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Tetrahedron Letters 45 (2004) 1279–1281

Tetrahedron Letters

$BiOClO_4$-mediated deprotection of silyl ethers

R. David Crouch,* Candice A. Romany, Anna C. Kreshock, Karina A. Menconi and Jennifer L. Zile

Department of Chemistry, Dickinson College, Box 1773, Carlisle, PA 17013, USA

Received 30 October 2003; revised 21 November 2003; accepted 24 November 2003

Abstract—TES- and TBS-protected alcohols undergo deprotection in good to excellent yield upon heating with 1 equiv of $BiOClO_4$-xH_2O in CH_2Cl_2. TBDPS- and TIPS-protected 2° alcohols are more resistant to deprotection. The use of this method in selective desilylation is, however, limited to the deprotection of alkyl silyl ethers in the presence of TBDPS-protected phenols.

As synthetic targets grow increasingly complex, protection/deprotection protocols continue to be of critical importance[1,2] and the development of methods for the manipulation of protecting groups remains an active area of investigation.[3] Silyl protecting groups are especially valuable when the molecule contains hydroxyl groups. Although protic acids and fluoride sources continue to be widely used for the removal of silyl protecting groups, a number of Lewis acids have been introduced to mediate desilylation reactions. Some recent examples from the literature include: BF_3–OEt_2,[4] BCl_3,[5] decaborane,[6] $Sc(OTf)_3$,[7] $InCl_3$,[8] $ZnBr_2$,[9] $Zn(BF_4)_2$,[10] $Ce(OTf)_4$,[11] and $CeCl_3$–$7H_2O$/NaI.[12] Of particular interest to us was the report that $BiBr_3$ in wet CH_3CN could effect deprotection of silyl ethers.[13] Bismuth reagents are noted for their relatively low cost and their low toxicity[14] and could serve as environmentally friendly reagents for desilylation.

A survey of the literature reveals a number of instances in which bismuth salts have served as Lewis acids including the hydrolysis of acetals,[15,16] ketals,[15,16] THP ethers,[17] acetonides,[18] and the opening of epoxides.[19] Recent reports of examples in which bismuth reagents have been used to remove silyl protecting groups include the use of $BiCl_3$/NaI in CH_3CN to selectively deprotect alkyl silyl ethers in the presence of aryl silyl ethers[20] and the deprotection of silyl ethers with $BiCl_3$, bismuth (III) trifluoroacetate and $Bi(OTf)_3$.[21] The drawbacks of the latter report are that most of the reactions are limited to TMS ethers and $Bi(OTf)_3$ is a robust Lewis acid, showing no selectivity among several silyl groups.[21] And, the preferred solvent in Lewis acid-mediated desilylations has been acetonitrile. We sought to investigate the use of inexpensive and mild bismuth reagents using common organic solvents and wish to report our findings.

Our initial work focused on the use of $BiCl_3$ and $Bi(NO_3)_3$ in CH_2Cl_2 in the desilylation of TBS-protected 3-phenyl-1-propanol. Even with the addition of NaI, which is known to increase the Lewis acidity of these salts,[22,23] only unreacted silyl ether was recovered. However, $BiOClO_4$-xH_2O[24] proved to produce excellent yields of deprotected alcohol in as little as 1 h. The results of our preliminary studies are summarized in Table 1.

Based on our previous work in using $ZnBr_2$ as a desilylation agent,[9] we chose to focus on CH_2Cl_2 as the solvent of choice. We subjected a series of silyl-protected alcohols to our optimal reaction conditions of 1 equiv of $BiOClO_4$-xH_2O in CH_2Cl_2 at 45 °C for 1 h and the results of these reactions are summarized in Table 2.

Our results show that $BiOClO_4$-xH_2O in CH_2Cl_2 is an effective reagent for the deprotection of 1° silyl ethers as well as TES- and TBS-protected 2° alcohols. Longer reaction times were required to achieve useful yields in the deprotection of TIPS- and TBDPS-protected 2° alcohols. TES- and TBS-protected phenols underwent desilylation in 1 h but TBDPS-protected phenols were largely unreactive under these conditions.

The reactivity of silyl protected alcohols is such that selective removal of one of these groups in the presence of

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* Corresponding author. Tel.: +1-717-245-1351; fax: +1-717-245-1995; e-mail: crouch@dickinson.edu

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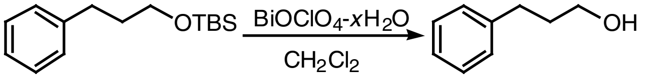
doi:10.1016/j.tetlet.2003.11.134

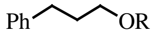
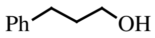
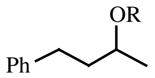
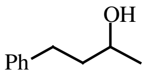
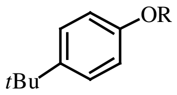
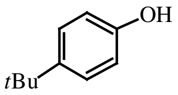
Table 1. Deprotection of TES-protected 3-phenyl-1-propanol



Entry	Equivalent of $BiOClO_4$	Temperature (°C)	Reaction time	Yield[a] (%)
1	1.0	25	1 h	26
2	2.0	25	1 h	87
3	2.0	25	5 h	67
4	2.0	25	2 days	94
5	1.0	45	1 h	92
6	0.5	45	2 days	45

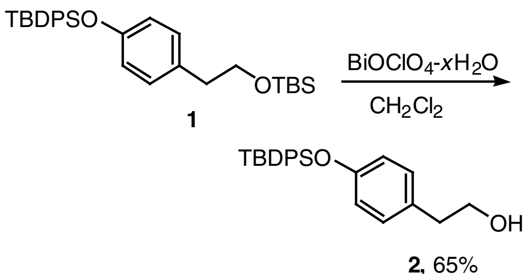
[a] Yields of isolated products were spectrally identical to authentic 3-phenyl-1-propanol.

Table 2. Deprotection of silyl ethers with $BiOClO_4$-xH_2O

Substrate	Product
	
R = TES	79%
TBS	92
TIPS	77
TBDPS	66
	
R = TES	85%
TBS	81
TIPS	32 (52)[a]
TBDPS	65 (94)[a]
	
R = TES	77%
TBS	85
TBDPS	<12

[a] Reaction time = overnight.

another is unlikely to be synthetically useful. But the stability of TBDPS-protected phenols to these conditions prompted us to investigate the selective deprotection of alkyl silyl ethers in the presence of TBDPS aryl ethers. Thus, a differentially protected bis-silyl ether 1 was prepared and heated for 3 h in the presence of 1 equiv of $BiOClO_4$-xH_2O to yield aryl silyl ether 2 in 65% yield (Eq. 1). The remainder of the product mixture included both unreacted bis-silyl ether **1** and the product of bis-desilylation with the former being predominant. Longer reaction times, however, led to the formation of more doubly deprotected product.



A typical procedure follows: To a stirring solution of 1 equiv of silyl ether in reagent grade CH_2Cl_2 (approximately 3 mL of solvent/mmol of substrate) was added 1.0 equiv of $BiOClO_4$-xH_2O. A reflux condenser was attached and the heterogeneous mixture was stirred at 45 °C until disappearance of silyl ether was observed by TLC (typically 1 h). The flask was cooled to room temperature, CH_2Cl_2 was added for volume and the reaction mixture was transferred to a separatory funnel. The organic layer was washed successively with H_2O, saturated $NaHCO_3$ (which made the organic layer cloudy) and brine. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. Column chromatography afforded the deprotected alcohol.

$BiOClO_4$-xH_2O is described as an oxidant[25] but no evidence of the product of oxidation of the alcohol was observed. In a control experiment, 3-phenyl-1-propanol was heated with $BiOClO_4$-xH_2O in CH_2Cl_2 overnight and the alcohol was recovered unchanged. Although we experienced no difficulties in handling this reagent, care should always be exercised when handling perchlorate salts.[24]

In summary, we have developed an easy-to-perform method for deprotecting silyl-protected alcohols that uses CH_2Cl_2, a readily available solvent. The method allows for deprotection of most alkyl silyl ethers. If a phenol is protected as a TBDPS ether, it may remain intact as an alkyl silyl ether is deprotected.

Acknowledgements

This research was partially supported by an award to Dickinson College under the Undergraduate Biological Science Education Program of the Howard Hughes Medical Institute and by the Arnold and Mabel Beckman Foundation through the Beckman Scholars Program.

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