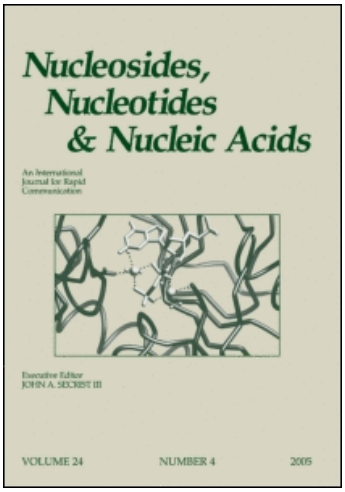

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AN IMPROVED SYNTHESIS OF 3'-KETO-5'-O-TRITYLTHYMIDINE

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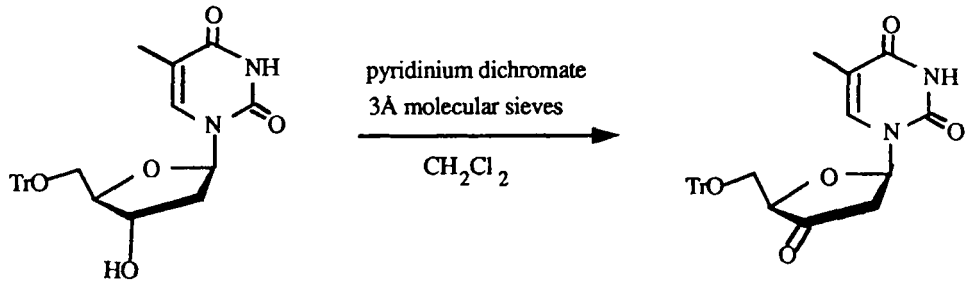
Abstract: The title compound is prepared in consistently high yield and purity by molecular sieve catalyzed pyridinium dichromate oxidation of 5'-O-tritylthymidine. Shortcomings of other preparations are described, and properties of the title compound are reported.

Because carbonyls may be transformed into a variety of other functional groups, ketonucleosides are potentially valuable intermediates for the synthesis of sugar-modified nucleosides. The usefulness of 3'-keto-5'-O-tritylthymidine (**2**) as an intermediate has been demonstrated in the recent syntheses of 3',3'-difluoro-3'-deoxythymidine[2] and 1-(2-deoxy-3-methyl-β-D-xylosyl)thymine[3]. We report here a method for the preparation of **2** from 5'-O-tritylthymidine (**1**) with several advantages over those previously reported.



1 **2**

Our ongoing efforts to prepare 3'-modified thymidines as potential inhibitors of viral transcription required large quantities of **2** in high purity. Several existing procedures for the preparation of ketonucleosides were considered. Moffat and co-workers[4,5] oxidized cytidine and uridine to their 2'- and 3'-keto derivatives with dimethylsulfoxide-based reagents. Our attempts to oxidize **1** with these reagents yielded mainly thymine and 2-trityloxymethyl-3(2H)-furanone, presumably by base-induced β-elimination. Schreiber and Ikemoto[6] recently reported the same results. Binkley et al.[7,8] prepared **2** in 61% yield (305 mg) by photolysis of the 3'-pyruvoyl ester of **1** in benzene. This procedure is difficult to carry out on a larger scale due to the finite capacities of common laboratory photochemical reactors and the low solubilities of **1** and **2** in the required solvent.

The chromium trioxide/pyridine/acetic anhydride reagent of Garegg and co-workers[9,10] was used by Hansske and Robins[11,12] to oxidize **1** to **2** in 87% yield (419 mg). Our attempts to repeat this procedure led to only partial success: yields were highly variable, and when product could be isolated at all, it was frequently contaminated with significant amounts of impurities, especially the previously mentioned products of β-elimination. Many of these impurities likely arose during a portion of this procedure where the product mixture is filtered through a short column of silica gel: the decomposition of **2** by silica gel to these products has been previously reported[8]. We have found that neutral alumina, activated carbon, and Florisil--even when deactivated-- also induce decomposition.

Since existing syntheses did not meet our needs, a new procedure based upon the oxidation method of Herscovici and co-workers[13,14] was developed. In our procedure, **1** in dichloromethane is oxidized at room temperature under anhydrous conditions by pyridinium dichromate in the presence of 3Å molecular sieve powder. Purification of the product is easily achieved by filtration through inert materials followed by recrystallization. Our procedure requires only common laboratory equipment and easily handled, commercially available reagents. The desired product **2** is obtained in consistently high yield and purity, and we have successfully run the reaction with as much as five grams of **1** at one time. Further scaleup should be possible but was not attempted.

The basic method of Herscovici and co-workers has been modified at times by adding catalytic amounts of dichloroacetic acid[13,14], acetic acid[15,16], or acetic anhydride[17,18] to the reaction mixture, resulting in improved reaction times and product yields in some cases. We found that no significant improvements to our procedure resulted from addition of these reagents; discoloration and minor decomposition of the product occurred in some cases. Also, several attempts were made to substitute nicotinic dichromate[19] for pyridinium

dichromate in the hope that workup would be simplified. However, yields of **2** varied considerably from run to run with this reagent, and its use was subsequently discontinued.

Experimental

General Information. NOTE: all reagents used in the reaction (especially the molecular sieve powder) must be dry, or lowered yields of product will result! Prior to use, 3Å molecular sieve powder (<10 μm particles-Sigma #M1885) was heated at 325 °C in a muffle furnace for at least three hours, then cooled in a dessicator. Dichloromethane (Fisher spectrometric grade) was eluted from a column of neutral alumina and stored over 3Å molecular sieve powder. Argon was dried by passage through a column of calcium sulfate (Drierite). 5'-O-Tritylthymidine (available from Sigma) was prepared by the method of Munson[20], recrystallized from toluene, and dried in a freeze drier. Elemental analysis and ^{1}H NMR spectroscopy indicated that the final product contained 10-11% toluene by weight. Pyridinium dichromate (available from Aldrich) was prepared by the method of Corey and Schmidt[21], ground to a powder with mortar and pestle, and dried in a vacuum oven. Ethyl acetate (Mallinkrodt spectrometric grade) was used as received.

Melting points were obtained with a Mel-Temp apparatus (Laboratory Devices, Inc.) set at 54 volts, yielding a heating rate of about 4 °C/minute between 170-185 °C. NMR spectra were obtained in $CDCl_3$ solutions with a Varian VXR-300 NMR spectrometer and were referenced to TMS. The diffuse reflectance infrared spectrum of **2** (as an approximately 10% w/w mixture with KBr which was ground five minutes in a Wiggle-Bug) was obtained with a Nicolet 20-SXB FTIR spectrometer equipped with a Spectra-Tech diffuse reflectance accessory and an MCT detector. HPLC analyses were performed with a Beckman Model 338 system interfaced to an IBM PS/2 Model 70 computer equipped with Beckman System Gold chromatography software. Samples were eluted from an Econosphere C18 column (5 μm, 80 Å, 250 x 4.6 mm; equipped with Direct-Connect C18 guard cartridge; Alltech Associates, Inc., Deerfield, IL) with 75/25 acetonitrile/water (Fisher HPLC grade) at 1.5 ml/min and detected at 254 nm. Elemental analyses were performed by Galbraith Laboratories, Inc. of Knoxville, Tennessee.

Synthesis Procedure. A slurry of 3Å molecular sieve powder (1.50 g) and pyridinium dichromate (1.50 g) in dichloromethane (10 mL) was magnetically stirred in a 50 mL round bottom flask at room temperature under argon. 5'-O-Tritylthymidine (1.25 g of a product containing 10% toluene) was added in one portion, and the sides of the flask

were washed down with more dichloromethane (10 mL). The color of the reaction mixture changed from light orange to dark brown within five minutes. The reaction was monitored by TLC (see below), and starting material was not detected after 45 minutes.

The reaction mixture was stirred at room temperature for one hour, then filtered on a Büchner funnel. The collected solids were washed with dichloromethane (25 mL), and the solvent was removed from the combined filtrates by rotary evaporation. The resulting brown solid was then suspended in ethyl acetate (200 mL) by sonicating the mixture for a few minutes in a laboratory ultrasonic bath. The suspension was first filtered through a PTFE filter (Millipore type FH, 0.45 mm pores) with a glass-fiber prefilter (Nalgene #281), then through a 2-3 cm plug of microcrystalline cellulose (Whatman #CC41) or 3Å molecular sieve powder (deposited as slurries with ethyl acetate) on a glass-fritted filter funnel. The plug was washed with ethyl acetate (25 mL). The solvent was removed from the combined filtrates by rotary evaporation to yield 1.05 g of light tan powder.

This powder was dissolved in a minimum volume of warm dichloromethane. About three volumes of carbon tetrachloride or diethyl ether were added, and the solution was allowed to stand. The fine white needles which formed were collected on a Büchner funnel and dried on the frit. The yield was 0.94 g (mp 179-182 °C). (Previous workers have recrystallized **2** from chloroform/carbon tetrachloride; however, this gives an amorphous solid melting at 172-176 °C). Samples recrystallized as above still contained (by NMR analysis) noticeable amounts of solvents that could not be removed by heating under vacuum. This problem was remedied by re-dissolving the crystals in dichloromethane, then removing it by rotary evaporation. After three such cycles the resulting white powder contained little solvent (which could now be removed by heating under vacuum). The final yield was 0.90 g (80%). This product melted at 182-184 °C (lit.[7,8] mp 171-174 °C). All products decomposed and re-solidified shortly after melting.

The product is a white powder stable indefinitely at room temperature. It is insoluble in alkanes, carbon tetrachloride, and water. It is very soluble in dichloromethane and chloroform (though dissolution occurs somewhat slowly); moderately soluble in ethyl acetate (approximately 5 mg/mL); and sparingly soluble in diethyl ether and benzene. Solutions in these solvents are stable; however, the product decomposes within six hours in solutions of dimethylsulfoxide[12], acetone, methanol, or acetonitrile.

Analyses. Useful information was still obtained from thin layer chromatography in spite of partial or complete decomposition of **2** on silica gel. Samples in dichloromethane were

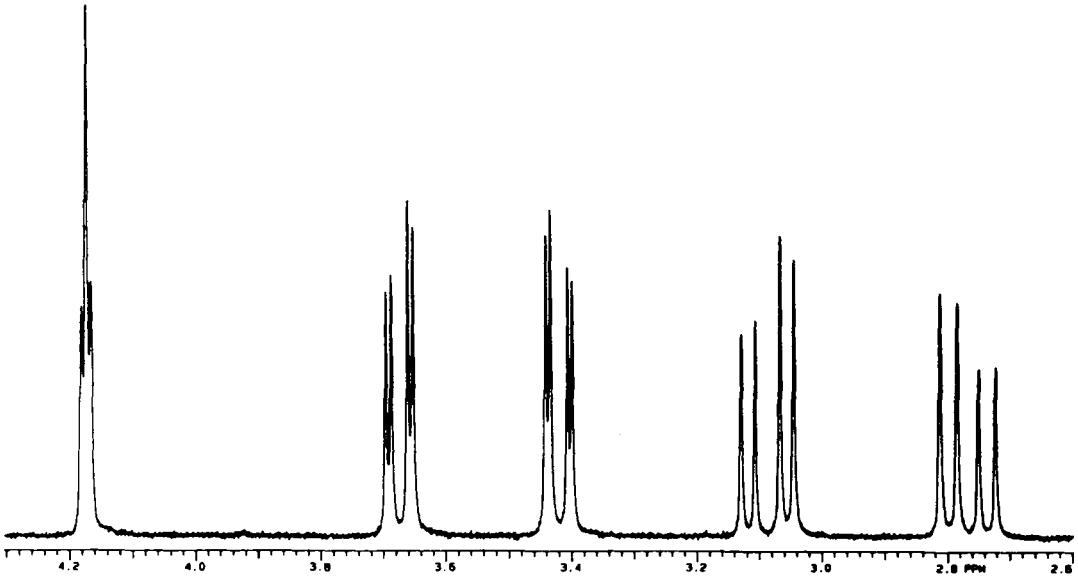


FIGURE 1. Portion of 300 MHz ^{1}H NMR spectrum of **2**.

spotted on silica gel TLC plates (Whatman #MK6F) and eluted with 95:5 dichloromethane/methanol solution. Spots were identified by comparison with the results from a pure sample of **1** and a sample of **2** fully decomposed with triethylamine. The following Rf values were noted: thymine, 0.08; **1**, 0.16; **2**, 0.32; and 2-trityloxymethyl-3(2H)-furanone, 0.74. The spot for **2** was usually but not always present, depending upon whether or not complete decomposition had occurred on the TLC plate. When a single drop of dichloroacetic acid was added to a solution of **2** in dichloromethane prior to spotting, a single spot (Rf=0.32) was observed.

Reverse-phase HPLC analysis of the product was investigated as an alternative to TLC. Its usefulness was also limited to the detection of remaining starting material due to decomposition of **2** in acetonitrile or methanol solution. The following retention times (in minutes) were noted: thymine, 1.67; **1**, 2.86; **2**, 3.47; 2-trityloxymethyl-3(2H)-furanone, 4.79.

The infrared spectrum of **2** was similar in appearance to that of **1** except for a strong absorption at 1766 cm^{-1}. The ^{1}H NMR spectrum (δ, $CDCl_3$) of **2** exhibited the following resonances (see also Figure 1): δ 8.72 (br s, H_3), 7.64 (unresolved q-appears as d with

shoulders, H_6), 7.20-7.40 (m, Ar), 6.57 (dd, $H_{1'}$), 4.17 (unresolved dd-appears as br t, $H_{4'}$), 3.67 (dd, $H_{5'A}$), 3.42 (dd, $H_{5'B}$), 3.09 (dd, $H_{2'A}$), 2.78 (dd, $H_{2'B}$), and 1.33 ppm (d, Me). The proton coupling constants were: $J_{Me\text{-}6}$=1.3 Hz, $J_{1'\text{-}2'A}$=6.7 Hz, $J_{1'\text{-}2'B}$=8.2 Hz, $J_{2'A\text{-}2'B}$=18.6 Hz, $J_{4'\text{-}5'A}$=2.6 Hz, $J_{4'\text{-}5'B}$=2.3 Hz, $J_{5'A\text{-}5'B}$=10.4 Hz. The ^{13}C NMR spectrum (δ, $CDCl_3$) of **2** exhibited the following resonances: δ 209.37 ($C_{3'}$), 163.39 (C_4), 150.34 (C_2), 143.00 (Ar), 134.92 (C_6), 128.60 (Ar), 128.12 (Ar), 127.54 (Ar), 112.43 (C_5), 87.69 ($Ph_3\underline{C}$), 81.45 ($C_{4'}$), 81.01 ($C_{1'}$), 63.14 ($C_{5'}$), 41.87 ($C_{2'}$), and 11.51 ppm (Me). Elemental analysis. Calculated for $C_{29}H_{26}N_2O_5$: C 72.18, H 5.43, N 5.81. Found: C 72.02, H 5.70, N 5.89.

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