

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

Teiichi Murakami, Masami Otsuka, Susumu Kobayashi, and Masaji
Ohno*

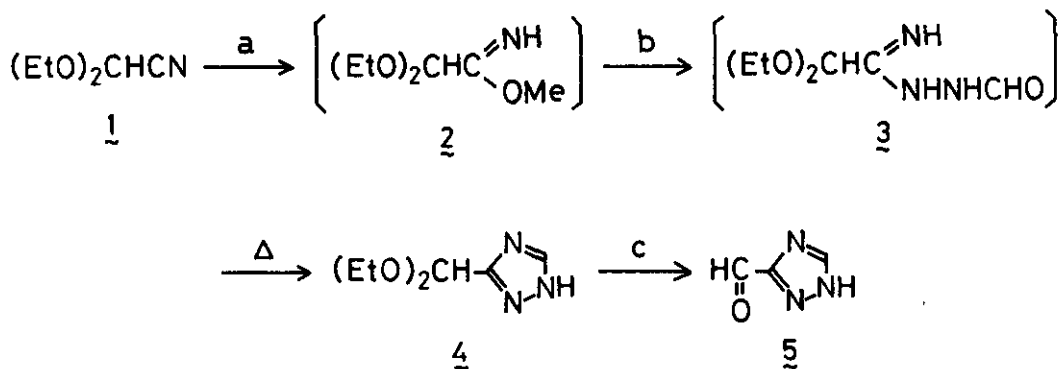
Faculty of Pharmaceutical Sciences, University of Tokyo,
Bunkyo-ku, Tokyo 113, Japan

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 pyrazomycin² 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 moiety⁴ 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 cyanide⁶ or triethyl orthoformate and acetyl cyanide⁷ or ethyl diethoxyacetate by treatment with ammonia followed by POCl₃.⁸ 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.

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

Chart 1



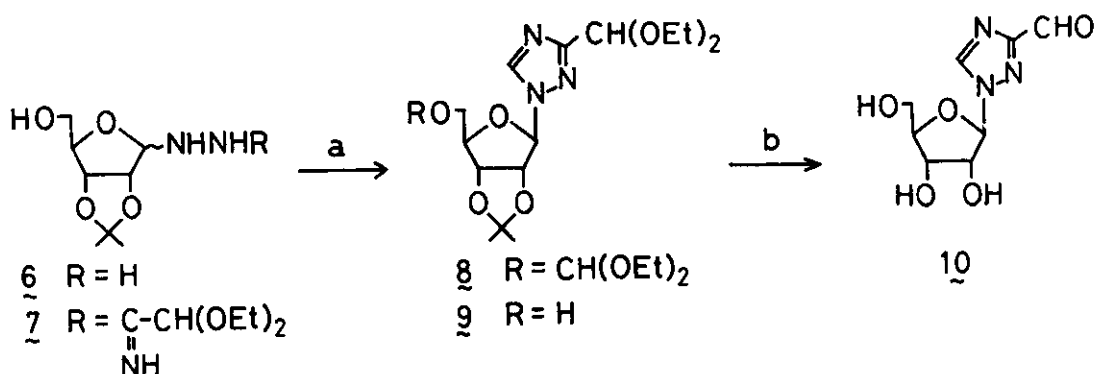
a, NaOMe / MeOH ; b, H₂NNHCHO ; c, 1N-HCl / Me₂CO

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 (Et₂O:CH₃COCH₃ = 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-carboxaldehyde¹⁰ (5, colorless foam, 93% yield) by treatment with 1N HCl in acetone at reflux for 3 h followed by neutralization with NaHCO₃, workup and chromatography on silica gel (CH₂Cl₂: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 ¹H-NMR in CD₃OD shows hemiacetal proton at δ 5.72 and an aromatic proton at δ 8.20, but ¹H-NMR in DMSO-d₆ 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 procedure¹² or trimethylsilyl derivatives,³ it is recognized that the isomeric distribution varies greatly with the substituents on the heterocycle. Therefore, hydrazino-ribose was used to obtain 3-formyl-1,2,4-triazole nucleoside regioselectively and to take advantage of diethoxyacetoneitrile 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 method¹³. (Chart 2) The

Chart 2



a. HC(OEt)₃ on 7 ; b. HCO₂H 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 (¹H-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 (Et₂O → AcOEt) and afforded a colorless syrup 9 in 39% overall yield from 6, showing M⁺+1, 344, and satisfactory IR, ¹H- and ¹³C-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 (CH₂Cl₂:MeOH=5:1), and complete removal of methanol under reduced pressure.¹⁰ The nucleoside 10 was converted to the oxime¹⁰ (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 CD₃OD/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.

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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 ¹H-NMR.
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