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Note

Acetylation of carbohydrates by transesterification using ethyl acetate and sodium hydride

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The acetylation of a carbohydrate is usually accomplished by treatment of the compound with acetic anhydride and a catalyst[1], such as pyridine, sodium acetate, perchloric acid, zinc chloride[2], ferric chloride[3] or 4-dimethylaminopyridine[4]. The preparation of esters by transesterification has been a much less common method[1], even though the reactions may proceed under mild conditions[5]. The acetylation of sucrose by transesterification using ethyl acetate was reported over 20 years ago by Hass *et al.*[6]. Recently, Posner *et al.*[7,8] demonstrated the selective acetylation of the primary hydroxyl groups of some partially derivatized monosaccharides by reaction with ethyl acetate and neutral alumina. This same reaction was extended, by Rana *et al.*[9], to partially derivatized disaccharides. The publication of these findings has prompted us to report that, in the course of studies in this laboratory, selective acetylation of the primary hydroxyl groups of various monosaccharide derivatives was observed when the compounds were heated with ethyl acetate and a stoichiometric amount of sodium hydride. These acetylations occurred more rapidly than those catalyzed by neutral alumina[8,9] and afforded comparable yields of the primary acetates (Table I). Sodium hydride is well known as a catalyst for the polymerization of caprolactam[10], and for carboxyalkylations using dialkyl carbonates[11], but its use for transesterification[12] has been limited to the formation of esters of β-hydroxyketones by reaction with ethyl carbonate[13], of *N*-benzyl-3-β-norgranatanol by reaction with methyl 2-cyclohexyl-2-phenylglycolate[14], and polyester formation[15].

Each of methyl α-D- and β-D-glucopyranoside and -galactopyranoside (**1**, **2**, **3**, and **4**, respectively) was subjected to transesterification by heating of the compound at 60–65° in ethyl acetate to which 4 mol of sodium hydride per mol of glycoside had been added. The methyl glycosides were almost insoluble in the reaction mixture, which was stirred continuously. The progress of the reaction was monitored by t.l.c.

TABLE I

RESULTS OF TRANSESTERIFICATION OF CARBOHYDRATE DERIVATIVES WITH SODIUM HYDRIDE AND ETHYL ACETATE

Compounds treated	*Reaction time for maximum yield (h)*	*Compounds obtained*[a]	*Yield (%)*	*Melting*[b] *point (degrees)*	*Specific*[b] *rotation* $[\alpha]_D^{20}$ *(degrees)*	*T.l.c. solvent*
1	7	Methyl 6-*O*-acetyl-α-D-glucopyranoside[20] (9)	43	Syrup	147.5 (*c* 1.7, acetone) [-150.1, acetone]	*D*
2	7	Methyl 6-*O*-acetyl-β-D-glucopyranoside[21]	40	129–130 [130]	32 (*c* 3, water) [32, water]	*D*
3	7	Methyl 6-*O*-acetyl-α-D-galactopyranoside[22]	32	157–158 [154–156]	−147.5 (*c* 0.39, ethanol) [-160, ethanol]	*D*
4	7	Two products	35 (combined)			*D*
5	2.5	6-*O*-Acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose[23]	18	142–144 [144–146]	6.5 (*c* 0.76, ethanol) [-6.3, ethanol]	*C*
6	4	3-*O*-Acetyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose[23]	75	58–60 [62]	37.4 (*c* 5, chloroform) [-38.5, chloroform]	*A*
7	2	Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside[21]	30	130 [133–134]	102.7 (*c* 0.39, chloroform) [-106.2, chloroform]	*B*
		Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside[21]	33	174–175 [176–177]	130.6 (*c* 0.36, chloroform) [114.1, chloroform]	
		Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside[24]	8.3	107–108 [109–110]	-74.2 (*c* 0.2, chloroform) [-72.1, chloroform]	
8	2	6-*O*-Acetyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[23]	75	107–108 [108]	-47.8 (*c* 1.5, chloroform) [-48.1, chloroform]	*A*

[a]The ^{1}H-n.m.r. and i.r. spectra of the product were consistent with the assigned structures. [b]Literature data in brackets.

These carbohydrate derivatives afforded a relatively large number of alternative sites for esterification. Nevertheless, after 7 h only one product was observed by t.l.c. from each of **1**, **2**, and **3**, and this was subsequently established to be the corresponding 6-acetate, which was isolated in yields of 30–45% based on the amount of starting compound (Table I).

The relative reactivities of the hydroxyl groups of carbohydrates have been studied extensively[16,17], and their ease of esterification has been shown to vary with reaction conditions. Gillet *et al.*[17] observed a decreased reactivity (toward protonation) of the secondary hydroxyl groups of methyl aldopyranosides relative to the corresponding aldopyranoses, but the reasons for this remain obscure. The selectivities reported herein are consistent with those data[17]. However, in most cases, alkyl glycosides afford mixtures of partially acetylated product[16,18], even with such a selective reagent as *N*-acetylimidazole[19], which produced each of the monoacetates[16] of **1**. Consequently, on this basis, the selectivity obtained upon treatment of **1**, **2**, and **3** with sodium hydride and ethyl acetate is remarkable.

The transesterification of carbohydrate derivatives that are moderately soluble in ethyl acetate exhibited decreased selectivity between primary and secondary hydroxyl groups. Thus, 1,2-*O*-isopropylidene-α-D-glucofuranose (**5**) afforded four products during the first 2.5 h of reaction under the present conditions. However, a marked preference for reaction at the primary hydroxyl group was evident from the isolation of 6-*O*-acetyl-1,2-*O*-isopropylidene-α-D-glucofuranose in 18% yield, a proportion that corresponds to ~50% of the reaction products. These data, and those acquired with 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**6**), methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**7**), and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**8**) (Table I) verified unambiguously the ability of sodium hydride–ethyl acetate to acetylate secondary hydroxyl groups of carbohydrate derivatives.

As just noted, the optimum yields of products were obtained after ~7 h of reaction; prolonging the reaction time did not afford any significant improvement. The unchanged substrates could be recovered from the reaction mixture by silicic acid column-chromatography. It is assumed that the reaction proceeds through the conjugate base of the sugar hydroxyl group, since no reaction occurs in the absence of sodium hydride. The yield of product and ease of reaction were temperature-dependent. At room temperature, the reaction was sluggish and required excessive time to form detectable amounts of product; at reflux temperature, the reaction mixture thickened rapidly, and low yields of product were obtained. The best results were observed when sodium hydride was added to a stirred mixture of substrate in ethyl acetate at room temperature and warmed to 60–65° over 0.5 h. It is probable that at elevated temperature polymeric compounds arising from aldol-type condensations of ethyl acetate become of major importance.

Very little product was isolated when the transesterification was performed in oxolane containing stoichiometric quantities of ethyl acetate and sodium hydride.

EXPERIMENTAL

General. — Melting points were determined with a Fisher–Johns apparatus, and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model 141 polarimeter at 20 ±2° using a 0.1-dm cell. Infrared (i.r.) spectra were recorded with a Perkin–Elmer Model 598 spectrophotometer. ^{1}H- and ^{13}C-N.m.r. spectra were recorded at 200 MHz with a Bruker CXP 200 spectrometer, and tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standard. T.l.c. was performed on precoated silica gel (60-F254) plates (0.25-mm layer of adsorbent). Compounds were located on the developed plates, after drying, by spraying with a solution containing ceric sulfate (1%), molybdic acid (1.5%), and sulfuric acid (10%) in water, and heating at 150°. Preparative separations were performed with dry-packed columns of silica gel G-60 (70–230 mesh). The solvent systems employed were as follows (v/v): (*A*) 14:1 chloroform–acetone; (*B*) 2:1 toluene–ethyl acetate; (*C*) 9:3:1 toluene–ethyl acetate–methanol; and (*D*) 1:1:1:1 toluene–chloroform–ethyl acetate–methanol. All evaporations were performed under reduced pressure at a bath temperature of ≤40°.

Preparation of methyl 6-O-acetyl-α-D-glucopyranoside (**9**) *by transesterification of* **1**. — Compound **1** (0.4 g) was dispersed in ethyl acetate (25 mL), and sodium hydride (4 mol per mol of **1**) was added; the suspension was stirred and warmed to 65 ±2°. The progress of the reaction was monitored by t.l.c. (solvent *D*). Maximum conversion of **1** into **9** was observed after ~7 h of reaction. The reaction mixture was allowed to cool to room temperature and was poured, with stirring, into 80% aqueous ethanol (30 mL) in which was suspended a small excess of Amberlite IR-120 cation-exchange resin (H^+). The resulting mixture was filtered through glass wool; the residue was washed with three 5-mL portions of 80% aqueous methanol, and the combined filtrate and wash solutions were evaporated. The syrupy residue was fractionated by chromatography with solvent *D* as eluent to afford **1** and **9** (see Table I).

Acetylation of other carbohydrate derivatives by transesterification. — The aforementioned procedure was utilized for the acetylation of compounds **2**–**8**. The reaction times, chromatographic solvents used, and product composition are reported in Table I.

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