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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 5031–5033

Regioselective acylation of 6-O-protected octyl β-D-glucopyranosides by DMAP catalysis

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Received 16 April 2007; accepted 17 May 2007
Available online 23 May 2007

Abstract—Regioselectivity of acylation of 6-O-protected octyl β-D-glucopyranosides was investigated. Treatment of octyl 6-*O*-methyl-β-D-glucopyranoside with isobutyric anhydride in the presence of DMAP in toluene at −40 °C gave 3-*O*-isobutyryl derivative in >99% regioselectivity. Similar treatment of octyl 6-*O*-TBS-β-D-glucopyranoside at −20 °C also gave 3-*O*-isobutyryl derivative in >99% regioselectivity.

1. Introduction

Regioselective functionalization of one of the multiple hydroxyl groups of carbohydrates has been receiving increasing synthetic attention. Selective acylation of a primary hydroxyl group of octyl β-D-glucopyranoside in the presence of three secondary hydroxyl groups has been achieved in ~100% selectivity by enzymatic methods.[1,2] Recently, Kattnig and Albert reported a method for selective acylation of octyl β-D-glucopyranoside with 4-dimethylaminopyridine (DMAP) and acetyl chloride to give the 6-*O*-acetyl derivative in 85% selectivity in 73% yield.[3] On the other hand, selective acylation of a secondary hydroxyl group of carbohydrates in the presence of a primary hydroxyl group is much more difficult. Yoshida and co-workers reported selective acylation of the secondary hydroxyl group at C(4) of octyl α-D-glucopyranoside in 61% selectivity with an acetic anhydride-DMAP system.[4] Recently, Griswold and Miller reported an excellent approach to the selective introduction of an acetyl group at a secondary hydroxyl group of octyl β-D-glucopyranoside by using peptide-based chiral catalysts, which gives the 4-*O*-acetyl derivative in 58% selectivity.[5] Highly selective diacylation of *p*-methoxyphenyl β-D-glucopyranoside on the primary hydroxyl group at C(6) and the secondary hydroxyl group at C(3) has also been reported by Wong and co-workers.[6] Since selective functionalization of the primary hydroxyl group at C(6) of glucopyranosides is possible, we investigated the selective acylation of 6-O-protected octyl β-D-glucopyranosides.

2. Results and discussion

Hu and Vesella reported that benzoylation of methyl 6-*O*-TBDPS-β-D-glucopyranoside with Oriyama's catalyst[7] and benzoyl chloride gave the 4-*O*-benzoyl derivative in 84% yield.[8] Moitessier and co-workers have also reported highly selective 3-O-acetylation of 6-O-protected methyl α-D-glucopyranoside in up to 93% selectivity, but in relatively low yields (40–65%).[9] We employed 6-O-protected octyl β-D-glucopyranosides instead of 6-O-protected methyl α-D-glucopyranosides because of their high solubility in non-polar solvents. Since regioselectivity of acylation is expected to originate in hydrogen-bonding networks of carbohydrates, non-polar solvents seem favorable to make hydrogen bonding more effectively.[4,9] While Moitessier employed bulky 6-O-protecting groups for the study of regioselective acylation, we chose the smallest protecting group, 6-*O*-Me, in order to minimize the steric effects.

Acylation of octyl 6-*O*-methyl-β-D-glucopyranoside was investigated with 10 mol % of DMAP and 1.1 mol equiv of isobutyric anhydride (Table 1). Isobutyric anhydride was chosen as an acylating agent because it shows high selectivity in the kinetic resolution of racemic alcohols[10] and also has a high k_{cat}/k_{uncat} ratio.[11] Reactions were conducted in non-polar solvents such as toluene and

Keywords: Acylation; Glucopyranoside; Regioselectivity; DMAP.
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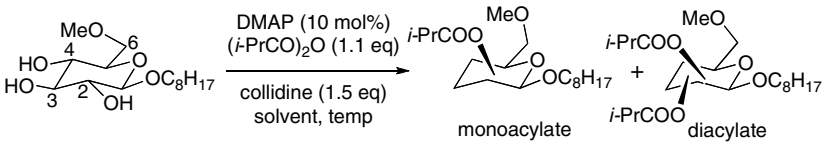
doi:10.1016/j.tetlet.2007.05.098

Table 1. Effects of solvents and temperature on regioselectivity of acylation of octyl 6-*O*-methyl-β-D-glucopyranoside with DMAP



Entry	Solvent	Temperature (°C)	Time (day)	Monoacylate (%)	Regioselectivity 4-*O*:3-*O*:2-*O*	Diacylate (%)	Recovery (%)
1[a]	Toluene	−20	2	85	1:99:0	12	1
2[b]	$CHCl_3$	−20	2	89	0:96:4	6	3
3[b]	THF	−20	2	79	5:91:4	15	2
4[b]	DMF	−20	2	63	13:73:14	20	11
5[a]	Toluene	20	1	74	4:92:4	17	5
6[a]	Toluene	−40	5	61	0:>99:0	12	23

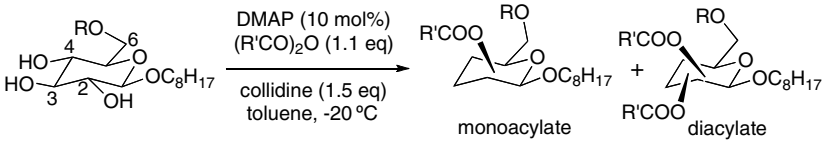
[a] The reactions were carried out with a substrate concentration of 0.08 M.
[b] The reactions were carried out with a substrate concentration of 0.1 M.

$CHCl_3$. Acylation of octyl β-D-glucopyranoside with 10 mol % of DMAP and 1.1 mol equiv of isobutyric anhydride in the presence of 2,4,6-collidine in toluene at −20 °C proceeded in a surprisingly high regioselectivity to give the 4-*O*-, 3-*O*-, and 2-*O*-isobutyryl derivative in a 1:99:0 ratio in a combined yield of 85% together with 12% of the diacylate and 1% recovery (entry 1). In $CHCl_3$, acylation took place also highly selectively to give the 3-*O*-isobutyryl derivative in 96% regioselectivity (entry 2). As expected, increasing the polarity of the solvent diminished the regioselectivity of the acylation. Acylation in THF or in DMF gave the 3-*O*-isobutyryl derivative in a decreased selectivity of 91% or 73%, respectively, together with increasing formation of the diacylate (entries 3 and 4). Having obtained the promising results in regioselective acylation in toluene, we then investigated the temperature effects. Lowering the temperature increased the regioselectivity of acylation (entries 1, 5, and 6). The reaction at −40 °C gave a perfect regioselectivity (>99%) for 3-O-acylation, although the reaction was very sluggish and monoacylation took place in 61% yield even after five days, together with 23% of recovery (entry 6). These temperature and solvent effects suggest that hydrogen-bonding interaction is critically involved in regioselective acylation.

Next, we investigated the scope of the regioselective acylation of 6-O-protected octyl β-D-glucopyranosides with various acid anhydrides. The results are summarized in Table 2. Acetylation (R′ = CH_3) of octyl 6-*O*-methyl-β-D-glucopyranoside with 10 mol % of DMAP at −20 °C in toluene gave the 3-*O*-acetyl surrogate in 98% regioselectivity and in 69% yield for monoacylation (entry 1). Benzolylation took place also in high regioselectivity to give octyl 3-*O*-benzoyl-6-*O*-methyl-β-D-glucopyranoside in 97% regioselectivity and in 93% yield for monoacylation (entry 2). Because of the poor solubility of octyl 6-*O*-acetyl-β-D-glucopyranoside in toluene, its benzolylation was performed in $CHCl_3$ to give the 3-*O*-benzoyl derivative in 93% regioselectivity (entry 3). Acetic anhydride, isobutyric anhydride, and benzoic anhydride were employed for acylation of octyl 6-*O*-TBS-β-D-glucopyranoside (entries 4–6). Highly regioselective 3-O-acylation proceeded with acetic anhydride or benzoic anhydride to give the 3-*O*-acetyl- or 3-*O*-benzoyl derivative in 84% or 83% regioselectivity, respectively (entries 4 and 6). Isobutyric anhydride was much more effective in regioselective acylation. Treatment of octyl 6-*O*-TBS-β-D-glucopyranoside with isobutyric anhydride in the presence of 10 mol % of DMAP and 2,4,6-colloidine in toluene at −20 °C gave octyl 3-*O*-isobutyryl-6-*O*-TBS-β-D-glucopyranoside in a perfect regioselectivity (>99%) and in 89% yield for monoacylation.[12]

Moitessier proposed that hydrogen-bonding interaction between pyridine nitrogen in 6-O-protecting group and the secondary hydroxyl group(s) of carbohydrates is critical for regioselective acylation.[9] In the present study, however, highly regioselective acylation was

Table 2. Regioselective acylation of 6-O-protected octyl β-D-glucopyranosides with DMAP



Entry	R	$(R'CO)_2O$	Time (day)	Monoacylate (%)	Regioselectivity 4-*O*:3-*O*:2-*O*	Diacylate (%)	Recovery (%)
1[a]	Me	Ac_2O	2	69	0:98:2	20	6
2[a]	Me	Bz_2O	3	93	0:97:3	3	3
3[b]	Ac	Bz_2O	3	78	0:93:7	15	0
4[a]	TBS	Ac_2O	2	84	9:84:7	13	0
5[a]	TBS	$(i\text{-}PrCO)_2O$	2	89	0:>99:0	10	0
6[a]	TBS	Bz_2O	7	80	5:83:12	1	16

[a] The reactions were carried out with a substrate concentration of 0.08 M.
[b] The reaction was carried out in $CHCl_3$ with a substrate concentration of 0.1 M because of poor solubility of the substrate in toluene.

observed in the absence of such a hydrogen bond acceptor in 6-O-protecting group. We assume that extremely high regioselectivity observed in the present study is the result from the intrinsically high reactivity of C(3)-OH based on intramolecular hydrogen-bonding networks of the 6-O-protected octyl β-D-glucopyranosides. The success in achieving high regioselectivity may rely on the proper choice of substrates and an acid anhydride. Substrates with high solubility in non-polar solvents should enhance the intramolecular hydrogen-bonding networks of the carbohydrates. Isobutyric anhydride works effectively in the discrimination of hydroxyl groups on acylation because of its steric effects as well as its high k_{cat}/k_{uncat} ratio.[11]

3. Conclusion

DMAP-catalyzed regioselective acylation of 6-O-protected octyl β-D-glucopyranoside has been developed. Isobutyric anhydride and toluene are the choices of acid anhydride and solvent, respectively, for achieving high regioselectivity. Under optimized conditions, acylation of octyl 6-*O*-methyl-β-D-glucopyranoside and octyl 6-*O*-TBS-β-D-glucopyranoside proceeded in a perfect regioselectivity to give the corresponding 3-*O*-acylates exclusively.

Acknowledgement

This work was supported by Grant-in-Aid for Scientific Research (A) from Ministry of Education, Culture, Sports, Science and Technology.

Supplementary data

^{1}H NMR and H–H COSY spectra of octyl 3-*O*-isobutyryl-6-*O*-TBS-β-D-glucopyranoside and ^{1}H NMR of octyl 3-*O*-isobutyryl-6-*O*-methyl-β-D-glucopyranoside. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.098.

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12. *Typical procedure for regioselective acylation of 6-O-protected octyl β-D-glucopyranoside* (Table 2, entry 5): Octyl 6-*O*-TBS-β-D-glucopyranoside (81 mg, 0.20 mmol), DMAP (2.4 mg, 0.020 mmol), and 2,4,6-collidine (40 μL, 0.30 mmol) were dissolved in toluene (2.5 mL) at 20 °C. After cooling the solution to −20 °C, isobutyric anhydride (36 μL, 0.22 mmol) was added to the mixture. The resulting mixture was stirred at −20 °C for 48 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (ethyl acetate/hexane = 30/70 to 50/50) to give pure octyl 3-*O*-isobutyryl-6-*O*-TBS-β-D-glucopyranoside (84 mg, 89%) as a single detectable monoacylate together with 11 mg (10%) of the corresponding diacylate. Analysis of the product was performed with 400 MHz ^{1}H NMR and H–H COSY spectrum.