Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

A New and Facile Synthetic Route to 1-Alkyl-2-Oxopropylphosphonates : 1-Alkylation with Subsequent Ozonolysis of 2-Methyl Allylic Phosphonates

Jun MoGil , Kwang YoungPark , Jung HwanHah & Dong YoungOh

SYNTHETIC COMMUNICATIONS, 28(19), 3601-3607 (1998)

A NEW AND FACILE SYNTHETIC ROUTE TO 1-ALKYL-2-OXOPROPYLPHOSPHONATES : 1-ALKYLATION WITH SUBSEQUENT OZONOLYSIS OF 2-METHYL ALLYLIC PHOSPHONATES

Jun Mo Gil, Kwang Young Park, Jung Hwan Hah and Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science and Technology, 373-1, Kusung-Dong, Yusung-Gu, Taejon, 305-701, Korea

Abstract: Alkylation of the 2-methyl allylic phosphonates is performed by treatment with *n*-BuLi, followed by addition of alkyl halides. The 1-alkyl-2-oxopropylphosphonates are obtained by the ozonolysis of the corresponding allylic phosphonates.

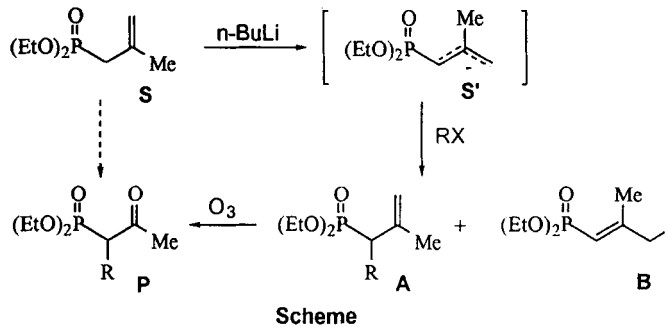
It is well known and established that 2-oxoalkylphosphonates[1] have long been of interest to the chemists. Their application in the formation of carbon-carbon double bond is especially interesting, since they display unique properties. For example, these reagents can be used to control regio- and stereoselectivity for olefin synthesis in homologation of aldehydes and ketones to α,β-unsaturated carbonyl compounds *via* the Wadsworth-Horner-Emmons condensation.[2]

Aside from the significant progress that expanded the Wadsworth-Horner-Emmons reaction, synthetic routes to 2-oxoalkylphosphonates are limited in terms of hard rigorous conditions and low yields due to the competetive reactions.[3] In the continuation of our work on the development of convenient synthetic routes to 2-

* To whom correspondence should be addressed

oxoalkylphosphonates, we have reported several such routes by the reactions of α-carbanionic alkylphosphonates with carboxylic acid chlorides[4] or nitrile compounds[5] and by the reactions of epoxysulphones or nitroalkenes with dialkyl hydrogen phosphite.[6] More recently, we have focused on the dephosphonylation of 1-alkyl-2-oxoalkylphosphonates as a new synthetic route to regioselectively alkylated ketones.[7] In the course of investigating this dephosphonylation , we found that 1-alkylations of 2-oxoalkylphosphonates are limited to active halides, take long time, and give low yields. This is in accord with an earlier report.[8] Moreover, it is hard to obtain only 1- monoalkylated products since the acidity of the α-proton shifts the reaction toward the formation of 1-dialkylated and 3-alkylated as well as 1-monoalkylated moieties. In contrast, 3-alkylations of 2-oxoalkylphosphonates *via* dianionic forms with various alkyl halides gives exclusively 3-monoalkylated 2-oxoalkylphosphonates with good yields.[9] Therefore, the specific alkylation at 3 carbon of 2-oxoalkylphosphonates makes 1-alkylated 2-oxopropylphosphonates useful reagents in organic synthesis and there has been strong demand for a facile synthesis of 1-alkyl-2-oxopropylphosphonates. In this paper, we wish to report our results on a new and facile synthesis of 1-alkyl-2-oxopropylphosphonates *via* 1-alkylation with subsequent ozonolysis of 2-methyl allylic phosphonates which are precursors of the butadiene moieties.[10]

Lithium derivative S' was allowed to react with alkyl halides. Nucleophilic addition of the allylic anion S' *via* its 1-carbon atom occured as a main reaction in good yields with traces of 3-alkylated adducts. When the substrate was cyclohexyl iodide, starting compound S was recovered with considerable amounts and 3-alkylated adducts increased remarkably. Ozonolysis had not any effect on phosphonyl group , but just converted olefin to corresponding carbonyl group. The



Scheme

Table Alkylation of 2-methyl allylanionic phosphonates & Ozonolysis of 1-alkylated 2-methyl allylic phosphonates

entry	RX	A/B [a]	yield (%) of A/B[b]	yield (%) of P[c]
1[d]	—	—	—	88
2	$CH_3(CH_2)_3I$	93/7	94	89
3	$PhCH_2Br$	90/10	93	90
4	$CH_3(CH_2)_4Br$	95/5	95	89
5		70/30	61[e]	86

a Determined on mixtures by ^1H NMR integration
b Total yields of A and B (A and B could not be separated by silica gel chromatography)
c Isolated yields of products from A
d 2-Methyl allylic phosphonates(**S**)
e **S** was recovered with considerable amount

structure of the products was unambiguously determined by NMR (^1H, ^{13}C, ^{31}P) spectroscopy, as the phosphorus coupling constants of vinylic carbons for the α- or β-position differ by $\Delta J_{C\text{-}P}$=180 Hz. The ratios of isomeric adducts formed by the addition of allylic anion S' *via* the 1- or 3-carbon were calculated by the ^1H NMR intergration.

In conclusion, we have developed a new and facile synthesis of 1-alkyl-2-oxopropylphosphonates from the corresponding allylic phosphonates, which can

undergo 3-alkylation and the subsequent Wadsworth-Horner-Emmons condensation to give α,β-unsaturated ketones.

General Experimental Procedure

The following provides a typical experimental procedure. *n*-Butyllithium (3.3 mmol) was added to a solution of **S** (0.57 g, 3 mmol) in THF (9 ml) at -78 °C under a positive pressure of nitrogen and the solution was stirred at this temperature for 1 h. Alkyl halide (3.3 mmol) in THF (3 ml) was added dropwise to the solution. After stirring for an additional 30 min at -78 °C, the reaction mixture was allowed to warm to room temperature. After stirring for 2 h at room temperature, the reaction was quenched by the addition of saturated aqueous NH_4Cl and the product (**A**+**B**) was isolated by extraction with diethyl ether(50 ml x 3), drying($MgSO_4$), evaporation, and silica gel chromatography(using a mixture of ethyl acetate and hexane(4/1) as an eluent). A stream of ozone was passed through a cold (-78 °C), dichloromethane (8 ml) solution dissolving alkylated allylic phosphonate until the distinctive blue color of ozone was observed. Ozone bubbling was then terminated, and the excess ozone was displaced by passing a stream of oxygen through the dichloromethane solution for 10 min. The solution was allowed to warm to room temperature, neat dimethyl sulfide(5 mmol) was added, and the solution was allowed to stir at refluxing dichloromethane. Concentration of the crude product, followed by silica gel chromatography(using ethyl acetate as an eluent) provided the 1-alkyl-2-oxopropylphosphonates(**P**).

Diethyl 1-butyl-2-oxopropyl phosphonate(2P): viscous oil; ^1H NMR(300 MHz, $CDCl_3$) δ 4.11-4.00(m, 4H), 3.06(ddd, 1H, *J*=24.32, 10.74, 3.65 Hz), 2.25(s, 3H), 2.10-1.85(m, 1H), 1.80-1.65(m, 1H), 1.30-1.23(m, 6H), 1.23-

1.10(m, 4H), 0.82(t, 3H, *J*=6.87 Hz); ^{13}C NMR(75 MHz, $CDCl_3$) δ 200.82(d, *J*=4.5 Hz), 62.45(d, *J*=14.78 Hz), 53.65(d, *J*=124.05 Hz), 31.01, 30.59(d, *J*=14.85 Hz), 26.06(d, *J*=5.18 Hz), 22.31, 16.26(d, *J*=6.0 Hz), 13.64.

Diethyl 1-pentyl-2-oxopropyl phosphonate(3P): viscous oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.12-4.00(m, 4H), 3.07(ddd, 1H, *J*=24.27, 10.78, 3.60 Hz), 2.25(s, 3H), 2.10-1.85(m, 1H), 1.80-1.60(m, 1H), 1.29-1.24(m, 6H), 1.24-1.15(m, 6H), 0.81(t, 3H, *J*=6.24 Hz); ^{13}C NMR(75 MHz, $CDCl_3$) δ 203.81(d, *J*=4.43 Hz), 62.47(t, *J*=6.98 Hz), 53.69(d, *J*=123.98 Hz), 31.37, 30.99, 28.11(d, *J*=14.55 Hz), 26.32(d, *J*=5.18 Hz), 22.21, 16.26(d, *J*=6.2 Hz), 13.83.

Diethyl 1-benzyl-2-oxopropyl phosphonate(4P): viscous oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ 7.22-7.07(m, 5H), 4.13-4.03(m, 4H), 3.45(ddd, 1H, *J*=23.99, 10.78, 3.38 Hz), 3.25-3.16(m, 1H), 3.08-3.02(m, 1H), 2.11(s, 3H), 1.31-1.13(m, 6H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 202.77(d, *J*=4.43 Hz), 138.80(d, *J*=15.75 Hz), 128.43, 128.34, 126.45, 62.59(dd, *J*=17.48, 6.68 Hz), 54.94(d, *J*=122.63 Hz), 32.03, 31.79(d, *J*=27.3 Hz), 16.21(d, *J*=6.0 Hz).

Diethyl 1-cyclohexyl-2-oxopropyl phosphonate(5P): viscous oil; ^{1}H NMR(300 MHz, $CDCl_3$) δ 4.14-4.04(m, 4H), 2.93(dd, 1H, *J*=20.76, 9.80 Hz), 2.10(s, 3H), 2.08-2.04(m, 1H), 1.75-1.59(m, 6H), 1.34-1.29(m, 6H), 1.29-1.08(m, 4H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 204.58(d, *J*=4.13 Hz), 62.22(dd, *J*=7.05, 2.55 Hz), 60.19(d, *J*=125.78 Hz), 37.30(d, *J*=4.58 Hz), 32.12(d, *J*=15.98 Hz), 31.62(d, *J*=0.68 Hz), 31.38, 25.95(d, *J*=5.48 Hz), 16.30(d, *J*=6.08 Hz).

REFERENCES

1. There are two kinds of name for this class of compounds : β-ketophosphonates and 2-oxoakylphosphonates. The former is common, but we prefer to the latter because the former de-emphasizes the important aspects of these compounds such as 1- or 3-alkylation.
2. For general reviews, see : (a) Maryanoff, B.E. ; Beitz, A. B. *Chem. Rev.*, **1989**, *89*, 863. (b) Wadsworth, W. S. Jr. *Org. React.(N. Y.)*, **1977**, *25*, 73. (c) Walker, B. J. *Organophosphorous Reagents in Organic Synthesis*; Cadogan, J. I. G. Ed.; Academic Press: New York, 1974 ; pp 155-206. (d) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, L.; Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1,chapter 3.1, pp 755-782. (e) Wadsworth, W. S., Emmons, W. D. *J. Am. Chem. Soc.*, **1961**, *83,* 1733
3. (a) Lichtenthaler, F. W. *Chem. Rev.*, **1961**, *61*, 607. (b) Honda, M. ; Katsuki, T. ; Yamaguchi, M. *Tetrahedron Lett.*, **1984**, *25*, 3857. (c) Corbel, B.; Medinger, L.; Healters, J.P.; Strutz, G. *Synthesis,* **1985**, 1048. (d) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.*, **1995**, *117,* 2931
4. Hong, S.; Chang, K.; Ku, B.; Oh, D. Y. *Tetrahedron Lett.*, **1989**, *30*, 3307
5. Lee, K.; Oh, D. Y. *Synthesis,* **1991**,213
6. (a) Ko, Y. J.; Oh, D. Y. *Tetrahedron Lett.* **1993**, *34*, 2147. (b)Kim, D. Y.; Lee, K.; Oh, D. Y. *J. Chem. Soc., Perkin Trans.1,* **1992**, 2451
7. (a) Hong, J. E.; Shin, W. S.; Jang, W. B.; Oh, D. Y. *J. Org. Chem.* **1996**, *61*, 2199. (b) Lee, S. Y.; Hong, J. E.; Jang, W.B.; Oh, D. Y.

Tetrahedron Letters **1997**, *38*, 4567. (c) Jang, W. B.; Shin, W. S.; Hong, J. E.; Lee, S. Y.; Oh, D. Y. *Synth. Comm.* **1997**,*27*,3333

8. Clark, R. D.; Kozar, L. G.; Heathcock, C. H. *Synthesis,* **1975**, 635.
9. Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.,* **1973**, *95,* 3071
10. Kondo, K.; Negishi, A.; Tunemoto, D. *Angew. Chem.* **1974**, *13*, 407.

(RECEIVED IN THE U.S.A. 07 APRIL 1998)