

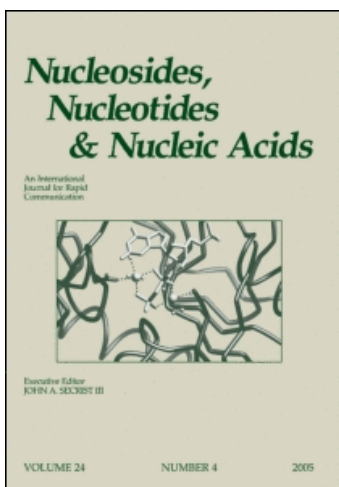
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Synthesis of [5'-Phosphoryl-N(α)]-oligonucleotidyl-peptides

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SYNTHESIS OF [5'-PHOSPHORYL-N(α)]-OLIGONUCLEOTIDYL-PEPTIDES

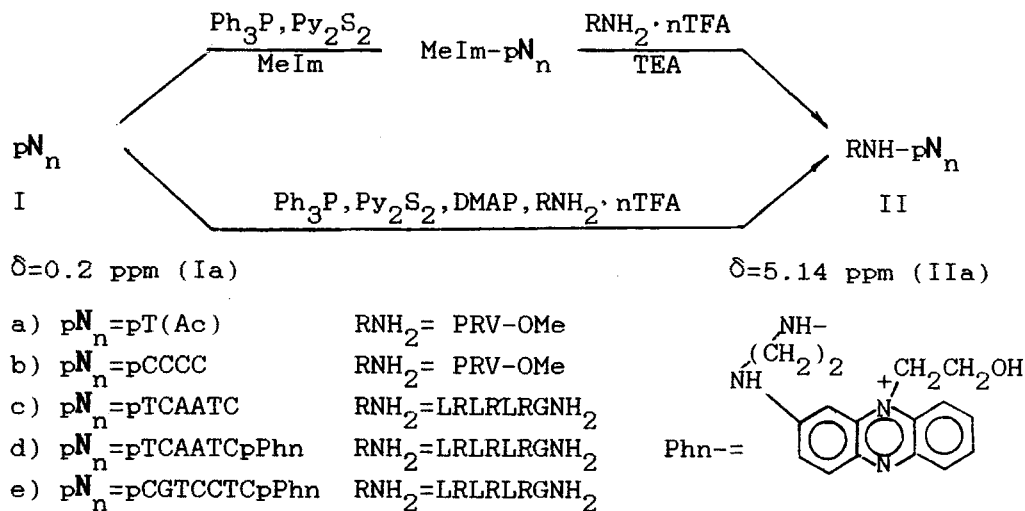
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ABSTRACT. An effective method for the synthesis of oligonucleotidyl-peptides via formation of a phosphoroamide bond between deblocked oligonucleotide and amino group of N-terminal amino acid was proposed.

To study structure and properties of covalently bound nucleotide-peptide complexes, nucleotidyl-peptides are used as model systems. The suggested method for covalent binding of deblocked oligonucleotides to the N-terminal amino group of peptides proved to be rather effective.

The reactions between an oligonucleotide (10^{-4} - 10^{-3} M) and a peptide (2.5×10^{-2} M) were carried out in anhydrous DMSO and DMF by triphenylphosphine (Ph_3P , 0.4 M) and



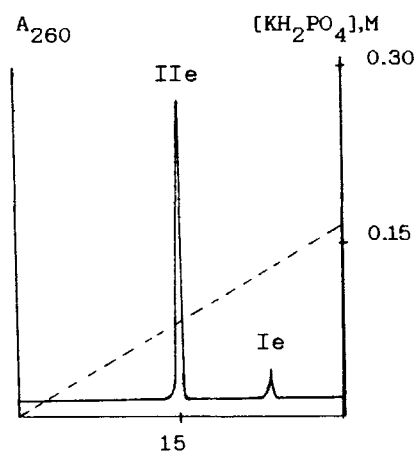


Fig.1.IEC of the reaction mixture containing IIE on a Polysyl CA 80 column.

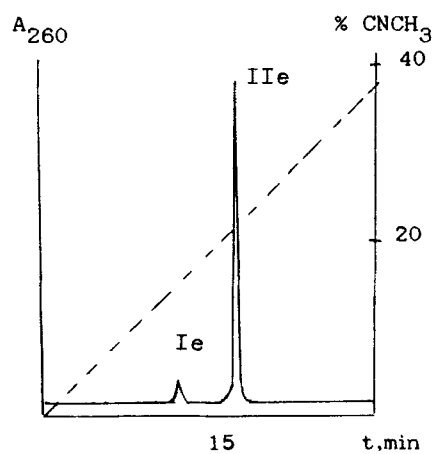


Fig.2.RPC of the reaction mixture containing IIE on a Lichrosorb RP 18 column.

2,2'-dipyridyldisulfide (Py_2S_2 , 0.4 M) in the presence of nucleophilic catalysts (1 M): 4-N'-N'-dimethylaminopyridine (DMAP) or 1-methylimidazole (MeIm).

According to the SCHEME the terminal phosphate of oligonucleotide must be activated prior to the addition of the peptide and TEA (0.2 M). In the case of DMAP, all components are mixed simultaneously and TEA is not added. All products were HPLC-purified with the yield of 70-80%.

The oligonucleotide-peptides bearing hydrophobic residues eluted from the column before the initial oligonucleotide (FIG.1) during IEC and after the initial oligonucleotide in RPC (FIG.2). The oligonucleotide-peptides are hydrolysed to yield parent oligonucleotides under conditions of phosphoroamide bond hydrolysis (20°C, 14 hr, pH 1).

The obtained results prove that oligonucleotidyl-peptides, including those bearing arginine residue, may be synthesized by our method to give a high yield.