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A convenient and economic method for the synthesis of mono-2-tosyl-β-cyclodextrin

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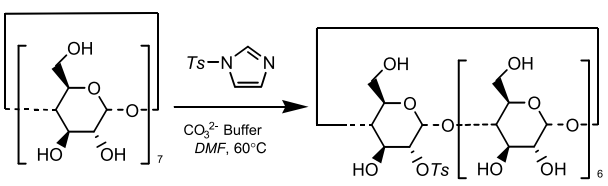
Abstract A convenient and economic method for the regioselective synthesis of mono-2-tosyl-β-cyclodextrin was achieved by using the combination of *N*-tosylimidazole and carbonate buffer in *DMF*, the reaction does not require strict anhydrous or specific basic catalysts.

Keywords Cyclodextrins; Mono-2-tosyl-β-cyclodextrin; Regioselective synthesis; Sulfonylimidazole.

Introduction

Cyclodextrins (*CD*s) are well-known cyclic oligosaccharides consisting of six or more *a*-1,4-linked D-glucopyranose units, which possess the secondary C–2 and C–3 hydroxyls on their more open face and the primary C–6 hydroxyls on the other face. Cyclodextrins have been widely used as artificial enzymes, sensors, drug delivery systems, and chiral reagents [1], owing to their hydrophobic and optically active interior. Since the more open secondary hydroxyl side of *CD*s is stated to be catalytically very important [2], modifications of this face are believed to produce valuable derivatives for catalysis, enzyme mimic, and chiral discrimination, *etc.* Mono-2-tosyl-β-cyclodextrin (**1**, Scheme 1) is a widely used intermediate for preparing other functional groups, and whose synthesis is still difficult [3]. In 1982, *Breslow* and *Ueno* demonstrated the authentically 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 [4]. In recent years, successful strategies were developed, *D'Souza* and co-workers sulfonylated the C–2 OH by deprotonation with NaH and subsequent reaction with sulfonyl chloride or sulfonyltriazole [5], this method needs the use of strong alkali as reactant. *Teranishi et al*. sulfonylated the C–2 OH with *N*-sulfonylimidazole in *DMF* by utilizing molecular sieves as promoters [6], which took long time for completion. *Hua Yu et al.* sulfonylated the C–2 OH with *N*-sulfonylimidazole in *DMF* by utilizing Cs_2CO_3 – an expensive catalyst [7]. Yields along these routes are usually 20–30%. Herein, we report a convenient and economic method for monosulfonylation of β-*CD* at the 2-position.



β-CD **1**

Scheme 1

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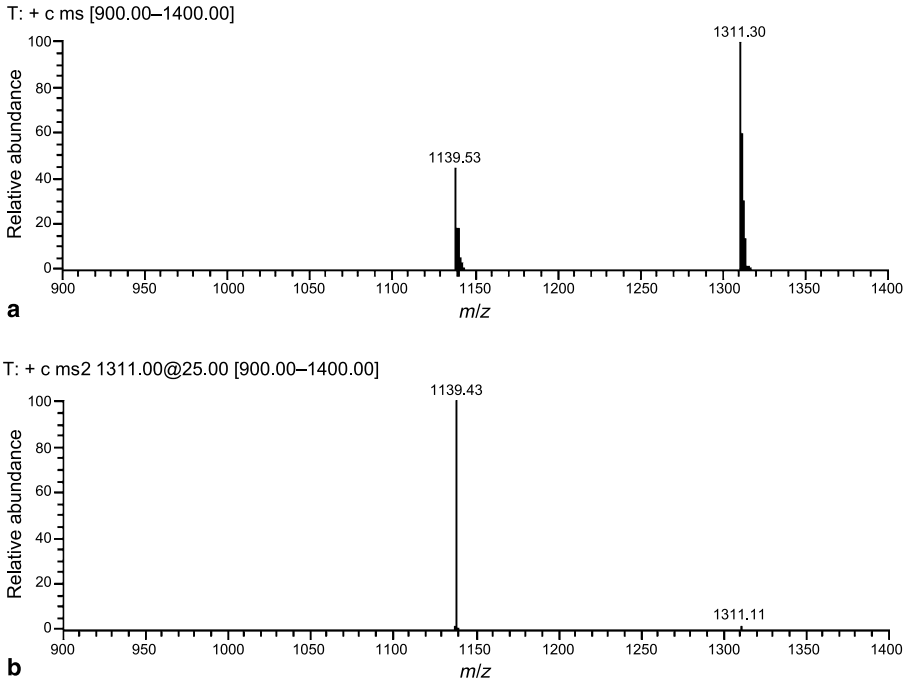

Fig. 1 ESI (+) mass spectra in the positive ion mode for (a) compound **1**; (b) ESI (+)-MS/MS of the ion of $m/z = 1311$

Results and discussion

In our work, we found that simply mixing *β-CD* with *N*-tosylimidazole in *DMF* did not result in an obvious reaction when heated at 60°C for 4 h. Carbonate buffer (*pH* 9.9) can efficiently promote the reaction. The reaction is highly regioselective at the 2-position, generating mainly monotosylate and a little ditosylates.

The optimized conditions for the synthesis of monotosylate are *β-CD*/*N*-sulfonylimidazole = 1/1 (mol/mol), *β-CD*/carbonate buffer = 1/6 (g/cm^3) at 60°C for 2 h. TLC demonstrated the formation of significant amounts of multitosylates under higher temperature and longer time.

The purity and structure were confirmed by TLC, ESI-MS, and NMR spectra. TLC on silica gel using *n*-butanol:ethanol:H_2O=5:4:3 (*v*/*v*) showed one spot at $R_f = 0.5$ for the product **1**. In the positive ion mode ESI-MS (Fig. 1), two peaks were observed at $m/z = 1139$ and 1311 corresponding to the monotosylate of *β-CD* ($M + Na^+$). MS/MS conformed that $m/z = 1139$ ion was produced from $m/z = 1311$ 1311 ion with the neutral loss of *Ts*OH. Those data indicated the product **1** was highly pure.

In conclusion, a convenient and economic method for the synthesis of mono-2-tosyl-*β*-cyclodextrin was developed, with the use of *N*-tosylimidazole in *DMF*-carbonate buffer solution in reasonable yield. The reaction does not require strict anhydrous or specific basic catalysts.

Experimental

NMR spectra were recorded on a Bruker AM-600 (^{1}H 600 and ^{13}C 150 MHz) in *DMSO*–d_6 solutions with *TMS* as a standard. The positive-ion ESI-MS^n 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 in Ref. [8]. 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 without further purification.

General experimental procedure

To a stirred solution of 2 g *β-CD* with one equiv of *N*-tosylimidazole in 60 cm^3 *DMF*, 12 cm^3 of 0.2 *M* carbonate buffer (*pH* 9.9) were added. The reaction mixture was heated at 60°C for 2 h. Then the mixture was neutralized with 1 *N* HCL, evaporated *in vacuo* to a volume of *ca.* 5, and 300 cm^3 acetone were added to precipitate cyclodextrin derivatives. The collected solid was subjected to a RP-18 column eluted with H_2O–*Me*OH; the eluent composition was gradually changed (*Me*OH–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 off, washed with acetone, and dried. Thus, 0.56 g pure **1** were obtained (28%). ^{1}H NMR

(600 MHz, *DMSO*–d_6): $\delta = 2.40$ (s, 3H), 3.23–3.80 (overlapping with HDO, m, 39H), 3.90 (t, 1H, $J = 8.3$ Hz), 4.05 (dd, 1H, $J = 10.0$, 3.3 Hz), 4.16 (d, 1H, $J = 3.6$ Hz), 4.40–4.49 (m, 7H), 4.83 (m, 7H), 5.62–5.73 (m, 10H), 5.76 (d, 1H, $J = 6.7$ Hz), 5.82 (d, 1H, $J = 6.2$ Hz), 5.85 (d, 1H, $J = 6.2$ Hz), 7.43 (d, 2H, $J = 8.2$ Hz), 7.84 (d, 2H, $J = 8.2$ Hz) ppm; ^{13}C NMR (150 MHz, *DMSO*–d_6): $\delta =$ 21.6, 60.2, 60.4, 69.8, 72.1, 72.3, 72.5, 72.7, 72.8, 72.9, 73.3, 73.4, 80.1, 81.3, 81.9, 82.0, 82.1, 98.6, 102.2, 102.4, 102.5, 128.5, 130.2, 133.3, 145.3 ppm. ^{1}H and ^{13}C NMR spectra were identical with the authentic mono-2-tosyl-β-cyclodextrin reported in Ref. [4].

Acknowledgements

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References

1. a) Breslow R (1994) Pure Appl Chem 66:1573; b) Breslow R (1995) Acc Chem Res 28:146; c) Breslow R, Dong SD (1998) Chem Rev 98:1997; d) Stainer CA, Alderman SJ, Claridge TD, Anderson HL (2002) Angew Chem Int Ed 41:1769; e) Hedges AR (1998) Chem Rev 98:2035; f) Uekama K, Hirayama F, Irie T (1998) Chem Rev 98:2045
2. a) D'Souza VT, Bender ML (1987) Acc Chem Res 20:146; b) Vanetten RL, Sebastian JF, Clowes GA, Bender ML (1967) J Am Chem Soc 89:3242
3. a) Yuan DQ, Tahara T, Chen WH, Okabe Y, Yang C, Yagi Y, Nogami Y, Fukudome M, Fujita K (2003) J Org Chem 68:9456; b) Khan AR, Forgo P, Stine KJ, D'Souza VT (1998) Chem Rev 98:1977
4. Ueno A, Breslow R (1982) Tetrahedron Lett 23:3451
5. a) Rong D, D'Souza VT (1990) Tetrahedron Lett 31:4275; b) Law H, Baussanne I, Garc Fernandez JM, Defaye (2003) J Carbohydr Res 338:451
6. a) Teranishi K, Watanabe K, Hisamatsu M, Yamada T (1998) J Carbohydr Chem 17:489; b) Teranishi K (2000) Chem Commun 1255; c) Teranishi K (2000) Tetrahedron Lett 41:7085; d) Teranishi K (2001) Tetrahedron Lett 42:5477
7. Yu H, Teramoto A, Fukudome M, Xie RG, Yuan DQ, Fujita K (2006) Tetrahedron Lett 47:8837
8. Hicks DR, Fraser Reid B (1974) Synthesis:203