Pergamon

Tetrahedron Letters, Vol. 35, No. 19, pp. 3033-3036, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0 00

0040-4039(94)E0500-W

A Mild Method for Selective Cleavage of Tetrahydropyranyl Ethers in the Presence of Other Acid-Labile Functionalities

Krishnan P. Nambiar* and Abhijit Mitra†

Department of Chemistry, University of California, Davis, CA 95616.

Abstract: A mild method for selective cleavage of tetrahydropyranyl ethers in the presence of other acid sensitive functionalities such as acetonides, methoxymethyl ethers, methylenedioxy ethers, mesitaldehyde acetals and t-butyldimethylsilyl ethers using Lewis acid-thiol system is described.

Selective introduction and removal of protecting groups is of great consequence in the synthesis of polyfunctional organic molecules. Tetrahydropyranylation of hydroxyl groups has been recognized as a useful and representative method for protection of alcohols.[1] It is highly desirable to have a method that would effect the selective removal of tetrahydropyranyl (THP) ethers in the presence of other functional groups that are sensitive to the acidic reaction conditions commonly used for their cleavage.[2-8] In this communication we describe a mild method for such a transformation.[9] We observed that Lewis acids in the presence of thiols at low concentration and low temperature are very effective in removing THP ethers in the presence of other acid-labile functional groups such as acetonides, methylenedioxy ethers, methoxymethyl ethers, mesitaldehyde acetals and t-butyl dimethylsilyl ethers in high yields.[10] Demethylation of methyl ethers using $BF_3.Et_2O$-thiol system,[11] dealkylation of esters and cleavage of alcoholic C-O bonds of lactones using aluminum halide-thiol system[12] and cleavage of methylenedioxy ethers using $AlBr_3$-ethanethiol[13] have been reported. These reactions were carried out at room temperature with excess Lewis acid and the reaction times were long. All these functionalities are stable to our reaction conditions used for the selective removal of THP ethers.

In a typical reaction, 10 mole percent of Lewis acid ($BF_3.Et_2O$) is added to a solution of the substrate in dry dichloromethane containing 5% (v/v) of ethanethiol at -20° C and the resulting solution is allowed to warm up to 0° C during a period of 30 minutes. The reaction mixture is poured into saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic extract is dried over anhydrous sodium sulfate, solvent evaporated under reduced pressure and the residue chromatographed on silica gel. In an alternate workup procedure, the Lewis acid is neutralized by adding triethyl amine, the reaction mixture evaporated under reduced pressure and the residue chromatographed on silica gel. Other Lewis acids such as BBr_3, $ZnBr_2$ and $ZnCl_2$ are also effective in this transformation.

The efficiency of this procedure for selective removal of THP ethers is illustrated using the examples shown in the table. THP ether groups in compounds **1** and **2** are selectively removed without affecting alkyl or aryl methoxymethyl ethers. The aryl methoxy group in **2** is also unaffected. The acetonide groups in compounds **3**, **4**, **5** and **6**; the alkyl methoxy group in **3** and mesitaldehyde acetal group in **5** are stable to THP ether cleavage conditions. t-Butyldimethylsilyl ethers are excellent hydroxyl protecting groups because of their ease of formation[14] and selective removal.[15] Under acidic conditions (eg. in 2:1 acetic acid-water at 25° C) t-butyl dimethylsilyl ether and THP ether are hydrolyzed at comparable rates. The Lewis acid-thiol system at low

---

† Present address: Department of Chemistry, Manhattan College, Riverdale, NY 10471.

Table

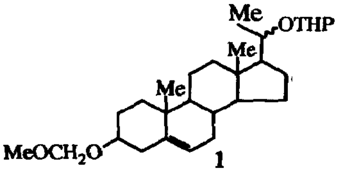
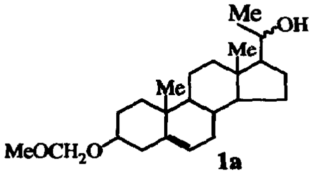
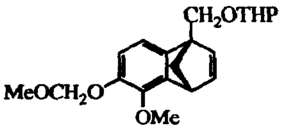
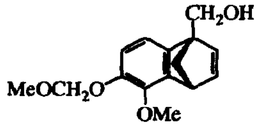
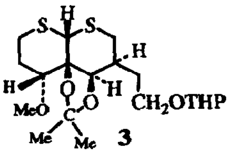
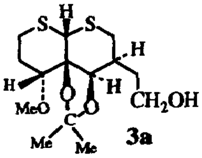
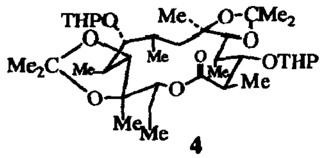
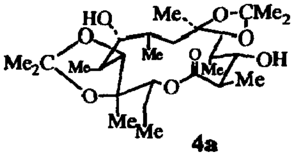
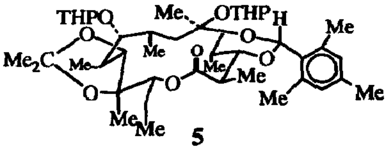
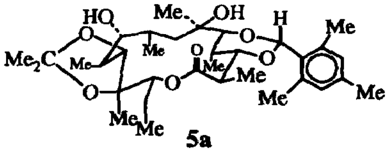
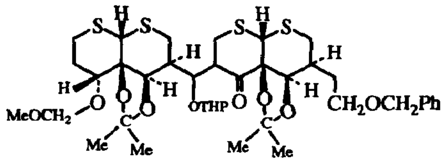
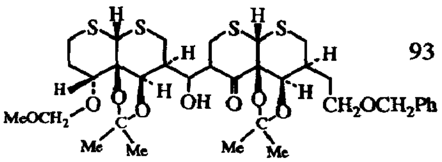
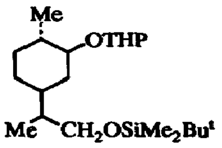
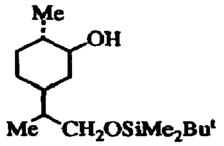
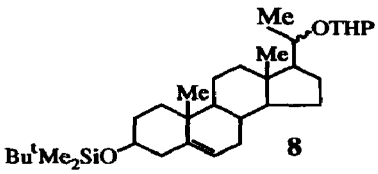
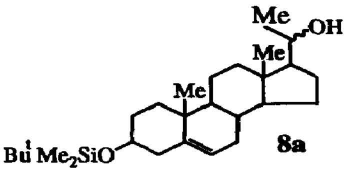
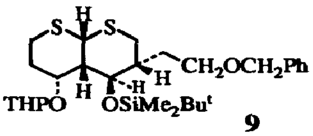
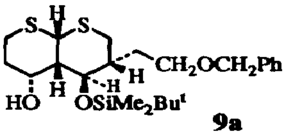
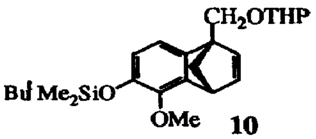
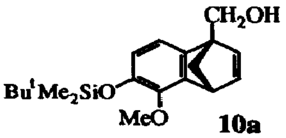
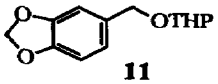
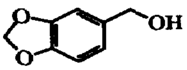
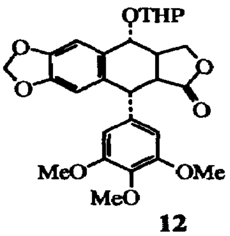
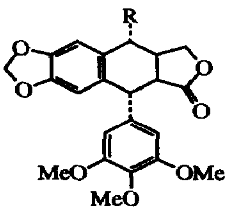
Substrate	Product	Yield (%)
 **1**	 **1a**	95
 **2**	 **2a**	91
 **3**	 **3a**	93
 **4**	 **4a**	83
 **5**	 **5a**	82
 **6**	 **6a**	93

Table (continued)

Substrate	Product	Yield (%)
 **7**	 **7a**	100
 **8**	 **8a**	94
 **9**	 **9a**	92
 **10**	 **10a**	94
 **11**	 **11a** R = OH **11b** R = SC_2H_5	77 23
 **12**	 **12a** R = OH **12b** R = SC_2H_5	75 8

temperature is capable of completely distinguishing between these two ether groups, cleaving only THP ethers (compounds **7-10**). Although dimethylaluminum chloride has been shown to remove THP ethers in the presence of t-butyldimethylsilyl ethers, this reagent also converts methoxymethyl ethers into ethyl ethers.[16] Both aromatic and aliphatic methoxymethyl ethers are stable to Lewis acid-thiol systems (compounds **1** and **2**). Aromatic methylenedioxy ethers are also stable to the reaction conditions (compounds **11** and **12**). In these two examples a small amount of the corresponding thioethers were formed as byproducts. Displacement of the OTHP moiety at benzylic positions having an electron donating para substituent seems to be competing with THP ether cleavage. The THP ether of benzyl alcohol under these reaction conditions gave benzyl alcohol in quantitative yield, no trace of the thioether was formed.

Acknowledgement. This research was in part supported by a grant from National Institutes of Health (GM 04229). We are grateful to the research group of the late Professor R. B. Woodward for the availability of some of the intermediates used in this study.

References and Notes

1. (a) Reese, C. B. In *Protecting Groups in Organic Chemistry* McOmie, J. F. W. Ed., Plenum Press: London, 1973, Chapter 3.
   (b) Fieser, L. F. and Fieser, M. *Reagents for Organic Synthesis* ; John Wiley and Sons, Inc.: New York, 1967, Vol. 1, p. 256.
   (c) Greene, T. W. and Wuts, P. G. M. *Protective Groups in Organic synthesis*, 2nd Ed. John Wiley and Sons, Inc.: New York, 1991, pp. 31-33.
2. (a) Sondheimer, F.; Stjernstrom, N and Rosenthal, D. *J. Org. Chem.* **1959**, *24*, 1280-1284.
   (b) Barry, P. J. and Craig, B. M. *Can J. Chem.* **1955**, *33*, 716-721.
3. Bernady, K. F.; Floyd, M. B.; Poletto, J. F.and Weiss, M. J. *J. Org. Chem.* **1979**, *44*, 1438-1447.
4. Miyashita, M.; Yoshikoshi, A. and Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772-3774.
5. Bongini, A.; Cardillo, G.; Orena, M.and Sandri, S. *Synthesis* **1979**, 618-620.
6. Beier, R. and Murdy, B. P.*Synth. Commun.* **1979**, *9*, 271-273.
7. Gigg, J. and Gigg, R. *J. Chem. Soc. C* **1967**, 431-434.
8. Corey, E. J.; Niva, H. and Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942-1943.
9. Nambiar, K. P. Presented in part at the National Meeting of the American Chemical Society , Philadelphia, PA, **1984**; paper ORGN 173.
10. All yields refer to compounds isolated after chromatography.
11. Node, M.; Hori, H. and Fujita, E. *J. C. S. Perkin I* **1976**, 2237-2240.
12. Node, M.; Nishide, K.; Sai, M.and Fujita, E. *Tetrahedron Letters* **1978**,*19*, 5211-5214.
13. Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.and Fujita, E. *Chemistry Letters* **1979**, 97-98.
14. Corey, E. J. and Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.
15. Corey, E. J. and Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549-2550.
16. Ogawa, Y. and Shibasaki, M. *Tetrahedron Letters*, **1984**, *25*, 663-664.

(*Received in USA* 4 *February* 1994; *revised* 3 *March* 1994; *accepted* 7 *March* 1994)