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Graphical Abstract

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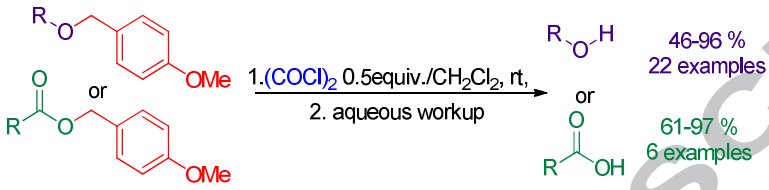
Ilangovan Andivelu[a, *] , Anandhan Karnambaram[a] and Kaushik Mahabir Prasad[b]



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Facile and selective deprotection of PMB ethers and esters using oxalyl chloride

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ABSTRACT

Oxalyl chloride, (0.5 equiv.) was found to cleave PMB group from alkyl, aryl PMB ethers and esters to give corresponding alcohol and acid in good yield. This method offers simple and efficient protocol for the selective deprotection of PMB ether and ester in DCE at ambient temperature.

1. Introduction

Selective masking and unmasking of ubiquitously found hydroxyl group, using a protecting group is one of the important transformations in the synthesis of complex organic molecules. The choice of protecting depends on its compatibility with other functional groups and set of reaction conditions used. Transformations relating to a hydroxyl group are likely to interfere with several functional groups such as amine, thiols, carboxylic acids, esters, ethers, etc. Although over 200 hydroxyl protecting groups have been reported so far, only a small fraction of them are in use.[1] Thus it requires development of conditions for selective protection and deprotection of hydroxyl group.

p-Methoxybenzyl group (PMB) is one of the widely used hydroxyl protecting group which shows orthogonality against a variety of protecting groups, including benzyl ethers, depending upon the deprotection method employed.[1] Different oxidizing agents such as DDQ,[2] CAN,[3] NBS,[4] iodine in methanol, clay supported ammonium nitrate[5] have been successfully utilized for PMB deprotection. Similarly, $NaCNBH_3/BF_3.OEt_2$,[6] Na in liq. NH_3[7] and H_2/Pd-C[8] have been used for the reductive removal of PMB group. Protic acids such as acetic acid,[9] 10% TFA in CH_2Cl_2, TfOH in the presence of 1,3-dimethoxybenzene,[10] and solid supported acids (Amberlyst-15, Lewatit, Dowex 2030, and Dowex 50X) in methanol[11] are known for the removal of PMB group. Lewis acids constitute the large number, among different type of reagents known for the deprotection of the PMB group. Lewis acids reported so far for the deprotection are $AlCl_3$-EtSH,[12] $CeCl_3.7H_2O$-NaI,[13] $Ce(OTf)_3$,[14] $ZrCl_4$,[15] $MgBr_2.OEt_2$-Me_2S,[16] Ag(I)SbF_6-1,3,5-trimethoxybenzene[17] (Figure 1). *N*-Chloro sulfonyl-*N*-benzylcarbamate formed as an intermediate by reaction between chlorosulfonyl isocyanate and PMB ethers must be hydrolyzed with NaOH to get back the alcohols.[18]

However, much of the reagents reported so far for the deprotection of PMB group has one or the other drawbacks. The major problem associated with oxidizing agents are the formation of inevitable anisaldehyde and side products due to the presence easily oxidisable functional groups such as sulphides, thiols, allyl etc., In case of acidic reagents, scavengers such as 1,3,5-trimethoxy benzene and thiols are to be used to avoid polymerization reaction of the PMB cation. Reagents such as $Ce(OTf)_3$ leads to a complex mixture of products with alcohols carrying double or triple bonds and AcOH as solvent gives rise to acetates instead of alcohol. Thus, there is a need for the development of simplified method for deprotection of PMB group.

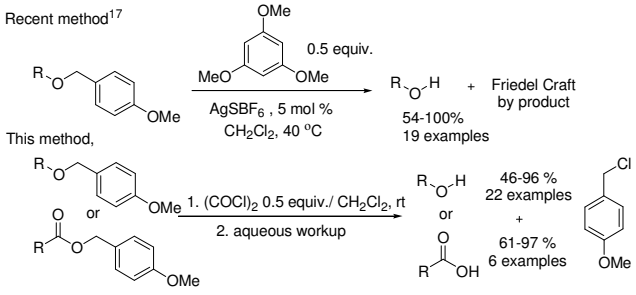

Figure-1. Background and reaction condition

Oxalyl chloride is one of the mild and widely used reagent for transformations such as preparation of acid chlorides,[19] chlorination,[20] three-component [3+2] cycloadditions,[21] reactions with organostannanes,[22] synthesis of cyclopentenones,[23] carbonylations,[24] as carbonyl synthon,[25] catalytic synthesis of N-heterocyclic ynones and ynediones,[26] and deprotection of secondary acetamides.[27] In the case of popularly known Swern

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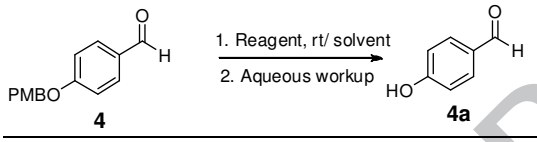
oxidation[28] of alcohols, dimethylchlorosulfonium chloride obtained by reaction of more than stoichiometric quantity of oxalyl chloride with DMSO is used as a mild oxidant.

Earlier, we demonstrated that a chlorinating agent such as $POCl_3$ could be used successfully for deprotection as well as trapping of the PMB cation generated to get 4-methoxybenzyl chloride and the deprotected alcohol.[29] In continuation of our interest on developing simple and selective method for the deprotection of hydroxyl protecting groups,[30] we examined readily available chlorinating agents such as $(COCl)_2$ and $SOCl_2$ as reagents for the removal of PMB group and found that $(COCl)_2$ could be used as an effective deprotecting agent for the selective removal of PMB group in high yield. Herein we present our results.

Our study began with examination of reaction of PMB ether **4**, independently with $(COCl)_2$ and $SOCl_2$ in different solvents at room temperature. The results are summarized in table-1. Compound **4** on reaction with 5 equiv. of $(COCl)_2$, without solvent, underwent PMB deprotection to give **4a** in 80% yield (entry 1). However, the yield increased substantially to 92% when the reaction was carried out in dichloroethane (DCE) using 1.5 equiv of $(COCl)_2$ (entry 5). The yield did not decrease when 0.5 equiv. of $(COCl)_2$ was used (entry 6). Further, lowering of quantity of $(COCl)_2$ to 0.2 equiv., lead to drop in the yield (entry 7). Change of solvent to DCM, THF or toluene lead to decrease in the yield (entries 2-4). When 1.5 or 0.5 equiv. of $SOCl_2$ was used in place of $(COCl)_2$ the yield was very low (entries 5 and 6). Thus $SOCl_2$ was found inferior to $(COCl)_2$ in the deprotection reaction. Based on these results the optimum condition for deprotection of PMB group was found to be 0.5 equiv. of $(COCl)_2$ in DCE at rt.

Table 1. Optimization experiments



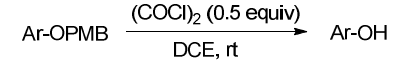
Entry	Solvent	Reagent (equiv) $(COCl)_2$	Reagent (equiv) $SOCl_2$	Time (h)	Yield[a] (%)
1.	Neat	5.0	-	10/-	80/-
2.	Toluene	0.5	-	24/-	70/-
3.	THF	0.5	-	10/-	80/-
4.	DCM	0.5	-	8/-	85/-
5.	DCE	1.5	1.5	5/24	92/56
6.	DCE	**0.5**	**0.5**	**5**/24	**92**/50
7.	DCE	0.2	-	9/-	88/-

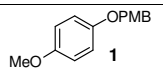
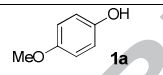
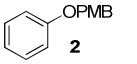
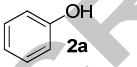
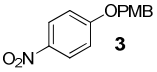
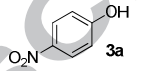
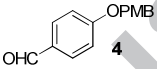
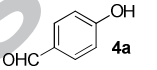
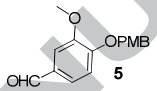
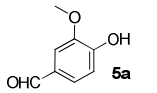
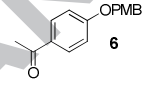
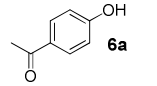
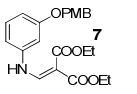
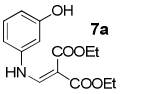
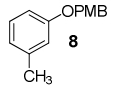
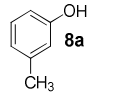
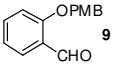
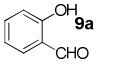
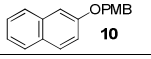
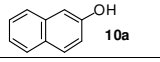
[a] Isolated yield,

Further, substrate scope was examined under the optimum reaction condition using different aryl PMB ethers and the results are summarized in table-2. Irrespective of the steric and electronic effect of the substituents present in the aromatic ring, all the substrates underwent deprotection successfully to provide corresponding phenol in high yield. While the substrates containing electron withdrawing substituents (entries 3-6) required longer time for complete removal of PMB group, unsubstituted substrates (entries 2 & 10) reacted rapidly. The presence of electron donating groups such as $–OCH_3$ and $–CH_3$ (entries 1, 8 table 2) lead to increase in rate of the deprotection.

Similarly, with 0.5 equiv. of oxalyl chloride, aliphatic substrates **11-22** underwent deprotection in less than 6 hours (Table 3). Functional groups such as acetyl, benzoyl, allyl, benzyl and prenyl groups (entries 3-7) remained intact and corresponding product was obtained in excellent yields. In case of compound **12** when a free hydroxyl group was present, the yield decreased substantially (entry-2). Although, there was no drop in rate of the reaction, slightly lower yield was observed in case of compounds **18** and **19** containing sensitive trityl and *t*-Bu groups (entries 7 and 8). No racemisation was observed in case of optically active substrates **20**, **21** and **22** and their corresponding products **20a**[31], **21a**[32] and **22a**,[33] respectively, were obtained in high yield (entries 10, 11 and 12). This was confirmed by recording optical rotation value for each compound. Further, the acetonide and benzylic ether functional groups present in the sugar derivative **22** was found to be compatible with the selective PMB deprotection condition.

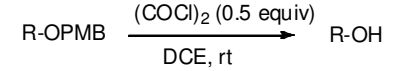
Table 2. Deprotection of Aryl PMB ethers[a]

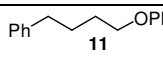
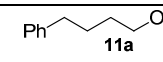
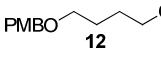
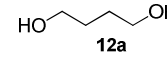
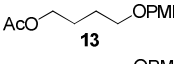
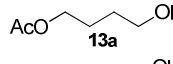
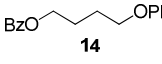
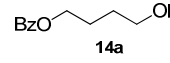
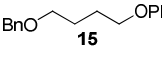
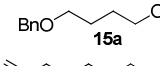
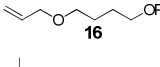
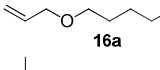
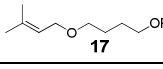
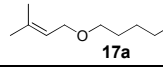


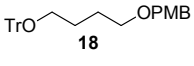
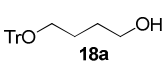
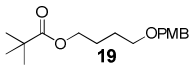
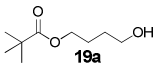
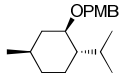
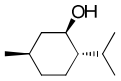
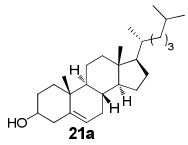
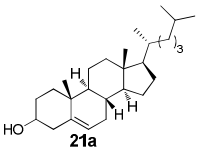
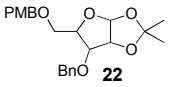
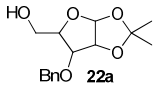
Entry	Substrate	Product	Time	Yield[b] (%)
1.			2 h 40 min	94
2.			2 h	93
3.			4 h	87
4.			5 h	96
5.			4 h 50 min	91
6.			4 h	92
7.			2 h	87
8.			1 h	85
9.			4 h 10 min	94
10.			2 h 10 min	85

[a] Reaction conditions: PMB ether (1 mmol), $(COCl)_2$ (0.5 mmol), DCE (5 mL), rt; [b] Isolated yield

Table 3. Selective deprotection of aliphatic PMB ethers[a]



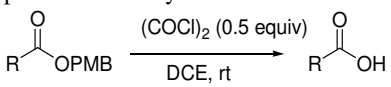
Entry	Starting material	Product	Time (h)	Yield[b] (%)
1			4 h	87
2			4 h	46[c]
3			2 h 30 min	86
4			4 h	81
5			5 h	85
6			5 h	87
7			5 h 50 min	89

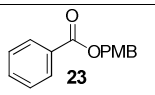
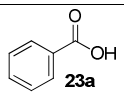
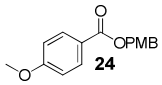
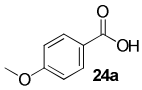
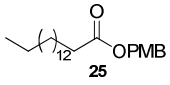
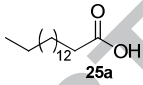
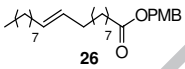
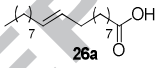
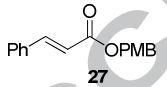
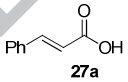
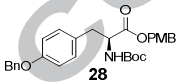
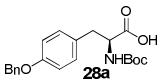
8	 **18**	 **18a**	2 h	60
9	 **19**	 **19a**	4 h	68
10	 **20**	 **20a**	3 h	70
11	 **21a**	 **21a**	2 h	77
12	 **22**	 **22a**	3 h	72

[a] PMB ether (1 mmol), $(COCl)_2$ (0.5 mmol), DCE (5 mL) at r t;
[b] Isolated yield [c] starting material recovered- 25%

Unlike several methods known for the deprotection of PMB ethers, there are only few mild methods reported for the deprotection of PMB esters. As a next part of the study we examined suitability of $(COCl)_2$ as a reagent for deprotection of PMB group present in different PMB esters. The results are summarized in Table 4.

Table 4. Deprotection of Aryl PMB esters[a]



Entry	Substrate	Product	Time	Yield[b] (%)
1	 **23**	 **23a**	2 h	82
2	 **24**	 **24a**	1 h 30 min	75
3	 **25**	 **25a**	4 h	97
4	 **26**	 **26a**	2 h 10 min	61
5	 **27**	 **27a**	5 h 50 min	73
6	 **28**	 **28a**	5 h	80

[a] PMB ether (1 mmol), $(COCl)_2$ (0.5 mmol), DCE (5 mL), r t; [b] Isolated yield

Both the aliphatic and aromatic esters delivered the corresponding acids (entries 1-6). Compared to compound **23**, marginal enhancement in the reactivity was observed in the case of compound **24** (entry 2). Almost quantitative yield of the product **25a** was observed in case of compound **25** containing no functional group (entry 4). Unexpectedly, oleic acid ester **26** (entry 3) and cinnamic acid ester **27**, containing double bond gave the products **26a** and **27a** in lower yield. As in the case of compound **28** (entry 6), the mild reaction condition didn't affect acid sensitive Boc group and the product **28a**[34] was obtained in good yield.

During the course of the reaction, we observed the formation of 4-methoxybenzylchloride and the deprotected alcohol only. Since oxalic acid diesters are stable compounds and do not undergo hydrolysis instantaneously, therefore we ruled out the formation of such side products. Based on this observation, we anticipated the formation of highly reactive intermediate, 3-chloro-3-alkoxy-oxiran-2-one, which is expected undergo decomposition quickly by losing carbon monoxide to give rise to stable compound alkoxy/aryloxycarbonylchloride. The formation of intermediate 3-chloro-3-alkoxy-oxiran-2-one can be justified due to the fact that similar compounds such as acetolactone [35] and oxalic anhydride are observed or detected in certain reactions of oxalyl chloride.[36] Based on these observations a plausible mechanism is proposed as shown below (Figure 2).

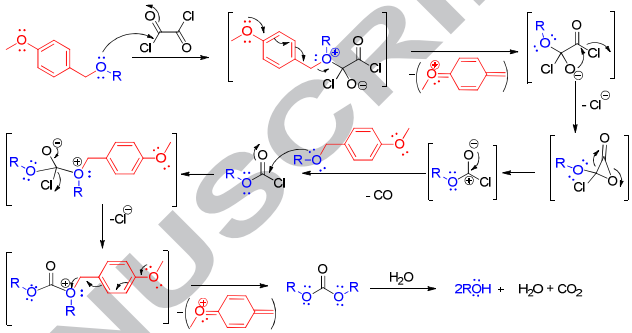


Figure 2. Plausible mechanism for the $(COCl)_2$ mediated deprotection of PMB group.

In conclusion, 0.5 equiv. of oxalyl chloride was successfully used for the highly selective deprotection of PMB group in aromatic, aliphatic, carbohydrate, steroid, terpenoid ethers as well as aromatic, aliphatic and amino acid esters. $SOCl_2$ was found to provide low yield compared to $(COCl)_2$. Besides being selective in its action against various acid and base sensitive functional groups, $(COCl)_2$ also meets some of the important characteristics of a successful deprotection agent such as non metallic reagent, short reaction time, reaction taking place at ambient temperature, easy isolation of the product and broad substrate scope. We hope that this mild and new method of deprotection of PMB group will be useful in synthetic organic chemistry.

Acknowledgments

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37. **General procedure for the deprotection of the PMB ethers and ester by $(COCl)_2$ (General Method D).** To a solution of the PMB ether or ester (1 equiv.) in DCE (5 mL), $(COCl)_2$ (0.5 equiv.) was added and stirred at room temperature. After completion of the reaction, it was quenched in ice water and the organic layer was separated and the aqueous layer was extracted with dichloroethane (2 x 5 mL). Combined organic layer was washed with brine solution, dried (Na_2SO_4), concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, EtOAc: Hexane= 2:8) to afford the corresponding alcohol.