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ORIGINAL PAPER

Efficient and improved syntheses of two key intermediates for functionalization of β-cyclodextrin at the secondary hydroxyl face

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Abstract A new and improved method for the regioselective synthesis of mono-2-tosyl-β-cyclodextrin was achieved under aqueous conditions that do not require large amounts of polar organic solvents such as *N*,*N*-dimethylformamide (DMF), specific basic catalysts such as Cs_2CO_3, or flammable bases such as NaH. Moreover, mono-2,3-mannoepoxy-β-cyclodextrin was also synthesized in the same reaction system by prolonging the reaction time.

Keywords Cyclodextrin · Mono-2-tosyl-β-cyclodextrin · Mono-2,3-mannoepoxy-β-cyclodextrin · Regioselective synthesis

Introduction

Cyclodextrins (CDs) are well-known cyclic oligosaccharides consisting of six or more α-1,4-linked D-glucopyranose units in which the secondary C-2 and C-3 hydroxyl groups are located on the more open face and the primary C-6 hydroxyl groups are on the other face. Owing to their hydrophobic and asymmetric interior, CDs and their derivatives have evolved into a versatile class of macrocyclic compounds with applications as artificial enzymes, sensors, drug delivery systems, and chiral reagents [1–8]. Since the more open secondary hydroxyl side of CDs is stated to be catalytically very important [9, 10], modifications of this face are believed to produce valuable derivatives for catalysis, enzyme mimicry, chiral discrimination, etc.

Selective introduction of functional groups into β-CD has been extensively studied for the primary hydroxyl face [11], but less well for the secondary hydroxyl face. The most commonly used method for selective introduction of one functional group at the secondary face is via activation of one hydroxyl group by sulfonylation, and research has focused on improving the preparation of mono-2-tosyl-β-CD (**1**) as the key intermediate, whose synthesis is still difficult [11–13]. In 1982, Breslow and Ueno [14] demonstrated the successful sulfonylation of the C-2 OH of β-CD by tosyl transfer from the *m*-nitrophenyl tosylate bound in the CD cavity, although in only ca. 10% yield. In recent years, several successful strategies have been developed, e.g., D'Souza and others [15, 16] sulfonylated the C-2 OH by deprotonation with NaH and subsequent reaction with sulfonyl chloride or sulfonyltriazole. This method needed the use of strong alkali as reactant. Yu et al. [17] sulfonylated the C-2 OH with *N*-sulfonylimidazole in *N*,*N*-dimethylformamide (DMF) by utilizing Cs_2CO_3—an expensive catalyst. In 2007, Strerath and co-workers [18] sulfonylated the C-2 OH with sulfonyl chloride under aqueous conditions by utilizing Na_2CO_3. Although this method was a facile one-step procedure, it used a highly reactive reagent and gave a mixture of C-2 and C-6 derivatives. *N*-Sulfonylimidazole is a highly selective acylating reagent [19] and is widely used for selective sulfonylation in saccharide chemistry. Herein, we report an efficient and improved method for monosulfonylation of β-CD at the 2-position (Scheme 1). Moreover, mono-2,3-mannoepoxy-β-CD (**2**), which is also an important intermediate [12, 20], was synthesized in the same reaction system by prolonging the reaction time.

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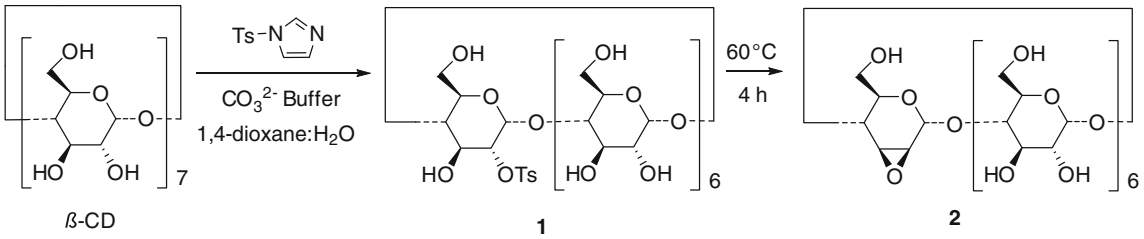

Scheme 1

Results and discussion

Of the three types of hydroxyl groups present in *β*-CD, those at the 6-position are the most basic and often most nucleophilic, those at the 2-position are the most acidic, and those at the 3-position are the most inaccessible. Thus, under normal circumstances, an electrophilic reagent attacks the 6-position, and more reactive reagents will attack the hydroxyl groups less selectively. In our work, we found that carbonate buffer (pH 9.9) can efficiently activate the hydroxyl groups at the 2-positions in a 1:1 mixture of 1,4-dioxane/water. The use of *N*-sulfonylimidazole as the sulfonating reagent rather than sulfonyl chloride has the following advantages: (1) *N*-sulfonylimidazole is a moderately reactive reagent, and it reacts more selectively with hydroxyl groups at the 2-positions than TsCl; (2) *N*-sulfonylimidazole is more resistant to hydrolysis than TsCl, which resulted in a higher yield of mono-2-tosyl-*β*-CD; (3) the only by-products of *N*-sulfonylimidazole are carbon dioxide and imidazole; the latter, being a relatively weak base, is unlikely to cause a distinct change of pH of the reaction system.

In an attempt to improve the yield of **1**, we varied several reaction parameters. First, it was shown that the maximum yield was obtained by using two molar equivalents of *N*-sulfonylimidazole; TLC demonstrated the formation of significant amounts of multitosylates with increasing amounts of *N*-sulfonylimidazole added during the reaction. Second, ESI–MS demonstrated the decreased abundance of **1** at longer reaction time and higher temperature with concomitant formation of significant amounts of mono-2,3-mannoepoxy-*β*-CD (**2**). It is noteworthy that **2** can also be synthesized under the same conditions simply by prolonging the reaction time.

In conclusion, an improved procedure for the preparation of mono-2-tosyl-*β*-CD was developed by using *N*-sulfonylimidazole as the sulfonating reagent in 1,4-dioxane/carbonate buffer solution in a reasonable yield. The reaction does not require large amounts of polar organic solvents such as DMF, specific basic catalysts such as Cs_2CO_3, or flammable bases such as NaH. In addition, mono-2,3-mannoepoxy-*β*-CD was also synthesized in the same reaction system by prolonging the reaction time.

Experimental

NMR spectra were recorded on Bruker AM-600 (^{1}H 600 MHz and ^{13}C 150 MHz) in D_2O and DMSO-d_6 solutions with TMS as the standard. The ESI–MS experiments were performed using a ThermoQuest Finnigan LCQ^{DECA} system equipped with an ESI source (ThermoQuest LC/MS Division, San Jose, CA, USA). *N*-Tosylimidazole was prepared according to the method described by Hicks and Fraser Reid [21]. Carbonate buffer (0.2 M, pH 9.9) was prepared by mixing equal volumes of 0.2 M sodium carbonate and 0.2 M sodium bicarbonate. All other chemicals were of commercial grade and used without further purification.

2^I-O-p-Tolylsulfonylcyclomaltoheptaose (**1**)

Carbonate buffer (20 cm^3, 0.2 M, pH 9.9) was added to a stirred solution of 2 g *β*-CD containing two equiv. of *N*-tosylimidazole in a 1:1 mixture of 1,4-dioxane/H_2O (40 cm^3). The reaction mixture was heated at 50 °C for 1 h. Then the mixture was neutralized with 1 N HCl, evaporated in vacuo to a volume of ca. 5 cm^3, and 300 cm^3 acetone was added to precipitate the cyclodextrin derivatives. The collected solid was loaded onto an RP-18 column and eluted with H_2O/MeOH. The eluent composition was gradually changed (MeOH/H_2O, 0–10–20–30%) until the pure product was eluted. The residue obtained after removal of the solvent was triturated with acetone, filtered, washed with acetone, and dried. Thus compound **1** was obtained in 34% yield (0.79 g). ESI–MS: m/z = 1,311 ($[M + Na]^+$); ^{1}H and ^{13}C NMR spectra were identical with those reported in the literature [14, 18].

Cyclo{4)-(2,3-anhydro-α-D-mannopyranosyl)-[(1 → 4)-α-D-glucopyranosyl]$_5$-(1 → 4)-α-D-glucopyranosyl-(1 →} (**2**)

Carbonate buffer (20 cm^3, 0.2 M, pH 9.9) was added to a stirred solution of 2 g *β*-CD containing two equiv. of *N*-tosylimidazole in a 1:1 mixture of 1,4-dioxane/H_2O (40 cm^3). The reaction mixture was heated at 50 °C for 1.5 h, and then 60 °C for another 4 h. The mixture was neutralized with 1 N HCl, evaporated in vacuo to a volume of ca. 5 cm^3, and 300 cm^3 of acetone was added to precipitate the cyclodextrin derivatives. The collected solid

was loaded onto an RP-18 column and eluted with H_2O/MeOH to give 0.82 g pure **2** (yield 41%). ESI–MS: m/z = 1,139 ($[M + Na]^+$); ^1H and ^{13}C NMR spectra were identical with those reported in the literature [22, 23].

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