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An efficient synthetic-route to prepare [2,3,6-tri-*O*-(2-bromo-2-methylpropionyl]-β-cyclodextrin)

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Abstract—The efficient approach for the synthesis of [2,3,6-tri-*O*-(2-bromo-2-methylpropionyl]-β-cyclodextrin) (21Br-β-CD) is described. The reaction between 2-bromoisobutyric bromide and β-cyclodextrin was performed directly in 1-methyl-2-pyrrolidione solvent, leading to much less complicated procedures and higher yield (up to 89.5%) compared with those reported previously (17% yield). The product is an extremely useful initiator in synthesizing star polymers with well-defined structures using atom transfer radical polymerization for biomedical applications.

1. Introduction

Star-like polymers have attracted enormous research interest in the past decade due to their unique solution and solid-state properties: Star polymers provide most of the properties of high molecular weight materials without the solution viscosity penalty of linear materials of similar molecular weight.[1] Living polymerization, atom transfer radical polymerization (ATRP) in particular, has been extensively used for the synthesis of star polymers through either a core-first method or an arm-first approach. In the arm-first method, monofunctional and living linear macromolecules are initially synthesized. The star is then formed either through the cross-linking by a difunctional comonomer during propagation[2] or by the connecting of a precise number of arms with a multifunctional terminating agent.[3] In contrast, in the core-first method, star polymers are made with a multifunctional initiator to induce the growth of the arms, which has been employed successfully to acquire well-defined stars with a discrete number of arms. For instance, several styrenic and (meth)acrylic star polymers have been prepared by the living radical polymerization using the multifunctional core of initiators such as cyclotriphosphazenes, cyclosiloxanes, and organic polyols.[4]

Star polymers have branches radiating from a central core that could be one atom, a small molecule, or a volume of material. β-Cyclodextrin (β-CD) is a cyclic oligosaccharide consisting of seven glucose units linked by α-1,4-glucosidic bonds. It has a specific steric structure of truncated conical shape with 1.53 and 0.78 nm of outer and inner periphery diameter, respectively.[5] The 21 substitutable hydroxyl groups on the outside surface of β-CD provide the possibility to make a core with 21 initiation sites for forming star polymers with 21 arms. In order to utilize ATRP to synthesize star polymers using β-CD as cores, it is essential to introduce halogens into the cyclodextrin.

Ohno et al.[6] first reported a β-CD initiator with 21 ATRP initiation sites and synthesized several neutral star polymers in an organic solvent. With the β-CD-based initiator, up to 21 arms could be created in star polymers. For the conventional star polymers, however, the number of arms is rarely greater than four. However, the synthetic route proposed by Ohno et al. was complicated and the yield was also low: the final yield of [2,3,6-tri-*O*-(2-bromo-2-methylpropionyl]-β-cyclodextrin) (i.e., 21Br-β-CD) through the reaction between β-CD and 2-bromoisobutyric anhydride only reached 17%. In view of previous reports using 2-bromopropionyl bromide or 2-bromoisobutyl bromide to directly modify the compounds containing hydroxyl groups to produce multifunctional initiators,[7,8] it appears to be feasible to synthesize the 21Br-β-CD directly with 2-bromoisobutyl bromide.

Keywords: 21Br-β-cyclodextrin; ATRP initiator; Star polymer.
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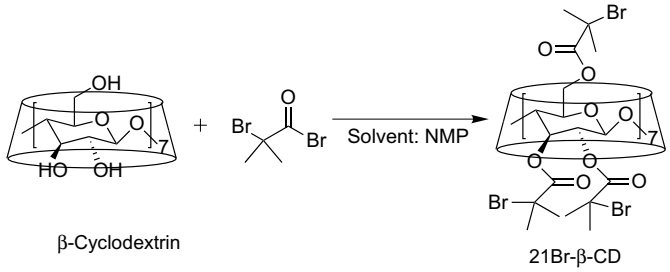


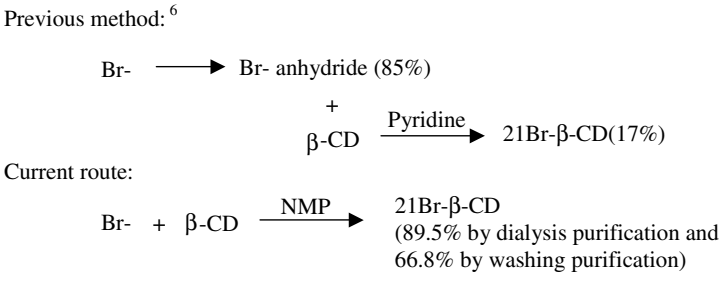
Scheme 1. Synthesis of 21Br-β-CD.

In this work, we developed a simplified route to synthesize the 21Br-β-CD initiator through reacting 2-bromoisobutyric bromide with β-cyclodextrin directly in 1-methyl-2-pyrrolidione solvent (see Scheme 1). The challenge lies on the solvent used for the synthesis. Pyridine is a good solvent for cyclodextrin, but it is immiscible with 2-bromoisobutyl bromide, inducing the precipitation observed in our trial experiments. As a result, the reaction yield was reduced significantly. The similar precipitation was also reported elsewhere[7] when 2-bromopropionyl bromide was used, and the precipitate was pyridine–HBr. In the work performed by Ohno et al.[6] the precipitation was avoided by replacing 2-bromoisobutyl bromide with 2-bromoisobutyric anhydride, which eliminated the formation of HBr when the anhydride reacted with β-CD, thus resulting in no pyridine–HBr precipitate. Alternatively, the problem can be solved if an appropriate solvent for β-CD is identified. The solvent is expected to be compatible with both 2-bromoisobutyl bromide and small amounts of HBr. 1-methyl-2-pyrrolidione (NMP) is one of such solvents. In this work, we focused on using NMP as solvent or reaction medium for the reaction between 2-bromoisobutyl bromide and β-CD. The results indicated that 21Br-β-CD was obtained at high yield: up to 89.5% based on dialysis purification and 66.8% according to the conventional washing purification. The process and yield comparisons between our current work and the previous research[6] are shown in Scheme 2. The 21Br-β-CD obtained is white powder, which is moderately soluble in aqueous solution and highly soluble in most organic solvents, including ether, toluene and dichloromethane. The aqueous solubility is extremely valuable in preparing water-soluble star polymers for various biomedical applications.

From the viewpoints of simple operation and effective yield, the present route provides a novel approach for the synthesis of 21Br-β-CD.

2. Synthesis of heptakis[2,3,6-tri-*O*-(2-bromo-2-methylpropionyl]-β-cyclodextrin) (21Br-β-CD)

β-CD (3.41 g, 3 mmol, vacuum dried at 80 °C over phosphorus pentoxide overnight immediately before use) was dissolved in 30 mL anhydrous 1-methyl-2-pyrrolidione (NMP) and was cooled to 0 °C. 2-bromoisobutyryl bromide (29.0 mL, 126 mmol) dissolved in anhydrous NMP (15 mL) at 0 °C was then added dropwise to the β-CD solution with magnetic stirring. The reaction temperature was maintained at 0 °C for 2 h and then allowed to rise slowly to ambient temperature after which the reaction was allowed to continue for 18 h. The brown solution obtained was concentrated in a vacuum oven for 24 h. There are two optional methods in purifying the concentrated syrup: (1) directly purify the syrup by dialysis (Spectra/Por dialysis membrane, MWCO 1000, Spectrum Laboratories Inc.) against distilled and de-ionized water, refreshing the water every 2 h for a period of 24 h. The pale yellow product obtained was concentrated in a vacuum oven and then crystallized in cold *n*-hexane to obtain a white precipitate (11.45 g, yield 89.5%); (2) dilute the syrup with 50 mL dichloromethane, and then wash sequentially with saturated $NaHCO_3$ aqueous solution (2×100 mL) and water (2×100 mL). The organic layer obtained was concentrated in a vacuum oven and then crystallized in cold *n*-hexane to produce a white precipitate (8.54 g, yield 66.8%). The structure of 21Br-β-CD was confirmed using: FTIR (zinc selenide): 2931 cm^{-1}



Scheme 2. Process and yield comparisons between the current work and the previous research in synthesizing 21Br-β-CD. Br–: 2-bromoisobutyric bromide; Br–anhydride: 2-bromoisobutyryl anhydride.

(ν_{C-H}), 1737 cm^{-1} ($\nu_{C=O}$), 1158 cm^{-1} (ν_{C-O-C}), 1039 and 1105 cm^{-1} (coupled ν_{C-C} and ν_{C-O}); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.2–2.2 (126H, CH_3), 3.5–5.5 (49H, residues of β-CD); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 30.8–31.3 (α-CH_3), 56.4 (C–Br), 64.0, 69.9–73.6, 74.4, 80.5, 98.6 (residues of β-CD), 171.3 (C=O). The characteristic peaks of the 21Br-β-CD synthesized in the current work appear to be identical with those reported by Ohno et al.[6]

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