Tetrahedron Letters 52 (2011) 4273–4276

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of *N*-vinyl 2,2-bisphosphonoaziridines from 1,1-bisphosphono-2-aza-1,3-dienes

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ARTICLE INFO

Article history:
Received 6 April 2011
Revised 27 May 2011
Accepted 31 May 2011
Available online 16 June 2011

Keywords:
Aminophosphonates
Azadienes
Aziridination

ABSTRACT

N-Vinyl 2,2-bisphosphonoaziridines are formed by treatment of 1,1-bisphosphono-2-aza-1,3-dienes with diazomethane. Depending on the substituents at the 4-position of the 1,1-bisphosphono-2-aza-1,3-dienes, exclusively 1-(ethenylamino)-2-phosphonoethenylphosphonates or mixtures of 1-(ethenylamino)-2-phosphonoethenylphosphonates and 2-imino-2-phosphonoethylphosphonates are obtained as side products.

Bisphosphonates are a major class of drugs for the treatment of bone diseases. They inhibit bone resorption by selective uptake and adsorption to mineral surfaces in the bone, where they are internalized by osteoclasts and interfere with specific biochemical processes. Bisphosphonates can be classified according to their mode of action. The more potent nitrogen-containing bisphosphonates or aminobisphosphonates act by inhibiting farnesyl diphosphate synthase, a key enzyme in the mevalonate pathway, and affect cellular activity and cell survival by interfering with protein prenylation and, therefore, the signaling functions of key regulatory proteins.[1–5] Aminobisphosphonates have also effects beyond the skeleton and are not selectively active on osteoclasts.[6] As a result, these compounds display direct antitumor effects.[5,7–11] Furthermore, aminobisphosphonate drugs constitute an attractive group as chemotherapeutic agents against protozoal diseases.[12]

Despite the importance of these aminobisphosphonates, heterocyclic geminal bisphosphonates with the phosphonate groups directly attached to the ring skeleton are scarcely reported in the literature.[13–18] During our ongoing efforts to further explore the class of azaheterocyclic phosphonates,[19,20] phosphonylated azadienes have been shown to be interesting precursors of phosphonylated aziridines,[21,22] phosphonylated β-lactams,[23] phosphonylated γ-lactams,[24] phosphonylated 2-oxazolidinones[25], and phosphonylated 2-imidazolidinones.[25] Recently, a new class of electron-deficient azadienes, that is, 1,1-bisphosphono-2-aza-1,3-dienes **1**, was synthesized by a 1,4-dehydrochlorination reaction of in situ formed *N*-bisphosphonomethyl α-chloroimines. These latter compounds were obtained by a condensation reaction between tetraethyl aminomethylbisphosphonate and α-chlorinated aldehydes.[26]

Herein, we describe the use of these 1,1-bisphosphono-2-aza-1,3-dienes **1** for the synthesis of *N*-vinyl 2,2-bisphosphonoaziridines **3**. To our knowledge, only one report has described the synthesis of 2,2-bisphosphonoaziridines up to now. Aziridination of 1,1-bisphosphonoethylene was carried out using a copper-catalyzed nitrogen transfer of a sulfonamide, mediated by iodosylbenzene to afford the corresponding *N*-sulfonyl 2,2-bisphosphonoaziridines.[27]

Besides the use of nitrenoids, the reaction between imines and diazo compounds has already proven its importance in the formation of aziridines.[28] As a consequence, this method was used for the synthesis of 2-phosphonoaziridines, either by a reaction of a phosphonylated diazo compound with an imine[29,30] or by a reaction between a phosphonylated imine and a diazo compound.[21,22]

In this context, 1,1-bisphosphono-2-aza-1,3-diene **1b** (R^1 = R^2 = Et) was treated with an excess of diazomethane (5–10 equiv) in Et_2O. After stirring the reaction mixture for 19 h at room temperature, all starting material was converted into three new products as was shown by ^{31}P NMR. Continuation of the reaction for about 25 h at room temperature resulted in a mixture of the same products, however appearing in different ratios. Subsequently, the solvent was evaporated in vacuo and the reaction products were identified using NMR-techniques (Scheme 1).

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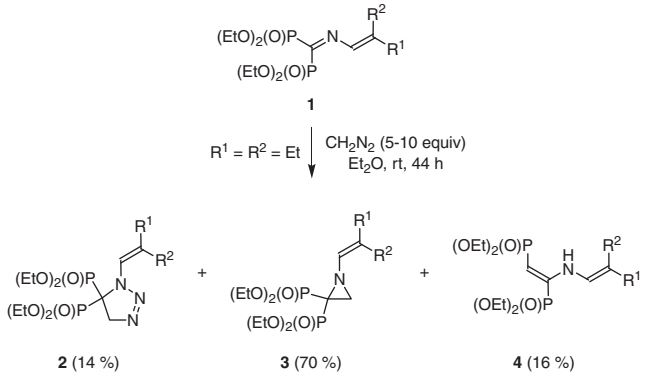
doi:10.1016/j.tetlet.2011.05.149



Scheme 1. Treatment of 1,1-bisphosphono-2-aza-1,3-diene **1b** with diazomethane.

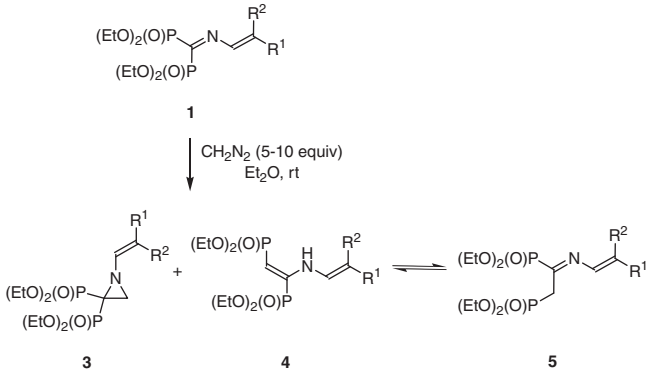
Because it was assumed that 1,2,3-triazoline **2** was a direct precursor of aziridine **3**, the other azadienes **1** were allowed to react with diazomethane until no 1,2,3-triazoline **2** was left in the reaction mixture, as was determined by ^{31}P NMR. In all cases, together with the formation of the *N*-vinyl 2,2-bisphosphonoaziridines **3**, the synthesis of the corresponding enamines **4** was observed. Performing the reaction in the dark or in day light did not have any influence on the reaction outcome. After evaporation of the solvent in vacuo, the two endproducts, **3** and **4**, were easily separated by chromatography on silica gel. In case non-aromatic substituents were present at the 4-position of the 1,1-bisphosphono-2-aza-1,3-dienes (**1a–c**), the isolation of the enaminophosphonates **4a–c** revealed the presence of small amounts of the corresponding 2-aza-1,3-dienes **5a–c**, whereas aromatic substituents at the 4-position (**1d–f**) exclusively led to the isolation of the enaminophosphonates **4**. Also noteworthy was the fact that the aromatic 1,1-bisphosphono-2-aza-1,3-dienes (**1d–f**) reacted markedly faster with diazomethane in comparison to the non-aromatic ones (**1a–c**) (Table 1).

Keeping these observations in mind, a mechanism for the reaction between the 1,1-bisphosphono-2-aza-1,3-dienes **1** and diazomethane was proposed. The 1,2,3-triazolines **2** are formed by a 1,3-dipolar cycloaddition of diazomethane and the C=N bond of the 1,1-bisphosphono-2-aza-1,3-dienes **1**. These intermediates **2** seem to be quite stable and are assumed to be the precursors for either the aziridines **3** and the enamines **4**. The formation of these latter compounds **4** can be explained by a nitrogen-assisted elimination of a diethyl phosphite anion, followed by a nucleophilic attack of this anion at the 4-position of the 1,2,3-triazolium ions **6**,[31] resulting in the elimination of nitrogen gas and formation of 2-aza-1,3-dienes **5**. These azadienes **5** are susceptible to an imine-enamine rearrangement, which results in the formation of the corresponding enaminophosphonates **4**. Clearly, the substituents at the 4-position of the azadienes **5** play a role in this rearrangement. Because of the presence of an excess of diazomethane in the reaction mixture, the aziridination of 2-aza-1,3-dienes **5** was considered as a competitive reaction, but the formation of these *N*-vinyl 2-phosphono-3-phosphonomethylaziridines was never observed. A possible alternative for the synthesis of the enaminophosphonates **4** would be the monodephosphonylation of the aziridines **3**, resulting in the formation of the azirinium ions, followed by a nucleophilic addition of the diethyl phosphite anion at the 3-position of the azirinium ion. However, this reaction was assumed to be quite unlikely to occur. Moreover, when one of the aziridines (**3a**) was heated in boiling THF for 21 h, only starting material was recovered, showing the thermal stability of the aziridines toward dephosphonylation reactions (Scheme 2).

The presence of the enaminophosphonates **4** after reaction of diazomethane with 1,1-bisphosphono-2-aza-1,3-dienes **1** was quite unexpected. Therefore, the synthesis of *N*-vinyl 2-ethoxycarbonyl-2-phosphonoaziridines was envisaged in order to investigate if a similar reaction outcome was obtained when 1-ethoxycarbonyl-1-phosphono-2-aza-1,3-dienes were reacted with diazomethane. The required 2-aza-1,3-diene **9** was synthesized starting from α-chloro aldehyde **7** and ethyl amino(diethylphosphono)acetate **8**[32] (Scheme 3) using a similar method as described for the formation of the 1,1-bisphosphono-2-aza-1,3-dienes **1**.[26]

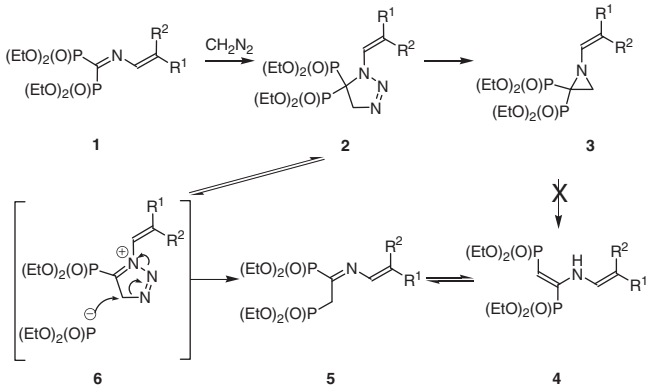
Next, azadiene **9** was submitted to a reaction with an excess of diazomethane. After 48 h of reaction at room temperature and subsequent evaporation of the solvent in vacuo, a mixture of compounds was recovered. With the help of ^{1}H NMR and ^{31}P NMR spectra, these compounds were identified as starting material **9** (29%), mainly aziridine **10** (51%) and in lesser extent 2-aza-1,3-diene **11** (20%) as an *E*/*Z*-mixture (major/minor: 83/17). There were no signs of the corresponding enamine. Sampling of this reaction mixture after 24 h had also revealed the presence of the

Table 1
Reaction between 1,1-bisphosphono-2-aza-1,3-dienes **1** and diazomethane with formation of *N*-vinyl 2,2-bisphosphono aziridines 3,1-(ethynylamino)-2-phosphonoethenylphosphonates **4** and 2-imino-2-phosphonoethylphosphonates **5**

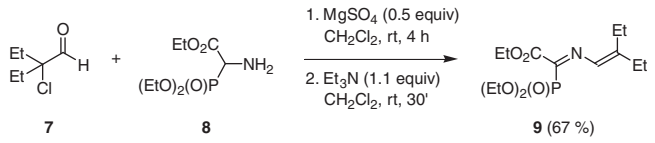


R^1	R^2	Reaction time (h)	3		4/5	
			Result	Yield[a] (%)	Result	Yield[a] (%) (ratio)[b]
Me	Me	44	**3a**	63	**4a**/**5a**	14 (80/20)
Et	Et	44	**3b**	68	**4b**/**5b**	14 (86/14)
$(CH_2)_5$		90	**3c**	67	**4c**/**5c**	17 (77/23)
Ph	Me	15	**3d**	79	**4d**/**5d**	9 (100/0)
Ph	Ph	15	**3e**	79	**4e**/**5e**	12 (100/0)
Cl	Ph	15	**3f**	72	**4f**/**5f**	19 (100/0)

[a] After chromatography (**4**+**5**).
[b] Determined by ^{31}P NMR.

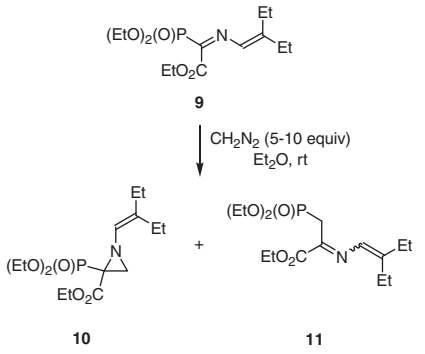


Scheme 2. Plausible reaction mechanism.



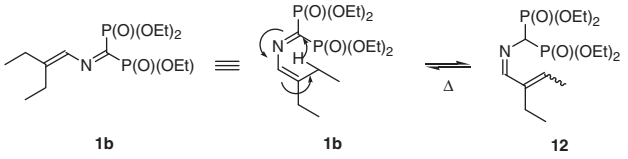
7 8 9 (67 %)

Scheme 3. Synthesis of 1-ethoxycarbonyl-1-phosphono-2-aza-1,3-diene **9**.



9 10 11

Scheme 4. Reaction between 1-ethoxycarbonyl-1-phosphono-2-aza-1,3-diene **9** and diazomethane with formation of *N*-vinyl 2-(ethoxycarbonyl)-2-phosphonoaziridine **10** and 1-(ethoxycarbonyl)-1-(phosphonomethyl)-2-aza-1,3-diene **11**.



1b 1b 12

Scheme 5. Thermally induced [1,5]-hydride shift of 1,1-bisphosphono-2-aza-1,3-diene **1b**.

intermediate 1,2,3-triazoline. Hence, a similar reaction course as described for the aziridination of the 1,1-bisphosphono-2-aza-1,3-dienes **1** (Scheme 2) was assumed to be plausible, with the only difference that azadiene **11** was formed rather than the corresponding enamine (Scheme 4).

In order to extend the scope of the aziridination of the 1,1-bisphosphono-2-aza-1,3-dienes **1**, some other diazo reagents, such as ethyl diazoacetate and trimethylsilyldiazomethane, were evaluated. At room temperature, none of these reagents were active toward azadiene **1b** ($R^1 = R^2 = Et$). However, when the same reactions were performed in toluene under reflux conditions, a transformation of the starting product occurred, not into the expected aziridine, but into 1-aza-1,3-diene **12**. The presence of this latter compound **12** could be rationalized by a thermal induced [1,5]-hydride shift of 1,1-bisphosphono-2-aza-1,3-diene **1b**. As expected, the formation of **12** was also observed when azadiene **1b** was heated in toluene without the presence of diazo reagents (Scheme 5).

In conclusion, it was shown that 1-vinyl-2,2-bisphosphonoaziridines **3** are formed by treatment of 1,1-bisphosphono-2-aza-1,3-dienes **1** with diazomethane[33]. As a side reaction, the formation of 1-(ethenylamino)-2-phosphonoethenylphosphonates **4** was also observed. Depending on the substituents at the 4-position of the 1,1-bisphosphono-2-aza-1,3-dienes, small amounts of the corresponding 2-aza-1,3-dienes **5** were also observed. Because of the particular reaction mechanism, it was not possible to drive the reaction toward the synthesis of one single reaction product. Aziridination of 1-ethoxycarbonyl-1-phosphono-2-aza-1,3-diene **9** with diazomethane revealed a similar reaction course. Other diazo reagents, such as ethyl diazoacetate and trimethylsilyldiazomethane, were not reactive toward the 1,1-bisphosphono-2-aza-1,3-dienes **1**, neither at room temperature nor at elevated temperatures. On the other hand, a thermal [1,5]-hydride shift of the isomerizable azadiene **1b** ($R^1 = R^2 = Et$) was observed.

Acknowledgments

Financial support for this research from the BOF (Bijzonder Onderzoeksfonds Universiteit Gent, Research Fund Ghent University) is gratefully acknowledged.

Supplementary data

Supplementary data (general information and spectroscopic data of all compounds synthesized with complete peak assignment. Copies of the ^1H NMR spectra and ^{13}C NMR spectra of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.149.

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31. Remark: To prove the presence of the 1,2,3-triazolium ions **6**, dimethyl phosphite was added (in 1, 20 and 120 equiv) to the reaction mixture of **1b** with diazomethane, after 4 h of reaction time. After completion of the reaction, the correct mass of the mixed bisphosphonylated products could be observed in minor amounts in LC–MS experiments (ES, Pos: 370 ($M+H^+$, 100). However, isolation of these mixed bisphosphonylated products was unsuccessful.
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33. *General procedure for the synthesis of N-vinyl 2,2-bisphosphono-aziridines 3,1-(ethenylamino)-2-phosphonoethenylphosphonates 4 and 2-imino-2-phosphonoethylphosphonates* **5**: To a solution of a 1,1-bisphosphono-2-aza-1,3-diene[26]

(0.50 mmol) in dry Et_2O (2 ml) was added an excess of freshly prepared diazomethane (2.5–5 mmol, 5–10 equiv), dissolved in dry Et_2O. The mixture was allowed to react at room temperature until completion as was determined by ^{31}P NMR (for reaction time, see Table 1). After evaporation of the solvent in vacuo, a mixture of compounds was obtained, which were easily separated by chromatography on silica gel. In case of azadienes **1a–c**, small amounts of the corresponding 2-aza-1,3-dienes **5a–c** were also isolated together with the enaminophosphonates **4a–c**. *Diethyl [2-(diethoxyphosphoryl)-1-(2-methylprop-1-en-1-yl)aziridin-2-yl]phosphonate* **3a**. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.33 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 1.34 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 1.64 (3H, br s, HC=CCH_3), 1.82 (3H, br s, HC=CCH_3), 2.63 (2H, t, $^3J_{HP}$ = 7.4 Hz, NCH_2), 4.12–4.28 (8H, m, 4 × CH_2CH_3), 5.75 (1H, br s, HC=CCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.5 (br s, 4 × CH_2CH_3), 17.3 (CH_3), 22.2 (CH_3), 35.9 (t, $^1J_{CP}$ = 180.0 Hz, CP_2), 38.3 (NCH_2), 62.88 (d, $^2J_{CP}$ = 3.5 Hz, CH_2CH_3), 62.92 (d, $^2J_{CP}$ = 3.5 Hz, CH_2CH_3), 63.26 (d, $^2J_{CP}$ = 3.5 Hz, CH_2CH_3), 63.30 (d, $^2J_{CP}$ = 3.5 Hz, CH_2CH_3), 127.5 (HC=CCH_3), 131.1 (t, $^3J_{CP}$ = 5.8 Hz, HC=CCH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 18.79. IR (cm^{-1}) ν_{max}: 1016 (br, P–O), 1248 (P=O). MS *m/z* (%): (ES, Pos) 370 ($M+H^+$, 100). Elem. Anal. Calcd for $C_{14}H_{29}NO_6P_2$: C, 45.53; H, 7.91; N, 3.79. Found: C, 45.67; H, 7.93; N, 3.79. Chromatography: CH_2Cl_2/CH_3CN (6/4) R_f = 0.31. Yield: 63%. *Diethyl (E)-2-(diethoxyphosphoryl)-1-(2-methylprop-1-en-1-ylamino)ethenyl-phosphonate* **4a**. Mixture of diethyl (*E*)-2-(diethoxyphosphoryl)-1-(2-methylprop-1-en-1-ylamino)-ethenylphosphonate **4a** and diethyl 2-(diethoxyphosphoryl)-1-(2-methylprop-1-en-1-ylimino)ethylphosphonate **5a** (ratio **4a**/**5a**:80/20). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 1.37 (6H, t, J = 7.2 Hz, 2 × CH_2CH_3), 1.67 (6H, br s, 2 × HC=CCH_3), 3.98–4.27 (8H, m, 4 × CH_2CH_3), 4.79 (1H, dd, J_{HP} = 19.3 Hz, J_{HP} = 12.1 Hz, PCH), 6.42 (1H, d, J = 11.6 Hz, HC=CCH_3), 9.27 (1H, dd, J = 33.0 Hz, J = 11.6 Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.1 (HC=CCH_3), 16.3 (d, $^3J_{CP}$ = 6.9 Hz, 2 × CH_2CH_3), 16.4 (d, $^3J_{CP}$ = 6.9 Hz, 2 × CH_2CH_3), 22.5 (HC=CCH_3), 61.8 (d, $^2J_{CP}$ = 4.6 Hz, 2 × CH_2CH_3), 63.2 (d, $^2J_{CP}$ = 5.8 Hz, 2 × CH_2CH_3), 85.2 (dd, $^1J_{CP}$ = 181.1 Hz, $^2J_{CP}$ = 13.9 Hz, PCH), 111.8 (HC=CCH_3), 121.4 (d, J_{CP} = 3.5 Hz, NCH), 148.5 (dd, $^1J_{CP}$ = 181.1 Hz, $^2J_{CP}$ = 3.5 Hz, NCP). ^{31}P NMR (121 MHz, $CDCl_3$) δ: 10.93 ($^3J_{PP}$ = 83.4 Hz), 23.15 ($^3J_{PP}$ = 83.4 Hz). IR (cm^{-1}) ν_{max}: 1025 (br, P–O), 1248 (P=O). MS *m/z* (%): (ES, Pos) 370 ($M+H^+$, 100). Elem. Anal. Calcd for $C_{14}H_{29}NO_6P_2$: C, 45.53; H, 7.91; N, 3.79. Found: C, 45.41; H, 7.88; N, 3.80. Chromatography: EtOAc (100%) R_f = 0.56. Yield: 14%.