A Mild and Selective Cleavage of *p*-Methoxybenzyl Ethers by CBr_4-MeOH

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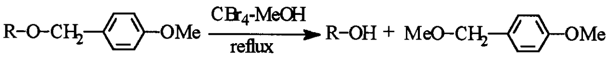
p-Methoxybenzyl ethers were selectively deprotected to the corresponding alcohols and phenols in high yields by CBr_4 in refluxing methanol under neutral reaction conditions.

Selective protection and deprotection of hydroxyl group is an important process in multi-step synthesis of complex natural products.[1] Among various hydroxyl protecting groups, the *p*-methoxybenzyl (PMB) ether is one of the most commonly used due to its stability towards a variety of reaction conditions and it can be removed selectively in the presence of benzyl ethers under mild conditions. Different methods are available for the selective removal of PMB group, which include Lewis acid catalysed cleavage by TMSCl-$SnCl_2$-anisole,[2] $AlCl_3$-EtSH,[3] Me_2BBr,[4] $BF_3{\cdot}Et_2O$-$NaCNBH_3$,[5] $MgBr_2$-Me_2S[6] and $CeCl_3{\cdot}7H_2O$-NaI[7] as well as oxidative cleavage[8] by DDQ, CAN and I_2-MeOH. Also, the cleavage of *p*-methoxybenzyl ether has been achieved by 10% solution of trifluoroacetic acid in dichloromethane.[9] However, inspite of their potential utility, some of these methods suffer from drawbacks like the use of heavy metals, lack of selectivity, unsatisfactory yields, expensive reagents and the use of strong oxidants. Although, the cleavage of *p*-methoxybenzyl ether has been reported by I_2-MeOH, the method involves longer reaction times resulting in moderate yields of the products. Moreover, iodine is hazardous and is not chemoselective in the presence of other functional groups present in the substrate. Consequently, the development of new methods with more efficacy, convenient procedures and better yeilds is desirable. Although the use of CBr_4 as catalyst and reagent for various transformations[10] is reported, it has not been used for the deprotection of PMB ethers.

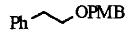
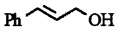
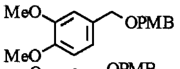
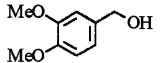
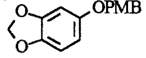
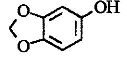
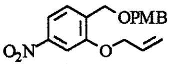
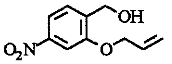
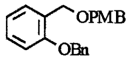
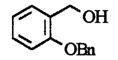
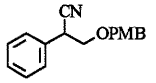
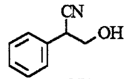
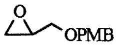
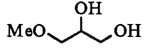
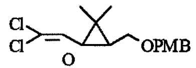
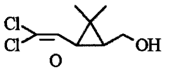
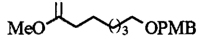
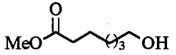
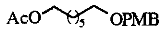
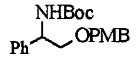
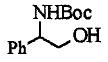
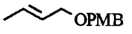
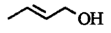
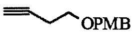
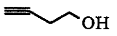
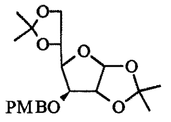
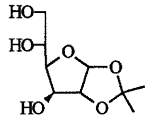
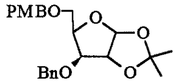
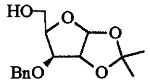
Herein, we report a new and efficient method for the selective removal of PMB group from the alcohols and phenols in the presence of benzyl ether and other functional groups. The deprotection proceeds smoothly by the treatment of the ether with a catalytic amount of CBr_4 in methanol at reflux temperature.



Scheme 1

Thus, *p*-methoxybenzyl ethers were cleaved selectively in the presence of other protecting groups like O-allyl, OBn, OPh, OMe, OBz, BOC, CBz and acetonide in the substrate. The results are summarised in the table. The advantage of the use of CBr_4 in methanol lies in its simplicity. Among various solvents studied, methanol is found to be more effective for this cleavage. The occurance of this cleavage may be attributed to the *in situ* formation of HBr itself by the reaction of CBr_4 with MeOH. To confirm the effect of the solvent the reactions were also carried out in refluxing acetonitrile in the presence of CBr_4

Table 1. Selective cleavage of *p*-Methoxybenzyl ethers by CBr_4-MeOH

Entry	Substrate	Product[a]	Reaction time/h	Yield %[b]
a.			6	87
b.			4	82
c.			3	93
d.			5	91
e.			7	87
f.			4	92
g.			6	85
h.			4	72
i.			5	84
j.			7	87
k.			6	91
l.			3	74[c]
m.			5	79
n.			6	83
o.			4	85
p.			3	90
q.			3	86
r.			4	70[d]
s.			3	73

[a] All products were characterised by IR, NMR and Mass spectra. [b] Isolated yields after column chromatography are reported. [c] Acetates were deprotected to the parent alcohol. [d] Primary ispropylidine group was cleaved under present reaction conditions.

which resulted in low to moderate yields of the products after a long reaction time. When the reactions were carried out with 10% CBr_4 the cleavage requires longer reaction times and anhydrous conditions to achieve comparable yields with 20% CBr_4. Neither expensive reagents nor overly acidic conditions are employed. Further, no precautions need to be taken to exclude moisture or oxygen from the reaction mixture. The method is compatible with other functional groups like nitro, cyano, olefinic, ester and cyclopropyl moieties in the molecule. If an oxirane ring is present in the substrate, a competitive reaction of nucleophilic ring opening of epoxide was observed along with the cleavage of PMB group. Further, the carbohydrate derivative entry(s) which contains an isopropylidine group, benzyl ether and glycosidic bond are unaffected under the present reaction conditions. However the deprotection is slow by CBr_4 in refluxing acetonitrile, various functional groups like acetates, THP ethers, epoxides and primary isopropylidine groups are unaffected.

The procedure for deprotection of PMB group is very simple. A mixture of ether (5 mmol) and CBr_4 (1 mmol) in distilled methanol (15 mL) was refluxed for an appropriate time as required to complete the reaction. After complete conversion as indicated by TLC, the reaction mass was cooled to room temperature and diluted with water and extracted twice with ether (2 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to yield crude product, which was purified by column chromatography on silica gel (Aldrich, 100–200 mesh, ethyl acetate: hexane, 1:9) to afford pure alcohol.

In conclusion, the letter describes a mild and efficient procedure for the selective removal of PMB ether group in the presence of benzyl ether using CBr_4 in refluxing methanol. The adopted procedure is simple, inexpensive, high yielding which makes it a useful addition to the existing methods.

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