A CONVENIENT STEREOSELECTIVE SYNTHESIS OF α-GLYCOSYL ESTERS

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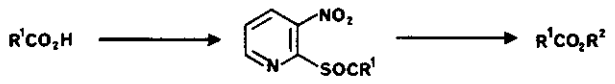
Abstract – The anomeric hydroxyl group of 2,3,4,6-tetra-O-benzyl-D-glucopyranose was esterified by reaction of the derived anomeric alkoxide with 2-acylthio-3-nitropyridines at −78°C. The resultant esters were obtained with high anomeric diastereoselectivity (α:β = 6.5:1 – 22:1). The method was extended to 2,3,4,6-tetra-O-methyl-D-glucopyranose (α:β 11:1) and 2,3,4,6-tetra-O-benzyl-D-mannopyranose (α only).

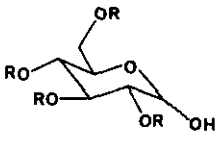
Recently, in connection with our studies on redox glycosidation[1], we required a stereoselective method for the synthesis of α-glycosyl esters. Many existing esterification procedures are hampered either by the lack of anomeric stereoselectivity or by their incompatibility with labile functionability[2]. Although excellent β-selective methods do exist[3], only the methodologies of Pfeffer et al.[3a] and Mukaiyama and Shoda[3c] lead to moderate α-diastereoselectivity. However the Pfeffer method is appropriate only for esterification using stable acid chlorides and the Mukaiyama method, in our hands, is complicated by epimerization and/or low yields when used to assemble glycosyl esters[4]. In this paper we report that 2-acylthio-3-nitropyridines are useful reagents for the preparation of glycosyl esters with moderate to excellent diastereoselectivities. Thus the carboxylic acids 1 were converted into the stable thioesters 2. Subsequent reaction of 2 with the pyranose anomeric alkoxides at −78°C gave the α-glycosyl esters 3.



1 2 3

In a typical procedure benzoic acid (25 mg) in dry CH_2Cl_2 (1 ml) was added to 3,3'-dinitro-2,2'-dipyridyl disulfide[5] (95 mg) and triphenylphosphine (80 mg) and the suspension was stirred for 3 h. Filtration and chromatography gave 2 (R^1 = Ph) (mp 89°C). n-Butyllithium (0.54 M; 0.20

ml) was added to 4a (65 mg) in dry THF (0.5 ml) at −78°C under nitrogen. After 10 min, 2(R' = Ph)(25 mg) in dry THF (0.5 ml) was added and stirring continued at −78°C[6] for 24 h. The mixture was added to saturated aqueous ammonium chloride (15 ml), extracted with diethyl ether, the extract was dried (Na_2SO_4) and evaporated Chromatography gave 6a (36 mg, 58%)(α:β 15·1). Further examples are summarized in the TABLE.



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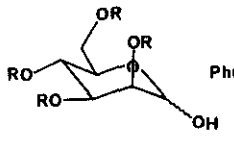
a R = $PhCH_2$
b R = Me



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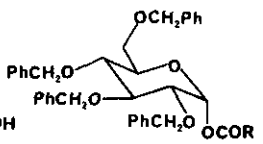
R = $PhCH_2$



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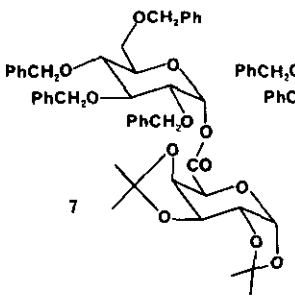
a R = Ph
b R = $Me(CH_2)_6$
c R = cyclohexyl



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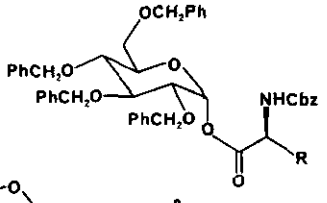

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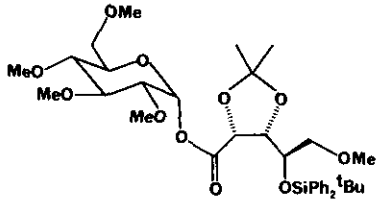
a R = i-$PrCH_2$
b R = i-Pr



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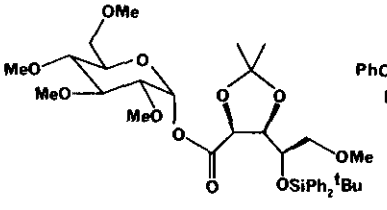

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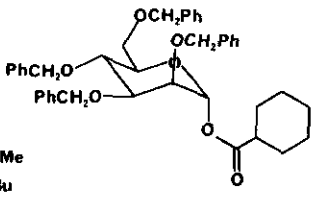

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Although the thioesters 2 were routinely isolated, their purification was not necessary for transesterification. In the *reaction of lyxonic acid* (entry h) the crude thioester was used to prepare 10 without any major effects on stereoselectivity or yield. It is clear from the TABLE that the reaction is general and successful even for hindered and highly *substituted systems* (entries c, g-i). While the reaction temperature had to be raised to −20°C in order to obtain

TABLE Preparation of α-Glycosyl Esters

Entry	Carbohydrate	Ester[7]	Yield % (α:β)[8]
a	4a	6a	58(16:1)
b	4a	6b	73(22:1)
c	4a	6c	83(20:1)
d	4a	7	94(9.5:1)
e	4a	8a	65(14:1)
f	4a	8b	66(6.5:1)
g[9]	4b	9	66(18:1)
h[9]	4b	10	67(11:1)
i	5	11	67(α only)

good yields of the galacturonic acid derivative (entry d), no major loss in selectivity was observed. In contrast to other esterification methods (DCC, 2-chloro-1-methylpyridinium iodide, 1,1'-carbonyldiimidazole) no epimerization was observed with α-substituted carbohydrate carboxylic acids (entries d, g, h) or with leucine (entry e). Valine, however, was partially epimerized (7%) during these esterification conditions. Alkoxide esterification is, in our opinion, the method of choice for the preparation of α-glycosyl esters. These are convenient precursors for α-linked disaccharides via redox glycosidation.

ACKNOWLEDGEMENTS

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4. Esterification to provide the ribonic acid derivative 9 with 2,3,4,6-tetra-O-methyl-D-glucopyranose (4b) using 2-chloro-1-methylpyridinium iodide led to C-2 epimerization of the acid and low yield. A. G. M. Barrett and B. C. B. Bezuidenhoudt, unpublished observations.

5. Prepared according to : R. Matsueda and R. Walter, Int. J. Peptide Protein Res., 1980, 16, 392.

6. The general procedure was changed for entry d. After metallation and stirring at −78°C for 3 h, the temperature was raised to −20°C and stirring continued for 60 h.

7. All new esters were fully authenticated by spectral data and microanalyses or high resolution mass ion measurements.

8. Anomeric ratios were determined by 300 or 400 MHz ^{1}H nmr spectroscopy.

9. The required carboxylic acids were prepared from the corresponding γ-lactones via the acyl indoles. See A. G. M. Barrett and D. Dhanak, Tetrahedron Lett., 1987, 28, 3327.

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