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ORIGINAL PAPER

Direct aroylation of β-cyclodextrin on the secondary hydroxyl face: a convenient equilibrium-dependent preparation of mono-3-aroyl-β-cyclodextrin via C2-*O*-aroyl to C3-*O*-aroyl group migration

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Abstract A new and convenient method is presented for the preparation of mono-3-*O*-benzoyl-β-cyclodextrin by direct regioselective benzoylation of β-cyclodextrin using *N*-benzoylimidazole in carbonate buffer solution. This process involved equilibrium-dependent C2-*O*-aroyl to C3-*O*-aroyl group migration to improve the yield.

Keywords Cyclodextrin · Benzoylation · Isomerization · Equilibrium

Introduction

Cyclodextrins (CDs) are well-known macrocyclic oligosaccharides which have hollow truncated cone structures capable of forming inclusion complexes with a variety of organic molecules in aqueous solutions. They have attracted widespread interest as hosts for building supramolecular structures, and their derivatives have evolved into a versatile class of host molecules with applications in enzyme mimics, molecular recognition, drug delivery, and chiral discrimination, to mention a few [1–4].

In recent years, selective benzoylation of the C-6 hydroxyl groups has been extensively studied, and the obtained mono-6-*O*-benzoyl-β-CDs have been used as novel supramolecular photosensitizing hosts in photochirogenesis [5–11]. Since the more open secondary hydroxyl face of CDs is stated to be catalytically very important [12–15], benzoylations of this face are believed to produce valuable derivatives for asymmetry catalysis. However only very few reactions are known to introduce a single benzoyl group at the secondary hydroxyl face of CDs, especially at the 3 position, presumably because hydroxyl groups at the 3 position are the most inaccessible and difficult to be modified [16]. Hao et al. [17] benzoylated one of the C-3 hydroxyl groups with benzoyl chloride in alkaline acetonitrile solution, but the isolated yield was relatively low (16 %). Herein, we describe a new and convenient method for the preparation of mono-3-*O*-benzoyl-β-CD by direct benzoylation of β-CD using *N*-benzoylimidazole in a carbonate buffer solution, an equilibrium process which involved C2-*O*-aroyl to C3-*O*-aroyl group migration to improve the yield (Scheme 1).

Results and discussion

In previous work [18], we developed a simple and efficient method for direct regioselective benzoylation of a single C-2 hydroxyl group of β-CD, and found that its hydrolysis occurred via benzoyl group migration, i.e., the C-3 hydroxyl group of β-CD attacked the carbonyl carbon of the C2-*O*-benzoyl group. Therefore, mono-3-*O*-benzoyl-β-CD can be prepared through isomerization of the corresponding mono-C2-*O*-benzoyl isomer.

A mixture of β-CD, one molar equivalent of *N*-(*p*-methylbenzoyl)imidazole, and carbonate buffer in DMF was stirred at 60 °C for 2 h. The reaction regioselectively generated mono-3-*O*-(*p*-methylbenzoyl)-β-CD (**1**), mono-2-*O*-(*p*-methylbenzoyl)-β-CD, and multi-benzoates. The mixture of mono-C2-*O*-benzoyl and mono-C3-*O*-benzoyl isomers (**1**), isolated by a simple open reversed-phase

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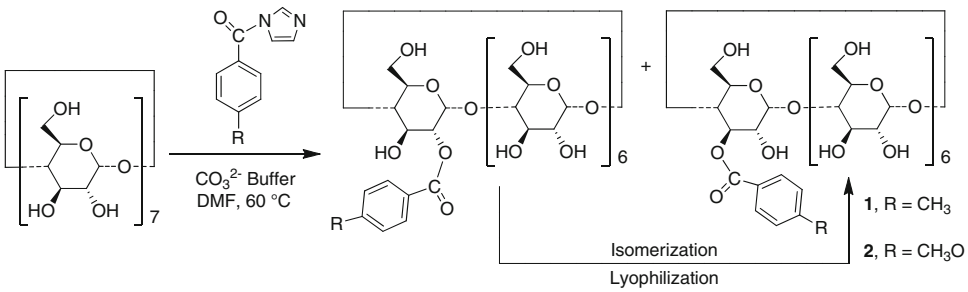
Scheme 1



column chromatography, was purified by preparative HPLC using 20 % aqueous MeOH as the eluent. The fractions containing the mono-C2-*O*-benzoyl isomer were concentrated under reduced pressure, dissolved in 20 % aqueous MeOH, heated at 50 °C for 1 h until the equilibrium of isomerization was established, and then purified by preparative HPLC. Through several isomerization and purification cycles, the mono-C3-*O*-benzoyl isomer (**1**) was obtained in good yield (39 %).

The structure of **1** was confirmed using ESI–MS and NMR spectra. Its ESI–MS spectrum exhibited the molecular ion $[M + Na]^+$ at $m/z = 1{,}275$. ^{13}C NMR spectroscopy is an effective technique for the analysis of cyclic oligosaccharides. Breslow [19] reported that aroylation of a hydroxyl group of CDs usually leads to a downfield chemical shift of the carbon carrying the hydroxyl (α carbon), but a small upfield chemical shift of the β carbon and a still smaller shift of the γ carbon. In the ^{13}C NMR spectra of **1**, the peak at $\delta = 78.5$ ppm (C-4′) clearly indicates that the substituent is at the 3 position of β-CD.

Using *N*-(*p*-methoxybenzoyl)imidazole as an aroylating reagent afforded **2** in 35 % yield.

In conclusion, mono-3-*O*-benzoyl-β-CD was prepared by direct benzoylation of β-CD on the secondary hydroxyl face using *N*-benzoylimidazole in carbonate buffer solution in good yield. The process involved an isomerization equilibrium, i.e., mono-2-*O*-benzoyl-β-CD was isomerized to the corresponding mono-3-*O*-benzoyl-β-CD. This benzoylation method can be highly useful for the preparation of other benzoates of β-CD as macrocyclic host molecules.

Experimental

Analytical and preparative HPLC column chromatographies were done using a Perkin-Elmer Series 200 HPLC system with a UV–Vis detector. A Kromasil 100-10-C18 column (4.6 mm × 250 mm) was used for the analytical HPLC, and a Zorbax SB-C18 column (10 mm × 250 mm) was used for preparative HPLC. NMR spectra were recorded on Bruker AM-600 spectrometer (^1H 600 MHz and ^{13}C 150 MHz) in DMSO-d_6 solutions with tetramethylsilane as 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). 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. *N*-Benzoylimidazole was prepared according to a literature procedure [20]. All other chemicals were of commercial grade and used without further purification.

General experimental procedure

To a stirred solution of 2 g β-CD (1.76 mmol) with one molar equiv. of *N*-benzoylimidazole in 60 cm^3 DMF, 12 cm^3 carbonate buffer (0.2 M, pH 9.9) was 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 cm^3, and 300 cm^3 of acetone was added to precipitate cyclodextrin derivatives. The collected solid was isolated on an open RP-18 column eluted with H_2O/MeOH (10–30 %) to give a mixture of mono-C2-*O*-benzoyl and mono-C3-*O*-benzoyl isomers. The mixture was dissolved in 70 cm^3 20 % aqueous MeOH, heated at 50 °C for 1 h, and then purified by preparative HPLC using 20 % aqueous MeOH as the eluent. The fractions containing the mono-C2-*O*-benzoyl isomer were evaporated in vacuo, dissolved in 30 cm^3 20 % aqueous MeOH, heated at 50 °C for 1 h, and purified by preparative HPLC. The processes were carried out twice, and all the fractions containing the mono-C3-*O*-benzoyl isomer were combined and lyophilized to give the pure mono-C3-*O*-benzoyl isomer.

Mono-3-O-(p-methylbenzoyl)-β-CD (**1**, $C_{50}H_{76}O_{36}$)
Yield 0.87 g (39 %); ESI–MS: $m/z = 1{,}275$ ($[M + Na]^+$); ^1H NMR (600 MHz, DMSO-d_6): $\delta = 2.35$ (s, 3H), 3.20–3.74 (m, 39H), 3.77 (t, 1H), 3.86 (br, 1H), 4.33–4.58 (m, 7H), 4.70–4.87 (m, 6H), 4.92 (d, 1H), 5.35 (t, 2H), 5.50–5.90 (m, 12H), 7.26 (d, 2H), 7.84 (d, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): $\delta = 21.5$, 60.4, 71.8, 72.2, 72.8, 73.1, 73.5, 75.1, 78.5 (C-4′), 81.7, 81.8, 82.0, 102.0, 102.2, 102.4, 128.9, 129.1, 129.9, 142.8, 166.1 ppm.

Mono-3-O-(p-methoxybenzoyl)-β-CD (**2**, $C_{50}H_{76}O_{37}$)
Yield 0.79 g (35 %); ESI–MS: $m/z = 1{,}291$ ($[M + Na]^+$); ^{1}H NMR (600 MHz, DMSO-d_6): $\delta = 3.20$–3.75 (m, 39H), 3.76 (t, 1H), 3.82 (s, 3H), 3.89 (br, 1H), 4.38–4.61 (m, 7H), 4.74–4.87 (m, 6H), 4.94 (d, 1H), 5.34 (t, 1H), 5.39 (br, 1H), 5.48–6.08 (m, 12H), 7.00 (d, 2H), 7.91 (d, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): $\delta = 55.8$, 60.4, 71.5, 71.9, 72.2, 72.5, 72.8, 73.1, 73.4, 75.0, 78.6 (C-4′), 81.8, 82.0, 82.1, 102.1, 102.3, 102.4, 113.9, 122.5, 131.9, 162.8, 165.8 ppm.

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