EFFICIENT SYNTHESIS OF 3-FORMYL-1,2,4-TRIAZOLE NUCLEOSIDE USING DIETHOXYACETONITRILE AS A SYNTHON†

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Abstract — Diethoxyacetonitrile has been shown to be an efficient and versatile synthon for the synthesis of 1,2,4-triazole heterocycle (5), and 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxaldehyde (10) has been synthesized regiospecifically for the nitrogens and stereospecifically for the ribosylation.

Certain azole nucleosides of both natural and synthetic origin have shown significant biological activity.[1] Among these are the C-nucleoside antibiotic pyrazomycin[2] and the synthetic nucleoside ribavirin.[3] Furthermore, it was recently disclosed that some nucleosides contain a formyl group in the base moiety. Nikkomycin X contains a 4-formyl-4-imidazolin-2-one moiety[4] and polyoxin N contains 3-formyl-4-hydroxypyrazole.[5] The objective of the investigation described herein was to develop a new methodology for the conversion of diethoxyacetonitrile to heterocyclic moiety of nucleosides structurally related to these biologically active compounds. Diethoxyacetonitrile is easily prepared from triethyl orthoformate and hydrogen cyanide[6] or triethyl orthoformate and acetyl cyanide[7] or ethyl diethoxyacetate by treatment with ammonia followed by $POCl_3$.[8] However, no systematic investigation has been carried out for the preparation of heterocyclic compounds using diethoxyacetonitrile as a synthon. Thus, we became interested in the selective conversion of the cyano group into various heterocyclic compounds, especially 1,2,4-triazole nucleoside of increasing importance.

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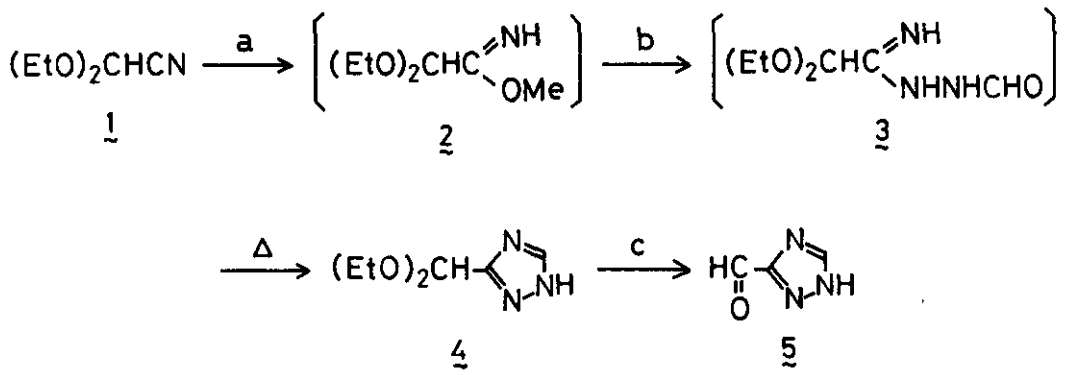
† Dedicated to Professor Dr. Tetsuji Kametani, the Pharmaceutical Institute, Tohoku University, in commemoration of his retirement from the University.

Chart 1



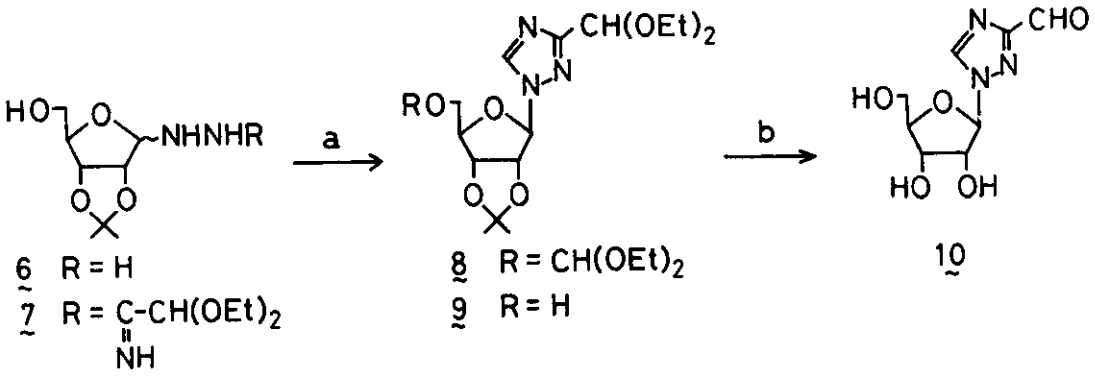
a, NaOMe / MeOH ; b, $H_2NNHCHO$; c, 1N-HCl / Me_2CO

Methyl diethoxyacetimidate (2) was prepared from diethoxyacetonitrile (1) in the presence of a catalytic amount of sodium methoxide in methanol at room temperature for 3 h under argon atmosphere, and the resulting solution was treated with equiv of formylhydrazine dissolved in methanol at room temperature for 12 h, depositing colorless crystals 3 .[9] Then, the reaction mixture was heated at reflux for 14 h. After neutralization with AcOH and removal of the solvent, a pale pink solid was obtained. It was purified by column chromatography on silica gel (Et_2O:CH_3COCH_3= 8:1) and afforded a colorless crystalline 1,2,4-triazole-3-carboxaldehyde diethyl acetal (4) in 90% yield, mp 68-70°C (recrystallized from n-hexane-ether). The acetal 4 was hydrolyzed to 1,2,4-triazole-3-carboxaldehyde[10] (5, colorless foam, 93% yield) by treatment with 1N HCl in acetone at reflux for 3 h followed by neutralization with $NaHCO_3$, workup and chromatography on silica gel (CH_2Cl_2:MeOH = 5:1). The aldehyde 5 can be purified by sublimation, showing yellow at 180°C with mp 200-202°C (dec.), and exhibits infrared carbonyl band (KBr) at 1694 cm^{-1}, and ^{1}H-NMR in CD_3OD shows hemiacetal proton at δ 5.72 and an aromatic proton at δ 8.20, but ^{1}H-NMR in DMSO-d_6 shows aldehyde proton at δ 9.98 and an aromatic proton at δ 8.78. The mass spectrum shows molecular ions corresponding to the aldehyde (M^+, 97), and was not to be dimeric hemiaminals.[11]

The present methodology essentially consists of a two-step reaction affording

1,2,4-triazole-3-carboxaldehyde in excellent overall yield (Chart 1), and can be applied to the synthesis of 3-substituted 1,2,4-triazole system. Although the most successful glycosylation is based on the acid-catalyzed fusion procedure[12] or trimethylsilyl derivatives,[3] it is recognized that the isomeric distribution varies greatly with the substituents on the heterocycle. Therefore, hydrazinoribose was used to obtain 3-formyl-1,2,4-triazole nucleoside regioselectively and to take advantage of diethoxyacetonitrile as an efficient and versatile synthon. The hydrazone 6 of 2,3-O-isopropylidene-D-ribose was prepared from 2,3-O-isopropylidene-D-ribose and hydrazine according to Schmidt's method[13]. (Chart 2) The

Chart 2



6 R = H

7 R = C(=NH)-CH(OEt)2

8 R = CH(OEt)2

9 R = H

10

a, $HC(OEt)_3$ on 7 ; b, HCO_2H on 9

acetimidate 2 (1.5 equiv) prepared as described above was gradually added to a methanol solution of the hydrazone 6, and the reaction mixture was stirred at room temperature for 3 h. A yellowish syrup (7) was obtained upon workup and directly treated with triethyl orthoformate, and the resulting solution was heated at reflux (120°C) for 1.5 h. After workup and complete removal of the excess orthoformate, and orange-red syrup was obtained and confirmed to be mainly 8, spectroscopically (^{1}H-NMR). The primary alcohol of 9 was generated by treatment with ethanol by heating at reflux for 8 h, affording a deep-red syrup upon workup. It was subjected to column chromatography on silica gel (Et_2O → AcOEt) and afforded a colorless syrup 9 in 39% overall yield from 6, showing M^++1, 344, and satisfactory IR, ^{1}H- and ^{13}C-NMR data. The diethoxyl and isopropylidene groups were hydrolyzed together by treatment with aqueous formic acid at 40°C for 10 h.

1-β-D-Ribofuranosyl-1,2,4-triazole-3-carboxaldehyde (10) was obtained in 68% yield as a colorless foam after workup, chromatography on silica gel (CH_2Cl_2:MeOH=5:1), and complete removal of methanol under reduced pressure.[10] The nucleoside 10 was converted to the oxime[10] (mp 151-153°C, M^++1 245). Evidence for the structure of the product 10 as β-configuration was obtained by comparison of the δ value (5.87 in CD_3OD/TMS) and the coupling constant $J_{1',2'}$ (3.5 Hz) for the anomeric proton with those of the triazole carboxamide nucleosides of known structure.[14] Formation of the α anomer corresponding to 8,9 and 10 was not detected in this procedure.

Acknowledgement: The work was financially supported in part by Grants-in-aid for Special Project Research from the Ministry of Education, Science and Culture of Japan.

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9. Compounds 2 and 3 were treated for further reaction without isolation, but they were easily confirmed to have the assigned structures by ^{1}H-NMR.
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Received, 23th July, 1980