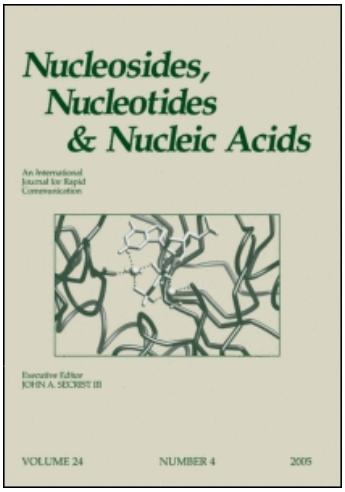

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Kwasi Agyei-aye[a]; Shijia Yan[a]; Anna K. Hebbler[a]; David C. Baker[a]
[a] Departments of Chemistry, The University of Alabama, Tuscaloosa, AL

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PREPARATION OF 2,3'-ANHYDROPYRIMIDINE NUCLEOSIDES USING N,N-DIETHYLAMINOSULFUR TRIFLUORIDE (DAST)

Kwasi Agyei-Aye, Shijia Yan, Anna K. Hebbler, and David C. Baker*

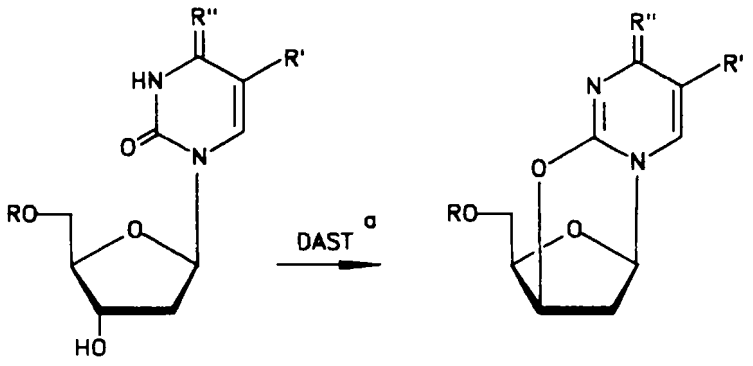
Department of Chemistry
The University of Alabama
Tuscaloosa, AL 35487-9671

Abstract. 2,3'-Anhydro-2'-deoxy-5'-O-(triphenylmethyl) and 5'-O-(monomethoxytriphenylmethyl) pyrimidine nucleosides of uracil, thymine, and cytosine were synthesized in a single step from their 2'-deoxy-5'-O-(triphenylmethyl) or 5'-O-(monomethoxytriphenylmethyl) precursors using N,N-diethylaminosulfur trifluoride (DAST). The anhydronucleosides were either isolated or directly converted to their respective 2-deoxy-β-D-threo-pentofuranosyl nucleosides using sodium hydroxide in ethanol.

Introduction

In recent years the synthesis of 2,3'-anhydropyrimidine nucleosides has become of paramount importance owing in part to these versatile intermediates[1] serving as precursors to 3'-modified pyrimidine nucleosides which have antitumor and antiviral properties,[2] particularly those (e.g., 3'-azido-2',3'-dideoxythymidine,[3,4] AZT) which have activity[5] against the HIV virus, the agent responsible for the development of acquired immune deficiency syndrome (AIDS).

2,3'-Anhydropyrimidine nucleosides, originally described in reports from Todd's laboratory,[6,7] have been synthesized by a variety of methods[1,8] which rely upon a good leaving group at the 3'-position of either β-D-ribofuranosyl- or 2-deoxy-β-D-erythro-pentofuranosyl pyrimidines. A frequently used procedure for anhydronucleoside formation is the two-step process of Fox[9,10] or Horwitz and coworkers,[11,12] as well as others,[13,14] which involves 3'-O-methanesul-



1a–c 2a–c

a: R = MMT,[b] R' = CH_3, R" = O
b: R = TR,[c] R' = H, R" = O
c: R = MMT,[b] R' = H, R" = NH

[a] DAST = diethylaminosulfur trifluoride; [b] MMT = monomethoxytrityl ($MeOPhPh_2C$) group; [c] TR = trityl (Ph_3C) group.

SCHEME 1

fonylation, followed by internal, base-induced displacement of the methanesulfonyloxy group. This method generally involves several hours' reaction time, extensive heating, or both, resulting in yields of ca. 80% from 2'-deoxy-5'-protected nucleosides. In the present study is reported a method using N,N-diethylaminosulfur trifluoride (DAST), a well-known fluorinating reagent,[15,16] which is very fast and efficient in producing 2,3'-anhydropyrimidine nucleosides from 5'-protected precursors.

Results and Discussion

Reaction of N,N-diethylaminosulfur trifluoride (2 equiv) with the appropriate 5'-protected pyrimidine nucleoside **1a-c** in dry dichloromethane proceeded quickly at room temperature to give the anhydronucleoside **2a-c** (Scheme 1 and Table 1). The reaction, when

Table 1. Amounts of Reagents and Yields of Products for Compounds 1a-c, 2a-c and 3a-c

Starting Nucleoside Compound No.	Amt. in Grams (mmol)	Vol. of CH_2Cl_2 in mL	Vol. of DAST in mL (mmol)	Anhydro Intermediate Compound No.	Amt. in Grams (% Yield)	Vol. of Triethylamine in mL (mmol)	Vol. of 1.0 M NaOH in mL (mmol)	Vol. of Ethanol in mL	Product Compound No.	Amt. in Grams (% Yield)
1a	9.23 (18.0)	250	4.80 (36.1)	2a	8.64 (97)	-	-	-	-	-
1a	6.50 (12.6)	180	3.40 (25.6)	-	-	7.00 (50.2)	54 (54)	400	3a	5.7 (89)
1b	9.40 (20.0)	1600	5.40 (40.6)	2b	8.60 (95)	-	-	-	-	-
1b	0.406 (0.86)	80	0.20 (1.51)	-	-	0.52 (3.73)	2.00 (2.00)	20	3b	0.351 (87)
1c	0.560 (1.12)	80	0.300 (2.27)	2c	0.480[a] (89)[a] 0.043[b] (8)[b]	-	-	-	-	-
1c	0.350 (0.70)	40	0.180 (1.36)	-	-	0.48 (3.44)	2.30 (2.30)	20	3c	0.260 (72)

[a] Based on crude product (HF salt). [b] Based on product (free base) from attempted purification by silica gel chromatography.

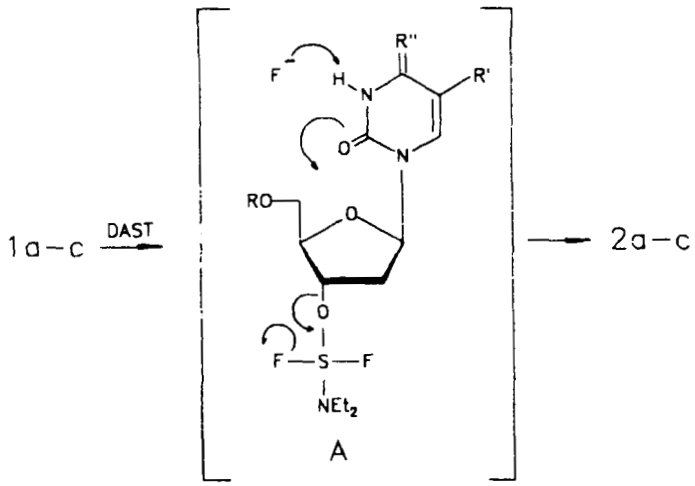
examined by TLC, was shown to be complete after only five min of reaction at room temperature. Workup and purification of the anhydronucleosides by column chromatography on silica gel furnished compounds **2a** and **2b** in high yield. Attempted isolation of 2,3'-anhydro-2'-deoxy-5'-O-(monomethoxytrityl)cytidine (**2c**), either by crystallization as the HF salt or as the free base (generated by treating the crude product with triethylamine) by column chromatography, resulted in nearly complete loss of the nucleoside, owing to its observed instability. Compound **2c** as the HF salt, however, was firmly identified on the basis of its ^{1}H NMR spectrum [Table 2: (Note chemical shift of the $=NH_2^+$.)], and by the fact that the crude product was ring-opened in base to give the 2-deoxy-β-D-threo-pentofuranosyl nucleoside **3c** in good yield (see discussion which follows). While no detailed study on the decomposition of **2c** was made, it is apparent that the molecule, a 2-deoxy nucleoside, suffers from extreme glycosylic bond instability.

The reaction of 2'-deoxy-5'-protected nucleosides with DAST is apparently facilitated by the ready formation of the alkoxy(dimethylamino)sulfur difluoride intermediate **A** (Scheme 2) which possesses nearly ideal leaving-group properties, giving rise to the anhydro compounds **2a-c** under the mildest of conditions. Intermediate **A** is not isolated; however, its presence is detected by TLC in the early stages of the reaction of **1c** as a fast-migrating zone that rapidly disappears with formation of the slower-migrating anhydronucleoside **2c**. Closure to the anhydro compounds **2a-c** may be promoted by the presence of F^- ions (generated by the initial reaction of the nucleoside -OH with DAST and maintained in excess by the elimination of the $-OSF_2NEt_2$ group as $O{=}SFNEt_2$)[15] which could serve as a base to abstract the H-N of the pyrimidine, thus facilitating ring closure of **A** to **2a-c**. Prolonging the reaction time beyond 5 min results in the formation of byproducts and a lowering of the yield of anhydronucleoside. The principal competing reaction, at least with 2'-deoxynucleosides, appears to be loss of the heterocyclic base. Interestingly enough, no product of 3'-fluorination,

Table 2. 200-MHz, ^{1}H NMR Spectral Data[a] for Compounds 2a-c and 3a-c in Methyl Sulfoxide-d_6

Compound No.	H-1'	H-2',2'a	H-3'	H-4'	H-5,5'a	$-OCH_3$	H-5 (Base)	H-6 (Base)	$5-CH_3$ (Base)	Ar	Others
2a	5.89d ($J_{1,2}$ 3.2Hz)	2.55m	5.32m[b]	4.43m	3.10m	3.73s	-	7.63s	1.77s	6.86d (J 8.7Hz) 7.24-7.50m	-
2b	5.48d ($J_{1,2}$ 3.5Hz)	2.64m	5.16m[b]	4.28m	3.38m	-	5.94d (J 7.1Hz)	7.05d (J 7.4Hz)	-	7.18-7.49m	-
2c	6.23d ($J_{1,2}$ 3.5Hz)	2.76m	5.62m[b]	4.54m	3.15m	3.74s	6.47d (J 7.1Hz)	8.16d (J 7.1Hz)	-	6.88d (J 8.7Hz) 7.24-7.36m	9.02s NH
3a	6.11d ($J_{1,2}$ 6.5Hz)	1.86 d (J 14.4Hz) 2.54m[d]	4.20m	4.09m	3.17-3.39dd[c,e] (J_1 10.2Hz, J_2 9.0Hz)	3.74s	-	7.61s	1.65s	6.90d (J 8.4Hz) 7.27-7.58m	5.21d (J 3.2Hz) 3'-OH 11.30s, NH
3b	6.10d ($J_{1,2}$ 7.0Hz)	1.83d (J 14.4Hz) 2.52m	4.04m	3.17-3.51m		-	5.43d (J 7.7Hz)	7.62d (J 8.01Hz)	-	7.23-7.44m	4.18bs -OH 11.51s, NH
3c	5.62d ($J_{1,2}$ 7.4Hz)	1.83d (J 14.6Hz) 2.49m[d]	4.08-4.16m		3.30dd[c,e] (J_1 11.4Hz, J_2 10.0Hz)	3.75s	6.05d (J 6.5Hz)	7.64d (J 7.4Hz)	-	6.90d (J 8.6Hz) 7.24-7.47m	5.13d, OH (J 3.1Hz) 7.12bs, $-NH_2$

[a] Spectra were obtained in methyl sulfoxide-d_6 with tetramethylsilane as internal standard. Chemical shifts (δ PPM) are downfield from Me_4Si. Spin-spin splittings are apparent, first-order values reported in Hz: b, broad; d, doublet; dd, doublet of doublets; m, multiplet; s, singlet. [b] Appears as a broad singlet. [c] AB of an ABX system. [d] Partially obscured by methyl sulfoxide. [e] Partially obscured by water.



a. R = MMT,[a] R' = CH_3, R" = O
b. R = TR[b], R' = H, R" = O
c. R = MMT[a], R' = H, R" = NH

[a] MMT = monomethoxytrityl ($MeOPhPh_2C$) group; [b] TR = trityl (Ph_3C) group.

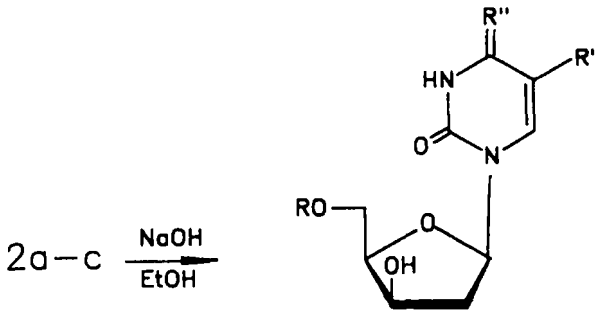
SCHEME 2

which is known with these compounds,[5] was detected under these mild conditions.

Inasmuch as the anhydronucleosides were produced in a state of high purity (ca. 95%, minimum, by ^1H NMR spectroscopy), the products were used directly in ring-opening reactions (Scheme 3) to give the 2-deoxy-β-D-threo-pentofuranosylnucleosides **3a–c**. The conversions, even with the cytosine example **2c**, which was essentially lost upon attempted silica gel purification, gave 72% of product in the direct conversion of **1c** to **3c**. Yields and other data are shown in Table 1.

Conclusions

The use of DAST provides a mild, high-yielding (89–97% yield for examples given) synthesis of 5'-protected-2,3'-anhydropyrimidine



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c. R = MMT[a], R' = H, R" = NH

[a] MMT = monomethoxytrityl ($MeOPhPh_2C$) group; [b] TR = trityl (Ph_3C) group.

SCHEME 3

nucleosides, and the reagent can be used in a convenient, one-pot synthesis of 2-deoxy-β-D-threo-pentofuranosylnucleosides via ring-opening of the anhydronucleoside with hydroxide ion. The reagent operates much in principle like the fluorinating reagent of Kowollik and coworkers,[17] which has also been used to synthesize 2,3'-anhydronucleosides; however, as the latter reagent is not commercially available and must be freshly prepared before use, DAST offers certain procedural advantages, especially for small-to-intermediate scale reactions.

Experimental

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus equipped with a Cole-Parmer model 8520-50 Digi-Sense digital thermometer that was calibrated with known standards. Solutions were evaporated at aspirator vacuum at ca. 40 °C.

^{1}H NMR spectra were determined at 200 MHz on ca. 0.1% solutions using a Nicolet NT-200 instrument. Chemical shifts are reported as δ (PPM) downfield from an internal standard of tetramethylsilane. Optical rotations at the sodium D-line were determined at the indicated temperature in methanol on a Perkin-Elmer model 241 spectropolarimeter using 1-dm cells. Thin-layer (TLC) and column chromatography were carried out using E. Merck silica gel products [aluminum-backed TLC plates with a 0.2-mm coating (cat. no. 5554) and bulk silica gel of 230 - 400 mesh ASTM (cat. no. 9385)]. TLC visualization was by 254-nm UV light and by spray/heat development using anisaldehyde-sulfuric acid reagent.[18] UV spectra were determined in methanol unless otherwise stated, on a Varian DMS 100 UV-visible spectrophotometer. Chemicals were of reagent grade and were used directly. Anhydrous dichloromethane was prepared by distillation from calcium hydride. Elemental analyses were carried out by Atlantic Microlab, Inc. of Atlanta, GA. Chloroform solvates of analytical samples were confirmed by ^{1}H NMR spectroscopy.

Preparation of 5'-O-(monomethoxytrityl)thymidine (1a), 2'-deoxy-5'-O-trityluridine (1b), and 2'-deoxy-5'-O-monomethoxytritylcytidine (1c). Compound **1a** was prepared by reaction of thymidine with monomethoxytrityl chloride in dry pyridine at 60 °C.[19] Compound **1b** was prepared by tritylation of 2'-deoxyuridine according to the published procedure.[20] Compound **1c** was prepared by the reported procedure[14] that involved first the protection of the amino group as its N,N-dimethylaminomethylene derivative, then reaction with monomethoxytrityl chloride.

Preparation of the anhydronucleoside intermediates 2a-c. General procedure. To a solution of an appropriate amount of the 5'-protected nucleoside **1a-c** (see Table 1) in dry dichloromethane maintained under a dry nitrogen atmosphere was added dropwise an appropriate amount of DAST, and the mixture was stirred at room temperature for 5 min. At the end of this time, the reaction was

Table 3. Physico-Chemical Data for Compounds 2a-c and 3a-c

Compound	UV Data Abs. (nm) (MeOH)	MP (°C)	Optical Rotation $[\alpha]_D^t$	c, MeOH	Formula	Elemental Analysis Calculated C	H	N	Found C	H	N	Ref.
2a	229	109-112	22° +4.7	1.42	$C_{30}H_{28}N_2O_5 \cdot 0.53\ CHCl_3$[a]	65.50	5.14	5.00	65.57	5.15	4.98	
2b	230	101-150 (indefinite)	24° +16.6	1.01								11,20
2c[b]	232	115-131	24° +35.5	0.51								14
3a	265	107-110	24° -16.9	2.12	$C_{30}H_{30}N_2O_6 \cdot 0.46\ CHCl_3$[a]	64.27	5.39	4.92	64.27	5.46	4.99	
3b	260	146 softens 158 bubbles 228-230 melts	22° -15.9	1.22								11,13
3c	270	149-151	22° +10.5	0.85								5

[a] Confirmed solvate by ^1H NMR spectroscopy. [b] HF salt.

quenched by careful addition of cold saturated aqueous sodium bicarbonate until there was no more effervescence and the mixture had turned turbid. The mixture was then separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate, and the solvent was evaporated to give a white solid, which was purified (See exception for compound **2c** noted in Table 1 and discussed in Discussion and Results.) by column chromatography, eluting with 95:5 chloroform - methanol to give the 2,3'-anhydro nucleoside **2a** and **2b** as a white solid. See Table 2 for ^{1}H NMR data and Table 3 for physico-chemical data for compounds **2a-c**.

Preparation of 1-(2-deoxy-β-D-threo-pentofuranosyl)pyrimidines 3a-c from 1a-c. General procedure. To a solution of an appropriate amount of the 5'-protected nucleoside **1a-c** in dry dichloromethane (Table 1), maintained under a dry nitrogen atmosphere, was added dropwise an appropriate amount of DAST, and the mixture was stirred at room temperature for 5 min. Triethylamine was added dropwise to the stirring mixture, and the solvent was subsequently evaporated. Dichloromethane was repeatedly added to and evaporated from the mixture, and the residual solid was dissolved in ethanol. To the ethanolic solution was added an appropriate amount of 1.0 M aqueous sodium hydroxide, and the mixture was heated under reflux for 45 min. The solvent was evaporated to about one-fourth the original volume and extracted twice with dichloromethane. The combined organic extract was dried over magnesium sulfate, and the solvent was evaporated. The resulting crude product was purified by column chromatography on silica gel, eluting with 95:5 chloroform - methanol to give compound **3a-c** as a white solid. For ^{1}H NMR data, see Table 2; for physico-chemical data, see Table 3.

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