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New Procedure for the Preparation of 2-(Trimethylsilyl)ethyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-ß-D-glucopyranoside and Other Alkyl ß-Glycosides

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Abstract: The title compound and other alkyl β-glycosides **1a-g** can be prepared in one step from commercially available 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**3**) and simple alcohols using camphorsulfonic acid as a promoter together with azeotropic removal of acetic acid.

Since its introduction in 1981 by Lipshutz[1] the 2-(trimethylsilyl)ethyl (TMSEt) group has played an increasingly important role in the protection and reaction chemistry of the anomeric center of carbohydrates.[2] The title ß-glycoside, 2-(trimethylsilyl)ethyl 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-ß-D-glucopyranoside (**1a**), is a useful starting material in the preparation of lipid A analogs,[3] sialoglycoconjugates,[4] and other amino sugars.[5] The TMSEt glycoside **1a** has been prepared by the Koenigs-Knorr reaction[2a] and by acid catalyzed ring-opening[5] of 2-methyl-(1,2-dideoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyrano)-[2,1-*d*]-2-oxazoline (**2**). Both of these procedures, however, involve multiple steps and the isolation of unstable intermediates. Although several excellent methods have been developed for the direct preparation of *N*-acylated 2-amino-2-deoxy-ß-D-glucopyranosides by Lewis acid-catalyzed glycosylation of the corresponding α- and/or ß-acetates,[6] these methods are not amenable to the synthesis of **1a** and other Lewis acid-sensitive glycosides.[2a,7] Here we report a mild, one-step procedure for the preparation of **1a** and other alkyl ß-glycosides from commercially available 2-acetamido-2-deoxy-1,3,4,6-tetra-*O*-acetyl-ß-D-glucopyranose (**3**).

Treatment of **3** with simple alcohols in the presence of a catalytic amount of camphorsulfonic acid (CSA) in benzene with azeotropic removal of acetic acid afforded the corresponding alkyl ß-glycosides **1a-g** in good yield (Table 1).[8] This method for the preparation of TMSEt glycoside **1a**, which was obtained in 87% isolated yield, compares very favorably with the two-step Koenigs-Knorr procedure (38-44% overall yield) and is operationally simpler and—in our experience—higher yielding than the oxazoline method. We have routinely carried out the preparation of **1a** and other glycosides shown in Table 1 on a multi-ten gram scale using this methodology.

A typical procedure is as follows. Preparation of **1a**: To a stirred solution of **3** (5.02 g, 12.8 mmol) and CSA (0.05 g, 0.2 mmol) in benzene (50 ml) under reflux was added a solution of 2-(trimethylsilyl)ethanol (3.2 g, 25.7 mmol) in benzene (20 ml) dropwise over 2 h. A constant reaction volume was maintained during the addition by using a Dean-Stark apparatus possessing a stopcock for continuous take-off. The addition of benzene (40 ml) and distillation of the azeotrope was continued for 4 h. The cooled reaction mixture was diluted with EtOAc, passed through a short column of silica gel, and concentrated. The crude product obtained was crystallized from EtOAc-hexanes to yield 5.0 g (87%) of **1a** as a colorless powder.

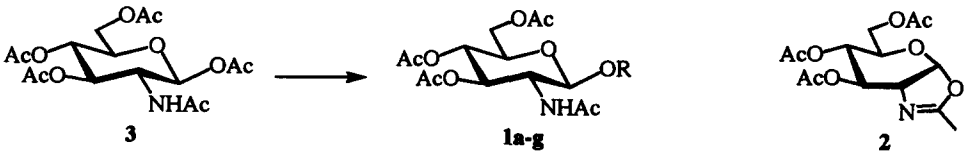

Table 1. Preparation of Alkyl 2-Acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-glucopyranosides (1)

Compound	R	Isolated Yield, %[a]	m.p. (°C)
1a	TMSEt	87	179-180
1b	Allyl	84	162-164
1c	Benzyl	92	160-162
1d	n-Butyl	88	142-145
1e	4-Pentenyl	86	127-129
1f	2-Methoxyethyl	84	145.5-146
1g	2,2,2-Trichloroethyl	52	184.5-185

[a]All products were characterized by ^{1}H- and ^{13}C-NMR. New compounds gave satisfactory elemental analyses.

Unlike the Helferich[9] synthesis of aryl glycosides from peracetylated sugars, the present method is highly stereoselective and does not lead to acid-catalyzed anomerization[10] of the initally formed β-glycoside.[11] The detection of oxazoline **2** (prepared from **3** with $SnCl_4$)[12] in the reaction by thin layer chromatography suggests that the protonated form of **2** is the reactive intermediate.

Further studies aimed at optimizing the reaction conditions by employing alternate solvents and an apparatus suitable for the simultaneous recycling of the distillate and removal of acetic acid are underway.

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8. In general, yields of **1** are lowered by 10-15% if the 80°C 2% AcOH/benzene azeotrope is not exploited for the removal of acetic acid. This is due presumably to the anomerization of **3** to the less reactive α-acetate.[12] However, in the case of weakly nucleophilic trichloroethanol, virtually none of the β-glycoside **1g** is formed in the absence of the azeotrope.
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