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Application of 1-Azidoalkylphosphonates in the Synthesis of Phosphonodipeptides and Other N-Substituted Aminophosphonates

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Efficient synthesis of diethyl 1-(isothiocyano)alkylphosphonates, and N-derivatives of diethyl 1-aminoalkylphosphonates as well as phosphonodipeptides were developed using diethyl 1-azidoalkylphosphonates as starting materials.

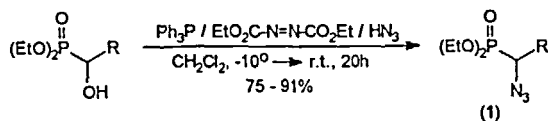
Keywords: diethyl 1-azidoalkylphosphonates; iminophosphoranes; phosphonodipeptides; diethyl (N-alkyl) 1-aminoalkylphosphonates; diethyl 1-(isothiocyano)alkylphosphonates

INTRODUCTION

Organic azides have been widely used in the synthesis especially for construction of heterocyclic systems and as precursors of the primary amino group.^[1] In turn, the presence of the phosphoryl moiety in the diethyl 1-azidoalkylphosphonates considerably extends synthetic applicability of these systems.

The Mitsunobu reaction,^[2] what was found by us^[3] and others,^[4] is the method of choice for the preparation of 1-azidoalkylphosphonates. According to the Scheme 1 diethyl 1-azidoalkylphosphonates^[3] (**1**) were obtained in high yields by the reaction of easily available diethyl 1-hydroxyalkylphosphonates with hydrazoic acid in the presence of triphenylphosphine/diethyl azodicarboxylate system. The title compounds are stable, distillable liquids and can be stored for unlimited time without any signs of decomposition.

Scheme 1



R: H, Me, Et, Pr, *i*-Pr, Bn, Ph

APPLICATION OF 1-AZIDOALKYLPHOSPHONATES IN THE SYNTHESIS OF N-SUBSTITUTED AMINOPHOSPHONATES AND PHOSPHONODIPEPTIDES

Recently, we have applied diethyl 1-azidoalkylphosphonates in the synthesis of 5-substituted 1-[1-(diethoxyphosphoryl)alkyl]-1*H*-1,2,3-triazoles^[5] and 1-alkenyl-1*H*-1,2,3-triazoles^[6] respectively.

We describe here efficient and simple methods for conversion of the title compounds (1) into diethyl 1-(isothiocyano)alkylphosphonates (2), N-(diethoxyphosphoryl) 1-aminoalkylphosphonates (3), and their N-alkyl analogs (4), N-(alkyl) 1-aminoalkylphosphonates (5) as well as O-ethyl 1-azidoalkylphosphonic acids (6) and derivatives of phosphonodipeptides (7-9). (Scheme 2). In most cases the Staudinger^[7] reaction is a key-step of these transformations.

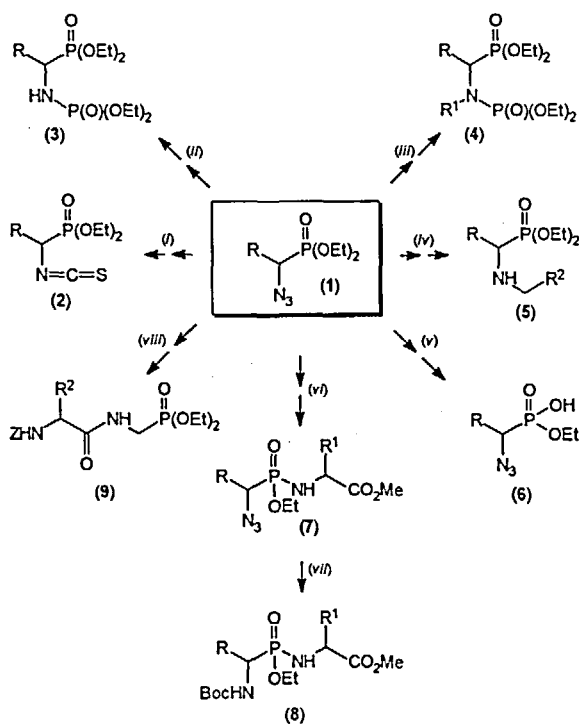
Thus, treatment of (1) with triphenylphosphine gave iminophosphoranes, which *in situ* were converted by carbon disulfide to novel class of phosphorylated isothiocyanates (2).

Similarly, iminophosphoranes formed *via* the Staudinger^[7] reaction between (1) and triethyl phosphite, were hydrolyzed with water or alkylated by means of alkyl halides to afford amino derivatives (3) and (4) respectively.

The aza-Wittig^[7] reaction of iminophosphoranes, obtained from (1) and triphenylphosphine, with appropriate aldehydes followed by immediate reduction of Schiff's bases thus formed with sodium borohydride, produced N-alkyl derivatives (5) with good yields.

The new methodology for the synthesis of phosphonodi-peptides has also been developed (Scheme 2).

Scheme 2



(i) $\text{Ph}_3\text{P}/\text{Benzene}$, r.t.; CS_2 , r.t. or reflux; (60-95%); (ii) $(\text{EtO})_3\text{P}/\text{THF}$, r.t.; H_2O reflux; (99%); (iii) $(\text{EtO})_3\text{P}/\text{THF}$, r.t.; R^1X reflux; (80-99%); (iv) $\text{Ph}_3\text{P}/\text{Benzene}$; R^2CHO ; NaBH_4 , r.t. or reflux; (65-96%); (v) LiBr or $\text{KOH}/\text{Ethanol}$, Δ ; (75-95%); (vi) COCl_2 ; $\text{Et}_3\text{N}/\text{Cl}$ $\text{H}_3\text{NCH}(\text{R}^1)\text{CO}_2\text{Me}$; (47-77%); (vii) $\text{H}_2\text{Pd-C}/\text{Boc}_2\text{O}$; (71-74%); (viii) $\text{Bu}_3\text{P}/\text{Toluene}$; $\text{ZHCH}(\text{R}^2)\text{CO}_2\text{H}$, Δ ; (50%).

Thus, O-ethyl 1-aminoalkylphosphonic acids (6), obtained by mono dealkylation of (1) with lithium bromide or potassium hydroxide, were coupled with amino acids esters to give the azide analogs of phosphonodipeptides (7). Next, compounds (7) were reduced with hydrogen in the presence of di-tert-butyl dicarbonate to Boc-derivatives of phosphonodipeptides (8).

By analogy to peptide chemistry,^[7,8] reaction of azide (1) with tributylphosphine followed by heating with Z-derivative of amino acids gave corresponding Z-derivative of phosphonodipeptide (9) with moderate yields.

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