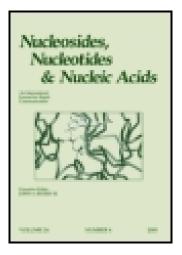
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# Nucleosides, Nucleotides and Nucleic Acids

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## Investigation of 1,3-Dipolar Cycloaddition Reactions of Unsaturated Nitrones in Ionic Liquids

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#### INVESTIGATION OF 1,3-DIPOLAR CYCLOADDITION REACTIONS OF UNSATURATED NITRONES IN IONIC LIQUIDS

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 $\Box$  The effect of the media (achiral and chiral ionic liquids) on the stereochemistry of intramolecular 1,3-dipolar cycloaddition reactions of D-galactose-derived  $\omega$ -unsaturated nitrones, leading to bicyclic isoxazolidines, has been investigated.

**Keywords** 1,3-dipolar cycloaddition; Bicyclic isoxazolidines; Ionic liquids; Nitronealkene cycloaddition; PNA analogues

#### **RESULTS AND DISCUSSION**

The recent advancements in the synthesis of peptide nucleic acids (PNA)<sup>[1,2]</sup> indicate that conformationally rigid PNAs derived from pyrrolidine rings<sup>[3,4]</sup> have outstanding biological features among the newly synthesized analogues. This fact prompted us to investigate the synthetic routes leading to new PNA analogues with azetidine moieties (ANA-1 and ANA-2, Figure 1)

Our synthetic strategy was based on the preparation of carbohydratebased bicyclic isoxazolidines that can further be elaborated into the target chiral azetidines. Herein we would like to report our preliminary results on intramolecular 1,3-dipolar cycloaddition reactions for the D-galacto series.

The reaction sequence shown in Scheme 1 was utilized since the simpler route, which involves iodination at the primary 6-hydroxyl group followed

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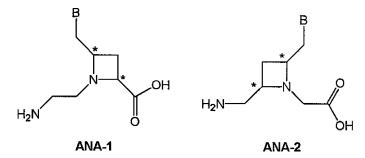
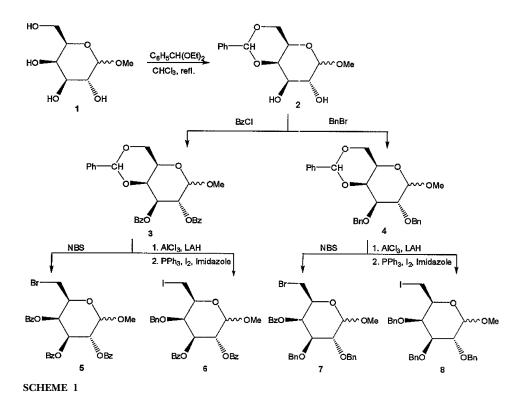
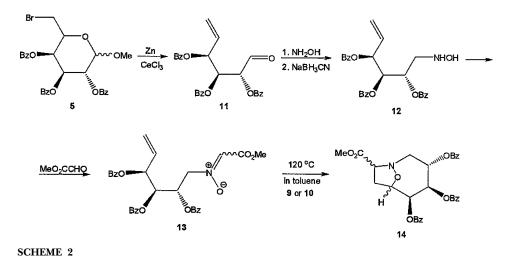


FIGURE 1 The structure of azetidine nucleic acid monomers ANA-1 and ANA-2.

by protection of the remaining secondary hydroxyl groups, failed. After selective protection of 4- and 6-hydroxyl groups of 1 as an acetal, the remaining free hydroxyl groups of compound 2 were protected either with benzoyl or benzyl protecting groups (3 and 4). The selective opening of the 4,6-*O*-benzylidene ring with *N*-bromosuccinimide<sup>[5]</sup> or with the LiAlH<sub>4</sub>-AlCl<sub>3</sub> reagent<sup>[6]</sup> provided a series of 6-deoxy-6-halo derivatives with different protecting group patterns (5–8). The oximes so obtained serve as building blocks for the synthesis of our target ANA derivatives (Scheme 2).





Starting from *N*-methyl-imidazole and L-alanine, ionic liquids  $9^{[7]}$  and  $10^{[8]}$  were prepared (Figure 2) to investigate the effect of media on the stereochemical outcome of cycloaddition reaction.

Starting from the bromine derivative 5, nitrone 13 was synthesized in four steps as depicted in Scheme 2. Nitrone 13 was heated in toluene in the presence of 9 and 10. The reactions carried out in toluene and in 9 furnished two isomers 14 out of the possible four diastereomers in ratios of ca. 3:1 and 8:1. In the presence of 10 only one isomer (the main product of the former two reacions) could be detected. Additionally, the conversion after 24 h at reflux was about 70% in toluene alone, whereas in the ionic liquids the starting nitrone 13 completely disappeared (TLC). The detailed NMR experiments to identify the absolute stereochemistry of the products formed are in progress.

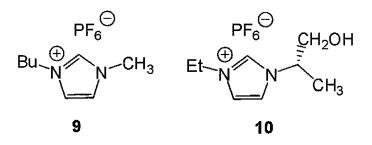


FIGURE 2 The structure of ionic liquids 9 and 10.

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