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Effective chemoselective deprotection of 3,4-dimethoxybenzyl (^{3,4}DMB) ethers in the presence of benzyl and *p*-methoxybenzyl (PMB) ethers by phenyliodine(III) bis(trifluoroacetate) (PIFA)

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ABSTRACT

In this Letter, a selective deprotection of the alcohol protecting 3,4-dimethoxybenzyl (^{3,4}DMB) group is described. The hypervalent iodine(III) reagent phenyliodine bis(trifluoroacetate) (PIFA) is found to be an efficient reagent for the chemoselective deprotection of ^{3,4}DMB ethers in the presence of benzyl, *p*-methoxybenzyl, methoxymethyl, *tert*-butyldimethylsilyl, and *tert*-butyldiphenylsilyl ethers under mild conditions. This is the first example of the selective deprotection of the ^{3,4}DMB group from a hydroxy group with PIFA.

The availability of effective methods for protection and, more importantly, the subsequent deprotection of functional groups play a major role in total synthesis. Protection of hydroxy groups as ethers, especially as benzyl-type ethers, has long been recognized as a valuable reaction.[1] This is mainly because benzyl ethers are stable under both acidic and basic reaction conditions and are relatively insensitive to various oxidizing and reducing agents as well. The *p*-methoxybenzyl (PMB or MPM) group is an especially useful protecting group and has been employed widely in the synthesis of complex natural products and carbohydrate chemistry.[1] Its utility lies in the fact that it is more readily cleaved oxidatively than unsubstituted benzyl (Bn) ethers.[1] There are various methods for removing the PMB group, including Lewis acid-catalyzed cleavage with $MeBBr_3$,[2] $BF_3{\cdot}OEt_2$–$NaCNBH_3$,[3] $AlCl_3$–EtSH,[4] and TMSCl–$SnCl_2$–anisole,[5] etc.[6] The oxidants that are used most frequently are 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[7] and ceric ammonium nitrate (CAN).[8] However, many of these procedures suffer from one or more drawbacks, for example, use of a heavy metal which is not ideal from an environmental point of view, lack of selectivity, unsatisfactory yield, or the necessity for anhydrous conditions.

Another important aspect of selective ether deprotection is to differentiate the same type of ethers, for example, PMB ethers versus 3,4-dimethoxybenzyl (^{3,4}DMB, DMPM, or veratryl)[9] ethers. Deprotection agents with such selectivity are more useful because initial removal can be carried out in a single step. In fact, the ^{3,4}DMB protecting group for the hydroxy function is more readily removed than the PMB group by DDQ oxidation under neutral conditions.[9a] In this context, there is still the need to devise a more environmentally friendly method, which has led us to investigate a new methodology that can carry out the selective deprotection of ^{3,4}DMB ethers in good-to-excellent yields (Scheme 1).

Recently, hypervalent iodine reagents, such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA), have been widely recognized as safe and useful oxidants having reactivities similar to those of the highly toxic heavy metal oxidizers.[10] Several novel methods using hypervalent iodine reagents have been developed for the syntheses of lactones by intramolecular C–O bond formation.[11] Kita and co-workers reported the cyclization of *para*-substituted phenol[12] or phenol ether derivatives[13] to spiro dienone lactones using PIDA and PIFA. These hypervalent iodine(III) reagents have also been used for the generation of aryl radical cations via a single-electron-transfer (SET) mechanism.[14] In addition, DDQ is a well-known electron accepter and forms charge transfer (CT) complexes with a variety of donors.[9a] Thus, a ^{3,4}DMB ether would also form a CT-complex with PIFA. It occurred to us that electron rich aromatic rings such as in ^{3,4}DMB ethers may be amenable to a similar deprotection reaction. Herein, we disclose an easy, efficient, and chemoselective deprotection method for ^{3,4}DMB ethers, which has no effect on PMB ethers (Scheme 1).

The influences of oxidants and solvents on the selective deprotection of L-(−)-maric acid derivative **1**, in which Bn, PMB, and ^{3,4}DMB ethers co-existed in the same molecule, leading to

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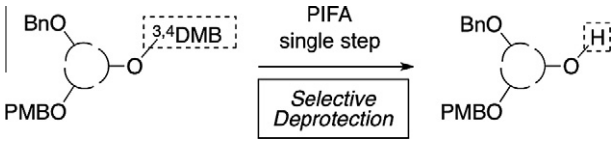


Scheme 1. Selective deprotection of a ^{3,4}DMB group.

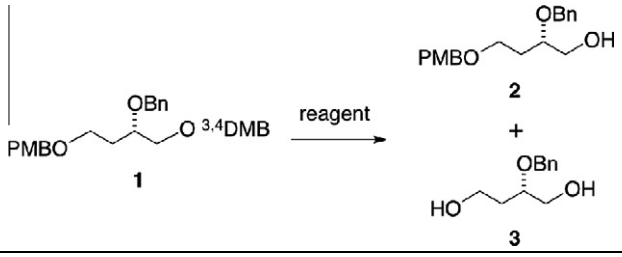
mono-alcohol **2**, are summarized in Table 1. The reaction was carried out in CH_2Cl_2–H_2O (18:1) at 0 °C for 30 min in the presence of DDQ (1.2 equiv) to give the desired alcohol product **2** in low yield (47%, entry 1). Under this condition, tri-protected alcohol **1** also undergoes facile cleavage of both the PMB and ^{3,4}DMB protecting groups to provide the benzyl diol **3** in 38% yield (entry 1). The deprotection of **1** using CAN (2.0 equiv) as oxidant at room temperature gave alcohol **2** with lower selectivity (30% for **2** and 59% for **3**, entry 2). Likewise, a similar trend is also observed when cooling the reaction of **1** to 0 °C. On the other hand, when **1** was treated with trifluoroacetic acid (TFA) (10 equiv), PIDA (10 equiv), and PIDA–TFA (10 equiv) using the same procedure, no removal of the ^{3,4}DMB group took place, even after 24 h at room temperature (entries 3–5). Next, PIFA was added in amounts ranging from 1.1 to 2.0 equiv in CH_2Cl_2 at room temperature (entries 6–8). Eventually, the best result was obtained when **1** was treated with flesh PIFA (2.0 equiv) in CH_2Cl_2 for 2 h at room temperature, producing the desired mono-alcohol **2** in high yield (94%, entry 8). These results clearly indicated that the use of PIFA (2.0 equiv) is essential for selective activation of the ^{3,4}DMB ether and efficient reaction progress. To elucidate the solvent effect on the selective deprotection, we also screened a number of solvents, such as CH_2Cl_2, toluene, DMF, MeOH, and THF, for the reaction of **1** and PIFA (2.0 equiv). As listed in Table 1 (entries 8–12), use of CH_2Cl_2 as the solvent provided the desired alcohol **2** with the highest selectivity. These results demonstrated that solvents have remarkable effects on the selectivities and rates of reaction. Nonpolar aprotic solvents, such as CH_2Cl_2 and toluene, gave good to excellent yields in a short time (94%, 2 h and 61%, 1.5 h, entries 8 and 9, respectively), whereas polar solvents, such as DMF, MeOH and THF, gave moderate chemical yields (35%, 38% and 57%, entries 10–12, respectively). We observed that the rate of deprotection of ^{3,4}DMB ether was accelerated in nonpolar aprotic solvents. It is noteworthy that this is the first example of the selective deprotection of the ^{3,4}DMB group from a hydroxy group with hypervalent iodine(III) reagent PIFA.

With these preliminary results in hand, we next examined the reaction scope and the results are summarized in Scheme 2. When tribenzyl-type ether-protected **4**, in which the two primary alcohols were protected with Bn and PMB groups and the secondary alcohol was protected with the ^{3,4}DMB group, was treated with 2.0 equiv of PIFA in CH_2Cl_2 at room temperature for 2 h, the ^{3,4}DMB group was removed to give the desired alcohol **5** with more than 98% selectivity (undesired diol less than 2% yield).

Under the optimized reaction conditions, a wide range of deprotective reactions of L-tartaric acid derivatives **6a–d** containing several other protective groups, such as methoxymethyl (MOM), *tert*-butyldimethylsilyl (TBS) and *tert*-butyldiphenylsilyl (TBDPS) ethers, with PIFA (2.0 equiv) were investigated and the results are shown in Table 2. As expected, the corresponding mono-alcohol products **7a** and **7d** were obtained in very good yields (96–98%, entries 1 and 5). Not surprisingly, due to the instability of the MOM moiety under acidic conditions, the TFA formed from reduction of the PIFA reagent cleaved the MOM ether, and provided dibenzyloxy diol **8** as the major product from **6b** (data not shown). Similarly, the ^{3,4}DMB–TBS compound **6c** did not furnish the desired TBS–protected diol **7c**, but afforded diol **8** as the major product due to the lability of the TBS moiety under non-basic conditions (entry 3). In the case of entries 2 and 4, the reaction of **6b** (having a MOM ether) or **6c** (having a TBS ether) was carried out under the usual conditions (PIFA, CH_2Cl_2, rt) in the presence of K_2CO_3 (10 equiv) as a base, to increase the selectivity of deprotected product **7b** or **7c**.

For a plausible mechanism of this selective deprotection, we believe that the cleavage of the ^{3,4}DMB ether proceeds by the same

Table 1
The result obtained from the selective deprotection of **1** with various oxidants and solvents

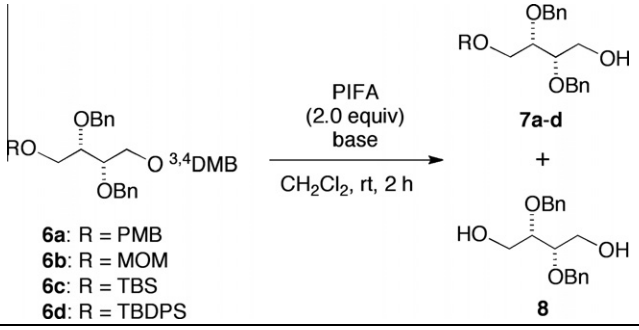


Entry	Reagent (equiv)	Solvent	Temp	Time (h)	Yield[a] (%)	
					2	**3**
1	DDQ (1.2)	CH_2Cl_2–H_2O[b]	0 °C	0.5	47	38
2	CAN (2.0)	CH_3CN–H_2O[c]	rt	0.5	30	59
3	TFA[d] (10)	CH_2C1_2	rt	24	NR[e]	
4	PIDA[f] (10)	CH_2C1_2	rt	24	NR	
5	PIDA–TFA (10)	CH_2C1_2	rt	24	NR	
6	PIFA (1.1)	CH_2Cl_2	rt	8	71	5
7	PIFA (1.5)	CH_2C1_2	rt	6	82	7
8	PIFA (2.0)	CH_2C1_2	rt	2	94	3
9	PIFA (2.0)	Toluene	rt	1.5	61	39
10	PIFA (2.0)	DMF	rt	24	35	39
11	PIFA (2.0)	MeOH	rt	24	38	45
12	PIFA (2.0)	THF	rt	12	57	40

[a] Isolated yield after purification.
[b] CH_2Cl_2–H_2O (18:l)
[c] CH_3CN–H_2O <18:1)
[d] TFA = trifluoroacetic acid
[e] NR: no reaction
[f] PIDA: phenyliodine(III) diacetate.

Scheme 2. The selective deprotection of **4** using PIFA.

Table 2
The selective deprotection of **6a–d** using PIFA



Entry	Substrate	Base (equiv)	Yield (%)	
			7a–d	**8**
1	**6a**	—	98	Trace
2	**6b**	K_2CO_3 (10)	81	10
3	**6c**	—	8	87
4	**6c**	K_2CO_3 (10)	68	26
5	**6d**	—	96	0

SET mechanism as described for debenzylation in the presence of DDQ.[9a,14] The ^{3,4}DMB ether is expected to be more reactive to the PIFA oxidation because it has a lower oxidation potential which makes it more electron-donating than the PMB group.[9a,15] Hence, benzylic oxidation with PIFA has been applied to the oxidative removal of the ^{3,4}DMB group, which proceeds by initial formation of the CT-complex between the electron-donative dimethoxybenzene ring and the electron-attractive PIFA, followed by dehydration and hydrolysis.

In conclusion, we have established that ^{3,4}DMB ethers can efficiently be deprotected by treatment with excess PIFA (2.0 equiv) in CH_2Cl_2 at room temperature. This reaction produces the corresponding alcohols in excellent yields and selectivities, thus providing a mild and efficient method for the chemoselective deprotection of ^{3,4}DMB ethers that does not require the use of generate toxic waste products. The use of the PIFA reagent system for organic synthetic transformations is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.049.

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