

## A Facile Synthesis of $\beta$ -Cyclodextrin Monoaldehyde

Jing HU<sup>1</sup>, Cheng Feng YE<sup>1</sup>, Yong De ZHAO<sup>2,\*</sup>, Jun Biao CHANG<sup>2</sup>, Rui Yun GUO<sup>2</sup>

<sup>1</sup>Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences  
Lanzhou 730000

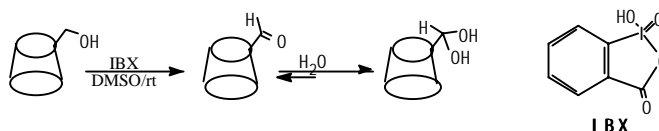
<sup>2</sup>Henan Institute of Chemistry, Zhengzhou 450002

**Abstract:**  $\beta$ -Cyclodextrin ( $\beta$ -CD) was directly oxidized in high yield to the corresponding monoaldehyde by cyclized 2-iodoxybenzoic acid (IBX) in DMSO.

**Keywords:** Cyclodextrin, oxidant, aldehyde.

Cyclodextrins and their derivatives have played important roles in such diverse fields as chiral separation, artificial enzymes, asymmetric synthesis and drug delivery<sup>1</sup>. The cyclodextrin monoaldehyde is a newly developed intermediate to synthesize novel derivatives through reductive amination in the presence of sodium cyanoborohydride<sup>2</sup>. The reported synthesis of cyclodextrin monoaldehyde involved the oxidation of  $\beta$ -CD monotosylate by DMSO in the presence of collidine or diisopropylethylamine<sup>3-4</sup>, or direct oxidation of  $\beta$ -CD with Dess-Martin periodinane (DMP)<sup>5</sup>. The latter method was encouraging on account of high yield and mild conditions. But long-term exposure to atmospheric moisture DMP resulted in hydrolysis to form monoacetylated product while the cyclized 2-iodoxybenzoic acid (IBX) was very stable and easily prepared<sup>6</sup>. On the other hand, Frigerio pointed out that IBX was also a mild oxidant for alcohols and 1, 2-diols in DMSO<sup>7</sup>. So we try to use IBX in place of DMP for the selective monooxidation of  $\beta$ -CD, and fortunately, met with success. (**Figure 1**)

**Figure 1.**



**General procedure.** To 0.5g dry  $\beta$ -CD in 4 ml DMSO in a stoppered flask 6 ml DMSO containing 1.3 eq. IBX<sup>8</sup> was added, allowed to react for 145 minutes, then 250 ml acetone was added. After filtration, the precipitate was dissolved in water, stirred for 1 hour, the white precipitate was removed by filtration. Lyophilization of the filtrate afforded the desired product. Yield was routinely better than 80%.

The time-based 400 MHz  $^1\text{H-NMR}$  shows the oxidation of  $\beta$ -CD by 1.3 equivalent IBX in  $\text{DMSO-d}_6$ . After 45 min, the characteristic single signal of the formyl proton is observed at  $\delta$  9.69 and a one C-5 proton doublet at  $\delta$  4.19 appears. At the same time, a new signal of an anomeric proton at  $\delta$  4.93 appears at the expense of signal at  $\delta$  4.83. After 145 min, the ratio of these two signals is about 1:6, indicative of monooxidation. This is consistent with the observations with Bieniarz<sup>5</sup>.

Notably, addition of a small amount of  $\text{D}_2\text{O}$  to the mixture, the formyl signal disappears and a new signal appears at  $\delta$  5.10, indicative of the conversion of  $\beta$ -CD to covalent hydrate.

Also, we discovered that the reaction time had a close relationship with the content of crystalline water of  $\beta$ -CD, which can accelerate the reaction. With longer reaction time or larger excess of the oxidant, the monoaldehyde product would be contaminated by di- and trialdehyde as evidenced by additional signals at  $\delta$  9.52 and  $\delta$  9.84 in  $^1\text{H-NMR}$ . So we suggest that the oxidation reaction be monitored by  $^1\text{H-NMR}$  for the exclusive formation of cyclodextrin monoaldehyde.

## References and notes

1. M. L. Bender and M. Komiyama, *"Cyclodextrin Chemistry"*, Springer-Verlag: New York, **1978**.
2. T. Carofiglio, R. Fornasier, G. Gennari, V. Lucchini, L. Simonato and U. Tonellato, *Tetrahedron Lett.* **1997**, 38 (45), 7919.
3. J. B. Huff and C. Bieniarz, *J. Org. Chem.* **1994**, 59, 7511.
4. J. Yoon, S. Hong, K. A. Martin and A. W. Bieniarz, *J. Org. Chem.* **1995**, 60, 2792.
5. M. J. Cornwell, J. B. Huff and C. Bieniarz, *Tetrahedron Lett.* **1995**, 36 (46) 8371.
6. D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.* **1991**, 113, 7277.
7. M. Frigerio and M. Santagostino, *Tetrahedron Lett.* **1994**, 35 (43), 8019.
8. IBX: 1-hydroxy-1, 2-benziodoxol-3 (1H)-one 1-oxide, prepared according to Dess-Martin procedure (ref.6), but further rinsed with anhydrous ether following the ethanol washings. m. p. 228-232°C (ref.6: 232-233°C)  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ) 7.84 (1H, t), 8.01 (2H, q), 8.14 (1H, d). Caution! IBX was reported to be explosive under impact or heating to  $>200^\circ\text{C}$ .

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