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Preliminary communication

Regioselective alkylation of carbohydrates in metal complexes

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The synthesis of oligosaccharides involves two major problems: the formation of glycosidic linkages with high stereoselectivity at C-1 of one sugar, and completely regioselective reaction of a specific hydroxyl group of a second carbohydrate or "aglycon". In view of recent advances in stereoselective glycosidation, argument may be made that the rate-limiting difficulties in oligosaccharide synthesis at this time involve the regioselective reaction of hydroxyl groups on the aglycon. This problem is usually addressed by selective protection of multiple hydroxyl groups.

The regioselective blocking-reactions most widely used are those that depend on a choice between axial and equatorial oxygen functions (the ortho ester[1] and the dibutylstannylene oxide methods[2]) and those that selectively convert the most acidic hydroxyl group into an anion for etherification (notably phase-transfer catalysis[3]). Ogawa[4] has also introduced selective activation of an equatorial secondary hydroxyl group adjacent to an axial hydroxyl group by means of bis(tributylstannylene) oxide.

A few examples of regioselective protection in a series of papers[5] by Avela, *et al.* have not attracted the attention they deserve. The authors have shown that copper chelates of the dianions of methyl 4,6-*O*-benzylidene-α- and β-D-glucopyranosides react with methyl iodide to give monosubstitution on O-3 preferentially. Furthermore, when copper complexes are made with the anomeric methyl 2,3-di-*O*-methyl-D-glucopyranosides, selective methylation occurs at either O-4 or O-6, depending upon the molar ratios of reactants. In addition, Avela's group has reported a survey of the use of other transition metals and selective acylation and alkylation of sucrose.

We have now found that Avela's approach holds promise of some generality, and complements other reported methods of regioselection. Its key feature is the deactivation of a dianion in the form of a copper(II) salt. As a result, the more-nucleophilic anion usually reacts preferentially with an alkyl iodide and disubstitution is virtually suppressed, undoubtedly because of the lesser second ionization.

Typically, in our experiments, a partially protected carbohydrate derivative (0.5 g) having two free hydroxyl groups was treated with 2 equiv. of sodium hydride (57% in mineral oil) in oxolane (tetrahydrofuran, THF) or dimethoxyethane (DME) (25 mL). Anhydrous copper(II) chloride (1 molar equiv.) was added to the stirred solution. Hydrogen evolution and formation of a green solution resulted and was usually complete in 5–20 min. The green solution was heated to boiling under reflux for 24 h with an excess of alkyl iodide (5 equiv.), and then cooled, treated with concentrated

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TABLE I

ALKYLATION OF 1:2:1 COPPER COMPLEXES OF CARBOHYDRATES

Compound A	*Solvent*	*Alkyl group*	*Percent composition*		
			2-O-	*3-O-*	*Compound A*
Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside[6]	THF	methyl	20	66	14
	DME	benzyl	18	74	8
	DME	allyl	19	77	4
Methyl 4,6-*O*-benzylidene-α-D-galactopyranoside[7]	DME	benzyl	29	68	3
	DME	allyl	29	68	3
Methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[8]	DME	allyl	19	81	
	THF	allyl	20	80	
Methyl 4,6-*O*-ethylidene-α-D-glucopyranoside[9]	DME	allyl	23	77	
	THF	allyl	20	80	
	DME	benzyl	32	68	
Methyl 4,6-di-*O*-benzyl-α-D-mannopyranoside[a]	DME	allyl	19	76	5
	THF	benzyl	15	85	
	THF	benzyl		95	5
			4-O-	*6-O-*	
Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside[10]	DME	allyl	61	15	24
	THF	allyl	36	31	33
	DME	benzyl	51	25	24
Methyl 2,3-di-*O*-benzyl-α-D-galactopyranoside[11]	DME	allyl	70	26	4
	DME	allyl	63	33	4
Methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside[12]	THF	methyl	100		
	DME	allyl	78	10	12
	THF	allyl	100		
	DME	benzyl	75	19	6
	THF	benzyl	100		
			3-O-	*4-O-*	
Methyl 2,6-di-*O*-benzyl-α-D-galactopyranoside[13]	DME	allyl	55	22	23
	DME	benzyl	48	29	23
			5-O-	*6-O-*	
3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose[14]	DME	allyl	50	40	10
	DME	benzyl	48	40	12
			2-O-	*6-O-*	
Methyl 3,4-*O*-isopropylidene-α-D-galactopyranoside[15]	DME	benzyl	35	34	31
			1-O-	*2-O-*	
3,4,6-Tri-*O*-benzyl-D-glucopyranose[16]	DME	allyl	0	0	(100)

[a] By benzylation of methyl 2,3-*O*-isopropylidene-α-D-mannopyranoside followed by acid hydrolysis of the isopropylidene group; m.p. 100.5–101°, $[\alpha]_D^{25}$ + 74.7° (*c* 1, chloroform).

ammonium hydroxide (4 mL) and water (10 mL), and evaporated to dryness to remove much of the excess alkyl iodide. The residue was treated with dilute ammonia and extracted with ethyl acetate. The aqueous layer was weakly acidified with M hydrochloric acid; sodium chloride and a small quantity of sodium thiosulfate were added, and the solution was again extracted with ethyl acetate. The combined organic phases were processed and chromatographed to separate the residual starting material and products from mineral oil and alkyl iodides or derived byproducts. The weights of residual starting material and monoalkylated products were determined, and the ratio of the two monoalkylated products was determined by the ratio of corresponding peak heights in ^{13}C-n.m.r. spectra. The ratio was checked in the peak areas of u.v. tracings of l.c. separations. The percent conversion of carbohydrate derivative into monoalkylated products was usually >85%. The regioselectivity is indicated in Table I.

A number of extensions and modifications of this general approach suggest themselves and are under investigation in this laboratory.

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