Pergamon

Tetrahedron Letters, Vol. 37, No. 7, pp. 991-994, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02360-7

The Regioselective Synthesis of Non-Glycosidically Linked Oligosaccharides

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Abstract: Dialkylstannylene acetals derived from a number of different carbohydrates were reacted with diacyl chlorides and disulfonyl chlorides in the presence of tertiary amines to give symmetrical non-glycosidically linked disaccharides with excellent regioselectivity and in excellent yield. The regioselectivity obtained was the same as that previously found in acylation reactions of the same substrates. In one case, a symmetric non-glycosidically linked trisaccharide was also obtained in excellent yield.

Although carbohydrate-protein binding plays an important role in biological recognition, the binding constants of proteins for individual carbohydrate molecules are small. Proteins achieve sufficient binding strength to carbohydrates on the surface of antibodies, viruses, bacteria, etc., by clustering the carbohydrate recognition domains of the proteins and also by recognizing clusters of carbohydrate molecules on the surfaces of these entities.[1] In order to develop therapeutic agents that mimic this binding, it will be necessary either to prepare clusters of carbohydrates or to make compounds that attach to the carbohydrate recognition sites on the protein but bind more strongly. Approaches to this problem previously described include synthesis of small native carbohydrate clusters[2] and preparation of carbohydrate dendrimers.[3,4] Here, we describe an efficient method for creating carbohydrate clusters that avoids the difficulties associated with glycoside formation, which is required for both of the previous approaches.

Dialkylstannylene acetals serve as convenient intermediates for obtaining highly regioselective substitution of diols and polyols.[5,6] We demonstrate here that use of difunctional or trifunctional electrophiles can result in the efficient formation of non-glycosidically linked disaccharides or trisaccharides. For instance, reaction of the dibutylstannylene acetal of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) with a variety of diacyl chlorides in the presence of triethylamine (TEA) results in non-glycosidically linked disaccharides in a highly regioselective manner as shown below.

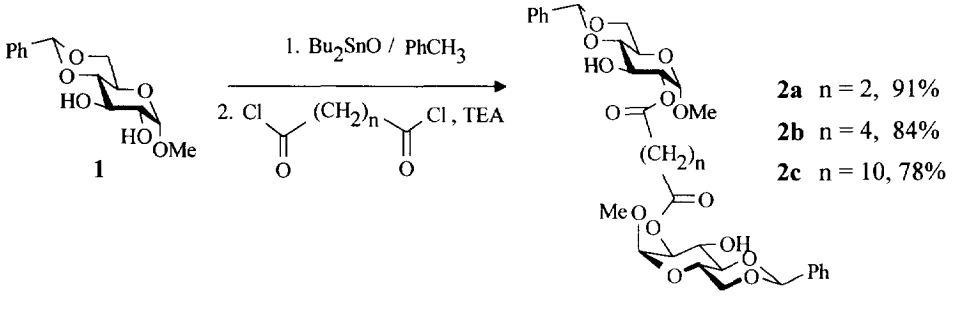
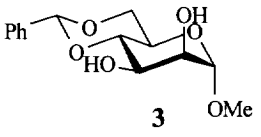


Table. Reactions Forming Non-Glycosidically Linked Disaccharides

Cmpd[a]	Linker		Reaction Conditions				Products[b]			
	acyl halide	eq.	Solvent	added base[c] (eq)	temp. (° C)	time (h)	2,2'-dimer	2,3'-dimer	3,3'-dimer	2,3-cyclic
1	**7**	0.4	toluene	TEA(1)	22	1	91			
1	**7**	0.5	toluene		22	1	58			21
1	**7**	0.48	toluene		0	2	72			6
1	**7**	1	toluene[d]		80	10	50			50
1	**8**	0.34	toluene	TEA (1)	22	0.83	84			
1	**9**	0.35	toluene	TEA(1)	22	1.5	78	12	trace	trace
1	**10**	0.43	toluene	TEA(1)	22	1	95			
1	**11**	0.34	toluene	TEA(1)	22	1	81			
3	**8**		toluene		22		21	43	18	10
3	**8**	0.42	toluene	TEA(1)	22	1	54	32	8	
3	**8**	0.42	toluene	NMI (10)	22	1	16	51	26	
3	**8**	0.42	toluene	DIA(1)	22	1	20	42	38	
3	**12**	0.43	toluene	TEA(1)	22	14	93	5		
4	**7**	0.44	dioxane	TEA(1)	22	10	72			
5	**10**	0.50	toluene	TEA(1)	22	0.33	97			
6	**10**	0.58	toluene	TEA(1)	22	2	77			

[a] Compounds were converted to dibutylstannylene acetals by reaction with dibutyltin oxide in toluene at reflux with azeotropic removal of water. [b] Isolated yields. All new products were fully characterized by measurement of physical constants, of ^{1}H and ^{13}C NMR spectra, and by analysis or by high resolution mass spectroscopy. [c] TEA = triethylamine, NMI = *N*-methylimidazole, DIA = diisopropylamine. [d] Under very dilute conditions, the concentration of **1** was 0.004 M.



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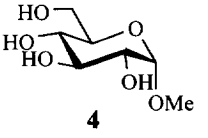

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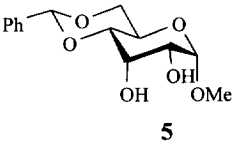

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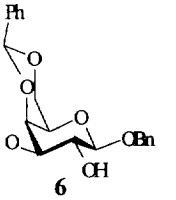

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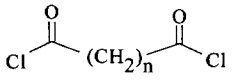
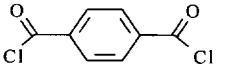


7 n = 2 **8** n = 4



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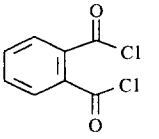

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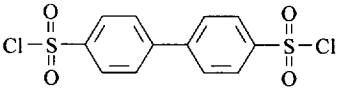
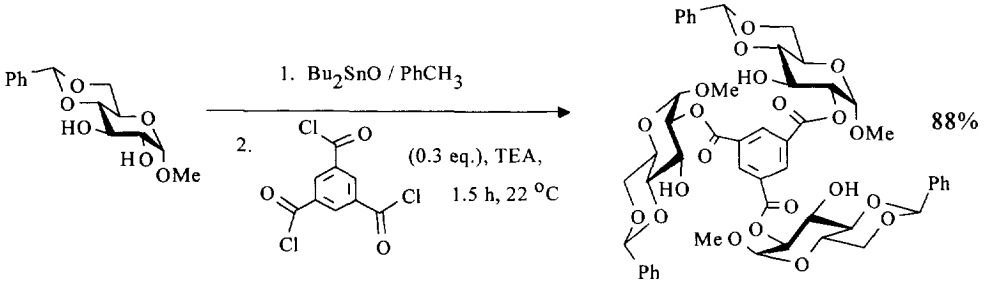


9 n = 10

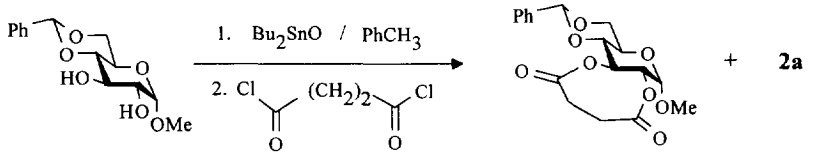
12

Analogous reactions performed with **1** and other sugars using a variety of difunctional electrophiles under different conditions are summarized in the Table. As noted in the Table, the dibutylstannylene acetals reacted fastest with diacyl chlorides in the presence of added nucleophiles or bases, such as TEA or NMI and under these conditions give symmetric non-glycosidically linked disaccharides in excellent yields. The regiochemistry of the products is what would be expected on the basis of previous reactions of these dibutylstannylene acetals with electrophiles.[4,5] The structures of the products can be established easily from their ^{1}H NMR spectra; those of the symmetric disaccharides contained signals assigned to carbohydrate and assigned to linker that integrated in the ratio of two to one. The signals of all carbohydrate protons were assigned by combinations of first-order analysis, and COSY and HETCOR experiments. The location of the acyl linker was determined unambiguously from the identity of the secondary proton that was most deshielded by the presence of the attached acyl group.

In addition, use of polyfunctional electrophiles leads to non-glycosidically linked oligosaccharides. Reaction of the dibutylstannylene acetal of **1** with 1,3,5-benzenetricarbonyl trichloride gave the corresponding non-glycosidically linked trisaccharide in excellent yield as shown below.



As listed in the Table, reactions performed in the absence of added nucleophiles or bases yielded in addition to the major product, small amounts of other products. One such product arises from intramolecular ring-closure from succinyl chloride to give a tricyclic product, termed the 2,3-cyclic product in the Table, and shown below. The yield of this byproduct was increased to 50% by using 1 equiv of succinyl chloride and performing the reaction in a very dilute solution in toluene.



With dibutylstannylene acetals derived from *trans*-diols, non-glycosidically linked disaccharides with structures other than that of the major symmetric compound were obtained only from a few reactions and then in

low yields. With one dibutylstannylene acetal, that derived from the *cis*-diol **3**, major amounts of the three possible disaccharides were obtained under several reaction conditions. TLC evidence suggested that in the reactions of **3**, the initial products obtained from the diacyl chlorides rearranged as the reaction progressed and during isolation. Similar rearrangements were observed in the benzoylation of the dialkylstannylene acetals of primary-secondary diols.[7] The products obtained using the disulfonyl chloride **12** did not rearrange during isolation. The major product obtained, the 2,2'-non-glycosidically linked disaccharide, had the same regiochemistry as that of the major product obtained in the benzoylation of the dibutylstannylene acetal of **3** performed in the absence of added nucleophiles.[8]

Repetitive application of reactions of this type could result in the rapid formation of large clusters. Valverde *et al.* have recently shown that carbohydrates having single free hydroxyl groups can be reacted with anhydrides, the product acids converted to acid chlorides, which then can be reacted with stannylene acetals of other sugars to produce non-symmetric non-glycosidically linked disaccharides with some of the same linkers as employed here.[9] Combination of these two methods would make a wide range of clusters available and the availability of a wide variety of possible linkers would allow adjustment of the distance between biologically active carbohydrate units to match that required for efficient binding. Investigations of some of these possibilities are in progress.

Acknowledgements. TBG thanks the Natural Sciences and Engineering Research Council of Canada for a research grant. HN thanks the Government of I. R. Iran for a graduate scholarship. We thank the Atlantic Region Magnetic Resonance Centre for NMR time.

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(*Received in USA* 17 *November* 1995; *accepted* 6 *December* 1995)