Tetrahedron Letters, Vol.32, No.30, pp 3627-3630, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

NUCLEOSIDE SYNTHESIS FROM THIOGLYCOSIDES

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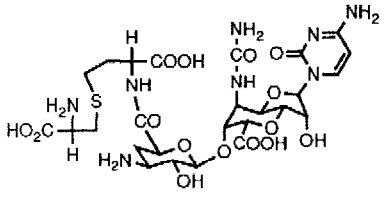
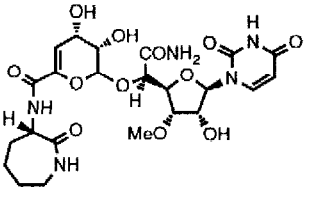
Key words: *N*-iodosuccinimide; triflic acid; *N*-glycosylation; nucleoside antibiotics; Vorbruggen coupling

Abstract: *Acetylated phenyl and methyl 1-thiofurano- and pyranosides react with silylated uracil, acetylcytosine, and benzoyladenine under the influence of NIS / triflic acid to generate the β-nucleoside derivatives in good yield.*

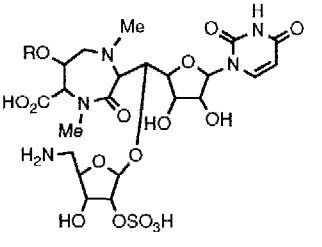
Complex nucleoside antibiotics,[1] such as ezomycin A_1 (**1**),[2] capuramycin (**2**),[3] and liposidomycin B (**3**),[4] present a number of synthetic challenges, not the least of which are the timing and manner of introducing the pyrimidine base. As an alternative to elaboration of a simple nucleoside, *N*-glycosylation of the pyrimidine with an appropriately activated carbohydrate portion can be carried out late in the synthesis. A survey of literature examples,[1,5-11] and our own experience with *S*-glycosylation using lincosamine derivatives,[12] reveals that Vorbruggen-type coupling of higher glycosyl acetates, while often successful, can be sluggish[13] or low-yielding[7,9] when there are many Lewis-basic heteroatoms to compete for the electrophilic activating reagent (usually TMS-OTf). Inasmuch as thioglycosides have been used to "store" and later activate the anomeric center for the synthesis of disaccharides,[14,15] we have investigated their use in nucleoside synthesis.[16] We report that the combination *N*-iodosuccinimide / triflic acid[14,17] specifically activates thioglycosides for efficient coupling with silylated nucleoside bases under mild conditions.



1: ezomycin A_1

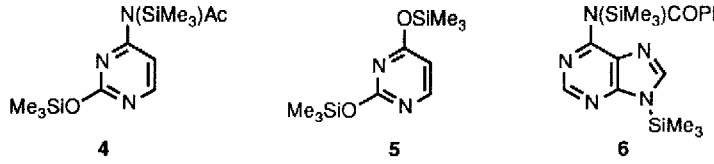


2: capuramycin



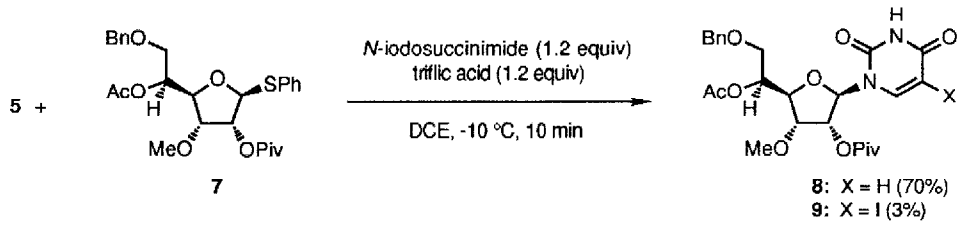
3: liposidomycin B

Table 1 shows the results of coupling various phenylthio- and methylthio-glycosides with the silylated nucleoside base derivatives 4-(*N*-trimethylsilyl)-acetamido-2-(trimethylsilyloxy)-pyrimidine (**4**), 2,4-bis(trimethylsilyloxy)-pyrimidine (**5**), and 9-(trimethylsilyl)-6-(*N*-trimethylsilyl)-benzamido-purine (**6**).[7,18] The reaction with *N*-iodosuccinimide / triflic acid proceeds within two hours at room temperature in dichloromethane or 1,2-dichloroethane (DCE) solution. Isolated yields (typically 70-90%) are comparable to those from glycosyl acetates.[1,5-11] Dimethyl(methylthio)sulfonium triflate[19] was used as the activating reagent in one example (entry 11) and produced the nucleoside **22a** in good yield (compare entry 9), although more forcing conditions were required.

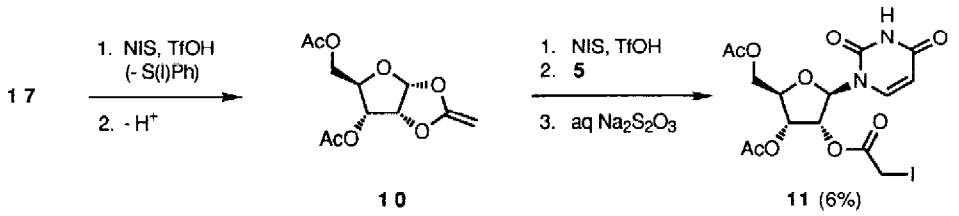


Acetylated thioglycoside substrates like **12**, **17**, and **21** are conveniently prepared from the corresponding anomeric acetates.[20] A variety of other thioglycosides, including **14a** and **14b**, are commercially available from Pfanstiehl; lincomycin penta-acetate **19** was prepared by acetylation of the antibiotic. Among the nucleoside products in Table 1, **13a**,[21] **13b**,[21] **15a**,[21] and **16**[22] are known compounds. By virtue of the participating group (acetoxy or phthalimido) at C-2', and regardless of the starting anomeric configuration, the nucleoside products are formed as β-anomers exclusively, according to their H-1'/H-2' coupling constants.

The coupling reaction was also carried out on an intermediate[23] (**7**) for a projected synthesis of capuramycin, as shown below. The reaction with pyrimidine **5** was complete within 10 min at -10 °C, and produced the desired nucleoside product **8** in good yield. A small amount of the ring-iodinated[24] product **9** was also formed, presumably as the result of reaction of an iodonium species[14] with **8**. The isolation of **9** underscores the need to monitor the time of coupling, which can be almost instantaneous,[14] and the amount of triflic acid.

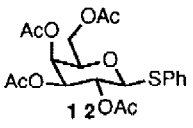
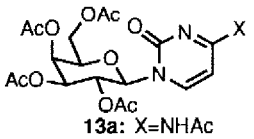
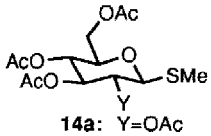
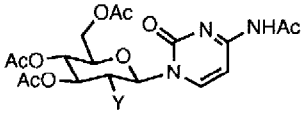
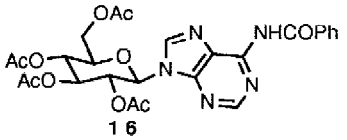
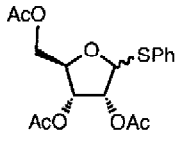
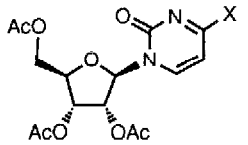
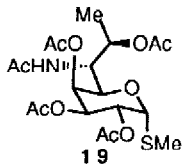
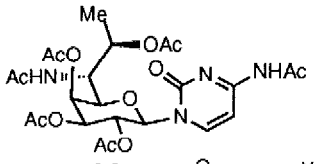
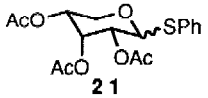
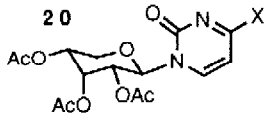


The reaction of **17** with **5** (entry 7, Table 1) provided evidence for another iodination process that can reduce the coupling yield. In addition to **18b**, a small quantity of an iodo acetate, possibly **11**, was isolated.[25] This product could arise by iodination of a ketene acetal intermediate **10**, as proposed below.



General Procedure for Nucleoside Synthesis. Trifluoromethanesulfonic acid (1.2 equiv) is added over several min to a stirred solution of the acetylated thioglycoside (1 equiv, 0.05 M), *N*-iodosuccinimide (1.2 - 2.5 equiv), and the silylated nucleoside base (**4**, **5**, or **6**; 1.2 - 1.5 equiv) in dry 1,2-dichloroethane at room temperature under an argon atmosphere. When TLC analysis indicates the disappearance of the thioglycoside (10 - 120 min), the reaction is treated with 10% aqueous sodium thiosulfate solution until the purple color is discharged. The organic layer is washed with water, dried over magnesium sulfate, concentrated, and chromatographed on silica gel by using 4:1 ethyl acetate / acetone or 19:1 dichloromethane / methanol as the eluant to afford the nucleoside derivative.

Table 1. Synthesis of Nucleosides from Thioglycosides [a]

Entry	Thioglycoside	Base	Conditions	Product	Yield (%)
1	 **12**	**4**	CH_2Cl_2, 30 min	 **13a:** X=NHAc	90
2	**12**	**5**	CH_2Cl_2, 45 min	**13b:** X=OH	83
3	 **14a:** Y=OAc	**4**	DCE, 1 h	 **15a:** Y=OAc	83
4	**14b:** Y=NPth	**4**	DCE, 1 h	**15b:** Y=NPth	70
5	**14a**	**6**	DCE, 2 h	 **16**	79
6	 **17**	**4**	CH_2Cl_2, 45 min	 **18a:** X=NHAc	81
7	**17**	**5**	CH_2Cl_2, 10 min	**18b:** X=OH	56
8	 **19**	**4**	DCE, 2 h	 **20**	85
9	 **21**	**4**	CH_2Cl_2, 30 min	 **22a:** X=NHAc	87
10	**21**	**5**	CH_2Cl_2, 30 min	**22b:** X=OH	80
11	**21**	**4**	$MeSSMe_2OTf$ CH_3CN, Δ, 30 min	**22a**	83

[a] For all entries except 11, the thioglycoside was treated with *N*-iodosuccinimide and triflic acid at room temperature in the solvent indicated, as described in the **General Procedure**.

Summary: A thioglycoside alternative to the usual Vorbruggen-type nucleoside synthesis has been developed. The reaction is characterized by mild conditions, short reaction times, and good yields, and is successful for complex nucleosides such as **8** and **20**.

Acknowledgments: We are grateful to the Charles and Johanna Busch Memorial Fund and Ciba-Geigy Corporation for financial support of this work, NSF grant CHEM-8300444 and NIH grant 1510RRO1486 for support of instrumentation, Andrew B. J. Naughton for assistance with NMR spectroscopy, Dr. David R. White (Upjohn Co.) for a generous gift of lincomycin, and Santosh Nandan for supplying compound **7**.

References and Notes

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23. Compound **7** was prepared from diacetone glucose in 9 steps (details to be published).
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25. Compound **11**: ^{1}H NMR ($CDCl_3$) δ 3.72 and 3.79 (2 H, AB quartet for $COCH_2I$, J = 10.2); CI-MS *m/z* 497 [$(M + 1)^+$, 42%], 385 [$(M^+ - C_4H_3N_2O_2)$, 100%].

(Received in USA 10 April 1991)