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

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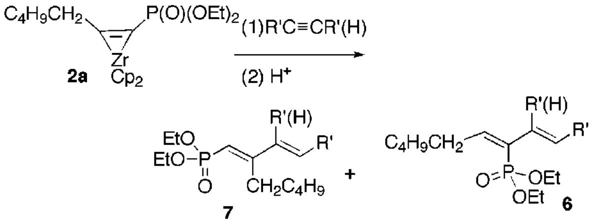
ABSTRACT



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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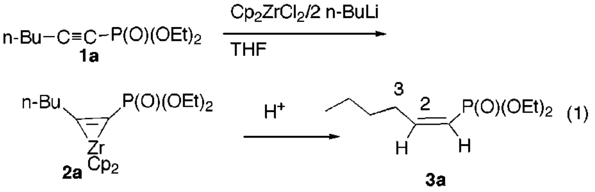
catalyst, and reaction time. Another very useful reaction of triple bonds that has not been applied to 1-alkynylphosphonates is the addition of zirconocene. Hydrolysis of the zirconacycles would provide *cis*-vinylphosphonates, and subsequent insertion reactions of the three-membered zirconacycles with 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 $Cp_2ZrCl_2/2n$-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). 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.

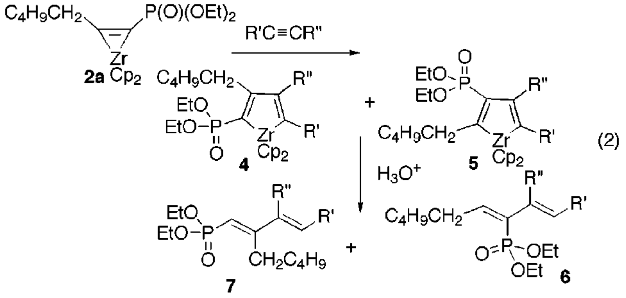
Table 1. Synthesis of **3** and Selected NMR Data

entry	R	yield,[a] %	*J* (Hz)	
			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%.

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), 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

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

entry	R″	R′	yield[a]%	*J* (Hz)		
				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.

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

entry	R″	R′	yield,[a] %	J_{H4-H5} (Hz)	J_{P-C3} (Hz)	J_{P-C4} (Hz)
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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(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).

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