An Efficient Synthesis of 3'-Azido-3'-deoxythymidine (AZT)

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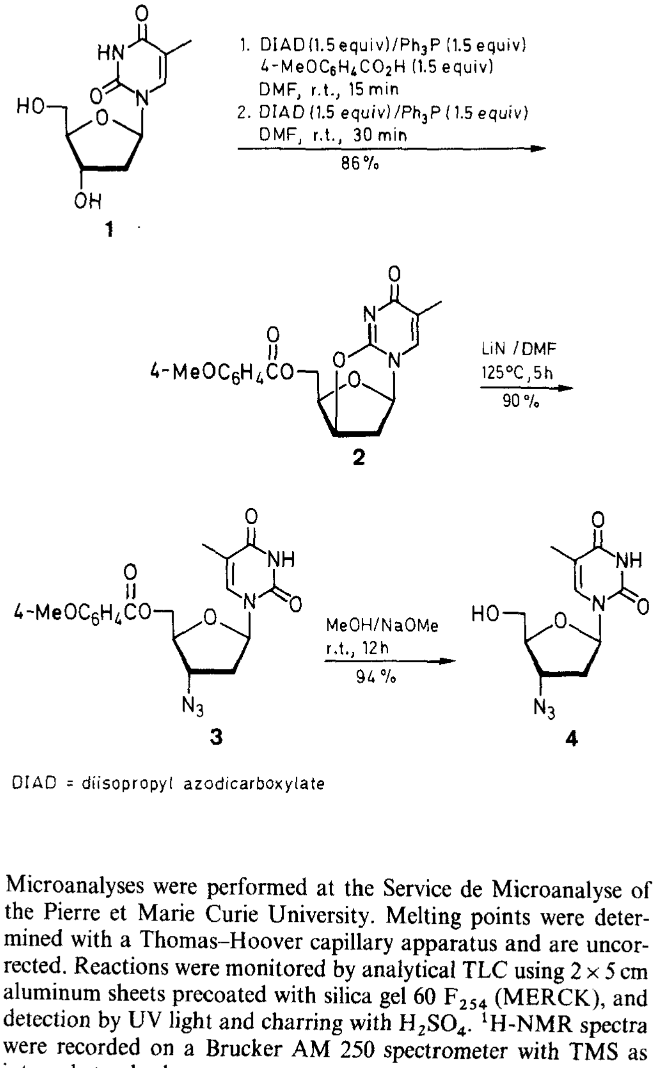
A very efficient synthesis of 3'-azido-3'-deoxythymidine (**4**) (AZT) from thymidine is described. The key step is a one-pot transformation of thymidine into 2,3'-anhydro-5'-*O*-(4-methoxybenzoyl)-thymidine (**2**) which is isolated by direct crystallization. Further ring opening of **2** with the azide ion and 5'-O-deprotection afforded AZT in 73 % overall yield.

Since the discovery of human immunodeficiency virus (HIV) as the causative agent of AIDS,[1] and the identification of HIV as a retrovirus, much research has been aimed at developing agents that could control or block the HIV replication process.[2] Among the numerous candidates the modified nucleoside 3'-azido-3'-deoxythymidine (**4**) (AZT) is, at present, the only drug receiving wide clinical usage. We report herein a very efficient synthesis of this compound.

Compound **4** can be prepared by modification of thymidine **1** or by condensation of a suitably functionalized sugar derivative with activated thymine. In the first approach, the problem to be solved is the substitution of the 3'-OH by an azido group with retention of configuration. Several solutions have already been proposed, and the first synthesis of AZT from thymidine involved a multistep double inversion at C-3'.[3] Later, other syntheses involving the opening of a 2,3'-anhydro derivative of thymidine by an azide ion were reported.[4,5] Coupling a 3-azido-2,3-dideoxypentofuranose derivative with activated thymine affords **4** together with the α-anomer.[6,7]

In the procedure described herein, thymidine is converted into 2,3'-anhydro-5'-*O*-(4-methoxybenzoyl)thymidine (**2**) by a one-pot transformation involving a tandem Mitsunobu reaction.[8] When a solution of **1** in dimethylformamide was treated with diisopropyl azodicarboxylate (DIAD, 1.5 equiv) in the presence of triphenylphosphine (Ph_3P, 1.5 equiv) and 4-methoxybenzoic acid (1.5 equiv) at room temperature, TLC analysis showed complete consumption of **1** within 15 minutes. Rather than isolating the intermediate 5'-ester it was found to be more convenient to complete the transformation into the 2,3'-anhydro derivative **2** by a further addition of triphenylphosphine (1.5 equiv) and DIAD (1.5 equiv). After stirring the reaction mixture for 30 min, the cyclization was complete. Compound **2** was precipitated by pouring the reaction mixture into diethyl ether. Filtration and drying afforded **2** in 86 % yield and good purity.

Ring opening of the 2,3'-anhydro derivative was cleanly achieved with lithium azide (1.5 equiv) in dimethylformamide at 125 °C. No cleavage of the 5'-ester function was observed under these conditions. Crystalline **3** was obtained in 90 % yield and was deprotected without purification. For the deprotection of the 5'-ester function, transesterification with methanol in the presence of sodium methoxide (1.15 equiv) was the best method. The methyl 4-methoxybenzoate formed was extracted with diethyl ether after addition of water. The aqueous phase was neutralized with acidic ion exchange resin and AZT was obtained in 94 % yield in good purity. This procedure allows the transformation of thymidine into AZT in 73 % overall yield and compares very favorably with methods previously described in the literature,[3-5] including recent publications.[9,10]



DIAD = diisopropyl azodicarboxylate

Microanalyses were performed at the Service de Microanalyse of the Pierre et Marie Curie University. Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. Reactions were monitored by analytical TLC using 2 × 5 cm aluminum sheets precoated with silica gel 60 F_{254} (MERCK), and detection by UV light and charring with H_2SO_4. ^{1}H-NMR spectra were recorded on a Brucker AM 250 spectrometer with TMS as internal standard.

2,3'-Anhydro-5'-*O*-(4-methoxybenzoyl)thymidine (2):

Thymidine (**1**; 3.63 g, 15 mmol) and Ph_3P (5.9 g, 22.5 mmol, 1.5 equiv) are dissolved in DMF (30 mL). To this stirred mixture a solution of DIAD (4.4 mL, 22.5 mmol, 1.5 equiv) im DMF (7 mL) and 4-methoxybenzoic acid (3.42 g, 22.5 mmol, 1.5 equiv) is added drop by drop and stirring is continued at r.t. for 15 min. The same quantity of Ph_3P and DIAD is then added. After 30 min. at r.t. the mixture is poured into Et_2O (370 mL) and the resulting suspension is chilled for 2 h. The white crystalline precipitate is isolated by suction and washed with Et_2O; yield: 4.63 g (86 %); mp 260 °C.

$C_{18}H_{18}N_2O_6$	calc.	C 60.33	H 5.06	N 7.81
(358.35)	found	60.18	5.02	7.68

^{1}H-NMR (DMSO-d_6/TMS): $\delta = 1.75$ (s, 3 H, 5-Me), 2.52, 2.61 (2 m, 2 H, $J_{gem} = 12.7$ Hz, $J_{vic} = 3.05$, 1.65 Hz, H-2'), 3.83 (s, 3 H, OCH_3), 4.30, 4.48 (daB, 2 H, $J_{gem} = 11.8$ Hz, $J_{vic} = 6.5$, 5.1 Hz, H-5'), 4.57 (dt, 1 H, $J_t = 6.1$ Hz, $J_d = 2.05$ Hz, H-4'), 5.41 (m, 1 H, H-3'), 5.90 (d, 1 H, $J = 3.2$ Hz, H-1'), 6.98, 7.86 (AB, 4 H, $J = 8.8$ Hz, C_6H_4), 7.56 (s, 1 H, H-6).

3′-Azido-3′-deoxy-5′-*O*-(4-methoxybenzoyl)thymidine (3):

Compound **2** (2.0 g, 5.6 mmol) and LiN_3 (412 mg, 8.4 mmol, 1.5 equiv) are suspended in DMF (10 mL) and the mixture is heated in an oil bath at 125 °C for 5 h. The orange homogeneous mixture is poured in H_2O (50 mL) containing 5 % aq HCl (4.1 mL, 1 equiv), EtOAc (20 mL), is added. The aqueous layer is extracted with EtOAc (2 × 10 mL) and the organic extract is washed with H_2O (10 mL), then with brine (10 mL). After drying (Na_2SO_4) the solvent is evaporated *in vacuo* to give **3** as a foamy solid; yield: 2.04 g (90 %); mp 57 °C (softened) – 165 °C (dec) (MeOH).

$C_{18}H_{19}N_5O_6$	calc.	C 53.87	H 4.77	N 17.44
(401.35)	found	53.68	4.81	17.22

IR (KBr): ν = 3210, 2130, 1700 (b) cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 1.71 (s, 3 H, 5Me), 2.35, 2.54 (2 m, 2 H, J_{gem} = 13.9 Hz, J_{vic} = 7.3, 6.65, 4.8 Hz, H-2′), 3.87 (s, 3 H, OCH_3), 4.21 (dt, 1 H, J_t = 3.6 Hz, J_d = 2.5 Hz), 4.35 (m, 1 H, H-3′), 4.53, 4.65 (dAB, 2 H, J_{gem} = 12.3 Hz, J_{vic} = 3.65, 3.3 Hz, H-5′), 6.18 (pseudo-t, 1 H, J = 6.5 Hz, H-1′), 6.95, 7.98 (AB, 4 H, J = 8.7 Hz, C_6H_4), 7.22 (s, 1 H, H-6), 9.36 (br s, 1 H, NH).

3′-Azido-3′-deoxythymidine (4):

Compound **3** (2.0 g, 5 mmol) is suspended in dry MeOH (20 mL), 1 M NaOMe in MeOH (5.75 mL, 1.15 equiv) is added and the mixture is stirred at r. t. overnight (12 h). H_2O (30 mL) is added and MeOH is evaporated. The aqueous solution is extracted with Et_2O (2 × 10 mL) then Amberlite IRN-77 (H^+ form, 2.0 g) is added and the mixture is stirred slowly at r. t. for 15 min. The resin is filtered, washed well with H_2O and the filtrate concentrated *in vacuo* to give a white glassy solid; yield: 1.26 g (94 %); mp 120 °C (*i*-PrOH) (Lit.[4] mp 120–122 °C (H_2O)).

$C_{10}H_{13}N_5O_4$	calc.	C 44.95	H 4.90	N 26.19
(267.2)	found	45.10	4.89	26.00

IR (KBr): ν = 3500, 3150, 2120, 1680 (b) cm^{-1}.

^{1}H-NMR (D_2O): δ = 1.70 (s, 3 H, 5-Me), 2.32 (pseudo-t, 2 H, J = 6.5 Hz, H-2′), 3.60, 3.70 (dAB, 2 H, J_{gem} = 12.6 Hz, J_{vic} = 4.6 Hz, H-5′), 3.83 (pseudo-q, 1 H, J = 4.7 Hz, H-4′), 4.18 (pseudo-q, 1 H, J = 6.4 Hz, H-3′), 6.02 (pseudo-t, 1 H, J = 6.5 Hz, H-1′), 7.46 (s, 1 H, H-6).

MS (CI NH_3): m/z = 268 (M^+ + 1), 285 (M^+ + 18).

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