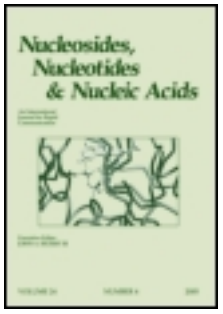

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SYNTHESIS OF FLUORINATED INDOLES AS RNA ANALOGUES

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□ *Nucleoside analogues are chemical means to investigate hydrogen bonds, base stacking, and solvation as the three predominant forces that are responsible for the stability of secondary structure of nucleic acids. To obtain deeper insight into the contributions of these interactions to RNA stability apart from the ones exerted by the predominant nucleosides we decided to synthesize some novel nucleic acid analogues where the nucleobases are replaced by fluoroindoles. Fluorinated indoles can be compared to fluorinated benzimidazoles to determine the role of nitrogen in five membered ring system. The synthesis of fluoroindole ribonucleosides is described here.*

Keywords Fluorinated inoles; RNA; fluorinated benzimidazoles

INTRODUCTION

A series of fluorobenzimidazole nucleosides has been already synthesized in our group.[1,2] The fluorobenzimidazole analogues investigated so far all show very similar properties. Thus, we decided to synthesize and evaluate the similar pattern of substitution on fluoroindoles. As the charge distribution and dipole moment between those two classes of compounds differ significantly, we expected also to observe differences in RNA oligonucleotide stability containing those building blocks. Here, we report strategies for the synthesis of fluoroindole building blocks.

SYNTHESIS

The synthesis of fluoroindoles (which are not commercial available) was achieved very efficiently in a four step procedure as shown in Figure 1.[3,4] Methyl azidoacetate, an intermediate in indole synthesis was synthesized by literature procedure.[5]

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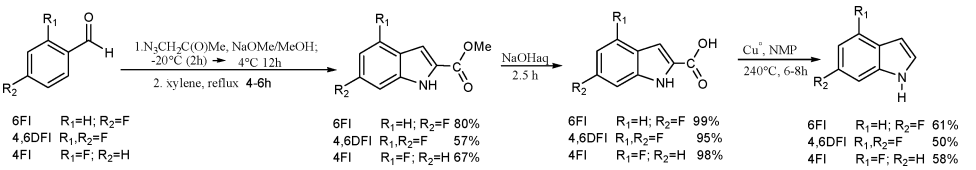

FIGURE 1 Synthesis of fluoroindoles.

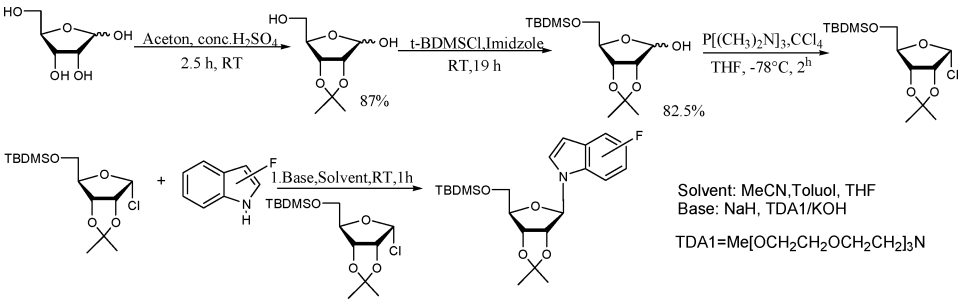

FIGURE 2 The direct glycosylation of fluoroindoles with halogenated ribose derivative.

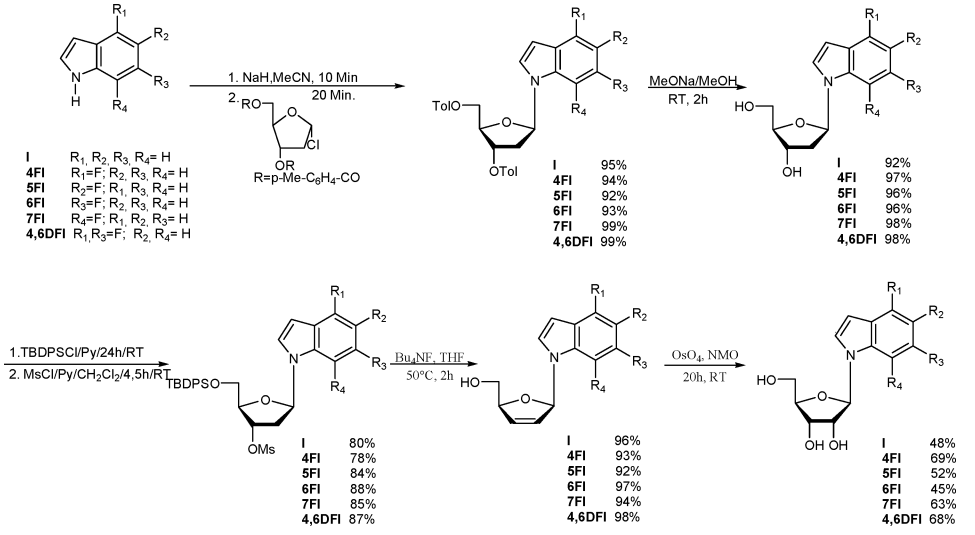

FIGURE 3 Efficient synthesis of fluoroindolenucleosides.

The direct synthesis of ribonucleosides (using halogenated ribose derivative) gave very poor yields below 5% and separation of the obtained products was very complicated[5] (Figure 2).

As none of the tried direct glycosylations was successful, we decided to synthesize first deoxy derivative and than the ribo derivative of the corresponding nucleosides as shown in Figure 3. For glycosylation, chlorodeoxyribose derivative was used.[6] The key point is that glycosylation reaction is very fast and, therefore, only ß isomer is obtained (isomerisation of the sugar

5 does not take place due to the fast reaction time). This reaction furnished the deoxynucleosides 1, 4FI-7FI, in very high yields (92–98%). The successive deprotection led to the corresponding unprotected ribose derivatives in almost quantitative yields. The synthesis of the ribo derivatives were then accomplished converting the deoxynucleosides into the corresponding riboderivatives. The synthesis of the ribo derivative was done in three steps with an overall yield of 57%. Despite the formal, "long way" of synthesis all procedures are worked out as routine and overall yields are very good[7] (Figure 3.).

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