Efficient Synthesis of α-Purine Nucleosides of 2-Deoxyribofuranose and 2-Deoxyribopyranose

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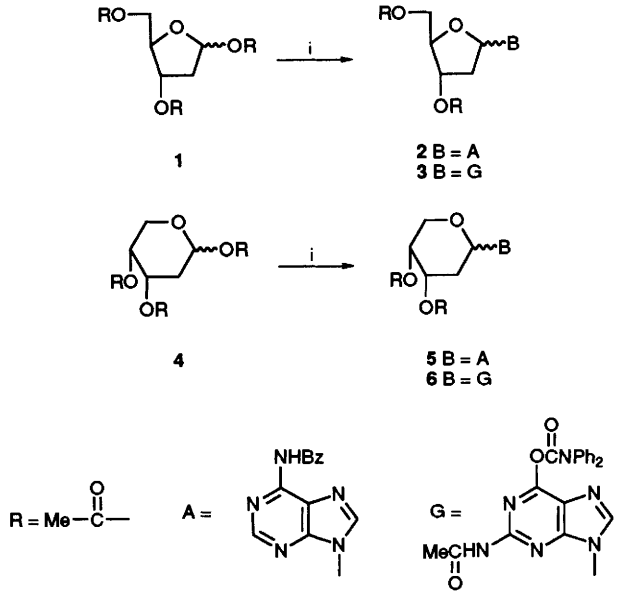
A high yield synthesis of α-purine nucleosides of 2-deoxyribofuranose and 2-deoxyribopyranose is reported starting from 1,3,5-tri-*O*-acetyl-2-deoxyribofuranose and 1,3,5-tri-*O*-acetyl-2-deoxyribopyranose with silylated purines under Lewis acid ($SnCl_4$) catalysed conditions.

Structural variants of oligodeoxynucleotides are valuable tools for studying protein-DNA interactions and are promising antisense agents in controlling gene expression.[1] α-Anomers of oligodeoxynucleotides[2] have been shown to form duplexes with complementary DNA or RNA *via* Watson–Crick hydrogen bonds.[3] The increased thermal stability of α/β duplexes[4] and their nuclease resistance[5] make them promising antisense therapeutic agents for *in vivo* application. Hence it is highly desirable to have stereoselective procedures that allow large scale synthesis. We have investigated the coupling reactions of various 2-deoxyribose derivatives with silylated bases in presence of Lewis acids. Here we report that the stannic chloride mediated coupling reactions of 1,3,5-tri-*O*-acetyl-2-deoxyribofuranose and 1,3,4-tri-*O*-acetyl-2-deoxyribopyranose with suitably protected purine derivatives proceed in very high yields and give excellent α-anomeric stereoselectivities. Suitably protected purines yield the desired N-9 regiochemistry while unprotected purines lead to mixtures of N-7 and N-9 regioisomers.[6] In comparison with the previous methods for preparation of α-anomers by Lewis acid catalysed conditions,[7] our method is highly efficient. Although our yields are comparable to the recently reported phase transfer glycosidation methods[8] our procedure gives higher α-anomeric selectivity in the case of adenosine. More significantly, our base protection scheme is superior for oligonucleotide synthesis by phosphoramidite or phosphodiester methods.

1,3,5-tri-*O*-acetyl-2-deoxyribose **1** was prepared starting from 2-deoxyribose.[9] *N*-benzoyl adenine (1.3 equiv.) was silylated using *N*,*O*-bistrimethylsilyl acetamide (BSA) (2.6 equiv.) in acetonitrile and the silyl derivative thus obtained was condensed with the sugar derivative **1** in the presence of $SnCl_4$ (1.3 equiv.) as devised by Vorbruggen *et. al.*[10] After 12 h of stirring at room temp., TLC showed the complete disappearance of starting material. After aqueous workup and chromatographic separation, compound **2** was isolated in 95% yield† with an α : β ratio of 78 : 22.‡ The sugar acetate **1** under the reaction conditions does not give rise to any side product, whereas the 1-*O*-methyl-3,5-di-*p*-toluoyl-2-deoxyribose under identical conditions gave the acyclic nucleosides arising via silylation of the ring oxygen[11] along with the expected cyclic nucleoside **2**. Furthermore the reaction proceeds to completion with only 1.3 equiv. of silylated base in a shorter period of time, yielding higher α-anomeric ratios. The choice of solvent, acetonitrile, proved to be critical for the success of the reaction. The reaction conducted in 1,2-dichloroethane under similar conditions resulted in a mixture of products from which the required nucleoside **2** was isolated in 60% yield with an anomeric ratio of α : β = 68 : 32.



Scheme 1 *Reagents and conditions*: i, B-[Si(Me)$_3$]$_2$, $SnCl_4$, MeCN, room temp.

Extension of this study to guanine nucleosides was then attempted. Of the several protecting groups[12] available for 6-*O*- of guanine, we chose diphenylcarbamoyl group,[13] since it gives an organic-soluble derivative for further elaborations. Treatment of the sugar acetate **1** with silylated 2-*N*-acetyl-6-*O*-diphenylcarbamoyl guanine (1.3 equiv.) in the presence of $SnCl_4$ (1.3 equiv.) in acetonitrile led to a mixture of products. Analysis of the products showed that the sugar acetate as well as the silylated guanine derivative undergoes decomposition. Similar guanine decomposition was also observed in the case of the reaction of 1-*O*-methyl-3,5-di-*p*-toluoyl-2-deoxyriboside with silylated guanine derivatives and 1.0 equiv. of $SnCl_4$. This observation prompted us to study the reaction with increasing amounts of $SnCl_4$. At 10 equiv. of $SnCl_4$ the reaction was complete in 16 h and the required nucleoside **3** was obtained in 80% yield with an anomeric ratio of α : β = 68 : 32. The reaction in 1,2-dichloroethane gave the nucleoside **3** in only 40% yield, with an anomeric ratio of α : β = 75 : 25. These results show that the success of the nucleoside synthesis depends not only on the reaction conditions, the sugar derivatives and the Lewis acid catalyst but also on the reacting nucleobase. The acetate protection for the hydroxy groups is a better choice than benzoyl, *p*-nitrobenzoyl or *p*-toluoyl groups, since the *O*-acetyl groups can be selectively cleaved without affecting the *N*-acetyl group.[14] Thus it avoids the additional steps needed in protecting the amino groups of purine nucleosides prior to phosphitylation.[7,15]

In the case of 2-deoxyribopyranose nucleosides, a recent report[16] showed the adenine derivative to be obtained in only 50% yield under Lewis acid ($SnCl_4$) catalysed conditions in 1,2-dichloroethane. Hence we reinvestigated this reaction using acetonitrile as the solvent. 1,3,5-tri-*O*-acetyl-2-deoxyribopyranose **4** was prepared by reacting 2-deoxyribose with acetic anhydride in pyridine. Reaction of the pyranose sugar acetate with silylated adenine (1.3 equiv.) in the presence of $SnCl_4$ (1.3 equiv.) gave the required nucleoside **5** in 85% yield, with an anomeric ratio of α : β = 52 : 48. Extending the reaction to guanine nucleoside was also successful. Treatment of the sugar derivative and the silylated 2-*N*-acetyl-6-*O*-diphenylcarbamoyl guanine in the presence of $SnCl_4$ (10 equiv.) gave the nucleoside **6** in 80% yield after chromatographic separation, with an anomeric ratio of α : β = 60 : 40.

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Footnotes

† All reported compounds showed satisfactory spectral data.
‡ Anomeric ratios were determined using ^{1}H NMR (300 MHz) spectrum by integration of 1′-H, 3′-H or 8-H protons for adenosine and guanosine derivatives. The α-anomer of 2-*N*-3′,5′-tri-*O*-acetyl-6-*O*-diphenylcarbamoyl-2′-deoxyguanosine is separable from the mixture by fractional crystallization (dichloromethane–diethyl ether = 1:1). Separation of the α-anomer of 6-*N*-benzoyl-3′,5′-di-*O*-acetyl-2′-deoxyadenosine proved to be difficult. However, α- and β-anomers of 6-*N*-benzoyl-5′-dimethoxytrityl-2′-deoxyadenosine are easily separable by silica gel chromatography (0–5% methanol in chloroform containing 0.1% pyridine).

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