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Control of hydroboration of 1-alkynylphosphonates, followed by Suzuki coupling provides regio- and stereospecific synthesis of di-substituted 1-alkenylphosphonates

Inna Pergament and Morris Srebnik*

Department of Medicinal Chemistry and Natural Products, School of Pharmacy, Hebrew University in Jerusalem, POB 12065, Jerusalem 91120, Israel

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Abstract—Hydroboration of 1-alkynylphosphonates can be controlled to place boron on either C1 or C2 of the triple bond by control of reaction conditions. Initial hydroboration occurs on C1 (kinetic product), which can be isomerized to place boron on C2 (thermodynamic product) by extended heating or by use of large amounts of catalyst. Suzuki reaction of the hydroboration products with aryliodides provides a regio- and stereospecific route to disubstituted vinylphosphonates

1-Alkenylphosphonates are very useful compounds for organic transformations[1] and for the synthesis of biologically active compounds.[2] Organometallic approaches to the synthesis of these compounds include *syn* addition of organocuprates to 1-alkynylphosphonates to give 2,2-disubstituted vinylphosphonates,[3] reaction of α-stannylated phosphonates with aldehydes to give E/Z mixtures of 1,2-disubstituted vinylphosphonates,[4] *anti* hydrotelluration of 1-alkynylphosphonates,[5] hydrozirconation of alkynes followed by phosphorylation.[6] Heck reactions using aryldiazonium salts,[7] α-lithiation of β-oxy or β-thio vinylphosphonates,[8] NaH catalyzed olefination of benzenesulfinylmethylphosphonates,[9] and addition of sodium organyl chalcogenolates to 1-alkynylphosphonates.[10] These methods and others at best give one regio or stereo isomer. In practice, mixtures are obtained. A regio- and stereoselective synthesis of disubstituted 1-alkenylphosphonates would be highly desirable.

We have recently reported the first study of the hydroboration of unsaturated phosphonates, including 1-alkynylphosphonates.[11] We could not explain the apparent random placement of boron on either C1 or C2 of the triple bond. This prompted us to investigate the hydroboration of 1-alkynylphosphonates in greater depth. In our work we discovered the factors that determine the placement of boron in 1-alkynylphosphonates. The results are the basis of this communication.

When alkynylphosphonates (^{31}P NMR ~−5 to −7 ppm), **1**, were hydroborated with pinacolborane (PBH) in CH_2Cl_2 at 25°C, a series of peaks appeared in the ^{31}P NMR in the range +15–20 ppm, which we attributed to coordination complexes between boron and phosphorus oxygens. Boron was directed to carbon C1 of the triple bond. Workup at this point provided one compound, **2**. Compounds **2** resonate in ^{31}P NMR in the +31 ppm range and their ^{11}B NMR shifts are around +30 ppm. ^{1}H NMR spectra were difficult to interpret because of overlapping signals. In ^{13}C NMR, carbon C1 could not be identified due to the boron quadrapole, but C2 resonated as a doublet (J_{CP} ~ 11 Hz) at about 160 ppm. If compounds **2** were heated to reflux in toluene, they slowly disappeared during 48 h and were replaced by new peaks in the GC–MS. These new peaks were identified as **4** on the basis of their NMR spectra. Subsequently, the reaction could be monitored by GC–MS. The conversion from **2** to **4** was accelerated by the addition of palladium salts.[12] We found that the nature of the catalyst affected the rate of conversion. The best catalyst for obtaining **4** was $PdCl_2$. Suzuki coupling is an important application of vinylboronates. Coupling of the vinylboronophosphonates with aryliodides would be expected to give stereodefined vinylphosphonates.[13] That indeed proved to be the case (Table 1). The best base for the coupling reaction was NaOH.[14] Addition of an aryliodide to

* Corresponding author. Tel.: 972-2-675-7301; fax: 972-2-675-8201; e-mail: msrebni@md2.huji.ac.il

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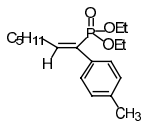
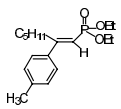
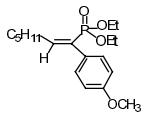
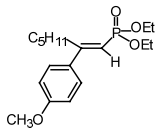
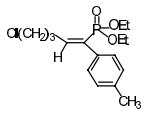
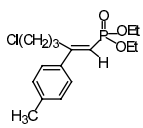
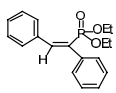
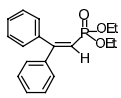
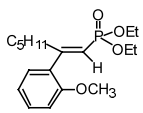
Table 1. Hydroboration–Suzuki reaction of 1-alkynyphosphonates **1**

Entry	R	ArI Method[a]	Product **3**, **5**	Yield (%)[b]
a	C_5H_{11}	*p*-C_6H_4-CH_3 **A**		72
b	C_5H_{11}	*p*-C_6H_4-CH_3 **B**		32
c	C_5H_{11}	*p*-C_6H_4-OCH_3 **A**		45
d	C_5H_{11}	*p*-C_6H_4-OCH_3 **B**		30
e	$Cl(CH_2)_3$	*p*-C_6H_4-CH_3 **A**		60
f	$Cl(CH_2)_3$	*p*-C_6H_4-CH_3 **B**		27
g	Ph	Ph **A**		20
h	Ph	Ph **B**		35
i	C_5H_{11}			37

[a] Suzuki reaction conditions for method **A**: NaOH (3 equiv.), $Pd(PPh)_2Cl_2$ (3 mol%), reflux in toluene during 2 h. Method B: NaOH (3 equiv.), $PdCl_2$ (more than 10 mol%), reflux in toluene during 24 h.

[b] Isolated yields after silica gel chromatography (~50 % EtOAc in P.E.).

either preformed **2** or **4** provided coupling products **3** and **5** (Fig. 1). In general, yields of **3** were good whereas yields of **5** were appreciably lower. However, in both cases only one coupling product was isolated.

Alternatively, a one-pot procedure was developed for synthesizing either **3** or **5**. Compounds **3** were exclusively synthesized by using a relatively low catalyst load (3 mol% Pd) and short reaction times (2 h in refluxing toluene), **method A**. Compounds **5** were obtained by using a higher catalyst load (>10 mol% Pd) and longer reaction times (24 h in refluxing toluene), **method B**. It is well known that thermal isomerization of pinacolboronates in the presence of transition metals ultimately places the boron atom on the least hindered carbon of the molecule by a series of hydroboration/dehydroboration steps.[15] Thus, we surmise that in the present case, the phosphonate group is the more sterically demanding than the R group of the alkyne. Apparently, under the more vigorous conditions of **method B**, isomerization of **2** to **4** occurred faster than coupling. That no equilibration occurred between **3** and **5** was established by control experiments. Thus, pure **3** was not converted to **5** under the conditions of the reaction. Attempts to trap pinacolborane with a terminal alkyne were unsuccessful. Apparently, PBH was intimately bound during the process and was not available for hydroboration. In each case essentially one coupling product was isolated, the other being present in less than 1% (by GC–MS). When 2-iodoanisole was used in the coupling reaction (Table 1, entry i), only one product could be obtained, regardless of conditions, corresponding to hydroboration occurring on C2. This is apparently due to greater steric requirements. All products were purified on silica gel and characterized by NMR. The stereochemistry was determined from J coupling constants.[16] Thus, for products **3** (hydrogen on double bond *trans* to phosphorus), J_{PH} was $\sim$48 Hz, and for compounds **5** (H1 is geminal to phosphorus) J_{PH} was $\sim$17 Hz. GC retention times of products **5** were 0.1 min more than retention times of compounds **3** and R_f values on TLC of products **5** were lower than those of products **3**. In the ^{31}P NMR of **3**, the chemical shifts are $\sim$1.5 ppm lower than the chemical shifts for compounds **5**. The yields of **3** and **5** were not optimized and although good to poor, only one isomer is obtained which is easily isolated. Owing to the great value of vinylphosphonates, the present procedure should be attractive.

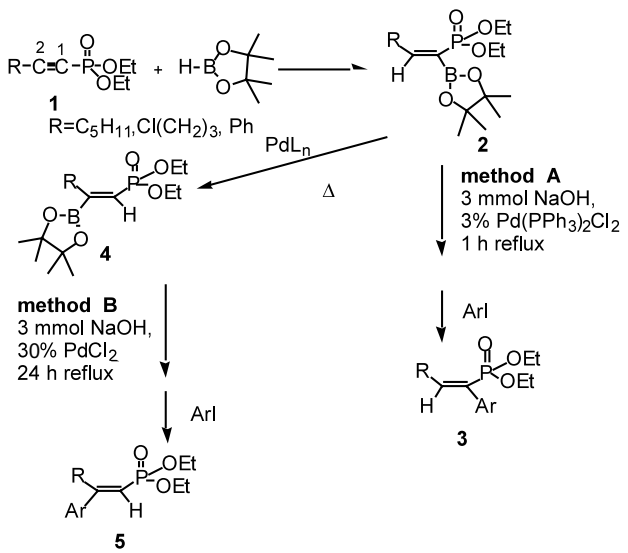


Figure 1. Hydroboration-coupling of alkynylphosphonates.

Preparation of **3a** and **5b** are typical. **Hydroboration**: Alkenylphosphonates (1 mmol) were dissolved in dry dichloromethane (1 ml) and pinacolborane (1.5 mmol) was added at 0°C. The reaction mixture was stirred at room temperature overnight. The solvent and excess of pinacolborane were removed in vacuo to obtain hydroboration product. **Suzuki coupling reaction of hydroboration products**: Solution of iodoaryl compound (1.2 mmol) in toluene (1 ml), catalyst ($Pd(PPh)_2Cl_2$, 3% mol in method **A** or, $PdCl_2$, 30% in method **B**) and base (NaOH, 3 mmol) were placed in the reaction flask equipped with a condenser, under nitrogen. The mixture was stirred at room temperature for 15 min. The product of hydroboration (1 mmol) was dissolved in toluene (1 ml) and this solution was added to the reaction flask. The mixture was refluxed for 2 h (method **A**) or 24 h (method **B**), then cooled to room temperature and filtered. The solution was evaporated to dryness and the residue was chromatographed on silica (EtOAc/PE). **NMR data of 3a**: ^1H NMR ($CDCl_3$): $\delta=0.92$ (t, 3H), 1.24 (t, 6H), 1.30–1.33 (m, 4H), 1.49 (t, 2H), 2.33 (s, 3H), 2.69 (dd, 2H), 4.03 (q, 4H), 6.31–6.47 (dt, 1H), 7.11 (d, 2H), 7.20 (d, 2H). ^{13}C NMR ($CDCl_3$): $\delta=14.19$, 16.55, 22.69, 25.07, 28.19, 30.89, 31.62, 61.56, 115.32, 117.76, 128.50, 128.94, 129.88–132.21 (d, $J_{PC}=196$ Hz), 137.09, 137.43, 152.81 (d, $J_{PC}=11$ Hz). ^{31}P NMR ($CDCl_3$): $\delta=15.62$ ($J_{PH}=49$ Hz). **NMR data of 5b**: ^1H NMR ($CDCl_3$): $\delta=0.84$ (t, 3H), 1.22 (t, 6H), 1.30–1.35 (m, 4H), 1.44 (t, 2H), 2.34 (s, 3H), 2.95 (dd, 2H), 4.10 (q, 4H), 5. 70–5.76 (d, 1H),7.15 (d, 2H), 7.32 (d, 2H). ^{13}C NMR ($CDCl_3$): $\delta=14.24$, 16.70, 21.43, 22.68, 28.87, 30.06, 32.78, 61.62, 111.67–114.21 (d, $J_{PC}=186$ Hz), 126.62, 129.44, 142.13. ^{31}P NMR ($CDCl_3$): $\delta=17.12$ ($J_{PH}=18$ Hz).

Acknowledgements

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