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Novel addition reactions of titanacycle phosphonates by tuning of Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl†

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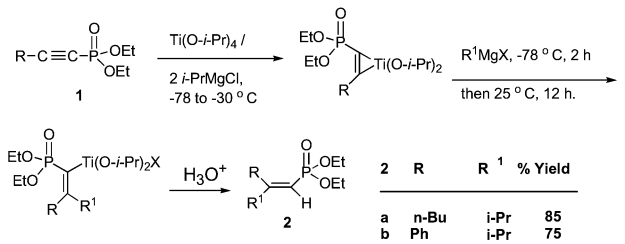
Di- or tri-substituted vinylphosphonates, 2–5, can be obtained in a highly regio- and stereoselective manner from 1-alkynylphosphonates, by manipulation of Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl.

Vinylphosphonates are an exceedingly important group of compounds.[1–7] Owing to their importance, there are various routes to the preparation of vinylphosphonates.[8–13] Recently, two groups have reported protocols based on carbocupration reactions of 1-alkynylphosphonates.[14] Since the cuprate reagents are derived from organolithium or Grignard reagents, they suffer from the same functional group incompatibility. Nevertheless, metallation of alkynylphosphonates is an attractive approach to the synthesis of highly substituted vinylphosphonates. In many instances, transition metal chemistry circumvents these problems. The Ti(O-*i*-Pr)$_4$/2RMgCl reagent initially discovered by Kulinkovich[15] and developed into a highly useful synthesis of cyclopropanols from esters,[16] has been further modified by Sato to add to alkynes and alkenes from which a variety of useful reagents and products can be obtained.[17] Its preparation from relatively inexpensive starting materials makes it an attractive alternative to divalent titanocene compounds. We have been interested in the chemistry of zirconacycle phosphonates as a means of preparing vinylphosphonates.[18] However, the potentially enhanced reactivity of titanacycle isopropoxides tempted our curiosity. Herein we report some interesting new reactions involving divalent titanium isopropoxides, which greatly expand the usefulness of this reagent and provide compounds not attainable with zirconacycles, thus complementing the reactions we have developed with the latter.

When the intermediate titanacycle prepared from 1-alkynylphosphonate,[19] **1**, and Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, was reacted with an additional equivalent of RMgX, followed by aqueous workup, the vinylphosphonate, **2**, was isolated (Scheme 1). This intrigued us. We assumed that two equiv. of *i*-PrMgCl went into the formation of the titanacycle. The other Grignard then attacked and inserted into the Ti–C bond (Scheme 1). The reaction did not proceed when the Grignard reagents were replaced by *n*-BuLi. Since the diisopropoxytitanacycle is a stable species at low temperature, it was reasonable to expect that replacement of the third equivalent of isopropylmagensium chloride by another Grignard would give the corresponding 1,4-addition product. This indeed proved to be the case. When phenyl- or ethylmagnesium bromide were used in step two (Scheme 1), aqueous workup provided the corresponding disubstituted vinyl phosphonates. Isopropyl derivatives were not detected. Yields were good to excellent.



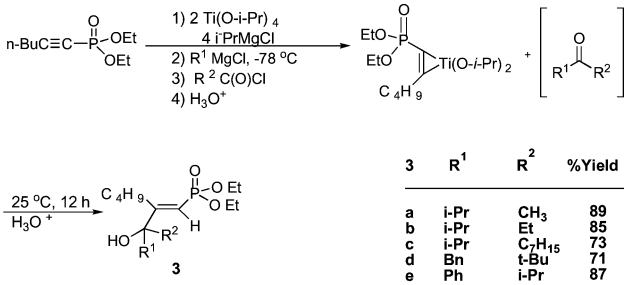
2	R	R 1	% Yield
a	n-Bu	i-Pr	85
b	Ph	i-Pr	75
c	Cl(CH$_2$)$_3$	i-Pr	63
d	n-Bu	Et	83
e	Ph	Et	77
f	n-Bu	Ph	84
g	Cl(CH$_3$)$_3$	Et	68

Scheme 1

The titanium reagent may be further modified. Reacting an alkynylphosphonate (1 mmol), Ti(O-*i*-Pr)$_4$ (2 mmol), *i*-PrMgCl (4 mmol) to allow formation of intermediates followed by addition of another equivalent of *i*-PrMgCl and an acyl chloride (1 mmol) overnight with warming to room temperature provided in good yields the isopropyl derivatives **3a**–**c** (Scheme 2).[20] A possible mechanism involves the *in-situ* formation of a ketone that then reacts with the titanacycle to form the allylic alcohol. As was the case in Scheme 1, another Grignard may be substituted for isopropyl Grignard. For **3d**, *i*-PrMgCl (4 mmol) was used followed by BnMgCl (1 mmol) and for **3e** *i*-PrMgCl (4 mmol) and PhMgCl (1 mmol) was then added. The ability to select different Grignards and acyl chlorides makes it possible to synthesize a very large number of compounds. In products **2** and **3**, coupling occurred on C2 ($^2J_{PH}$ = 17.1–18.6 Hz). On the other hand the stereochemistry of compounds **2** and **3** was determined by the carbon–phosphorus coupling constant $^3J_{PC}$. The large $^3J_{PC}$ of the allylic carbon in R_1, **2**, or the alcohol carbon in **3** (20.3–24.1 Hz) compared to the small $^3J_{PC}$ of the allylic carbon of R in **2** or the *n*-Bu carbon in **3** (6.3–8.0 Hz) is indicative that both R_1 and the alcohol groups are *trans* to phosphorus, whereas R and *n*-Bu are *cis*. Although the above isomer **2** was the major product, in some cases another stereoisomer was detected, ~10%, in which R_1 is *cis* to phosphorus, and R is *trans*, **2b**, **2f**.

Interesting C–C bond formations occurred when the initially formed titanacycle was allowed to react with stoichiometric amounts of PhMgBr and an acid chloride (Scheme 3). Products **4** were obtained in good yields along with **2f** (~30%). A possible mechanism involves attack by the Grignard on an intermediate cyclopropene oxide.[21] The sequence is equivalent to *syn* addition of a Grignard followed by an aldehyde.[22]

The reaction takes a somewhat different course when a Cu(I) catalyst (10 mol%) is added, followed by an acyl chloride. Under these conditions, double insertion with C–C bond formation occurred to give **5** (Scheme 4).

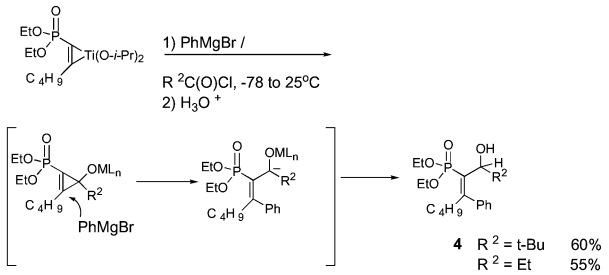


3	R^1	R^2	%Yield
a	i-Pr	CH$_3$	89
b	i-Pr	Et	85
c	i-Pr	C$_7$H$_{15}$	73
d	Bn	t-Bu	71
e	Ph	i-Pr	87

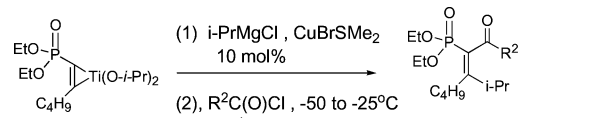
Scheme 2

† Electronic supplementary information (ESI): further experimental details. See http://www.rsc.org/suppdata/cc/b2/b209149f/

DOI: 10.1039/b209149f



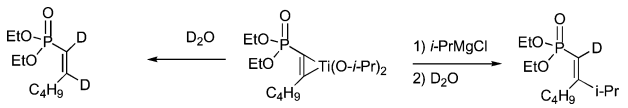
Scheme 3



5	R^2	Yield %
a	t-Bu	78
b	Ph	30
c	Et	35

Scheme 4

The regioselectivity of compounds **4** and **5** was determined by $^3J_{PC}$ and $^2J_{PC}$. Since $^3J_{PC}$ of the *i*-Pr carbon, **5**, or the $^3J_{PC}$ of the Ph carbon, **4**, (19.1–23.0 Hz) is larger than the $^2J_{PC}$ of the carbonyl in **5** or the alcohol carbon in **4**, (12.4–15.8 Hz), coupling of the isopropyl group in compounds **5**, or the phenyl group in compounds **4**, of the Grignard reagents must have occurred on C2 while coupling of the acid chlorides occurred on C1. In addition, the stereochemistry of compounds **4** and **5** was also determined by $^3J_{PC}$. The large $^3J_{PC}$ of the *i*-Pr carbon, **5**, or Ph carbon, **4**, (20.0–23.0 Hz), and the small $^3J_{PC}$ of the *n*-Bu carbon, **4** and **5** (6.3–8.3 Hz), is indicative that the *i*-Pr group in **5** and the Ph ring in **4** are *trans* to phosphorus while the *n*-Bu is *cis*. A series of labeling experiments with D_2O were carried out to determine that the actual intermediates involved were titanacycles. Thus GCMS analysis of the product obtained by treatment of the intermediate titanacycle formed from diethyl 1-hexynylphosphonate gave $M^+ = 222$, indicative of the *cis*-1,2-dideuteriovinylphosphonate (Scheme 5). D_2O workup after addition of *i*-PrMgCl to the same titanacycle provided the monodeuterio product, $M^+ = 263$.



Scheme 5

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22 In point of fact addition of an aldehyde gave a complex mixture of products.