed by $^1$H NMR spectroscopy.




**Scheme 2.**

the stereoselectivity; condensation between the bulkiest oxaphospholene and benzaldehyde gave the best *syn* diastereoselectivity (*syn*:*anti* = 4.9:1). In contrast, we found that increasing the bulkiness had a very little effect on the stereochemistry of our aldol products.

We presumed that the observed ratio of *syn* and *anti* isomers is associated with the methoxy substituent at C-5 on the 1,2$\lambda^5$-oxaphospholene and with the oxygen anion in the possible enolate intermediate after cleavage of apical P–O bond in the oxaphospholene. Our postulated mechanism is that the methoxy group at C-5 in the oxaphospholene ring allows equilibrium between *E*/*Z* enolates which results in almost similar ratio of *syn* and *anti* isomers. Additional experiments are in progress to examine the influence of other phosphites and enones on the stereochemical outcome of the phosphonate-containing aldol products. In addition, microwave-assisted condensation reaction of 1,2$\lambda^5$-oxaphospholene intermediate and benzaldehyde appears to reduce the reaction time dramatically. This reaction was carried out neat and the phosphonate product could be obtained in 30 min at 120 °C (employing an average microwave power of 200 W). We are currently improving the reaction conditions and will report the results with other outcome soon.

Relative stereochemistry of the aldol products **3–7** were determined by comparison of their spectral data with the corresponding product independently prepared by the use of Mukaiyama's enolate of compound **1** (Scheme 2).[3,8] The phosphonate-containing aldol compounds, **3s**–**5s** (*syn* isomers), were independently synthesized via the reaction of the 9-BBN boron enolate of **1** with the aldehydes in question (yield 60–70%). This Mukaiyama enolate procedure is known to produce *syn* aldol stereochemistry and was utilized to compare with our *syn* product obtained from the condensation reaction. The NMR data ($^1$H, $^{13}$C, and $^{31}$P) as well as IR and MS were identical with the corresponding spectra for the *syn* isomer.

In conclusion, we have been able to synthesize P(V)-2,2,2-trialkoxy-2,2-dihydro-5-methoxy-1,2$\lambda^5$-oxaphospholenes as a new type of enolate, and have shown its application through the synthesis of variously substituted phosphonates.

Hydrolysis of the oxaphospholene intermediate gave access to a number of esterphosphonate and amidophosphonate derivatives. We have also accomplished aldol reaction of the oxaphospholene intermediate with several aldehydes as electrophiles under mild and neutral conditions to produce γ-hydroxy-γ-methoxy-γ-oxaphosphonates. These phosphonates, because of the ester moiety, can be easily converted into various functional groups and in addition, this intermediate can be used for the chain elongation in the synthesis of diverse bioactive compounds.

## Acknowledgments

We thank the Regional Technology Innovation Program of the Ministry of Knowledge Economy (MKE), Korea, for financial support (Grant No. RTI05-01-02). This work was also supported by the start-up fund provided by Roosevelt University.

## Supplementary data

Supplementary data (representative experimental details for the synthesis and the characterization data for key intermediates are provided.) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.059.

## References and notes

1. (a) Sikorski, J. A.; Logusch, E. W. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; pp 739–805; (b) Eto, M. In *Handbook of Organophosphorus Chemistry*; Engel, R., Ed.; Marcel Dekker: New York, 1992; pp 807–873.
2. (a) Kalir, A.; Kalir, H. H.. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley and Sons: New York, 1996; Vol. 4, pp 767–780; (b) Engel, R. *Chem. Rev.* **1977**, *77*, 349–367; (c) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237–12273; (d) Knowles, J. R.; Orr, G. A. *Biochem. J.* **1974**, *141*, 721–723; (e) Kim, C. U.; Misco, P. F.; Luh, B. Y.; Hitchcock, M. J. M.; Ghazzouli, I.; Martin, J. C. *J. Med. Chem.* **1991**, *34*, 2286–2294; (f) Varki, A. *Glycobiology* **1993**, *3*, 97–130.
3. McClure, C. K.; Jung, K. Y. *J. Org. Chem.* **1991**, *56*, 2326–2332.
4. McClure, C. K.; Jung, K. Y.; Grote, C. W.; Hansen, K. *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, *75*, 23–26.
5. Hwang, J. M.; Kwon, H. B.; Lee, S. B.; Jung, K. Y. *Bull. Korean Chem. Soc.* **2009**, *30*, 239–241.
6. (a) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899–931; (b) Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P. *Tetrahedron Lett.* **1995**, *36*, 2483–2486; (c) Zamova, A. M.; Molodykh, Zh. V.; Kudryavtseva, L. A.; Teplyakova, L. V.; Fedorov, S. B.; Ivanov, B. E. *Pharm. Chem. J.* **1986**, *20*, 774–777.
7. General procedure for the preparation of condensation products **(3–7)**. A mixture of distilled enone (1 equiv) and triethylphosphite (1 equiv) was stirred for 3–4 days at room temperature. Unreacted triethylphosphite was removed under vacuum at 55 °C (12 mmHg). To the 2,2,2-triethoxy-5-methoxy-1,2$\gamma^5$-oxaphospholene (1.0 mmol), in a flame-dried flask under argon, was added freshly distilled aldehyde (1.2–1.6 mmol) and stirred at ambient temperature (0 °C for the reactions with acetaldehyde) and monitored by $^1$H NMR spectroscopy. For the condensations with benzaldehyde, the oxaphospholene was diluted with $CH_2Cl_2$ prior to addition of aldehyde. The reaction mixture was then heated to 40 °C and monitored as mentioned above by taking aliquots from each reaction. After disappearance of the 2,2,2-triethoxy-1,2$\gamma^5$-oxaphospholene, distilled water (10.0 mL) was added to the reaction mixture. The mixture was allowed to stir for 8–10 h, and the crude product was extracted with $CH_2Cl_2$. The combined organic extracts were washed with distilled water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. After initial purification of the crude product with flash column chromatography to remove most of unwanted material, all of the combined mixture of diastereomers was separated with HPLC using $CH_2Cl_2$.
8. Mukaiyama, T.; Inoue, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174–178.