Tetrahedron Letters 51 (2010) 3772–3774

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of β-aminovinylphosphonates by organocatalytic nucleophilic displacement of acetate with amines

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ARTICLE INFO

Article history:
Received 25 March 2010
Revised 10 May 2010
Accepted 12 May 2010
Available online 20 May 2010

Keywords:
β-Aminovinylphosphonates
Organocatalysis
Morita–Baylis–Hillman derivatives
1,4-Diazabicyclo[2.2.2] octane
Diethyl (α-acetoxymethyl) vinylphosphonate

ABSTRACT

The synthesis of diethyl β-aminovinylphosphonates **2** from acetoxy phosphonate **1** is described. The reaction entails an organocatalyzed substitution of the acetoxy group by primary or secondary amines. The use of a catalytic amount of DABCO is necessary if the amine is not nucleophilic enough, otherwise a strong nucleophilic amine can react without organocatalyst. The reaction led to a series of functionalized title compounds in good to excellent yields.

Functionalized vinylphosphonates constitute an important class of building blocks for which numerous synthetic methods have been reported.[1] In this area, β-aminovinylphosphonates, although much less studied, have received attention due to their use for the preparation of β-aminophosphonic acid derivatives[2] which display diverse biological activities such as antibiotics,[3] enzymes inhibitors,[4] anti HIV[5] and anti inflammatory agents.[6] In addition, they are used for the synthesis of hydroxyphosphonates or α-aminoesters[7] and 2,4-disubstituted tetrahydrothiophenes.[8]

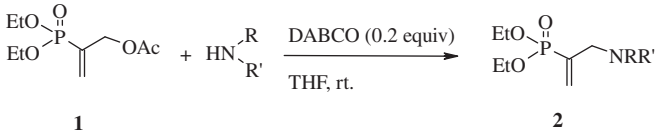
β-Aminovinylphosphonates have been obtained via Mannich reactions[9] or from dimethyl 3-chloropropene phosphonate.[10] On the other hand, *N*-(alkoxycarbonyl) β-aminovinylphosphonates were prepared by aziridination of dialkyl (1-trimethylsilanylmethyl-vinyl)phosphonates followed by silyl group elimination and aziridine ring opening,[11] by aldol-type addition of ethylphosphonate to trifluoromethyl-substituted imines followed by treatment with *m*-chloroperbenzoic acid,[12] from *N*-Boc aminoethylidene-1,1-bisphosphonates[13] and very recently by S_N2 displacement of 1,2-dibromo-2-propene followed by a nickel-catalyzed Arbusov reaction.[14] Finally, Krische and co-workers[15] reported a triphenylphosphine-catalyzed allylic substitution of Morita–Baylis–Hillman (MBH) 2-(diethylphosphonyl)-substituted allylic acetates with 4,5-dichlorophthalimide as the nucleophile. The synthesis of 2-amino-1-cycloalkenylphosphonates has also been reported using an amine-induced cyclization of ω-halo alkynylphosphonates.[16]

We wish to describe here an alternate synthesis of diethyl aminovinylphosphonates **2** using a displacement reaction of the acetate group in diethyl (α-acetoxymethyl) vinylphosphonate **1** by amines (Scheme 1). The reaction may occur spontaneously or in the presence of 20 mol % of DABCO (1,4-diazabicyclo[2.2.2] octane) as organocatalyst,[17] depending on the nature of the nucleophilic amine.

Compound **1** was obtained by standard acetylation[18] of diethyl (α-hydroxymethyl) vinylphosphonate[19] and formally corresponds to the acetylated MBH adduct of diethyl vinylphosphonate and formaldehyde.

As shown in Table 1, several primary and secondary amines reacted with **1** in THF at room temperature in the presence of 20 mol % DABCO, leading to β-aminovinylphosphonates **2** in good to excellent yields.

The DABCO-induced substitution of allylic MBH acetates is the subject of numerous reports,[20] and involves the DABCO-acetate



1 2

Scheme 1. Synthesis of β-aminovinyl phosphonates **2**.

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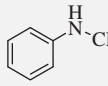
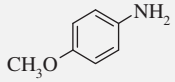
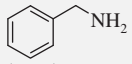
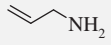
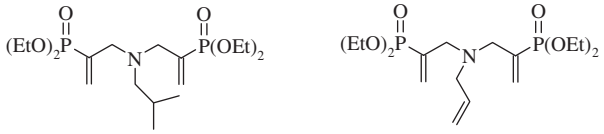
doi:10.1016/j.tetlet.2010.05.050

Table 1
Synthesis of β-aminovinylphosphonates **2** from acetoxyphosphonate **1**[a]

Entry	Amine	Yield (%)	
		Without DABCO	With DABCO (0.2 equiv)
1		10[b]	98
2		No reaction	91
3		2[b]	95
4		93	[c]
5	$(n\text{-Bu})_2NH$	83	[c]
6	$i\text{-BuNH}_2$	68[d]	71[e]
7		98	[c]
8		60[f]	67[g]

[a] Reactions were carried out with **1** (100 mg; 0.42 mmol), amine (0.47 mmol, 1.1 equiv) and DABCO (9.5 mg; 0.085 mmol, 0.2 equiv) in THF (1.5 mL) at rt for 24 h.
[b] Conversion measured by ^{31}P NMR.
[c] Not performed.
[d] Dialkylated product **3** was also obtained (25% yield).
[e] Dialkylated product **3** was also obtained (18% yield).
[f] Dialkylated product **4** was also obtained (35% yield).
[g] Dialkylated product **4** was also obtained (21% yield).



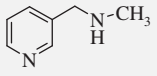
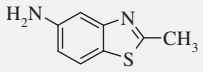
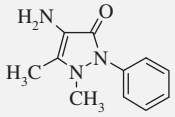
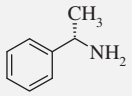
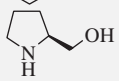
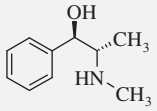
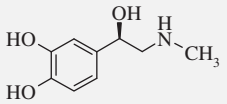
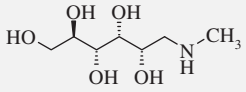
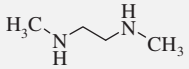
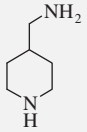
3 **4**

Figure 1.

salt intermediate which further yields the substitution product with regeneration of DABCO. The organocatalyst DABCO is essential for aromatic amines, that is, aniline (entry 1) which gives 98% yield of aminophosphonate (vs 10% conversion without DABCO), *N*-methyl aniline which does not react in the absence of organocatalyst (entry 2) and for anisidine (entry 3).

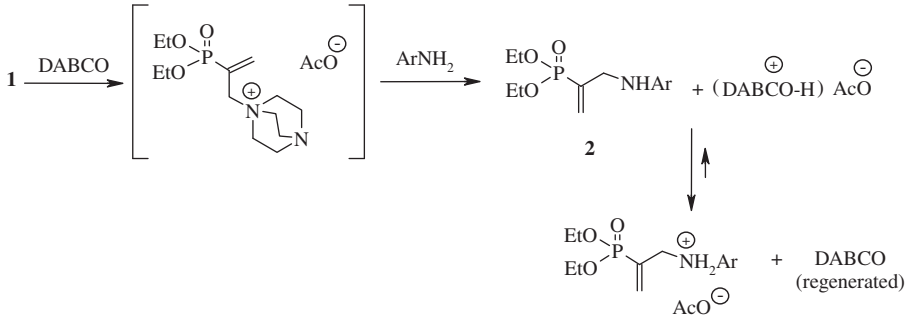
However, we found that the use of DABCO is not essential in the case of aliphatic amines which led to the expected aminovinylphosphonates by simple reaction with **1** (entries 4–8). This

Table 2
Synthesis of novel functionalized β-aminovinylphosphonates **2** from **1**[a]

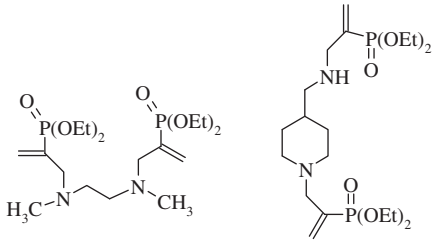
Entry	Amine	DABCO[b] (equiv)	Yield (%)
1		–	99
2		0.2	93
3		0.2	76
4		–	98
5		–	82
6		–	87
7		0.2	81
8		–	83
9[c]		–	60[d]
10[c]		–	58[d]

[a] Reactions were carried out with **1** (100 mg; 0.42 mmol), amine (0.47 mmol, 1.1 equiv) and DABCO (9.5 mg; 0.085 mmol, 0.2 equiv) in THF (1.5 mL) at rt for 24 h.
[b] DABCO was used if necessary.
[c] Reactions were carried out in the presence of 2 equiv of **1**.
[d] Yield of bisphosphonate (dialkylated product).

feature can be accounted for by a higher nucleophilic character of the amine and is due to the direct substitution of allylic MBH acetates by amines (or azides) in the absence of organocatalyst.[21] Furthermore, the formation of bisphosphonates **3** and **4** (Fig. 1) as a result of the dialkylation reaction was encountered in the case of isobutylamine (entry 6) and allylamine (entry 7), respectively.



Scheme 2. Mechanism for the synthesis of **2**.



5 6

Figure 2.

The presence of DABCO in these cases did not improve notably the selectivity.

Using 1.1 equiv of nucleophilic amine is sufficient to drive the reaction to completion. This suggests that even if the nucleophilic amine is partially consumed by evolved acetic acid to give the corresponding salt, it can be regenerated by proton exchange with the reaction product **2** already formed, thus leading to the acetate salt of **2**, together with liberated amine. When using aromatic amines where DABCO must be present, the substitution of the DABCO salt by amine regenerates DABCO along with acetic acid. According to the pK_a values for aniline and DABCO, one might expect a selective protonation of DABCO which should be deactivated. However, the higher concentration of **2** (compared to that of [DABCO−H]$^+$) presumably helps in shifting the equilibrium towards the regeneration of DABCO from its acetate salt (Scheme 2).

Encouraged by these results, we were interested in expanding the scope of the reaction to the synthesis of more complex β-aminovinylphosphonates by using different primary and secondary amines (Table 2), the reactions being carried out in the presence of DABCO, if necessary.

Thus, the reaction led to a facile route to heterocyclic derivatives **2** (entries 1–3), whereas enantiopure amine (entry 4) or aminoalcohols (entries 5–8) yielded chiral derivatives. In the case of diamines, the reaction led to unseparable complex mixtures, presumably mono- and bisphosphonates together with other byproducts. However, bisphosphonates **5** and **6** (Fig. 2) could eventually be obtained in satisfactory yields when the reactions were performed with 2 equiv of **1** (entries 9 and 10).

In summary, we have shown that functionalized β-aminovinylphosphonates can be easily obtained from **1** by an organocatalyzed substitution reaction of acetate by amines. This can lead to functionalized derivatives as well as chiral compounds, the reaction being performed at room temperature, using only a slight excess of amine, this feature being interesting in the case of amines whose preparation is multistep and time consuming. Depending on the nucleophilic character of this amine, using a catalytic amount of DABCO as the initiator is necessary, but a strong nucleophilic amine can react alone.

Acknowledgements

Financial support as a 'Ministère de la Recherche et de la Technologie' grant to Cécile Garzon and from C.N.R.S. is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.050.

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18. *Synthesis of* **1**: To a cooled (0 °C) solution of diethyl 3-hydroxyprop-1-en-2-ylphosphonate (1 g, 5.15 mmol), dimethylaminopyridine (0.038 g, 0.31 mmol, 0.06 equiv) and triethylamine (1.1 mL, 7.7 mmol, 1.5 equiv) in dichloromethane (10 mL) was added dropwise a solution of acetic anhydride (0.54 mL, 5.7 mmol, 1.1 equiv) in dichloromethane (30 mL) and the mixture was stirred at room temperature for 3 h. It was then washed with 15% Na_2CO_3 until pH 9, with 5% HCl (pH 2) and brine. After drying over $MgSO_4$, filtration and removal of solvents, the residue was purified by flash chromatography (ethyl acetate/methanol, 95:5) to furnish **1** as a colourless oil (1.02 g, 84% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, $^3J_{HH}$ = 7.0 Hz, 6H), 2.10 (s, 3H), 4.10 (qt, $^3J_{HH}$ = $^3J_{HP}$ = 7.1 Hz, 4H), 4.72 (dt, $^3J_{HP}$ = 8.8 Hz, $^4J_{HH'}$ = $^4J_{HH}$ = 1,5 Hz, 2H), 6.05 (dq, $^3J_{HP}$ = 46.0 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.5 Hz, 1H), 6.20 (dq, $^3J_{HP}$ = 22.5 Hz, $^2J_{HH}$ = $^4J_{HH}$ = 1.5 Hz, 1H). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 16.3 (d, $^3J_{PC}$ = 6.3 Hz), 20.8 (s, CH_3), 62.1 (d, $^2J_{PC}$ = 5.7 Hz), 62.8 (d, $^2J_{PC}$ = 17.8 Hz), 130.9 (d, $^2J_{PC'}$ = 6.9 Hz), 134.6 (d, $^1J_{PC'}$ = 177.8 Hz), 170.2 (s, C=O). ^{31}P NMR (121.49 MHz, $CDCl_3$): 17.0 ppm.
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