A Simple Method for the Selective Deprotection of *p*-Methoxybenzyl Ethers by Cerium(III) Chloride Heptahydrate and Sodium Iodide

Anna Cappa, Enrico Marcantoni,* and Elisabetta Torregiani

Dipartimento di Scienze Chimiche, via S. Agostino 1, I-62032 Camerino (MC), Italy

Giuseppe Bartoli,* Maria Cristina Bellucci, Marcella Bosco, and Letizia Sambri

Dipartimento di Chimica Organica "A. Mangini", v.le Risorgimento 4, I-40136 Bologna, Italy

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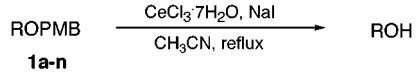
Introduction

Chemoselective transformation of polyfunctional compounds is a challenging problem in organic synthesis, especially in the cases where sensitive structural features limit reagent choice. Although much recent work has dealt with the development of methods and procedures general and efficient enough to be employed across a wide range of substrate molecules, hitherto the chemistry of protective groups continues to be an active area of research. There are hundreds of protective groups that can be introduced and removed by a variety of methods, but new and milder methods continue to be developed for both the introduction and cleavage of many of the existing protective groups.[1] For this reason, protection and deprotection of hydroxyl groups have been given considerable attention in recent years, not only because of their fundamental importance, but also as to their role for multistep synthesis of complex natural products such as polyketide-derived macrolide and polyether antibiotics. The synthesis of polyhydroxylated compounds[2,3] often requires orthogonal protecting strategies to distinguish between hydroxyl groups. In the realm of hydroxyl protecting groups, benzyl ethers, both substituted and unsubstituted, are among the most common because of their stability toward acid, alkali, and a number of other reagents. To be able to remove selectively a substituted benzyl ether in the presence of an unsubstituted benzyl ether under mild conditions is of great benefit. The *p*-methoxybenzyl (PMB) group is one of the most useful groups for alcohol protection because it can be selectively cleaved in the presence of unsubstituted benzyl ethers. There are various methods for selectively removing the PMB group which include Lewis acid-catalyzed cleavege with MeBBr,[4] $BF_3{\cdot}OEt_2-NaCNBH_3$,[5] $AlCl_3-EtSH$,[6] and a combination of $TMSCl-SnCl_2$−anisole.[7] The oxidation, either electrolytically,[8] or chemically by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[9,10] or ceric ammonium nitrate (CAN),[11] have been reported. Also, the cleavage of the PMB ether has been accomplished using a 10% solution of trifluoroacetic acid[12] or using clay-supported ammonium nitrate under microwave irradiation.[13] Many of these procedures suffer from one or more drawbacks: use of a heavy metal which not ideal from an environment point of view, lack of selectivity, unsatisfactory yield,[14] cost of the reagent, or necessity of anhydrous conditions. In this context there is still the need to devise a method with environmental consciousness using inexpensive reagents, and this has led us to investigate a new methodology, which is able to carry out the selective deprotection of PMB ether with good-to-excellent yields.

Scheme 1



Over recent years, lanthanide salt mediated Lewis acid reactions has attracted tremendous interest throughout scientific communities.[15] Their low toxicity, ease of handing, and low cost make lanthanide derivative species attractive alternatives to their classical competitors such as $TiCl_4$. For this, in the course of our studies on the use of cerium(III) chloride in organic reactions,[16] we have developed new methods for deprotection of organic functional groups.[17] Thus, we have considered the possibility of using cerium(III) chloride heptahydrate to promote the cleavage of PMB ethers. In the same way that other Lewis acids promote this reaction of deprotection, $CeCl_3$ should also lead to activated PMB ethers for being resolved to parent hydroxy compound. Now we describe here that the cleavage of the *p*-methoxybenzyl protecting group of alcohols and phenols in the presence of benzyl

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(14) The oxidative removal of the PMB group requires the combination of aqueous solvent organic and DDQ, and under these aqueous conditions the 2,3-dichloro-5,6-dicyano-1,4-benzoquinone is reduced to the corresponding 1,4-diphenol derivative, which may result in acidic conditions.
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ether and other sensitive functional groups can be effectively realized by the combination of cerium(III) chloride with a soft nucleophile such as sodium iodide (Scheme 1).

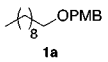
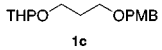
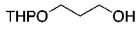
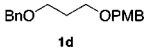
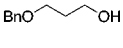
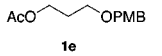
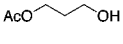
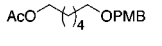
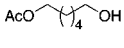
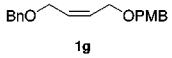
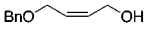
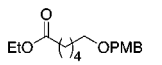
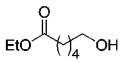
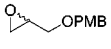
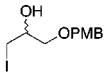
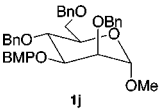
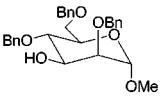
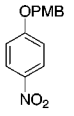
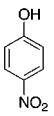
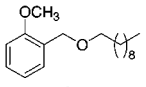
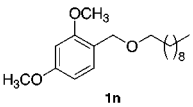
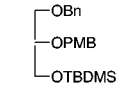
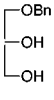
Results and Discussion

The treatment at room temperature of PMB ether **1a** with $CeCl_3 \cdot 7H_2O$ in the presence of NaI in acetonitrile gave 1-decanol only 5% after 3 days. However, to obtain high yield of free alcohol, refluxing the reaction mixture for 24 h is sufficient (entry 1, Table 1). The procedure for deprotection of PMB ether **1a** is very simple. The ether was stirred with a suspension of $CeCl_3 \cdot 7H_2O$ and NaI in acetonitrile at reflux temperature for a certain period of time as required to complete the reaction (TLC or GC). Usual workup and evaporation of solvent followed by purification through column chromatography furnished the pure alcohol. In general, 1.5 equiv of $CeCl_3 \cdot 7H_2O$ and 1.0 equiv of NaI was found to give the best results. The use of a higher excess of cerium(III) chloride (5.0 equiv) led to similar results, but lower amounts (e.g., 0.5 equiv) gave lower chemical yields.

A wide range of structurally varied PMB ethers have been subjected to cleavage with $CeCl_3 \cdot 7H_2O$/NaI by this procedure to provide the corresponding alcohols in good yields. Selected examples of the present reaction are shown in Table 1 which summarizes some important findings. Our initial observation was that acetonitrile provides to be a superior reaction solvent to tetrahydrofuran (THF) or dichloromethane (DCM). In fact, for the cleavage of 1-decyl PMB ether **1a**, it was found that in acetonitrile the reaction is complete after 24 h, whereas in THF or DCM the substrate, under the same conditions, had barely reacted after a much longer period of time, 65 h and 5 days, respectively. These results are probably due to appreciable dissociation and higher solubility of cerium(III) chloride in acetonitrile,[19] much more than in THF or DCM. Thus, electrostatic activation of the oxygen ether atom will be stronger, and for this reason, we did not try to extend the range of choices with solvents which strongly coordinate cerium(III) such as acetone, ethyl acetate, and DMF. It is known, indeed, that these solvents form remarkably stable 1:1 complexes in which the solvent molecule is bonded to the metal via lone pairs of oxygen atoms.[20]

The complex $CeCl_3 \cdot 7H_2O$/NaI cleaved selectively PMB ethers in the presence of other protecting groups for alcohols (entries 3−7, Table 1). It should be noted that the treatment of benzyl *p*-methoxybenzyl ethers **1d** and **1g** with $CeCl_3 \cdot 7H_2O$/NaI gave only the benzyl alcohols without a trace of *p*-methoxybenzyl alcohols, and no *Z*−*E* isomerization of double bond was observed (entry 7, Table 1). The starting ether **1o** (entry 15, Table 1) also provide another example of the selective cleavage of a *p*-methoxybenzyl (PMB) ether in the presence of a benzyl (Bn) ether, and this entry is a reflection of the substantially longer time required for the cleavage of a PMB ether than a *tert*-butyldimethylsilyl (TBDMS) ether,[17b] the most

Table 1. Cleavage of PMB Ethers by $CeCl_3 \cdot 7H_2O$ and NaI in Acetonitrile at Reflux Temperature

Entry	Starting material[a]	time	Product[b]	Yield, %[c]
1	 **1a**	24 h		90
2	 **1b**	48 h		88
3	 **1c**	30 h		75
4	 **1d**	24 h		89
5	 **1e**	24 h		90
6	 **1f**	32 h		92
7	 **1g**	15 h		89
8	 **1h**	24 h		93
9	 **1i**	4 h		49
10	 **1j**	24 h		90
11	 **1k**	48 h		86
12	 **1l**	21 h		89
13	 **1m**	24 h		91
14	 **1n**	7.5 h[d]		97
15	 **1o**	24 h	 **1o**	89

[a] *p*-Methoxybenzyl ethers were prepared by conventional methods.[18] [b] All products were identified by their IR, NMR, and GC/MS spectra. [c] Yields of products isolated by column chromatography. [d] Room temperature.

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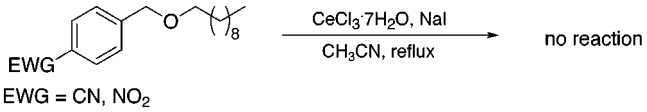
Scheme 2

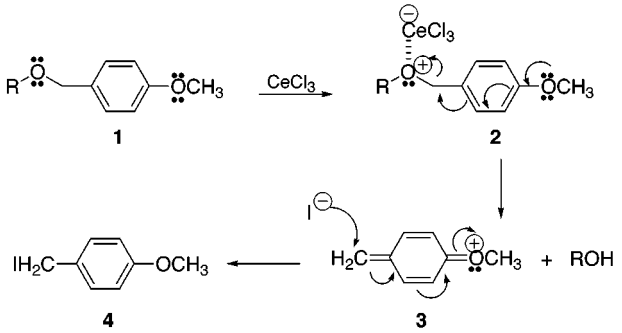


popular silicon-containing protecting group used in organic synthesis.[1a] In this context, the major usefulness of this deprotection is in the selective cleavage of PMB ether in the presence of primary tetrahydropyranyl ether (entry 3, Table 1). PMB ethers were also selectively cleaved in the presence of other functional groups, such as ester function (entry 8, Table 1). When the methyl 2,4,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-D-mannopyranoside **1j**,[21] which contains a benzyl ether and glycosidic function, was subjected to the action of our procedure, the parent alcohol was obtained in good yield (entry 10, Table 1). On the other hand, we observed that if an oxirane ring is present in the ether substrate **1i**, no PMB ether cleavage was obtained, but nucleophilic opening of ring was much more rapid than deprotection (entry 9, Table 1).

Having established the conditions for the selective cleavage of PMB ether of various alcohols, we have also investigated the possibility of cleavage of aryl PMB ethers[22] (entries 11, and 12, Table 1). The PMB ether of phenol **1k** on reaction with our system gave the desired product without contamination of product from *ortho*-alkylation.[23] The rate of this deprotection is improved in the case of **1l**, in which the *para* position was occupied by nitro group moiety. This has led us to test whether the electronic properties of the aromatic group can influence the rate of cleavage, which should in turn guide the development of hydroxyl protecting groups with different reactivities. Indeed, we have observed that the rate of cleavage can be affected by the electronic properties of the aromatic ring, and there is considerable acceleration by electron-donating substituents (entry 14, Table 1). Although no difference in reactivity was observed between compounds **1a** and **1m**, the deprotection of the corresponding 2,4-dimethoxy derivative **1n**[24] proceeded more rapidly under the same conditions and was completed within 7.5 h at room temperature. Certainly, the substitution of the electron-withdrawing group onto the aromatic ring severely retards the deprotection, and when *p*-cyano- and *p*-nitrobenzyl ethers are used, only starting materials were recovered in all cases even after prolonged reaction times (Scheme 2).

For the mechanism of this deprotection of PMB ether, Scheme 3 illustrates a proposed pathway for the reaction. We believe that the cleavage of the PMB ether proceeds by the same mechanism as described for debenzylation of benzyl ethers in the presence of a stoichiometric amount of Lewis acid.[25] Cerium(III) chloride would

Scheme 3



coordinate to the PMB ether oxygen (Scheme 3) to form a complexed oxygen species **2**, which then undergoes electronic delocalization to liberate the parent alcohol and the oxonium **3**. Compound **3** is trapped by nucleophilic attack of I^- to afford the *p*-methoxybenzyl iodide **4**, as identified by GC-MS. We believe, then, that the addition of 1 mol equiv of NaI provides the external noncomplexed nucleophile, which is necessary as a trap for the quinone methide intermediate **3**. In fact, in the absence of NaI, the treatment of PMB ether **1a** with $CeCl_3 \cdot 7H_2O$ alone furnished the desired alcohol in 55% yield contaminated by impurities after longer times (7 days at reflux). The major products identified by GC-MS, other than the isolated alcohol, were *p*-methoxybenzyl alcohol and chiefly *p*-methoxybenzyl chloride. Given these results, we have thought to change the agent for serving in the trap role. Unfortunately, the treatment of PMB ether **1a** with $CeCl_3 \cdot 7H_2O$ and with additional trapping agent such as NaCl in acetonitrile gave the parent alcohol only 60% after one week at reflux temperature. Since NaCl is less soluble in acetonitrile than NaI, we have also investigated the possibility that CsF, which is very soluble, could work as trapping agent. But the yield of deprotected alcohol was lower than in previous cases. Therefore, we believe that the addition of 1 mol equiv of NaI is crucial in these deprotections in obtaining high yields of deprotected alcohol compounds. Moreover, it should be noted that no deprotection occurred when conventional Lewis acids ($BF_3 \cdot OEt_2$, $TiCl_4$) were used, whereas the use of $CeCl_3$ promoted the PMB ether cleavage. We presume that the standard Lewis acids formed strong NaI−Lewis acid complexes, which neutralized the Lewis acid and, in addition, removed some of the iodide from the system so that there is less reagent available for the reaction. In contrast, $CeCl_3$, being a much harder Lewis acid, is likely to form a weaker and more labile NaI−Lewis acid complex. This complex may still function as a Lewis acid as there should still be free sites on the metal to allow coordination of the ether and therefore promote the deprotection.

In conclusion, we have shown that this $CeCl_3 \cdot 7H_2O$/NaI-promoted procedure provides an efficient methodology for an highly selective deprotection of *p*-methoxybenzyl ethers and demostrates a useful protocol for the attainment of free hydroxylated compounds. The other notable advantages offered by this procedure are the simplicity in operation (no special apparatus or techniques required), and the mild nature of cerium(III) chloride[26] in comparison to $TiCl_4$ and other Lewis acids.

(21) Izumi, M.; Suhara, Y.; Ichikawa, Y. *J. Org. Chem.* **1998**, *63*, 4811.

(22) Aryl PMB ethers were prepared using the standard procedure employing PMBCl and K_2CO_3 in refluxing acetone.

(23) Hart, L. S.; Waddington, C. R. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1607.

(24) The 2,4-dimethoxybenzyl ether was usually synthesized as follow: To a stirred suspension of NaH in DMF was added a THF solution of 2,4-dimethoxybenzyl alcohol at 0 °C. After evolution of H_2 ceased, a THF solution of decyl chloride was added, and the mixture was stirred for several hours. Usual workup gave the ether in almost quantitative yield.

(25) Fuji, K.; Ichikawa, Y.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.

(26) Imamoto, T. *Lanthanides in Organic Synthesis*; Academic Press: New York, 1994; and references therein.

Moreover, its compatibility with sensitive functionalities such as OBn, CO_2Et, and double bonds allows us to believe that this method will find many useful applications in organic synthesis.

Experimental Section

General. ^1H NMR spectra were recorded at 200 MHz using residual $CHCl_3$ (7.26 ppm) as reference. Mass spactra were determined on a HP5890 Series II capillary GC operating in split mode with helium carrier gas and fitted with a mass selective detector (MSD). Analytical TLC were performed on Merck silica gel plates (60F-254) using UV light. Flash column chromatography[27] was carried out using silica gel (Merck: 0.040−0.063 mm).

Representative Procedure for the $CeCl_3 \cdot 7H_2O$/NaI Cleavage of *p*-Methoxybenzyl Ethers. Deprotection of Methyl 2,4,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-D-mannopyranoside To Provide Methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (entry 10, Table 1). To a solution of methyl 2,4,6-tri-*O*-benzyl-3-*O*-(4-methoxybenzyl)-α-D-mannopyranoside **1j**[28] (1.0 mmol) in acetonitrile (10 mL) were added $CeCl_3 \cdot 7H_2O$ (1.5 mmol) and NaI (1.0 mmol), and the resulting mixture was stirred at reflux temperature for 24 h (no starting material remains as monitored by TLC). The reaction mixture was diluted with Et_2O and treated with 0.5 N HCl (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed twice with saturated aqueous $NaHCO_3$ and saturated brine solution and dried over Na_2SO_4. The solvent was then removed under reduced pressure, and the crude product was purified by flash chromatography (eluent: hexanes−ethyl acetate 85:15) to give methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (90% yield) as a syrup: ^1H NMR ($CDCl_3$) δ 2.32 (1H, d, J = 9.6 Hz), 3.35 (3H, s), 3.80−3.62 (5H, m), 3.96−3.90 (1H, m), 4.58−4.49 (3H, m), 4.65 (1H, d, J = 12.1 Hz), 4.76 (1H, d, J = 11.7 Hz), 4.83 (1H, d, J = 1.5 Hz), 4.85 (1H, d, J = 10.9 Hz), 7.25−7.40 (15H, m).

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(28) Compound **1j** was prepared in two steps from the commercially available methyl α-D-mannopyranoside: (a) Bu_2SnO, MeOH, PMBCl, CsF, DMF, (89%); (b) NaH, BnBr, DMF, (92%).

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