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Deprotection of silyl ethers using $ZnBr_2$ and H_2O in CH_2Cl_2

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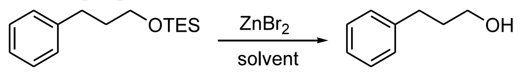
Abstract—TES- and TBS-protected alcohols undergo deprotection upon treatment with excess $ZnBr_2$ and water in CH_2Cl_2 at 44–50°C. TIPS-protected alcohols also undergo deprotection but at slower rates. TBDPS-protected alcohols and silyl-protected phenols are unreactive under these conditions, allowing for selective deprotection of differentially-protected bis-silyl ethers.

Protection/deprotection sequences continue to be crucially important in natural product synthesis and in the preparation of other complex organic molecules.[1–3] Silyl protecting groups are of particular value when intermediate compounds contain hydroxyl groups and the development of new methods for their attachment and removal remains an active area of research. Although protic acids and fluoride sources continue to be widely used to deprotect silyl ethers, a number of Lewis acids have been shown to be effective in promoting desilylation of protected alcohols.[1–3] Examples from the recent literature include: BF_3,[4] BCl_3,[5] $PdCl_2(CH_3CN)_2$,[6] $BiBr_3$,[7] $Sc(OTf)_3$,[8] $InCl_3$,[9] cerium(III) chloride heptahydrate/NaI,[10] $Zn(BF_4)_2$[11] and $Ce(OTf)_4$.[12] Although many of these reagents provide the added advantage of promoting selective desilylation of bis-silyl ethers,[13] some have not been systematically studied.[4,5] Others require the use of relatively expensive reagents[8,10,12] and most require the use of CH_3CN. We have developed a method that employs $ZnBr_2$[14] and water in CH_2Cl_2 to remove some silyl groups from protected primary and secondary alcohols and wish to share our results.

A recent communication described the use of excess $ZnBr_2$ in CH_2Cl_2 to deprotect *t*-butyl esters and *t*-butyl ethers under especially mild conditions.[15] Earlier work in our laboratory showed that $ZnCl_2/H_2O$ in CH_2Cl_2 effected the desilylation of TES-protected alcohols.[16] Unfortunately, those results were unreliable. Based on Wu's results, we thought $ZnBr_2$ might be more dependable than $ZnCl_2$ in removing TES groups and set out to investigate the possible utility of this system. The results of our preliminary studies are summarized in Table 1.

Reactions were initially performed using 5.0 equiv. of $ZnBr_2$ and no water was added, in accord with Wu's

Table 1. Deprotection of TES-protected 3-phenyl-1-propanol[a]



Entry	$ZnBr_2$ (equiv.)	H_2O (equiv.)	Solvent	Temperature (°C)	Reaction time (h)	Yield (%)
1	5.0	0	CH_2Cl_2	25	3	77
2	5.0	0	CH_2Cl_2	25	Overnight	76
3	5.0	0	CH_2Cl_2	43	3	84
4	5.0	0	CH_2Cl_2	43	6	85
5	5.0	5.0	CH_2Cl_2	25	3	82
6	5.0	5.0	CH_2Cl_2	45–50	3	87
7	5.0	5.0	$ClCH_2CH_2Cl$	86	2.5	70

[a] Products were isolated via column chromatography and found to be spectrally identical to authentic 3-phenyl-1-propanol.

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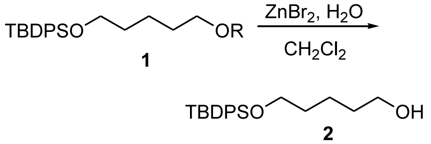
work.[14] In general, reactions in reagent grade CH_2Cl_2 produced desilylated product in a narrow range of yields. Marginal improvement was observed when 5.0 equiv. of water was added and when the reaction was heated. The use of reagent grade solvent without drying and adding water has previously been advantageous in silyl deprotection reactions.[12] Decreasing the amount of $ZnBr_2$ and/or water failed to improve product yield. Similarly, attempts to use 1,2-dichloroethane as solvent and allow an increase in the reaction temperature failed to improve yields. The optimized conditions were 5.0 equiv. of $ZnBr_2$ and 5.0 equiv. of water in CH_2Cl_2 at 45–50°C for 3 h.

A typical procedure follows: To a stirring solution of 1 equiv. of silyl ether in reagent grade CH_2Cl_2 (approximately 4 mL of solvent/mmol of substrate) was added 5.0 equiv. of anhydrous $ZnBr_2$ followed by 5.0 equiv. of water. A water condenser was affixed and the heterogeneous mixture then stirred at 45–50°C for 3 h when TLC showed the reaction to be complete. The flask was cooled to room temperature and CH_2Cl_2 was added for volume. The contents of the flask were transferred to a separatory funnel, the flask being rinsed with additional CH_2Cl_2. The organic layer was then washed twice with water and twice with saturated aqueous $NaHCO_3$. The organic layer was dried with $MgSO_4$, filtered and concentrated in vacuo. Purification of the crude product mixture was achieved using column chromatography.

To our surprise,[16] other silyl protecting groups were also removed under these reaction conditions. These results are summarized in Table 2. TBS-protected primary alcohols as well as TES- and TBS-protected secondary alcohols underwent deprotection cleanly. TIPS-protected primary and secondary alcohols also underwent deprotection but longer reaction times were required than for less sterically hindered silyl groups. Attempts to deprotect silyl-protected phenols failed (Table 2). In every instance, silyl ether was the only product recovered. This result was not entirely surprising given the relative resistance of silyl-protected phenols to mildly acidic hydrolysis.[17]

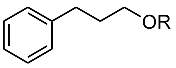
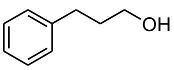
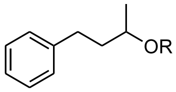
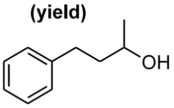
It is noteworthy that TBDPS-protected alcohols were largely unreacted after 24 h, pointing to the potential use of this method in selectively deprotecting bis-silyl ethers. This possibility was tested using bis-silyl ethers **1** which were subjected to our reaction conditions and produced selectively deprotected alcohols **2**[9] in good yields. Selective desilylation of TES- or TBS-protected alcohols in the presence of TIPS-protected alcohols is less likely since a significant amount of the TIPS group was removed in 3 h.

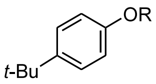
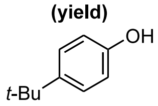


a R = TES 78%
b TBS 84%

The stability of silyl-protected phenols to these conditions prompted us to investigate whether or not our method might also serve as a useful means for the selective deprotection of alkyl silyl ethers in the presence of aryl silyl ethers.[8,9,13,17–25] Thus, bis-silyl ethers **3** were prepared and subjected to our deprotection protocol, yielding selectively deprotected alcohols **4**.[26] No evidence of deprotection of the aryl silyl ether was observed in either case.[27,28]

Table 2. Deprotection of silyl ethers[a]

substrate	product (yield)	substrate	product (yield)
			
R = TES	87	R = TES	85
TBS	83 (82)[b]	TBS	85
TIPS	81[c]	TIPS	44 (73)[c]
TBDPS	0[c,d]	TBDPS	0[c]

substrate	product (yield)
	
R = TBS	0
TIPS	0[d]
TBDPS	0[d]

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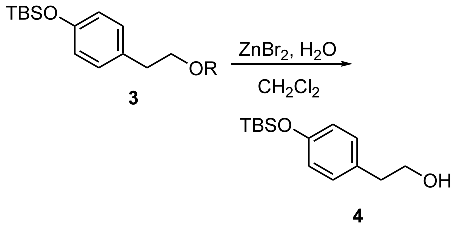
[a] all products were isolated via column chromatography and found to be spectrally identical to commercially-avalable alcohol or phenol.

[b] reaction at room temperature

[c] reaction time was 24 hours

[d] >90% silyl ether was recovered



a R = TES 87%
b TBS 85%

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 selective deprotection of alkyl silyl ethers in the presence of aryl silyl ethers. If protecting groups are carefully chosen (i.e. one group is TBDPS), this method also allows selective deprotection of one silyl-protected alcohol in the presence of another.

Acknowledgements

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26. ^{1}H NMR data for: (a) **3a** ($CDCl_3$, 300 MHz) δ 0.15 (s, 6H), 0.53 (q, 6H), 0.89 (t, 9H), 2.74 (t, $J=7.5$ Hz, 2H), 3.74 (t, $J=7.5$ Hz, 2H), 6.73 (d, $J=8.4$ Hz, 2H), 7.03 (d, $J=8.4$ Hz, 2H); (b) **3b** ($CDCl_3$, 300 MHz) δ 0.03 (s, 6H), 0.19 (s, 6H), 0.87 (s, 9H), 0.98 (s, 9H), 2.75 (t, $J=7.0$ Hz, 2H), 3.78 (t, $J=7.0$ Hz, 2H), 6.75 (d, $J=8.5$ Hz, 2H), 7.05 (d, $J=8.5$ Hz, 2H); (c) **4** ($CDCl_3$, 300 MHz) δ 0.19 (s, 6H), 0.98 (s, 9H), 2.79 (t, $J=6.6$ Hz, 2H), 3.81 (t, $J=6.6$ Hz, 2H), 6.77 (d, $J=6.4$ Hz, 2H), 7.08 (d, $J=6.5$ Hz, 2H).
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