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Highly Selective Oxidative Cleavage of β-Cyclodextrin−Epoxide/Aziridine Complexes with IBX in Water†

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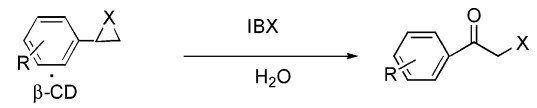
Abstract: Water, an environmentally friendly reaction medium, has been utilized for the reaction of IBX with various epoxides **1** and aziridines **2** as their β-cyclodextrin complexes to afford for the first time α-hydroxyketones **3** and α-aminoketones **4**, respectively.

In our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins,[1] we have been exploring the direct synthesis of α-hydroxyketones and α-aminoketones from the easily accessible and inexpensive epoxides and aziridines, respectively, using a mild and environmentally friendly oxidizing agent with water as a solvent. These α-hydroxyketones and α-aminoketones are widely used as synthetic intermediates of high significance in organic and medicinal chemistry.[2] Our attention was drawn to hypervalent Iodine reagents, which are gaining increasing importance as mild oxidizing agents.[3] Among them, 2-Iodoxybenzoic acid (IBX) is evolving as the reagent of choice due to easy handling, stability to longer shelf life, tolerance to moisture, and zero toxic waste generation. We report herein, the utility of IBX for the first time for the synthesis of α-hydroxyketones **3** and α-aminoketones **4** from the corresponding epoxides **1** and aziridines **2** as their β-cyclodextrin complexes in an aqueous medium.

Cyclodextrins, which are cyclic oligosaccharides with hydrophobic cavities, mimic enzymes in their capability to bind substrates selectively and catalyze chemical reactions. They catalyze reactions by supramolecular catalysis involving reversible formation of host−guest complexes by noncovalent bonding. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus, mimicking of biochemical selectivity, which shows shape and substrate selectivity, with the reactions being carried out in water will be superior to chemical selectivity. Hence, the oxidation of various epoxides and aziridines was carried out as their β-cyclodextrin complexes in water using IBX. Since β-cyclodextrin is the least expensive among the cyclodextrins, it has been utilized as the complexing host.

SCHEME 1



R= H, Br, Cl, Me, OMe and NO_2

1. X = O
2. X = NTs
3. X = OH
4. X = NHTs

The β-CD inclusion complexes of epoxide **1**/aziridine **2** prepared in water as described by us earlier[1] were reacted in situ with IBX at room temperature to obtain the title compounds **3** and **4** (Scheme 1). The yields obtained, up to 92%, were also impressive (Table 1). All the compounds were characterized by IR, Mass, ^{1}H NMR spectral data and by comparison with the known compounds.[4] The reduced IBX, i.e., IBA can be recovered and oxidized to IBX as described earlier.[5] β-CD can also be recovered and reused. However, these reactions when carried out, with an epoxide as an example, in the presence of a protic component (HCl) to see the effect of "nonhost" participation in activation yielded halohydrin as the major product (52%) along with the desired keto alcohol (44%). In addition, a variety of other parameters have also been studied to see the importance of these CD-catalyzed reactions. The reaction of epoxide/aziridine and IBX when carried out in the absence of CD in DMSO, where both the substrates are soluble in an organic solvent, gave a mixture of products, i.e., epoxide yielded keto alcohol (60%) and diol (30%), whereas aziridine gave ketoamine (55%) and amino alcohol (44%). This was also the case in other organic solvents (for example, the reaction of epoxide in methanol yielded keto alcohol (40%) and diol (55%).

The product formation from the respective epoxides/aziridines in these CD-catalyzed reactions in water has been postulated and confirmed by spectroscopic evidence as follows: the fact that these reactions do not take place in the absence of cyclodextrins and also that IBX is insoluble in water shows the essential role of cyclodextrin. It appears that the cyclodextrin not only activates the epoxide/aziridine but also forms a CD−IBX complex

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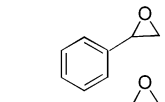
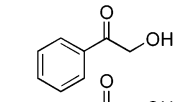
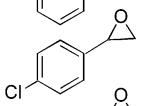
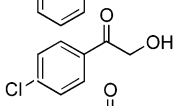
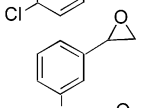
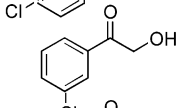
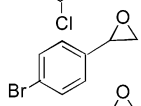
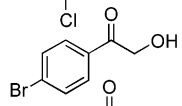
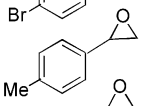
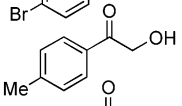
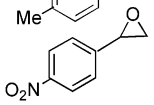
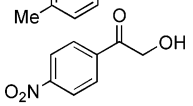
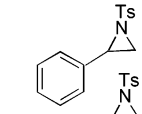
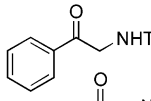
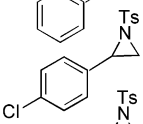
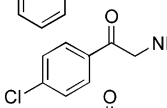
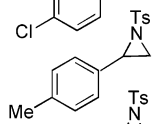
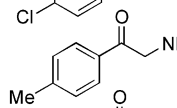
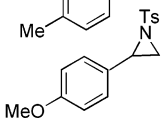
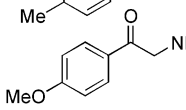
TABLE 1. Reaction of IBX with *β*-CD Complexes of Epoxides/Aziridines

Entry	Epoxide	Product [a]	Yield [b](%)
1			90
2			92
3			90
4			92
5			91
6			82
7			92
8			90
9			90
10			84

[a] All products were reported previously in literature.[4] [b] Yields of products isolated after column chromatography.

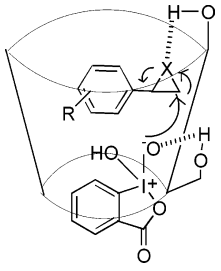


FIGURE 1.

through H-bonding (Figure 1), which first oxidizes the epoxide to 1,2-diol and aziridine to α-amino alcohol, which is further oxidized at the secondary position to give the respective ketones. Evidence to this mechanistic approach was deduced from ^{1}H NMR and IR spectroscopy. These studies were undertaken with styrene epoxide as a representative example. A comparison of the ^{1}H NMR spectra (D_2O) of *β*-CD, *β*-CD−styrene epoxide complex, *β*-CD−IBX complex, and freeze-dried reaction mixtures of the CD complex with IBX at 3, 6, and 12 h was undertaken. It could be seen from Figure 2 that there is a clear upfield shift of H_3 (0.028 ppm) and H_5 (0.045 ppm) protons of cyclodextrin in CD−styrene epoxide

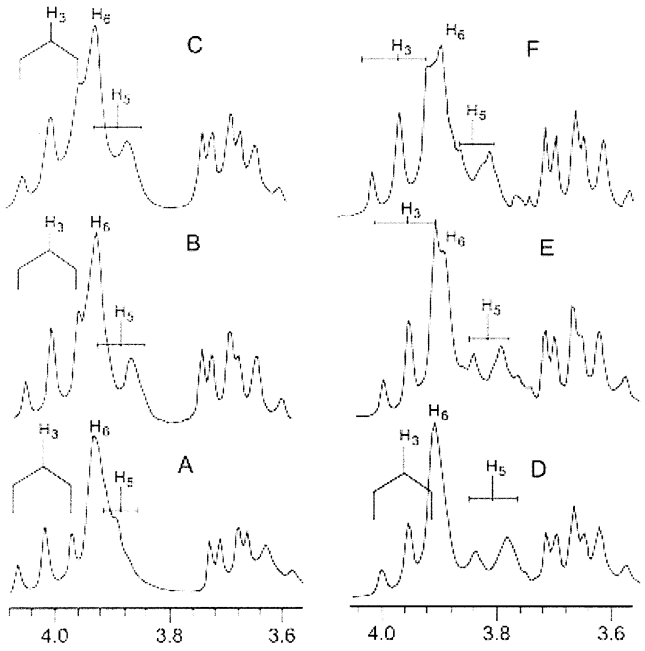


FIGURE 2. A, *β*-CD; B, *β*-CD−epoxide complex; C, *β*-CD−IBX complex; D, 3 h reaction; E, 6 h reaction; F, 12 h reaction.

complex as compared to CD, indicating the formation of an inclusion complex of epoxide with *β*-CD.[7] An upfield shift of H_3 and H_5 protons was also observed in *β*-CD−IBX complex. However, it can be observed from the spectra of the reaction mixtures of *β*-CD−epoxide complex and IBX at 3, 6, and 12 h that with these complexes, apart from retaining the upfield character of H_3 and H_5 protons with subtle changes, there is also an upfield shift of H_6 proton, i.e., 0.03 ppm at 3 h and 0.034 ppm at 6 and 12h reactions; this indicates the complexation of IBX at the primary side of cyclodextrin. From these ^{1}H NMR studies, it could be seen that the epoxide/aziridine while still being retained in the cavity, IBX complexes from the primary side (Figure 1) for the reaction to proceed.

Thus, we have demonstrated for the first time that the highly valuable synthons α-hydroxyketones **3** and α-aminoketones **4** can be generated directly from the easily accessible epoxides/aziridines in the presence of *β*-cyclodextrin and IBX in water. To our knowledge, this is the first reported synthesis of α-aminoketones directly from the aziridines in a single step. The reaction may be considered as simple from a practical point of view and has great potential for future applications.

Experimental Section

Materials. Epoxides and aziridines were prepared as described earlier.[6]

General Procedure. The epoxide **1**/aziridine **2** (1 mmol) dissolved in acetone (2 mL) was added to an aqueous solution of *β*-cyclodextrin (1 mmol of *β*-CD in 20 mL of water) at 60 °C and allowed to cool to room temperature. Then, IBX (1 mmol)

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was added while stirring, and stirring was continued for 12 h at room temperature. The reaction mixture was extracted with ethyl acetate (3 × 15 mL), dried, and concentrated in a vacuum. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (8:2) as an eluent.

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