

A Practical Synthesis of Ethyl 1,2,4-Triazole-3-Carboxylate and its use in the Formation of Chiral 1',2'-*seco*-Nucleosides of Ribavirin [1]

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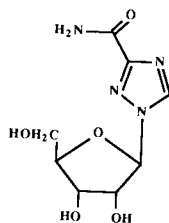
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A practical and efficient synthesis of ethyl 1,2,4-triazole-3-carboxylate (**6a**, R'' = H) from ethyl carboethoxyformimidate hydrochloride (**7**) is described. Alkylation of this heterocycle with the chloromethyl ethers of 1,3-*O*-dibenzylbutane-1,2*R*,3*S*-triol (**8a**) and 1,3,4-*O*-tribenzylbutane-1,2*R*,3*S*,4-tetrol (**8b**), followed by conversion of the ester function to the amide and deprotection, furnished the chiral 1',2'-*seco*-nucleosides of ribavirin, **11a** and **11b**, respectively.

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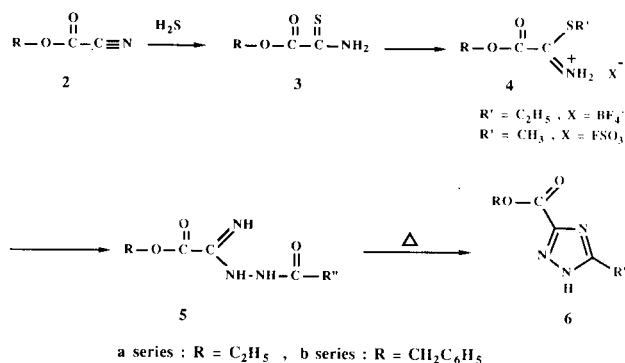
In an attempt to find additional broad-spectrum anti-viral agents like ribavirin (**1**, 1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide), synthetic programs were initiated involving chemical modifications of this nucleoside [2]. Some of these studies focused on altering the sugar moiety and a variety of *N*(1)-pentofuranosyl analogues were prepared [2]. A more recent addition to this category was an acyclic *N*(1)-derivative possessing the DHPG-type side chain [3]. In an effort to synthesize additional acyclic analogues of ribavirin, especially those which retain the chirality and carbon framework of the natural pentoses, we undertook the preparation of 1',2'-*seco*-nucleosides **11** of **1**. During this synthetic study, we became aware that a practical, chemical route to 1,2,4-triazole-3-carboxylic esters was needed. Such heterocycles are valuable synthons in the chemical synthesis of ribavirin analogues [4,5]. Methods for the preparation of such esters exist [5,6], but a shorter and more efficient approach to these heterocycles was desired. We now wish to describe a convenient synthesis of ethyl 1,2,4-triazole-3-carboxylate **6a**, (R'' = H) and its use in the preparation of 1',2'-*seco*-analogues of ribavirin.



1

A literature search concerning the syntheses of 1,2,4-triazole esters revealed that ethyl 5-methyl-1,2,4-triazole-3-carboxylate **6a** (R'' = CH₃) [7] could be prepared in 34% overall yield starting with ethyl 2-thiooxamate (**3a**, Scheme 1). Alkylation of **3a** with either triethylxonium tetrafluoroborate or methyl fluorosulfonate

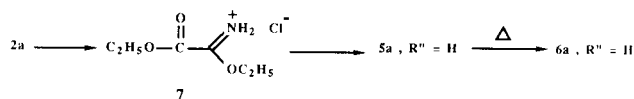
Scheme 1



afforded the corresponding thioformimidates **4a** [8] which were then reacted with acetylhydrazide to furnish the amidrazone **5a** (R'' = CH₃). This intermediate upon thermal cyclization provided **6a** (R'' = CH₃). The same synthetic methodology was used by Ohno and coworkers [5] to prepare benzyl 1,2,4-triazole-3-carboxylate (**6b**, R'' = H). However, their synthesis started with benzyl cyanofornate (**2b**) [10] and they subsequently reacted **4b** (R' = C₂H₅ and X = BF₄⁻) with formyl hydrazine instead of acetylhydrazide to obtain **5b** (R'' = H).

The present procedure (Scheme 2) is shorter and avoids the thiation-alkylation steps. It uses the hydrochloride **7** of ethyl carboethoxyformimidate [11] which can be conveniently synthesized from ethyl cyanofornate [12]. Reaction

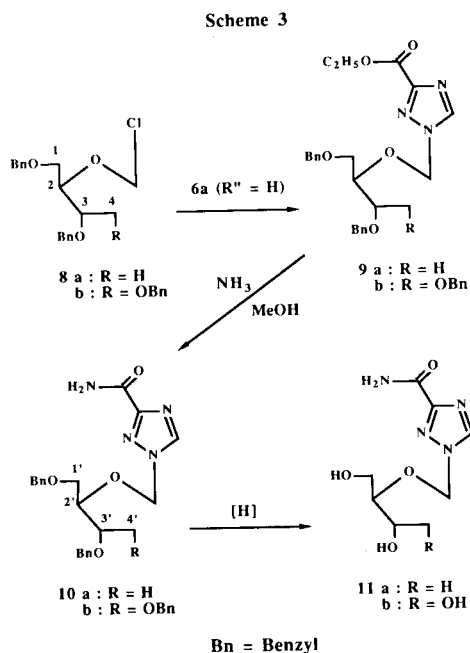
Scheme 2



of **7** with formyl hydrazine at 5° furnished **5a** (R'' = H, 99%) which when heated at 165° cyclized to **6a** (R'' = H)

in near-quantitative yield [13].

We now turned our attention to coupling this synthon with the protected, chiral chloromethyl ethers **8a** and **8b** (Scheme 3). The corresponding precursors of **8a** and **8b**, *i.e.*, 1,3-*O*-dibenzylbutane-1,2*R*,3*S*-triol and 1,3,4-*O*-tribenzylbutane-1,2*R*,3*S*,4-tetrol, were prepared from D-isoscorbic acid [14]. Chloromethylation of these chirons was carried out with paraformaldehyde and hydrogen chloride gas in dichloromethane at 0° [15a]. The percent purity of **8a** and **8b** was determined by integration of the



characteristic OCH_2Cl resonance which appears approximately at δ 5.6 in the ^1H nmr spectrum. In our hands, we found the percent of chloromethylation to range between 80 to 90% [15b]. Treatment of **8a** and **8b** with silylated **6a** ($\text{R}'' = \text{H}$) furnished the blocked 1',2'-*seco*-nucleosides **9a** and **9b**, respectively. In each case, a small amount of the 5-carboxylate isomer was isolated from the reaction mixture.

The site of alkylation on the 1,2,4-triazole ring was determined by ^1H nmr spectroscopy. The 1',2'-*seco*-nucleosides prepared in this study followed the same trend observed for 3- and 5-substituted 1- β -D-ribofuranosyl-1,2,4-triazoles [16]. The C(3)H proton chemical shift of the 5-substituted isomer is more shielded (*ca.* δ 7.9) than than the C(5)H signal of the 3-substituted isomer (*ca.* δ 8.2) whereas the proton chemical shift for OCH_2N methylene of the 3-isomer appears at higher field (*ca.* δ 5.6) as compared to the signal of the 5-substituted isomer (*ca.* δ 6.0). This spectral feature provides a rapid and convenient method to assign the site of attachment of similar acyclic chains on the 1,2,4-triazole-3-carboxylic ester ring.

The ester function of **9a** and **9b** was easily converted to the carboxamide moiety using methanolic ammonia at room temperature. Debenzylation of the acyclic side chain was accomplished by transfer hydrogenation over Pearlman's catalyst [17]. These last two steps were near-quantitative and provided the desired 1',2'-*seco*-nucleosides **11a** and **11b** in reasonable overall yields.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting apparatus and are uncorrected. The ^1H nmr spectra were obtained with a Varian EM-390 spectrometer. The chemical shifts are expressed in parts per million with respect to TMS. Thin layer chromatography was run on precoated (0.2 mm) silica gel 60 F-254 plates manufactured by EM Laboratories, Inc., and short-wave ultraviolet light (254 nm) was used to detect the uv-absorbing spots. Silica gel (Merck, 230-400 mesh, 60A) suitable for chromatographic use was employed for column chromatography. All solvent proportions are by volume unless otherwise stated. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

Ethyl carboethoxyformimidate hydrochloride (**7**) was obtained according to reference [12] with minor modifications. Therefore, we have included our procedure for the synthesis of **7**.

Ethyl Carboethoxyformimidate Hydrochloride (**7**).

Ethyl cyanofornate (Aldrich, 16.5 g, 167 mmoles) was added to a solution of absolute ethanol (7.8 g, 170 mmoles) and anhydrous diethyl ether (25 ml). The solution was stirred and maintained between -35° and -15° . Dry hydrogen chloride gas was bubbled into the reaction mixture until 18 g were absorbed. The reaction flask was tightly stoppered and placed in a freezer for six days. The precipitated solid was collected by filtration, washed with dry ether, and dried in a vacuum desiccator over sodium hydroxide/phosphorus pentoxide to furnish 23.9 g of **7** (79%).

Ethyl β -Formylloxalamidrazone (**5a**, $\text{R}'' = \text{H}$).

To a cold solution (5°) of formyl hydrazine (Aldrich, 3.31 g, 55.1 mmoles) in dry, AR-methanol (50 ml) was added a cold solution of **7** (10.0 g, 55.1 mmoles) in AR-methanol (25 ml). The reaction mixture was stirred at 10 minutes and then neutralized with reagent grade sodium bicarbonate (4.63 g, 55.1 mmoles) which was previously dissolved in water (30 ml). The solution was filtered, concentrated *in vacuo* to near-dryness, and the precipitated product collected by filtration (8.67 g, 98.9%; mp 149 - 151°). Recrystallization from ethyl acetate provided the pure amidrazone, mp 152 - 153° ; ^1H nmr (DMSO- d_6): δ 1.25 (t, 3, CH_3), 4.20 (q, 2, CH_2), 6.20-6.60 (m, 2, NH), 8.43 (s, 1, CHO), 10.20 (s, 1, NH).

Anal. Calcd. for $\text{C}_5\text{H}_9\text{N}_3\text{O}_2$: C, 37.73; H, 5.70; N, 26.40. Found: C, 37.88; H, 5.45; N, 26.30.

Ethyl 1,2,4-Triazole-3-carboxylate (**6a**, $\text{R}'' = \text{H}$).

Compound **5a** ($\text{R}'' = \text{H}$, 4.44 g, 27.9 mmoles) was placed in a sublimation apparatus and heated at 165° (oil bath) under vacuum. After heating for 10 minutes, the molten material solidified and was allowed to cool. The crystalline residue was recrystallized from absolute ethanol to afford **6a** ($\text{R}'' = \text{H}$) (3.80 g, 97%), mp 169 - 171° ; ^1H nmr (DMSO- d_6): δ 1.32 (t, 3, CH_3), 4.30 (q, 2, CH_2), 8.51 (s, 1, C(5)H), 14.69 (br s, 1, NH).

Anal. Calcd. for $\text{C}_7\text{H}_9\text{N}_3\text{O}_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.34; H, 4.90; N, 29.60.

2*R*-Chloromethoxy-1,3*S*-dibenzylxybutane (**8a**).

1,3-*O*-Dibenzylbutane-1,2*R*,3*S*-triol [14b] (10.74 g, 37 mmoles) was dissolved in 65 ml of dry dichloromethane (distilled from phosphorus pentoxide) to which 1.7 g of paraformaldehyde was added. The reaction mixture was cooled in an ice bath and hydrogen chloride gas (dried through concentrated sulfuric acid) was passed through the stirred solution for 4 hours. Next, anhydrous calcium chloride was added and the

suspension stirred for 5 minutes. It was then filtered and the filtrate was concentrated under diminished pressure to furnish 12.68 g of an oily material, which contains 84% of the chloromethyl ether **8a** as indicated by ¹H nmr spectroscopy.

2R-Chloromethoxy-1,3S,4-tribenzyloxybutane (**8b**).

Treatment of 1,3,4-tribenzyloxy-D-erythritol [14b] (15.86 g, 40 mmoles) with paraformaldehyde (1.83 g) in the presence of hydrogen chloride gas, as described for **8a**, afforded 17.81 g of a liquid product. The ¹H nmr indicated that it contained 81% of the title chloromethyl ether **8b**.

Ethyl 1-[(1,3S-Dibenzyloxy-2R-butoxy)methyl]-1,2,4-triazole-3-carboxylate (**9a**).

Ethyl 1,2,4-triazole-3-carboxylate (3.53 g, 25 mmoles) and ammonium sulfate in hexamethyldisilazane (HMDS, 90 ml) were heated at reflux for 5 hours. The excess HMDS was distilled off under reduced pressure and the silylated triazole ester was treated with **8a** (9.54 g, 24 mmoles) in acetonitrile (155 ml) and in the presence of tetraethylammonium iodide (38 mg). The resulting mixture was stirred at reflux for 4.5 hours and then 3 days at room temperature. The acetonitrile was removed *in vacuo* and the remaining residue was dissolved in dichloromethane (40 ml). This solution was washed with water, a 10% sodium thiosulfate solution, water, and brine, and then dried over anhydrous magnesium sulfate. The solvent was removed under diminished pressure and the resulting syrup (9.94 g) was applied to a silica gel column (200 g) and the column eluted with hexane-ethyl acetate (65/35, v/v). Fractions containing uv-active material were pooled and evaporated to afford pure ethyl 1-[(1,3S-dibenzyloxy-2R-butoxy)methyl]-1,2,4-triazole-5-carboxylate (0.09 g, 0.8%) and **9a** (7.02 g, 64%). Physical constants of **9a** are: $[\alpha]_D^{25} = -0.21$ (c = 2.405, ethanol); ¹H nmr (deuteriochloroform): δ 1.08 (d, 3, CH₃), 1.37 (t, 3, OCH₂CH₃), 3.3-4.08 (m, 4), 4.23-4.63 (m, 6, CH₂C₆H₅ and OCH₂CH₃), 5.68 (s, 2, OCH₂N), 7.25 (br s, 10, CH₂C₆H₅), 8.27 (s, 1, C(5)H).

Anal. Calcd. for C₂₄H₂₉N₃O₅: C, 65.59; H, 6.65; N, 9.56. Found: C, 65.40; H, 6.72; N, 9.53.

Ethyl 1-[(1,3S,4-tribenzyloxy-2R-butoxy)methyl]-1,2,4-triazole-3-carboxylate (**9b**).

The synthetic procedure was identical to that described for **9a**. Ethyl 1,2,4-triazole-3-carboxylate (1.19 g, 8.43 mmoles) was silylated and condensed with **8b** (6.66 mmoles as based on percent purity) in acetonitrile (60 ml) containing tetraethylammonium iodide (16 mg). Work-up and chromatography provided 310 mg (6.8%) of ethyl 1-[(1,3S,4-tribenzyloxy-2R-butoxy)methyl]-1,2,4-triazole-5-carboxylate and 1.52 g (33%) of the title compound **9b** [18] as colorless gums. Physical constants for **9b** are: $[\alpha]_D^{25} = -3.22$ (c = 1.645, ethanol); ¹H nmr (deuteriochloroform): δ 1.37 (t, 3, CH₂CH₃), 3.17-4.2 (m, 6), 4.27-4.73 (m, 8, CH₂C₆H₅ and CH₂CH₃), 5.63 (s, 2, OCH₂N), 7.25 (s, 15, CH₂C₆H₅), 8.2 (s, 1, C(5)H).

Anal. Calcd. for C₃₁H₃₅N₃O₆: C, 67.54; H, 6.42; N, 7.65. Found: C, 67.52; H, 6.54; N, 7.80.

1-[(1,3S-Dibenzyloxy-2R-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**10a**).

A solution of **9a** (4.7 g, 10 mmoles) in 100 ml of methanolic ammonia (previously saturated at -10°) was allowed to stand at room temperature for 3 days in a sealed flask. The solvent was removed under diminished pressure to provide crystalline **10a** (4.33 g, 98%). An analytical sample was prepared by recrystallization from ethanol, mp 124-125°; $[\alpha]_D^{25} = -2.19$ (c = 1.184, chloroform); ¹H nmr (deuteriochloroform): δ 1.1 (d, 3, CH₃), 3.33-4.12 (m, 4), 4.43 (*q*_{AB} J = 12 Hz, 2, CH₂C₆H₅), 4.43 (s, 2, CH₂C₆H₅), 5.68 (s, 2, OCH₂N), 6.78-7.07 (br s, 2, CONH₂, deuterium oxide exchangeable), 7.25 (br s, 10, CH₂C₆H₅), 8.2 (s, 1, C(5)H).

Anal. Calcd. for C₂₂H₂₆N₄O₄: C, 64.38; H, 6.38; N, 13.65. Found: C, 64.65; H, 6.37; N, 13.58.

1-[(1,3S,4-Tribenzyloxy-2R-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**10b**).

The synthetic procedure was similar to that described for **10a**. Compound **9b** (889 mg, 1.63 mmoles) afforded the title compound **10b** (770 mg, 92%) as a gum, $[\alpha]_D^{25} = -5.90$ (c = 1.365, ethanol); ¹H nmr (deuteriochloroform): δ 3.2-4.22 (m, 6), 4.33-4.78 (m, 6, CH₂C₆H₅), 5.6 (s, 2, OCH₂N), 6.8-7.67 (m, 17, CH₂C₆H₅ and NH₂, deuterium oxide exchangeable), 8.18 (s, 1, C(5)H).

Anal. Calcd. for C₂₉H₃₂N₄O₅: C, 67.43; H, 6.24; N, 10.85. Found: C, 67.38; H, 6.54; N, 11.07.

1-[(1,3S-dihydroxy-2R-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**11a**).

Compound **10a** (4.07 g, 9.92 mmoles) was dissolved in absolute ethanol (75 ml) and to this solution was added 20% Palladous hydroxide/C (1.1 g) and cyclohexene (19 ml). This mixture was heated at reflux for 6 hours and, while hot, filtered through a celite pad. The pad was washed with hot ethanol, the wash and filtrate were combined, and evaporated to dryness to furnish a quantitative yield of **11a** as a gum. This material was dissolved in a minimal amount of distilled water and lyophilized to provide a colorless solid, mp 79-84°; $[\alpha]_D^{25} = -7.8$ (c = 2.75, ethanol); ¹H nmr (DMSO-d₆): δ 0.88 (d, 3, CH₃), 3.17-3.8 (m, 4), 4.45-4.83 (m, 2, OH, deuterium oxide exchangeable), 5.67 (s, 2, OCH₂N), 7.62 (br d, 2, NH₂, deuterium oxide exchangeable), 8.73 (s, 1, C(5)H).

Anal. Calcd. for C₈H₁₄N₄O₄: C, 41.76; H, 6.13; N, 24.34. Found: C, 42.00; H, 6.17; N, 24.19.

1-[(1,3S,4-Trihydroxy-2R-butoxy)methyl]-1,2,4-triazole-3-carboxamide (**11b**).

Transfer hydrogenation of 679 mg (1.32 mmoles) of **10b** was carried out as described in the preceding experiment. A quantitative yield of **11a** was obtained. This material was dissolved in water and lyophilized to a white solid, mp 71-73°; $[\alpha]_D^{25} = -9.47$ (c = 1.995, ethanol); ¹H nmr (DMSO-d₆): δ 2.93-3.78 (m, 6), 3.96-4.87 (m, 3, OH, deuterium oxide exchangeable), 5.63 (s, 2, OCH₂N), 7.59 (br d, 2, NH₂, deuterium oxide exchangeable), 8.68 (s, 1, C(5)H).

Anal. Calcd. for C₈H₁₄N₄O₅: C, 39.03; H, 5.73; N, 22.76. Found: C, 39.21; H, 5.80; N, 22.54.

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which was generously supplied to us by Drs. Roland K. Robins and Ganapathi R. Revankar of the Nucleic Acid Research Institute, Costa Mesa, California.

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[18] Alkylation of methyl 1,2,4-triazole-3-carboxylate (2.57 g, 20 mmoles) with 8.9 g of **8b** (81% pure, 16.4 mmoles) furnished methyl 1-[(1,3S,4-tribenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-5-carboxylate (2.05 g, 19%) and methyl 1-[(1,3S,4-tribenzyloxy-2*R*-butoxy)methyl]-1,2,4-triazole-3-carboxylate (3.34 g, 31%). Physical data for the 5-carboxylate are: $[\alpha]_D^{25} = -1.9$ ($c = 2.105$, ethanol); ^1H nmr (deuteriochloroform): δ 3.3-3.75 (m, 5), 3.85 (s, 3, OCH₃), 4.02-4.25 (m, 1), 4.32-4.68 (m, 6, CH₂C₆H₅), 5.97 (s, 2, OCH₂N), 7.23 (br s, 15, CH₂C₆H₅), 7.87 (s, 1, C(3)H).

Anal. Calcd. for C₃₀H₃₃N₃O₆: C, 67.79; H, 6.26; N, 7.90. Found: C, 68.08; H, 6.03; N, 7.90.

Physical constants of the 3-carboxylate are: $[\alpha]_D^{25} = -3.66$ ($c = 1.91$, ethanol); ^1H nmr (deuteriochloroform): δ 3.25-4.23 (m, 6), 3.87 (s, 3, OCH₃), 4.27-4.75 (m, 6, CH₂C₆H₅), 5.6 (s, 2, OCH₂N), 7.22 (br s, 15, CH₂C₆H₅), 8.17 (s, 1, C(5)H).

Anal. Calcd. for C₃₀H₃₃N₃O₆: C, 67.79; H, 6.26; N, 7.90. Found: C, 67.74; H, 6.01; N, 7.90.