

Copper(II) Chloride Dihydrate: A Catalytic Agent for the Deprotection of Tetrahydropyranyl Ethers (THP Ethers) and 1-Ethoxyethyl Ethers (EE Ethers)†

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Tetrahydropyranyl ethers (THP groups) and 1-ethoxyethyl ethers (EE groups) are removed upon refluxing in 95% EtOH or Me₂CO–H₂O (95:5) in the presence of a catalytic amount of copper(II) chloride dihydrate (2–5 mol%).

Protecting groups play an important role in organic synthesis. Among the various methods for protecting hydroxy groups, the formation of tetrahydropyranyl ethers (THP groups) is one of the most widely used methods because of their easy formation and inertness to various reaction conditions. The deprotection of THP groups is usually under dilute aqueous acidic condition, such as acetic acid, *p*-toluenesulfonic acid or boric acid, *etc.*¹ In recent years, a number of different methods have been reported for the deprotection of THP groups.² Nevertheless, it is still desirable to develop alternative and milder conditions to remove protecting groups. We report here a simple and efficient process for the removal of THP groups and related 1-ethoxyethyl ethers (EE groups),¹ in which only a catalytic amount of

copper(II) chloride dihydrate is required. In addition, we also investigated the ability of CuCl₂·2H₂O to cleave the structurally related cyclic dioxolane derivatives, which are common protective groups for carbonyl groups.¹

A number of THP and EE ethers with different structures were prepared according to standard procedures.³ The THP ethers were subjected to reflux in 95% EtOH containing 5 mol% of copper(II) chloride dihydrate (Scheme 1). Under such conditions all the THP groups investigated in our study were cleanly and completely removed within 2–3 h, and the corresponding alcohols were isolated in good yields. Some acid sensitive functional groups, such as epoxide and tertiary hydroxy groups, were found to tolerate this condition (Table 1, entries 10 and 11).⁴ EE groups can be similarly

Table 1 Deprotection of THP and EE ethers with a catalytic amount of CuCl₂·H₂O

Entry	Compound	Reaction time ^a /h	Isolated yield (%)	Entry	Compound	Reaction time ^a /h	Isolated yield (%)
1	Me(CH ₂) ₂₁ OTHP	3.0	91	10		1.5	78
2		2.0	89	11		1.5	91
3	EtO ₂ C–	3.0	92	12		2.0	91
4		2.0	98	13	Me(CH ₂) ₉ OEE	1.0	92
5		2.5	90 ^b	14		1.0	91
6		2.0	92	15		1.0	92
7		2.0	93	16		1.0	96
8		3.0	93	17		1.0	95
9	OHC–	2.0	92				

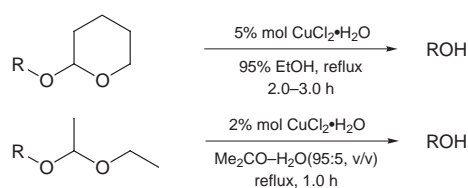
^a Reaction conditions: for THP ethers, 5 mol% of CuCl₂·H₂O was refluxed with the protected compound in 95% EtOH. For EE ethers, 2% mol of CuCl₂·H₂O was refluxed with the protected compound in Me₂CO–H₂O (95:5, v/v). ^b Both THP and dioxolane groups were removed, and the isolated product was epiandrosterone. ^c The reaction was run under an N₂ atmosphere.

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removed under the same condition. As expected, we found it was easier to remove EE groups and the solvent could be replaced by Me₂CO–H₂O (95:5 v/v). The removal of THP groups with Me₂CO–H₂O (95:5) as solvent is however, slow. For example, refluxing Me[CH₂]₂₁OTHP with 5% mol

$\text{CuCl}_2 \cdot \text{H}_2\text{O}$ in $\text{Me}_2\text{CO}-\text{H}_2\text{O}$ (95:5 v/v) for 6 h gave the parent alcohol in only 25% isolated yield.



Scheme 1

In order to gain some insight into the mechanism of this novel deprotection process, we investigated the reaction with anhydrous CuCl_2 in anhydrous EtOH. We found that both THP and EE groups could be removed as efficiently as when using $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in H_2O -containing EtOH. Therefore, H_2O is not indispensable for these reactions. However, refluxing of EE protected compound with anhydrous CuCl_2 in anhydrous acetone led to decomposition to several unidentified products. Additionally THF- H_2O (95:5 v/v) was an unsuitable solvent for deprotection and led to no reaction after refluxing for several hours. We also tested $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ and $\text{Cu}(\text{acac})_2$ and found them to be ineffective in the deprotection of THP or EE groups under the same conditions.

Since an aqueous solution of CuCl_2 is acidic (pH 3.6 in 0.2M aqueous solution), it is most possible that these deprotection reactions are simply acid-catalyzed hydrolysis of acetals. However, considering the catalytic amount of CuCl_2 in the reaction system, it is also likely that metal complexation is involved in the reaction so as to facilitate. Sen *et al.* recently reported that $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ could remove THP protecting groups.⁵ It seems likely that these processes have some common feature in the reaction pathway. However, the detailed mechanism for CuCl_2 -promoted deprotection is still unclear.

In Table 1 (entry 5), both THP and dioxolane groups in the 3 β -OH and 17-oxo-protected epiandrosterone were found to be removed under the CuCl_2 -promoted deprotection conditions. This suggests that dioxolane groups in general might be also removed under the same reaction conditions. We then investigated the ability of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ to cleave cyclic dioxolane derivatives. Thus, ketals and acetals were prepared according to standard procedures,¹ and the deprotection was conducted under the same conditions as for the THP ethers and results are summarized in Table 2. Although the deprotection indeed worked in most of cases, the reaction generally takes longer than for corresponding deprotection of THP or EE groups. In several cases, the reaction did not proceed to completion (Table 2, entries 3, 4 and 5). In one case, the acetal group was not cleaved and the starting material was recovered unchanged (entry 6).

In conclusion, we have discovered an efficient method for the deprotection of THP and EE groups. The reaction is remarkably simple and requires only a catalytic amount of inexpensive and readily available copper(II) chloride dihydrate.

Experimental

$\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ was obtained from Beijing Chemical Reagent Co., China and anhydrous CuCl_2 was purchased from Aldrich. All solvents were distilled prior to use. 100–200 Mesh silica gel (Qingdao, China) was employed for column chromatography purification. THP ethers, EE ethers and dioxolane derivatives were prepared by standard procedures and characterized by ^1H (200 MHz) and ^{13}C NMR (50 MHz).

General Procedure for Deprotection with $\text{CuCl}_2 \cdot \text{H}_2\text{O}$.—The protected compound (1 mmol) was dissolved in 95% EtOH (10 mL) or $\text{Me}_2\text{CO}-\text{H}_2\text{O}$ (95:5 v/v; 10 mL). To the solution was added

Table 2 Deprotection of cyclic dioxolanes with a catalytic amount of $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ ^a

Entry	Compound	Reaction time ^a /h	Isolated yield (%)
1		3.0	90 ^b
2		2.5	94 ^b
3		5.5	95(5) ^c
4		7.5	47(53) ^c
5		4.5	90(10) ^c
6		3.5	0(100) ^c

^a Reaction conditions: $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ was refluxed with the protected compound in 95% EtOH. ^b 5% mol $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ was used. The deprotections were complete, and the yields refer to isolated yield. ^c 10% mol $\text{CuCl}_2 \cdot \text{H}_2\text{O}$ was used. The reactions were not complete. The relative yields were estimated by ^1H NMR and the numbers in parentheses refer to unreacted materials.

$\text{CuCl}_2 \cdot \text{H}_2\text{O}$ (0.05 or 0.01 mmol and the homogenous solution was heated under gentle reflux until completion of the reaction (monitored by TLC). After cooling, the solvent was removed by evaporation. Diethyl ether (30 mL) was added to the residue, and the mixture was washed with H_2O and saturated aqueous NaCl. The ethereal solution was dried over anhydrous MgSO_4 . Removal of the drying agent and the solvent gave a crude product, which was purified by column chromatography with silica gel. The pure parent compound was identified by comparison with an authentic sample (TLC, ^1H NMR, ^{13}C NMR).

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