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Nucleosides and Nucleotides. 114. A Convenient Method for the Synthesis of 3-Deazapurine Nucleosides from AICA-Riboside[1]

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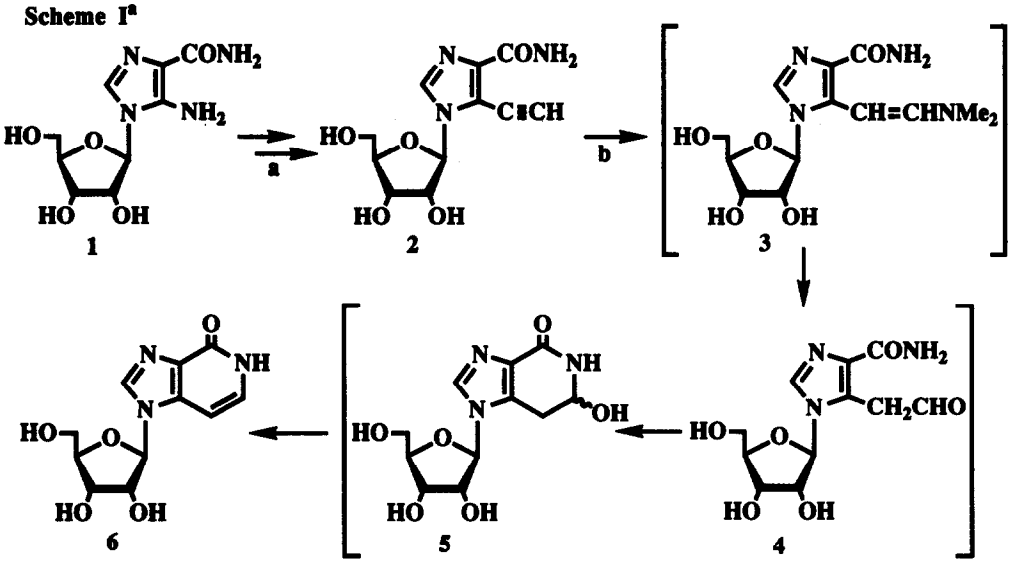
Key Words: nucleoside; 3-deazapurine nucleoside; 3-deazaadenosine; 3-deazaguanosine; 3-deazainosine; acetylene; antiviral agent

Abstract: 3-Deazapurine nucleosides, 3-deazainosine (**6**), 3-deazaguanosine (**12**), and 3-deazaadenosine (**17**), were synthesized from 5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamide (**2**) or -4-carbonitrile (**13**), which were readily obtained from AICA-riboside, via intramolecular ring closure.

Since the original isolation of the antibiotics toyocamycin and tubercidine, and subsequent structural elucidation of these antibiotics as 7-deazapurine nucleosides, numerous deazapurine nucleosides have been synthesized in the search for anticancer and antiviral agents. Interesting compounds in this category are the 3-deazapurine nucleosides, especially 3-deaza-adenosine and -guanosine. 3-Deazaadenosine was found to be a potent inhibitor of *S*-adenosylhomocysteine hydrolase.[2] It was also reported that the nucleoside inhibits the reverse transcriptase of HIV-1.[3] On the other hand, 3-deazaguanosine has demonstrated potent antiviral activity *in vitro* against a variety of DNA and RNA viruses[4] as well as *in vivo* activity against L1210 leukemia and adenocarcinoma 755 in mice.[5] 2'-Deoxy analogues of 3-deazapurine nucleoside were also used as valuable probes for study of protein-nucleic acid interactions.[6] In spite of the interesting biological and pharmacological properties of the 3-deazapurine nucleosides, almost all of the synthetic methods so far reported involved classical condensation methods with appropriate 3-deazapurines and sugars, which suffer from regio- and stereochemical disadvantages.[7] Therefore, it seems worthwhile to develop a new general synthetic route from readily available nucleosides which will be free from these disadvantages. To achieve our purpose, a most straightforward route is to synthesize 4-carboxamidoimidazole nucleosides having formyl- and cyano-methylene groups at the 5-position, followed by ring closure of these nucleosides to make the target nucleosides. We have already reported the introduction of alkynyl groups into the 5-position of such imidazole nucleosides, which was easily obtained from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA-riboside, **1**), by organopalladium chemistry.[8] Since modification of terminal alkynes has already been demonstrated as a Willgerodt-Kindler reaction,[9] we apply this methodology to 5-ethynyl-1-β-D-ribofuranosylimidazole-4-carboxamede (**2**) and -4-carbonitrile (**13**) to find out a new convenient method for the synthesis of 3-deazapurine nucleosides.

Treatment of **2** with 50% aqueous dimethylamine in EtOH at 80 °C in a sealed tube, followed by 50% aqueous acetic acid–EtOH (1: 1) gave the desired 3-deazainosine (**6**)[10] in 64% yield. In this reaction, a series of reactions (hydroamination of **2**, hydrolysis of **3**, intramolecular ring closure of **4**, and dehydration from **5**) could proceed successively. Treatment of **5** with acetic acid accelerated the formation of **6**.

Scheme I[a]

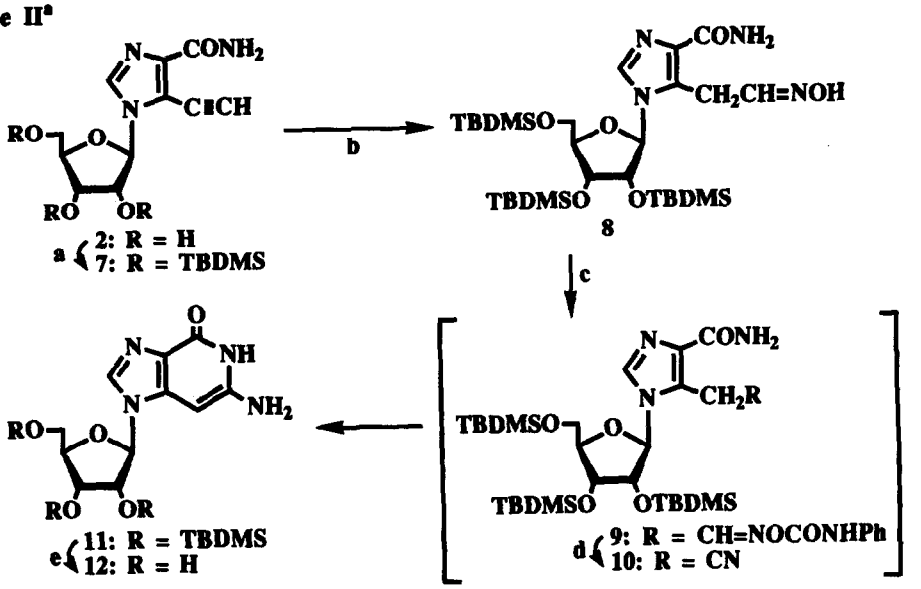


[a]a) ref. 8; b) 50% aq. Me_2NH in EtOH, 80 °C, 5.5 h, then 50% aq. AcOH in EtOH, room temperature.

For the synthesis of 3-deazaguanosine (**12**), it could be easily prepared if the formyl group in **4** reacts with hydroxylamine faster than the intramolecular ring closure to **5**. Compound **2** was first silylated with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of imidazole in *N*, *N*-dimethylformamide (DMF) to give **7** in 92% yield. After hydroamination of **7** was carried out at 50 °C with 50% aqueous dimethylamine, hydroxylamine hydrochloride and acetic acid were then added to the reaction mixture. The desired **8** was obtained in 91% yield without formation of the 3-deazainosine derivative. After several attempts, we found phenyl isocyanate as the choice for dehydration. Treatment of **8** with phenyl isocyanate in benzene gave intermediate **9**, which was subsequently heated in EtOH–5% aqueous sodium carbonate at 100 °C to give **11** in 56% yield from **8** via intermediate **10**. Compound **11** was then deprotected by tetrabutylammonium fluoride (TBAF) to give 3-deazaguanosine (**12**)[10] in 78% yield.

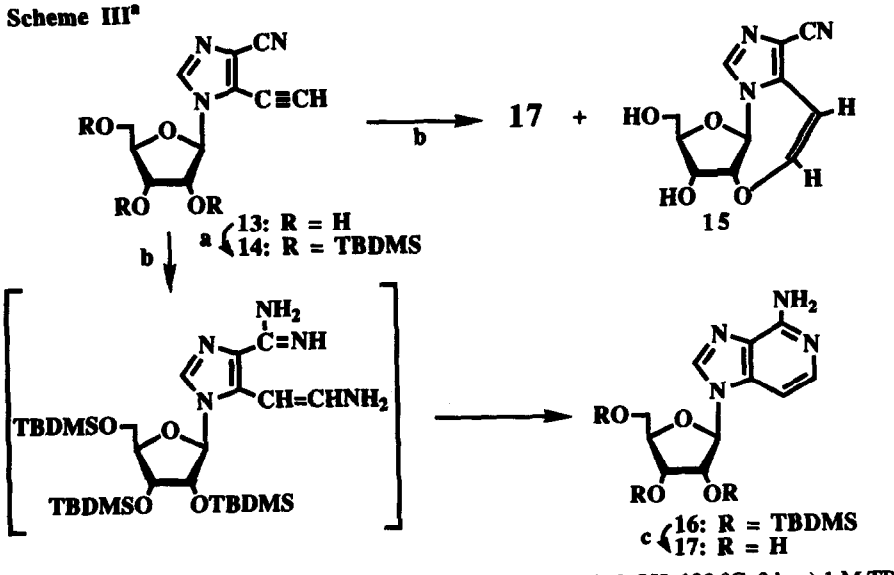
The route for the synthesis of 3-deazaadenosine (**17**) was similarly based on the knowledge that intramolecular ring closure proceeds between substituents of the imidazole ring. That is to say, it could be prepared if both hydroamination to 5-ethynyl group and conversion of the 4-cyano group to the corresponding 4-amidino group proceed at the same time. We first used **13** as a starting material, which was obtained in a similar manner as **2**[8b], with methanolic ammonia at 120 °C in a sealed tube. The desired **17** was obtained in only 17% yield along with 5, 2'-*O*-cycloetheno derivative **15**[11], which might be obtained by a direct reaction between the 2'-hydroxyl and the 5-ethynyl groups. In this reaction, it is thought that the transformation of the cyano group to the amidino group would be a rate-determining step, therefore, formation of **15** is of greater advantage than of **17** in unprotected form. Consequently, the hydroxyl groups of the sugar moiety were protected with TBDMSCl to give **14** in 83% yield. When **14** was treated with methanolic ammonia as above, 3-deazaadenosine derivative **16** was obtained in 76% yield. Compound **16** was then deprotected to give 3-deazaadenosine (**17**).[10] In this method, **17** was obtained as a free form which is free from the perplexing problems reported by Mizuno *et al.* before.[12]

Scheme II[a]



[a]a) TBDMSCl, imidazole in DMF, room temperature; b) 50% aq. Me_2NH in EtOH, 50 °C, 8 h, then NH_2OH·HCl, AcOH, room temperature; c) PhNCO in benzene, room temperature, 1.5 h; d) 5% aq. Na_2CO_3–EtOH, 100 °C, 1.5 h; e) 1 M TBAF in THF.

Scheme III[a]



[a]a) TBDMSCl, imidazole in DMF, room temperature; b) NH_3 / MeOH, 120 °C, 3 h; c) 1 M TBAF in THF.

We concluded that 3-deazapurine nucleosides, 3-deazainosine, 3-deazaguanosine, and 3-deazaadenosine, were conveniently synthesized from AICA-riboside. This method can be generalized and used for the synthesis of a wide variety of 3-deazapurine derivatives.

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10. Physical constants of **6**, **12**, and **17** were identical in all respects with those reported.[7]
11. **15**: mp 198-201° C; MS *m/z* 249 (M^+); ^1H NMR (DMSO-d_6) δ 7.77 (s, 1H, H-2), 6.79 (d, 1H, J = 7.7 Hz, vinyl proton), 5.84 (d, 1H, J = 4.4 Hz, 3'-OH), 5.69 (d, 1H, J = 6.0 Hz, H-1'), 5.66 (d, 1H, vinyl proton), 4.96 (dd, 1H, J = 5.0, 6.0 Hz, 5'-OH), 4.40 (dd, 1H, J = 4.9 Hz, H-2'), 4.34 (m, 1H, H-3'), 4.24 (m, 1H, H-4'), 3.48 (m, 2H, H-5', 5"); Anal. Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.99; H, 4.48; N, 17.01.
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