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A facile sulfonylation method enabling direct syntheses of per(2-*O*-sulfonyl)-β-cyclodextrins

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Abstract—Cs_2CO_3 was found to efficiently catalyze the reaction of β-cyclodextrin and *N*-tosylimidazole. Stirring β-cyclodextrin and *N*-tosylimidazole in 1/1.2 molar ratio in DMF in the presence of catalytic amount of Cs_2CO_3 at rt for 1.5 h afforded 2^A-mono-(*O*-tosyl)-β-cyclodextrin in 32% yield. The $2^A,2^B$-, $2^A,2^C$- and $2^A,2^D$-ditosylates were isolated in ca. 6–7% yields, respectively, when β-cyclodextrin and *N*-tosylimidazole were used in 1/2.5 molar ratio. The charge of excess (10 equiv) of *N*-tosylimidazole ensured a one-step direct (protection-free) synthesis of the per(2-*O*-tosyl)-β-cyclodextrin in 5% isolated yield. *N*-(*m*-Nitrobenzenesulfonyl)-imidazole even allowed a much faster access to the corresponding persulfonate in only 1 h reaction.

1. Introduction

β-Cyclodextrin (CD), a cyclic heptamer of α-(1→4)-D-glucopyranose having a hydrophobic cavity for guest-binding, and its functional derivatives are actively studied in various fields including chiral discrimination, drug delivery and catalysis.[1] Functionalization of the secondary face of β-CD often takes the 2-sulfonates as the key intermediates whose syntheses are still difficult.[2] In 1982, Breslow and Ueno demonstrated the first successful sulfonylation of the 2-OH of β-CD by tosyl transfer from the *m*-nitrophenyl tosylate bound in the CD cavity, making a landmark in the selective functionalization of CDs.[3] Years later, D'Souza and co-workers sulfonylated the 2-OH by deprotonation with NaH and subsequent reaction with sulfonyl chloride or sulfonyltriazole.[4] This method can be used to sulfonylate any two 2-OH groups of β-CD[5] but the use of strong alkali as reactant in large excess may cause side reactions and inconvenience in manipulation. Teranishi et al.[6] sulfonylated the 2-OH with *N*-sulfonylimidazole in DMF by utilizing molecular sieves as promoters. To our knowledge, this reaction is generally very slow and even the mono-sulfonylation takes long time for completion. On the other hand, per(2-*O*-sulfonyl)-β-CDs proved to be very important for the mono-facial modification of the secondary side and creation of novel cyclooligosaccharides,[7] but their syntheses require the protection of all the 6-OHs before sulfonylation of all the 2-OHs.[8] Herein, we describe the Cs_2CO_3-catalyzed reaction of CD with *N*-sulfonylimidazole that allows facile mono- and disulfonylations of the secondary side of β-CD (Scheme 1), and the first protection-free synthesis of per(2-*O*-sulfonyl)-β-CDs.

Simply mixing CDs with an *N*-sulfonylimidazole in DMF does not result in obvious reaction. Cs_2CO_3 can efficiently promote the reaction and a catalytic amount of the carbonate is sufficient to ensure a fast sulfonylation. As shown by the HPLC (Fig. 1) of the reaction mixture of β-CD with *N*-tosylimidazole, the reaction is highly regio-selective, generating only one mono-tosylate without any other regio-isomers being recognized. HPLC analysis indicated that this mono-tosylate is identical to authentic 2^A-mono(*O*-tosyl)-β-CD synthesized by the literature method. In agreement with the high selectivity, the HPLC demonstrated 3 peaks in the region of ditosylates.

The optimized conditions for the syntheses of mono-tosylate and the ditosylates are β-CD/*N*-tosylimidazole/

Keywords: Cyclodextrin; Modification; Sulfonylation; Synthesis.
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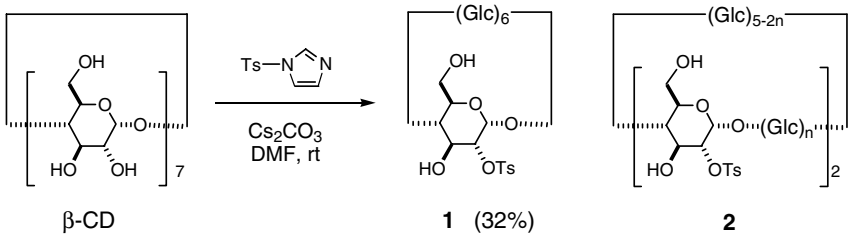


Scheme 1.

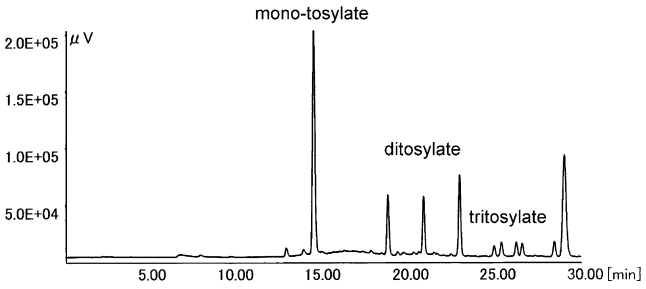


Figure 1. HPLC of the reaction mixture of β-CD and *N*-tosylimidazole. Reagents and conditions: β-CD/*N*-tosylimidazole/Cs_2CO_3 = 1/1.2/0.2 in molar ratio, in DMF, rt, 2 h. HPLC condition: Cosmosil packed 5C18-AR-II column (4.6 × 150 mm), gradient elution from water to 50% aq CH_3CN in 30 min, flow rate at 0.7 ml/min, detection at $\lambda = 260$ nm.

Cs_2CO_3 = ca. 1/1.2/0.2 (rt, ca. 1.5 h) and 1/2.5/0.2 (rt, ca.1.5 h), respectively. Quantification of the products by HPLC revealed that, under these reaction conditions, the formation of both mono- and ditosylates approached to the completion in ca. 1.5 h (Fig. 2). By reacting β-CD (5g) with *N*-tosylimidazole (1.17 g) in the presence of Cs_2CO_3 (0.288 g) in DMF (17 mL) at rt for 1.5 h, the 2^A-mono(*O*-tosyl)-β-CD (**1**) was isolated in 32% yield by chromatography of the reaction mixture on a reversed-phase column. The structure of **1** was confirmed by comparing the HPLC retention time and NMR spectra with the authentic sample obtained by the traditional methods. Reaction of β-CD (1 mmol) with *N*-tosylimidazole (2.5 mmol) in the presence of Cs_2CO_3 (0.2 mmol) in DMF (5 mL) at rt for 1.5 h gave, in addition to 19% **1**, the three ditosylates in ca. 6–7% isolated yields, respectively.

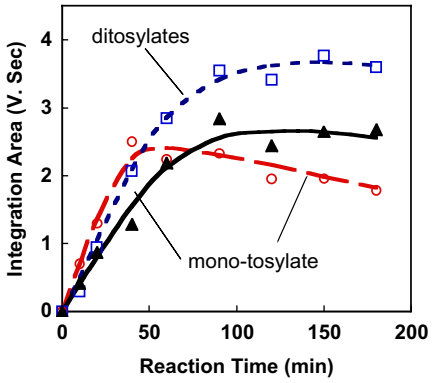
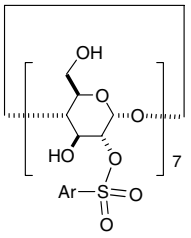


Figure 2. Products formation in the Cs_2CO_3-catalyzed sulfonylation reaction of β-CD. β-CD/*N*-tosylimidazole/Cs_2CO_3 = 1/1.2/0.2 (solid line) or 1/2.5/0.2 (broken lines) in molar ratio, DMF, rt. HPLC condition is the same as described in Figure 1.

Anhydrous condition is not necessary for this reaction. DMF–H_2O (5:1) as mixed solvent also gave similar results although the reaction proceeded much slower because of the poor solubility of the *N*-sulfonylimidazole in water.[9] A survey of proper catalysts for this reaction suggested that Cs_2CO_3 is of choice because it is slightly soluble in DMF. Organic bases such as triethylamine and imidazole failed to catalyze the reaction.

Since the present Cs_2CO_3-catalyzed sulfonylation reaction avoids the strong basic condition and proceeds smoothly to higher substitution degree, we explored the possibility of sulfonylating all the 2-OHs without protection of primary side. A survey of the reaction condition indicated that a molar ratio of β-CD/*N*-tosylimidazole/Cs_2CO_3 = 1/10/0.2 is suitable for the synthesis of the per(2-*O*-sulfonyl)-β-CD. A preparative reaction at a gram-scale in DMF (rt, overnight) gave the per(2-*O*-tosyl)-β-CD **3** in 5% isolated yield after repeated reversed-phase column chromatography. The structure and purity were confirmed by TOF-MS together with NMR spectra which demonstrated only one set of signals both for the protons and carbons. All the nuclei of the saccharides demonstrated normal chemical shifts that are very similar to those of the corresponding individuals of β-CD except H-2 and C-2 which resonate at much lower fields than those of β-CD. This observation supports the per-2-*O*-sulfonylation.



3 Ar = *p*-tolyl
4 Ar = *m*-nitrophenyl

The reaction process was traced by HPLC and the result showed that the reaction proceeded readily at the early stage but significantly slowed down at the late stage, especially for sulfonylation of the last 2-OH. Prolonged

reaction time led to partial formation of epoxides. Upon utilizing the more reactive *N*-(*m*-nitrobenzenesulfonyl)imidazole, the reaction takes only 1 h to proceed to a similar extent under the same condition as that of *N*-tosylimidazole. The reaction of 1 mmol β-CD in DMF (rt, 1 h) gave the per(2-sulfonate) **4** in 7% yield. The structure and purity were confirmed by NMR spectra (Fig. 3). Successful introduction of 7 sulfonyl groups to β-CD was confirmed by the comparison of the integration area in the aromatic range with that of the sugar range of the ^{1}H NMR spectrum. Both the proton and carbon NMR spectra demonstrated only one kind of sugar units together with one kind of aromatic substituents, indicating that the sulfonate is C_7-symmetrical and all the sugar units are magnetically equivalent. Assignments of the spectra with the aid of 2D NMR experiments revealed that both the H-2 and C-2 of the glucose displayed significant downfield shifts while all the other nuclei did not show large difference from those of β-CD, which indicated that all the 2-OH were sulfonylated. The splitting patterns of most protons were clearly displayed and were in consistence with the structure. The coupling constants relating the sugar part, $J_{1,2} = 3.5$, $J_{2,3} = 9.5$, $J_{3,4} =$ ca. 8.9 and $J_{3,4} =$ ca. 8.9 Hz, are quite similar to the corresponding ones of β-CD, implying that there is no significant difference between **4** and β-CD in the conformation of their sugar units.

In conclusion, a facile access to the 2-OH of β-CD was established by taking Cs_2CO_3 as catalyst for the reaction β-CD with *N*-sulfonylimidazoles in DMF. This methodology has the advantage of a fast and clean reaction, facile manipulation and stable results for the monosulfonates. It also ensured the first direct sulfonylation of all the 2-OHs simply by charging excess of *N*-sulfonylimidazole and the per(2-sulfonate) was synthesized in 7% yield by a 1-h reaction at rt.

2. Experimental

^{1}H and ^{13}C NMR spectra were determined with a Varian 500 MHz NMR spectrometer by setting the frequency at 500 MHz for ^{1}H spectra and at 125 MHz for ^{13}C spectra. MALDI-TOF-MS spectra (positive) were recorded on Applied Biosystems Voyager System 6336 spectrometer using 2,5-dihydroxybenzoic acid as a matrix.

2.1. 2^A-Mono(*O*-tosyl)-β-CD (1) and 2^A,2^X-di(*O*-tosyl)-β-CDs (2)

β-CD (5 g, 4.4 mmol) and *N*-tosylimidazole (1.17 g, 5.3 mmol) are dissolved in DMF (17 ml), and Cs_2CO_3 (288 mg, 0.88 mmol) was added. The suspended mixture was stirred at rt for 1.5 h, diluted with water, acidified with 1 N HCl (2 ml) and membrane-filtered. The filtrate was subjected to chromatography on a reversed-phase Lobar column (Rp-18, size C). Elution of the column with water (0.5 L) and a subsequent gradient from water to 25% aq C_2H_5OH solution (a total 2 L) afforded 2^A-mono(*O*-tosyl)-β-CD **1** (1.81 g, 32%) together with the recovery of β-CD (1.64 g, 33%). Continued elution of the column with a second gradient from 25% to 45% aq C_2H_5OH solution (a total 2 L) gave the 2^A,2^D-, 2^A,2^C-, and 2^A,2^B-di(*O*-tosyl)-β-CDs (**2**) in 4–7% yield for each isomer.

The structures of all the sulfonates were confirmed by direct comparison with authentic samples by HPLC and NMR measurements.

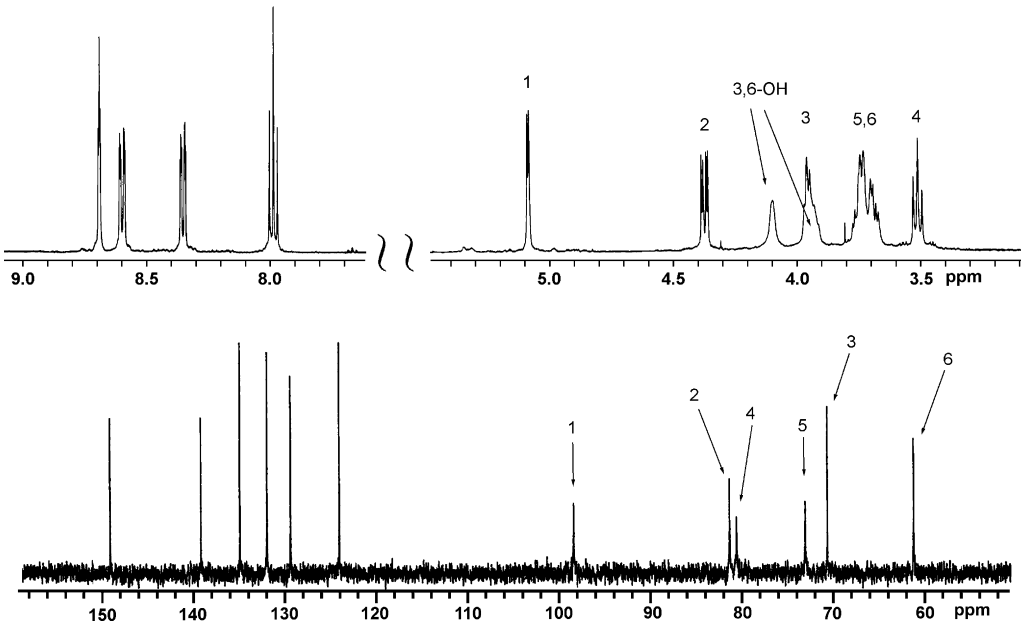


Figure 3. The ^{1}H and ^{13}C NMR spectra of per[2-*O*-(*m*-nitrobenzenesulfonyl)]-β-CD **4** in acetone-d_6 (TMS int.). The assignments were done with the aid of 2D NMR experiments.

2.2. Per(2-*O*-tosyl)-β-CD (3)

β-CD (1.0 g, 0.88 mmol), *N*-tosylimidazole (1.9 g, 8.6 mmol) and Cs_2CO_3 (65 mg, 0.2 mmol) were added in DMF (5 ml), and the resultant mixture was stirred overnight at rt. The reaction mixture was then added to water, acidified and extracted with ethyl acetate. The organic phase was evaporated and the residue was dissolved in 50% aq CH_3CN, membrane-filtered and applied to column chromatography (Rp-18, size C). Elution of the column with 50% aq CH_3CN (1 L) followed by a gradient of 50–90% aq CH_3CN (a total 2 L) afforded the crude per(2-tosylate) (160 mg, 8%). Repeated chromatography on the same reversed-phase column (gradient elution from 60% to 70% aq CH_3CN) gave the pure per(2-tosylate) **3** (98 mg, 5%). TOF-MS: *m*/*z* 2235 ($[M+Na]^+$). ^1H NMR ($CDCl_3$, TMS int): δ_H 7.78 (2H), 7.31 (2H), 5.06 (1H, H-1), ca. 4.4 (v.br, 1H, OH), 4.37 (1H, H-2), 3.78 (2H, H-3, H-6), 3.69 (1H, H-6′), 3.60 (1H, H-5), 3.43 (1H, H-4), 3.12 ppm (1H, OH); ^{13}C NMR ($CDCl_3$, TMS int): δ_C 145.3, 132.8, 129.7, 128.5 (Ar), 99.4 (C-1), 81.7 (C-4), 79.3 (C-2), 71.7 (C-5), 70.1 (C-3), 60.9 (C-6), 21.7 ppm (CH_3).

2.3. Per[2-*O*-(*m*-nitrobenzenesulfonyl)]-β-CD (4)

The mixture of β-CD (1.13 g, 1 mmol), *m*-nitrobenzenesulfonyl imidazole (2.5 g, 10 mmol) and $CsCO_3$ (65.2 mg 0.2 mmol) in DMF (5 ml) was stirred at rt for 1 h and then taken in 50% aq CH_3CN (1 L). After membrane filtration, the filtrate was subjected to column chromatography (Rp-18, size C). Elution of the column with 50% aq CH_3CN afforded per[2-*O*-(*m*-nitrophenylsulfonyl)-β-CD **(4)** (172 mg, 7.1%). ^1H NMR (acetone-d_6, TMS int): δ 8.69 (s, 7H), 8.68 (d, $^3J_{H,H} = 8.4$ Hz, 7H), 8.35 (d, $^3J_{H,H} = 8.5$ Hz, 7H), 7.99 (t, $^3J_{H,H} = 8.4$ Hz, 7H) (Ar–H); 5.08 (d, $^3J_{H,H} = 3.5$ Hz, 7H, H-1), 4.37 (dd, $^3J_{H,H} = 3.5$, 9.5 Hz, 7H, H-2), 4.10 (br, 7H, 3- or 6-OH), 3.97–3.90 (m, 14H, H-3 and 6- or 3-OH), 3.78–3.65 (m, 21H, H-5 and H-6), 3.51 ppm (t, $^3J_{H,H} = 8.9$ Hz, 7H, H-4). ^{13}C MNR (acetone-d_6, TMS int): δ 149.2, 139.2, 134.4, 132.0, 129.6, 124.1 (Ar–C); 98.7 (C-1), 81.5 (C-2), 80.7 (C-4), 73.1 (C-5), 70.7 (C-3), 61.3 ppm (C-6).

Conversion of per[2-*O*-(*m*-nitrobenzenesulfonyl)]-β-CD (**4**) to the per(2,3-mannoepoxy)-β-CD was carried out by stirring **4** (100 mg) and Cs_2CO_3 (180 mg) in DMF overnight at rt. Chromatography of the reaction mixture on reversed-phase Lobar column (Size B, elution with a gradient of 0–40% aq CH_3CN) afforded the per-epoxide (27 mg, 65%). TOF-MS: *m*/*z* 1031 (M+Na), 1047 (M+K). ^{13}C MNR (DMSO-d_6, TMS int): δ 94.7, 69.2, 67.6, 60.4, 53.0, 48.6 ppm.

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