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A Simple and Efficient Hydrolyzing Method for Tetrahydropyranyl Ethers

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Abstract: A series of tetrahydropyranyl ethers are hydrolyzed to the corresponding alcohols in a CBr_4 / CH_3OH (5% / 5mL) reaction system under refluxing. This method also enables to deprotect other functionalities such as acetals and ketals.

The reaction of selective introduction and removal of protective groups is an important tool in organic synthesis.[1] Transformation of alcohols into their corresponding ethers or acetals/ketals has been recognized as a common and useful method for protection of hydroxyl groups.[2,3] Tetrahydropyranyl ether (ROTHP, a mixed acetal) is one of the most widely used protective groups employed in organic synthesis because of its low cost and stability to various reaction conditions. THP ethers are resistant in basic conditions required for ester hydrolysis whereas are labile to acidic conditions such as HCl/MeOH/THF,[4] AcOH/THF/H_2O,[5] PPTS/EtOH,[6,7] TsOH/MeOH,[8] BF_3/ethanethiol,[9] $MgBr_2$,[10] $FeCl_3/SiO_2$,[11] Me_2AlCl,[12] Amberlyst H-15/MeOH.[13] Recently, our laboratory reported a novel and selective hydrolyzing method for acetals and ketals.[14] A series of cyclic and acyclic acetals and ketals were deprotected to their corresponding carbonyl compounds by a catalytic amount of CBr_4 in a CH_3CN / H_2O solvent mixture under different energy source, thermal or ultrasound. We expected that this type of hydrolyzing system can be further extended to the application of deprotecting tetrahydropyranyl ethers. Herewith, we wish to report a simple deprotective reaction of tetrahydropyranyl ethers in a CBr_4 / CH_3OH mixture under refluxing conditions (Scheme 1).

Scheme 1

$$\text{R-OTHP} \xrightarrow[\text{reflux (65 °C)}]{\text{CBr}_4\text{ / MeOH (5\% / 5mL)}} \text{R-OH}$$

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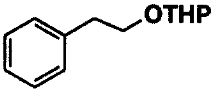
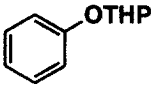
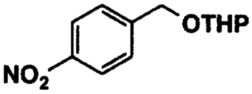
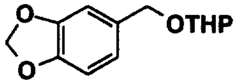
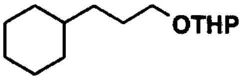
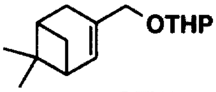
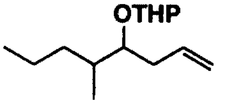
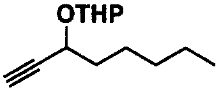
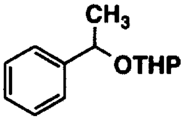
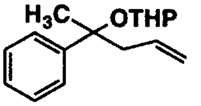
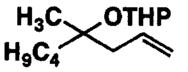
The typical procedure for hydrolyzing tetrahydropyranyl ether to the corresponding alcohol follows: A solution of tetrahydropyranyl ether (1.0 mmol) and CBr_4 (0.05 mmol) in anhydrous CH_3OH (5 mL/ROTHP mmol) is refluxed at 65 °C for 0.5-3 hours. The solution was cooled to room temperature and poured into an

Table 1. Hydrolysis of tetrahydropyranyl ethers

Entry	Substrate	Time (Hour)	Yield[a]
1		3	96%
2		1	91%
3		1.5	93%
4		1	89%
5		0.5	89%
6		2.5	90%
7		1.5	99%
8		3	95%
9		0.5	93%
10		1	90%
11		1	90%
12		1	96%

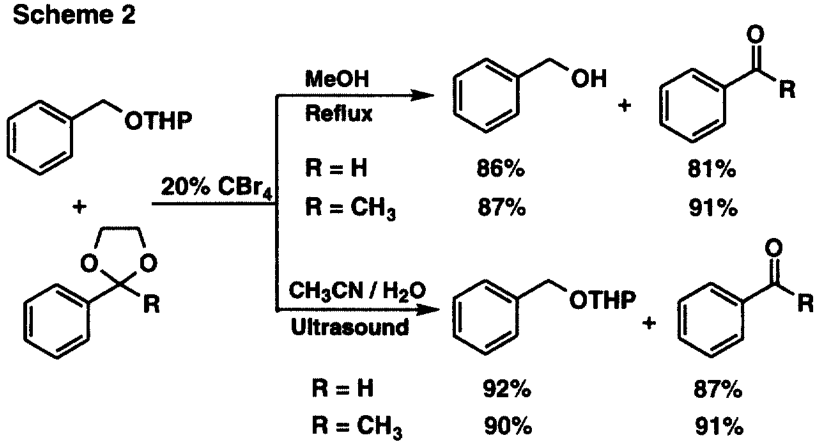
a. The yields were determined after chromatographic purification.

aqueous $NaHCO_3$ solution (5%, 10 mL) and then extracted with diethyl ether (3 x 10mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Further purification was achieved on a silica gel flash chromatography with ethyl acetate/hexane. A series of tetrahydropyranyl ethers were hydrolyzed and the results are shown in Table 1. Primary, secondary, tertiary and phenolic tetrahydropyranyl ethers could be deprotected to their corresponding alcohols in high yields.

We firstly investigated the hydrolysis of tetrahydropyranyl ethers under the previously reported $CBr_4/CH_3CN/H_2O$ reaction conditions using thermal or ultrasound as energy source and alcohol was produced in very low yield (<15%). Then, we chosed CH_3OH (more common solvent for hydrolysis of ROTHP) instead of CH_3CN. A mixture of ROTHP (Entry 1, 1.0 eq.), CBr_4 (0.5 eq.) and CH_3OH/H_2O (3 mL/2 mL) was refluxed for 3 hours and a 77% yield of deprotected product was obtained. Interestingly, we observed that hydrolysis was faster and complete when a dry solvent was used. Thus, a mixture of ROTHP (Entry 1, 1.0 eq.), CBr_4 (0.5 eq.) and anhydrous CH_3OH[15] (5 mL) was refluxed for 2.5 hours and a 88% yield of deprotected product was formed. We also found that a catalytic amount of CBr_4 was sufficiently enough for the hydrolysis and a higher yield (96%) was achieved when 0.05 eq of CBr_4 was used. It should be noted that yield was decreased when more CBr_4 was used. Other alcoholic solvents such as ethanol and *iso*propanol also can be used for the ROTHP hydrolysis.

It is highly desirable to have a method that would effect the selective removal of expected functional groups in the presence of tetrahydropyranyl ethers that are sensetive to the acidic reaction conditions commonly used for their cleavage. We investigated the hydrolysis of a mixture of acetal/ketal under such conditions. 1,3-Dioxolane also was hydrolyzed to the corresponding carbonyl compound under $CBr_4/MeOH$ reaction conditions. A mixture of a tetrahydropyranyl ether (0.5 eq.) and an 1,3-dioxolane (0.5 eq.) was refluxed in a $CBr_4/MeOH$ (0.2 eq./5 mL) reaction system for one hour and 86% of benzyl alcohol and 81% yield of benzaldehyde[16] were obtained separately (Scheme 2). When a CH_3CN/H_2O mixture was used as solvent and ultrasound as energy source, the tetrahydropyranyl ethers were stable under the reaction conditions whereas the 1,3-dioxolanes were hydrolyzed to the corresponding carbonyl functionality.

Scheme 2



These results lead us to further investigate this type of distinctive hydrolyzing procedure between different functional groups such as methyloxymethyl ether (ROMOM), methoxyethoxymethyl ether (ROMEM) and silyl esters ($RCO_2SiR'_3$) and the studies are underway.

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15. Methanol was distilled from magnesium turnings and recirculated prior to use.
16. The yield is lower because the product is highly volatile.