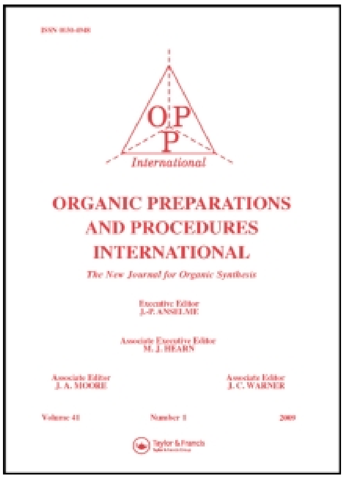

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Vasu Nair[a]; Greg S. Buenger[a]
[a] Department of Chemistry, University of Iowa, Iowa City, IA

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REGIOSPECIFIC 5'-SILYLATION OF NUCLEOSIDES

Vasu Nair* and Greg S. Buenger

Department of Chemistry, University of Iowa, Iowa City, IA 52242

There has been considerable interest in recent years in the synthesis of carbohydrate-modified nucleoside analogues because of the potential of these compounds to exhibit antiviral activities. Some examples of such antiviral nucleosides include 3'-azidothymidine (AZT),[1] 2',3'-dideoxynucleosides,[2,3] 2',3'-didehydro-2',3'-dideoxynucleosides,[4] and 2'- or 3'-substituted 2',3'-dideoxynucleosides.[5-9] Synthetic access to these compounds and other novel carbohydrate modified nucleosides require the regiospecific protection of the 5'-hydroxyl group prior to chemical modification at the 2'- and/or 3'-position. Stable silyl protecting groups are becoming increasingly important in nucleoside synthesis. This paper reports on the utilization of N,N-dimethylaminopyridine (DMAP) as a catalyst for the regiospecific silylation of the 5'-hydroxyl group of natural and synthetic purine and pyrimidine nucleosides. The 5'-silylated compounds are potentially useful intermediates for the synthesis of sugar-modified nucleosides. The procedure described complements previously

a) B = adenine b) B = guanine c) B = thymine d) B = cytosine
e) B = purine f) B = 2-aminopurine g) B = 8-bromoadenine

reported methods.[10,11] However, in terms of generality of application to both natural and non-natural nucleosides, we believe that its simplicity makes it superior to these methods.

The stable silyl protecting system chosen for this study was the *t*-butyldimethylsilyl group. A number of natural and synthetic nucleosides (**1a-g**) were chosen as representative examples for this study. For example, when the synthetic nucleoside, 8-bromoadenosine (**1g**), was treated with *t*-butyldimethylsilyl chloride (TBDMSiCl), triethylamine, and DMAP in N,N-dimethylformamide (DMF)-dichloromethane at room temperature for 4 h, 8-bromo-5'-*t*-butyldimethylsilyl adenosine was produced in 76 % yield (Table 1). Small amounts of unreacted 8-bromoadenosine and disilylated nucleosides were also isolated. Under the same conditions with the literature procedure,[11] we obtained only a 43% yield of product. Similarly, much higher yields were also obtained with our procedure in the case of 2-aminonebularine (**2f**). In order to establish the generality of this experimental approach, five natural nucleosides (**1a-e**) were also converted with complete reproducibility to their corresponding 5'-silyl ethers **2a-e** in excellent yields (Table 1).

All of the silylations were done using catalytic amounts of DMAP which was constantly regenerated in the reaction mixture by triethylamine. The use of DMAP permits greater selectivity for silylation of the primary alcohol (5'-CH_2OH)) versus the secondary alcohols (2'-OH and 3'-OH) of the carbohydrate moiety.[12] Also, the best results were obtained when slightly more than one equivalent of TBDMSiCl was used in the silylation reaction. Increasing the amount of silylating agent in excess of this amount resulted in an increase in the formation of multiply silylated nucleoside. It should be noted that the base moieties of the nucleosides do not need to be protected in these conversions. The 5'-silylated nucleosides were identified by UV, mass spectral and ^1H nmr data (Table 2) and by comparison of the physical data available in the literature for the known compounds.

TABLE 1. Yields, mps and UV data for Compounds 2a-g.

Starting Compound	Reaction Time (hr)	Product	Yield (%)	mp.(solvent)[b] (lit. mp. [°C])	UV (EtOH) λ_{max} (ε)
Adenosine	6	2a	85	179-181° (178-180°)[10]	259.5 (10400)
Guanosine	6	2b	70	dec. 200° (dec. 205°)[13]	254.5 (5915) 275.0 sh(3775)
Thymidine	9	2c	70	197-198°[c] (198-199°)[14]	208.5 (9090) 267.0 (9115)
Cytidine	9	2d	80	182-185°[c] (160-163°)[13]	235.0 (5150) 274.0 (6300)
Nebularine	12	2e	67 [83][a]	113-115°	262.0 (6190)
2-Amino-nebularine	5	2f	70	164-167°	309.0 (6900) 246.0 (5980)
8-Bromo-adenosine	4	2g	76	189-192°	264.0 (14840)

a) Conversion after recovery of starting material b) Water unless otherwise noted c) EtOH-H_2O

EXPERIMENTAL SECTION

Mps were determined on a Thomas-Hoover melting point apparatus fitted with a microscope and are uncorrected. Nmr spectra were recorded on Bruker WM 360 and MSL 300 instruments. Ultraviolet data were taken on a Gilford Response spectrophotometer. Mass spectra at 30 eV were obtained on a Hewlett Packard 5985 GC/MS system. All new compounds gave satisfactory elemental analyses.

General Procedure for Regiospecific Silylation.- A mixture of nucleoside (2 mmol), *t*-butyldimethylsilyl chloride (2.2 mmol), triethylamine (2 mmol), N,N-dimethylaminopyridine (0.3 mmol), N,N-dimethylformamide (10 ml), and dichloromethane (5 ml) was stirred at room temperature under nitrogen for 4-12 h. The solvents were evaporated and the residue was taken up in 5% methanol/chloroform and purified by flash chromatography on silica gel (230-400 mesh) with 5-10 % methanol/chloroform as the eluting solvent. The products were crystallized from ethanol/water or water.

TABLE 2. Mass Spectra and ^{1}H nmr data for Compounds 2a-g.

Product	MS m/e (rel. int. %)	^{1}H-nmr (DMSO-d_6) δ [ppm]
2a	366 (1.2); 324 (53.5); 178 (100); 164 (30.7); 136 (56.2); 135 (11.1)	0.04 (s, 6H); 0.87 (s, 9H); 3.82 (m, 3H); 4.17 (m, 1H); 4.55 (m, 1H); 5.21 (d, 1H); 5.53 (d, 1H); 5.92 (d, 1H); 7.26 (br.s, 2H); 8.15 (s, 1H); 8.28 (s, 1H)
2b	397 (3.4); 340 (29.9); 308 (19.5); 194 (80.8); 152 (49.4); 151 (79.3)	0.04 (s, 6H); 0.87 (s, 9H); 3.76 (m, 2H); 3.87 (m, 1H); 4.08 (m, 1H); 4.32 (m, 1H); 5.17 (d, 1H); 5.47 (d, 1H); 5.69 (d, 1H); 6.71 (br.s, 2H); 7.82 (s, 1H); 10.8 (s, 1H)
2c	299 (24.9); 281 (100); 263 (29.9); 213 (18.6); 183 (53.4); 165 (30.9); 127 (44.3)	0.07 (s, 6H); 0.88 (s, 9H); 1.77 (s, 3H); 2.06 (m, 2H); 3.77 (m, 3H); 4.20 (m, 1H); 5.27 (m, 1H); 6.17 (t, 1H); 7.46 (s, 1H); 11.2 (s, 1H)
2d	300 (7.0); 282 (10.8); 186 (22.3); 168 (34.8); 140 (27.3); 112 (100)	0.08 (s, 6H); 0.89 (s, 9H); 3.89 (br.m, 5H); 5.00 (br.s, 1H); 5.35 (br.s, 1H); 5.76 (m, 2H); 7.24 (br.s, 2H); 7.81 (d, 1H)
2e	351 (0.6); 309 (26.2); 163 (100); 149 (21.1); 121 (63.4); 120 (2.9)	0.03 (s, 6H); 0.85 (s, 9H); 3.84 (m, 2H); 3.99 (m, 1H); 4.21 (m, 1H); 4.66 (m, 1H); 5.24 (d, 1H); 5.59 (d, 1H); 6.06 (d, 1H), 8.76 (s, 1H); 8.96 (s, 1H); 9.19 (s, 1H)
2f	381 (0.5); 366 (1.5); 324 (71.5); 178 (100); 136 (34.0); 135 (17.2)	0.04 (s, 6H); 0.87 (s, 9H); 3.79 (m, 2H); 3.92 (m, 1H); 4.12 (m, 1H); 4.47 (m, 1H); 5.22 (d, 1H); 5.53 (d, 1H); 5.85 (d, 1H); 6.53 (br.s, 2H); 8.21 (s, 1H); 8.59 (s, 1H)
2g	404 (34.2); 402 (34.6); 258 (72.2); 256 (75.3); 216 (59.8); 214 (69.3)	-0.06 (s, 6H); 0.79 (s, 9H); 3.85 (m, 3H); 4.34 (m, 1H); 5.16-5.48 (m, 3H); 5.81 (d, 1H); 7.41 (br.s, 2H); 8.11 (s, 1H)

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