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A stereoselective palladium-catalyzed synthesis of amino alkenyl geminal bisphosphonates

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Abstract—The synthesis of amino alkenyl geminal bisphosphonates is carried out via the palladium-catalyzed ring opening of tetraethyl 2-vinyl-1,1-cyclopropane bisphosphonate **1** in the presence of a secondary amine at room temperature. The reaction proceeds with complete regio- and stereoselectivity.

Geminal bisphosphonates and their related acids are stable analogues of pyrophosphates and constitute an important class of pharmacologically active molecules. They bind to the bone mineral and inhibit the resorption of living bone.[1] A number of these compounds have found clinical use in the treatment of bone diseases such as Paget's disease, myeloma, bone metastases and osteoporosis.[2] Some others have also been proven to be efficient anti-inflammatory agents,[3] or exhibit antiprotozoal activity.[4]

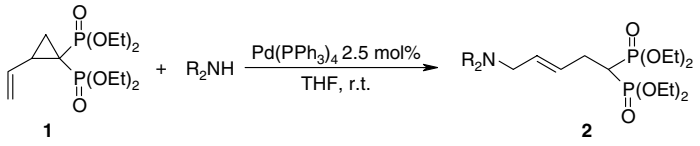
This interesting behaviour led to the development of a number of methods for the synthesis of bisphosphonates, including alkylation of tetraalkyl methylene bisphosphonate,[5] nucleophilic addition to ethylidene bisphosphonate esters,[6] enolate chemistry,[7] pentacovalent organophosphorus chemistry,[8] Diels–Alder reactions[9] and radical chemistry.[10]

The biological activities of these compounds are determined by the nature of the alkyl moiety bound to the bisphosphonic structure as well as the chemical groups located on the alkyl chain, with nitrogen-containing homologues amongst the most potent antiresorptives.[5a,8] They are also able to promote γδT cell activation.[11]

We report here the synthesis of a new class of amino functionalized bisphosphonates **2** via a palladium-catalyzed ring opening of tetraethyl 2-vinyl-1,1-cyclopropane bisphosphonate **1** with amines (Scheme 1).

This reaction is well documented for the related dialkyl 2-vinyl-1,1-cyclopropane dicarboxylates with soft carbon nucleophiles[12] and amines.[13]

Compound **1** was conveniently prepared in 83% yield by reacting stoichiometric amounts of 1,4-dibromobut-2-ene



1 2

Scheme 1.

Keywords: Bisphosphonates; Palladium; Vinylcyclopropanes; Tetraethyl 2-vinyl-1,1-cyclopropane bisphosphonate.
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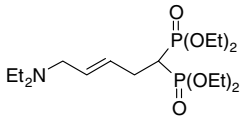
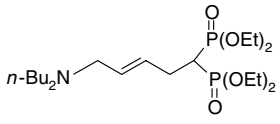
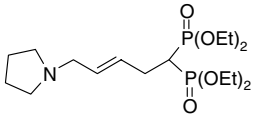
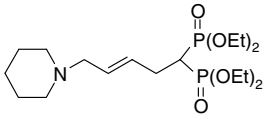
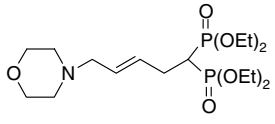
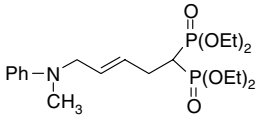
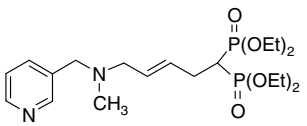
and tetraethyl methylene bisphosphonate in the presence of 2 equiv of sodium hydride at room temperature.[14]

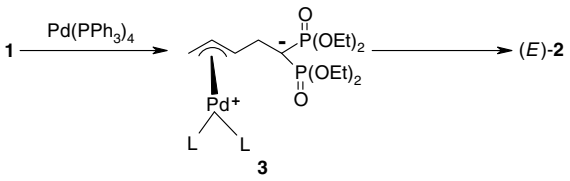
Next, the palladium-catalyzed synthesis was carried out by reacting **1** with 1.5 equiv of a secondary amine in the presence of 2.5 mol% of palladium tetrakis(triphenylphosphine) at room temperature[15] (Table 1).

The reaction is regio- and stereoselective, and the (*E*) geometry for the double bond was deduced from the $^3J_{HH}$ coupling constants for the ethylenic protons (ca. 15 Hz). It is known that activated vinylcyclopropanes react with palladium(0) complexes to produce (π-allyl)palladium intermediates.[12] Accordingly, the reaction of **1** with palladium tetrakis(triphenylphosphine) must generate the complex **3** which leads to bisphosphonates **2** upon attack of the amine to the less substituted carbon of the (π-allyl) moiety (Scheme 2).

Thus, the reaction allows the synthesis of bisphosphonates **2** in which the amino moiety may include alkyl or cycloalkyl substituents (entries 1–5), as well as aromatic rings (entry 6). The easy introduction of the (3-pyr-

Table 1. Palladium-catalyzed reaction of **1** with secondary amines

Entry	Amine	Product	Yield (%)
1	Diethylamine	 **2a**	88
2	Di(*n*-butyl)amine	 **2b**	92
3	Pyrrolidine	 **2c**	83
4	Piperidine	 **2d**	85
5	Morpholine	 **2e**	92
6	*N*-Methylaniline	 **2f**	93
7	*N*-Methyl-*N*-(3-pyridylmethyl)amine	 **2g**	75



Scheme 2.

idylmethyl)amino group (entry 7) constitutes an interesting access to heterocycle-substituted amino phosphonates.

Aromatic amines (pyrrole, carbazole) were not able to promote the reaction, presumably because of their less pronounced nucleophilic character. The use of their sodium salts (generated by prior reaction with sodium hydride) did not enhance their reactivity.

It is noteworthy that primary amines did not react, even in refluxing THF and upon prolonged reaction. This is rather surprising since allylic palladium-catalyzed amination is known to proceed readily with these substrates.[16]

In conclusion, the reaction described herein allows an easy synthesis of a new class of amino bisphosphonates **2** under mild conditions with good yields from **1**. Furthermore, the presence of the double bond in **2** may allow further functionalization, which can be useful for a structure–activity relationship study. Studies in this area as well as the evaluation of the biological activities of **2** are currently in progress.

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14. Synthesis of **1**: 1.8 g of 60% sodium hydride in mineral oil (45 mmol) was washed with petroleum ether (2×10 mL) and suspended in anhydrous THF (20 mL). A mixture of tetraethyl methylene bisphosphonate (4.55 g, 15.8 mmol) and 1,4-dibromobut-2-ene (3.43 g, 16 mmol) dissolved in THF (30 mL) was added dropwise with stirring at room temperature over 1 h, and the mixture was stirred at rt overnight. A 1 M HCl solution (50 mL) was added dropwise, and most of the THF was removed in vacuo. The mixture was then extracted with dichloromethane (4×30 mL), the combined extracts were washed with satd aqueous NaCl, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Kugelrohr distillation (130 °C/0.001 Torr) afforded pure **1** (4.45 g, 83%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.32$ (m, 12H), 1.66 (m, 2H), 2.52 (m, 1H), 4.11 (m, 8H), 5.13 (d, $J = 10.2$ Hz, 1H), 5.34 (d, $J = 17.0$ Hz, 1H), 6.06 (dt, $J = 17.0$ Hz, $J = 10.2$ Hz). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 16.3$, 17.5, 17.9 (dd, $J = 169$ Hz, $J = 167$ Hz), 28.6, 62.5 (d, $J = 7$ Hz), 118.3, 134.8. ^{31}P NMR (121.49 MHz, $CDCl_3$): $\delta = 22.9$ (d, $J = 20.8$ Hz), 24.2 (d, $J = 20.8$ Hz). IR (neat): 2983, 2932, 1443, 1248, 1165, 1097, 1027 cm^{-1}. MS (ESI): $m/z = 341$ [M+H$^+$]. Anal. calcd for $C_{13}H_{26}O_6P_2$: C, 45.88; H, 7.65; O, 28.23. Found: C, 45.98; H, 7.68; O, 28.31.
15. Typical procedure: To a stirred solution of tetrakis(triphenylphosphine)palladium (15 mg, 0.013 mmol) in anhydrous THF (2 mL) under argon was added a solution of **1** (170 mg, 0.5 mmol) in THF (1 mL) followed by a solution of diethylamine (73 mg, 1 mmol) in THF (1 mL), and the mixture was stirred at rt overnight. The solvent was removed in vacuo, the residue was dissolved in ethyl acetate (10 mL) and washed with 2% HCl until pH = 1. The combined aqueous washings were brought to pH = 10 by addition of solid K_2CO_3 and extracted with dichloromethane (3×10 mL). The combined extracts were washed with satd aqueous NaCl, dried with $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, methanol) to afford **2a** (182 mg, 88%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.0$ Hz, 6H),

1.25 (t, $J = 7.2$ Hz, 12H), 2.15–2.33 (m, 1H), 2.41 (q, $J = 7.0$ Hz, 4H), 2.5–2.67 (m, 2H), 2.92 (d, $J = 6.4$ Hz, 2H), 4.08 (quint., $J_{HP} = 7.2$ Hz, $J_{HH} = 7.2$ Hz, 8H), 5.53 (dt, $J = 15.1$ Hz, $J = 6.6$ Hz, 1H), 5.64 (dt, $J = 15.1$ Hz, $J = 6.6$ Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 11.5$, 16.2, 28.5, 37.3 (t, $J_{PC} = 134$ Hz), 46.3, 54.8, 62.3 (d, $J_{PC} = 7.5$ Hz), 129.4, 130.3 (d, $J_{PC} = 7.5$ Hz). ^{31}P NMR (121.49 MHz, $CDCl_3$): $\delta = 24.3$. IR (neat): 2977, 2931, 1741, 1441, 1251, 1165, 1029 cm^{-1}. MS (ESI): $m/z = 414$ [M+H$^+$].

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