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Mild deprotection of PMB ethers using *tert*-butyl bromide

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ABSTRACT

A convenient and high yielding method for the cleavage and scavenging of *p*-methoxybenzyl protecting group of several alcohols using *tert*-butyl bromide in refluxing acetonitrile is described. Under these mild conditions other protecting groups such as acid sensitive allyl, benzyl, and Me_3CPh_2Si ethers, or isopropylidene acetals were unchanged. Interestingly, a selective alkoxy-PMB cleavage was observed in the presence of a PMB phenoxy ether.

Introduction

One important tool in the total synthesis of natural products is the mild and selective cleavage of hydroxyl protecting group. According to the functional group diversity of such molecules, cleavage conditions should be as mild as possible and orthogonal to other hydroxyl protecting groups. The *para*-methoxybenzyl ether (PMB) is one of the most common hydroxyl protecting groups since it is generally stable toward a large panel of reaction conditions and can be selectively cleaved.[1] Numerous methodologies exist for the selective removal of the PMB group including oxidative condition with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[2] which has been then optimized using NBS or co-oxidants such as $HClO_4$, HIO_4, HNO_3, $FeCl_3$, and $Mn(OAc)_3$ to minimize the use of DDQ.[3] Ceric ammonium nitrate (CAN) can also be used for the oxidative cleavage of PMB ethers.[4] These oxidative conditions led to a major drawback with the formation of side products such as 4-anisaldehyde or dichlorodicyanohydroquinone. Later on, anodic oxidation[5] and photoredox catalysis[6] have been used as other oxidative cleavages of PMB ethers. Reductive cleavage of PMB ethers was alternatively described using the $NaCNBH_3$–$BF_3{\cdot}Et_2O$[7] system but gave rise to another side product, 4-methylanisole. This method is also not suitable for compounds with reducible and acid sensitive functional groups. A lot of effort has been put on the combination of a Lewis acid and a soft nucleophile, such as $AlCl_3$–dimethylaniline,[8a] $MgBr_2$–Me_2S,[8b] $CeCl_3{\cdot}7H_2O$–NaI,[8c] $SnCl_4$–PhSH,[8d] $ZrCl_4$–CH_3CN,[8e] $Ce(OTf)_3$,[8f] or TMSI-TPP,[8g] as mild cleavage conditions. PMB ethers are generally stable under mild acidic conditions but can be cleaved in the presence of strong acids in certain conditions. For instance, acetic acid at 90 °C,[9] 10% trifluoroacetic acid in dichloromethane,[10] trifluoroacetic, methanesulfonic, or triflic acid with 1,3-dimethoxybenzene in toluene,[11] or TFA-anisole in dichloromethane,[12] or triflic acid with *N*-methyl-*p*-toluenesulfonamide, cleaved efficiently PMB ethers. Functionalized resins such as sulfonamide-functionalized ('safety-catch') could also be used.[13] Iodohydric acid-mediated deprotection of PMB ethers has also been described with extension to other alkoxymethyl.[14] Just recently, a combination of $Ag(I)SbF_6$ (5 mol %) and 1,3,5-trimethoxybenzene (0.5 equiv),[15] $POCl_3$ (0.5 equiv) in dichloroethane,[16a] oxalyl chloride in dichloroethane,[16b] and proton-exchanged montmorillonite[16c] was reported as useful reagents for the deprotection. In case of acidic catalysis, if the conjugate is a weak nucleophile, scavengers have to be used to avoid production of dimers and polymeric products resulting from the self-condensation of the released PMB cation.[17] This can be bypassed if strong nucleophiles such as Cl^- are formed during the protection simplifying the work up procedure.[8e,16] Very recently, a self-cleaving PMB deprotection catalyzed by $FeCl_3$ was described, leading when quantitative, to the mother alcohols without purification.[18]

During the course of our studies toward the synthesis of the polyol part of Amphidinol-3,[19] we carried out the reduction of hydroxysulfoxide **1** into the corresponding sulfide **2** using *tert*-butyl bromide[20] in refluxing chloroform (Scheme 1). To our surprise, the dihydroxysulfide **2** was isolated as a major product of this reaction, in which the reduction of the sulfinyl group

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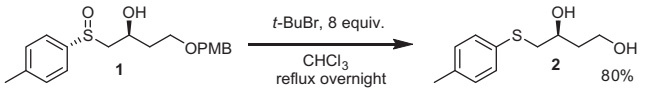


Scheme 1. Sulfinyl group reduction and PMB cleavage of compound 1 under Tenca et al.[20]

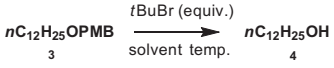
occurred, but the PMB group protecting the primary alcohol was also cleaved.

Since nothing concerning the use of *tert*-butyl bromide for ethers cleavage was reported in the literature, we wanted to explore the possibility of using this readily available reagent as a general method to deprotect PMB ethers. Our study began with examination of reaction of PMB ether **3** with varying amounts of *t*-BuBr in different solvents at different temperatures. The results are summarized in Table 1.

Fair yields (12–20%) of the alcohol **4** were obtained with 8 equiv of *t*-BuBr in DMF and DCM, and no reaction was observed in Et_2O (entries 3–6). Surprisingly, application of Tenca's conditions[20] leads to lower yield of alcohol **4** (entry 1) compared to diol **2** (Scheme 1). Best solvent was refluxing acetonitrile, although the yield decreased when lower temperature or long reaction times were used (entries 7, 8 and 10). The highest yield (92%) was obtained by adding only 1.1 equiv of *t*-BuBr in refluxing acetonitrile in 1 h reaction time (entry 12). Larger or substoichiometric amount (5, 8, 0.5 equiv) of *t*-BuBr leads to a drop in the yield (entry 7, 9 and 11).

The versatility of *t*-BuBr (1.1 equiv) as a PMB deprotection reagent was tested using various ethers under the optimum reaction conditions (Table 2).[21] All the PMB ethers were prepared from the corresponding alcohols using the adapted protocol of Rai and Basu.[22] *t*-BuBr (1.1 equiv) in refluxing acetonitrile cleaved the PMB ethers of primary, secondary, and hindered tertiary alcohols without alteration of optical information in excellent yields (72–92%, entries 1–7). The PMB ether of primary alcohols could be chemoselectively removed in the presence of primary or secondary benzyl[23] and allyl ethers (entries 14, 15 and 30) or acetate, benzoate, and pivalate esters (entries 8, 9 and 34) as well as phthalimide protected amine (entry 18). Similar selectivity was observed with secondary PMB ethers (entries 24, 28 and 29). These conditions are mild enough so that even substrates that have a trityl (entry 13), a TBDPS (entries 11, 26 and 32), an acetonide (entry

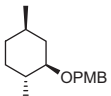
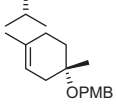
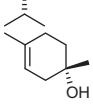
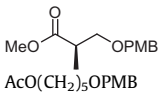
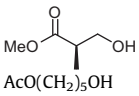
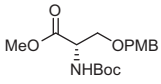
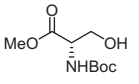
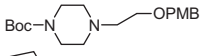
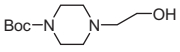
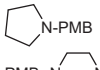
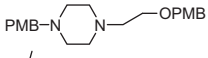
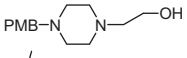
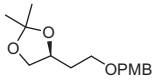
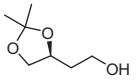
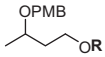
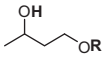
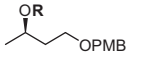
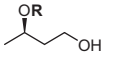
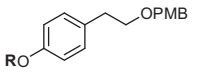
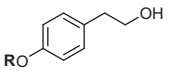
Table 1
Cleavage of the PMB ether 3



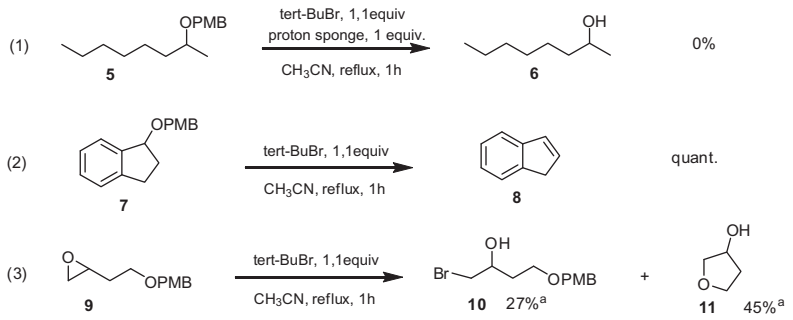
Entry	Equivalent	Solvent	Time	Temperature	Yield[a] (%)
1	8	$CHCl_3$	Over-night	Reflux	55
2	4	$CHCl_3$	Over-night	Reflux	20
3	8	DMF	Over-night	RT	12
4	8	DMF	Over-night	50 °C	12
5	8	Et_2O	Over-night	Reflux	0
6	8	DCM	Over-night	Reflux	20
7	8	CH_3CN	Over-night	Reflux	77
8	8	CH_3CN	72 h	RT	30
9	0.5	CH_3CN	Over-night	Reflux	33
10	5	CH_3CN	36 h	Reflux	60
11	2	CH_3CN	Over-night	Reflux	70
12	1.1	CH_3CN	1 h	Reflux	92

[a] Isolated yields.

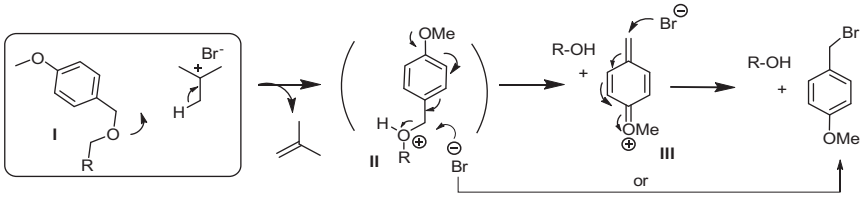
Table 2
Selective cleavage of the PMB group of different ethers by *t*-BuBr (1.1 equiv) in refluxing acetonitrile

Entry	Substrate	Product	Time	Yield (%)
1	*n*-Dodecanyl-OPMB	*n*-Dodecanol	1 h	92
2	*i*-Octanyl-OPMB	*i*-Octanol	45 mn	99
3	Adamantanyl-OPMB	Adamantanol	45 mn	91
4			1 h	93
5			1 h	87[a]
6			1 h	90[a]
7			50 mn	72[a]
8	$AcO(CH_2)_5OPMB$	$AcO(CH_2)_5OH$	1 h	76
9	$BzO(CH_2)_5OPMB$	$BzO(CH_2)_5OH$	1 h	81
10	$TBSO(CH_2)_5OPMB$	$TBSO(CH_2)_5OH$	80 mn	50[b]
11	$TBDPSO(CH_2)_5OPMB$	$TBDPSO(CH_2)_5OH$	80 mn	85
12	$MOMO(CH_2)_5OPMB$	$MOMO(CH_2)_5OH$	1 h	0[b,c]
13	$TrO(CH_2)_5OPMB$	$TrO(CH_2)_5OH$	1 h	65[b]
14	$BnO(CH_2)_5OPMB$	$BnO(CH_2)_5OH$	1 h	88
15	$AllylO(CH_2)_5OPMB$	$AllylO(CH_2)_5OH$	1 h	85
16	$BocNH(CH_2)_3OPMB$	$BocNH(CH_2)_3OH$	2 h	0[b,c]
17	$CbzNH(CH_2)_3OPMB$	$CbzNH(CH_2)_3OH$	1.5 h	32[b,c]
18	$PhthNH(CH_2)_3OPMB$	$PhthNH(CH_2)_3OH$	1.5 h	95
19			30 mn	10[b,c]
20			30 mn	15[b,c]
21		No reaction	12 h	0[d]
22			80 mn	86[d]
23			1 h	88
				See Ref. 24
24	R = Bn	—	1 h	89
25	R = TBS	—	1 h	40[b,c]
26	R = TBDPS	—	80 mn	85
27	R = MEM	—	50 mn	0[b,c]
28	R = Piv	—	1 h	95
29	R = allyl	—	1 h	93
				See Ref. 25
30	R = Bn	—	1 h	91
31	R = TBS	—	45 mn	30
32	R = TBDPS	—	75 mn	82
33	R = MEM	—	1 h	5[b,c]
34	R = Piv	—	1 h	92
				
35	R = Me	—	30 mn	98
36	R = Bn	—	20 mn	93
37	R = MOM	—	15 mn	16[b,c]
38	R = TBDPS	—	20 mn	68
39	R = PMB	—	20 mn	62

[a] No loss of optical integrity.
[b] No selective deprotection.
[c] Complete deprotection is mainly observed if 2 equiv of *t*-BuBr are used (diol not isolated).
[d] 2.2 equiv of *t*-BuBr used.



Scheme 2. Proof of acid generation in the reaction mixture. (a) Isolated yields. Other undetermined products were present in the crude.



Scheme 3. Proposed mechanism of deprotection by *t*-BuBr.

23) were readily converted into the corresponding alcohol in 65–85% yields. Similarly, selective removal of aliphatic PMB ether was achieved in the presence of different phenoxy ethers except when phenol is protected by a MOM group (entries 35–38). Furthermore, a useful yield of a mono-deprotected *p*-hydroxyphenylethanol was attainable from starting bis-PMB ether (entry 39). However, alcohols with more acid-sensitive protecting groups such as MOM or MEM ether (entries 12, 27 and 33), TBS (entries 10, 25 and 31), and Boc- or Cbz-protected amines (entries 16, 17, 19 and 20) could not be selectively cleaved by this method. In the cases of TBS ethers, we found that the PMB group was cleaved faster than the silyl group, but not fast enough to give synthetically useful yields of mono-deprotected products.

We tried to adapt our method to the cleavage of PMB amine (entry 21). Even using a large excess of *t*-BuBr (2.2 equiv) no reaction occurred. The stability of PMB-amine under our conditions was advantageously applied to the selective removing of PMB ether in excellent yield (86%, entry 22). During the course of the reaction, we observed 4-methoxybenzylbromide which was transformed into the corresponding alcohol after work up. The chemoselectivity observed in Table 2 prompted us to investigate if an in situ generation of acid in the reaction mixture could occur. If this hypothesis was effective, we argue that addition of proton sponge should buffer acid and inhibit the deprotection reaction. In fact, no conversion from PMB ether **5** to the corresponding alcohol **6** was observed in the presence of 1 equiv of proton sponge (Scheme 2, Eq. 1). The quantitative formation of indene **8** from PMB ether **7** and of the mixture (1/2) of bromohydrin **10** and 3-hydroxytetrahydrofuran **11** from epoxy-ether **9** resulting, respectively, from an acid-catalyzed deshydration (Eq. 2) or epoxide ring-opening (Eq. 3) supports acid generation in the medium.

The deprotection process is fairly general even though the mechanism of acid generation may have different origins. Direct hydrogen bromide generation from *t*-BuBr in refluxing acetonitrile has to be rejected since no bromocyclohexane was observed after treatment of cyclohexene under our deprotection conditions.[26] A suitable mechanism is proposed based on these observations, as shown in Scheme 3.

Complex **II** formed between the PMB ether **I** and *t*-BuBr after liberation of isobutene should undergo elimination of the stabilized PMB cation **III** in acetonitrile, which in turn should lead by bromide attack to the formation of PMB bromide and the deprotected alcohol. The latter can result from nucleophilic substitution of bromide on the oxonium cation **II**.

In conclusion, we have discovered novel and quite mild conditions for the removal of PMB ethers using *t*-BuBr as a single reagent for the deprotection as well scavenging of the PMB cation, avoiding the use of external trapping reagents. This method is selective against various acid and base sensitive functional groups.

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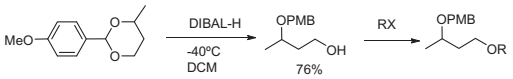
24. 

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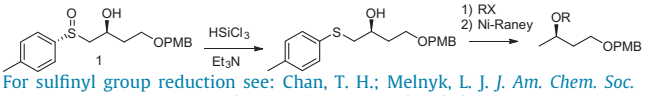
25. 

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