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Mild and Efficient Removal of Hydroxyethyl Unit from 2-Hydroxyethyl Ether Derivatives Leading to Alcohols

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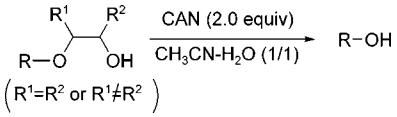
ABSTRACT

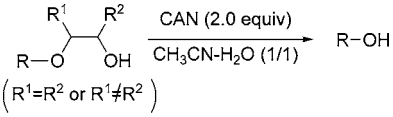


CAN is a good reagent for the transformation of 2-hydroxyethyl ether units to alcohols. Significantly, many functional groups can tolerate the reaction conditions, although they do not survive under many previously reported removal conditions. The reaction mechanism is clarified.

The transformation of 2-hydroxyethyl ether units to alcohols is very important, especially for asymmetric synthesis with C_2-symmetric chiral acetals from chiral 2,3-butanediol or chiral hydrobenzoin, because such units are formed by the cleavage of the C−O bond of the dioxolane rings in the nucleophilic substitution reactions. The usual method for the removal of 2-hydroxyethyl ether units from 2,3-butanediol involves a multistep sequence, i.e., oxidation of a secondary alcohol and then Birch reduction[1] or Baeyer−Villiger reaction followed by methanolysis.[2] On the other hand, for the 2-hydroxyethyl ether units derived from chiral hydrobenzoin, (1) oxidation of the secondary alcohol followed by reductive elimination[3] or (2) Birch reduction or hydrogenolysis are usually used.[4] However, such reactions are not applicable to compounds having labile functions such as carbonyl, halogen, and olefin groups. Recently, asymmetric synthesis using a chiral hydrobenzoin has increased rapidly because of the ready availability of optically pure hydrobenzoin via the Sharpless asymmetric dihydroxylation of *trans*-stilbene.[5]

We now present a very mild, efficient, and highly general one-pot removal method for 2-hydroxyethyl ether units to give alcohols (Scheme 1).

Scheme 1. Transformation of 2-Hydroxyethyl Ethers to Alcohols



Quite recently, we wanted to obtain an alcohol **2** from **1** by removal of the 2-hydroxy-1,2-diphenylethylene unit. We succeeded in effecting this transformation with cerium ammonium nitrate (CAN), the desired alcohol **2** being obtained in good yield (Table 1, entry 1).[6] On the other hand, the usual way to remove the 2-hydroxy-1,2-diphenylethyl unit, i.e., the Birch reduction or hydrogenolysis, led to poor results, giving a complex mixture due to the presence of the iodide and lactone moieties (entries 2, 3). Other reaction conditions, i.e., phenyliodine diacetate (PIDA)−I_2,[7] Pb-

(1) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088.
(2) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371.
(3) Alexakis, A.; Trevitt, G. P.; Bernardinelli, *J. Am. Chem. Soc.* **2001**, *123*, 4358.
(4) Fujioka, H.; Kitagawa, H.; Nagatomi, Y.; Kita, Y. *J. Org. Chem.* **1996**, *61*, 7309.
(5) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302.

(6) Fujioka, H.; Ohba, Y.; Hirose, H.; Murai, K.; Kita, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 734.

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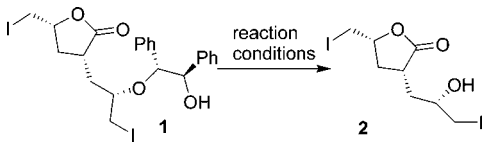
Table 1. Attempts for Removal of 2-Hydroxy-1,2-diphenylethyl Unit of **1**



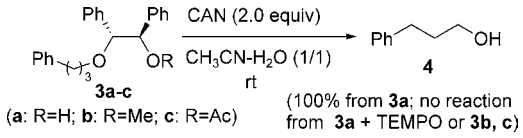
entry	conditions	yield
1	CAN/CH_3CN-H_2O	80%
2	Birch reduction[a]	decomp
3	hydrogenation[b]	decomp
4	PIDA, I_2[c]	decomp
5	$Pb(OAc)_4$[d]	nd[g]
6	$RuCl_3$, $NaIO_4$[a]	decomp
7	DDQ[f]	nr

[a] Ca (10 equiv), EtOH (10 equiv)/liquid NH_3, Et_2O. [b] $Pd(OH)_2$ (0.1 equiv)/EtOH, H_2 (1 atm). [c] Phenyl iodine diacetate (PIDA) (2.5 equiv), I_2 (1 equiv). [d] $Pb(OAc)_4$ (1.2 equiv), pH 7 buffer (0.1 M)/MeOH−CH_2Cl_2 = 1/2. [e] $RuCl_3 \cdot 3H_2O$ (2.2 mol %), $NaIO_4$ (20 equiv)/$CH_3Cn-CCl_4$ = 1/1. [f] DDQ (2 equiv), $CH_2Cl_2-H_2O$ = 18/1. [g] Major product was the compound reduced to iodines.

$(OAc)_4$,[8] and $RuCl_3-NaIO_4$,[9] usually used for the removal of the 2-hydroxyethyl unit from the *N*-2-hydroxyethyl-*N*-alkylamine, also gave poor results (entries 4−6). It is noteworthy that DDQ,[10] which is interchangeable with CAN in many cases, did not work at all in this case (entry 7, Table 1). Although the CAN method has previously been applied to the compounds derived from 1,2-di-(4-methoxyphenyl)-1,2-diol,[11] it appears that the authors went to the trouble of preparing a rather special diol, 1,2-di-(4-methoxyphenyl)-1,2-diol, for deprotection by CAN because the deprotection of 4-methoxyphenylmethyl ethers by CAN is widely recognized.[12,13] On the other hand, no report for the deprotection of the compounds derived from hydrobenzoin or other diols by CAN has appeared, to the best of our knowledge. Furthermore, the reaction mechanism for the deprotection of the compounds derived from 1,2-di-(4-methoxyphenyl)-1,2-diol was also not discussed. Therefore, we studied this reaction and its mechanism in detail.

(7) Boto, A.; Hernandes, R.; Montoya, A.; Suarez, E. *Tetrahedron Lett.* **2004**, *45*, 1559.
(8) Chakraborty, T. K.; Reddy, G. V. *J. Org. Chem.* **1992**, *57*, 5462.
(9) Ranganathan, D.; Saini, S. *J. Am. Chem. Soc.* **1991**, *113*, 1042.
(10) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(11) (a) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162. (b) Andrus, M. B.; Meredith, E. L.; Simmons, B. L.; Soma Sekhar, B. B. V.; Hicken, E. J. *Org. Lett.* **2002**, *4*, 3549. (c) Andrus, M. B.; Mendenhall, K. G.; Meredith, E. L.; Soma Sekhar, B. B. V. *Tetrahedron Lett.* **2002**, *43*, 1789. (d) Andrus, M. B.; Meredith, E. L.; Soma Sekhar, B. B. V. *Org. Lett.* **2001**, *3*, 259.
(12) Andrus et al. developed a new asymmetric aldol reaction first using the chiral diol, (*S*,*S*)-hydrobenzoin, as a chiral auxiliary and then hydrogenation for its removal (Andrus, M. B.; Soma, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035). However, the method was not applied to compounds having functional groups labile under hydrogenolysis conditions (ref 11c). For the total synthesis of (+)-geldanamycins, they used 1,2-di-(4-methoxyphenyl)-1,2-diol as the chiral diol (refs 11a,b,d).
(13) Green, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, 1999.

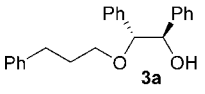
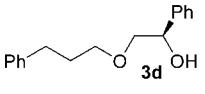
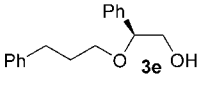
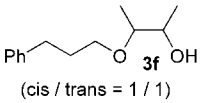
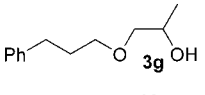
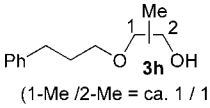
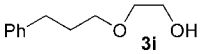
Scheme 2



The reactions of the 2-hydroxy-1,2-diphenylethyl ether derivatives **3a**−**c** of 3-phenylpropanol **4** were first examined. The reaction of the hydroxy compound **3a** proceeded smoothly to give the alcohol **4** in quantitative yield; on the other hand, the addition of 4-amino-(2,2,5,5-tetramethylpiperidine-*N*-oxide) (TEMPO), a radical scavenger, or *O*-protected compounds (Me−ether **3b** and acetate **3c**) did not afford the alcohol **4** at all, and the starting materials were recovered (Scheme 2).

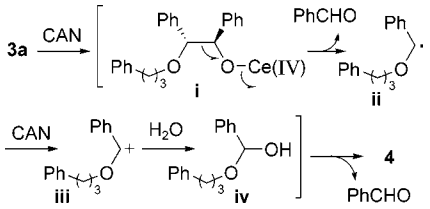
The reaction worked well for various 2-hydroxyethyl ether compounds of 3-phenylpropanol **4** (Table 2); thus, the 2-hydroxy-1,2-diphenylethyl group **3a** (entry 1), 2-hydroxy-2- or 1-phenylethyl groups **3d** or **3e** (entries 2, 3), and 2-hydroxy-2,3-dimethyl group **3f** (entry 4) all gave the alcohol **4** in good yields. It is noteworthy that 2-hydroxy-2-methyl compound **3g** and 2-hydroxy-monomethylated mixture (1-Me and 2-Me (**3g**) mixture) **3h** still gave **4** in good yields, although excess CAN and longer reaction times

Table 2. Reactions of Various 2-Hydroxytheyl Ethers of 3-Phenylpropanol **4** with CAN (2.0 equiv) in CH_3CN-H_2O (1/1) at Room Temperature.

entry	substrate	reaction time	yield of **4**
1	 **3a**	30 min	100%
2	 **3d**	30 min	100%
3	 **3e**	30 min	92%
4	 **3f** (cis / trans = 1 / 1)	30 min	80%
5	 **3g**	6 h	80%[a]
6	 **3h** (1-Me /2-Me = ca. 1 / 1)	10 h	66%[b]
7	 **3i**	>12 hr	No reaction[c]

[a] Reaction was carried out using 4.0 equiv of CAN. [b] Reaction was carried out using 6.0 equiv of CAN. [c] Reaction was carried out using 6.0 equiv of CAN at 60 °C.

Scheme 3. Reaction Mechanism of **3a**



were necessary (entries 5, 6), while the reaction of the unsubstituted 2-hydroxyethyl compound **3i** did not proceed (entry 7).

The results in Scheme 2 and Table 2 suggested the reaction mechanism shown in Scheme 3. The reaction is rationalized using the 2-hydroxy-1,2-diphenyethyl ether **3a**. We contend that the following sequence is in operation: The first step involves formation of the O−Ce(IV) bond to give **i**. Radical cleavage of the C−C bond then occurs to give the radical intermediate **ii**. Single-electron transfer then proceeds to give the cationic species **iii**. Finally, nucleophilic addition of water occurs to give hemiacetal **iv**, which breaks down to give the alcohol **4** and benzaldehyde.[14,15] This mechanistic proposal involving radical cleavage was confirmed from the fact that the reaction of **3a** did not proceed at all in the presence of the radical scavenger, TEMPO, as already described.

Table 3 shows the results of various substrates **5**. Many functional groups such as esters **5a**,**b** (entries 1, 2), olefins **5c**,**d** (entries 3, 4), Me−ether **5e** (entry 5), Bn−ether **5f** (entry 6), acetate **5g** (entry 7), tosylate **5h** (entry 8), and iodine **5i** (entry 9) tolerated these reaction conditions, whereas *p*-methoxybenzyl (PMB)−ether **5j** gave the diol **6h**. These facts show that the reaction here is very mild and has a wide generality.

The significant advantages of our method were also clarified by the successful reactions of compounds **7**[16] and **10a**,**b**[6] (Scheme 4), which contain functional groups such as bromine, olefin, and acetal units in **7** and iodine, acetal, and nitrile units in **10a**,**b**. A domino three-step sequence was also shown to be viable for converting **7** into the ene bromo lactol **8**, which exists as a 2:1 mixture of hemiacetals.[17] Its structure was determined by its conversion to lactone **9**. Compounds **10a**,**b** also gave the acetals **11a**,**b** in a single operation. These would allow for new chiral synthones because they have many functional groups for further transformation.

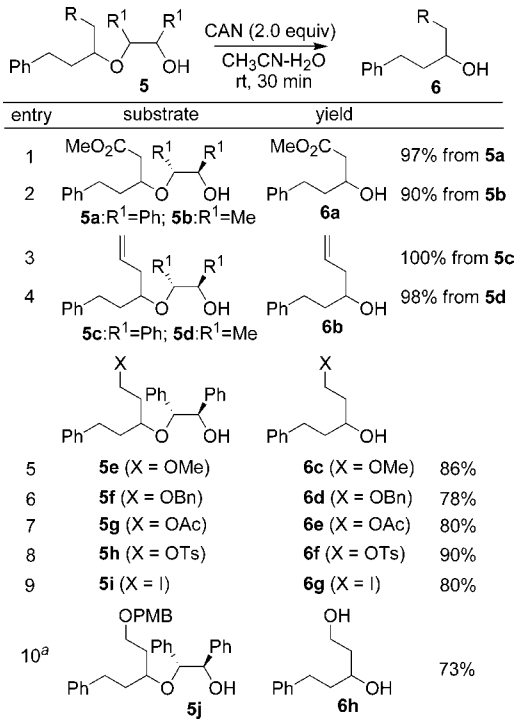
(14) For oxidative cleavage of 1,2-glycols by CAN for reference, see: Trahanovsky, W. S.; Gilmore, J. R.; Heaton, P. C. *J. Org. Chem.* **1973**, *38*, 760.

(15) Formation of benzaldehyde in the reaction mixtures from **3a**,**d**,**e** was determined by ^{1}H NMR.

(16) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825.

(17) For deprotection of acetals by CAN, see: (a) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Markó, I. E. *Tetrahedron* **2003**, *59*, 8989. (b) Markó, I. E.; Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C. *Angew. Chem., Int. Ed.* **1999**, *38*, 3207. For hydrolysis of acetal units in compounds **7** and **10**, the reactions were carried out at 60 °C and excess amounts of CAN were used.

Table 3. Reactions of Various 2-Hydroxyethyl Ethers (**5**)

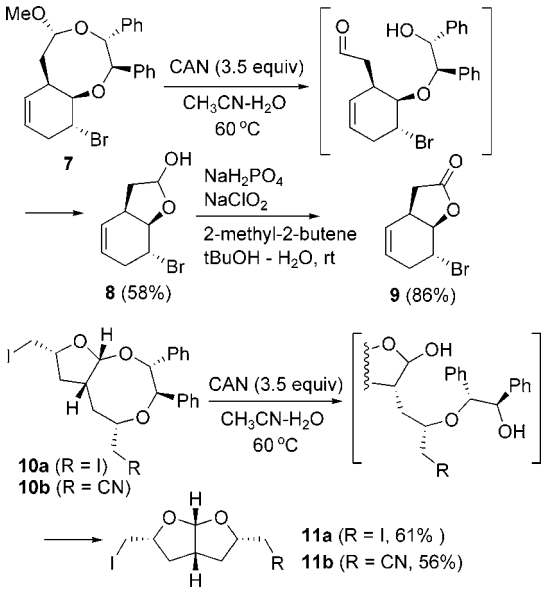


entry	substrate	yield
1	**5a**:R^1=Ph; **5b**:R^1=Me	**6a** 97% from **5a**
2		**6a** 90% from **5b**
3	**5c**:R^1=Ph; **5d**:R^1=Me	**6b** 100% from **5c**
4		**6b** 98% from **5d**
5	**5e** (X = OMe)	**6c** (X = OMe) 86%
6	**5f** (X = OBn)	**6d** (X = OBn) 78%
7	**5g** (X = OAc)	**6e** (X = OAc) 80%
8	**5h** (X = OTs)	**6f** (X = OTs) 90%
9	**5i** (X = I)	**6g** (X = I) 80%
10[a]	**5j**	**6h** 73%

[a] Performed with 4.0 equiv of CAN.

In conclusion, we proved that CAN deprotects a variety of ethers derived from various diols, including hydrobenzoin. We have also clarified its reaction mechanism. The reaction is very mild and efficient, and many functional groups are tolerant of the reaction. Therefore, this study adds a new aspect to synthetic organic chemistry and is potentially

Scheme 4. Domino-Type Reactions



important in asymmetric synthesis involving C_2-symmetric diols as described in the introduction of this Letter.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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