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A NEW, FACILE METHOD FOR CLEAVAGE OF ACETALS AND DITHIOACETALS IN CARBOHYDRATE DERIVATIVES

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Abstract: Treatment of carbohydrate acetals and dithioacetals with a dilute solution of iodine in methanol provides a simple, convenient, and high-yielding process for cleavage of the acetal functions.

The reagent system, iodine and methanol, has been reported[1,2] to open oxirane rings to afford β-methoxy alcohols. We report here that this reagent system is a highly efficient one for the cleavage of acetal and dithioacetal groupings in carbohydrate derivatives, groupings which find wide application in synthetic carbohydrate chemistry.[3,4] Benzylidine, ethylidene and isopropylidene acetals can be cleaved at room temperature or by heating at reflux temperature for a short period. If two acetal groupings are present in the molecule, one of them can be removed selectively. Simple glycosides and disaccharides do not undergo cleavage of their glycosidic linkages under the conditions employed. Also, acetyl groups survive the reaction conditions. However, if the reaction mixture is heated at reflux temperature for a prolonged period, carbohydrates having a free hydroxyl group at the anomeric center are converted into methyl glycosides. It is noteworthy that methyl glycofuranosides preponderate in the mixtures of glycosides that are formed, a result that resembles that generally observed in the case of the acid-catalyzed, Fischer glycoside synthesis.[5]

The synthetic procedure involves simply keeping a solution of the acetal in 0.5—1.0% iodine in methanol (w/v) at room temperature or at reflux temperature until TLC shows the consumption of the substrate. Processing consists of reduction of iodine using, for example, sodium thiosulfate, evaporation of the solvent, and extraction of the residue using an appropriate non-aqueous solvent such as chloroform; in some cases isolation was effected by conversion of the carbohydrate product into a per-O-acetylated derivative. The results obtained using a variety of carbohydrate acetals are shown in Table I. The overall yields are usually high.

The acetal-cleavage reactions presumably involve initially a complexation of an iodine species with one of the oxygen atoms; a subsequent reaction with methanol would lead to the free alcohols. On this basis it would be expected that dithioacetals should undergo facile cleavage, since the soft acid, iodine, would be expected to complex readily with the soft sulfur site. Indeed, treatment of D-arabinose diethyl dithioacetal

Table I. Cleavage of Carbohydrate Acetals and Dithioacetals Using Iodine and Methanol

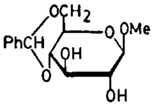
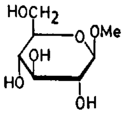
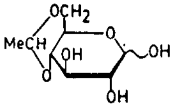
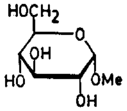
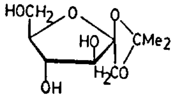
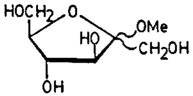
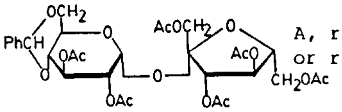
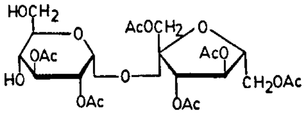
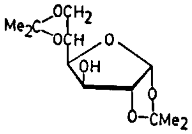
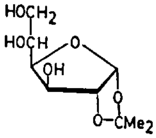
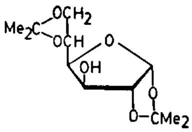
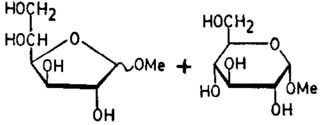
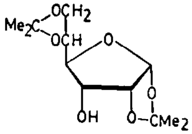
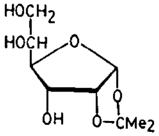
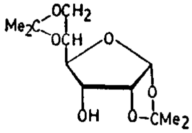
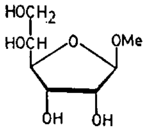
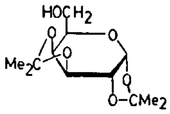
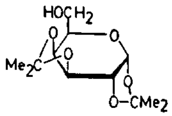
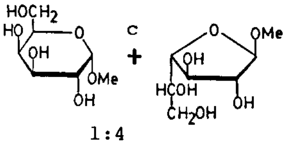
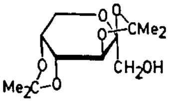
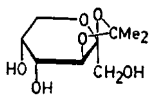
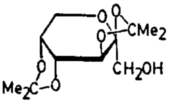
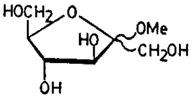
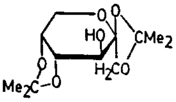
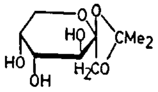
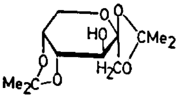
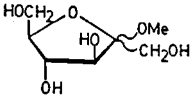
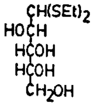
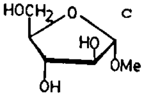
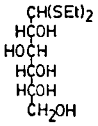
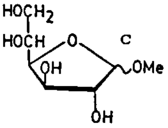
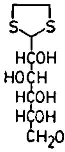
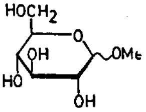
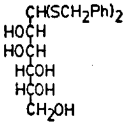
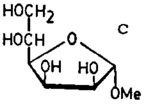
substrate	reaction conditions[a]	compounds obtained[b]	overall yield, %
	A, reflux, 30·min		>90
	A, room temp, 16 h, or reflux, 6.5 h		85
	A, room temp, 14 h, or reflux, 7 h	 3(α):7(β)	90—95
	A, room temp, 24 h, or reflux, 2.5 h		85—90
	B, room temp, 24 h, or reflux, 1—1.5 h		80
	B, reflux, 4 h	 4.2(α):4.6(β):1.2	80
	A, room temp, 24 h, or reflux, 4.5 h		65—70
	A, room temp, 36 h, or reflux, 10 h	[c]	85—90
	A, room temp, 100 h	starting material[d]	—
	A, reflux, 4 h	 1:4	51

Table I (Continued)

substrate	reaction conditions[a]	compounds obtained[b]	overall yield, %
	A, room temp, 6 h		35
	A, room temp, 14 h, or reflux, 6 h	 1.5(α):8.5(β)	90
	A, room temp, 6 h		75
	A, room temp, 24 h, or reflux, 6 h	 1(α):9(β)	90
	A, room temp, 48 h	 [c]	70
	A, room temp, 32 h	 [c] 1(α):2(β)	74
	A, reflux, 18 h	 4(α):1(β)	90
	A, room temp, 24 h	 [c]	76

[a] Solution A: 1% iodine in methanol (w/v); solution B: 0.5% iodine in methanol (w/v).
[b] Structures of compounds were established by comparison by TLC and/or HPLC with authentic samples, or by comparison of ^1H and ^{13}C NMR spectral data and physical constants with literature values. [c] Isolated as the per-O-acetylated derivative. [d] Thin-layer chromatographic evidence.

with a 1% solution of iodine in methanol afforded, after ∿2 days at room temperature, methyl α-D-arabinofuranoside in 70% yield. Other examples of the removal of dithioacetal groupings under mild conditions are given in Table I. It was found that cleavage of the dithioacetal grouping in D-glucose ethylene dithioacetal required heating at reflux temperature; it is known that mercury(II) chloride-catalyzed hydrolysis of ethylene dithioacetals occurs slowly.[6]

Developments in protective-group strategy, including the formation and cleavage of acetals, continue to be of interest in synthetic carbohydrate chemistry.[7,8] The attractiveness of the reagent system described here stems from its simplicity, convenience, versatility, and the high yields of the cleavage products. Various aspects of the process are currently under investigation in this laboratory.

Acknowledgement

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