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LITHIATION OF AN IMIDAZOLE NUCLEOSIDE AT THE C-5 POSITION. SYNTHESIS OF 3-DEAZAGUANOSINE FROM URIDINE

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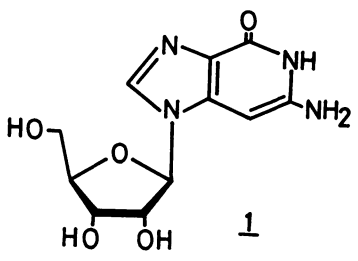
3-Deazaguanosine, an antiviral nucleoside, was synthesized from uridine via lithiation of a C-2 protected imidazole nucleoside, which has been devised as a method for introducing various functionalities to the C-5 position. This furnished the first successful example of the conversion of a naturally occurring nucleoside to a deazapurine nucleoside.

Although numerous studies to introduce a variety of functionalities to aromatic or hetero aromatic compounds by means of lithiation have been undertaken,[1] its application to nucleoside chemistry has only recently become recognized as a practically useful method. We have reported on lithiation of pyrimidine and purine nucleosides which furnished general access to modification of their base moieties.[2]

As part of our continuing work on the utilization of lithiation for synthetic purpose in nucleoside field, we were interested in lithiation of imidazole nucleosides which has been so far unknown.

In this communication, we would like to report that chlorine atom in the C-2 position of imidazole nucleoside serves as a protecting group during the lithiation with LDA to provide an efficient method for the introduction of various types of substituents to the C-5 position and a new route to 3-deazaguanosine (1), an antiviral nucleoside.[3]



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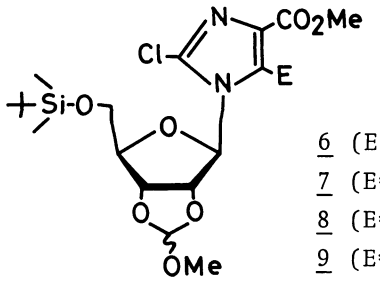
It is well known that lithiation of 1-substituted imidazoles occurs at the carbon between nitrogen atoms.[4] Thus, to generate the C-5 anion, protection of its C-2 position may be necessary. This suggests that compound 2, which can be obtained from uridine in relatively large quantity,[5,6] would be useful for our purpose. That is, 2-chloroimidazole nucleoside 3 accessible from 2 might be a good candidate for the lithiation at the C-5, provided that the C-2 protecting group is compatible with lithiation and removable under mild conditions.

Compound 2 was esterified, chlorinated and deacetylated according to the published procedures[6] to give 3. The sugar hydroxyl groups in 3 were protected by

the 2',3'-O-methoxymethylidene and 5'-O-TBDMS (tert-butyldimethylsilyl) groups, since removal of the 2',3'-O-isopropylidene and 5'-O-methoxymethyl groups previously used for uridine[2] caused cleavage of the glycosidic bond in the case of 3. Compound 4 was prepared in 89% yield by orthoester exchange (trimethyl orthoformate/p-TsOH/DMF) followed by treatment with an activated silica gel to remove 5'-O-protection.[7] Subsequent silylation (TBDMSCl/pyridine) of 4 gave a fully protected derivative (6) in 95% yield.

As LDA (lithium diisopropylamide) is a non-nucleophilic lithiating agent which is suitable for the metallation of nucleoside having a halogen substituent,[2,8] lithiation of 5 was carried out with LDA. When 5 in THF was added to a THF solution of LDA (1.8 eq) below -70 °C, a yellow solution of the anion resulted. Addition of MeI (1.8 eq) to the mixture (below -70 °C, 1.5 h) produced 5-methyl derivative (6: E= Me) in 83% yield. The structure of 6 was clear from disappearance of H-5 in its PMR spectrum and its MS spectrum (M^+: m/z 462 and 464).[9] It should be mentioned that products derived from the cleavage of C-Cl bond or the ester function in 5 were not detected in any appreciable amount in this reaction. We have also examined the reactions of the lithiated species of 5 with other electrophiles such as methyl chloroformate, benzoyl chloride, diphenyl disulfide and trimethylsilyl chloride. All these electrophiles gave the corresponding 5-substituted products (7-10) in high yields as shown in parentheses.



6 (E= Me, 83%)
7 (E= CO_2Me, 86%)
8 (E= COPh, 86%)
9 (E= SPh, 84%)
10 (E= $SiMe_3$, 87%)

We next intended to apply this method for the synthesis of 3-deazaguanosine (1), since it could overcome regio- and stereochemical problems encountered when classical condensation method is employed.[10,11]

Compound 5 was treated with LDA followed by HCOOEt (below -70 °C, 1 h) to produce 5-formyl derivative which was reduced by $NaBH_4$ in a one-pot manner to give 5-hydroxymethylated product (11) in 78% yield. The C-2 chlorine atom in 11, thus used as a protecting group, was subjected to hydrogenolytic cleavage (10% Pd-C/ 3 atm of H_2/Et_3N/MeOH) to leave 12 (90%). Chlorination of the hydroxymethyl group in 12 was first carried out in the presence of a bulky acid acceptor, 2,6-lutidine, to prevent the formation of a quarternary ammonium salt. It revealed, however, that partial deprotection of the sugar part took place during this reaction, presumably due to an acidic nature of 2,6-lutidinium salt formed. The use of Et_3N effected quantitative conversion of 12 to 13 (1.5 eq of MsCl/1.5 eq of Et_3N/DMF). 5-Cyanomethyl derivative (14) was obtained in 86% yield by nucleophilic substitution of 13 with cyanide anion in the presence of a crown ether (KCN/18-crown-6/benzene).

Cyclization of 14 to obtain a protected 3-deazaguanosine (15) was conducted with 28% NH_4OH/MeOH in a sealed tube at 80 °C for 2 h. Upon cooling the reaction mixture, 15 was separated as crystals (45%, mp 231-233 °C decomp). Formation of 15 was verified by PMR (DMSO-d_6: δ 5.63, NH_2; δ 6.08 and 7.80, two aromatic protons) and MS (M^+: m/z 438, B+1: m/z 150) spectroscopy.

Finally, treatment of 15 with 20% AcOH followed by dilute NH_4OH effected con-

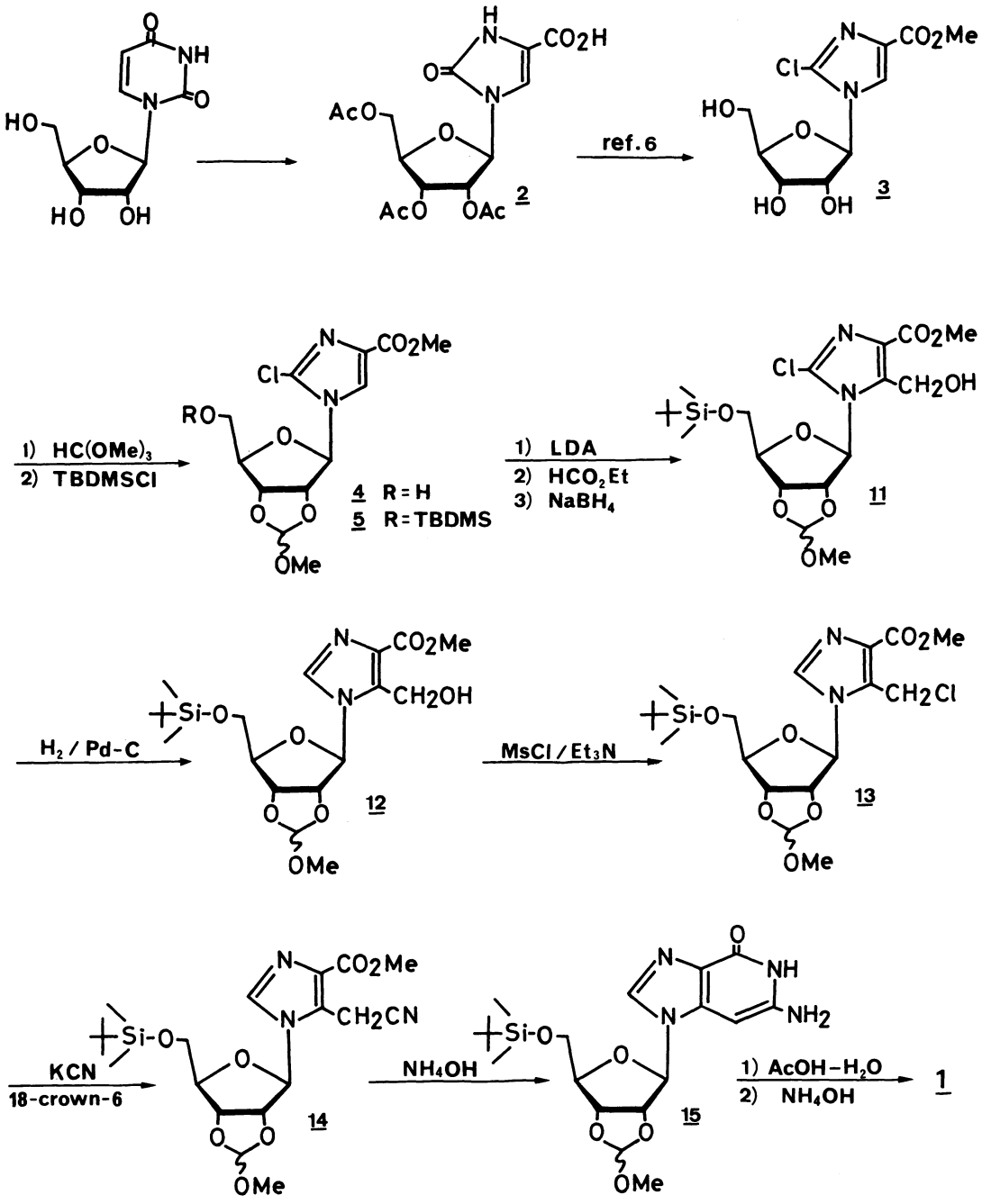


Chart 1.

current deprotection of the methoxymethylidene and TBDMS groups leading to 3-deazaguanosine (1: 80%, mp 254-256 °C decomp). Omission of the light was essential during deprotection, otherwise formation of a more polar product was observed. Physical constants of 1, thus obtained, are identical in all respects with those reported.[3)]

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