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THE SYNTHESIS OF, AND STUDIES ON, 2'-C-MODIFIED NUCLEOTIDES

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ABSTRACT

The synthesis of uridine monomers containing either a 2'-deoxy-2'-C-methylcyano or ethylcyano group is described. These monomers are intended for incorporation into oligonucleotides to investigate a proposed duplex-stabilising effect exerted by 2'-tethered amide groups.

Previously we have investigated the synthesis of several functionalized 2'-C-branched nucleosides with the long term aim of constructing ribozymes with enhanced functionality and nuclease resistance. Encouragingly, preliminary studies have shown that the incorporation of these 2'-C-modified residues into dinucleoside monophosphates confers considerable resistance to nucleases (1). Related to this work Sproat and co-workers have shown that 2'-O-carbamoylmethyl containing oligonucleotides show higher affinity for RNA than those which contain the simple 2'-O-alkyl or allyl modification (2). These results suggest, that in addition to the known beneficial effect of the 2'-oxygen, the amide group itself has some stabilising effect on the duplex. To further investigate this effect we describe here the synthesis of monomers that will enable the incorporation of 2'-C-branched nucleosides containing an amide functionality appended to either a 1 or 2 carbon alkyl chain (Fig. 1).

We have previously experienced difficulties in incorporating amide-functionalised nucleoside monomers into oligonucleotides due to either poor phosphorylation

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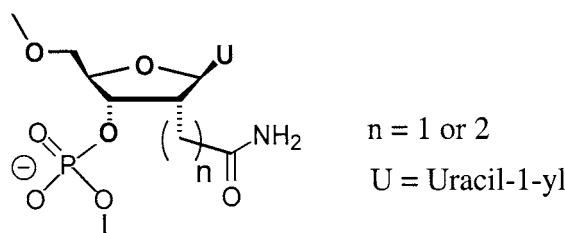


Figure 1.

to generate the amidite or dehydration of the amide to the nitrile during the iodine oxidation step (1). It seemed appropriate therefore to prepare the amidite monomers containing a nitrile group which could be converted by aminolysis to the amide. This approach has been successfully developed by Sproat and co-workers (2).

The synthesis of the required 2'-C-cyanoethyl- (1) and 2'-C-cyanomethyl- (2) uridine mononucleosides, from a common aldehyde precursor (3), is shown in Figure 2.

Model studies have shown that the cyanoethyl derivative 1 is cleanly converted to the corresponding amide by treatment with concentrated aqueous ammonia at 60°C. Following dimethoxytritylation and phosphitylation the cyanoethyl derivative 1 has been incorporated into oligonucleotides using standard automated procedures.

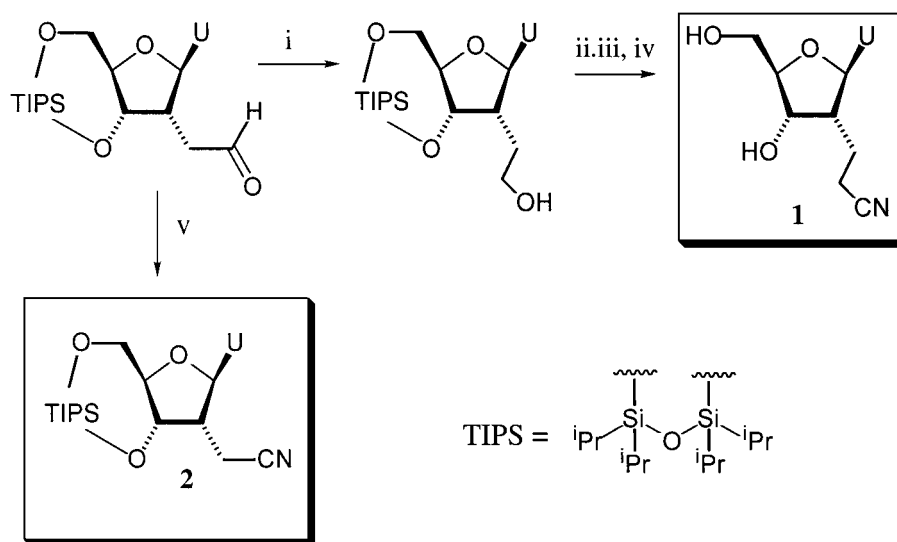


Figure 2. Reagents and Conditions i) NaBH_4 , MeOH, 81%; ii) MeSO_2Cl , pyridine, 87%; iii) NaCN, DMSO, 120°C, 71%; iv) $\text{NEt}_3 \cdot 3\text{HF}$, THF, 80%; v) $\text{NH}_2\text{OH} \cdot \text{HCl}$, CHCl_3 , SeO_2 .



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