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cis-Vinylphosphonates and 1,3-Butadienylphosphonates by Zirconation of 1-Alkynylphosphonates

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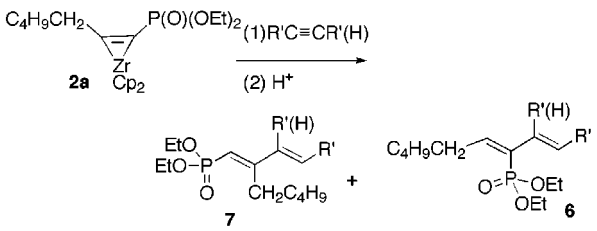
ABSTRACT



Addition of "zirconocene" to 1-alkynylphosphonates gives three-membered zirconacylces that can be hydrolyzed to *cis*-vinylphosphonates or further reacted with alkynes/hydrolysis to give substituted (*Z*,*E*)- and (*E*,*E*)-1,3-butadienylphosphonates.

Although 1-alkynylphosphonates have been known since 1957 and their synthesis was developed in the 1960s,[1] addition reactions of organometallics remain relatively unexplored and include *syn* addition of organocuprates to 1-alkynylphosphonates to give 2,2-disubstituted vinylphosphonates,[2] reaction of α-stannylated phosphonates with aldehydes to give *E/Z* mixtures of 1,2-disubstituted vinylphosphontaes,[3] *anti* hydrotelluration of 1-alkynylphosphonates,[4] Heck reactions using aryldiazonium salts,[5] α-lithiation of β-oxy or β-thio vinylphosphontes,[6] NaH-catalyzed olefination of benzenesulfinylmethylphosphonates,[7] and addition of sodium organyl chalcogenolates to 1-alkynylphosphonates.[8] These reactions provide access to 1-alkenylphosphonates that are very useful compounds for organic transformations[9] and for the synthesis of biologically active compounds.[10] We have recently started to investigate the addition of organometallic reagents to 1-alkynylphosphonates. Thus, we have discovered that the hydroboration of 1-alkynylphosphonates can be controlled to place boron on either C1 or C2 of the triple bond by proper use of base,

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(1) Iorga, B.; Eymery, F.; Carmichael, D.; Savignac, P. *Eur. J. Org. Chem.* **2000**, 3103.

(2) (a) Cristau, H.-J.; Mbianda, X. Y.; Beziat, Y.; Gasc, M.-B. *J. Organomet. Chem.* **1997**, *529*, 301. (b) Gil, J. M.; Oh, D. Y. *J. Org. Chem.* **1999**, *64*, 2950.

(3) Mimouni, N.; About-Jaudet, E.; Collignon, N.; Savignac, Ph. *Synth. Commun.* **1991**, *21*, 2341.

(4) Jang, W. B.; Oh, D. Y.; Lee, C.-W. *Tetrahedron Lett.* **2000**, *41*, 5103.

(5) Brunner, H.; Le Cousturier de Courcy, N.; Genêt, J.-P. *Synlett* **2000**, 210.

(6) Kouno. R.; Okauchi, T.; Nakamura, M.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1998**, *63*, 6239.

(7) Shen, Y.; Jiang, G.-F. *Synthesis* **2000**, 99.

(8) Braga, A. L.; Alves, E. F.; Silveira, C. C.; Andrade de, L. H. *Tetrahedron Lett.* **2000**, *41*, 161.

(9) For a recent review, see: (a) Minami I, T.; Motoyoshiya, J. *Synthesis* **1992**, 333. Selected recent reactions of vinylphosphonates include the following. Aziridination: (b) Kim, D. Y.; Rhie, D. Y. *Tetrahedron* **1997**, *53*, 13603. Epoxidation: (c) Cristau, H.-J.; Mbianda, X. Y.; Geze, A.; Beziat, Y.; Gasc, M.-B. *J. Organomet. Chem.* **1998**, *571*, 189. Organocuprate addition: (d) Afarinkia, K.; Binch, H. M.; Modi, C. *Tetrahedron Lett.* **1998**, *39*, 7419. C-glycosylation, (e) Junker, H.-D.; Fessner, W.-D. *Tetrahedron Lett.* **1998**, *39*, 269.

(10) As intermediates in drugs or biological investigative compounds: (a) Harnden, M. R.; Parkin, A.; Parratt, M. J.; Perkins, R. M. *J. Med. Chem.* **1993**, *36*, 1343. (b) Smeyers, Y. G.; Romero-Sanchez, F. J.; Hernandez-Laguna, A.; Fernandez-Ibanez, N.; Galvez-Ruano, E.; Arias-Perez, S. *J. Pharm. Sci.* **1987**, *76*, 753. (c) Megati, S.; Phadtare, S.; Zemlicka, J. *J. Org. Chem.* **1992**, *57*, 2320. (d) Lazrek, H. B.; Rochdi, A.; Khaider, H.; Barascut, J. L.; Imbach, J. L.; Balzarini, J.; Witvrouw, M.; Pannecouque, C.; De Clerq, E. *Tetrahedron* **1998**, *54*, 3807. (e) Smith, P. W.; Chamiec, A. J.; Chung-G.; Cobley, K. N.; Duncan, K.; Howes, P. D.; Whittington, A. R.; Wood, M. R. *J. Antibiot. Tokyo* **1995**, *4 8*, 73. Agrochemicals: (e) Chance, L. H.; Moreau, J. P. U.S. Patent 3910886, 1975.

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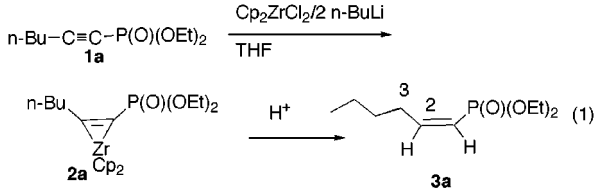
catalyst, and reaction time. Another very useful reaction of triple bonds that has not been applied to 1-alkynylphosphonates is the addition of zirconocene. Hydrolysis of the zirconacycles would provide *cis*-vinylphosphonates, and subsequent insertion reactions of the three-membered zirconacycles with various electrophiles would provide access to functionalized vinylphosphonates.[11] In the context of this paper, we explored the insertion of alkynes to provide substituted 1,3-butadienylphosphonates.

cis-Vinyphosphonates are useful intermediates in organic transformations.[9a] Reduction of 1-alkynylphosphonates with hydrogen under various conditions has been reported. Generally, mixtures of *cis*- and *trans*-vinylphosphonates are obtained.[12] When diethyl butynylphosphonate[13] was treated with Cp_2ZrCl_2/2*n*-BuLi,[11] and hydrolyzed, GCMS analysis indicated complete conversion. *cis*-Diethyl 1-butenylphosphonate was obtained as a single isomer in 76% isolated yield (eq 1).[14]



The reaction is general, isolated yields are excellent, and only the *cis*-vinylphosphonates, **3**, are obtained (Table 1).

Table 1. Synthesis of **3** and Selected NMR Data

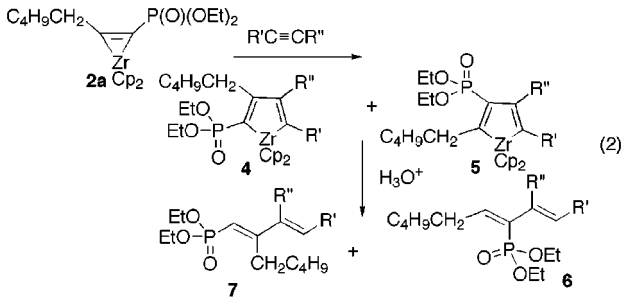
			J (Hz)	
entry	R	yield,[a] %	J_{P-H2}	J_{P-C3}
a	C_4H_9	79	53.1	8
b	C_5H_{11}	76	53.1	8
c	ClC_3H_6	63	52.5	8.3
d	Ph	76	51.5	8.8
e	$TBDMSOC_3H_6$	78	52.6	8.1

[a] Isolated yields. GCMS conversion was >99%, except for entry **e**, 85%.

The stereochemistry of the **3** was determined from the coupling constants obtained from the NMR data where both the $^3J_{P-H2}$ coupling constant (~50 Hz) and the small $^3J_{P-C3}$ (~8 Hz) indicates that H2 is *trans* to phosphonate group and that the R group is *cis*. Table 1 shows select coupling constants of vinylphosphonates obtained by reaction of 1-alkynylphosphonates with "zirconocene" followed by hydrolysis.

A further utilization of the three-membered zirconacycles, **2**, in this work was the investigation of alkyne insertion. This would lead to 1,3-butadienylphosphonates. The latter are interesting compounds that undergo a variety of reactions including 1,3-additions,[15] cycloaddition with CH_2N_2,[16] and [2 + 2] cycloadditions.[17] They have been prepared by isomerization of 1-alkynylphosphonates in the presence of palladium salts,[18] by Knoevenagel reaction,[17] by reaction of unsaturated cyanophosphonates with *N*-tosylsulfonylimines,[19] and by procedures similar to the preparation of vinylphosphonates.[9a]

When zirconacycles **2** (R = $C_4H_9CH_2$) were treated with a different alkyne (both terminal and internal alkynes were used), and the reaction mixture was hydrolyzed, two isomeric products were detected by GCMS, **6** and **7**, and isolated by silica gel chromatography (eq 2). Presumably, they arise from



zirconocyles **5** and **4**. Other possible isomeric 1,3-butadienylphosphonates were not isolated, apparently due to unfavorable steric interactions between the R′ groups of the incoming alkyne, the phosphonate, and $C_4H_9CH_2$ groups of the zirconacycle.

Results are listed in Tables 2 and 3.With terminal alkynes, **6** was the major isomer in all cases, apparently due to steric considerations. With an internal alkyne (Table 2, entry e),

Table 2. Synthesis of **6** and Selected NMR Data

				J (Hz)		
entry	R″	R′	yield[a]%	J_{H4-H5}	J_{P-H2}	J_{P-C3}
a	H	C_4H_9	68	15.4	48.8	5.4
b	H	C_5H_{11}	60	15.7	48.9	5.6
c	H	Ph	73	16.2	48.9	6.5
d	H	C_3H_6Cl	57	15.9	54.0	6.6
e	C_2H_5	C_2H_5	<3%[b]			

[a] Isolated yield GCMS conversion for combined **6** and **7** was >99%. [b] Not isolated.

compound **7e** was essentially the only product isolated (Table 3), **6e** being obtained in less than 3%. The structures of compounds **6** were determined by NMR spectroscopy. The doublet of triplets in the double bond region 6.5−6.2 ppm indicates that the alkyne coupling occurred on C1. Also, the

(11) (a) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (b) Negishi, E. In *Comprehensive Organic Synthesis;* Paquette, L. A., Ed.; Pergamon Press: New York, 1991; Vol. 5, p 1163.

(12) (a) L'vova, S. D.; Kozlov, Yu. P.; Gunar, V. I. *J. Gen. Chem. USSR (Engl. Transl.)* **1977**, *47*, 1153; *Zh. Obshch. Khim.* **1977,** *47*, 1251. (b) Rudinskas, A. J.; Hullar, T. L. *J. Org. Chem.* **1976**, *41*, 2411. (c) Cristau, H.-J.; Gase, M.-B.; Mbianda, X. Y. *J. Organomet. Chem.* **1994**, *474*, C14. (d) Cristau, H.-J.; Mbianda, X. Y.; Beziat, Y.; Gase, M.-B. *J. Organomet. Chem.* **1997**, *529*, 301. (e) Blackburn, G. M.; Forster, A. R.; Guo, M.-J.; taylor, G. E. *J. Chem. Soc., Perkin Trans. 1* **1979**, *44*, 865. In one example, hydrogenation of di-*n*-butyl 3-hydroxy-1-propynylphosphonate, the use of Pd/$BaSO_4$ provided the desired *cis*-olefin in 95% yield: (f) Machida, Y.; Saito, I. *J. Org. Chem.* **1979**, *44*, 856.

Table 3. Synthesis of **7** and Selected NMR Data

				J (Hz)		
entry	R″	R′	yield,[a] %	J_{H4-H5}	J_{P-C3}	J_{P-C4}
a	H	C_4H_9	15	15.9	5.6	28
b	H	C_5H_{11}	19	15.8	5.6	27.8
c	H	Ph	11	17.2	5.7	26.7
d	H	C_3H_6Cl	20	15.9	6.4	26.6
e	C_2H_5	C_2H_5	83		6.5	23

[a] Isolated yields. GCMS conversion for combined **6** and **7** was >99%.

large $^3J_{P-H2}$ coupling constant (~50 Hz) and the relatively small $^3J_{P-C3}$ coupling constant (5−6 Hz) indicate that the stereochemistry of the C1−C2 double bond is *Z*. The coupling constants $^3J_{H4-H5}$ (15−16 Hz) indicate that the hydrogens are *trans*. Thus compounds **6** have a *Z*,*E* configuration for the double bonds.

In a similar manner the structures of compounds **7** were determined. The doublet in the region 5.3−5.5 ppm corresponds to the hydrogen on the C1. This indicates that the alkyne coupling occurred on C2. Also, the large $^3J_{P-C4}$ coupling constants (23−28 Hz) and the relatively small $^3J_{P-C3}$ coupling constant (5.6−6.5 Hz) indicate that the stereochemistry of the C1−C2 double bond is *E* in compounds **7**. In addition, the multiplet (H4−H5) in the region 6.3−5.9 ppm corresponds to two vinylic hydrogens with a coupling constant $^3J_{HH}$ (15.8−17.2 Hz) indicative of the *E* configuration. Thus compounds **7** are the *E*,*E* isomers (Table 3).

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Supporting Information Available: Experimental procedures and full NMR data This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) All 1-alkynylphosphonates were prepared by reaction of the corresponding lithium acetylide with diethyl chlorophosphates: (a) Poss, A. J.; Belter, R. K. *J. Org. Chem.* **1987**, *52*, 4810. (b) Acheson, R. M.; Ansell, P. J *J. Chem. Soc., Perkin Trans. 1* **1987**, 1275. (c) Knierzinger, A.; Grieder, A.; Schönholzer, P. *Helv. Chim. Acta* **1991**, *74*, 517. (d) Ruder, S. M.; Norwood, B. K. *Tetrahedron Lett.* **1994**, *35*, 3473. (e) Saalfrank, R. W.; Welch, A.; Haubner, M.; Bauer, U. *Liebigs Ann.* **1996**, 171. (f) Gil, J. M.; Sung, J. W.; Park, C. P.' Oh, D. Y. *Synth. Commun.* **1997**, *27*, 3171.

(14) To 1 mmol (0.292 g) of zirconocene dichloride dissolved in 5 mL of dry THF was added 2 mmol (1.25 mL of *n*-BuLi 1.6 M in hexane) dropwise at −78 °C. The mixture was stirred for 3 h, then 0.9 mmol of 1-alkynylphosphonate was added, and the mixture was slowly warmed to 25 °C and stirred overnight. The mixture was worked up with dilute aqueous HCl, and the vinylphosphonate was extracted in ether and separated on a silica gel column (80% petroleum ether: 20% ethyl acetate).

(15) Martin, S. F.; Garrison, P. J. *Synthesis* **1982**, 394.

(16) Minami, T.; Tokomasu, S.; Mimasu, R.; Hirao, I. *Chem. Lett.* **1985**, 1099.

(17) Okauchi, T.; Kakiuchi, T.; Kitamura, N.; Utsunomiya, T.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1997**, *62*, 8419.

(18) Ma, C. L.; Lu, X. Y.; Ma, Y. X. *Main Group Metal Chem.* **1995**, *18*, 391.

(19) Shen, Y.; Jiang, G.-F.; Sun, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3495.