Synthesis of 2',5'-Dideoxy-5'-Substituted Pyrimidine Nucleosides *via* Intramolecular Glycosylation

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5'-Azido-5'-deoxy and 5'-arylthio-5'-deoxy pyrimidine nucleosides were synthesized employing intramolecular glycosylation, in which a reaction intermediate was treated *in situ* with an azide salt or thiol.

In recent years, 5'-amino-5'-deoxy or 5'-deoxy-5'-thio nucleosides have been of considerable interest as antiviral agents[1-3] as well as components of antisence oligonucleotides.[4-8] In particular, the replacement of the phosphodiester parts in natural 2'-deoxyoligonucleotides by sulfide- or amide-modified linkages is currently an active area of research because it is expected to increase the stability against nuclease, while the affinity and the specificity for the complementary RNA target is maintained. Therefore, an efficient synthetic approach to 2',5'-dideoxy-5'-substituted nucleosides is still desirable.

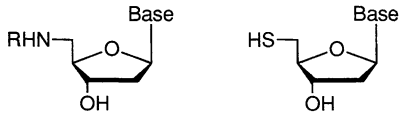
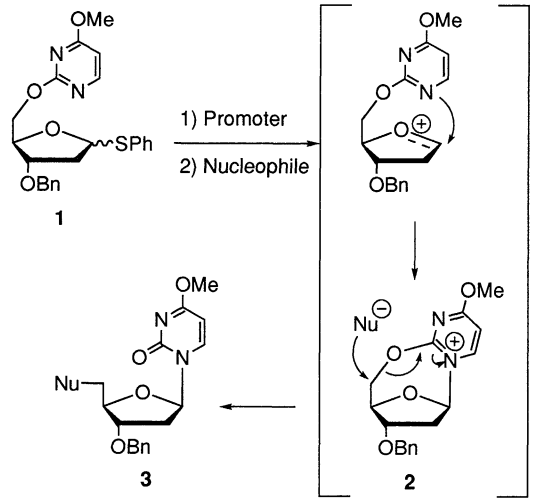


Figure 1.

In earlier reports,[9] we described a stereocontrolled method for the synthesis of deoxy-β-nucleosides employing intramolecular glycosylation. In our continuing research for the application of this approach to the preparation of a variety of nucleoside derivatives, we noticed a potential of the intramolecular glycosylation as a method for introducing nucleophilic substituents at the 5' position of pyrimidine nucleosides. Scheme 1 shows our synthetic strategy. After activation of the thioglycoside **1**, treatment of a pyrimidinium intermediate **2** with an appropriate nucleophile *in situ* would allow a nucleophilic attack at the 5' position to proceed, thus providing the 5'-substituted nucleoside. Herein, we describe the preliminary results obtained from the reactions with several nitrogen and sulfur nucleophiles.



Scheme 1.

The substrate for the intramolecular glycosylation, **1**, was prepared from phenyl 3-*O*-benzyl-2-deoxy-1-thio-D-ribofuranoside and 2-chloro-4-methoxypyrimidine as previously described.[9] Usually, the intramolecular glycosylation is undertaken by activation with dimethyl(methylthio)sulfonium tetrafluoroborate at –20 °C for 1 h, followed by treatment with a 1 M aqueous solution of sodium hydroxide at 0 °C for 1 h in order to hydrolyze the pyrimidinium intermediate **2**. In place of this basic hydrolysis, our initial efforts focused on the substitution with nitrogen nucleophiles.[10] The attempted addition of sodium azide to intermediate **2** resulted in the production of only the usual nucleoside (**3**, Nu=OH), probably due to insolubility of the azide salt. However, a solution to this problem was found by using tetrabutylammonium azide as the nucleophile. Treatment of the intermediate **2** with two equivalents of tetrabutylammonium azide provided the 5'-azido-5'-deoxy derivative in 71% yield (run 1 in Table 1). In contrast, an attempt to directly introduce an amino function at the 5 position using benzylamine was unsuccessful. Although polar material was detected in the reaction mixture, it decomposed during purification with silica gel chromatography. Consequently, any pure compounds couldn't be obtained from this reaction at all.

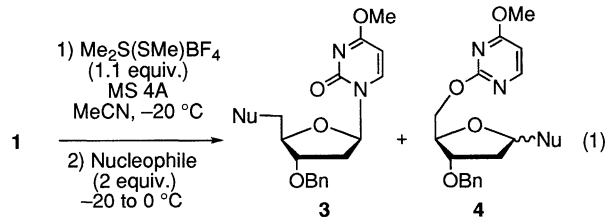
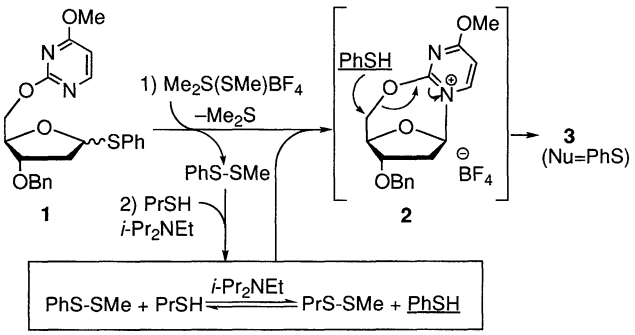


Table 1.

Run	Nucleophile	Yields/%		
		Nu	**3**	**4**
1	$Bu_4N{\cdot}N_3$	N_3	71	7
2	$BnNH_2$	BnNH	—	—
3	PhSH	PhS	70 (+ Nu=OH, 12%)	—
4	PhSH/*i*-Pr_2NEt	PhS	74	—
5	*p*-$NO_2C_6H_4SH$/*i*-Pr_2NEt	*p*-$NO_2C_6H_4S$	75	—
6	*p*-$MeOC_6H_4SH$/*i*-Pr_2NEt	*p*-$MeOC_6H_4S$	37 (+ Nu=PhS, 40%)	—
7	PrSH/*i*-Pr_2NEt	PrS	— (Nu=PhS, 56%)	—

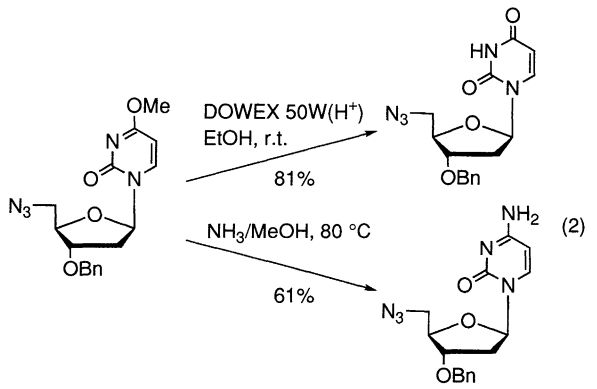
We next turned our attention to the introduction of a sulfur function at the 5' position. The reaction with thiophenol gave the desired 5'-deoxy-5'-phenylthio nucleoside **3**[11] in 70% yield along with a 7% yield of the 5'-hydrolyzed product (run 3). In this case, tetrafluoroboric acid is formed with the progress of the substitution. In order to capture the acid, a similar reaction was next conducted in the presence of Hünig base. As a result, the production of the byproduct was suppressed, but the yield of **3** was not improved so much (run 4). Likewise, *p*-nitrothiophenol provided 5'-*p*-nitrophenylthio nucleoside **3** in 75% yield (run 5) whereas, to our surprise, the reaction with *p*-methoxythiophenol gave a mixture of 5'-*p*-methoxyphenylthio and 5'-phenylthio nucleosides in 77% combined yields (run 6). Moreover, in the reaction using an alkanethiol, PrSH, no 5'-propylthio-substituted nucleoside was produced and, instead, 5'-phenylthio nucleoside was isolated in 56% yield. When this reaction was carried out without the base, hydrolyzed products (**3** and **4**, Nu=OH), resulting from work-up with water, were major products (total 77%), along with a small amount of the 5'-phenylthio product, again (6%). On the basis of these findings, we propose a mechanism for the formation of phenylthio-substituted product as described in Scheme 2. The interconversion of methyl phenyl disulfide to methyl propyl disulfide occurs rapidly to produce thiophenol *in situ*, which reacts with intermediate **2** to afford 5'-phenylthio product, whereas propanethiol cannot react with **2**. *p*-Nitrothiophenol doesn't undergo such a interconversion because its thiolate ion is more stable than that of thiophenol under the basic conditions. Hence, the substitution proceeds with only *p*-nitrothiophenol. By contrast, in the reaction of *p*-methoxythiophenol, both anions of *p*-methoxythiophenol and thiophenol exist at equilibrium in nearly equal amounts. Consequently, ca. 1:1 mixture of 5'-substituted products were produced.



Scheme 2.

Finally, the 5'-azido derivative was converted into the corresponding 2'-deoxyuridine by acidic hydrolysis and into the 2'-deoxycytidine by treatment with ammonia in methanol, respectively (Eq. 2). The azido function can be reduced to amine according to a known method.[5]

While the introduction of sulfur function has not been optimized at this point, the simplicity, mild conditions and reasonable yields of the reactions with azide and some arenethiols provides a useful method to prepare certain 5'-substituted nucleosides. Further



study of the usefulness of this method in the preparation of nucleoside intermediates, including the investigation of reactions with other nucleophiles is in progress.

References and Notes

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1 A. Eleuteri, C. B. Reese, and Q. Song, *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2237.

2 C. McGuigan, S. Turner, N. Mahmood, and A. J. Hay, *Bioorg. Med. Chem. Lett.*, **6**, 2445 (1996).

3 P. Wentworth Jr and K. D. Janda, *J. Chem. Soc., Chem. Commun.*, **1996**, 2097.

4 B. Meng, S. H. Kawai, D. Wang, G. Just, P. A. Giannaris, and M. J. Damha, *Angew. Chem., Int. Ed. Engl.*, **32**, 729 (1993); I. Idziak, G. Just, M. J. Damha, and P. A. Giannaris, *Tetrahedron Lett.*, **34**, 5417 (1993); C. G. Yannopoulos, W.-Q. Zhou, P. Nower, D. Peoc'h, Y. S. Sanghvi, and G. Just, *Synlett*, **1997**, 378.

5 A. De Mesmaeker, J. Lebreton, A. Waldner, V. Fritsch, R. M. Wolf, and S. M. Freier, *Synlett*, **1993**, 733; J. Lebreton, A. Waldner, C. Lesueur, and A. De Mesmaeker, *Synlett*, **1994**, 137; A. De Mesmaeker, A. Waldner, J. Lebreton, P. Hoffmann, V. Fritsch, R. M. Wolf, and S. M. Freier, *Angew. Chem., Int. Ed. Engl.*, **33**, 226 (199[illegible]); A. De Mesmaeker, C. Lesueur, M.-O. Bévière, A. Waldner, V. Fritsch, and R. M. Wolf, *Angew. Chem., Int. Ed. Engl.*, **35**, 2790 (1996).

6 G. Stork, C. Zhang, S. Gryaznov, and R. Schultz, *Tetrahedron Lett.*, **36**, 6387 (1995).

7 L. De Napoli, A. Iadonisi, D. Montesarchio, M.Varra, and G. Piccialli, *Bioorg. Med. Chem. Lett.*, **5**, 1647 (1995).

8 M. J. Robins, S. Sarker, M. Xie, W. Zhang, and M. A. Peterson, *Tetrahedron Lett.*, **37**, 3921 (1996).

9 K. Sujino and H. Sugimura, *Chem. Lett.*, **1993**, 1187; K. Sujino and H. Sugimura, *Tetrahedron Lett.*, **35**, 1883 (1994); K. Sujino and H. Sugimura, *J. Chem. Soc., Chem. Commun.*, **1994**, 2541; H. Sugimura, M. Motegi, and K. Sujino, *Nucleosides Nucleotides*, **14**, 413 (1995); H. Sugimura and K. Sujino, *Nucleosides Nucleotides*, **17**, 53 (1998).

10 A typical procedure is as follows. To a solution of **1** (0.2 mmol) in MeCN (50 cm^3) was added powdered molecular sieves 4A (0.5 g) under Ar. The solution was cooled to –20 °C, and $Me_2S(SMe)BF_4$ (0.22 mmol) was then added. After 1 h, a nucleophile (and Hünig base) (0.4 mmol each) was added to the reaction mixture. The mixture was stirred for 2 h at the same temperature, and then allowed to warm to 0 °C for over 1 h. After saturated aqueous NH_4Cl was added, the solution was stirred at room temperature for 30 min, then filtered through Celite and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was chromatographed on silica gel (hexane-AcOEt) to provide **3**.

11 The structure was confirmed by comparison of spectral data with those obtained from an authentic sample, which was prepared by phenylthiolation of a previously obtained compound (**3**, Nu=OH) according to the literature; I. Nakagawa, K. Aki, and T. Hata, *J. Chem. Soc., Perkin Trans. 1*, **1983**, 1315.