Bisallylphosphonates

Substituted 1,4-Bisallylphosphonates: Preparation from 1-Alkynylphosphonates and Ti(O*i*Pr)$_4$/2 *i*PrMgCl[**]

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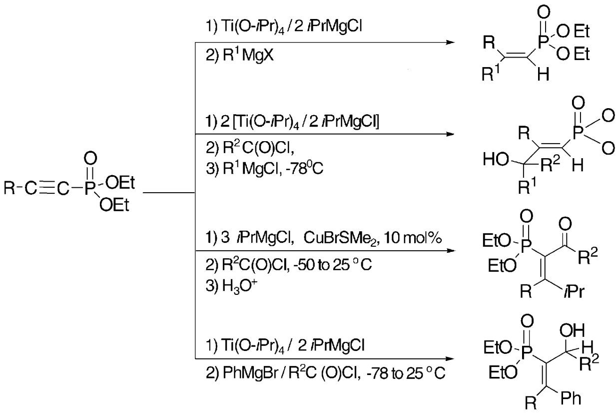
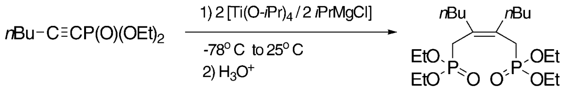
Bisphosphonates have wide range of applications,[1] Among the various types of bisphosphonates, the 1,4-bisphosphonates are potent inhibitors of yeast glyceraldehyde-3-phosphate dehydrogenase, and phosphoglycerate kinase,[2,3] which disturbs the production of ATP and causes cardiovascular respiratory disorders. Surprisingly, the methods of synthesis of 1,4-bisphosphonates are limited. Among these methods is the Michaelis–Arbuzov reaction of the appropriate alkylbromides and triethyl phosphite,[4] the Michaelis–Baker synthesis,[3,5] and catalytic cross-coupling of 1,4-diiodobutadiene with two equivalents of diethyl phosphite.[6] Recently, we began exploring the chemistry of titanacycle alkoxides.[7] These intermediates undergo a series of reactions with electrophiles that depends on the 1:2 stoichiometry of Ti(O*i*Pr)$_4$ and *i*PrMgCl and of additives, such as CuBrSMe$_2$. A variety of di- and trisubstituted vinylphosphonates may be prepared in a regio- and stereoselective manner (Scheme 1).



Scheme 1. Synthesis of di- and trisubstituted vinylphosphonates.

Indeed, these titanacycles display a much richer chemistry than the corresponding zirconacycles. Thus, whereas the titanacycles react with imines, the corresponding zirconacycles do not.[8] The reactions of the zirconacyclopropenes with the various nucleophiles took place at room temperature.[9] On the other hand, nucleophiles added to the titanacyclopropenes at low temperature (−30 °C to −50 °C). In addition, a longer time was required for the reactions of zirconacycles than for those with Ti^{II} complexes. Warming the reactions of 1-alkenylphosphonate zirconacycles to room temperature produced *cis*-vinylphosphonate after hydrolysis.[9d] In general, titanacyclopropenes generated from Grignard reagents are not stable at temperatures above −30 °C.[10] However, herein we offer evidence that under certain conditions Ti^{II} complexes generated from Grignard reagents are stable and report the synthesis of novel 1,4-bisphosphonates by a straightforward one-pot reaction.

When the diethyl 1-hexynylphosphonate was treated with two equivalents of the Ti(O*i*Pr)$_4$/2 *i*PrMgCl reagent,[11] allowed to warm to 25° C, and hydrolyzed, an unexpected compound was formed. Dimerization had occurred which gave, not the expected 1,3-butadienylphosphonate but rather the 1,4-bisallylphosphonate **1b** which was isolated as the only product in about 75 % yield [Eq. (1)].



1b

(1)

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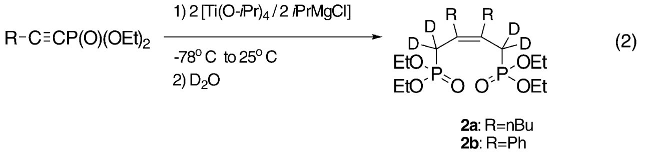
To explore the formation of **1b**, the reaction mixture was quenched with D_2O. GC-MS analysis of the D_2O quenched product **2a** indicated that four atoms of deuterium had been incorporated [Eq. (2)]. The phenyl analogue **2a** also showed incorporation of four deuterium atoms (Table 1). The symmetry of deuterium incorporation is consistent with the ^{1}H NMR and ^{13}C NMR spectra.



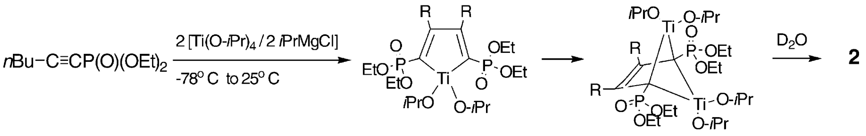
2a: R=nBu
2b: R=Ph

(2)

Table 1: Yields and select ^{31}P NMR spectroscopic data for the deuterated compounds **2**.

2	R	^{31}P NMR δ	$^2J_{PH}$	Yield % NMR (isolated)
a	Ph	27.49	–	80 (65)
b	*n*Bu	29.15	–	82 (68)

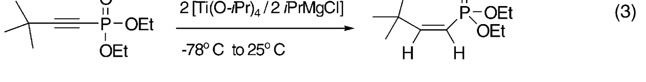
To explain the incorporation of four deuterium atoms, four C–Ti bonds are required. This situation requires that two Ti atoms are incorporated into the intermediate leading to **1** or **2**. A possible structure accounting for the deuterium incorporation would be the dinuclear complex **4** which could be generated from the initial cyclization product, **3**, by addition of another equivalent of the Ti(O*i*Pr)$_4$ (Scheme 2). The nature of dinuclear titanocene complexes depends on the stoichiometry and nature of the reaction conditions.[12] However, to our knowledge, dinuclear titanium alkoxide complexes have not been reported. Repeated attempts to isolate and characterize **4** have thus far been unsuccessful.



3 **4**

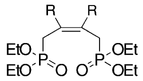
Scheme 2. proposed intermediate in the formation of **2**.

The formation of compounds **1** was investigated with several 1-alkynylphosphonates. The results are shown in Table 2. The reaction is very clean and yields are high. The only failure was when (3,3-dimethyl-but-1-ynyl)-phosphonic acid diethyl ester was used. Only the corresponding *cis*-vinylphosphonate was isolated [Eq. (3)].



(3)

Table 2: Yields and select ^{31}P NMR spectroscopic data of **1**.



1	R	^{31}P NMR δ	$^2J_{PH}$	Yield % NMR (isolated)
a	*n*Pentyl	29.06	19.2	95 (76)
b	*n*Bu	28.97	20.2	93 (75)
c	Ph	27.65	18.9	85 (71)
d	$Cl\text{-}CH_2CH_2CH_2$	28.39	19.2	85 (72)
e	*m*-F_3CPh	26.44	19.5	80 (63)

The structure of compounds **1** was determined by GC-MS, LC-MS, and NMR spectroscopic data (Table 2). The presence of only one phosphorus resonance signal in the ^{31}P NMR, and phosphorus couplings in the ^{1}H NMR and ^{13}C NMR spectra, all indicated that compounds **1** had a symmetrical structure in which homo coupling occurred on C2. The ^{31}P resonances for the different compounds **1** lie in the range $\delta = 26.4$–29.06 and are indicative that the phosphorus is coupled to an sp^3 carbon. Usually, when the phosphorus is coupled to an sp^2 carbon, it resonates in the range $\delta \approx 10$–20 ppm, and when coupled to an sp carbon, it resonates in the range $-8-0$ ppm. The doublets found in the range $\delta = 2.69$–3.37 ppm with $^2J_{PH}$ (18.9–20.2 Hz) in the ^{1}H NMR spectra are consistent with the presence of a methylene group adjacent to phosphorus. (The doublet is absent in compounds **2**, Table 2). This assignment is corroborated by the doublet in the ^{13}C NMR spectrum at $\delta \approx 29.5$ ppm, with $^1J_{PC}$ 133.3–140.3 Hz (see Supporting Information). Furthermore, the intensity of the signal at $\delta \approx 129$ ppm is consistent with the presence of two symmetrical vinylic carbon atoms.

Several other electrophiles were investigated. Bromine and iodine gave products **5**.[13] This reaction can be explained by initial complexation of the halogen with one of the titanium atoms of **4**, followed by oxidative elimination to **3** and $X_2Ti(OiPr)_2$ (Scheme 3).[14] The latter alkoxide then is halogenated in the usual manner.

In conclusion, the formation of **1** is very facile. Even with one equivalent of Ti(O*i*Pr)$_4$/2*i*PrMgCl, only **1** and starting material were obtained at 25 °C. However, the reaction with one equivalent of Ti(O*i*Pr)$_4$/2*i*PrMgCl and alkynylphosphonate at −30 °C resulted in the formation of *cis*-vinylphosphonates after workup at −30 °C. Thus, although zirconium and titanium belong to the same group differences in reactivity between Zr^{II} and Ti^{II} complexes were observed in the present reaction. The same reaction conditions using $[ZrCp_2Cl_2]/2\,n$BuLi (Negishi's reagent; Cp = C_5H_5) resulted only in *cis*-vinylphosphonate formation, that is, no homo-coupling products were detected. This result is probably due to the larger steric requirements of the zirconocene complex.

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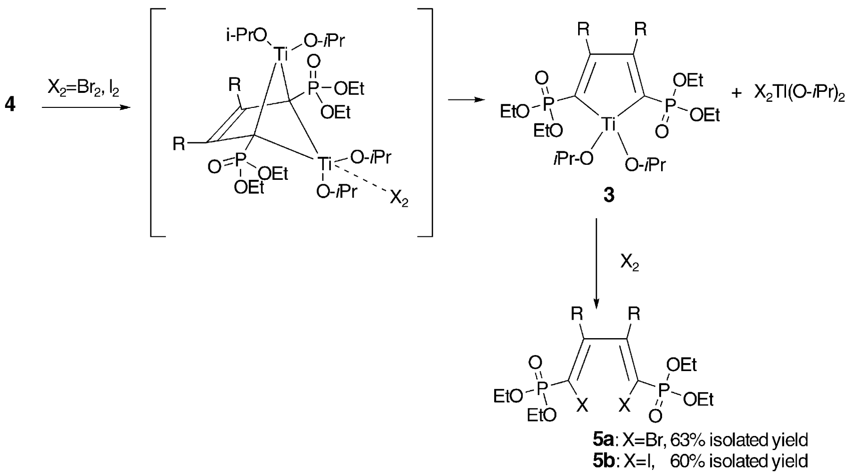

Scheme 3. Proposed mechanism for preparation of **5**.

Keywords: alkoxides · alkynes · C–C coupling · phosphonates · titanium

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