# One-step Conversion of Thymidine into 2,3′-Anhydro Derivatives

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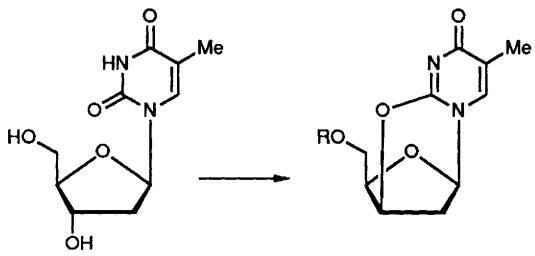
2,3′-Anhydro derivatives of thymidine are obtained in *ca.* 80% yield by a one-pot transformation involving a tandem Mitsunobu reaction.

The search for efficient syntheses of 2,3′-anhydro derivatives of thymidine (**1**) is of interest because these compounds are precursors of many 2′,3′-dideoxynucleosides which have proved to be selective inhibitors of HIV-1 replication,[1] some of which are used for the treatment of patients with AIDS.

We report herein a very efficient one-pot conversion of (**1**) into 2,3′-anhydro derivatives. Originally, transformation of (**1**) into the 2,3′-anhydro derivative (**2**) involved several steps.[2,3] Later, Kowollik *et al.*[4] reported a one-step procedure in which (**1**) was heated at 70 °C in the presence of 2-chloro-1-diethylamino-1,1,2-trifluoroethane to afford the 2,3′-anhydro derivative (**2**). Recently, (**2**) was obtained by heating (**1**) at 150 °C in the presence of diphenyl sulphite.[5] Although these are useful procedures we believe that the method described herein has advantages in that the reagents are readily available, the reactions are conducted under mild conditions, and the isolation of pure products is very facile.

We thought that an intramolecular Mitsunobu reaction[6] could be a way to achieve the 2,3′-cyclisation. Mitsunobu, whilst attempting to prepare 3′-phosphate esters, has observed intramolecular 2,3′-cyclisation when 5′-*O*-protected 2′-deoxynucleosides are treated with triphenylphosphine and diethyl azodicarboxylate in the presence of dibenzyl phosphate.[7] When an unprotected 2′-deoxynucleoside is employed as starting material, we have observed that 2,5′-cyclisation is the preferred process.[8] Since it is well established that this reaction proceeds better with less hindered alcohols and more acidic incoming groups ($ArCO_2H > ArOH$),[6] we decided to sequentially protect the 5′-OH as an ester function and achieve the cyclisation. When a solution of (**1**) in dimethylformamide (DMF) was treated with di-isopropyl azodicarboxylate (DIAD, 1.5 equiv.) in the presence of triphenylphosphine ($Ph_3P$, 1.5 equiv.) and benzoic acid ($PhCO_2H$, 1.5 equiv.) at room temperature, TLC analysis showed complete consumption of (**1**) within 15 min. Rather than isolating the intermediate 5′-ester it was found more convenient to complete the transformation to (**2a**) by further addition of $Ph_3P$ (1.5 equiv.) and DIAD (1.5 equiv.). After stirring the reaction mixture for <1 h the product (**2a**) was precipitated by pouring the mixture into ether. Filtration and drying gave (**2a**) in 86% yield and good purity.† Our results with selected aromatic carboxylic acids are shown in Table 1. In all cases, TLC analysis indicated that the transformation was very efficient. The differences in isolated yield are related to solubility differences of the products in DMF/$Et_2O$. In some cases (entries 3,4) the 2,3′-anhydro derivative could be isolated by cooling the reaction mixture and filtration of the precipitate.

Cleavage of the 5′-*O*-ester function without opening the anhydro ring is possible if mild conditions are employed




(**1**)

(**2**) R = H
(**2a**) R = PhCO
(**2n**)* R = ArCO

*See Table 1

† All described compounds gave analytical and spectral data in agreement with their structure. *E.g.*, $^1H$ NMR ($CDCl_3$) for (**2a**): δ 1.88 (s, 5 Me), 2.48 and 2.68 (2 m, $J_{gem}$ 12.9, $J_{vic}$ 3.5 Hz, H-2′ and H-2″), 4.46 and 4.63 (dAB, $J_{gem}$ 10.5, $J_{vic}$ 5.5 Hz, H-5′ and H-5″), 4.55 (m, H-4′), 5.27 (br. s, H-3′), 5.51 (d, J 3.5 Hz, H-1′), 6.93 (s, H-6), 7.38—7.99 (m, Ph).

**Table 1**

| Entry | R | Product | Isolated yield/% | M.p. /°C |
|---|---|---|---|---|
| 1 | Benzoyl | (**2a**) | 86 | 242 |
| 2 | 4-Methoxybenzoyl | (**2b**) | 80 | 238—240 |
| 3 | 4-Methoxybenzoyl | (**2b**) | 76 | |
| 4 | 4-Nitrobenzoyl | (**2c**) | 66 | >300 |
| 5 | 2-Furoyl | (**2d**) | 75 | 260 |
| 6 | 3,5-Dinitrobenzoyl | (**2e**) | 90 | 258 |
| 7 | 3,4-Dimethoxybenzoyl | (**2f**) | 84 | 240 |
| 8 | 2-Bromobenzoyl | (**2g**) | 65 | 238 |
| 9 | 2,6-Dichlorobenzoyl | (**2h**) | 76 | 222 |

(catalytic NaOMe, MeOH, room temp., 75% yield) but, since these 2,3′-anhydro derivatives (**2**) have very low solubility in organic solvents, the 5′-*O*-protected derivatives are more suitable for further transformations.

The conversion of thymidine (**1**) into the corresponding 2,3′-anhydro derivatives, described herein, compares very favourably with other syntheses described in the literature.[2—5]

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