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ORIGINAL PAPER

Direct regioselective benzoylation of a single C-2 hydroxyl group of β-cyclodextrin and its hydrolysis via benzoyl group migration

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Abstract A simple and efficient method for the direct regioselective benzoylation of a single C-2 hydroxyl group of β-cyclodextrin was developed by using a combination of *N*,*N*′-carbonyldiimidazole and carbonate buffer in 1,4-dioxane, which does not require highly reactive reagents such as acyl chloride, or toxic solvents such as acetonitrile. Moreover, hydrolysis of the product was determined to occur via benzoyl group migration.

Keywords Cyclodextrin · Regioselective benzoylation · Benzoyl group migration · Hydrolysis

Introduction

Cyclodextrins (CDs) are well-known macrocyclic compounds consisting of six or more glucose units linked together by α-1,4 linkages to form torus-like structures, which possess the secondary C-2 and C-3 hydroxyl groups on their more open face and the primary C-6 hydroxyl groups on the other face. Owing to their hydrophobic and asymmetric interior, derivatives of CDs have evolved into a versatile class of host molecules with applications in artificial enzymes, biomimetic materials, drug delivery systems, and chiral reagents [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 widely used as novel supramolecular photosensitizing hosts in photochirogenesis [5–10]. However only very few examples are known of the introduction of a single benzoyl group at the secondary face of CDs. Regioselective benzoylation of a single C-2 hydroxyl group of β-CD is still difficult, because of the competitive reaction of the primary face and purification of the synthesized cyclodextrin derivatives [11]. Hao et al. [12] monoacylated β-CD on the secondary hydroxyl face with acyl chloride in alkaline acetonitrile solution, a method which involved a toxic solvent and a highly reactive reagent. Moreover, this reaction gave a mixture of C-2, C-3, and C-6 monoacylated derivatives.

Herein, we describe a simple and efficient method for the direct regioselective benzoylation of a single C-2 hydroxyl group of β-CD, and report that the product's hydrolysis occurs via benzoyl group migration (Scheme 1).

Results and discussion

In previous work, we found that carbonate buffer (pH 9.9) can efficiently activate the C-2 OH of β-CD in a 1:1 mixture of 1,4-dioxane/water, and regioselectively promote reactions at the 2-position [13, 14]. *N*,*N*′-Carbonyldiimidazole is a useful, general carboxylic acid-activating reagent [15], and the only by-products are carbon dioxide and imidazole ($pK_A = 6.80$) which, being a relatively weak base, is unlikely to cause a distinct change of pH value of the reaction system. Therefore, mono-2-*O*-(*p*-methylbenzoyl)-β-CD (**1**) and mono-2-*O*-(*p*-methoxybenzoyl)-β-CD (**2**)

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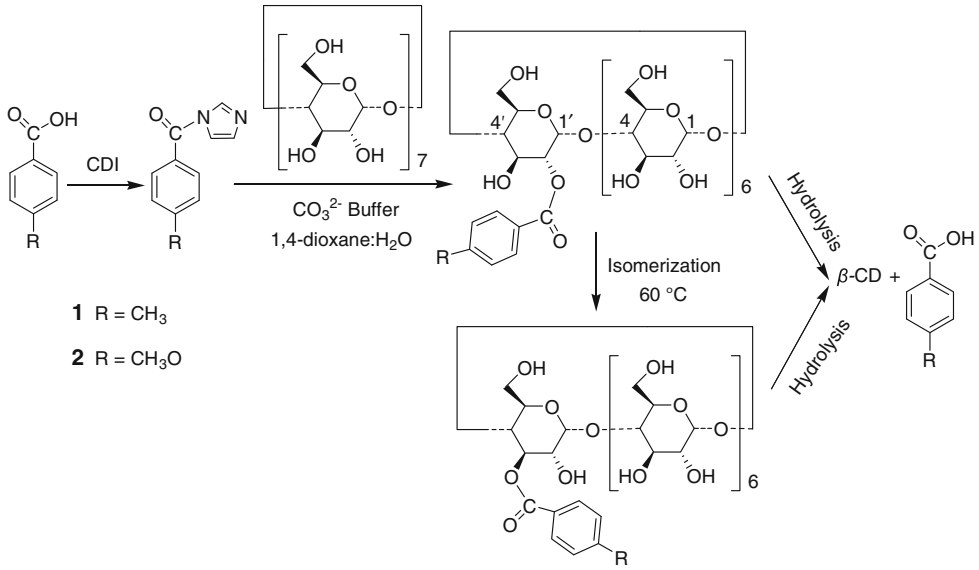
Scheme 1



were prepared in a simple, two-step sequence via a one-pot reaction. In the first step, on the basis of TLC analysis, the reactions between aromatic acids and *N*,*N*′-carbonyldiimidazole were quantitative in 1,4-dioxane within 2 h at room temperature. In the second step, the couplings of benzoyls to the C-2 hydroxyl group of *β*-CD were accomplished in the carbonate buffer at 50 °C for 1 h. ESI–MS demonstrated that the contents of the crude products were monobenzoate, dibenzoates, tribenzoates, and a little of the tetrabenzoates.

The structure of **1** was characterized by ESI–MS and NMR spectra. Its ESI–MS spectrum exhibited the molecular ion $[M + Na]^+$ at $m/z = 1{,}275$ (Fig. 1a). ^{13}C NMR spectroscopy is an effective technique for the analysis of cyclic oligosaccharides. As elegantly explained by Breslow [16], usually, arylation of a hydroxyl group of CDs 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 an even smaller shift of the *γ*-carbon. As shown in Fig. 2a, the ^{13}C NMR spectrum of **1** has a peak at $\delta = 98.6$ ppm (C-1′); this, together with the lack of change in the shift of C-6 of the substituted glucose unit with respect to unsubstituted glucose units, indicates that the benzoyl substituent is at the 2-position and not the 6- or 3-positions of *β*-CD.

In the preliminary hydrolysis experiment of **1** (Fig. 1), initially, the positive ion mode ESI–MS spectrum exhibited only one molecular ion $[M + Na]^+$ at $m/z = 1{,}275$. After 1 h at 60 °C in 20% aqueous MeOH, two peaks were observed at $m/z = 1{,}275$ and 1,157. As shown in Fig. 2, a new peak appeared at $\delta = 78.5$ ppm in the corresponding ^{13}C NMR spectra; this peak indicated that the *p*-methylbenzoyl group was attached to the C-3 hydroxyl group of *β*-CD [16]. Therefore, **1** was partly isomerized to the corresponding mono-3-*O*-(*p*-methylbenzoyl)-*β*-CD. Similar

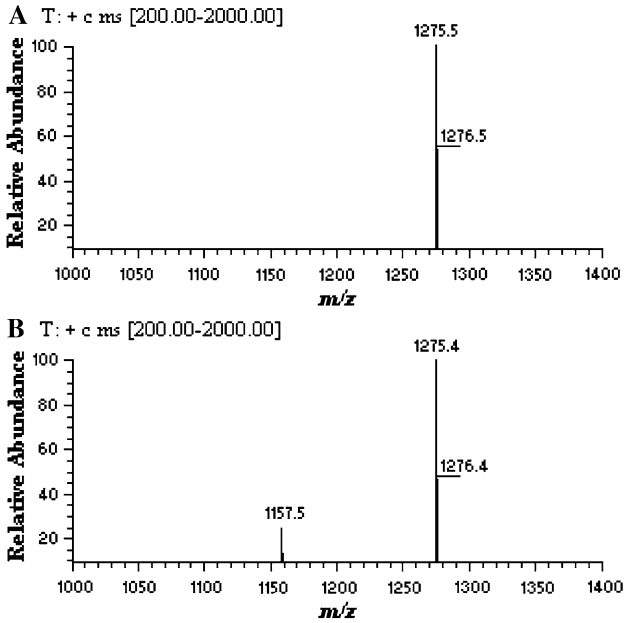


Fig. 1 ESI(+) mass spectra of **1** initially (**a**) and after being heated at 60 °C for 1 h (**b**)

results were obtained using *p*-methoxybenzoic acid as the reaction reagent, as shown in Figs. 3 and 4.

On the basis on the above facts, ester hydrolysis occurred via benzoyl group migration, i.e., the C-3 hydroxyl group of *β*-CD attacked the carbonyl carbon of the adjacent benzoyl group, which resulted in isomerization.

In conclusion, a simple and efficient method for the direct regioselective benzoylation of a single C-2 hydroxyl group of *β*-CD was developed by using the combination of *N*,*N*′-carbonyldiimidazole and carbonate buffer in 1,4-dioxane, which does not require highly reactive reagents

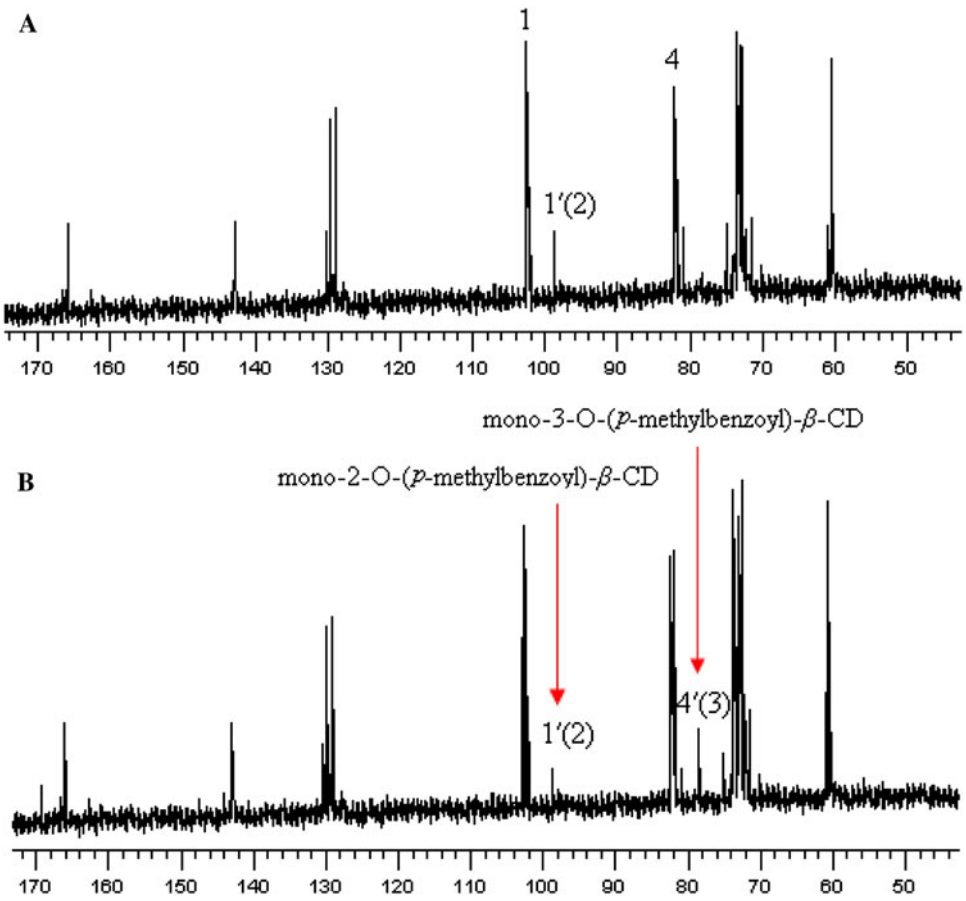


Fig. 2 ^{13}C NMR (150 MHz) spectra of **1** initially (**a**) and after being heated at 60 °C for 1 h (**b**). The *numbers* indicate the peak assignments

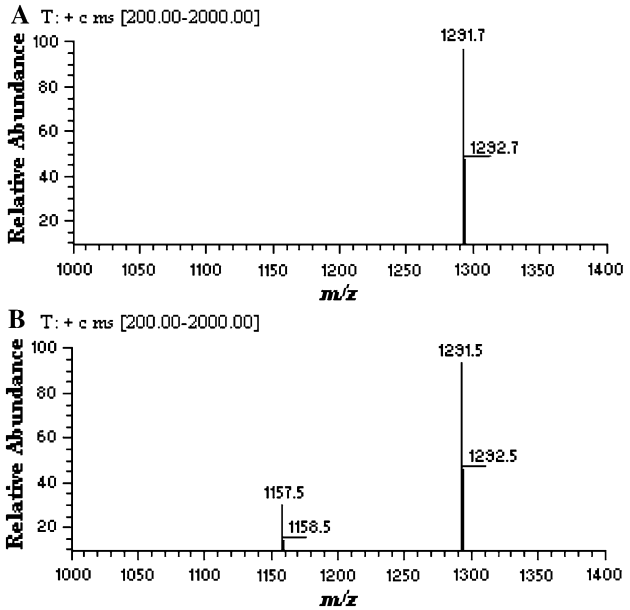


Fig. 3 ESI(+) mass spectra of **2** initially (**a**) and after being heated at 60 °C for 1 h (**b**)

such as acyl chloride, or toxic solvents such as CH_3CN. In addition, hydrolysis of the product occurred via benzoyl group migration.

Experimental

Preparative HPLC separations were carried out with a Perkin-Elmer Series 200 HPLC system equipped with a UV/Vis detector and a ZORBAX SB-C18 column (10 × 250 mm). 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. All other chemicals were of commercial grade and were used without further purification.

General experimental procedure

To a solution of 2.65 mmol aromatic acid in 20 cm^3 anhydrous 1,4-dioxane, 1.2 equivalents of *N*,*N*′-carbonyldiimidazole (CDI) was added at room temperature. After stirring for 2 h, 1.76 mmol β-CD and 20 cm^3 of 0.2 M carbonate buffer (pH 9.9) were added. The reaction mixture was heated at 50 °C for 1 h. Then the mixture was

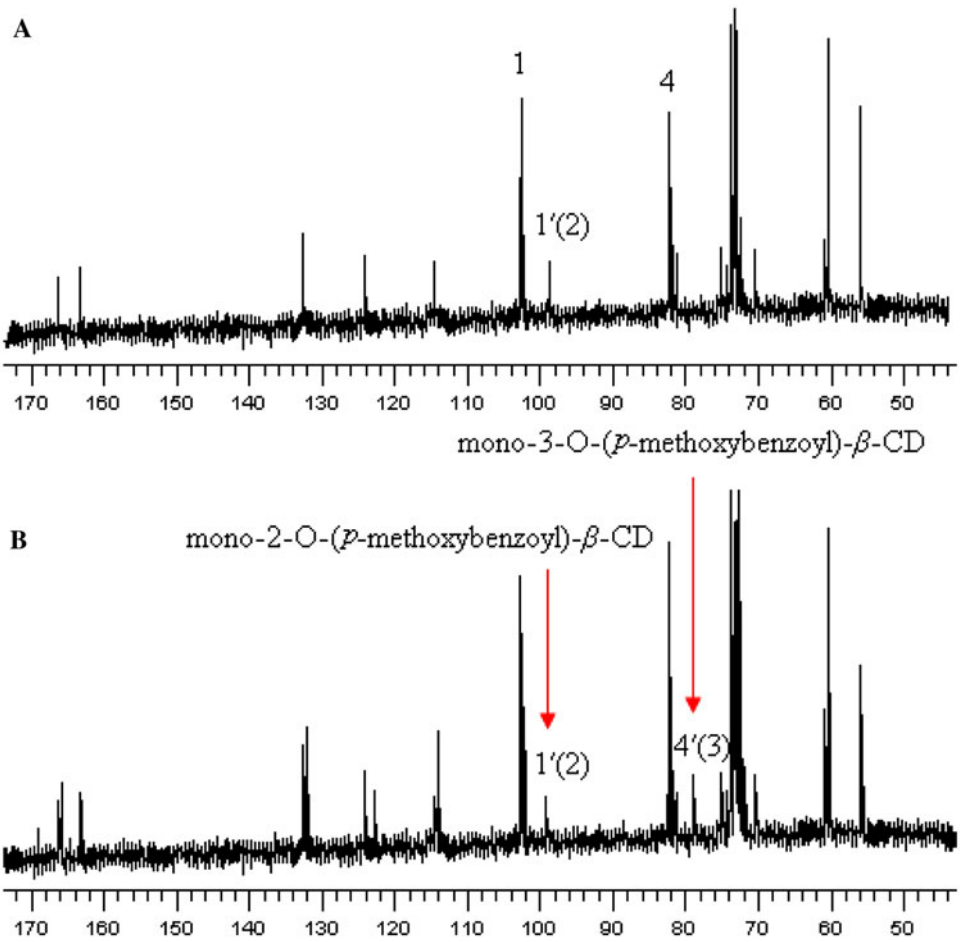


Fig. 4 ^{13}C NMR (150 MHz) spectra of **2** initially (**a**) and after being heated at 60 °C for 1 h (**b**). The *numbers* indicate the peak assignments

neutralized with 1 M HCl, evaporated in vacuo to a volume of ca. 5 cm^3, and 300 cm^3 acetone was added to precipitate the cyclodextrin derivatives. The crude products were separated by preparative HPLC using 20% aqueous MeOH as eluent, collected, and lyophilized.

Mono-2-O-(p-methylbenzoyl)-β-cyclodextrin (**1**, $C_{50}H_{76}O_{36}$)
Yield 0.27 g (12%); ESI–MS: m/z = 1,275 ($[M + Na]^+$); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 2.36 (s, 3H), 3.22–3.73 (m, 39H), 3.76 (t, 1H), 3.85 (br, 1H), 4.32–4.60 (m, 7H), 4.72–4.85 (m, 6H), 4.89 (d, 1H), 5.17 (d, 1H), 5.34 (t, 1H), 5.53–5.90 (m, 12H), 7.28 (d, 2H), 7.95 (d, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 21.6, 60.4, 71.4, 71.8, 72.5, 73.0, 73.4, 75.0, 80.9, 81.8, 82.0, 98.7 (C-1′), 102.0, 102.3, 102.4, 129.1, 129.5, 130.2, 143.1, 166.3 ppm.

Mono-2-O-(p-methoxybenzoyl)-β-cyclodextrin (**2**, $C_{50}H_{76}O_{37}$)
Yield 0.41 g (18%); ESI–MS: m/z = 1,291 ($[M + Na]^+$); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.20–3.74 (m, 39H), 3.77 (t, 1H), 3.83 (s, 3H), 3.88 (br, 1H), 4.39-4.70 (m, 7H), 4.75–4.86 (m, 6H), 4.90 (d, 1H), 5.16 (d, 1H), 5.39 (t, 1H), 5.50–6.00 (m, 12H), 7.01 (d, 2H), 8.03 (d, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 55.9, 60.6, 70.1, 71.5, 72.2, 72.6, 72.8, 73.0, 73.5, 74.9, 81.1, 81.8, 82.0, 98.8 (C-1′), 102.0, 102.3, 102.4, 114.1, 123.8, 132.3, 162.9, 166.0 ppm.

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