SELECTIVE PROTECTION OF HYDROXY GROUP AT C6 POSITION OF GLUCOSE DERIVATIVES

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ABSTRACT

6-*O*-Benzyl derivatives and 6-*O*-toluoyl derivatives, **2a–f** and **3a–f,** were prepared in high yields from glucose derivatives **1a–f** through multi-level anion formation using an excess of sodium hydride (4 eq.).

INTRODUCTION

It is necessary to protect many hydroxyl groups in each carbohydrate before glycosylation for the synthesis of glycoconjugates. In general, the primary hydroxyl group at the C6 position of monosaccharides like glucose or galactose is more reactive than the other hydroxyl groups at C2-C4 positions because of less steric hindrance, and bulky triphenylmethyl (Tr) /1/, pivaloyl (Piv) /2/ and *t*-butyldiphenylsilyl (TBDPS) /3-5/ have been widely used as protecting groups. More general protection by acetylation /6/, benzoylation /7-9/ and alkylation are not very selective for the protection of primary alcohols. Although a facile synthetic route using reductive ring-opening of 4,6-benzylidene acetals /10/ has been developed to generate 6-*O*-benzyl-hexopyranoside derivatives, the direct protection of the desired hydroxyl group may prove more selective.

In this report, we investigated a simple method to selectively alkylate and acylate the C6 terminal hydroxyl group of glucose derivatives **1a–f.** Difficulties in selective protection of the C6 hydroxyl group originates from its non-selectivity towards acylation and alkylation compared to C2–C4 hydroxyl groups.

RESULTS AND DISCUSSION

The benzylation of 1-*O*-protected glucoses **1a–f** in DMF with sodium hydride (NaH, 1.3 eq.) and benzyl bromide (BnBr, 1.3 eq.) under various conditions consistently produced the 6-*O*-benzyl glucose derivatives in poor yields. We then examined the same benzylation with NaH (2 eq.) and BnBr (1–2 eq.), but the yield was always lower than 50%. Finally, we investigated the benzylation and toluoylation (*p*-methyl benzoylation) of multi-anion of **1a–f,** like their corr-

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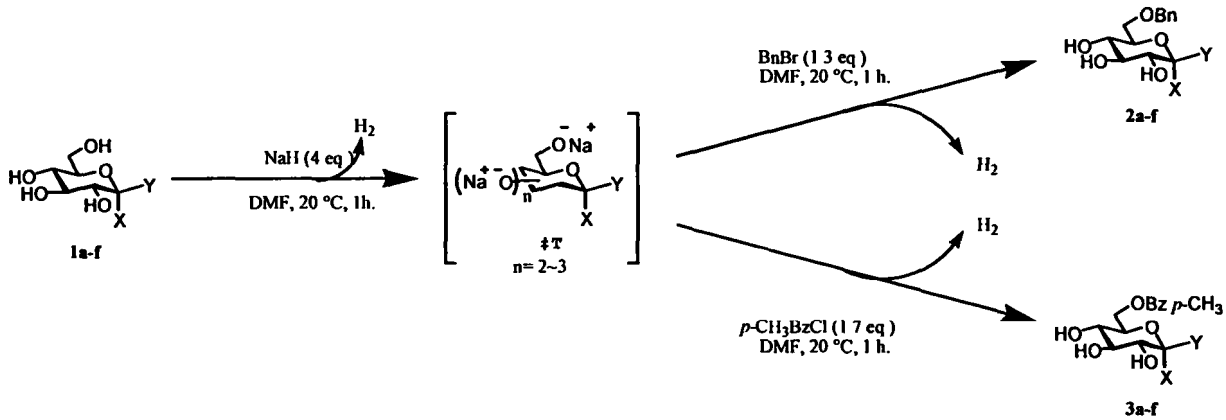

Scheme 1: Benzylation and toluoylation of protected glucose **1a–f**.

Table 1; Benzylation of glycoside derivatives **1a–f**

entry	s.m.	X	Y	NaH	BnBr	product (Yield)
1	**1a**	H	OPh	4 eq.	1.3 eq.	**2a** (63%)
2	**1b**	H	OCH_3	4 eq.	1.3 eq.	**2b** (69%)
3	**1c**	H	OMP*	4 eq.	1.3 eq.	**2c** (73%)
4	**1d**	H	SPh	4 eq.	1.3 eq.	**2d** (73%)
5	**1e**	OPh	H	4 eq.	1.3 eq.	**2e** (<30%)
6	**1f**	OCH_3	H	4 eq.	1.3 eq.	**2f** (<30%)

*MP= *p*-methoxy phenyl

Table 2; Toluoylation of glycoside derivatives **1a–f**

entry	s.m.	X	Y	NaH	*p*-CH_3BzCl	product (Yield)
7	**1a**	H	OPh	4 eq.	1.7 eq.	**3a** (57%)
8	**1b**	H	OCH_3	4 eq.	1.7 eq.	**3b** (61%)
9	**1c**	H	OMP*	4 eq.	1.7 eq.	**3c** (76%)
10	**1d**	H	SPh	4 eq.	1.7 eq.	**3d** (81%)
11	**1e**	OPh	H	4 eq.	1.7 eq.	**3e** (74%)
12	**1f**	OCH_3	H	4 eq.	1.7 eq.	**3f** (61%)

*MP= *p*-methoxy phenyl

esponding tri- and tetra- anions, using NaH (4.0 eq.) in DMF. Reaction conditions and yields after silica gel purification are shown in Tables 1 and 2.

The reaction was carried out under the following representative conditions. In entry 1 (Table 1), the 1β-*O*-phenyl

glucose (**1a**: 100 mg) was first stirred with NaH (4.0 eq) in DMF (3 mL) for 1 h at 20 °C to effort the multi-anion. And then BnBr (1.3 eq.) was added to the reaction mixture and stirred for another 1h at the same temperature. The reaction mixture was neutralized by adding acetic acid and diluted with ethyl acetate and washed 3 times with brine and the ethyl acetate solution was dried with anhydrous sodium sulphate and concentrated. 6-*O*-Monobenzyl derivative **2a** was obtained in 63% yield using silica gel open column chromatography. The structure was determined to be 6-*O*-benzyl derivertive **2a** by ^{1}H-NMR spectra of **2a** and its per-acetate. As shown in entries 2–4 (Table 1), 6-*O*-Bn-derivatives **2b–d** were also obtained in high yields from 1β-protected glucose derivatives **1b–d**. On the other hand, the benzylation yields of α-protected isomers **1e** and **1f** were low as shown in entry 5 and 6. These results suggest that anionic alkoxide at 2–position of **1e** and **1f** is also reactive without the steric hindrance to give many isomers in entry 5 and 6.

The 6-*O*-monotoluoylation of glucose derivatives through multi-anion formation with sodium hydride (4 eq.) is shown in Table 2. When toluoyl chloride (1.7 eq.) was added to the multi-anion **I**, 6-*O*-monotoluoyl derivatives **3a–f** were synthesised from glucose derivatives **1a–f** in 57–81% yields. The toluoylation of 1α-substituted glucose derivatives **1e** and **1f** gave 6-*O*-mono-substituted **3e** (74%) and **3f** (61%), respectively. These results suggested that the reason why 6-*O*-monotoluoyl derivertives **3a–f** were produced preferentially is that the C2 anionic alkoxide hardly reacted with bulky acyl chloride (toluoyl chloride).

The yields of benzylation or toluoylation using over 5eq of sodium hydride were almost constant, but the yields using 1~3 eq of sodium hydride were low. Therefore, we presume the multianion prepaired with 4 eq sodium hydride to be two or three anion per molecule. But the positions of anionic alkoxides is currently being studied.

In summary, 6-*O*-benzyl **2a–d** and 6-*O*-toluoyl derivatives **3a–f** were generated in good yields. Further applications of these selective functionalisations to another complex carbohydrate are currently in progress.

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