



Cerium(IV) sulfate tetrahydrate: a catalytic and highly chemoselective deprotection of THP, MOM, and BOM ethers



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ABSTRACT

Tetrahydropyranyl (THP), methoxymethyl (MOM), and benzyloxymethyl (BOM) phenyl/alkyl ethers were efficiently cleaved to the corresponding parent hydroxyl compounds in good yields using catalytic amounts of Ce(SO₄)₂·4H₂O by microwave-assisted or conventional heating in methanol solution. Intramolecular and competitive experiments demonstrated the chemoselective deprotection of THP ethers in the presence of triisopropylsilyl (TIPS) and *tert*-butyldiphenylsilyl (TBDPS) phenyl ethers.

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Tetrahydropyranyl (THP) ethers were one of the first¹ generally useful protecting groups for alcohols to be adopted and they are still widely used today in multistep organic syntheses.² The particular merits of THP group are its ease of introduction, the low cost of dihydropyran, and its stability under a wide range of reaction conditions. A drawback of THP group is the formation of an additional stereocenter, therefore, methoxymethyl (MOM) and benzyloxymethyl (BOM) ethers may be used instead THP of ethers.

Several methods for THP,³ MOM,⁴ and BOM⁵ ether removal have been reported. The most common methods involve acid hydrolysis; however, these methodologies are inappropriate in the case of acid sensitive molecules. Thus, there is a need to develop new alternatives to remove THP, MOM, and BOM ethers under mild and preferably catalytic conditions. Recently, various inorganic salts⁶ have shown promise for THP ether cleavage, particularly, cerium ammonium nitrate (CAN)⁷ are the unique cerium based inorganic reagent reported for depyranylation, but their scope and selectivity in the presence of silyl ethers have not been explored.

During one of our current research programs, we observed that menthol protected as THP ether **1a** was cleaved within minutes upon microwave heating in methanol containing cerium(IV) sulfate tetrahydrate. As a consequence of the above results, we

decided to investigate the Ce(SO₄)₂·4H₂O cleavage of tetrahydropyranyl ether **1a** in more detail.

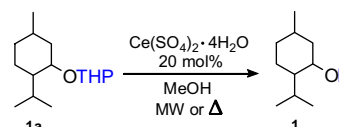


Table 1

Deprotection of THP ethers using 20 mol % Ce(SO₄)₂·4H₂O in methanol by microwave (MW) or conventional heating (Δ)

Entry	Substrate	Alcohol ^a	Yield ^{b,c} (%)	
			MW ^d	Δ ^e
1	2a	2	92	92
2	3a	3	94	96
3	4a	4	87	90
4	5a	5	94	90
5	6a	6	90	93
6	7a	7	86	88
7	8a	8	Trace	Trace
8	9a	9	NR	NR

^a Confirmed by comparison with ¹H NMR and ¹³C NMR with authentic sample.

^b Yields refer to chromatographically pure isolated compounds.

^c In some cases no reaction occurred (NR) or product yields were very low and ca. 90–95% of starting material was recovered.

^d 130 °C, 20 min.

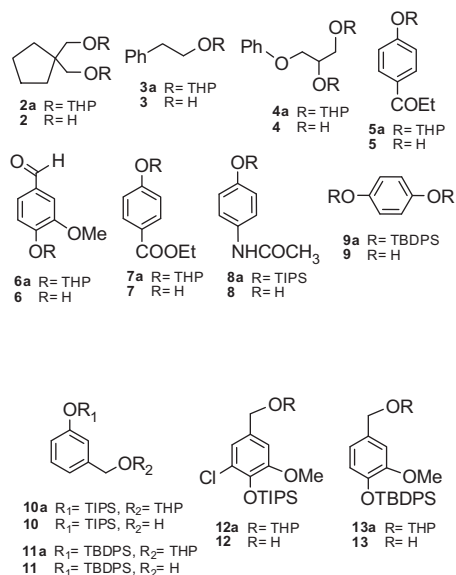
^e 60 °C, 12 h.

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The optimized conditions for the microwave assisted⁸ cleavage of **1a** were heating at 130 °C for 20 min in methanol containing 20 mol % $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$. With this catalyst concentration, cleavage of **1a** was slow at room temperature, but heating (conventional) at 60 °C resulted in acceptable reaction rates, and a 12 h reaction period was adopted as the standard.⁹

Cleavage of a series of THP ethers was then examined under these optimized conditions (Table 1). Our method demonstrated that THP alkyl and aryl ethers were very efficiently cleaved in high yields. Interestingly, when we studied the deprotection of TIPS (entry 7) and TBDPS (entry 8) ethers of phenols using our method, these were cleaved in trace amounts or not at all.



Data in Table 1 clearly indicate that selective cleavage of THP ethers in the presence of silyl phenyl ethers should be possible. Indeed, the results presented in Table 2 demonstrate that THP alkyl ethers are cleanly and efficiently removed in the presence of phenolic TIPS (entries 1 and 2) or phenolic TBDPS (entries 3 and 4) ethers within the same molecule.¹⁰

In addition, we carried out competition experiments to demonstrate that phenolic THP protected species can be cleanly cleaved in the presence of other phenols protected as TIPS (Table 3, entry 1) or TBDPS (entry 2) ether.¹⁰

On the other hand, we decided to explore the scope of our method in similar protecting groups such as methoxymethyl (MOM) and benzyloxymethyl (BOM) ethers. Table 4 shows the

Table 2

Chemoselectivity deprotection of THP alkyl ethers in the presence of TIPS and TBDPS phenyl ethers

Entry	Substrate	Product ^a	Yield ^b (%)	
			MW ^c	Δ ^d
1	10a	10	92	88
2	12a	12	93	95
3	11a	11	95	95
4	13a	13	90	90

^a Confirmed by comparison with ¹H NMR and ¹³C NMR with authentic sample.

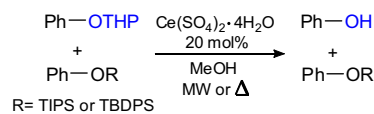
^b Yields refer to chromatographically pure isolated compounds.

^c 130 °C, 20 min.

^d 60 °C, 12 h.

Table 3

Cleavage of THP phenyl ethers in the presence of silyl phenyl ethers by competition experiments



Entry	Substrate	Product ^a (Yield %) ^b	
		Δ ^c	MW ^d
1	6a + 8a	6 (88) + 8a (94)	6 (90) + 8a (95)
2	7a + 9a	7 (90) + 9a (96)	7 (93) + 9a (94)

^a Confirmed by comparison with ¹H NMR and ¹³C NMR with authentic sample.

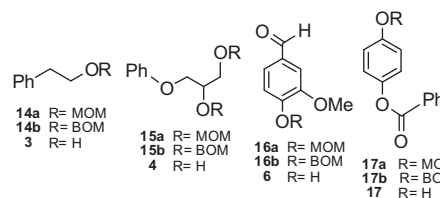
^b Yields refer to chromatographically pure isolated compounds.

^c 60 °C, 12 h.

^d 130 °C, 20 min.

Table 4

Deprotection of MOM and BOM alkyl/aryl ethers using 20 mol % $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$ in methanol by microwave (MW) or conventional heating (Δ)



Entry	Substrate	Product ^a	Yield ^b (%)	
			MW ^c	Δ ^d
1	14a	3	87	84
2	14b	3	86	90
3	15a	4	90	88
4	15b	4	85	86
5	16a	6	87	85
6	16b	6	90	85
7	17a	17	80	90
8	17b	17	82	87

^a Confirmed by comparison with ¹H NMR and ¹³C NMR with authentic sample.

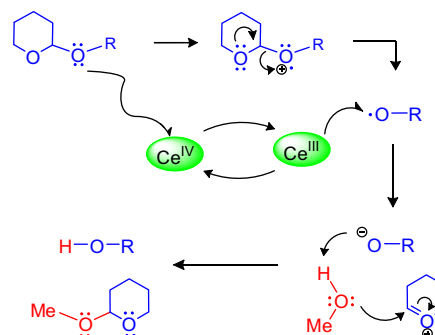
^b Yields refer to chromatographically pure isolated compounds.

^c 130 °C, 20 min.

^d 60 °C, 12 h.

cleavage of MOM (entries 1 and 3) and BOM (entries 2 and 4) ethers of alcohols as well as MOM (entries 5 and 7) and BOM (entries 6 and 8) ethers of phenols in good yields.

The chemistry of Ce(IV) as a powerful one-electron oxidants in organic synthesis is well known.¹¹ The electron-transfer processes by O/Ce(IV) in the deprotection of several protective groups have been proposed¹² and demonstrated¹³ previously. Therefore, herein we propose a plausible mechanism (Scheme 1) for the removal of the THP group from organic molecules by using $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$.



Scheme 1. An O/Ce redox cycle is a proposed plausible mechanism for the cleavage of THP ethers.

An essential step in depyranlylation reaction involves oxidation of tetrahydropyranyl ether to give the corresponding radical cation while the reduction of Ce^{IV} – Ce^{III} takes place. Radical cations then undergo fragmentation to give an alkoxy radical. Then, reduction of alkoxy radical to alkoxide allows regeneration of Ce^{IV} from Ce^{III} . Finally, protonation of alkoxide by methanol produces free alcohol.

In conclusion, we report that catalytic cerium(IV) sulfate tetrahydrate in methanol solution, affects the efficient, facile, mild, and selective deprotection of THP, MOM, and BOM ethers. Furthermore, we demonstrated that THP ethers are efficiently cleaved in the presence of phenols protected as triisopropylsilyl or *tert*-butyldi-phenylsilyl ethers. The noteworthy feature of this deprotection method, in addition to its selectivity, is that $Ce(SO_4)_2 \cdot 4H_2O$ is readily available, easily handled, and of relatively low toxicity.

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Supplementary data

Supplementary data (characterization data of all compounds and copies of 1H NMR and ^{13}C NMR spectra) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2013.10.117>.

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- Microwave Irradiation Procedure*: A 10-mL reaction vessel was charged with a magnetic stir bar, 0.4 mmol of THP ether and 20 mol % $Ce(SO_4)_2 \cdot 4H_2O$ in 2 mL of MeOH. A septum cap was affixed; the vessel was placed in the microwave cavity of an Anton-Paar microwave equipment. The stirring reaction mixture was irradiated at 130 °C for 20 min. After cooling to room temperature, TLC indicated the disappearance of starting material. The solid cerium sulfate was filtered off and the solvent was removed under reduced pressure. Column chromatography afforded pure alcohol. All products were spectrally identical with authentic alcohols.
- Conventional Heating Procedure*: A 10-mL round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. Then were added 0.4 mmol of THP ether and 20 mol % $Ce(SO_4)_2 \cdot 4H_2O$ in 2 mL of MeOH. The reaction mixture was stirred at 60 °C for 12 h. After cooling to room temperature, TLC indicated the disappearance of starting material. The solid cerium sulfate was filtered off and the solvent was removed under reduced pressure. Column chromatography afforded pure alcohol. All products were spectrally identical with authentic alcohols.
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