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# Synthesis of 3-Phosphorylated 2-Aza-1,3-dienes from Imines Derived from Bisphosphonates.

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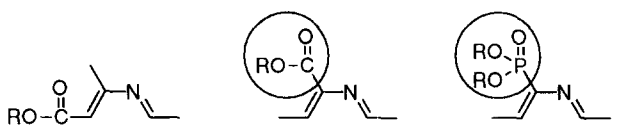
**Abstract.**

A synthesis of 2-aza-1,3-butadienes **3** substituted with a phosphonate group in the 3-position is described. The key step is the olefination reaction of bisphosphonylalkyl imino compounds **2**, with aldehydes in the presence of base. Heterocyclisation of 2-azatrienes **5** afforded substituted 2-phosphorylated pyridines **6**.


2-Aza-1,3-butadienes represent an important class of compounds, and have become useful key intermediates in organic synthesis for the construction of both heterocyclic systems and open chain polyfunctionalized compounds [1]. The synthesis and some reactions of electronically neutral 2-azadienes [2], as well as of heterodienes with electron-donating substituents [3], have been reported. However, electron-poor 2-azadienes have received much less attention, probably owing to the lack of general methods for their synthesis [1]. Azabutadienes of this type were limited to 3- or 4-substituted electron-deficient heterodienes derived from α- [4] (**Ib,** Scheme 1) or β-amino acids [5] (**Ia**, Scheme 1) as well as to 4,4- [6a] and to 3,4-electron-withdrawing substituted 2-azadienes [5a,6b,c], and these kinds of electron-poor 2 azadienes derived from amino acids (**I**) have been used not only in the synthesis of heterocyclic systems through cycloaddition reactions [4-7] but also for the synthesis of functionalized amino acid derivatives [8].




Ia Ib II

**Scheme 1**

Nevertheless, 1-aminoalkylphosphonic acids, the phosphonic analogues of important amino acids, and their phosphapeptide derivatives, are a unique class of simple mimetics of amino

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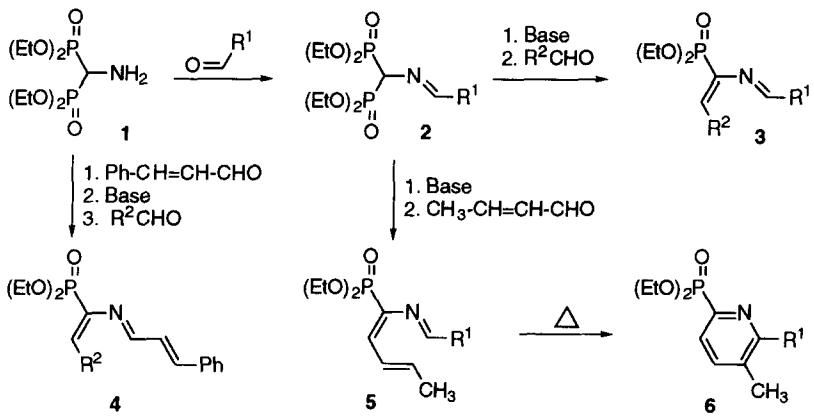
acids and peptides and they constitute a new type of compound with interesting biological properties [9,10]. With this in mind and taking into account our previous studies of the synthesis [4e,5] and reactivity of electron-poor 2-azadienes derived from α- [4e,7a,e] and β-amino acids [5] **I** we are interested in the design of new 2-azadienes (**II**, Scheme 1) derived from α-aminophosphonates which involve the isosteric replacement of the carboxylate ester group of compounds **I** by the phosphonic ester. To the best of our knowledge, the synthesis of 2-azadienes **II** with a phosphonate in the 3 position of the acyclic system has not been reported. These substituents could regulate important biological functions and could increase the biological activity of these types of compounds and of their derivatives, in a similar way to that reported for other pharmaceuticals [9]. Retrosynthetically, we envisaged obtaining these compounds **3** by olefination reactions of aldehydes and imines derived from bisphosphonates **2**, prepared by condensation of aldehydes and α-aminomethyldiphosphonate **1** (Scheme 2). In this context, we have previously used β-functionalized imines or enamines derived from phosphazenes, phosphonium salts, phosphine oxides and phosphonates for the construction of carbon-carbon double bonds in the synthesis of acyclic derivatives such as oximes [11a,b], allylamines [11c], hydrazones [11d], azadienes [11e], aminodienes[11f] and β-amino functionalized compounds [11g,h].




**Scheme 2**

The required imines **2**,[1] derived from bisphosphonates, were easily prepared by simple condensation reaction of α-aminomethyldiphosphonate **1** [12] and aromatic, heteroaromatic and α,β-unsaturated aldehydes (See Scheme 2 and Table 1). The spectral data are in agreement with structure **2**. Thus, in the $^{31}$P-NMR spectrum of compound **2a**, the phosphoryl groups resonate at $\delta_P$ = 16.0 ppm, while the $^1$H-NMR spectrum of this compound **2a** showed absorption at $\delta_H$ = 4.35 ppm for the methine proton, as a well resolved triplet with a $^2J_{PH}$ = 18 Hz. Subsequent olefination reactions of imines derived from bisphosphonates **2** with aldehydes were performed. Methyl lithium and the superbase BTPP

[1] All new compounds reported here gave satisfactory elemental analysis. Spectral data for **2a**: $\nu_{max}$ (film) 1629, 1257, 1030 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.30 (12H, m, 4 x $CH_3$-$CH_2$), 2.35 (3H, s, $CH_3$-Ph), 4.20 (8H, m, 4 x $CH_2$), 4.35 (1H, t, $^2J_{PH}$ 18.0 Hz, CHP), 7.16-7.64 (4H, m, Harom); 8.25 (1H, t, $^4J_{PH}$ 4.2 Hz, CH=N) ppm; $\delta_P$ (120MHz, $CDCl_3$) 16.01 ppm; $\delta_C$ (75.4 MHz, $CDCl_3$) 16.1 (s, $CH_3$-$CH_2$), 21.2 (s, $CH_3$-Ph), 63.2 (s, $CH_3$-$CH_2$), 67.8 (t, $^1J_{CP}$ 149.2 Hz, CHP), 128.2, 129.5 (2s, Carom-H), 132.3, 135.6 (2s, Carom-C), 167.3 (t, $^3J_{CP}$ 15.4 Hz, CH=N) ppm; m/z 288 ($M^+$-$NCC_6H_4CH_3$, 100).

(t-Butyl-tris(tetramethylene) phosphazene) were the initial bases chosen for the generation of the carbanion derived from the bisphosphonate, but owing to the partially stabilized nature of the carbanion it was thought that a weaker base such as cesium carbonate ($Cs_2CO_3$) in THF/iPrOH would suffice [13]. In addition the use of this base does not require special precautions and provides excellent yields (see table 1). Compounds **3** were characterized by their spectroscopic data.[2] Thus, the mass spectrum of **3a** showed a molecular ion peak (*m/z* 371, 100 %), while in the $^{31}$P-NMR spectrum of compound **3a** the phosphoryl group resonate at $\delta_P$ = 14.3 ppm, and the $^1$H-NMR spectrum of this compound **3a** showed absorption at $\delta_H$ = 7.05 and 8.56 ppm for the vinylic and imine protons, the first one as a well resolved doublet with $^3J_{PH}$ = 16.6 Hz.

This methodology, used for the preparation of 2-azadienes derived from phosphonates **3**, can also be applied to the synthesis of 3-azatriene **4** (Table 1, entry 6) when the corresponding α,β-unsaturated imine **2** derived from the bisphosphonate is used. Likewise, 2-azatriene **5** (Table 1, entry 7) derived from phosphonate was prepared by the olefination reaction of the imine **2** with crotonaldehyde in the presence of cesium carbonate ($Cs_2CO_3$) as base in THF/iPrOH. Thermal 6-electrocyclization at 110°C of 2-azahexa-1,3,5-triene **5** provides 2-phosphonyl-pyridine **6** (Scheme 2) in a 50% yield. However, heating 3-azahexa-1,3,5-triene **4** at 105°C does not allow the preparation of the corresponding pyridine, the starting phosphonyl-azatriene **4** being recovered. These results are consistent with previously reported thermal 6π-electrocyclization processes by us [14a] and by others [14b] in the case of azatrienes derived from α-aminoacids.

Table 1.
Imines **2**, 2-azadienes and azatrienes **3, 4, 5** and pyridine **6** obtained.

| Entry | Comp. | $R^1$ | $R^2$ | Yield (%)[a] |
|---|---|---|---|---|
| 1 | **2a** | *p*-Me-Ph | — | 87 |
| 2 | **2b** |  | — | 65 |
| 3 | **2c** | (E)-Ph-CH=CH | — | 70 |
| 4 | **3a** | *p*-Me-Ph | *p*-Me-Ph | 67 |
| 5 | **3b** |  | Me | 75 |
| 6 | **4** | — | *p*-$NO_2$-Ph | 60 |
| 7 | **5** | *p*-Me-Ph | — | 70 |
| 8 | **6** | *p*-Me-Ph | — | 60 |

[a] Yield of products after flash chromatography. All compounds were isolated as yellow oils except compound **4** (yellow crystals, m.p. 95-96°C).

In conclusion, we here describe a simple method for the synthesis of azadienes **3**, azatrienes **4** and **5** and pyridine **6** derived from α-aminophosphonates, making use of readily available starting materials. Aminoalkyl bisphosphonate derivatives have generated great

[2] Spectral data for **3a**: $\upsilon_{max}$ (film) 1608, 1247, 1023 cm$^{-1}$; $\delta_H$ (300 MHz, $CDCl_3$) 1.26 (6H, t, $^3J_{HH}$ 7.0 Hz, 2 x $CH_3$-$CH_2$), 2.26, 2.35 (6H, 2s, 2 x $CH_3$-Ph), 4.11 (4H, q, $^3J_{HH}$ 7.0 Hz, 2 x $CH_2$), 7.05 (1H, d, $^3J_{PH}$ 16.6 Hz, CH=C), 7.09-7.70 (8H, m, Harom); 8.56 (1H, s, CH=N) ppm; $\delta_P$ (120MHz, $CDCl_3$) 14.3 ppm; $\delta_C$ (75.4 MHz, $CDCl_3$) 16.2 (s, $CH_3$-$CH_2$), 21.3, 21.5 (2s, $CH_3$-Ph), 62.1 (s, $CH_3$-$CH_2$), 128.7, 128.9, 129.4, 131.3 (4s, Carom-H), 131.9 (d, $^3J_{CP}$ 19.1 Hz, Carom-C), 132.6 (d, $^2J_{CP}$ 22.7 Hz, CH=C), 133.7, 138.7, 142.1 (Carom-C), 136.2 (d, $^1J_{CP}$ 175.2 Hz, CP), 162.1 (d, $^3J_{CP}$ 9.6 Hz, CH=N) ppm; m/z 371 ($M^+$, 100).

interest recently in medicinal chemistry as anti-inflammatory agents and for the treatment of bone diseases [15]. Further studies on 3-phosphonyl azadienes and imines derived from bisphosphonates are now in progress in our laboratory.

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