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Deprotection of *t*-Butyldimethylsiloxy (TBDMS) Protecting Group with Catalytic Copper (II) Chloride Dihydrate

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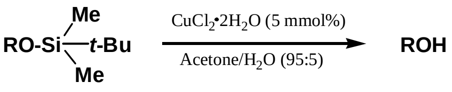
Abstract: *t*-Butyldimethylsilyl (TBDMS) ether can be cleaved upon refluxing in acetone/H_2O (95 : 5) in the presence of a catalytic amount of copper (II) chloride dihydrate (5 mmol %).

Keywords: TBDMS ether, deprotection, copper (II) chloride dihydrate.

The protection of functional group is unavoidable in multi-step organic synthesis. Along with tetrahydropyranyl (THP) ethers, *t*-butyldimethylsilyl (TBDMS) ethers have been widely used for protecting hydroxyl groups. TBDMS ether is more stable to hydrolysis than trimethylsilyl ether, but is still readily cleaved by a variety of selective conditions[1]. The deprotection of TBDMS is usually under mild acidic conditions [AcOH/H_2O/THF, 3:1:1[2], or BF_3 $Et_2O/CHCl_3$[3], *etc.*[4]], or with a fluoride ion[2,5]. Although those deprotection conditions have been widely applied in organic synthesis, there is still a need to look for alternative and milder condition for the deprotection of TBDMS ethers. We have recently reported that catalytic amount of cheap and readily available copper (II) chloride dihydrate ($CuCl_2{\cdot}2H_2O$) can efficiently cleave THP ethers[6]. In this communication, we further describe the successful removal of TBDMS ether by $CuCl_2{\cdot}2H_2O$ under catalytic condition (**Scheme 1**).

Scheme 1

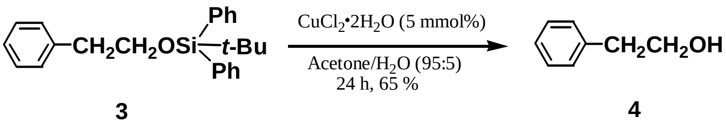


1 **2**

The TBDMS ethers with different structures were prepared by the literature procedure in good yields[2]. The deprotection was performed by refluxing the TBDMS ether in acetone/H_2O (95/5) containing 5 mmol % of $CuCl_2{\cdot}2H_2O$. Under this condition, the TBDMS ethers investigated in our study were completely removed within 2 to 30 h. The corresponding parent alcohol was isolated in moderate to excellent yield by column chromatography. The results are summarized in **Table 1**.

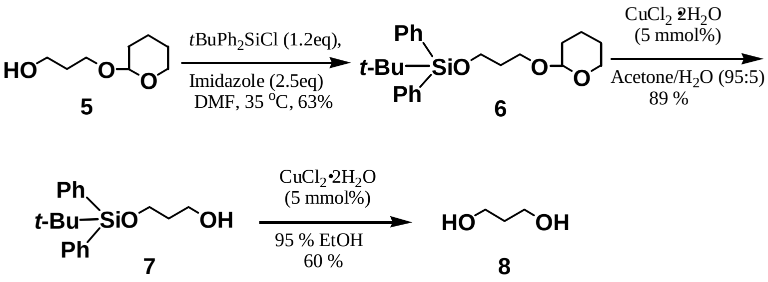
In order to know if this novel deprotection is general for silyl ether, we proceed to investigate deprotection of *t*-butyldiphenylsilyl ether, which is more stable than TBDMS ether. Thus, *t*-butyldiphenylsilyl ether **3** was prepared and then hydrolyzed in acetone/H_2O (95/5) in the presence of $CuCl_2 \cdot 2H_2O$ (**Scheme 2**). We found that this protecting group could also be cleaved under this condition, although the reaction took longer time than the corresponding TBDMS ether.

Scheme 2



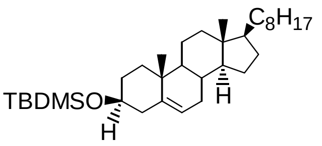
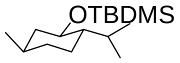
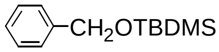
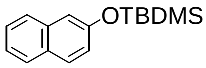
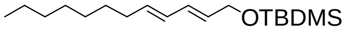
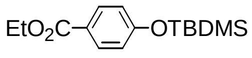
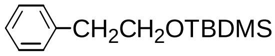
Since the selective removal of one protecting group in the presence of another in the same molecule is often required in organic synthesis[7], we further investigated the possibility to selectively remove one protecting group by $CuCl_2 \cdot 2H_2O$ when both THP ether and *t*-butyldiphenylsilyl ether are present. We have previously reported that THP ether can also be cleaved by $CuCl_2 \cdot 2H_2O$[6], but the reaction generally needs higher temperature with 95 % alcohol as solvent. Thus, as shown in **Scheme 3**, sequential protection of the 1,3-propandiol with THP and *t*-butyldiphenylsilyl groups gave compound **6**. In contradiction to our initial expectation, deprotection of compound **6** by refluxing with $CuCl_2 \cdot H_2O$ in acetone/H_2O (95/5) resulted in the selective removal of THP group to give **7** in 89 % isolated yield. The *t*-butyldiphenylsilyl ether of **7** can be further removed by refluxing it with $CuCl_2 \cdot 2H_2O$ in 95 % EtOH. This example demonstrates that by careful control of the reaction condition, it is possible to selectively remove THP ether in the presence of *t*-butyldiphenylsilyl ether. However, the scope and limitation of the selectivity needs further investigation.

Scheme 3



In summary, we have shown an alternative method for the deprotection of TBDMS ethers by catalytic amount of $CuCl_2 \cdot 2H_2O$. The reaction condition is nearly neutral, and the reagent is readily available. Therefore, this novel method should find application in organic synthesis.

Table 1. Deprotection of TBDMS Ethers Catalytic Amount of $CuCl_2 \cdot 2H_2O$

Entry	Compound	Reaction Time (h)	Isolated Yield (%)
1	$CH_3(CH_2)_9OTBDMS$	3	86
2		6.5	99
3		6	97
4		6	98
5		30	80
6		2	97
7		24	50
8		3	99
9	$CH_3(CH_2)_{21}OTBDMS$	2	99

General procedure for the deprotection with $CuCl_2 \cdot 2H_2O$: The TBDMS ether (1 mmol) was dissolved in acetone/H_2O (95/5, 10 mL). To the solution was added $CuCl_2 \cdot 2H_2O$ (0.05 mmol) and the homogenous solution was heated under gentle reflux until completion of the reaction, as indicated by TLC check. The solvent was evaporated and the residue was subjected to column chromatography with silica gel. The pure parent alcohol was compared with an authentic sample (TLC and ^1H NMR).

Acknowledgment

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