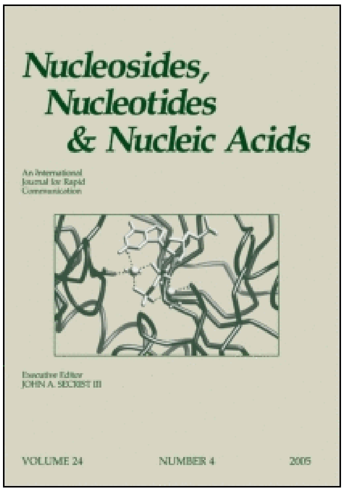

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A New Reagent for the Formation of Anhydronucleosides

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NOTE

A NEW REAGENT FOR THE FORMATION OF ANHYDRONUCLEOSIDES

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Abstract: 5'-O-Trityl-thymidine reacts with excess perfluorobutanesulfonyl fluoride/DBU in toluene to 5'-O-trityl-2,3'-anhydrothymidine in 75% yield. Free thymidine gives rise to 4',5'-dehydro-2,3'-anhydrothymidine and to 5'-fluoro-2,3'-anhydrothymidine.

Among the different reagents for the formation of anhydropyrimidine nucleosides such as triphenylphosphine-azoester[1-4)], $POCl_3$-H_2O[5-8)], $SOCl_2$[7,8)], SO_2Cl_2[9)], diphenyl carbonate [10-13)], $Si(OAc)_4$[14)] and 2-acetoxybenzoyl chloride[15)], the reactive but relatively unstable 2α-acetoxyisobutyryl chloride[16] gave in our hands consistently the highest yields of 2,2'-anhydropyrimidine nucleosides. Due to the instability of 2α-acetoxyisobutyryl chloride, however , particularly on extended storage, we became interested in a chemically stable and lower priced alternative to this reagent.

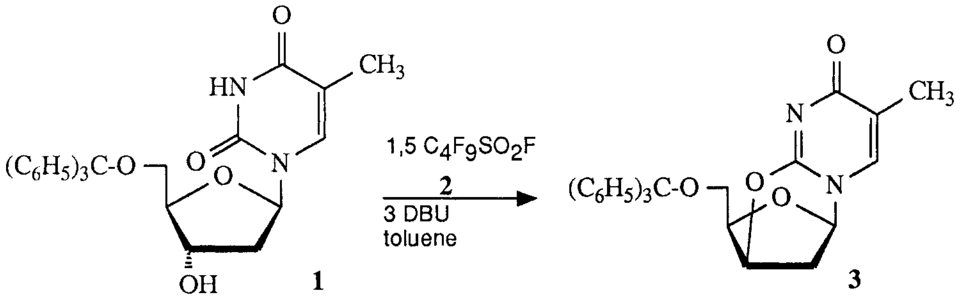
We have recently observed that the very stable and readily accessible n-perfluorobutanesulfonyl fluoride **2** ($C_4F_9SO_2F$; bp = 64-65°) as well as n-perfluorooctanesulfonyl fluoride ($C_8F_{17}SO_2F$: bp = 154-155°), the mixted anhydrides between the perfluoroalkanesulfonic acids and hydrogen fluoride, react readily with primary or secondary alcohols in the presence of 1,8-diaza-bicyclo[5,4,0]undecen-7-ene (DBU) in toluene to give under Walden inversion the corresponding fluorides in much higher yields [17)] than with diethylaminosulfur trifluoride (DAST) [18)].

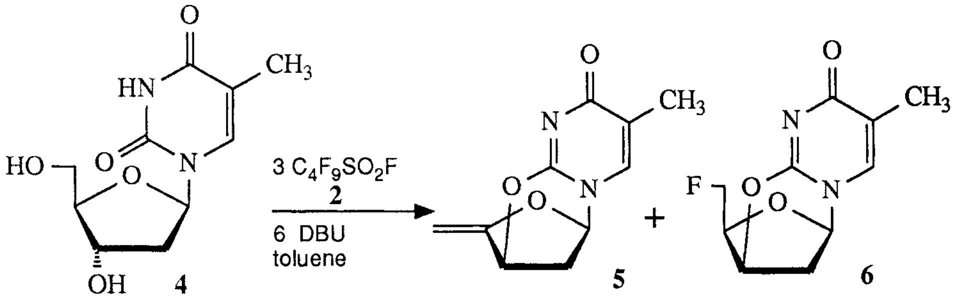
Consequently, we have reacted 5'-O-trityl-thymidine **1** with $C_4F_9SO_2F$ **2** in toluene in the presence of DBU and obtained after workup and crystallization the known 5'-O-trityl-2,3'-anhydrothymidine **3** [20)] in >75% yield.

Dedicated to Professor Y. Mizuno on the occasion of his 75th birthday

The analoguos reaction of a suspension of free thymidine **4** in toluene with excess of $C_4F_9SO_2F$ **2** and DBU afforded *via* the corresponding 3',5'-bis-O-nonaflate the 4',5'-dehydro-2,3'-anhydrothymidine **5**, which was isolated on chromatography on a column of SiO_2 in 15% yield, besides 42% of crude 5'-fluoro-2,3'-anhydrothymidine **6** which crystallized to give pure **6**[21].

These two examples demonstrate that the combination of $C_4F_9SO_2F$ **2** (or $C_8F_{17}SO_2F$) and DBU in toluene or more polar solvents such as acetonitrile might turn out to be a useful alternative for small as well as large scale preparations of anhydro nucleosides.





EXPERIMENTAL

5'-O-Trityl-2,3'-anhydrothymidine 3

A stirred suspension of 1.21 g (2,5 mmol) of 5'-O-trityl-thymidine [19] **1** in 20 abs. toluene became a clear solution on addition of 1.1 ml (7.5 mmol) of DBU. On subsequent slow addition of 0.67 g (3.75 mmol) perfluorobutanesulfonyl fluoride **2** the reaction temperature rose to 30°C. After 2 h the reaction mixture was concentrated in vacuo, the residue taken up in CH_2Cl_2-ice cold sat. $NaHCO_3$ and the organic phase dried (Na_2SO_4). After evaporation, the residue (2.39 g) was chromatographed in acetone - isopropanol (3:2) on a column of 120 g SiO_2 (E. Merck). After a forrun of 375 ml, the subsequent 750 ml eluate furnished crude **3**, which crystallized from ethanol to give in several crops 0.84 g (75%) of pure **3** mp. 218-221° (lit.[20)] mp. = 226-227°)

3 MS (EI) $^{m}/_{z}$= 466(M^+), 389 (M-C_6H_5), 243 ($C(C_6H_5)_3^+$, 223, 165, MS (CI) $^{m}/_{z}$= 467 (M+H^+), 262, 243, 200; ^{1}H-NMR($CDCl_3$) δ=1.95 (s, 3H, C^5-CH_3), 2.36-2.63 (m, 2H , H-2'), 3.35-3.40 (m, 2H, H-5'), 4.23-4.29 (m, 1H, H-4'), 5.14 (br, 1H, H-3'), 5.43 (d, J=3.7 Hz, 1H, H-1'), 6.91 (s, 1H , H-6), 7.2-7.46 (m. 15H.)

Anal. calcd. for $C_{29}H_{26}N_2O_4$ (466.51) C 74.66, H 5.62, N 6.01 Found: C 74.41, H 5.61, N 5.87

4.5-Dehydro-2,3'-anhydrothymidine **5** and 5'-fluoro-2,3'-anhydrothymidine **6**

To a suspension of 1.21 g (5 mmol) thymidine **4** and 3.36 ml (22.5 mmol) of DBU in 40 ml abs. toluene were added slowly 2.05 ml (11 mmol) $C_4F_9SO_2F$ **2** with stirring, where upon the reaction mixture turned yellow and two phases formed on 18 h standing. Evaporation and workup with CH_2Cl_2-sat. ice cold aqueous $NaHCO_3$-solution gave 9.05 crude product, which was chromatographed in acetone on a column of 120 g SiO_2. After 1.1 l forrun giving 4.84 g material containing traces of unreacted thymidine **4**, subsequent elution with 375 ml of acetone-isopropanol (9:1) furnished 0.14 g (13.6%) of **5**, whereas the following 500 ml eluted 0.47 g (41.6%) of crude **6**, from which 0.05 g of pure **6** mp. 215-217°C crystallized on standing in ethanol.

5 MS (EI) $^{m}/_{z}$=206 (M^+), 164, 127, 125, 110, 96, 81

MS (CI) $^{m}/_{z}$=224 (M+NH_4^+)207(M+H^+)184, 167, 153, 134, 131, 114

^{1}H-NMR (DMSO-D_6) δ=1.69 (s, 3H, C^5-CH_3), 2.47-2.68 (m, 2H,H-2'), 4.48-4.72 (m, 2H, H_5'), 5.53 (s, 1H, H_3'), 6.2 (d, J=3, 8 Hz, 1H, H-1'), 7.64 (s, 1H, H-6)

6 MS (EI) $^{m}/_{z}$= 226 (M^+) 206 (M-HF) 177, 150, 226 (Thymine) 110, 101, 81, 53

MS (CI) $^{m}/_{z}$= 244 (M+MH_4^+) 227(M+H^+), 207, 115, 98, 81

^{1}H-NMR (DMSO-D_6) δ= 1.75 (s, 3H, C^5-CH_3), 2.45-2.63 (m, 2H,3H-2'), 4.39-4.8 (m, 3H, H-5'+ H-4'), 5.36 (s, 1H, H-3'), 5.9 (d, J=3.8 Hz, 1H, H-1'), 7.69 (s, 1H, H-6)

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