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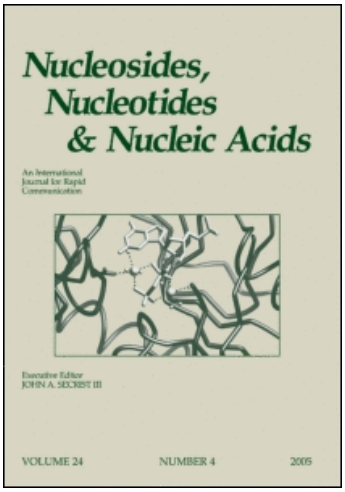

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Lithiation-Stannylation Chemistry of Nucleosides

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LITHIATION-STANNYLATION CHEMISTRY OF NUCLEOSIDES

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ABSTRACT: Two examples of anionic stannyl migration practically useful for nucleoside synthesis are presented. One involves the migration from the 8- to 2-position of 6-chloropurine derivatives, which provided a new entry to 2-substituted purine nucleosides. The other is that from the 6- to 2'-position of 1',2'-unsaturated uridine. The latter enabled the preparation of a hitheroto unknown class of nucleoside analogues, 2'-substituted 1',2'-unsaturated uridines.

Lithiation when used for the base-modification of nucleosides provides certain advantages over usual nucleophilic substitution: 1) the reaction can be carried out under very mild conditions, and 2) a considerable scope can be expected with respect to the reacting electrophiles.[1)] Two examples of stannyl migration observed in our lithiation studies of nucleosides are the present subjects.

Although the lithiation of 6-chloropurine nucleosides such as **1** with LDA takes place exclusively at the 8-position,[2)] reaction of the 8-lithiated species with Bu_3SnCl was found to result in the formation of the 2-stannylated product **2**. Several experiments suggested that the mechanism involves initial stannylation at the 8-position, which was followed by an intermolecular anionic stannyl migration. The 2-stannylated product **2** can be prepared in almost quantitative yield under optimized conditions where LTMP was employed in place of LDA. Manipulation of the stannyl group can be performed either at stage **2** or after converting to the adenosine derivative **3** to give various types

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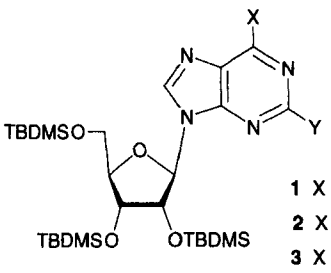
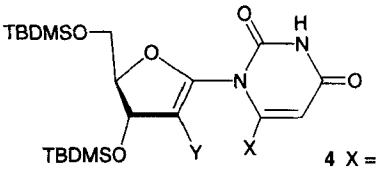
(halogeno, benzyl, phenyl, allyl, alkenyl, and alkynyl) of 2-substituted derivatives. This chemistry has been shown to be applicable to the synthesis of the 2-substituted analogs



1 X = Cl, Y = H
2 X = Cl, Y = $SnBu_3$
3 X = NH_2, Y = $SnBu_3$



4 X = H, Y = H
5 X = $SnBu_3$, Y = H
6 X = H, Y = $SnBu_3$
7 X = H, Y = I

of adenine nucleoside antibiotics, such as neplanocin A[3] and cordycepin.[4]

It has been known that LDA effects regioselective lithiation of uridine derivatives at the 6-position.[1] The LDA lithiation of 1',2'-unsaturated uridine **4**, first reported by Robins and Trip,[5] also follows the above selectivity, forming the 6-stannylated product **5** upon reacting with Bu_3SnCl. However, further LDA treatment of **5** gives the 2'-stannyl derivative **6** as a result of deprotonation of H-2' and subsequent intramolecular stannyl migration. This migration is encouraged by the use of LTMP as well as by the presence of HMPA. Iodination of the 2'-stannyl group in **6** can be carried out simply by reacting with iodine in THF. Both **6** and **7** serve as substrates for C-C bond forming reaction (Me, Ph, benzyl, and vinyl) at the 2'-position through organostannane chemistry.

Despite the reported instability of the deprotected 1',2'-unsaturated uridine,[5] desilylation of these 2'-substituted derivatives with NH_4F gave the corresponding free nucleosides uniformly in high yields.[6]

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