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Efficient and Selective Synthesis of Glycofuranosyl Azides and Nucleosides from Cyclic 1,2-Thiocarbonate Sugars

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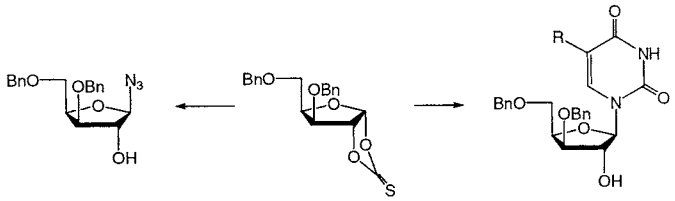
ABSTRACT



Cyclic 1,2-thiocarbonate sugars are convenient starting materials for the selective and efficient preparation of glycofuranosyl azides and nucleosides by regio- and stereoselective thiocarbonate ring-opening.

The biological role of nucleoside-related compounds[1] keeps the development of more efficient synthetic methods as a permanent current topic due to the importance of this type of compounds in the development of new lines of antineoplastic therapeutic agents.[2] The greatest challenge is the achievement of a good stereoselectivity to avoid the formation of α/β diastereomeric mixtures, which are difficult to separate. In other cases, the employment of strong glycosylating promoters or conditions limits the use of many protecting groups.[3]

Cyclic 1,2-thiocarbonate sugars[4] are stable compounds that are easily prepared and handled. They have previously been employed as glycosyl donors in glycosidation reactions by sulfur methylation that promotes the attack of the glycosyl acceptor.[4,5] Other related glycosyl donors are cyclic 1,2-sulfite sugars that have also been employed for nucleoside synthesis[6] using persilylated pyrimidinic bases with good yields and, in some cases, stereoselectivities. Nevertheless, in these reactions, the opening of the 1,2-cyclic sulfite ring usually requires long reaction times and high temperatures.

Glycosyl azides are important intermediates for the synthesis of a wide variety of sugar derivatives. For their synthesis, three general methods are normally used: (a) reaction of glycosyl halides with metal azides or tetramethylguanidium azide[7] under homogeneous conditions[8] or by using phase transfer catalysts,[9] (b) reaction of glycosyl esters with trimethylsilyl azide in the presence of a Lewis acid

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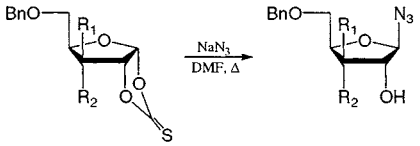
catalyst,[8c,10] and (c) reaction of cyclic 1,2-sulfite sugar derivatives with sodium azide.[6b,11]

Considering the particular charge density at the anomeric carbon of the cyclic 1,2-thiocarbonate sugars as a consequence of the concurrence of the sugar and thiocarbonate rings, we thought that these bicyclic compounds should be easily opened by attack with nucleophiles such as sodium azide allowing the synthesis of the corresponding glycosyl azides. This hypothesis was corroborated when compounds **1** and **2** were treated with sodium azide,[12] leading to the corresponding 3,5-di-*O*-benzyl-β-D-*xylo* (**3**) and the already described 3,5-di-*O*-benzyl-β-D-*ribo*furanosyl azide (**4**)[11] in 95 and 90% yields, respectively (Scheme 1).

Scheme 1. Thiocarbonate Ring-Opening with NaN_3



1 R_1 = OBn, R_2 = H
2 R_1 = H, R_2 = OBn

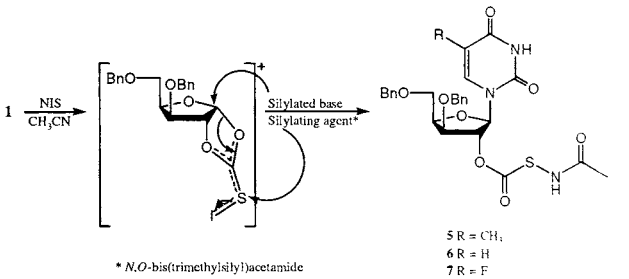
3 R_1 = OBn, R_2 = H
4 R_1 = H, R_2 = OBn

On the basis of these satisfactory results, we thought that the pyrimidinic bases could also be used as nucleophiles for the opening of cyclic 1,2-thiocarbonate sugars, allowing an easy access to nucleosides. Preliminary experiments were carried out using thymine as a nucleophile, but treatment of this base with compound **1** using NaH or DBU led to complex mixtures.

Sugimura[13] has previously reported the use of NBS to promote nucleosidation of thioglycosides achieving good yields with moderate stereoselectivity in a variety of examples. Taking this antecedent into consideration, we chose NIS as the promoter for the nucleosidation of cyclic 1,2-thiocarbonates sugars. The use of NIS proves to be particularly efficient when persilylated pyrimidinic bases (thymine, uracil, and 5-fluoruracil) were used as nucleophilic agents and acetonitrile as a solvent. The thiocarbonate ring-opening of compound **1** was thus effectively achieved at room temperature, and β-nucleosides **5**−**7** were exclusively obtained in high yields having the hydroxyl group at C-2′ protected as indicated in Scheme 2.

Yields were drastically affected by the number of equivalents of the pyrimidine base used and the proportion of the

Scheme 2. General Mechanism for the Nucleosidation Process



* *N*,*O*-bis(trimethylsilyl)acetamide

5 R = CH_3
6 R = H
7 R = F

disposable silylating agent [*N*,*O*-bis(trimethylsilyl) acetamide] (Table 1). The better results correspond to the use of

Table 1. Optimization of the Nucleosidation Process: Yields of **5**−**7**

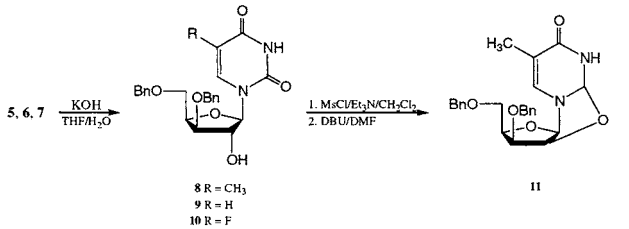
	base[a]		silylating agent[b]	
compd	1 equiv	2 equiv	4 equiv	6 equiv
5	29	73	86	90
6	25	39	70	76
7	26	43	57	71

[a] In all cases, 2 equiv of silylating agent was employed. [b] In all cases, 2 equiv of nucleobase was employed.

2 equiv of base and a large excess of silylating agent (see General Method).[14]

To demonstrate unequivocally the β-configuration at the anomeric position of nucleosides **5**−**7**, the substituent at C-2′ was first removed by basic (KOH, DABCO) or acid ($KHSO_4$) treatment leading to the corresponding nucleosides **8**−**10** in almost quantitative yield. Compound **8** was then mesylated and treated with DBU to obtain the tricycle **11**, which showed physical and spectroscopic data identical to those previously described (Scheme 3).[15]

Scheme 3. Chemical Correlation Demonstrating the Obtained β-1′ Configuration



8 R = CH_3
9 R = H
10 R = F

11

In summary, we report a new methodology for the synthesis of glycofuranosyl azides and nucleosides using cyclic 1,2-thiocarbonate sugars as readily available and useful starting materials. The reactions were shown to be mild, fast, and selective, allowing the isolation of only one of the

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(12) **General Procedure for Azide Glycosidation.** To a stirred solution of **1** (1.12 g, 3.0 mmol) in DMF (10 mL) was added NaN_3 (585 mg, 9.0 mmol), and the mixture was heated at 60 °C until TLC indicated the disappearance of the starting material (15 min). Water (100 mL) was then added and the solution extracted with toluene (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated, giving a residue that was purified by column chromatography (ether−hexane 2:1) to achieve **3** (1.02 g, 95%).

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anomers. It could be anticipated that this approach should constitute an adequate method for the synthesis of a wide variety of nucleoside derivatives. Studies with other cyclic 1,2-thiocarbonate sugars are currently under investigation.

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Supporting Information Available: Complete IR, mass spectra, $[\alpha]_D$, and NMR data of products **3**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) **General Procedure for Nucleosidation.** To a stirred suspension of thymine (252 mg, 2 mmol) in CH_3CN (15 mL) was added *N*,*O*-bis-(trimethylsilyl)acetamide (1.5 mL, 6 mmol). Once the thymine was dissolved (15 min), compound **1** (372 mg, 1 mmol) and NIS (450 mg, 2 mmol) were added, and the solution stirred at room temperature until TLC indicated the disappearance of the starting material (10 min). After evaporation, the crude was dissolved in CH_2Cl_2 (25 mL) and the solution washed successively with $NaHCO_3$ saturated aqueous solution, water, 10% $Na_2S_2O_3$ solution, and water. The organic layer was dried over $MgSO_4$ and evaporated, giving a residue that was purified by column chromatography (CH_2Cl_2−MeOH 25:1) to achieve **5** (500 mg, 90%).

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