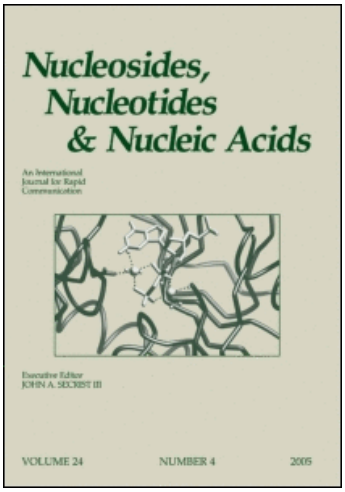

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Novel Synthesis of 2′-O Modified Oligonucleotides by Solid Phase Fragment Condensation

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INTRODUCTION

Oligonucleotides modified at 2′-OH position have attracted much attention from a biological and medicinal point of view because they have a number of advantageous properties for their application to antisense and antigene medicines. For example, they can bind to complementary RNA with higher affinity than native oligoDNA, and they are more resistant to nuclease degradation. It has been shown by the researchers of ISIS Pharmaceuticals Ltd. that ''gapmer technology'' combining this type of modification and sulfurization of phosphate backbone of oligonucleotides makes it possible to apply chemically modified oligonucleotides to antisense therapy.[1]

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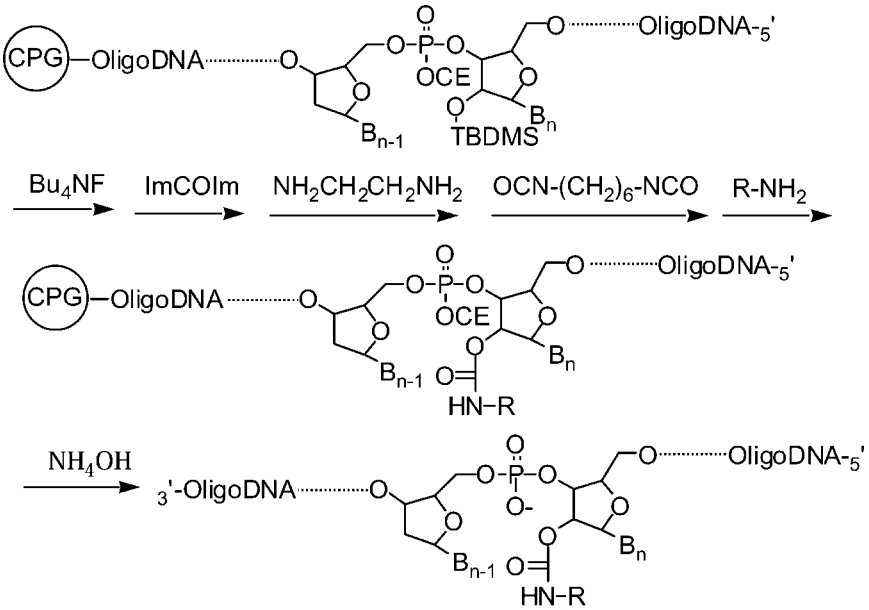
Almost of synthetic methods of them so far studied requires a preparation of phosphoramidite derivatives of the respective 2′-O modified nucleosides and the preparation sometimes includes complicated and prolonged steps. The present paper describes about the development of a novel method for the synthesis of 2′-O modified oligonucleotides by solid phase fragment condensation (SPFC).[2]

RESULTS AND DISCUSSIONS

This method involves a coupling of an amine derivative to an oligonucleotide fragment at 2′-O position on solid phase. (Sch. 1) Oligonucleotides including ribonucleotides with 2′-OH groups protected by *t*-butyldimethylsilyl (TBDMS) groups assembled on CPG support by a standard cyanoethylphosphoramidite chemistry were treated with tetrabutylammonium fluoride (TBAF) to remove TBDMS and set 2′-OH groups free. The CPG linked oligonucleotides were then reacted with carbonyldiimidazole (CDI) and amine derivatives, sequentially. After treatment with aqueous ammonia at 50°C for 5 h, the modified oligonucleotides were purified by RPHPLC two times (DMT on and DMT off) to give 2′-O modified oligonucleotides in 15–30% yields. Protected peptide fragments bearing a free amino group, amino sugars, polyamines, and any other amine derivatives can be employed in the present



Scheme 1. Synthesis of 2′-O modified oligonucleotides by SPFC.

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method. Since the present method requires only commercially available phosphoramidites and allows the modification of ribonucleotide moieties of any positions of oligonucleotides at one time, it can be applied to the synthesis of any types of 2′-O modified oligonucleotides.

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