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REGIOSELECTIVE SYNTEHSIS OF VIRAZOLE USING BENZYL CYANOFORMATE AS A SYNTHON

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An antiviral nucleoside or virazole was synthesized efficiently and regioselectively starting with benzyl cyanoformate.

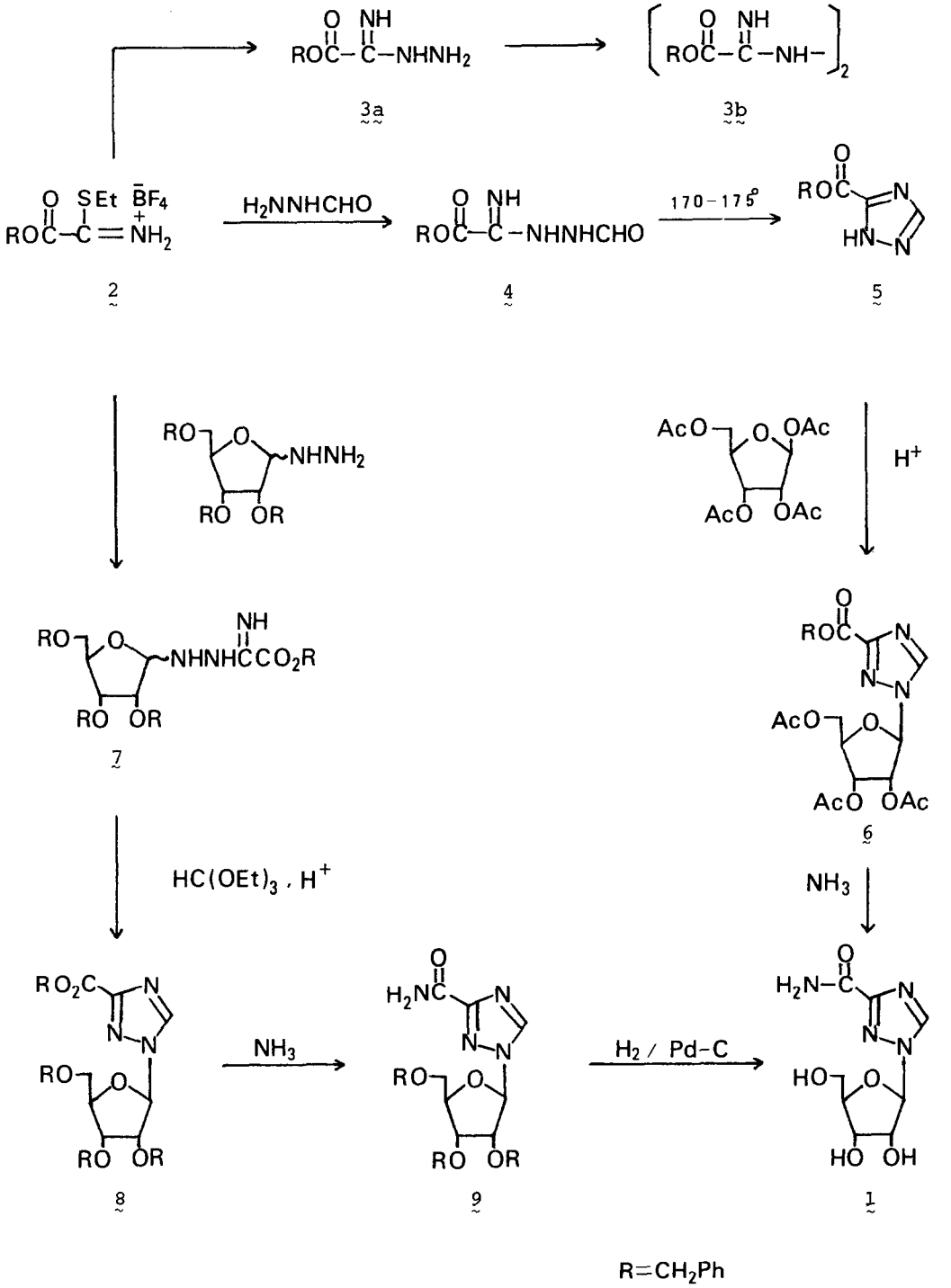
In the foregoing paper[1] we described an efficient route to a variety of N-substituted or N-unsubstituted amidinoformic acids. The objective of the investigation described herein was to develop methodology for the conversion of benzyl cyanoformate to heterocyclic moiety of some nucleosides of biological interest. Virazole, 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (1), was first synthesized in 1972 and has been described as the first broad-spectrum antiviral agent which is not an interferon inducer[2] and of potential medicinal importance[3]. Since then, a considerable attention has been paid on the biological and chemical studies of such nucleosides synthetically derived[4]. However, there are a few reports[5,6] concerning the synthesis of 1,2,4-triazole-3-carboxamide which is obtained by starting from oxalic acid and aminoguanidine[5] or acetylaminothiourea[6] or 3-cyano-1,2,4-triazole[7], and there are two methods, acid-catalyzed fusion procedure[5] and fermentation process[6], as for the ribosylation of the base.

We report here unique and regioselective synthesis of virazole by two different approaches starting with benzyl cyanoformate and hydrazine derivatives. Tetrafluoroborate of 1-carbobenzyloxyethylthioformimidate 2 obtained from benzyl cyanoformate[1] is inactive to amino derivatives such as urea, thiourea or guanidine, but active to hydrazine affording 3b in 65% yield by treatment with an excess amount of hydrazine hydrate in methylene chloride at 0°C. The result showed that the expected intermediate 3a first formed reacted further with 2 more rapidly. The control reaction to get only the hydrazine derivative 3a seemed to be difficult. Therefore, it was considered to be necessary to protect one of the amino group of hydrazine properly and designed to use the protecting group in such a way that can be transformed into the triazole nucleus or virazole structure itself at a later stage. Thus, formyl hydrazine and D-ribose hydrazide easily available were chosen as the nucleophiles to ethylthioformimidate 2. Treatment of 2 with formylhydrazine in methanol at 0° for 5 min followed by neutralization with $NaHCO_3$ afforded 4 in 88% yield, mp 163-165°; IR (KBr): 3380, 3308, 3200, 1740, 1640, 1603 cm^{-1}; PMR (DMSO-d_6/TMS) δ 10.20 (d. J=9Hz for -CHO).

Heating of 4 itself at 170-175° simply afforded benzyl 1,2,4-triazole-3-carboxylate in almost quantitative yield, mp 195-197°; IR (KBr) 3264, 1702, 1467 cm^{-1}; PMR (DMSO-d_6) δ 8.56 (s, 1H for aromatic proton). The easy formation of the triazole nucleus 5 is striking, since acethydrazide derivative of 2 (R=$PhCH_2$) resisted to ring formation by heating at 215-220° affording decomposed products[8]. Ribosylation of 5 with 2 equivalent amount of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose was carried out in the presence of bis-p-nitrophenylhydrogen phosphate (13 mol %) at 160-165°[2,9], affording a colorless syrup 6 in 71% yield after silica gel column chromatography using ether as an eluent. Treatment of the blocked benzyl ester nucleoside 6 with methanolic ammonia provided 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide (1) in 77% yield, mp 180-182°; IR (KBr) 3472, 3320, 1703, 1670, 1610, 1500, 1486 cm^{-1}; $[\alpha]_D^{20}$ -38° (c 1.0 H_2O); PMR δ 8.88 (s, 1H for H-5) 5.84 (d, 1H J=3Hz for H-1'). NOE was clearly observed between H-5 and H-1' protons (18% enhancement of the integrated area of H-5 by irradiation of H-1' and 15% enhancement of that of H-1' by irradiation of H-5), supporting 1 N-substituted β-nucleoside structure[10]. Witkowski and co-workers[2] obtained 2 N-substituted isomer as a by-product (one-tenth of 1) from the reaction of 5 (R=Me) and peracetylribofuranose, but in our case the by-product was hardly recognized by careful study of PMR of the crude product of 6 and 1. Therefore, it should be mentioned here that benzyl ester more strongly influence regioselectivity in such ribosylation than that of methyl ester.

Ribofuranosulhydrazine derivatives easily obtained from 2,3,5-tri-O-benzyl-D-ribose or 2,3-O-isopropylidene-D-ribose were elegantly used for the synthesis of pyrazole and allopurinol ribosides by Schmidt and his co-workers[11]. Such a hydrazine was considered to be a good candidate for the heterocycle of virazole, since it already attaches to D-ribose and may react with 2 with no ambiguity about the location of N-sugar linkage, and may form triazole nucleus by adding C_1-unit at the final stage. Thus, 2 was treated with 2,3,5-tri-O-benzyl-D-ribose hydrazone in methylene chloride at room temperature for 5 min and followed by neutralization with $NaHCO_3$, affording 7 as an oily material. Since 7 is unstable even on silica gel column, it was used without purification for the next reaction. Addition of C_1-unit was the most difficult stage. After a systematic survey of acid-catalyzed ring formation of 7 with triethylorthoformate used as the C_1-unit and also as the solvent, 1-(2,3,5-tri-O-benzyl-β-D-ribofuranosyl-)1,2,4-triazole-3-carboxylic acid benzyl ester (8) was obtained in 65% (HCl) and 79% (p-TsOH) yields based on 2. The reaction product 8 is a mixture of β- and α-nucleosides in a ratio of 8:1 based on the PMR analysis. Attempt to separate the mixture with TLC was unsuccessful, so it was treated with methanolic ammonia affording 9 in 80% yield and the benzyl groups of 9 was removed by common hydrogenolysis in methanol with Pd-C in the presence of HCl and 1 was obtained in the hydrochloride form. The hydrochloride was made free with Dowex-1 (OH^- form) to give 1 in excellent yield. This synthetic approach is completely regiospecific as for the glycosidic bond, but not highly stereoselective, yielding β and α

Scheme I


3a
3b
2
4
5
7
6
8
9
1
$H_2NNHCHO$
170-175°
$HC(OEt)_3 \cdot H^+$
NH_3
H_2 / Pd-C
H^+
$R=CH_2Ph$

anomeric mixture in a ratio of 8:1. The methodology developed here can be applied for a variety of other heterocycles and nucleosides and further investigations are continuing in our laboratories[12].

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References and Notes

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