Letter

# Selective deprotection of tetrahydropyranyl ethers catalysed by β-cyclodextrin in water†

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**The hydrolysis of tetrahydropyranyl ethers to alcohols catalysed by β-cyclodextrin proceeds in water under neutral conditions.**

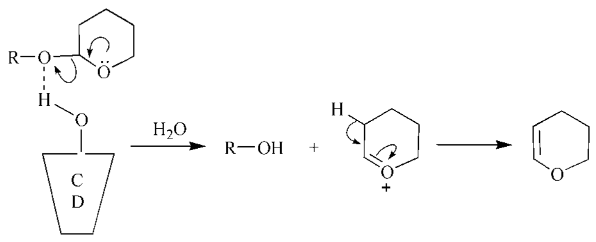
Selective protection and deprotection of functional groups is of great significance in organic synthesis. Amongst these procedures, tetrahydropyranylation of hydroxyl groups has been recognised as a method of choice for the protection of alcohols and phenols due to the ease of installation and stability in the presence of most nonacidic reagents of the tetrahydropyranyl group.[1] However, most of the general methods used for the cleavage of tetrahydropyranyl (THP) ethers involve a variety of catalysts, such as $MgBr_2$, $Me_2AlCl$, $(NCSBu_2Sn)_2O$, MeOH–HCl, $NaBH_3CN–BF_3 \cdot OEt_2$, $Ph_3PBr$, DDQ, *etc.*[2] There are also examples that, under neutral conditions in aqueous or non-aqueous media, involve expensive and toxic reagents.[2f,h,3] Apart from this, some of these methods produce considerable amounts of side products. Keeping in view the range of catalysts and the complexity of procedures involved, we felt there was a need to develop an alternate and mild approach for the selective removal of the THP group in the presence of other sensitive functional groups, preferably under neutral conditions. The best choice would be through supramolecular catalysis, but this still remains a goal yet to be attained.

In our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins in water,[4] we report herein a simple methodology for the deprotection of THP ethers catalysed by β-cyclodextrin (β-CD) in water (Scheme 1).

Cyclodextrins, which are cyclic oligosaccharides, exert a microenvironmental effect that can lead to selective reactions. They catalyse reactions by supramolecular catalysis through non-covalent bonding, as seen in enzymes. These reactions can be carried out effectively in water, which is an environmentally benign solvent under neutral conditions, and also do not generate any toxic waste products. This supramolecular catalysis involving cyclodextrins has been applied to the deprotection of THP ethers. It was carried out by dissolving β-cyclodextrin in water, followed by addition of the THP ether. The yields of the products obtained were in the range 70–90% (Table 1). Though this reaction takes place in the presence of α-CD also, β-CD will be the preferred catalyst due to its easy accessibility and low cost. These reactions can be efficiently carried out with only a catalytic amount of the cyclodextrin (0.1 mol of CD per mol of the substrate). The cyclodextrin can also be recovered and reused. These reactions, when carried out in the absence of cyclodextrin, show no deprotection of THP ethers. The fact that the deprotection of THP ethers does not take place in the presence of other carbohydrates such as glucose conclusively proves the role of cyclodextrin. This methodology is also very effective in deprotecting the THP group in the presence of other sensitive functionalities such as acetonide, methylenedioxy, *O*-methyl, *O*-benzyl, *N*-Boc, formyl, silyl and ester groups. Here, the role of CD appears to be to activate the THP ether by hydrogen bonding, as shown in Scheme 2, thus facilitating the hydrolysis.

In conclusion, this methodology involving cyclodextrin in water is the first of its kind for deprotecting THP ethers and has several advantages over the existing methodologies.

**Scheme 1**



**Scheme 2**

## Experimental

The substrate tetrahydropyranyl ethers (Table 1) were made as reported in the literature.[2j,l] β-Cyclodextrin was procured from Sterling Organics Ltd., U.K. Typical procedure is the following: β-cyclodextrin (0.1 mmol) was dissolved in water (25 ml) at 60 °C; tetrahydropyranyl ether (1 mmol) in methanol (1 ml) was added slowly with stirring. The stirring was continued at 50 °C for the specified time (Table 1). It was cooled to room temperature, extracted with ethyl acetate (2 × 30 ml), dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The crude product was purified by silica gel column chromatography using ethyl acetate–hexane (3 : 7) as eluent. All the products were characterized by $^1H$ NMR and mass spectral data and compared with the data reported in the literature for the authentic samples.[2a,b,d,i–m]

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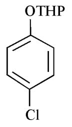
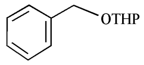
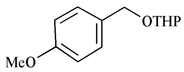
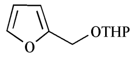
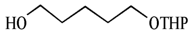
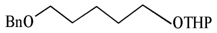
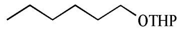
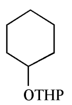
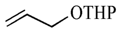
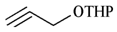
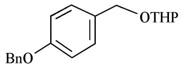
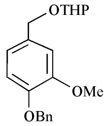
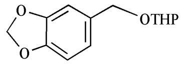
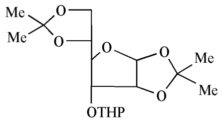
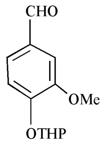
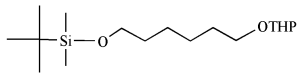
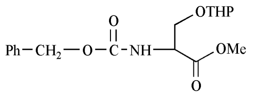
**Table 1** CD catalysed hydrolysis of tetrahydropyranyl ethers

| Substrate | Time/h | Yield[a] (%) |
|---|---|---|
|  | 8 | 85 |
|  | 8.5 | 84 |
|  | 9 | 85 |
|  | 9 | 80 |
|  | 10 | 75 |
|  | 10 | 75 |
|  | 10 | 70 |
|  | 10 | 80 |
|  | 8 | 85 |
|  | 8 | 85 |
|  | 9 | 90 |
|  | 9 | 86 |
|  | 10 | 80 |
|  | 12 | 75 |
|  | 12 | 80 |
|  | 10 | 75 |
|  | 10 | 80 |

[a] Isolated yield.

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