ORGANIC
LETTERS

1999
Vol. 1, No. 5
769−771

Selective Rhenium-Catalyzed Oxidation of Secondary Alcohols with Methyl Sulfoxide in the Presence of Ethylene Glycol, a Convenient One-Pot Synthesis of Ketals

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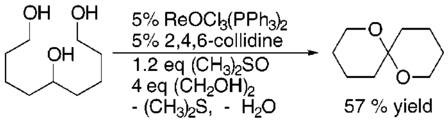
Received June 22, 1999

ABSTRACT



Secondary alcohols are oxidized preferentially by DMSO and the catalyst $ReOCl_3(PPh_3)_2$ in the presence of ethylene glycol and refluxing toluene, producing the corresponding ketals. The reactions are rapid, and proceed in very good to excellent yields. The byproducts of the reaction, methyl sulfide and water, are easily removed. No epoxidation or other common side reactions were observed. This direct oxidative transformation of alcohols to the protected ketal derivatives should have broad synthetic applicability.

The oxidation of alcohols to carbonyl compounds is a fundamental transformation in organic synthesis. While many different reagents are available, there remains a constant need for the development of new oxidants with improved chemoselectivity.[1,2] Other desirable characteristics for a reagent are stability, low cost, and minimal concomitant waste.[3] Sulfoxide-based Swern oxidations are frequently used to oxidize primary and secondary alcohols,[4] although this method requires anhydrous solvents, low temperatures, an amine base, and a strong electrophile to generate the reactive sulfonium ion. Consideration of the hypothetical reaction of 2-propanol with methyl sulfoxide eq 1 illustrates the potential advantages of a catalytic process, since water and methyl sulfide are the only byproducts. The stability of methyl sulfoxide constitutes the greatest challenge toward the development of this catalytic process. Transition metals such as rhenium are capable of activating sulfoxides for other synthetically useful oxidation reactions.[5] Recently, allylic and

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(1) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; London, 1981. (b) Hudlucky, M. *Oxidations in Organic Chemistry*; American Chemical Society: Washington, D.C., 1990. (c) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, 2nd ed.; John Wiley & Sons: New York, 1992. (d) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599.

(2) A variety of metals catalyze the oxidation of alcohols with hydrogen peroxide (a) Clerici, M. G. *Stud. Surf. Sci. Catal.* **1993**, *78*, 21. The high reactivity of peroxides can lead to other reactions such as the following: alkene epoxidation [(b) Trost, B. M.; Masuyama, Y. *Tetrahedron Lett.* **1984**, *25*, 173], oxidative cleavage of diols [(c) Ishii, Y.; Yamawaki, K.; Yoshida, T.; Ura, T.; Ogawa, M. *J. Org. Chem.* **1987**, *52*, 1868; (d) Kaneda, K.; Kawanishi, Y.; Jitsukawa, K.; Teranishi, S. *Tetrahedron Lett.* **1983**, *24*, 5009], and ether oxidation [(e) Murray, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. *Tetrahedron Lett.* **1995**, *36*, 6415; (f) Zauche, T. H.; Espenson, J. H. *Inorg. Chem.* **1998**, *37*, 6827; (g) Espenson, J. H.; Zhu, Z.; Zauche, T. H. *J. Org. Chem.* **1999**, *64*, 1191].

(3) Aerobic oxidations selective for primary alcohols have been catalyzed by copper [(a) Chaudhuri, P.; Hess, M.; Flörke, U.; Wieghardt, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2217], palladium [(b) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185; (c) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *Tetrahedron Lett.* **1998**, *39*, 6011], and ruthenium [(d) Hanyu, A.; Takezawa, E.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1998**, *39*, 5557].

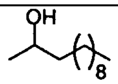
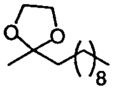
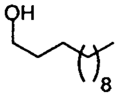
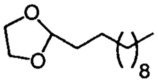
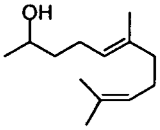
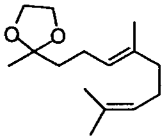
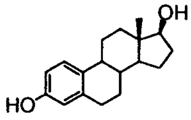
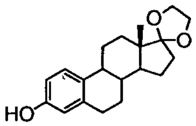
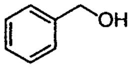
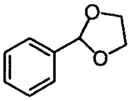
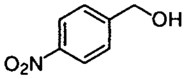
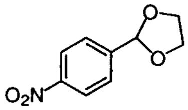
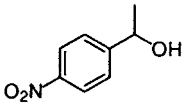
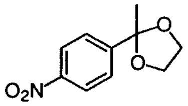
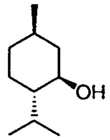
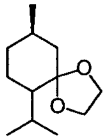
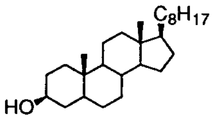
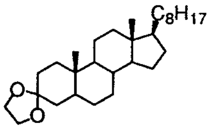
(4) Tidwell, T. T. *Synthesis* **1990**, 857.

(5) (a) Arterburn, J. B.; Nelson, S. L. *J. Org. Chem.*, **1996**, *61*, 2260. (b) Arterburn, J. B.; Perry, M. C. *Tetrahedron Lett.* **1996**, *37*, 7941. (c) Arterburn, J. B.; Perry, M. C.; Nelson, S. L.; Dible, B. R.; Holguin, M. S. *J. Am. Chem. Soc.* **1997**, *119*, 9309.

(6) Lorber, C. Y.; Pauls, I.; Osborn, J. A. *Bull. Soc. Chim. Fr.* **1996**, *133*, 755.

10.1021/ol990755e CCC: $18.00

Table 1. Rhenium-Catalyzed Alcohol Oxidation with DMSO and Ethylene Glycol[7]

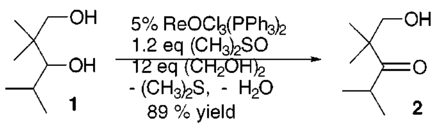
entry	substrate	product	yield (%)	ketone	method	time (hrs)
1			86[a]	5	A	5
2			85[a]		A[d]	23
3			82[a]	6	A	5
4			82[a]	18	A	5
5			87[a]		B	5
6			92[a]		A	5
7			88[a]		A	5
8			67[b,c] 81[b,c]	17 8	A B	5 7
9			93[a] 100[a]		A B	5 5

[a] Isolated by chromatography on silica gel. [b] Isolated by bulb-to-bulb distillation. [c] Product contained 14% isomenthone ketal. [d] Additional DMSO and ethylene glycol were required.

benzylic alcohols were catalytically oxidized with sulfoxides using *cis*-dioxomolybdenum(VI) complexes.[6] In this communication, we describe a new catalytic rhenium–ethylene glycol system which selectively oxidizes secondary alcohols with methyl sulfoxide, and conveniently produces the corresponding ethylene ketals.

$$(CH_3)_2CH(OH) + Me_2SO \rightarrow (CH_3)_2C(O) + H_2O + Me_2S \quad (1)$$

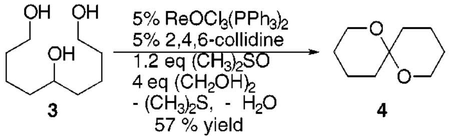
We had initially observed low yields of ketone products from the catalytic oxidation of secondary alcohols with $ReOCl_3(PPh_3)_2$ and methyl sulfoxide in refluxing toluene and found that primary alcohols were even less reactive under these conditions. Interestingly, a dramatic increase in reactivity resulted from the addition of ethylene glycol. The preferential reactivity of secondary alcohols in this system was evident from the reaction of diol **1**, which was completely oxidized to ketone **2** after 1 h, 89% yield.



When our investigation was extended to include less-hindered alcohol substrates, we found that ketals were obtained as the major products from further reaction of the ketones with ethylene glycol under the mild Lewis acidic conditions Table 1.[7] The oxidation of 2-dodecanol using the standard conditions produced the ketal and ketone in 86% and 5% isolated yields, respectively (entry 1). The oxidation of the primary alcohol 1-dodecanol to the acetal was significantly slower and required additional methyl sulfoxide, ethylene glycol, and a longer reaction time (entry 2).[8] Alcohols were selectively oxidized in the presence of alkenes, and no oxidative cyclization typical of rhenium(VII) trioxo complexes occurred with the diene-ol substrate (entry 3).[9] The phenol group was also unaffected during the oxidative ketalization of the secondary alcohol in β-estradiol (entry 4).

The oxidation of benzyl alcohol under these conditions was problematic due to the competing formation of ether byproducts which result from ionization to the benzylic carbocation. Consistent with this explanation, the 4-nitro-substituted analogues were oxidized in high yield without producing the ether byproducts (entries 6 and 7). The yield of acetal from the oxidation of benzyl alcohol was dramatically improved by the addition of a small amount of the mild base 2,4,6-collidine as a buffer (method B, entry 5). The yields of ketals from the oxidation of secondary alkyl alcohols were also slightly improved (entries 8 and 9). Epimerization of the α-position occurred during the reaction of menthol, producing a 6:1 mixture of menthone:isomenthone ketals (entry 8).

The direct oxidative transformation of alcohols to the protected ketal derivative is unprecedented in the alcohol oxidation literature to the best of our awareness, and this procedure should have broad synthetic applicability. As further evidence of the synthetic utility of this method, we carried out a one-step synthesis of the olive fly ketal **4** by directly oxidizing 1,5,9-nonanetriol **3**. Here preferential intramolecular ketal formation occurred, giving the volatile spiro ketal product in 57% isolated yield.[10]



The dramatic difference in reactivity due to ethylene glycol implicates its possible role as a chelating ligand.[11] Chelating ligands are known to favor the formation of *cis*-dioxo d^2 octahedral metal complexes, which are typically more reactive than the *trans* isomers.[12,13] *cis*-Dioxorhenium(VII) complexes containing the chelating hydridotris(1-pyrazolyl)-borate ligand are known to stoichiometrically oxidize coordinated alcohols.[14] The faster rate for the oxidation of secondary alcohols is consistent with a mechanism where decomposition of a metalloester intermediate is the rate-determining step.[2b] Mechanistic investigations, and further development of synthetic applications are currently in progress.

Acknowledgment. The authors thank the USAMRC DAMD17-97-1-7120 for financial support.

Supporting Information Available: Detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[7] **General Procedure. Method A.** The alcohol (1 mmol), ethylene glycol (4 mmol), DMSO (2.1 mmol), and $Re(O)Cl_3(PPh_3)_2$ (0.05 mmol) in toluene (5 mL) was refluxed using a Dean−Stark apparatus. Additional portions of ethylene glycol (8 mmol) were added to the reaction mixture after 1 h and 3 h. After 5 h, the reaction mixture was washed with $NaHCO_3$ and H_2O, dried $MgSO_4$, and purified by chromatography or bulb-to-bulb distillation. **Method B.** 2,4,6-Collidine (3.3 μL, 0.025 mmol) was also included. Ketones were efficiently converted to the ketals when they were added to the reaction mixture.

[8] Ethylene glycol was consumed slowly during the reaction.

[9] (a)Tang, S.; Kennedy, R. M. *Tetrahedron Lett.* **1992**, *33*, 5303. (b) McDonald, F. E.; Singhi, A. D. *Tetrahedron Lett.* **1997**, *38*, 7683. (c) Towne, T. B.; McDonald, F. E. *J. Am. Chem. Soc.* **1997**, *119*, 6022. (d) Sinha, S. C.; Keinan, E.; Sinha, S. C. *J. Am. Chem. Soc.* **1998**, *120*, 9076.

[10] Reddy, G. B.; Mitra, R. B. *Synth. Commun.* **1986**, *16*, 1723.

[11] Rhenium(VII) trioxo diol complexes of the tertiary diol pinacol have been synthesized: Edwards, P. G.; Jokela, J.; Lehtonen, A.; Sillanpää, R. *J. Chem. Soc., Dalton Trans.* **1998**, 3287.

[12] Demachy, I.; Jean, Y. *New J. Chem.* **1996**, *20*, 53.

[13] Reaction mixtures containing 1,3-propanediol, a ligand with a larger “bite angle”, were not effective for oxidizing alcohols. Interestingly, diol **1** also reacted with the catalyst and DMSO in the absence of ethylene glycol to produce ketone **2**. This observation is consistent with the enhanced chelating ability of this diol relative to 1,3-propanediol due to the Thorpe−Ingold effect.

[14] (a) DuMez, D. D.; Mayer, J. M. *Inorg. Chem.* **1995**, *34*, 6396. (b) DuMez, D. D.; Mayer, J. M. *Inorg. Chem.* **1998**, *37*, 445.