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Tetrahedron Letters 49 (2008) 2875–2877
Tetrahedron Letters

Carbamoylphosphonates Part 7. An efficient method for the synthesis of hindered carbamoylphosphonates using 4-nitrophenoxycarbonylphosphonate diesters

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Received 31 January 2008; revised 22 February 2008; accepted 6 March 2008
Available online 18 March 2008

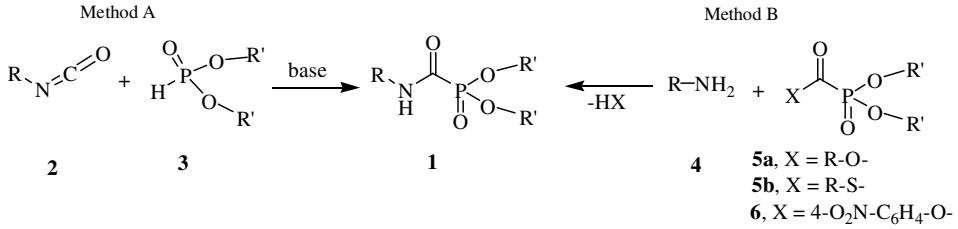
Abstract

Hindered primary amines that resist other reagents can be converted to carbamoylphosphonates by means of 4-nitrophenoxycarbonylphosphonate diesters in high yields and under mild conditions.

We have recently reported that some carbamoylphosphonic acids (CPOs, **1**, R′ = H) are capable of inhibiting matrix metalloproteinases (MMPs) in vitro,[1] and in vivo.[2,3]

Carbamoylphosphonates have been known for almost a century. The first compound of this class, the parent diethyl carbamoylphosphonate, $H_2NCOP(O)(OEt)_2$, was prepared by reacting triethyl phosphonoformate and anhydrous ammonia in an alcohol solvent for several weeks (**5a**, Method B, Scheme 1).[4] Later, substituted carbamoylphosphonates were prepared by the Arbuzov reactions of carbamoyl chlorides with trialkyl phosphites[5] or by the addition of dialkyl H-phosphonates **3** to alkyl or aryl isocyanates[6] (**2**, Method A, Scheme 1). Subsequently, it was found that this reaction could be accelerated significantly by base catalysis.[7]

Another convenient synthetic approach to compounds **1** is based on the reaction of trialkyl phosphonothiolformates[8] **5b** with ammonia[9] or an amine (**4**, Method B, Scheme 1). The latter approach is particularly convenient when a series of N-substituted carbamoylphosphonates are required as it uses a common, phosphorus-containing, starting material, **5b**, which can be reacted with many primary and secondary amines, instead of needing the synthesis of isocyanates **2** (Scheme 1). Triethyl phosphonothiolformate (**5b**, R = R′ = Et) reacts with amines via the cleavage of the *S*-acyl bond,[9] as opposed



Scheme 1.

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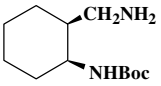
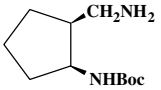
doi:10.1016/j.tetlet.2008.03.036

Table 1
Comparison of the efficiency of 4-nitrophenoxycarbonylphosphonate (**6**) and phosphonothiolformate (**5**) as reagents in carbamoylphosphonate synthesis

$$\underset{\mathbf{4}}{\text{R-NH}_2} + \underset{\mathbf{5}\text{ or }\mathbf{6}}{\text{X-CO-P(O)(OR')}_2} \rightarrow \underset{\mathbf{1}}{\text{R-NH-CO-P(O)(OR')}_2} + \text{H-X}$$

Reagent	**6** X = 4-O_2N–C_6H_4O–		**5b**, X = EtS–	
Starting material	Solvent	Product yield[a] (%) (reaction time, 1 h)[b]	Solvent (catalyst)	Product Yield[a] (%) (reaction time h)[b]
4, R–NH_2 *tert*-Bu–NH_2	MeCN	65	MeCN	30 (48)
1-Adamantyl–NH_2	DMF	83	DMF	0 (24)
	MeCN	50	MeCN (DMAP)	0 (72)
	DCM	85	MeCN	0 (24)

[a] Yields were determined by ^{31}P NMR spectral examination of the crude reaction mixtures.
[b] All reactions were performed at room temperature.

to *P*-acyl fission, which is the characteristic behavioral pattern of simple acylphosphonate diesters toward nucleophiles.[10] The phosphonate diesters **1** (R′ = alkyl) can subsequently be dealkylated with bromotrimethylsilane[11] (TMSBr) in chloroform[12] followed by methanolysis to the corresponding *N*-(*cyclo*)alkylcarbamoylphosphonic acids CPOs, **1**, R′ = H). As has been pointed out, some CPOs are active as MMP inhibitors, and are potentially useful in the treatment of various diseases such as cancer metastasis,[2,3,13] arthritis, and several other connective tissue-related disorders that have been shown to be mediated by MMPs.[13]

For our further studies we required CPOs derived from sterically hindered, tertiary alkyl- or 2-substituted cycloalkylamines. Attempts to obtain these using reagent **5b** (Method B, Scheme 1), however, were unsuccessful even under harsh conditions, and in the presence of 4-*N*,*N*-dimethylaminopyridine (DMAP) as catalyst, apparently due to its poor reactivity. We considered that the problem could be overcome by increasing the electrophilicity of the carbonyl group in **5b**, simply by substituting 'X' with a stronger electron-withdrawing group. Comparison of the pK_a values of the two leaving groups EtSH (pK_a = 10.6) with that of 4-nitrophenol (pK_a = 7.15) revealed three orders of magnitude difference between the two values. Therefore, we examined 4-nitrophenylphosphonoformate diethyl[14] and diisopropyl[15] esters, (abbreviated as Et–NPPF and *i*Pr–NPPF, respectively) **6a**, and **6b** as reagents in these syntheses. Indeed, we found that reagents **6** reacted rapidly with sterically hindered amines (that reacted only sluggishly or not at all with **5b**) to give the corresponding CPOs under mild conditions. The results of the reactions of four representative sterically hindered amines with the two reagents **5b** and **6** are shown in Table 1. The application of 'NPPF' esters **6** for the synthesis of CPOs has not been reported previously.

The reactions were carried out by mixing the reactants in a wide variety of solvents, such as hydrocarbons, halogenated hydrocarbons, ethers, amides (e.g., DMF) nitriles, amines and pyridine. An advantage of the reactions is that the salts of amines can also be used, as the free bases can be generated in situ by adding a strongly basic tertiary amine such as diisopropylethylamine to the reaction mixture. The onset of the reaction usually occurs instantly after mixing the reagents at room temperature as indicated by the appearance of the intense yellow color of the 4-nitrophenolate anion. Another convenient aspect of the method is that the difference in ^{31}P NMR chemical shifts between reagent **6** ($\delta = -6$ to -8 ppm) and the CPO products ($\delta = -2$ to -4 ppm) is sufficiently large to allow monitoring the progress of the reaction directly by ^{31}P NMR spectroscopy. At the end of the reaction, the 4-nitrophenol byproduct can be removed from the reaction mixture by extraction with 0.5 M NaOH solution. If the solvent used for the reaction is water soluble it must be replaced with dichloromethane. All the carbamoylphosphonate esters prepared are new compounds. They have been dealkylated by a treatment with TMSBr[11] to give the corresponding carbamoylphosphonic acids, which have been characterized by elemental analysis and by ^{1}H and ^{31}P NMR spectroscopy.

Acknowledgements

This work was supported in part by the Ministry of Science of Israel and in part by The German Israeli Foundation for Scientific Research and Development (GIF) to E.B. and R.R. and, in part, by the Grass Center for Drug Design and Synthesis of Novel Therapeutics. R.R. and E.B. are affiliated with the David R. Bloom Center of Pharmacy, in the School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem.

Supplementary data

Experimental procedures and analytical data of the compounds shown in Table 1 and of additional CPOs syn-

thesized using 4-nitrophenoxycarbonylphosphonate esters **6**, can be found in the Supplementary data associated with this article in the online version, at doi:10.1016/j.tetlet.2008.03.036.

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