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3'-Substituted Pyrimidines via Alkylation-opening of 2,3'-Cyclothymidine

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Substituted thymidine derivatives are of interest because of their potential antiviral properties. We demonstrate a general strategy for synthesis of 3'-substituted thymidine derivatives, consisting of activation via N-3 alkylation of 2,3'-cyclothymidine followed by nucleophilic opening at the 3'-position. Examples include demonstration of carbon-carbon bond formation at the 3'-position.

Pyrimidine derivatives substituted at 3'-carbon are of interest as potential antivirals and as important intermediates towards the synthesis of certain internucleoside linkers in antisense DNA.[1] Synthesis of several 3'-substituted thymidine derivatives were described recently, however no general method has been described and formation of carbon-carbon bonds at the 3'-position remains a challenging task.[2] Cyclonucleosides in general are of continuing interest in organic chemistry.[3] The 2,3'-cyclothymidine **1** has been widely investigated and is a potential precursor to a variety of 3'-substituted thymidine derivatives. Azide ring opening of cyclothymidine produces 3'-azido-3'-deoxythymidine (AZT), the first approved drug for treatment of acquired immune deficiency syndrome.[4] Two other reports on the opening of cyclothymidine ring at 3'-carbon have appeared, featuring sulfur[5] and selenium[6] nucleophiles. Such reactions of 2,3'-cyclothymidine have required elevated temperatures and long reaction times. We report the synthesis of a broad variety of 3'-substituted thymidine derivatives via a novel activation-opening reaction of 2,3'-cyclothymidine.[7]

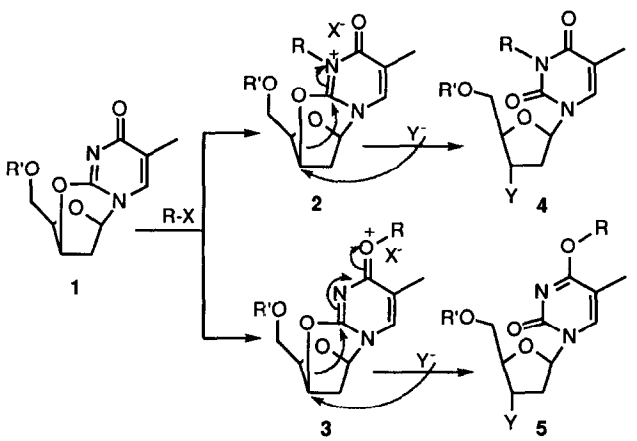
Alkylation at the N-3 atom of **1** results in intermediate **2** having a quaternary nitrogen atom.[8] It was reasoned that the positively charged heteroaromatic pyrimidine ring coupled with the conformational strain existing in the fused oxazine ring (Scheme I) would lead to facile ring opening under relatively mild conditions, allowing even weak nucleophiles to cause substitution at the 3'-position.

Thus, when 5'-dimethoxytrityl-2,3'-cyclothymidine **1**[5] was treated with methyl trifluoromethane sulfonate (methyl triflate) in anhydrous THF in the presence of a small amount of 2,6-di-t-butyl-4-methylpyridine, immediate disappearance of starting material and formation of a polar product was observed by TLC. Since, the triflate counter-anion is non-nucleophilic, experimentation with a variety of nucleophiles

was possible to probe the effectiveness of this activation procedure. Introduction of lithium azide at 10 °C led to immediate formation of a less polar product. After isolation by chromatography, characterization revealed this to be 5'-O-dimethoxytrityl-N-methyl-3'-azido thymidine **4a**, (yield 85%; Table I). Thus opening was achieved rapidly, under mild conditions and in high yield.[9] The product **4a**, was subjected to detritylation by 3% trichloroacetic acid in CH_2Cl_2 to give N-methyl-AZT **4b**. A minor product **5a** (5-10%), resulted from alkylation at C-4 oxygen atom followed by 3'-opening with azide.

When water is introduced to the active intermediate **2**, hydroxide substitution at the 3'-atom gave N-methyl thymidine **4c**. The 3'-bromo, 3'-iodo, and 3'-thiocyanato derivatives **4d**, **4e** and **4f** respectively were prepared in high yield with equal ease, by treatment of activated cyclothymidine with sodium bromide, sodium iodide and sodium thiocyanate respectively. When opening was attempted with vinyl magnesium bromide, the 3'-bromo derivative **4d**, but not the expected 3'-vinyl derivative, was obtained in high yield. We were particularly interested in ring opening with the cyano nucleophile, however reactions with lithium, sodium, potassium or n-tetrabutyl ammonium cyanide led only to the hydroxide (H_2O) opening product to give N-methyl-thymidine **4c**. An interesting reaction was observed when **2** was treated with an excess of cuprous cyanide. A clean opening reaction was observed by TLC, however upon isolation and spectral characterization the product was identified as N-methyl-3'-carboxylate **4g**. The cyanide ion opened the activated 2,3'-ring in **2** but then presumably was hydrolyzed to the carboxylate in the presence of cuprous ion. We are further examining this reaction as it may constitute a general method for cyanide hydrolysis. Another carbon-carbon bond formation was achieved at the 3'-position when **2** was treated with dimethyl sodiomalonate (2 eqv.) to give **4h** in 50% yield.

Scheme I



We briefly explored activation of the 2,3'-ring by alkylation with removable groups. Thus cyclothymidine **1** reacted rapidly with benzyl triflate[10] and lithium azide to give after detritylation N-benzyl-AZT **4k**. Reaction of **1** with 2-cyanoethyl bromide resulted in N-cyanoethyl-3'-bromothymidine **4m**.

Table I. List of compounds prepared via alkylation-opening of 1

Product	R=	Y=	RX/Y	Rxn times:[a] Alkylation/opening	% yield
4a	CH_3	N_3	CH_3OTf/LiN_3	10/20 min	85%
5a	CH_3	N_3	CH_3OTf/LiN_3	10/20 min	9%
4b (R'=H)[b]	CH_3	N_3	------	--------	90%
4c	CH_3	OH	CH_3OTf/H_2O	10/40 min	90%
4d[c]	CH_3	Br	$CH_3OTf/NaBr$	10/20 min	70%
4e	CH_3	I	CH_3OTf/NaI	10/20 min	90%
4f	CH_3	SCN	$CH_3OTf/NaSCN$	10/20 min	60%
4g	CH_3	COOH[d]	$CH_3OTf/CuCN$	10 min/24 h (r. t.)	65%
4h	CH_3	$CH(CO_2Me)_2$	$CH_3OTf/NaCH(CO_2Me)_2$[e]	10 min/2h	50%
4k (R'=H)[f]	CH_2Ph	N_3	$PhCH_2OTf/LiN_3$	10 min (-20 °C)/20 min	90%
4m	CH_2CH_2CN	Br	$CNCH_2CH_2Br$	4h (65 °C)[g]	60%

a) Reaction temperature is 10 °C unless otherwise noted. b) Obtained by detritylation of **4a**. c) This compound was also obtained when opening was attempted with vinyl-magnesium bromide. Yield: 50%. d) Carboxylic acid presumably formed via hydrolysis of CN. e) Dimethyl sodiomalonate was generated from dimethylmalonate and sodium hydride in THF. f) Detritylation occurs in-situ. g) Opening by bromide counter anion.

The above alkylation-opening reaction makes possible opening of cyclothymidine with a broad selection of nucleophiles under exceptionally mild conditions. Nucleophillic displacement is clearly facilitated by the generation of the strained electron-deficient tricyclic system **2** and should prove to be a valuable methodology. This provides a rapid and efficient method for synthesis of N-3-substituted AZT derivatives, for which activity against HIV-replication has recently been described.[11]

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9. **General procedure and data for representative compounds. 4a**: Methyl triflate (1 mM; 113 μL) was added dropwise via syringe to a solution of 5'-dimethoxytrityl-2,3'-cyclothymidine[5] (1 mM; 526 mg) and 2,6-di-t-butyl-4-methyl pyridine (0.25 mM; 50 mg) in anhydrous THF (20 mL) under N_2 at 10 °C. After 10 minutes, lithium azide (80 mg) was added as solid under a steady N_2 flow and the reaction was allowed to stir for 2 h. Water (5 mL) was added and the reaction was extracted into ethyl acetate, organic layers washed with brine and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography (silica gel; 20 % EtOAc/Hexanes). Yield: 495 mg; 85%. Rf: 0.6 (50% EtOAc/Hexanes). IR (film): 2106 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.56, (s, 1 H), 7.38-7.21 (m, 9 H), 6.81 (d, J = 9 Hz; 4 H), 6.26 (t, J = 6.3 Hz; 1 H), 4.30 (q, J = 7 Hz; 1 H), 3.95 (m, 1 H), 3.76 (s, 1 H), 3.45 (ABq, J = 11, J = 3 Hz, Δν = 73 Hz; 2 H), 3.31 (s, 3H), 2.42 (m, 2 H), 1.5 (s, 3 H). MS (FAB): m/z 584.4 $(M+H)^+$. Anal Calcd. for $C_{32}H_{33}N_5O_6.0.5H_2O$: C, 64.92; H, 5.79; N, 11.82. Found: C, 64.54; H, 5.46; N, 11.57. **Data for 4g:** Yield: 65%. Rf: 0.57 (40% EtOAc/Hexanes). MS (FAB): m/z 587.1 $(M+H)^+$. ^1H NMR (300 MHz, $CDCl_3$): δ 8.0, (s, 1 H), 7.56 (s, 1 H), 7.35 - 7.2 (m, 9 H), 6.79 (d, J = 9 Hz; 4 H), 6.42 (m, 1 H), 5.49 (m, 1H), 4.12 (m, 1 H), 3.74 (s, 1 H), 3.44 - 3.40 (m, 2 H), 3.30 (s, 3H), 2.46 - 2.42 (m, 2 H), 1.38 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 160.9, 159.5, 152.0, 144.8, 135.8, 135.7, 133.7, 130.7, 128.6, 127.8, 113.8, 111.2, 87.6, 85.5, 84.1, 75.3, 63.8, 55.6, 38.3, 28.2, 12.7. Anal Calcd. for $C_{33}H_{34}N_2O_8$: C, 67.60; H, 5.84; N, 4.78. Found: C, 68.00; H, 5.90; N, 4.93.
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