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Zirconium(IV) Chloride Catalyzed New and Efficient Protocol for the Selective Cleavage of *p*-Methoxybenzyl Ethers[†]

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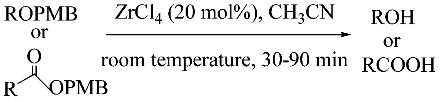
Abstract: A highly selective and efficient method for the unmasking of *p*-methoxybenzyl (PMB) ethers and esters has been developed by use of 20 mol % of zirconium(IV) chloride as Lewis acid in acetonitrile. The present method is very fast, and the conditions are tolerable to a variety of acid/base-sensitive protecting groups and substrates such as carbohydrates, terpenes, and amino acids. The products are obtained in good to high yields.

Selective and efficient masking and unmasking[1,2] of hydroxyl groups play a crucial role in organic synthesis, with a special reference to polyhydroxylated compounds. Of the several benzyl ether type protecting groups reported, *p*-methoxybenzyl (PMB)[3] ether enjoys a unique position due to the ease of its introduction and removal. PMB group demasking, in general, is mediated either by oxidizing agents (i.e., DDQ,[3] CAN,[4] and DDQ−Mn(OAc)$_3$[5]) or by Lewis acids[6] and other methods.[7] Lewis acid mediated removal of PMB groups suffers from the use of (a) reagents in stoichiometric quantities ($BF_3{\cdot}OEt_2$, $CeCl_3{\cdot}7H_2O$, Me_2BBr), (b) added reagents (ex. NaI, EtSH, anisole, etc.), and (c) sometimes longer reaction times. In spite of the availability of a variety of methods for PMB deprotection, development of milder and new methods is warranted to overcome the above drawbacks. We have previously reported efficient protocols for the PMB protection[8] of alcohols using catalytic Yb(OTf)$_3$ and unmasking[5] with 20 mol % of DDQ−Mn(OAc)$_3$. In continuation of our studies on the masking/unmasking of the hydroxyl groups,[9] herein we report an efficient $ZrCl_4$-catalyzed[10] protocol for the deprotection of PMB ethers and esters in short reaction times and good to high yields (eq **1**).



(1)

Thus, PMB ether **1** on treatment with $ZrCl_4$ (20 mol %) in CH_3CN at room temperature underwent a facile deprotection of PMB group in 30 min and gave **1a** in 86% yield (Table 1). Having observed efficient unmasking of **1**, to study the generality of the protocol, PMB ethers were prepared from a variety of substrates having different protecting groups and submitted to the new protocol using $ZrCl_4$ as Lewis acid. Accordingly, PMB ethers **3** and **4**, having acid-sensitive THP and MEM ethers, respectively, underwent smooth demasking of the PMB group in 40 min to give the products **3a** (85%) and **4a** (79%), respectively. PMB ethers **5** and **6**, having base-sensitive groups such as Ac and Bz, also underwent efficient PMB removal in 45 min to give **5a** (92%) and **6a** (88%). In a further study on ethers **7** and **8** with *O*-allyl and *O*-prenyl ethers, respectively, the $ZrCl_4$ (20 mol %)-catalyzed cleavage was effected in 45 min to give the alcohols **7a** (88%) and **8a** (90%), respectively.

Similarly, compound **9**, containing an acid-sensitive isopropylidene group as well as a glycosidic bond, when treated with $ZrCl_4$, gave the alcohol **9a** (82%) in 45 min, while carbohydrate derivative **10** having a glycosidic bond and a benzyl group furnished **10a** (89%) in 45 min very efficiently. Further, $ZrCl_4$-catalyzed PMB deprotection of terpenoidal ethers viz. **11** with a primary OH group and **12** with a secondary OH group was smooth in furnishing the corresponding alcohols **11a** (76%) and **12a** (78%) in 60 min.

In a further study, aminol **13** having a NHBoc group underwent smooth deprotection to give **13a** in 82% yield, while **14** with trityl group gave diol **14a** by a simultaneous deprotection of both the trityl and PMB groups. Further, esters **15**−**17** were deprotected with $ZrCl_4$ (20 mol %) to give the corresponding acids **15a**−**17a**, amply indicating that PMB esters also can be cleaved with equal ease as PMB ethers.

A comparative study on the PMB deprotection was conducted with different Lewis acids such as $AlCl_3$, $BiCl_3$, $TiCl_4$, and $FeCl_3$, the results of which is indicated in Table 2. For example, when **1** was treated with $TiCl_4$ and $FeCl_3$

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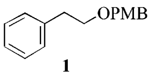
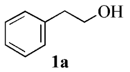
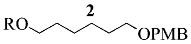
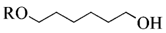
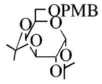
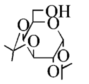
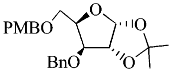
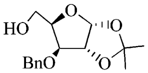
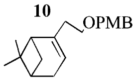
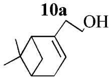
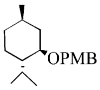
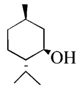
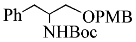
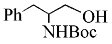
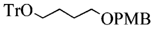
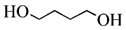
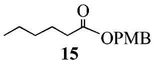
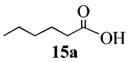
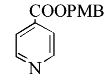
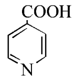
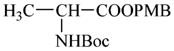
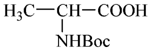
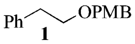
TABLE 1. $ZrCl_4$-Catalyzed Deprotection of PMB Etheres and Esters

S.No	STARTING MATERIAL	PRODUCT	TIME (min)	YIELD (%)
1	 **1**	 **1a**	30	86
2	$CH_3(CH_2)_6CH_2OPMB$ **2**	$CH_3(CH_2)_6CH_2OH$ **2a**	30	82
3				
	3 R= THP	**3a** R= THP	40	85
	4 R= MEM	**4a** R= MEM	40	79
	5 R= Ac	**5a** R= Ac	45	92
	6 R= Bz	**6a** R= Bz	45	88
	7 R= Allyl	**7a** R= Allyl	45	88
	8 R= Prenyl	**8a** R= Prenyl	45	90
4	 **9**	 **9a**	45	82
5	 **10**	 **10a**	45	89
6	 **11**	 **11a**	60	76
7	 **12**	 **12a**	60	78
8	 **13**	 **13a**	45	82
9	 **14**	 **14a**	45	76
10	 **15**	 **15a**	60	86
11	 **16**	 **16a**	90	67
12	 $\mathrm{H_3C{-}\underset{\underset{NHBoc}{\vert}}{CH}{-}COOPMB}$ **17**	 $\mathrm{H_3C{-}\underset{\underset{NHBoc}{\vert}}{CH}{-}COOH}$ **17a**	90	72

[a] All the products were identified by IR, ^1H NMR, mass, and TLC analysis with authentic samples.

TABLE 2. Comparative PMB Deprotection Study with Different Lewis Acids

Lewis acid (20 mol%), rt	$ZrCl_4$	$AlCl_3$	$BiCl_3$	$TiCl_4$	$FeCl_3$
substrate  **1**	30 min 86%	45 min 47%	incomplete reaction (24 h)	No reaction (24 h)	No reaction (24 h)

there was no reaction, while with $BiCl_3$ the reaction was incomplete; however, $AlCl_3$ gave the product in moderate yield (47%), thus indicating that $ZrCl_4$ is superior over the reagents studied for the PMB deprotection.

In conclusion, we observed that 20 mol % of $ZrCl_4$ in CH_3CN is a very efficient reagent for the cleavage of PMB ethers and esters. The efficacy of the present protocol is that it is catalytic and unmasking is effected in preference over benzyl and allylic ethers (allyl and prenyl). In addition, acid- and base-sensitive groups as well as substrates such as carbohydrates, terpenes, and amino acids well tolerate the reaction conditions. Further, the unmasking is performed in a shorter duration to result in good to high yields of the products. Thus, the new protocol using $ZrCl_4$ (20 mol %), due to its milder conditions, shorter reaction times, and higher yields, might find wide use for PMB deprotection in organic synthesis and in peptide chemistry.

Experimental Section

To a stirred solution of PMB ether/ester (1 mmol) in dry acetonitrile was added $ZrCl_4$ (0.2 mmol), and the mixture was stirred at room temperature until the starting material completely disappeared (TLC analysis). The solvent was removed under reduced pressure and the residue treated with EtOAc (20 mL). It was washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel 60−120; hexanes−EtOAc) to furnish the alcohols/acids, which were characterized by IR, ^1H NMR, and mass spectra.

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Supporting Information Available: Spectral data for all compounds along with a detailed experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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