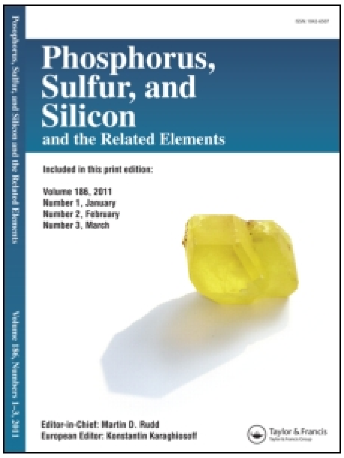

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of New α-Heterocyclic α-Aminophosphonates

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To cite this Article Boukallaba, K. , Elachqar, A. , Hallaoui, A. El , Alami, A. , Hajji, S. El , Labriti, B. , Martinez, J. and Rolland, V.(2006) 'Synthesis of New α-Heterocyclic α-Aminophosphonates', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 4, 819 — 823

To link to this Article: DOI: 10.1080/10426500500272046

URL: http://dx.doi.org/10.1080/10426500500272046

Phosphorus, Sulfur, and Silicon, 181:819–823, 2006
Copyright © Taylor & Francis Group, LLC
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500272046

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α-heterocyclic α-aminophosphonates were obtained in good yields by N*-alkylation of several nitrogen heterocycles with α-azido-α-aminophosphonate **1**.*[1]

Keywords α-Azido-α-aminophosphonate; heterocycle; N-alkylation

INTRODUCTION

Aminophosphonic acids are considered mimics of the corresponding α-aminocarboxylic acid.[2] The phosphonic moiety has long been established as a bioisostere of a carboxyl unit. These features explain the large range of biological activities[3] displayed by the members of this important class of compounds and the applications they have found ranging from medicine to agriculture, for example, as antibiotics,[4] enzyme inhibitors,[5] anticancer agents,[6] and herbicides.[7] These biological properties mostly are associated with the tetrahedral structure of the phosphonyl group acting as a "transition-state analogue (p 694)."[8]

Moreover, because of their ability to mimic transition states of hydrolysis, phosphonic acid derivatives having heteroatoms at the

Received May 24, 2005; accepted June 9, 2005.

We thank the CNRST-Morocco for financial support (Programs PROTARS D13/03).

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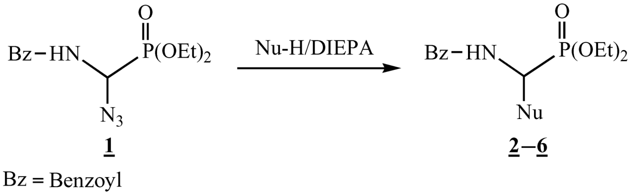
α-and/or β-positions have been shown recently to be inhibitors of various enzymes, including HIV-protease and human collagenase.[3,9]

The literature reports numerous methods of the synthesis of α-aminophosphonates.[10] However, to our knowledge, there are few methods available to their heterocyclic analogues.[3c,7,11]

Continuing our work concerning the preparation of heterocyclic α-aminoacids,[12] we report in this article the synthesis of new α-heterocyclic α-aminophosphonates.

RESULTS

Organic azides have proved to be efficient key intermediates in organic synthesis for the construction of heterocyclic systems by cycloaddition reactions, while the substitution of the azide group has received much less attention. We therefore used this last method for the preparation of α-heterocyclic α-aminophosphonates **2**–**6** (Scheme 1).



SCHEME 1

Diethyl α-azido-α-aminomethylphosphonate **1** was obtained by the reaction[1] of sodium azide with the α-bromo-α-amino phosphonic ester. The title compound is stable and can be stored for an unlimited time without any signs of decomposition. The α-bromo-α-aminophosphonic ester also can be used and gives satisfactory results; the azide **1** is used especially for its stability.

The reactions of different heterocyclic nucleophiles (benzimidazole, imidazole, pyrazole, 3,5-dimethylpyrazole, and 1,2,4-triazole) with **1** were conducted at r.t. in acetone in the presence of DIEPA (diisopropylethylamine); results are summarized in Table I. No progress of reaction was observed when pyrrole, indole or carbazole was used as a heterocycle.

Products **2**–**6** all were analyzed by HPLC, LC-MS (ESI Electrospray) and ^{1}H NMR. As shown in Table I, the N-alkylation products were obtained in good to high chemical yields (70–94%) by this method and exhibit high purity (82–99%).

Product **6** was identified as the N_1-isomer on the basis of literature data[13,14] and the chemical shifts of the triazolic proton.

TABLE I Synthesis of α-Heterocyclic α-Aminophosphonate Derivatives 2–6

Product	Nu-H	M.P. (°C)	Reaction time (h)	Yield (%)	HPLC Ret. time (min)	HPLC* purity (%)
2	Benzimidazole	135–137	16	94	8.3	86.5
3	Imidazole	135–137	16	80	6.7	82.0
4	Pyrazole	93–95	48	85	9.0	85.5
5	3,5-dimethylpyrazole	121–123	48	70	10.0	99.0
6	1,2,4-triazole	131–133	48	85	8.2	82.0

*Analytic HPLC were performed on a Waters apparatus with millenium program using a linear gradient of CH_3CN in H_2O with 0.1% TFA in 20 min.

In conclusion, the method described here provides a new and simple access to α-heterocyclic aminophosphonates starting from the appropriate azide 1. The N-alkylation of nitrogen heterocycles with azide occurred under very mild conditions and led to the desired products with good to excellent yields.

EXPERIMENTAL

Melting points were obtained on a electrothermal melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC-250 MHz spectrometer in $CDCl_3$, using TMS as internal standard and coupling constants are reported in Hertz. LC-MS identification by electrospray on a micromass ESI Platform II. Analytic HPLC were performed on a Waters apparatus with millenium program using a linear gradient of CH_3CN in H_2O with 0.1% TFA in 20 min.

Typical Procedure for N-Alkylation

To a stirred acetone solution (10 mL) of nitrogen heterocyclic compound (2.86 mmol) and diisopropylethylamine (3.12 mmol), diethyl 1-azido-1-(benzoylamino)methylphosphonate 1 (2.6 mmol) was added. The mixture was stirred at r.t. and the reaction was followed by TLC (Kiesegel Merck 60F524). The solvent was evaporated under vacuum, and the residue was dissolved with a saturated aqueous solution of ammonium chloride (20 mL) and extracted with dichloromethane (3 × 20 mL). The organic layer was dried with sodium sulfate (Na_2SO_4), and the solvent was removed. The product was purified wherever necessary by column chromatography on silica gel using ether/hexane or ether/methanol as an eluant to afford the pure N-alkylated product.

2: Rf = 0.18 (ether)
^{1}H NMR ($CDCl_3$)δ : 0.90 (t, 3H, J = 7 Hz); 1.30 (t, 3H, J = 7 Hz); 3.70–4.20 (m, 4H, OCH_2); 6.85 (dd, 1H_a, $^2J_{H-P}$ = 18.41 Hz, $^3J_{H-H}$ = 9.60 Hz); 7.15–7.75 (m, 10H, 9H_{arom} + NH); 8.35 (s, 1H, H_{Benzi}).
MS (electrospray) m/z = 388 [M + 1]

3: Rf = 0.3 (ether-methanol 95/5)
^{1}H NMR ($CDCl_3$)δ: 1.05 (t, 3H, J = 7 Hz, CH_3); 1.25 (t, 3H, J = 7 Hz); 3.70–4.15 (m, 4H, OCH_2); 6.60 (dd, 1H_a, $^2J_{H-P}$ = 17.29 Hz, $^3J_{H-H}$ = 9.73 Hz); 6.97(s, 1H, H_{imid}); 7.30 (s, 1H, H_{imid}); 7.32–7.46 (m, 3H, H_{arom}); 7.80 (m, 2H, H_{arom}); 7.83 (s, 1H, H_{imid}); 8.48 (m, 1H, NH).
MS (electrospray) m/z = 338 [M + 1]

4: Rf = 0.4 (ether)
^{1}H NMR ($CDCl_3$)δ: 1.15 (3H, t, J = 7 Hz, CH_3); 1.35 (3H, t, J = 7 Hz); 3.85–4.25 (m, 4H, OCH_2); 6.30(t, 1H, H_{pyr}); 6.80 (dd, 1H_a, $^2J_{H-P}$ = 16.45 Hz, $^3J_{H-H}$ = 9.75 Hz); 7.42–7.50 (m, 3H, H_{arom}); 7.55 (d, 1H, H_{pyr}); 7.78 (d, 1H, H_{pyr}); 7.86 (m, 2H, H_{arom}); 7.96 (1H, m, NH).
MS (electrospray) m/z = 338 [M + 1]

5 : Rf = 0.38 (ether)
^{1}H NMR ($CDCl_3$)δ: 1.10 (t, 3H, J = 7.04 Hz, CH_3); 1.30 (t, 3H, J = 7.04 Hz); 2.22 (s, 3H, H_{CH3} pyrazole); 2.38 (s, 3H, H_{CH3}pyrazole); 3.85–4.20 (m, 4H, OCH_2); 5.72 (s, 1H, H_{pyr}); 6.45 (dd, 1H_a, $^2J_{H-P}$ = 16.35 Hz, $^3J_{H-H}$ = 9.73 Hz); 7.32–7.46 (m, 3H, H_{arom}); 7.55 (m, 1H, NH); 7.36–7.47 (m, 2H, H_{arom}).
MS (electrospray) m/z = 366 [M + 1]

6 : Rf = 0.15 (ether)
^{1}H NMR ($CDCl_3$)δ: 1.10 (t, 3H, J = 7 Hz, CH_3); 1.30 (t, 3H, J = 7 Hz); 3.90–4.20 (m, 4H, OCH_2); 6.75 (dd, 1H_a, $^2J_{H-P}$ = 17.00 Hz, $^3J_{H-H}$ = 9.70 Hz); 7.35–7.48 (m, 3H, H_{arom}); 7.78–7.84 (m, 2H, H_{arom}); 7.95 (s, 1H, H_{tria}); 7.90–8.00 (m, 1H, NH); 8.40 (s, 1H, H_{tria}).
MS (electrospray) m/z = 339 [M + 1]

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