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Simple and efficient method for the synthesis of 2′,3′-didehydro-3′-deoxythymidine (d4T)

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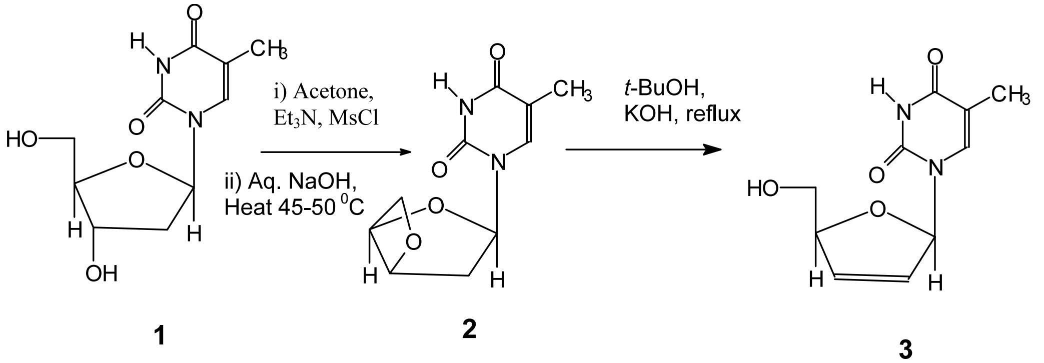
Abstract—2′,3′-Didehydro-3′-deoxythymidine (d4T) is an orally active antiviral drug used in the treatment of AIDS. A novel two-step synthetic method was developed for the synthesis of d4T using inexpensive reagents. An improvement in the yield was achieved for the conversion of the intermediate oxetane to d4T. This is the first simple and efficient method for the large-scale synthesis of d4T. © 2003 Elsevier Science Ltd. All rights reserved.

Acquired Immuno Deficiency Syndrome (AIDS) is an infectious disease caused by human T-cell lymphotropic virus type III/lymphadenopathy virus (HTLV-III/LAV), recently termed as the human immuno deficiency virus.[1] Several compounds with different chemical structures i.e. 2′,3′-dideoxycytidine (ddc), 2′,3′-dideoxyadenosin (ddA),[2] dideoxyinosine (ddI),[3] 3-azidoguanosine,[4] 3′-fluoro-3′-deoxy thymidine (FDDT),[5] zidovudine (AZT),[6] lamivudine (3TC),[7] and stavudine (d4T)[8] have been reported to exhibit significant inhibitory effect against HIV. Among these, AZT, 3TC and d4T have proven to be the most potent antiviral agents and are approved by the drug authorities of many countries for the treatment of AIDS.

Although 2′,3′-didehydro-3′-deoxythymidine (stavudine), is a promising drug for the treatment of AIDS, there is no economically viable method for its synthesis. Although a few methods are available in the literature,[8c,9,10] they are tedious, not feasible for large-scale synthesis, give poor yields and usually require expensive reagents. Stavudine (d4T) was first synthesised by Horwitz et al., by two different methods.[9,10] The first route involved conversion of 3′,5′-anhydrothymidine to stavudine by an elimination reaction under strongly basic conditions. The second route also involved subjecting the 5′-O-protected 2,3′-anhydrothymidine to a ring opening elimination reaction under basic conditions followed by deprotection to yield d4T. Both methods involved the use of a strong base and polar solvents such as DMSO or DMF. Hence high vacuum and high temperatures are required to distil these solvents from the reaction mixtures. Prolonged exposure to basic conditions at high temper-



Scheme 1.

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atures leads to decomposition of d4T to give thymine as an undesired product thereby decreasing the overall yield and purity of the product. To overcome these drawbacks, Starret et al.,[8c] made an attempt to improve the process for the synthesis of d4T. In this method, 3′,5′-anhydrothymidine was subjected to an elimination reaction using a strong base (t-BuO$^-$K$^+$) in polar solvents like DMSO/DMF similar to Horwitz et al.[10] After completion of the reaction, the potassium salt of d4T was precipitated by adding solvents such as toluene, ethyl acetate, and acetone. The resultant salt was redissolved in the minimum quantity of water, neutralised with an acid and the precipitated d4T was recrystallised from acetone. Although this method is considered an improved method, it retains a few drawbacks. Isolation of the potassium salt is very tedious, as it is highly hygroscopic and usually it should be used immediately in the next step. The neutralisation of the potassium salt is an exothermic process, which leads to decomposition of the d4T to thymine as an undesired side product.

Here, we report a two-step method (Scheme 1) involving inexpensive reagents and non-hazardous solvents, which can be conveniently applied for industrial scale synthesis. In the first step, thymidine was converted to the intermediate dimesylated thymidine by reacting with 2 equiv. of methane sulfonyl chloride in acetone, in the presence of triethylamine. After concentrating the solvent, the reaction mass was treated with aqueous sodium hydroxide to obtain the reactive intermediate 3′,5′-anhydrothymidine (an oxetane). In the second step, the oxetane was subjected to an elimination reaction by treatment with potassium hydroxide in t-butanol. After completion of the reaction, methanol was added, the mixture was neutralised with HCl gas in isopropyl alcohol, and the precipitated potassium chloride was filtered. Upon concentration of the solvent, the product was recrystallised from acetone to yield stavudine. In the first step, thymidine was directly converted to the oxetane using acetone instead of hazardous pyridine as reported for earlier processes.[8c,9,10] During the second step, the reaction time was reduced from 18–20 h to 2–3 h. This step involves the use of the relatively mild base KOH and t-BuOH as solvent compared to earlier processes,[8c,9,10] which use t-BuO$^-$K$^+$ as base and DMSO or DMF as solvent.

In the above process, the first step involves preparation of 3′,5′-anhydrothymidine intermediate **2** starting from thymidine **1**. This was obtained by the reaction of thymidine with 2 equiv. of methanesulfonyl chloride, followed by reaction with aqueous sodium hydroxide. During the conversion of dimesylthymidine to 3′,5′-anhydrothymidine, the primary mesylate undergoes hydrolysis by the action of the base, and subsequently displaces the secondary mesylate through intramolecular nucleophilic substitution. The second step involves abstraction of the proton (C^1-2) from the oxetane in the presence of potassium hydroxide, followed by ring opening to obtain d4T via an E_2 mechanism.

In summary, we report an inexpensive, two step method, which can be conveniently applied to the large-scale synthesis of d4T.

Typical procedure:

Preparation of 3′,5′-anhydrothymidine 2:

To a stirred solution of β-thymidine **1** (200 g, 0.82 mol) in acetone, triethylamine was added. To this solution distilled methanesulfonyl chloride (198.2 g, 1.73 mol) was added in portions, while maintaining the temperature of reaction between 30 and 35°C. After the addition was complete the reaction was slowly brought to 40–45°C and stirred for about 5 h. The solvent was concentrated and the residue was cooled to room temperature. 20% Sodium hydroxide was added until a pH of 10 was attained and the solution was heated to 45–50°C for 2 h. After completion of the reaction, it was cooled to 5°C and neutralised with acetic acid. The precipitated solid was filtered and washed with water to give 108 g (58%) of 3′,5′-anhydrothymidine. mp 189–192°C; lit[8c] 188–190°C.

^{1}H NMR (200 MHz, DMSO-d_6): 11.34 (s, 1H, NH), 8.0 (s, 1H, H-6), 6.53 (t, 1H, J=5.4 Hz, H-1′), 5.48 (m, 1H, H-3′), 4.89 and 4.68 (m, 2H, H-5′), 4.02 (d, 1H, J=8.0 Hz, H-4′), 2.47 (m, 2H, H-2^1), 1.77 (s, 3H, CH_3).

Preparation of 2′,3′-didehydro-3′-deoxythymidine 3:

To a stirred solution of 3′,5′-anhydrothymidine **2** (100 g, 0.44 mol) in t-BuOH (600 mL), potassium hydroxide (80 g, 1.42 mol) was added in portions over a period of 20–30 min. The solution was heated to 55–60°C and maintained at this temperature for 2 h. After completion of the reaction, it was cooled to room temperature and methanol (400 mL) was added slowly to give a clear solution. This was then neutralised with hydrochloric acid (HCl gas in IPA). Precipitated potassium chloride was filtered and the clear filtrate was concentrated under vacuum to give crude d4T, which was recrystallised from acetone to yield a colourless solid (85 g, 85%). mp 165–166°C; lit[10] 165–166°C, $[\alpha]_D^{25}$ −44 (c 0.7, water); lit[10] $[\alpha]_D^{25}$ −42 (c 0.69, water).

IR (KBr): 3463, 3159, 3033, 1691, 1496, 1116, 1093 cm^{-1}.

^{1}H NMR (200 MHz, DMSO-d_6): 11.28 (s, 1H, NH), 7.64 (s, 1H, H-6), 6.82 (d, 1H, J=1.4 Hz, H-1′), 6.40 (d, 1H, J=1.5 Hz, H-3′), 5.92 (dd, 1H, J=1.1, 3.8 Hz, H-2′), 5.03 (m, 1H, OH), 4.76 (s, 1H, H-4′), 3.62 (m, 2H, H-5′), 1.72 (s, 3H, CH_3).

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