An Improved and Alternative Method for the Preparation of Per(6-bromo-6-deoxy)cyclodextrins

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Received 12 August 2011; revised 31 August 2011

Dedicated to Professor Biao Yu, Shanghai Institute of Organic Chemistry, on the occasion of his 45th birthday and in recognition of his brilliant contributions to glycochemistry

Abstract: A practical and efficient approach to the regioselective synthesis of per(6-bromo-6-deoxy)cyclodextrins is described. The method utilizes the easily accessible (chloro(phenylthio)methylene)dimethylammonium chloride (CPMA), circumventing disadvantages of earlier protocols.

Key words: regioselective bromination, cyclodextrins, CPMA

α-Cyclodextrin, β-cyclodextrin, and γ-cyclodextrin are natural oligomers consisting of six, seven, and eight D-glucopyranose residues, respectively, linked by α-1,4-glycosidic bonds into a macrocycle. Currently, there is increasing interest in modified cyclodextrins for applications in the areas of supramolecular chemistry and materials science. Through modification, cyclodextrins become effective templates for the generation of a wide range of molecular hosts.[1] Per(6-bromo-6-deoxy)cyclodextrins, in particular, have emerged as a typical class of fascinating modifiers and significant precursors suitable for further synthetic transformations. Other derivatives of cyclodextrins, in which all primary hydroxy groups are replaced by such important functionalities as azido,[2] amino,[3] and thiol groups,[2b] may be efficiently synthesized from the perbrominated cyclodextrins. All of these monofacially substituted analogues function not only as scaffolds of diverse multivalent systems of biologically active compounds,[4] but also as supramolecular building blocks[5] and drug delivery systems.[6]

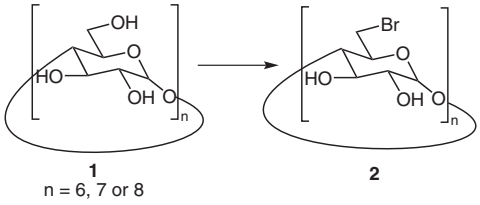
A common approach for perbromination on the primary side is the treatment of cyclodextrins with traditional brominating reagents such as $MeSO_2Br$,[7] the Vilsmeier–Haack reagent,[2b,8] and Ph_3P–NBS[9] in *N*,*N*-dimethylformamide under prolonged heating. These reagents, however, suffer from many practical drawbacks. $MeSO_2Br$ is usually inaccessible due to its high price and strong toxicity. The Vilsmeier salt is quite sensitive to moisture and comparatively difficult to handle; in particular, its relatively poor shelf life necessitates the prompt, fresh preparation prior to use. Furthermore, the removal of excess Vilsmeier salt from the reaction system requires a large amount of a strong base, such as sodium methoxide, in the workup. The use of triphenylphosphine is associated closely with the inconvenience of generating stoichiometric triphenylphosphine oxide as byproduct. To circumvent these problems and to establish the regioselective substitution at the C-6 position of the glucose repeat units as a general methodology, a facile, robust, and mild alternative to per(6-bromo-6-deoxy)cyclodextrins is required.

A recent methodology revealed that (chloro(phenylthio)methylene)dimethylammonium chloride (CPMA), a readily accessible reagent, can mildly and selectively halogenate primary hydroxy groups in the presence of unprotected secondary hydroxy groups.[10] The protocol led us to envisage that the reactions of free carbohydrate derivatives such as cyclodextrins with the reagent may produce 6-deoxyhalocyclodextrins. Here, we report a mild and regioselective procedure for the efficient conversion of cyclodextrins into per-6-brominated derivatives.

In our study, bis(trichloromethyl) carbonate (BTC), instead of phosgene, was adopted due to its higher safety in the preparation of CPMA. CPMA, which was easily prepared on large scale, was further demonstrated to be a stable solid reagent. We observed that the halogenating reagent (2.0 equiv per glucose unit) reacted with β-cyclodextrin (**1**, n = 7) in the presence of tetrabutylammonium bromide (2.0 equiv per glucose unit) in anhydrous *N*,*N*-dimethylformamide to afford per(6-bromo-6-deoxy)-β-cyclodextrin (**2**, n = 7) in a good yield. This protocol also led to efficient and total bromination at the C-6 position when applied to α- or γ-cyclodextrin (Scheme 1). The reactions smoothly proceeded at room temperature without heating. No undesired byproducts could be detected by ^1H and ^{13}C NMR spectroscopy. Tetrabutylammonium bromide and the resulting thiocarbamate in the reactions are highly soluble in acetone so that they can be conveniently washed out. During the workup of products, no base such as sodium methoxide was required. The pure products can be isolated from the reaction mixture by evaporation of the solvent and subsequent simple filtration and washing. No chromatography or crystallization is necessary, thus this protocol is potentially applicable to the wholesale preparation of per(6-bromo-6-deoxy)cyclodextrins.

In conclusion, a novel method based on an accessible, shelf stable, and efficient reagent for selectively perbro-

SYNTHESIS 2011, No. 22, pp 3612–3614
Advanced online publication: 26.09.2011
DOI: 10.1055/s-0030-1260241; Art ID: H80011SS



Scheme 1 *Reagents and conditions*: CPMA, TBAB, DMF, r.t., >90%.

minating the primary face of cyclodextrins has been described. The practicable protocol allows for the production of large amounts of the title compounds, which are versatile building blocks in cyclodextrin chemistry.

The α-, β-, and γ-cyclodextrins were recrystallized from water and dried over P_2O_5 under reduced pressure in a drying pistol at 110 °C prior to use. All the reagents and solvents were commercial products and used as received, unless otherwise noted. DMF was distilled over CaH_2 prior to use. TLC was performed on precoated plates of silica gel 60 F_{254} using EtOAc–*i*-PrOH–concd aq NH_3–H_2O (1:5:3:1) as eluent; visualization of spots was effected by charring with 20% (v/v) H_2SO_4 in EtOH. Optical rotations were measured with a JASCO DIP-370 digital polarimeter, using a sodium lamp (λ = 589 nm) at 20 °C. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer at 400 MHz in DMSO-d_6 with references at δ = 2.49 ppm and 39.50 ppm (DMSO), or in $CDCl_3$ with references at 7.26 ppm ($CHCl_3$) and 77.0 ppm ($CDCl_3$), respectively. High-resolution mass spectra (HRMS) were recorded on a Bruker APEX II mass spectrometer using electrospray ionization (ESI).

Per(6-bromo-6-deoxy)cyclodextrins 2; General Procedure

To a soln of CPMA (2 equiv per glucose unit) in anhyd DMF (100 mL) was added freshly dried α-, β-, or γ-cyclodextrin (**1**, n = 6, 7, or 8; 4 mmol) and anhyd TBAB (2 equiv per glucose unit) with stirring at r.t. After the reaction was complete, as monitored by TLC, DMF was removed under reduced pressure and the resulting residue was poured into sat. Na_2CO_3 soln (100 mL); the reaction mixture was allowed to stir for another 1 h. Addition of cold acetone (200 mL) gave a precipitate which was collected by filtration and exhaustively washed with H_2O and acetone to yield **2** as a white solid.

Hexakis(6-bromo-6-deoxy)-α-cyclodextrin (2, n = 6)

Yield: 5.2 g (96%).

$[\alpha]_D^{20}$ +97.4 (*c* 1.0, DMF); R_f = 0.53.

^{1}H NMR (DMSO-d_6): δ = 3.34 (d, *J* = 8.8 Hz, 12 H, H-6), 3.59–3.67 (m, 12 H, H-2, H-4), 3.80 (t, *J* = 8.4 Hz, 6 H, H-3), 3.99 (d, *J* = 10.0 Hz, 6 H, H-5), 4.95 (s, 6 H, H-1), 5.86 (s, 6 H, OH-3), 5.98 (d, *J* = 8.0 Hz, 6 H, OH-2).

^{13}C NMR (DMSO-d_6): δ = 102.59 (C1), 85.10 (C4), 72.76 (C3), 72.53 (C2), 71.49 (C5), 34.88 (C6).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{36}H_{54}O_{24}NaBr_6$: 1366.8003; found: 1366.8049.

Heptakis(6-bromo-6-deoxy)-β-cyclodextrin (2, n = 7)

Yield: 5.8 g (92%).

$[\alpha]_D^{20}$ +91.2 (*c* 1.0, DMF); R_f = 0.71.

^{1}H NMR (DMSO-d_6): δ = 3.34 (d, *J* = 10.0 Hz, 14 H, H-6), 3.59–3.66 (m, 14 H, H-2, H-4), 3.86 (t, *J* = 8.4 Hz, 7 H, H-3), 3.99 (d, *J* = 10.0 Hz, 7 H, H-5), 4.95 (s, 7 H, H-l), 5.88 (s, 7 H, OH-3), 5.98 (d, *J* = 8.0 Hz, 7 H, OH-2).

^{13}C NMR (DMSO-d_6): δ = 102.58 (C1), 85.10 (C4), 72.75 (C3), 72.52 (C2), 71.47 (C5), 34.91 (C6).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{42}H_{63}O_{28}NaBr_7$: 1590.7687; found: 1590.7724.

Octakis(6-bromo-6-deoxy)-γ-cyclodextrin (2, n = 8)

Yield: 6.8 g (95%).

$[\alpha]_D^{20}$ +113.6 (*c* 1.0, DMF); R_f = 0.60.

^{1}H NMR (DMSO-d_6): δ = 3.35 (s, 16 H, H-6), 3.61–3.62 (m, 16 H, H-2, H-4), 3.79 (s, 8 H, H-3), 3.96 (d, *J* = 10.0 Hz, 8 H, H-5), 4.94 (s, 8 H, H-1), 5.85 (s, 8 H, OH-3), 5.97 (d, *J* = 5.6 Hz, 8 H, OH-2).

^{13}C NMR (DMSO-d_6): δ = 102.60 (C1), 85.12 (C4), 72.79 (C3), 72.55 (C2), 71.52 (C5), 34.88 (C6).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{48}H_{72}O_{32}NaBr_8$: 1814.7371; found: 1814.7428.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This work was financially supported by the Fundamental Research Funds for Lanzhou University (lzujbky-2009-27 and lzujbky-2011-136).

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