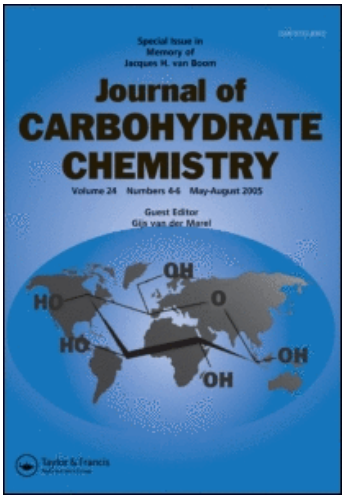

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COMMUNICATION

EFFICIENT REGIOSELECTIVE SYNTHESIS OF MONO-2-*O*-SULFONYL-CYCLODEXTRINS BY THE COMBINATION OF SULFONYL IMIDAZOLE AND MOLECULAR SIEVES

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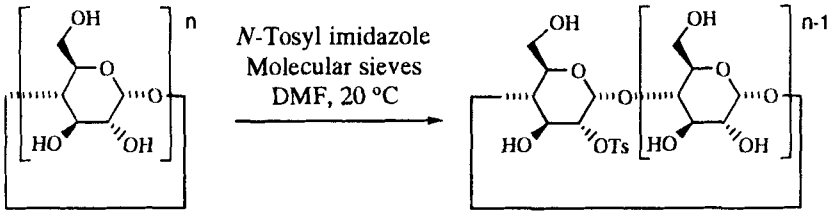
Cyclodextrins are cyclic oligosaccharides consisting of six or more α-1,4-linked D-glucopyranose units, which possess primary hydroxyl groups at the C-6 positions and secondary hydroxyl groups at the C-2 and C-3 positions. Because cyclodextrins have a hydrophobic and optically active interior, they have been utilized as transporters of hydrophobic molecules and small molecular mimics of enzymes. The chemical modification of cyclodextrins has been investigated in order to improve these characteristics. Sulfonations of the primary or secondary hydroxyl groups of cyclodextrin have been applied for further functionalization of cyclodextrin, and several methods for regioselective sulfonations have been developed. Among these strategies, selective monotosylation of the C-6 hydroxyl group is done relatively easily by reaction of α or β-cyclodextrin and *p*-toluenesulfonyl chloride in pyridine[1,2] or in alkaline aqueous solution.[3,4] However, sulfonation of the secondary hydroxyl groups is more difficult and new sulfonation methods must be developed to provide precursors for cyclodextrin analogues such as amino and sulfide analogues. Several strategies for the sulfonation of one C-2 hydroxyl group have been reported. However, because reaction conditions can require specific sulfonation reagents,[5] alkaline conditions,[3-7] strict anhydrous conditions,[8,9] or use of protected C-6 hydroxyl groups,[10,11] the methodology is not convenient to employ.

During our studies of the sulfonation of cyclodextrins using sulfonyl imidazoles, we found that the addition of molecular sieves resulted not only in a markedly enhanced reactivity but also in good regioselectivity. In this paper, we report a convenient and high regioselective sulfonation onto one C-2-hydroxyl group of α- and β-cyclodextrins, in which a combination of sulfonyl imidazole and molecular sieves is used.



1a : n = 6
3 : n = 7

Reaction of α-cyclodextrin in *N,N*-dimethylformamide (DMF) in the presence of *p*-toluenesulfonyl imidazole (0.85 equiv.) and freshly activated powder molecular sieves 4A (250 wt.%, on the basis of α-cyclodextrin), followed by isolation using reverse-phase column chromatography, gave a mixture of mono-2-*p*-toluenesulfonate **1a** and mono-3-*p*-toluenesulfonate **1b** with 35 and 2% yields, respectively. No mono-6-*p*-toluenesulfonate **1c** was formed. Product analysis was by high-performance liquid chromatography. Sulfonates **1a** and **1b** were identical with the authentic sulfonyl compounds by ^{1}H NMR, FABMS, TLC and high-performance liquid chromatography analyses.[5,8] When molecular sieves were not added to the reaction solvent, the sulfonates were not observed. Moreover, it is noteworthy that using *p*-toluenesulfonyl chloride instead of *p*-toluenesulfonyl imidazole in *N,N*-dimethylformamide in the presence of molecular sieves did not yield any sulfonate esters. The amount of added *p*-toluenesulfonyl imidazole in the reaction mixture was then varied to see how the yield of **1a** was affected. It was determined that the yields were practically the same. When the same reaction was run in *N,N*-dimethylacetamide, and in 1-methyl-2-pyrrolidinone instead of *N,N*-dimethylformamide, **1a** was isolated in 24% yield along with **1b** (2% yield) and **1c** (1% yield), and **1a** in 30% yield with **1b** (2% yield) and **1c** (1% yield), respectively. The reaction in pyridine, in which the sulfonation of α-cyclodextrin with *p*-toluenesulfonyl chloride affords 6-*p*-toluensulfonate **1c**,[1] resulted in the generation of the expected product **1a** in a 16% yield without **1b** or **1c**. Among the solvents tried, *N,N*-dimethylformamide was found to be best for the sulfonation at the C-2 hydroxyl groups. The amount of molecular sieves did not influence the reaction regioselectivity, but an increase in the amount of molecular sieves decreased the time needed for sulfonation. A 250 wt.% addition of molecular sieves 4A on the basis of α-cyclodextrin was sufficient

to provide a convenient reaction. Molecular sieves 3A and 13X were also substituted in the sulfonation and did not affect the regioselectivity. When pellet form molecular sieves 4A, involving a binder, were used, the sulfonation was not affected. These results showed that the differences in the composition and structure of molecular sieves do not practically affect the sulfonation. The yield of 35% was accompanied by generation of disulfonates (18% yield) and recovery of α-cyclodextrin (35% yield). Using *p-tert*-butylbenzenesulfonyl imidazole, which contains a bulky alkyl group, resulted in a 41% isolated yield of mono-2-*p-tert*-butylbenzenesusulfonate **2** without mono-3- and mono-6-sulfonates.

The effect of water on this sulfonation was investigated in order to ascertain if the elimination of moisture from the reaction system by the molecular sieves was important for the sulfonation. Dried molecular sieves 4A (0.5 g), which were able to absorb 0.13 g of water, was stirred for several mixtures with *N,N*-dimethylformamide and water at 20 °C for 1 day. To the mixture was added *p*-toluenesulfonyl imidazole and α-cyclodextrin (0.20 g) containing 6.8 mg of water as determined by the Karl Fischer method. In the case of the addition of 0.48 g of water, which is probably sufficient to inactivate the ability of eliminating moisture by molecular sieves, the regioselectivity and yield in the sulfonation was the same as in the case of water not being added. Further increase in the amount of water resulted in a slight decrease in the yield of **1a** and a slight decrease in the reaction rate. These results clearly indicate that the role of molecular sieves is not to protect the sulfonation system from moisture and that anhydrous conditions are not needed for this regioselective C-2 sulfonation.

To check if the sulfonation by the combination of *p*-toluenesulfonyl imidazole and molecular sieves can be applied to aliphatic alcohols, such as cyclohexylmethanol, cyclohexanol, and *trans*-1,2-cyclohexanediol, reactions were tried under the same conditions. It was found that the sulfonation using *p*-toluenesulfonyl imidazole and molecular sieves did not proceed with these alcohols. In the case of β-cyclodextrin as a substrate, regioselective mono C-2 hydroxyl sulfonation was achieved in a 36% yield. The product was identified by comparison with the authentic sulfonyl compound from ^{1}H NMR, FABMS, TLC and high-performance liquid chromatography analyses.[8] Mono C-3 and mono C-6 sulfonation products were not produced. Thus, it has been shown that regioselective sulfonation using *p*-toluenesulfonyl imidazole and molecular sieves can be applied to cyclodextrins in particular. Pregel and Buncel reported the sulfonation at one C-2 hydroxyl group of heptakis (6-*O-tert*-butyldimethylsilyl)-β-cyclodextrin with *p*-toluenesulfonyl imidazole and sodium methoxide in refluxed chloroform.[10] However, such an approach was deemed less convenient because of the requirement for protection

and deprotection of C-6 hydroxyl groups, strong alkaline conditions and low-yields of the mono-2-*O*-sulfonyl-cyclodextrins.

The incorporation of aluminum in the molecular sieve framework results in a negative charge, which is compensated by a cation, Na^+, K^+, or Ca^{2+}. The negative charges may selectively influence the C-2 hydroxyl groups of cyclodextrin and cause certain activations such as weakening the bond between the proton and oxygen atom of the hydroxyl groups and increasing nucleophilicity of the oxygen atoms. The C-2 hydroxyl groups are the most acidic hydroxyl groups of cyclodextrin and more acidic than ordinary alcohols.[9] Molecular sieves, however, cannot completely deprotonate the protons of the C-2 hydroxyl groups. If the deprotonation was extensive, cyclodextrin could react with *p*-toluenesulfonyl chloride under alkaline reaction conditions similar to those reported by many researchers.[3,4,6,9] Possibly hydrogen bonds are formed between the nitrogen atoms of *p*-toluenesulfonyl imidazole and the protons of the C-2 hydroxyl groups, activating them for selective sulfonation.

In conclusion, we have found that the combination of sulfonyl imidazole and molecular sieves achieves the suitable regioselective mono C-2 hydroxyl sulfonation of cyclodextrin. The presence of water in this system does not obstruct the sulfonation; therefore, the role of molecular sieves cannot be due to their water-trapping properties. This property of the system makes the sulfonation convenient, not requiring strict anhydrous conditions. This sulfonation can be done under mild non-alkaline conditions, at room temperature, without decomposition of the sulfonate.

EXPERIMENTAL

General methods. HPLC analysis and isolation were done using a JASCO GULLIVER HPLC system with a MD-910 three-dimensional UV-VIS detector. A Fuji Silysia Chromatorex-ODS DU0005MT column (4.6 mm x 150 mm) was used for the analysis. For preparative chromatograpy, a Fuji Silysia Chromatorex-ODS DM1020T was used. Elution conditions for HPLC for analysis: elution with 0 : 100 EtOH/H_2O to 35 : 65 EtOH/H_2O at a flow rate of 0.8 mL/min for 30 min. Analytical TLC was performed on Merck Kieselgel 60 F254 precoated, glass-backed, 0.25 mm layer-thickness. The TLC eluant was 5:4:3 *n*-BuOH/EtOH/H_2O. Compounds were visualized under a UV lamp or sprayed with *p*-anisaldehyde-HOAc-H_2SO_4-EtOH solution. ^1H NMR for a mixture of **1a** and **1b**, **2**, and **3** were recorded with a JEOL JNM-A500 spectrometer in D_2O at 50 °C using *tert*-butyl alcohol as an internal reference. ^1H NMR chemical shifts were assigned on the basis of ^1H-^1H COSY, DEPT ^{13}C NMR, and ^1H-

^{13}C COSY. ^{1}H NMR for *p-tert*-butylbenzenesulfonyl imidazole was recorded in $CDCl_3$ at 20 °C using tetramethylsilane as an internal reference. Chemical shift values are reported in δ (ppm) relative to internal standard and coupling constants (*J*) are in Hz. FAB mass spectra (positive) were measured with a JEOL DX-303 instrument using glycerol as a matrix. Elemental analyses were measured with a Yanaco CHNCORDER MT-3 instrument. Cyclodextrins, molecular sieves 3A, 4A, imidazole, and solvents were purchased from Nacalai Tesque INC. (Kyoto, Japan) and powder form molecular sieves 13X, *p*-toluenesulfonyl imidazole and *p-tert*-butylbenzenesulfonyl chloride were purchased from Aldrich Chemical Co. (St. Louis, MO, U.S.A.). α-Cyclodextrin and β-cyclodextrin were dried for 12 h at 140 °C under vacuum.

Typical procedure for the reaction of cyclodextrin with sulfonyl imidazole and molecular sieves. To a solution of α-cyclodextrin (0.2 g, 0.20 mmol) and *p*-toluenesulfonyl imidazole (0.17 mmol) in 6.0 mL of DMF was added freshly activated powder molecular sieves 4A (0.50 g), and the mixture was stirred for 50 h. Molecular sieves were removed by filtration through Celite and the filtrate was concentrated under reduced pressure to dryness. The filtrate was subjected to ODS column chromatography to give a mixture of **1a** and **1b** in about 18 : 1 ratio (0.098 g, 40% yield).

Mono-2-*p*-toluenesulfonyl-α-cyclodextrin (1a).[4,6,8,9,12] Yield 35% as determined by HPLC analysis.

Mono-2-*p-tert*-butylbenzenesulfonyl-α-cyclodextrin (2). Yield 0.105 g (41%); ^{1}H NMR (D_2O, 50 °C): δ 1.35 (9H, s, $C(CH_3)_3$), 3.30 (1H, t, *J* 9.2 Hz, H-4 of glucose unit without Ts group), 3.5-4.0 (m, protons of α-CD), 4.13 (1H, t, *J* 9.8 Hz, H-3 of glucose unit with Ts group), 4.38 (1H, dd, *J* 3.7, 9.8 Hz, H-2 of glucose unit with Ts group), 4.76 (1H, d, *J* 3.7 Hz, H-1 of glucose unit with Ts group), 5.0-5.05 (5H, m, H-1 of glucose units without Ts group), 7.74 (2H, d, *J* 8.5 Hz, ArH), and 7.99 (2H, d, *J* 8.5 Hz, ArH).

Anal. Calcd for $C_{46}H_{72}O_{32}S + 3H_2O$: C, 45.17: H, 6.42. Found: C, 45.32; H, 6.40. FABMS *m/z* 1191 ($M+Na^+$).

Mono-2-*p*-toluenesulfonyl-β-cyclodextrin (3). (This compound was reported in references 4, 5, 8, and 9, but complete characterization data are not presented). Yield 0.087 g (36%); ^{1}H NMR (D_2O, 50 °C): δ 2.44 (3H, s, CH_3), 3.37 (1H, t, *J* 9.2 Hz, H-4 of glucose unit without Ts group), 3.5-4.0 (m, protons of β-CD), 4.12 (1H, t, *J* 9.2 Hz, H-3 of glucose unit with Ts group), 4.32 (1H, dd, *J* 3.1, 9.2 Hz, H-2 of glucose unit with Ts group), 4.96 (1H, d, *J* 3.1 Hz, H-1 of glucose unit with Ts group), 5.0-5.1 (6H, m, H-1 of glucose units without Ts group), 7.47 (2H, d, *J* 8.6 Hz, ArH), and 7.92 (2H, d, *J* 8.6 Hz, ArH).

Anal. Calcd for $C_{49}H_{76}O_{37}S + 5H_2O$: C, 42.67: H, 6.29. Found: C, 43.02; H, 6.33. FABMS *m/z* 1289 ($M+1^+$).

***p-tert*-Butylbenzenesulfonyl imidazole.** To a solution of imidazole (0.32 g, 4.7 mmol) in 15 mL of DMF was added 60% NaH (0.18 g, 4.5 mmol) at 0 °C, and the mixture was stirred for 15 min. To the mixture was added *p-tert*-butylbenzenesulfonyl chloride (1.0 g, 4.3 mmol) at 0 °C, and then the mixture was stirred at room temperature for 1 h. The mixture was added to a mixture of cold water (50 mL), hexane (30 mL), and EtOAc (10 mL), and the product extracted with organic solvent. The organic phase was washed with water (30 mL), dried over anhydrous Na_2SO_4, and concentrated. The product was crystallized from hexane to give *p-tert*-butylbenzenesulfonyl imidazole (0.73 g, 64%). ^1H NMR ($CDCl_3$): δ 1.33 (9H, s, $C(CH_3)_3$), 7.09 (1H, s, imidazole-H), 7.31 (1H, s, imidazole-H), 7.56 (2H, d, *J* 8.5 Hz, ArH), 7.85 (2H, d, *J* 8.5 Hz, ArH), and 8.02 (1H, s, imidazole-H).

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REFERENCES

1. L. D. Melton and K. N. Slessor, *Carbohydr. Res.*, **18**, 29 (1971).
2. Y. Matsui and A. Okimoto, *Bull. Chem. Soc. Jpn.*, **51**, 3030 (1978).
3. S. Onozuka, M. Kojima, K. Hattori, and F. Toda, *Bull. Chem. Soc. Jpn.*, **53**, 3221 (1980).
4. K. Takahashi, K. Hattori and F. Toda, *Tetrahedron Lett.*, **25**, 3331 (1984).
5. A. Ueno and R. Breslow, *Tetrahedron Lett.*, **23**, 3451 (1982).
6. K. Fujita, S. Nagamura and T. Imoto, *Tetrahedron Lett.*, **25**, 5673 (1984).
7. K. Fujita, S. Nagamura, T. Imoto, T. Tahara and T. Koga, *J. Am. Chem. Soc.*, **107**, 3233 (1985).
8. T. Murakami, K. Harata and S. Morimoto, *Tetrahedron Lett.*, **28**, 321 (1987).
9. D. Rong and V. T. D'Souza, *Tetrahedron Lett.*, **31**, 4275 (1990).
10. M. J. Pregel and E. Buncel, *Can. J. Chem.*, **69**, 130 (1991).
11. F. Venema, C. M. Baselier, E. van Dienst, B. H. M. Ruël, M. C. Feiters, J. F. J. Engbersen, D. N. Reinhoudt and R. J. M. Nolte, *Tetrahedron Lett.*, **35**, 1773 (1994).
12. H. Ikeda, Y. Nagano, Y. Du, T. Ikeda and F. Toda, *Tetrahedron Lett.*, **35**, 5045 (1990).