Facile One-Step Synthesis of Mono-2-(*p*-Tolylsulfonyl)-β-cyclodextrin under Aqueous Conditions

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Received 21 September 2006; revised 30 October 2006

Abstract: A new and convenient method is presented for the synthesis of mono-2-(*p*-tolylsulfonyl)-β-cyclodextrin under aqueous conditions that does not require large amounts of polar organic solvents such as DMF, metal-containing reagents such as dibutyltin oxide, or flammable bases such as NaH. Yields are typically around 20%.

Key words: cyclodextrins, sulfonates, regioselectivity, host-guest systems

Cyclodextrins, cyclic oligosaccharides composed of six (α), seven (β), or eight (γ) α-1,4-linked D-anhydroglucose units, and their derivatives have evolved into a versatile class of macrocyclic compounds with applications in basic research,[1] for example in the synthesis and investigation of artificial receptors, sensors, and enzyme mimics,[2] and in industry.[3] Derivatization of cyclodextrins can involve the complete or incomplete statistical conversion of the hydroxyl groups along the ring into, for example, ethers or esters, or the selective modification of a few or only one of these OH groups.[1a,4] The latter is often achieved by tosylation followed by substitution of the resulting sulfonate with an appropriate nucleophile such as a halide, an azide, or a thiol. The reaction of β-cyclodextrin (**1**) with *p*-toluenesulfonyl chloride in aqueous alkaline medium, for example, selectively yields mono-6-(*p*-tolylsulfonyl)-β-cyclodextrin[5] while the corresponding mono-2-(*p*-tolylsulfonyl)-β-cyclodextrin (**2**) is more difficult to obtain (Figure 1). Successful strategies involve the reaction of anhydrous **1** with *p*-toluenesulfonyl chloride in anhydrous DMF using NaH as base[6] or a mixture of dibutyltin oxide and triethylamine.[7] A three-step reaction sequence has also been developed that proceeds via a β-cyclodextrin derivative with all primary hydroxyl groups protected by TBDMS ethers.[8] Yields along these routes are usually 20–30%.

Since **2** is a valuable starting material, particularly in supramolecular chemistry, for the synthesis of β-cyclodextrin derivatives with substituents along the wider rim of the cavity,[1a] we sought after a simpler way to synthesize this compound. The results of our investigations are reported here.

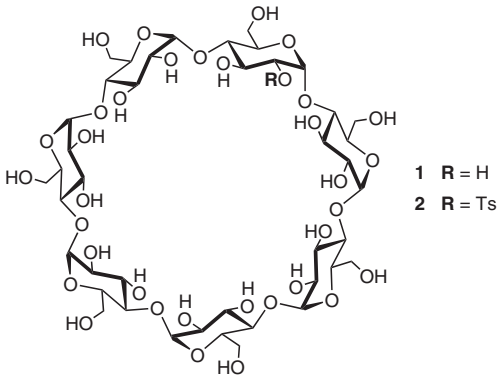

Figure 1

Regioselective monotosylation of **1** at a 6-hydroxyl group in aqueous solution has been attributed to the formation of an inclusion complex between **1** and *p*-toluenesulfonyl chloride which brings the sulfonyl chloride group in close proximity to the primary hydroxyl group of an anhydroglucose unit.[1a,5a] Indeed, in solvents such as DMF in which no complexes are formed, reaction occurs preferentially in the 2-position because of the higher acidity of the corresponding hydroxyl group with respect to a primary 6-OH.[9] We reasoned that addition of a co-solvent, that reduces solvent polarity, to an aqueous solution of **1**, should also direct tosylation into the 2-position, as it should weaken the stability of the *p*-toluenesulfonyl chloride complex. This effect should be even more pronounced if the molecules of the co-solvent are able to compete with the tosylation agent in binding to **1**. An ideal co-solvent would therefore be one that is chemically inert, completely miscible with water, relatively non-polar and a weak binder to **1**.

To test this assumption, we investigated the effect of solvent composition on the tosylation of **1** (4.4 mmol) in the presence of one equivalent of *p*-toluenesulfonyl chloride and three equivalents of NaOH. As expected, in water regioselective formation of mono-6-(*p*-tolylsulfonyl)-β-cyclodextrin was observed. In a 1:1 mixture of 1,4-dioxane–water, however, only formation of **2** could be detected, clearly demonstrating the strong influence of the solvent on the regioselectivity of the reaction. Presumably, the presence of 1,4-dioxane in the reaction medium does indeed prevent the formation of the inclusion complex between *p*-toluenesulfonyl chloride and **1**. This effect might solely be due to the reduction of solvent polarity but for-

SYNTHESIS 2007, No. 3, pp 0348–0350
Advanced online publication: 12.01.2007
DOI: 10.1055/s-2007-965885; Art ID: T14706SS

mation of a dioxane inclusion complex, that is known for α-cyclodextrin,[10] can be a contributing factor.

HPLC was used to quantify the ratio between **2** and unreacted starting material **1** in the reaction mixtures. It has to be noted that accurate detection of **1** and **2** required the use of a refractive index (RI) detector which in turn prevented us from running the chromatographic separations with a solvent gradient.[11] Unfortunately, under isocratic conditions higher substituted products were not visible in the chromatograms due to large retention times and significant line broadening. HPLC therefore only gave information about the ratio between **2** and **1** in solution and did not allow us to estimate the overall yield of the reaction.

Under the initial conditions, tosylation of **1** resulted in a ratio between product and starting material of 19:81. From there we improved the synthesis of **2** by varying several reaction parameters. First, an increase of the amount of *p*-toluenesulfonyl chloride added during the reaction from one to three equivalents shifted the ratio of **2**:**1** to 29:71 in favor of the desired product. Second, the use of weaker bases, the additional advantage of which is that they reduce the risk of tosyl elimination in **2** to give *manno*-2,3-epoxycyclodextrin,[12] also proved to be beneficial. In the presence of three equivalents of Na_2CO_3, for example, a **2**:**1** ratio of 53:47 was observed. Triethylamine had a similar effect. Finally, the ratio between **2** and **1** approached 65:35 when the reaction was performed at 50 °C. TLC also indicated a high conversion of the starting material under these conditions while simultaneously demonstrating the formation of significant amounts of higher tosylated products. Since additional modifications of the reaction conditions did not cause any further improvements we then concentrated on establishing an appropriate procedure for the isolation of **2**.

Separation of **2** from the starting material, the side products, and the salts could easily be achieved chromatographically on a RP-18 column affording pure **2** in overall yields of ca. 20%. Alternatively, the excess of **1** could be precipitated from the reaction mixture as the *p*-xylene complex after evaporation of the organic solvent. Attempts to crystallize the product from the filtrate failed most probably because the dissolved tosylate salts prevented the crystallization of **2** by forming an inclusion complex with the cyclodextrin. Indeed, if tosylate was removed by additional treatment of the filtrate with the chloride form of an anion exchange resin, recrystallization of the product from a concentrated aqueous solution became possible.

The latter result indicated that the use of an anion-exchange resin as base during the reaction could be an attractive way to avoid free salts in the reaction mixture that interfere during the recrystallization step. Indeed, treatment of **1** in 1,4-dioxane–water with three equivalents of *p*-toluenesulfonyl chloride at 50 °C in the presence of the carbonate form of an anion exchange resin yielded **2** with a **2**:**1** ratio of 37:63. Although this conversion rate is lower than the one determined for the reaction in homogeneous solution, product isolation now could simply be achieved by evaporation of the organic solvent, removal of insoluble higher substituted products by filtration, and recrystallization. In this way, compound **2** was obtained in similar yields as in the presence of Na_2CO_3 but without the need of a chromatographic purification step. Chromatographic purification did furnish purer product, however, because higher tosylated products could not be removed completely by recrystallization. The properties of pure **2** are in full agreement with previously published data.[6,7,8a,12]

In conclusion, we have developed a new and convenient method for the synthesis of **2** under aqueous conditions without the need to use large amounts of polar organic solvents such as DMF, metal-containing reagents such as dibutyltin oxide, or flammable bases such as NaH. This should make our procedure an attractive alternative to those previously described.

^1H and ^{13}C NMR spectra were recorded on Bruker DPX 400 and Bruker Avance 600 spectrometers. CHN analysis was performed in the Pharmaceutical Institute of the Heinrich-Heine-University, Düsseldorf. The analytical HPLC equipment consisted of an isocratic pump (Waters 510), an RI detector (Latek, 8110), and a RP-18 column (Bischoff, ProntoSIL 120-5-C18-ace-EPS 5.0 μm). The eluent was 18.5% MeOH–H_2O. Preparative chromatographic separations were carried out using a LiChroprep RP-18 column (Merck, prepacked column size C, 40-63 μm). β-Cyclodextrin was purchased from Wacker (Cavamax W7), anion exchange resin from Aldrich (Amberlite IRA-400, 1.4 meq/mL). Technical grade 1,4-dioxane was used without further purification. Reactions were monitored with silica gel 60 F_{254} TLC plates (Merck) by using *n*-butanol–EtOH–H_2O (4:3:3) as eluent. The plates were developed by spraying with a 5% H_2SO_4–EtOH solution followed by heating with a heat gun.

Tosylation of β-Cyclodextrin; Reaction in Homogeneous Solution

β-Cyclodextrin (5.0 g, 4.4 mmol) and Na_2CO_3 (1.4 g, 13.2 mmol) were dissolved in a mixture of H_2O–1,4-dioxane 1:1 (80 mL). The solution was heated to 50 °C and a solution of *p*-toluenesulfonyl chloride (2.5 g, 13.2 mmol) in 1,4-dioxane (20 mL) was added dropwise over the course of 1 h under stirring. Stirring was continued at 50 °C for 30 min. Afterward, the mixture was neutralized with aq 1 M HCl and evaporated in vacuo to a volume of ca. 10 mL. The residue was subjected to a RP-18 column conditioned with H_2O. Eluent composition was gradually changed [EtOH–H_2O, 5% → 10% → 15%] until the pure product eluted with the last solvent mixture. The residue obtained after removal of the solvent was triturated with acetone, filtered, washed with acetone, and dried; yield: 1.3 g (23%).

Tosylation of β-Cyclodextrin; Reaction in the Presence of an Ion Exchange Resin

β-Cyclodextrin (5.0 g, 4.4 mmol) and the anion-exchange resin Amberlite IRA-400 loaded with carbonate (65 mL) were suspended in a mixture of H_2O–1,4-dioxane 1:1 (80 mL). The solution was heated to 50 °C, and a solution of *p*-toluenesulfonyl chloride (2.5 g, 13.2 mmol) in 1,4-dioxane (20 mL) was added dropwise over the course of 1 h under stirring. Stirring was continued at 50 °C for 30 min. Afterward, the resin was filtered off, washed with 1,4-dioxane–H_2O (1:1), and the filtrate was evaporated in vacuo to a volume of ca. 10 mL. The residue was diluted with H_2O (140 mL) and the solution was stirred vigorously for 1 h. Insoluble material was filtered off by using a glass frit (P4), and the solvent was evaporated to dryness in

vacuo. The residue was triturated with acetone, filtered, dried and recrystallized from hot H_2O (20 mL). Upon cooling, the product precipitated very slowly. After 7 d at 4 °C, the product was collected by filtration, washed with a small amount of cold water and acetone, and dried (0.7 g). Another batch of 0.4 g was obtained by reducing the volume of the filtrate to 10 mL and storing the solution at 4 °C for additional 7 d. According to TLC, the material thus obtained was contaminated with higher tosylated β-cyclodextrins; yield: 1.1 g (19%). Impurities could be removed almost quantitatively by another recrystallization from 10 mL of water, which, however, reduced the yield to 0.4 g (7%).

^{1}H NMR (400 MHz, D_2O–DMSO-d_6, 1:1): δ = 2.39 (s, 3 H), 3.24 (t, ^3J = 9.2 Hz, 1 H), 3.36–3.80 (m, 39 H), 3.95 (t, ^3J = 9.2 Hz, 1 H), 4.19 (dd, ^3J = 10.0, 2.9 Hz, 1 H), 4.74 (d, ^3J = 3.5 Hz, 1 H), 4.90 (br s, 6 H), 7.46 (d, ^3J = 8.3 Hz, 2 H), 7.86 (d, ^3J = 8.3 Hz, 2 H).

^{13}C NMR (125 MHz, D_2O–DMSO-d_6, 1:1): δ = 22.6, 61.2, 61.3, 61.5, 70.9, 73.0, 73.2, 73.3, 73.4, 73.5, 73.6, 74.5, 74.6, 80.9, 82.3, 82.6, 82.7, 82.8, 99.8, 103.3, 103.4, 129.7, 131.7, 133.3, 147.9.

Anal. Calcd for $C_{49}H_{76}O_{37}S{\cdot}7\ H_2O$ (1415.3): C, 41.58; H, 6.41. Found: C, 41.73; H, 6.26.

Acknowledgment

Financial support from Cognis GmbH & Co. KG, Düsseldorf, Germany is gratefully acknowledged. We also thank D. Mampe, A. Rathjens, T. Stalberg, and H. Rößler for helpful discussions.

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