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Highly Efficient Deprotection of Aromatic Acetals under Neutral Conditions Using β-Cyclodextrin in Water†

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Abstract: Aromatic acetals have been deprotected to the corresponding aldehydes under biomimetic conditions for the first time using β-cyclodextrin in water under neutral conditions, thereby overcoming many of the drawbacks associated with earlier methodologies. This method, apart from being simple with regard to recycling of the catalyst, also has the potential for industrial applications.

Acetals are the most commonly used protecting groups for carbonyl compounds in the course of total synthesis, and hence many reagents have been developed for their deprotection. The deprotection is accomplished by a variety of methods utilizing aqueous acid hydrolysis,[1] transition metals and Lewis acids,[2] phosphorus-based reagents,[3] silicon-based reagents,[4] montmorillonite K10,[5] (trimethylsilyl)bis(fluorosulfinyl)imide,[6] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[7] etc. However, there are severe limitations with these methodologies such as elevated temperatures, lower yields, and corrosive and acidic reagents leading to lower selectivities. Hence, considerable efforts have been directed toward the development of mild and selective methods for acetal deprotection.

In our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins in water,[8] we report herein, for the first time, a practical and efficient method for the deprotection of aromatic acetals catalyzed by β-cyclodextrin in water under neutral conditions. Though there are earlier reports of utilizing cyclodextrins under acid-catalyzed conditions for aryl acetal hydrolysis, wherein β- and γ-cyclodextrins slowed the reaction[9] and strong binding with β-cyclodextrin led to reduced activity,[10] the present methodology has the advantage of performing the acetal hydrolysis under neutral conditions in water with a catalytic amount of β-cyclodextrin.

Cyclodextrins (CDs), which are cyclic oligosaccharides with hydrophobic cavities, exert microenvironmental effects leading to selective reactions. They catalyze

SCHEME 1

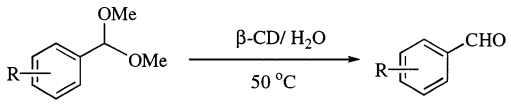
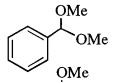
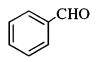
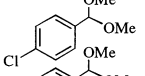
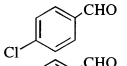
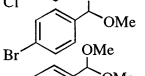
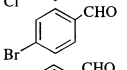
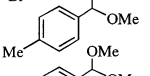
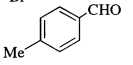
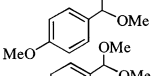
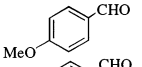
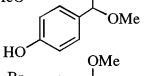
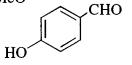
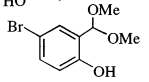
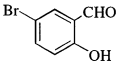
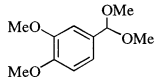
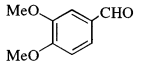
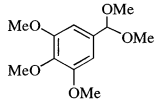
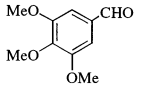
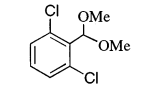
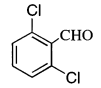
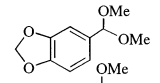
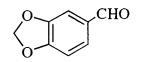
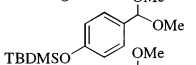
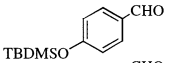
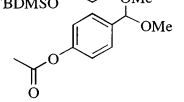
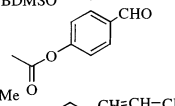
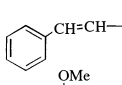
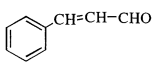
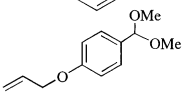
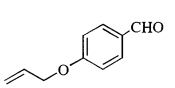


TABLE 1. Deprotection of Aromatic Acetals with β-cyclodextrin/ Water

Entry	Substrate	Product[a]	Time(h)	Yield(%)[b]
1			8	80
2			8	92
3			8	88
4			10	83
5			10	90
6			10	82
7			10	80
8			10	85
9			10	78
10			10	80
11			8	85
12			8	84
13			12	82
14			12	86
15			12	82

[a] All products were reported previously in the literature.[11] [b] Yield refers to isolated product.

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reactions involving supramolecular catalysis through noncovalent bonding as seen in enzymes. These biomimetic reactions can be effectively carried out in water under neutral conditions without generating any toxic waste products. Thus, mimicking biochemical conditions with the reactions being carried out in water will be superior to chemical selectivity. This background has prompted us to attempt the deprotection of acetals of various aromatic aldehydes using CDs in water, as this is one of the most useful synthetic transformations (Scheme 1).

The reactions were carried out by dissolving β-cyclodextrin in water at 50 °C followed by the addition of acetal and stirring at that temperature. The results are summarized in Table 1. The yields were impressive and realized between 80 and 90% in most cases. Benzaldehyde dimethyl acetal (entry-1) and substituted benzaldehyde acetals such as bromo, chloro, methyl, methoxy, methylene dioxy, hydroxy, and OTBDMS (entries 2−12) were all converted to the corresponding aldehydes in good yields in reaction times ranging from 8 to 10 h, whereas acetals with acetyl, allyloxy, and double-bond conjugation (entries 13−15) have taken longer reaction times up to 12 h. These reactions can be effectively carried out with only a catalytic amount of cyclodextrin, i.e., 0.1 mol of CD per mole of the substrate. These reactions do not take place in the absence of CD. Cyclodextrin can also be recovered and reused. This methodology, apart from having the advantage of neutral conditions and aqueous medium, is also compatible in the presence of various other functional groups such as OMe, OTBDMS, OAc, allyloxy, methylenedioxy, and conjugated double bonds to acetals. Though these reactions do take place with acetals of aliphatic aldehydes, the yields are less than satisfactory. For example, the acetals of octanal and decanal react very slowly, taking up to 24 h and yielding products in the range of 20% with the recovery of starting materials. Here the role of CD appears to be to activate the acetal group by hydrogen bonding, thereby facilitating its cleavage in the presence of water. This reaction also takes place in the presence of α-CD, but β-CD is the preferred catalyst because of its easy accessibility and economic viability.

In conclusion, this work demonstrates cyclodextrin to be a highly efficient catalyst for the first time for the deprotection of aromatic acetals in water. This straightforward methodology using water as the reaction medium and β-cyclodextrin as the reusable catalyst may find potential applications in industry.

Experimental Section

Materials. Acetals were either purchased commercially or synthesized as reported in the literature.[12]

General Procedure for Deprotection. In a typical procedure, β-cyclodextrin (0.1 mmol) was dissolved in 20 mL of water by heating at 50 °C, and acetal (1 mmol) in methanol (1 mL) was added slowly; the mixture was stirred at this temperature for the required length of time (Table 1). The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 20 mL). The combined organic extract was washed with water (2 × 10 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The product obtained was further purified by column chromatography on silica gel (100−200 mesh) using 9:1 hexane/ethyl acetate. The products were identified by comparison of their NMR, IR, TLC, and mixed TLC analysis with those of authentic samples.

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