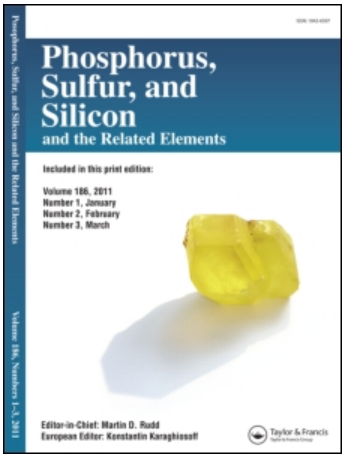

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Application of 1-Azidoalkylphosphonates in the Synthesis of Phosphonodipeptides and Other N-Substituted Aminophosphonates

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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.

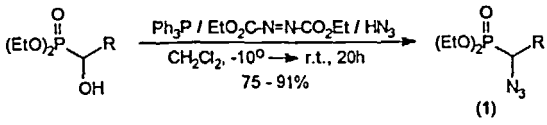
Keywords: diethyl 1-azidoalkylphosphonates; iminophosphoranes; phosphonodipeptides; diethyl (N-alkyl) 1-aminoalkylphosphonates; diethyl 1-(isothiocyano)alkylphosphonates

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.

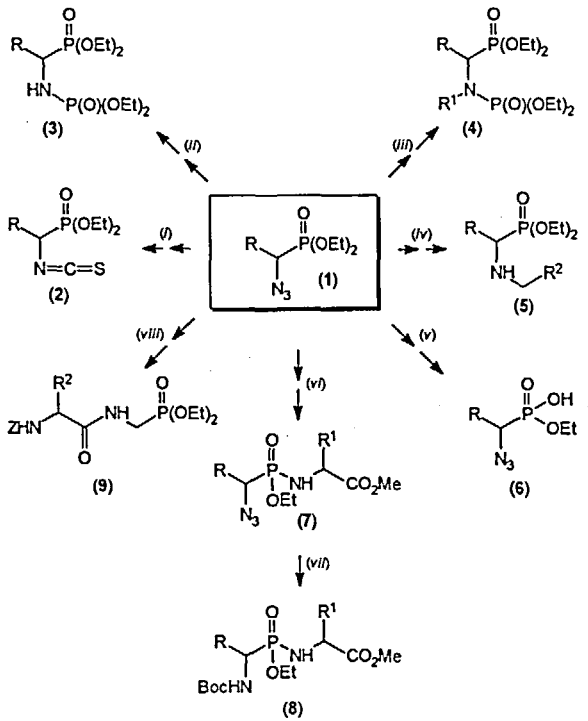
Thus, treatment of (**1**) with triphenylphosphine gave iminophosphoranes, which *in situ* were converted by carbon disulfide to novel class of phosphorylated isothiocyanates (**2**).

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 phosphonodipeptides has also been developed (Scheme 2).

Scheme 2



(*i*) Ph_3P/Benzene, r.t.; CS_2, r.t. or reflux; (60-95%); (*ii*) $(EtO)_3P$/THF, r.t.;H_2O reflux;(99%); (*iii*) $(EtO)_3P$/THF, r.t.; R^1X reflux;(80-99%); (*iv*) Ph_3P/Benzene; R^2CHO; $NaBH_4$, r.t. or reflux;(65-96%); (*v*) LiBr or KOH /Ethanol, Δ; (75-95%); (*vi*) $COCl_2$; $Et_3N/Cl^{\ominus}H_3\overset{\oplus}{N}CH(R^1)CO_2Me$; (47-77%); (*vii*)$H_2$/Pd-C/$Boc_2O$;(71-74%); (*viii*) Bu_3P/Toluene; $ZHNCH(R^2)CO_2H$, 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.

Acknowledgments

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