Simple and Regioselective Reductive Cleavage of Tetrahydropyranyl Ethers to Alcohols

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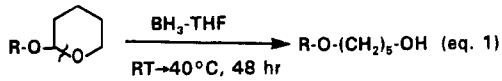
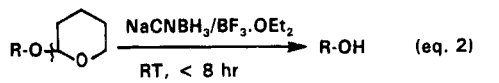
Received October 11, 1994

Selective introduction and removal of protecting groups is of great significance in organic synthesis. Acetals and ketals are protected carbonyl compounds which can be reduced to either ethers or hydrocarbons under a variety of reducing conditions, *e.g.*, trialkylsilanes in the presence of Bronsted or Lewis acids.[1] Tetrahydropyranyl (THP) ethers are mixed acetals (inter- and intramolecular) of 5-hydroxyvaleraldehyde and alcohols and are well established as protecting groups for alcohols because of their ease of formation and stability to various conditions. For the deprotection of the THP ethers, quite often a transacetalization methodology is opted, mainly because under normal hydrolytic conditions, sometimes the byproduct formed in the reaction, 5-hydroxyvaleraldehyde, is problematic during workup and purification procedures. It occurred to us that reductive cleavage of the *exo* C–O bond of THP ethers provides a convenient method for the deprotection of THP ethers, since the low-boiling, cyclic ether tetrahydropyran (H-THP) will become the byproduct. Recently, Cossy *et al.*[2] reported that reductive cleavage of THP ethers using 2 equiv of BH_3–THF furnishes 5-(alkyloxy)pentanols *via* the cleavage of the *endo* C–O bond (eq 1) in a regioselective manner. In

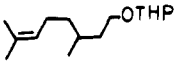
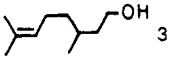
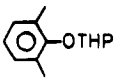
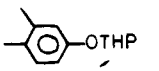
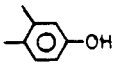
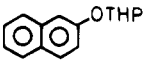
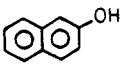
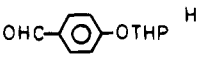
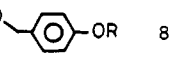




contrast, we have discovered that reductive cleavage using sodium cyanoborohydride in the presence of 1 equiv of BF_3·OEt_2 in dry THF efficiently cleaves the *exo* C–O bond of the THP ethers furnishing the corresponding alcohols in a highly regioselective manner (eq 2), which in turn provided an alternative, simple, and efficient nonhydrolytic method for the removal of the THP protecting group.[3]

A range of THP ethers[4] were prepared from the corresponding alcohols including naphthol and phenols using standard procedures (DHP and PPTS in CH_2Cl_2) and subjected to reductive cleavage using sodium cyanoborohydride and BF_3·OEt_2 in dry THF at room temperature.

Table 1. Reductive Cleavage of THP Ethers[a]

Entry	R-O-THP	Product	Time	Yield
(1)	$^nC_{12}H_{25}$-O-THP	$^nC_{12}H_{25}$-OH	2 h	90%
(2)	Cholesteryl-THP	Cholesterol	3 h	68%
(3)			3 h	80%
(4)			8 h	92%
(5)			8 h	95%
(6)			8 h	90%
(7)			8 h[b]	83%[c]

A R = THP; B R = H

[a] Yields (unoptimized) refer to isolated and chromatographically pure products. [b] When the reaction was stopped at 1 h, only product A[5] was obtained. [c] 5:3 mixture of the compounds A and B.

The results are summarized in Table 1. All the reactions were clean and completed in less than 8 h. The corresponding alcohols were obtained in very good yields. However, in contrast, the allyl and benzyl THP ethers were found to generate mixture of products under these conditions. It is worth mentioning that in the case of aliphatic THP ethers when the reaction was carried out under dilute conditions (0.1 M) varying amounts (10–30%) of 5-(alkyloxy)pentanols were also formed. In the last entry, quite expectedly, the aldehyde reduced faster than the THP ether furnishing the corresponding[5] benzyl alcohol.[6]

In conclusion, we have discovered a simple, convenient, and highly regioselective nonhydrolytic method for the removal of the THP protecting group using a combination of sodium cyanoborohydride and boron trifluoride etherate in THF.

Experimental Section

General Procedure of the BF_3·OEt_2-Catalyzed Reductive Cleavage of THP Ethers to Alcohols with Sodium Cyanoborohydride. Sodium cyanoborohydride (1.5 mmol) was added to a magnetically stirred solution of the THP ether (1 mmol) and BF_3·OEt_2 (1 mmol) in dry THF (2 mL), and the reaction mixture was stirred at room temperature until the completion of the reaction (monitored by TLC analysis). Aqueous sodium bicarbonate solution was added to the reaction mixture and extracted with ether (5 mL × 2). The ether extract was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification of the residue over a silica gel (5 g) column using a combination of ethyl acetate and hexane as solvent furnished hydroxy compounds, which were identified by comparison (TLC, IR, and ^1H NMR spectra) with authentic compounds.

Acknowledgment. J.A.S. and R.V. thank the I.I.Sc., Bangalore, and U.G.C., New Delhi, respectively, for the award of research fellowships.

JO941704S

(1) For the reductive cleavage of ketals and acetals, see: Bartels, B.; Hunter, R. *J. Org. Chem.* **1993**, *58*, 6756 and references cited therein.

(2) Cossy, J.; Bellosta, V.; Müller, M. C. *Tetrahedron Lett.* **1992**, *33*, 5045.

(3) For earlier methods of deprotection of THP ethers, see: Nambiar, K. P.; Mitra, A. *Tetrahedron Lett.* **1994**, *35*, 3033 and references cited therein.

(4) (a) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772. (b) Olah, G. A.; Husain, A.; Singh, B. P. *Synthesis* **1983**, 892. (c) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618. (d) Vig, O. P.; Sharma, S. D.; Vig, R.; Kumar, S. D. *Indian J. Chem. Sect. B* **1979**, *18B*, 31. (e) Pinhey, J. T.; Xuan, P. T. *Aust. J. Chem.* **1988**, *41*, 69. (f) Diner, U. E.; Brown, R. K. *Can. J. Chem.* **1967**, *45*, 2547. (g) Kuroda, T.; Hisamura, K.; Matsukuma, I.; Nishikawa, H.; Nakamizo, N. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 674.

(5) Taylor, G. N.; Stillwagon, L. E.; Houlihan, F. M.; Wolf, T. M.; Sogah, D. V.; Hertler, W. R. *Chem. Mater.* **1991**, *3*, 1031.

(6) Subsequently, it was observed that excess sodium cyanoborohydride and BF_3·OEt_2 deoxygenates aryl ketones: Srikrishna, A.; Sattigeri, J. A.; Viswajanani, R.; Yelamaggad, C. V. *Synlett* **1995**, 93.

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