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Novel One-Pot Synthesis of 3-Amino-1-alkenylphophonates by Addition of Imines to Alkynylphosphonate Titanium(II) Complexes

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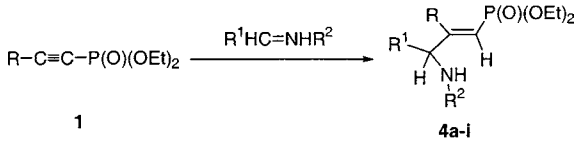
ABSTRACT



1 4a-i

A new method of synthesis of 3-amino-1-alkenylphosphonates is described. It involves the addition of imines to the alkynylphosphonate titanium(II) complexes 2, which are prepared in situ from 1-alkynylphosphonates and Ti(O-*i*-Pr)$_4$/2 equiv of *i*-PrMgCl. Compounds 4a–i were obtained regio- and stereoselectivily in high yields.

Vinylphosphonates are compounds that have a wide range of applications in many areas such as copolymers,[1] polymer additives,[2] flame retardants,[3] intermediates for drugs,[4] agrochemicals,[5] in further transformations,[6] and other applications.[7] Due to their importance, their preparation methods are varied.[8]

The presence of a nitrogen atom at any position of phosphonates in the carbon skeleton enhances the potential of these types of compounds. Generally, aminophosphonates are an important class of compounds because of their unique utilities as antibiotics,[9] herbicides,[10] antifungal,[11] enzyme inhibitors,[12] and pharmacological agents.[13] Among the various types of aminophosphonates, the 3-aminophosphonates originally were isolated from microorganisms[14] and subsequently synthesized to confirm the structures. They were also prepared from (1-hydroxy-2-alkyl)phosphonates by the reac-

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(7) For a complete list, see the IBM patent database on the Internet at: www.delphion.com.

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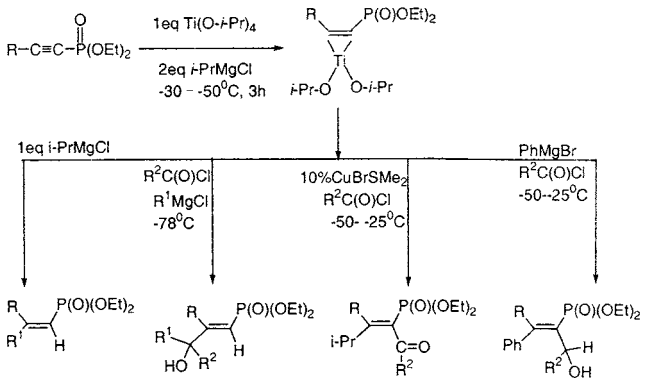
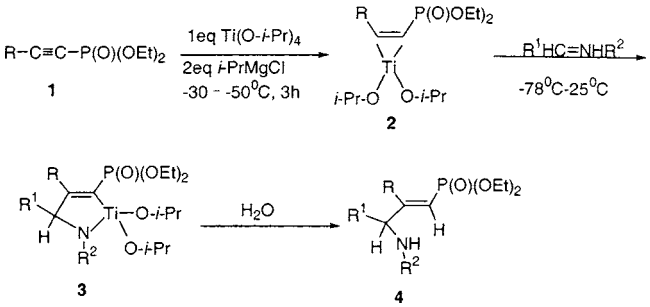
tion with triphenylphosphine, diethylazidodicarboxylate, and hydrogen azide, followed by 1,3 rearangement of the allylic α-azidophosphonates[15] or by the addition of diethyl methylphosphonite to 2-cyclohexenone followed by amino acid formation.[12b] Another method involves a seven-stage process starting from Michael addition of dimethyl methylphosphonate to 4-chloro-β-nitrostyrene and catalytic reduction of the nitro group, followed by hydrolysis of the resulting amine.[16] Recently, we reported some interesting reactions of alkynylphosphonates with divalent titanium isopropoxides to produce various types of di- and trisubstituted vinylphosphonates (Scheme 1).[17] The in situ-generated divalent titanium com-

Scheme 1



plex was initially discovered by Kulinkovich.[18] It is prepared from available and inexpensive starting materials, i.e., Ti-(*O*-*i*-Pr)$_4$ and 2 equiv of *i*-RrMgX (X = Cl, Br). It has been used to synthesize cyclopropanols from esters[19] and shown to add to alkynes or alkenes, which in turn react with various electrophiles to produce many useful and interesting products.[20] Herein, we extend our work to prepare 3-amino-1-alkenyl-phosphonates by addition of imine to the alkynylphosphonate titanium(II) (Scheme 2).

Scheme 2



Various types of imines efficiently reacted with the alkynylphosphonate titanium(II) complex **2**, prepared from 1-alkynylphosphonates, and Ti(*O*-*i*-Pr)$_4$/2 equiv of i-PrMgCl to produce the desired 3-amino-1-alkenylphosphonates in high yields as shown in Table 1. This one-pot reaction is general and proceeds with aliphatic and aromatic substituents on both the vinylic carbon and the nitrogen atom of the imine, in high yields.

Table 1. 3-Amino-1-alkenylphosphonates **4a**−**i** Obtained from Addition of Imines to the Alkynylphosphonate Titanacycles

entry	R	R^1	R^2	^{31}P yield[a]	isolated yield
4a	Ph	*p*-tolyl	Me	97%	79%
4b	Ph	*p*-MeO-Ph	*i*-Pr	95%	78%
4c	*n*-Bu	Et	Bz	95%	80%
4d	*n*-Bu	Ph	Bz	98%	85%
4e	*n*-Bu	Ph	Ph	95%	75%
4f	*n*-Bu	Ph	*i*-Pr	98%	79%
4g	*n*-Bu	*p*-MeO-Ph	*i*-Pr	98%	81%
4h	1-ClPr	Ph	Ph	95%	70%
4i	1-ClPr	Ph	Bz	90%	71%

[a] Determined by ^{31}P NMR of the reaction mixture.

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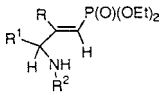
We found that 3 equiv of the freshly distilled imine is essential for reaching the maximum yield. However, the excess imine was recovered by silica gel chromatography during the isolation of the reaction mixture. The course of the reaction was followed by ^{31}P NMR on aliquots prepared by quenching with distilled water and extraction with ethyl acetate. Changing the reaction sequence, i.e., adding the alkynylphosphonate to imine titanium(II) complex, produced the 3-amino-1-alkenylphosphonate in much lower yields (<50%) in addition to many other nonidentified side products. Only one isomer of the 3-aminovinylphosphonate was produced, in which carbon−carbon bond formation occurred on C2 of the titanacycle. This regioselectivity seems to be controlled by steric factors. The regiochemistry was determined by ^{1}H NMR spectroscopy, which showed a doublet in the region (5.0−6.3 ppm) for the hydrogen on C1 split by phosphorus, with J_{PH} values (18.0−19.9 Hz). The stereochemistry of **4** was determined by NMR analysis of the carbon−phosphorus coupling constant. The large $^{3}J_{PC}$ of the amino carbon (19.2−23.8 Hz) compared to the smaller values of $^{3}J_{PC}$ of the vinylic carbon of R (6.2−8.1 Hz) is consistent with trans arrangement of the amino group to phosphorus and cis configuration of the vinylic carbon of R with respect to phosphorus, as shown in Table 2. Previous methods for the synthesis of 3-aminophosphonates are multistep, are not general, and suffer from overall low yield. Finally, the present alkynylphosphonate titanium(II) complexes have proven to be complementary with our work with phosphonate zirconocene complexes, since in our previous work all attempts to add imines to alkynylphosphonate zirconacycles did not succeed.[21]

Table 2. Selected NMR Data of **4**



4a-i

entry	$^{3}J_{PC}$ (Hz) allylic amino carbon	$^{3}J_{PC}$ (Hz) allylic carbon of R	^{31}P NMR	$^{2}J_{PH}$
4a	19.2	8.1	17.98	18.6
4b	21.2	7.1	19.49	18.9
4c	19.2	7.5	18.15	18.15
4d	20.3	6.9	19.59	18.6
4e	21.4	6.2	19.59	18.0
4f	20.4	6.9	20.01	18.9
4g	23.8	7.1	18.10	18.6
4h	22.2	7.1	18.00	18.5
4i	20.3	6.9	20.11	19.9

In summary, we have developed a new synthetic route for the preparation of 3-amino-1-alkenylphosphonates by addition of the imines to the alkynylphosphonate titanacycles. This methodology has the advantages of being one-pot, general, and regio- and stereoselective. In addition, it is done under mild conditions using inexpensive and available reagents.

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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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