Synthesis of 3′-Isocyano-3′-deoxythymidine

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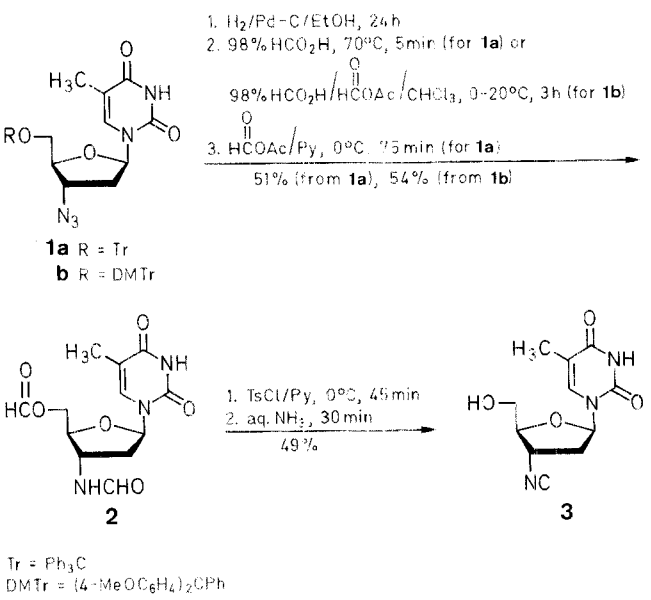
Dedicated to Prof. Dr. Hans Rudolph on the occasion of his 60th birthday.

The synthesis of 3′-isocyano-3′-deoxythymidine (**3**) from the corresponding 5′-protected azido derivatives **1a, b** is reported.

3′-Azido-3′-deoxythymidine (**1**, R = H, AZT), and other 2′-,3′-dideoxynucleosides inhibit the replication of HIV.[1-3] However, *in vivo*, AZT produces severe side-effects. Therefore, the search continues for nucleoside analogs with more selective antiviral activity. Recently, 3′-cyano-3′-deoxythymidine[4] and some 3′-cyano-3′-deoxy-β-D-arabinonucleosides[5] have been synthesized as candidates for antiviral agents. Here we report the synthesis of 3′-isocyano-3′-deoxythymidine (**3**) from thymidine derivatives **1a, b**.

3′-Azido-3′-deoxy-5′-*O*-tritylthymidine (**1a**)[6] and the corresponding 5′-*O*-dimethoxytrityl compound **1b** (prepared from 5′-*O*-dimethoxytritylthymidine in analogy to **1a** without isolation of intermediates in 87% overall yield) are converted into the corresponding 3′-amines by hydrogenation in the presence of palladium on carbon in ethanol/formic acid at 20°C. The trityl and the dimethoxytrityl groups are completely cleaved from the protected thymidine derivatives under these conditions.[7] In contrast, the trityl protecting groups are stable on the azide derivatives. The detritylation of 3′-amino-3′-deoxythymidines is achieved by acidolysis with formic acid, hot for trityl, cold and dilute for dimethoxytrityl. Subsequently, the resulting 3′-amino-3′-deoxythymidine is *O,N*-diformylated by treatment with an excess of formyl acetate. Dehydration by means of tosyl chloride in pyridine[8,9] is the method of choice for converting **2** via its 5′-*O*-formylisocyanide derivative and subsequent cleavage of the 5′-*O*-formyl group with aqueous ammonia into the target 3′-isocyano-3′-deoxythymidine (**3**).



In analogy to the synthesis of **1** (R = H), we tried to introduce the formamido or the isocyano group by direct nucleophilic substitution of various suitable leaving groups at the 3′-position of thymidine derivatives, such as its 3′-*O*-triflate, 3′-*O*-mesyl-, or 2,3′-anhydrothymidine, in order to reduce the number of steps in the synthesis of **3**. Neither the reaction with trimethylsilyl cyanide in the presence of zinc iodide, nor the nucleophilic substitution by various formamide derivatives succeeded. Sodium formamide,[11,12] sodium diformylamide,[13] and *o*-nitrosulfenylformamide[14] were tested under various conditions, but no reaction took place. In some cases elimination to 5′-*O*-trityl-2′,3′-dideoxythymidinene was observed, because the formamide anion is of lower nucleophilicity but of higher basicity than the azide anion.

In conclusion, we have demonstrated a facile synthesis of 3′-isocyano-3′-deoxythymidine (**3**), sustaining the interest in simple methods for the synthesis of biologically important 3′-substituted nucleosides.[15]

The NMR spectra were measured on Bruker AM 360 spectrometer (360.13 MHz for ^{1}H-, 90.56 MHz for ^{13}C-) with TMS as internal standard. The IR spectra were recorded on a Perkin-Elmer Model 177 Infrared spectrophotometer. Melting points were determined with Büchi SMP-20 apparatus in capillaries and are uncorrected. Flash chromatography was done on TLC silica gel 60, 20–45 μm (Amicon), or TLC silica gel 60 H, 15 μm (Merck) using $CHCl_3$/EtOH (9:1) $CHCl_3$/EtOH/Et_3N (90:9:1) as eluents. Reactions were monitored by analytical TLC using 2 × 5 cm TLC plates: silica gel 60 F_{254}, layer thickness 0.25 mm. All reactions were performed under a blanket of argon.

3′-Formamido-3′-deoxy-5′-formylthymidine (2):

From **1a**: 3′-Azido-3′-deoxy-5′-*O*-tritylthymidine (**1a**; 1.90 g, 3.73 mmol) is dissolved in dry EtOH (50 mL) and hydrogenated (24 h, 1.1 bar) in the presence of 10% Pd/C (400 mg). After filtration the solvent is evaporated. The crude product is dissolved in 98% formic acid (20 mL)

and kept at 70°C for 5 min. The solvent is evaporated *in vacuo*, the residue is dissolved in dry pyridine (20 mL), and formyl acetate (5 mL) is added. After 75 min at 0°C the solvent is evaporated *in vacuo*. The residue is purified by flash chromatography on silica gel using $CHCl_3$/EtOH (9:1) as eluent to give **2** as a white powder; yield: 590 mg (51%, based on **1a**); mp 75°C (shrinking), 216°C (dec); R_f ($CHCl_3$/EtOH, 8:2) = 0.33.

From **1b**: The same compound is obtained from **1b** by dissolving the crude hydrogenation product (2.1 g, 3.9 mmol) in $CHCl_3$ (20 mL). 98% Formic acid (8 mL) and formyl acetate (10 mL) are added at 0°C. After 3 h without additional cooling an excess of MeOH is added at 0°C and the solvent evaporated. Chromatography as above gives **2** as a white powder; yield: 0.78 g (54%, based on **1b**).

$C_{12}H_{15}N_3O_6$	calc.	C 48.48	H 5.09	N 14.13
(297.3)	found	48.65	4.99	13.95

^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ = 1.89 (d, 3H, J = 1 Hz, CH_3); 2.32 (m, 2H, H-2'); 4.07 (dt, 1H, J_t = 5.4 Hz, J_d = 3.3 Hz, H-4'); 4.40, 4.44 (dAB, 2H, J_{gem} = 12.2 Hz, J_{vic} = 3.25, 5.28 Hz, H-5'); 4.52 (pseudo-quint, 1H, J = 7.4 Hz, H-3'); 6.28 (pseudo-t, 1H, J = 6.5 Hz, H-1'); 7.34 (m, 1H, H-6); 8.10 (s, 1H, CHO); 8.18 (s, 1H, CHO); 8.41 (d, 1H, J = 7.4 Hz, 3'-NH); 11.11 (br s, 1H, 3-NH).

^{13}C-NMR ($CDCl_3$/DMSO-d_6): δ = 11.45 (CH_3); 35.80 (C-2'); 46.90, 62.30 (C-5', C-3'); 80.51, 83.05 (C-1', C-4'); 109.69 (C-5); 134.00 (C-6); 149.50, 163.08 (2 × C=O); 159.54, 160.20 (2 × CHO).

3'-Isocyano-3'-deoxythymidine (3):

Tosyl chloride (400 mg, 2.1 mmol) is added to 3'-formamido-3'-deoxy-5'-*O*-formylthymidine (**2**; 560 mg, 1.9 mmol) in dry pyridine (7 mL) at 0°C. After 45 min conc. aq. ammonia (2 mL) is added dropwise, and after 0.5 h the mixture is evaporated to dryness *in vacuo*. The residue is subjected to flash chromatography on silica gel using $CHCl_3$/EtOH/Et_3N (90:9:1) as eluent. The chromatographed product is recrystallized from EtOH to give an amorphous solid; yield: 230 mg (49%); mp 147°C (shrinking), 154°C (dec); R_f ($CHCl_3$/EtOH, 8:2) = 0.62.

$C_{11}H_{13}N_3O_4$	calc.	C 52.58	H 5.21	N 16.73
(251.2)	found	52.68	5.20	16.54

IR (KBr): ν = 3470, 2140, 1680 cm^{-1}.

^{1}H-NMR ($CDCl_3$/DMSO-d_6): δ = 1.83 (d, 3H, J = 1 Hz, CH_3); 2.51 (m, 2H, H-2'); 3.76, 3.84 (after D_2O exchange, dAB, 2H, J = 12.4, 2.6 Hz, H-5'); 4.13 (dt, 1H, $J_{4',5'}$ = 2.6 Hz, $J_{3',4'}$ = 4.7 Hz, H-4'); 4.44 (dt, 1H, J_t = 4.9 Hz, J_d = 7.7 Hz, H-3'); 5.38 (t, 1H, J = 5.1 Hz, OH, exchangeable with D_2O); 6.26 (pseudo-t, 1H, J = 6.5 Hz, H-1'); 7.63 (m, 1H, H-6); 11.25 (br s, 1H, NH).

^{13}C-NMR ($CDCl_3$/DMSOd_6): δ = 11.75 (CH_3); 37.95 (C-2'); 50.84, 59.80 (C-5', C-3'); 83.58, 84.57 (C-1', C-4'); 110.05 (C-5); 134.92 (C-6); 149.91, 163.51 (2 × C=O); 157.80 (N=C).

Note added in proof:
After submission of our manuscript a paper appeared, describing the preparation of the title compound by a different method.[16]

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