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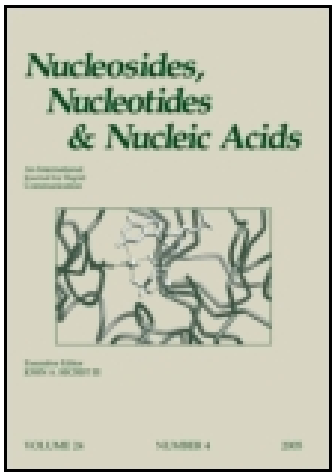

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AN INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION REACTION TOWARDS THE SYNTHESIS OF CHIRAL AZETIDINE NUCLEOSIDE ANALOGUES: THE D-GLUCO CASE

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AN INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION REACTION TOWARDS THE SYNTHESIS OF CHIRAL AZETIDINE NUCLEOSIDE ANALOGUES: THE D-*GLUCO* CASE

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▫ *The diastereoselective intramolecular 1,3-dipolar cycloaddition reaction of unsaturated nitrones, derived from methyl α-D-glucopyranoside with 2-furaldehyde and 2-(benzyloxy)acetaldehyde has been studied. In our pevious studies with 2-furaldehyde, the cycloaddition resulted 3 diastereoisomers in a 3:1:1 ratio. In this article, how the number of the possible isomers generated by 1,3-cycloaddition could be reduced from 4 to 1 when 2-(benzyloxy)acetaldehyde was employed as an aldehyde is shown.*

RESULTS AND DISCUSSION

In an attempt to overcome some of the undesirable properties of peptide nucleic acids (PNAs), we have designed conformationally restricted, chiral azetidine nucleic acids (ANAs). The key step in the synthesis of the ANA monomers, which are needed for construction of the oligomers, is a diastereoselective intramolecular 1,3-dipolar cycloaddition reaction involving unsaturated nitrones derived from carbohydrate precursors (Figure 1). The intramolecular 1,3-

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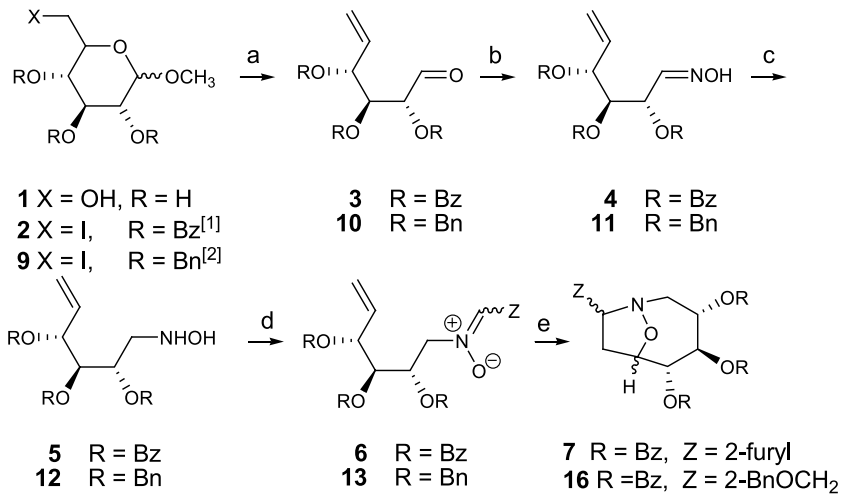

FIGURE 1 a) Zn, sonication[3] or Zn and Co(II)-phthalocyanine,[4] b) $NH_2OH \cdot HCl$, $NaHCO_3$,[5] c) $NaBH_3CN$, HCl/dioxane, d) 2-furaldehyde or 2-(benzyloxy)acetaldehyde, toluene, 4 Å MS, 50°C, 18 h, e) toluene, 120°C, 4 Å MS, Lewis acid catalysts, **7**, 16: 9-oxa-1-azabicyclo[4.2.1]nonane skeleton.

dipolar cycloaddition has the potential to reduce the number of possible resulting isomers by virtue of steric constraint. Thus, condensation of the hydroxylamines (**5** and **12**) with different aldehydes 2-furaldehyde (**14**), 2-(benzyloxy)acetaldehyde (**15**), took place successfully at 60–90°C (toluene, 4 Å MS) to afford the corresponding unsaturated nitrones. Subsequent ring closure yielded heterocycles (**7a–d** and **16**) as diastereomeric mixtures.

The effect of side chain protection on the regio- and diastereoselectivity of the intramolecular 1,3-cycloaddition has been studied in detail for the D-*gluco* series. The reaction involving the benzyl protected nitrone (**13**) proved to be sluggish (toluene, reflux, 1 week) and low-yielding; therefore, it was abandoned. All the cycloaddition products isolated exhibited the same regiochemistry. After 12–48 h, the benzoyl protected nitrone was found to afford only 9-oxa-1-azabicyclo[4.2.1]-nonane diastereoisomers **7b–7d** (Figure 2). We were unable to isolate the fourth diastereoisomer (**7a**) as it was produced in a negligible amount. We assume that the alternative 8-oxa-1-azabicyclo[4.2.1]nonane derivatives did not form because of steric hindrance between the furyl chain and oxazepane ring.

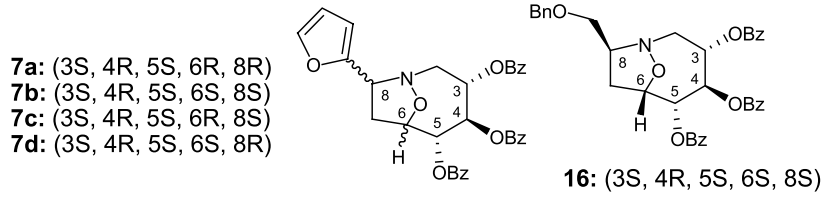

FIGURE 2 The structure of diastereoisomers **7a–7d** and **16**.

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The effect of different Lewis acid catalysts ($ZnCl_2$, $MgCl_2$, BF_3OEt_2), solvents (toluene, benzene, dioxane) and time (12–48 h) on yields and diastereomeric ratios have been examined in detail for reactions involving 2-furaldehyde (**14**). It was found that **7b** was the main isomer in all cases (except when dioxane and $ZnCl_2$ was used). We have ascertained that the best solvent for this reaction is toluene in presence of $MgCl_2$ as a Lewis acid catalyst (90% yield). The use of a hard Lewis acid catalyst caused elimination of the benzoyl protecting group and, sometimes, decomposition and conversion of the furyl group, too (yields: 17–32%). The stereoselectivity of the reaction did not alter much under the conditions explored. The cycloaddition was found to afford three 9-oxa-1-azabicyclo[4.2.1]nonane diastereomers in a 3:1:1 ratio.

Condensation of 2-(benzyloxy)acetaldehyde (**15**) with benzoyl protected hydroxylamine (**5**) resulted in formation of the single cycloaddition product (**16**), bearing the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton (Figure 2), and the expected intermediate unsaturated nitrone was not observed. The reaction took place at 90°C (toluene, 4 Å MS) without the addition of a Lewis acid catalyst. This surprising result implies that we could potentially reduce the number of the possible diastereoisomers generated by the intramolecular 1,3-cycloaddition from 4 to 1. The NMR measurements ^{1}H, ^{13}C, HSQC, and HMBC suggest the same *trans* arrangement for protons H-6 and H-8 in **16**. We have determined both the configuration of the newly formed chiral centers *(C-6, C-8)*, and the conformation of the 1,2-oxazepane ring for the all diastereoisomers **7b–7d** and **16**. Finally, the results show that the single isomer of **16** has the same configuration and conformation as the main isomer, **7b**. As a conclusion, various isoxazolidine precursors of chiral azetidine moieties have been successfully synthesised by employing an intramolecular 1,3-dipolar cycloaddition. Out of the three aldehydes examined to date, two of them, aldehydes **14** and **15** have been shown to be suitable candidates for use in this reaction. Our preliminary studies have also found that, when **15** is employed, one diastereoisomer of 9-oxa-1-azabicyclo[4.2.1]nonane is formed exclusively, out of a possible four. The configuration and conformation of the diastereoisomers of the resulting cycloadducts have been examined in detail using NMR studies. The effect of Lewis acid catalysts and solvents on yield and diastereomeric ratios have been investigated.

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