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Direct synthesis of carbonyl compounds from THP ethers with IBX in the presence of β-cyclodextrin in water

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Abstract—Water, an environmentally friendly reaction medium, has been utilized for the oxidative deprotection of tetrahydropyranyl ethers **1** with IBX at room temperature in the presence of β-cyclodextrin to give the corresponding carbonyl compounds **2**.
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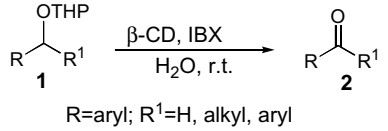
There are many catalysts reported for the tetrahydropyranylation of alcohols and the cleavage of tetrahydropyranyl ethers to their parent alcohols,[1] but the direct synthesis of carbonyl compounds from tetrahydropyranyl ethers is not widespread in the literature.[2] However, in view of the importance of oxidative deprotection of THP ethers, a number of reagents have been studied such as iron(III) nitrate with clay and montmorillonite K-10,[3] $AgBrO_3$ and $NaBrO_3$ in the presence of $AlCl_3$,[1] benzyltriphenylphosphonium peroxymonosulfate with bismuth chloride,[4] tetramethylammonium chlorochromate,[5] PCC (pyridinium chlorochromate),[2b] $(^nBuPPh_3)_2S_2O_8$ (*n*-butyltriphenylphosphonium peroxodisulfate),[6] CPCC (3-carboxypyridinium chlorochromate),[2c] chromium(VI) oxide,[7] etc. The utility of chromium(VI) reagents in oxidative transformations is compromised due to their inherent toxicity and the potential danger in handling its complexes. Apart from this, many of these methods have severe limitations such as tedious work-up, long reaction times, low yields, high temperatures and also the use of anhydrous organic solvents, Lewis acid catalysts, expensive reagents, etc. Thus, the introduction of new methods, inexpensive reagents and environmentally friendly reaction conditions for such functional group transformations is still in demand.

In continuation of our investigations on organic reactions catalyzed by β-cyclodextrin in aqueous medium,[8] we explored the oxidative deprotection of THP ethers using 2-iodoxybenzoic acid (IBX), which is a mild and environmentally friendly oxidizing agent.

Amongst various oxidizing agents, IBX, a hypervalent iodine reagent, attracted our attention due to its low toxicity,[9] ease of handling and moisture stability. We report herein the utility of IBX for the direct synthesis of carbonyl compounds from their corresponding THP protected alcohols catalyzed by β-cyclodextrin in water (Scheme 1).[10] Cyclodextrins are cyclic oligosaccharides, which exert microenvironmental effects. They promote reactions by supramolecular catalysis through non-covalent bonding as seen in enzymes.

The yields obtained were impressive ranging up to 96%. No over-oxidation products were detected in the case of aldehydes. The yields were diminished when a $-NO_2$ group was present on the aromatic ring (Table 1, entry 6) due to a decrease in the nucleophilicity of the alcoholic oxygen, since the reaction proceeds via nucleophilic attack of the alcoholic oxygen on IBX. Longer reaction times had no impact on the yield. The yields from THP ethers with an aromatic moiety were comparatively better than those from saturated THP ethers



Scheme 1.

Keywords: THP ethers; IBX; Oxidative deprotection; Carbonyl compounds; β-Cyclodextrin; Water.
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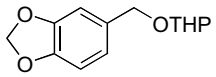
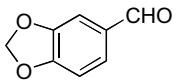
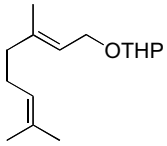
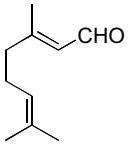
Table 1. Oxidative deprotection of THP ethers with IBX in the presence of β-CD in water

Entry	Substrate	Product[a]	Time (min)	Yield (%)[b]
1	$C_6H_5CH_2OTHP$	C_6H_5CHO	60	96
2	*p*-$BrC_6H_4CH_2OTHP$	*p*-BrC_6H_4CHO	40	90
3	*p*-$ClC_6H_4CH_2OTHP$	*p*-ClC_6H_4CHO	40	90
4	*p*-$MeC_6H_4CH_2OTHP$	*p*-MeC_6H_4CHO	45	92
5	*p*-$MeOC_6H_4CH_2OTHP$	*p*-$MeOC_6H_4CHO$	40	95
6	*p*-$NO_2C_6H_4CH_2OTHP$	*p*-$NO_2C_6H_4CHO$	90	70
7	$C_6H_{11}OTHP$	$C_6H_{10}O$	60	65
8	$C_6H_5CH(CH_3)OTHP$	$C_6H_5COCH_3$	50	95
9	*p*-$MeC_6H_4CH(CH_3)OTHP$	*p*-$MeC_6H_4COCH_3$	45	90
10	*p*-$BrC_6H_4CH(CH_3)OTHP$	*p*-$BrC_6H_4COCH_3$	40	95
11	*p*-$ClC_6H_4CH(CH_3)OTHP$	*p*-$ClC_6H_4COCH_3$	45	90
12	*p*-$THPOC_6H_4CH(CH_3)OTHP$	*p*-$THPOC_6H_4COCH_3$	60	86
13	*p*-$TBDMSOC_6H_4CH(CH_3)OTHP$	*p*-$TBDMSOC_6H_4COCH_3$	110	90
14	*p*-TBDMSO-*m*-$MeOC_6H_4CH(CH_3)OTHP$	*p*-TBDMSO-*m*-$MeOC_6H_4COCH_3$	120	88
15	$C_6H_5CH(OTHP)C_6H_5$	$C_6H_5COC_6H_5$	50	94
16	*p*-$TBDMSOCH_2C_6H_4CH(CH_3)OTHP$	*p*-$TBDMSOCH_2C_6H_4COCH_3$	120	85
17	$C_6H_5CH(OH)CH_2OTHP$	$C_6H_5COCH_2OH$	65	87
18	*p*-$ClC_6H_4CH(OH)CH_2OTHP$	*p*-$ClC_6H_4COCH_2OH$	70	90
19	$C_6H_5CH(OTHP)CH_2OTHP$	$C_6H_5COCH_2OH$	85	86
20	$C_6H_5CH{=}CHCH_2OTHP$	$C_6H_5CH{=}CHCHO$	90	88
21			80	90
22			90	85

[a] All the products are known compounds.[1]
[b] Yields of isolated products after column chromatography.

(Table 1, entry 7). When both –OTBDMS and –OTHP groups were present in the same substrate, –OTHP was selectively cleaved (Table 1, entry 16). In the case of substrates **17**, **18** and **19**, keto alcohols were the only products formed and resulted from oxidation of the benzyl alcohol due to the ease with which the α-hydrogen can be abstracted.[11] In these reactions the role of cyclodextrin appears to be to activate the tetrahydropyranyl ethers by hydrogen bonding and thereby facilitating the hydrolysis. Since the β-cyclodextrin cavity is hydrophobic in nature it may also be forming reversible complexes with the THP ethers. These reactions were efficiently carried out using a catalytic amount of β-cyclodextrin (0.1 mmol). β-Cyclodextrin is inexpensive and could also be recovered and reused.

When glycerol was used as solvent no reaction was observed. The reaction was also performed without IBX. Only deprotection occurred and no oxidized product was isolated. In the absence of β-cyclodextrin, no deprotection took place and hence no oxidation occurred.

The present methodology has the advantage of performing the in situ oxidative deprotection of tetrahydropyranyl ethers in water with IBX and a catalytic amount of β-cyclodextrin. It is an economical and user-friendly protocol.

Acknowledgements

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10. *Experimental procedure*: To a solution of β-cyclodextrin (0.1 mmol) in distilled water (15 mL) at room temperature was added the tetrahydropyranyl ether (1.0 mmol) in acetone (2 mL) followed by IBX (1.0 mmol). The resulting mixture was stirred at room temperature until the reaction was complete (TLC). The product was then extracted with ethyl acetate and the organic phase dried (anhydrous Na_2SO_4) and concentrated under vacuum. The crude product thus obtained was purified by column chromatography on silica-gel [*n*-hexane–ethyl acetate 9.7:0.3, except in the case of keto alcohols (**17**, **18** and **19**) where it was 9.0:1.0]. The aqueous phase was lyophilized to recover the β-cyclodextrin.
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