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AN IMPROVED METHOD FOR THE SYNTHESIS OF N-PHENOXYACETYLRIBONUCLEOSIDES

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ABSTRACT

N-phenoxyacetylribonucleosides were prepared efficiently from the reaction of ribonucleosides with phenoxyacetylchloride and 1,2,4-triazole(for adenosine and cytidine) or 1-hydroxybenzotriazole (for guanosine).

INTRODUCTION

The potential use of ribozymes as the therapeutic agents has led to an increased interest in the facile and rapid synthesis of oligoribonucleotides and their analogs.[1,2] One of the positive

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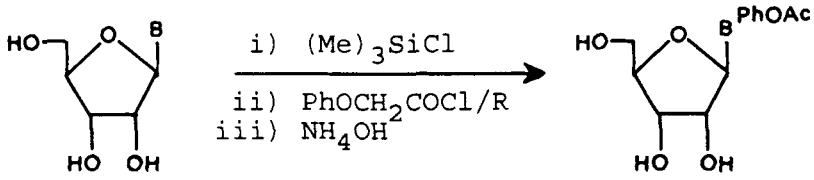
improvement in this direction would be to have a convenient procedure for the rapid and efficient synthesis of protected ribonucleosides, which are the primary building blocks in the synthesis of oligoribonucleotides of biological importance. In this communication, we have focussed our attention for improving the procedure for efficient synthesis of base protected nucleosides.

Various acyl groups have been introduced over the decades on the exocyclic amino function of adenosine, cytidine and guanosine. Phenoxyacetyl group has become the most common acyl protecting group because of its mild deprotection condition.[3,4] Introduction of this group is ususally carried out by phenoxyacetylchloride or phenoxyaceticanhydride[5] or a mixture of phenoxyacetylchloride and 1-hydroxybenzotriazole (HOBT),[6,7] using the 'transient protection method'.[8] But all the above methods have one or more drawbacks e.g. give moderate yields (49-65%), require longer reaction time or need an additional purification step because of colored side products.

We have found that N-phenoxyacetyltriazole, prepared by the addition of equimolar amount of phenoxyacetylchloride to 1,2,4-triazole,dissolved in acetonitrile:pyridine (1:1), can be used directly as an excellent acylating reagent for cytidine and adenosine. With this reagent, N^4-phenoxyacetylcytidine (2c) is obtained in 88% yield which is much higher than the previously reported method (64%)[6]. Exocyclic amino group of adenosine being less nucleophilic than that of cytidine took 7 h at 55°C to give N-phenoxyacetyl-adenosine (2a) in 70% yield. Finally, guanosine was acylated by this reagent, but the results were disappointing. In this case,the reported acylating reagent (mixture of phenoxyacetylchloride and 1-hydroxybenzotriazole) was found to be more suitable for the synthesis of N-phenoxyacetylguanosine (2b)[2] (yield 70%) when the reaction was performed at 55°C. It also reduced the reaction time to 5 h from the previously reported 17 h[7]. Thus, the method, described above for the preparation of N-phenoxyacetylribonucleosides is superior to the previously reported method. The products obtained



1(a-c) 2(a-c)

B : a) adenin-9-yl, b) guanin-9-yl, c) cytosin-1-yl

R : 1(a,c) = 1,2,4-triazole, 1(b) = HOBT

SCHEME

by this method do not require any chromatographic purification step.This method can be used in deoxy series too.

EXPERIMENTAL

TLC : Silica gel plates with flourescent indicator 254 nm., layer thickness 0.2 mm (Fluka), detection by UV. Melting points were determined with the capillary method and are uncorrected. Proton magnetic resonance spectra (^{1}H- NMR) were recorded on a Hitachi Perkin Elmer (60MHz) nmr instrument.

Synthesis of N-phenoxyacetylribonucleosides :

Trimethysilylchloride (9.5 ml,75 mmol) was added dropwise to the suspension of 10 mmol nucleoside in

anhydrous pyridine (60 ml) and the reaction mixture was stirred for 45 min. Meanwhile,phenoxy-acetylchloride (2.1 ml,15 mmol) was added dropwise to 1,2,4-triazole (1.03 g, 15 mmol for adenosine and cytidine) or HOBT (2.02 g, 15 mmol for guanosine) dissolved in acetonitrile (20 ml) and pyridine (20 ml). The acylating reagent thus formed, was added portionwise to the flask containing transiently protected nucleoside. The reaction was stirred for 2.5 h at room temparature for cytidine, 7 h at 55°C for adenosine and 5 h at 55°C for guanosine. During this time the reaction was complete as shown by TLC. Water (10 ml) was added followed after 25% ammonium hydroxide (5 ml). The solution was concentrated to remove pyridine, redissolved in water (100 ml for A,C ; 200 ml for G) and extracted with dichloromethane (80 ml). During the extraction, white product precipitated from the aqueous layer. For 2a, Rf = 0.6 and 2b, Rf = 0.34 in dichloromethane:methanol, 8:2 ; and for 2c,Rf = 0.26 in chloroform:methanol, 9:1. For compound 2a, m.p.132-133°C (lit.[5] 132-134°C); 2b, m.p. 168-170°C (lit.[5] 168-170°C) and 2c, m.p.175-176°C. The product obtained were

characterized by ^{1}H-NMR and comparison with authentic samples.[5]

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