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Selective *ortho*-cleavage of methoxymethyl- and 4-methoxybenzyl ethers

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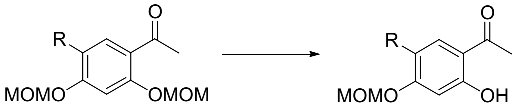
Abstract—Iodine in methanol has been found to be an effective catalyst system for the cleavage of alkoxymethyl ethers. This catalyst system is particularly useful for the selective removal of *ortho*-methoxymethyl- and *ortho*-(4-methoxybenzyl) ethers in the presence of their *para*-counterparts. Further investigation of various metal salts in methanol for their ability to cleave alkoxymethyl ethers revealed high-valent salts as effective catalysts, presumably through the release of small quantities of HCl.

In the field of organic synthesis, mild removal of protecting groups is often necessary, especially for complex or sensitive substrates. Molecules bearing multiple identical protecting groups have additional challenges associated with them if a selective deprotection is necessary later in the synthesis. In the course of our research, we needed to develop a method to selectively remove a methoxymethyl (MOM) group from the 2-position of bis-MOM protected 5-substituted-2,4-dihydroxyacetophenones (Scheme 1). We felt such a selective deprotection should be possible, as other protecting groups have been cleaved from similarly functionalized scaffolds.[1] Ideally, the method used would be mild, easy to set up/work up, and not require special handling techniques or anhydrous solvents. We were attracted to the work by Szarek whereby his group utilized 1 wt% of iodine in methanol to cleave silyl ethers, 4-methoxybenzyl ethers (PMB), and acetonides to their respective alcohols.[2] Subsequent research demonstrated that the I_2/MeOH catalyst system is capable of removing tetrahydropyranyl[3] and trityl[4] protecting groups as well as mediate transesterification.[5] Additionally, I_2/MeOH was also used to selectively cleave aliphatic silyl ethers in the presence of their phenolic counterparts in high yield.[6]

Iodine has been shown to react with methanol in the gas phase, generating hydrogen iodide and other products.[7] Acid generation in the liquid phase is also suggested as I_2/MeOH solutions have been shown to be mildly acidic.[6] Additionally, only alcohols bearing an α-hydrogen to the –OH group are effective solvents for this reaction.[3] Presumably, oxidation of the alcoholic solvent by iodine at this position is necessary to generate catalytic amounts of HI.



Scheme 1.

While I_2/MeOH had been used to cleave acetonides, we were unsure whether this reagent system would be effective at the removal of the more robust methoxymethyl ethers. When we first utilized this reagent system[8] we were delighted to observe selective deprotection of 5-chloro-2,4-dihydroxyacetophenone at the 2-position[9] in 76% yield (Table 1, entry 1). The reaction proceeded at room temperature in 8 h using reagent grade methanol without additional purification or drying. Longer reaction times resulted in greater amounts of di-deprotected material. Encouraged by this result, other substrates were subjected to the reaction conditions in an effort to elucidate the scope of the observed selectivity. Acids and amides (entries 2A and 3)[10,11] were well tolerated, giving useful yields (70–94%) of mono-deprotected products. MOM esters were cleaved along

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Keywords: Selective cleavage; MOM; PMB; Iodine; Methanol; Solvolysis.

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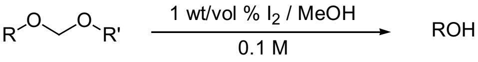
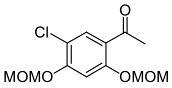
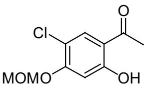
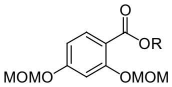
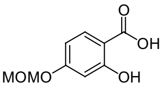
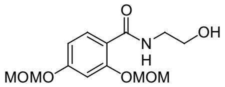
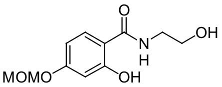
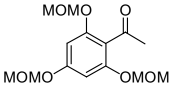
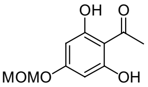
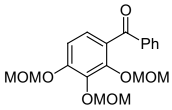
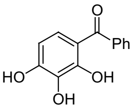
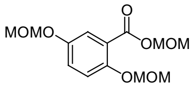
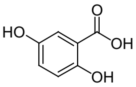
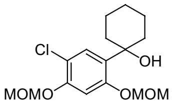
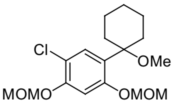
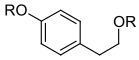
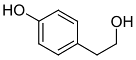
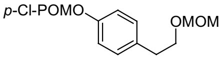
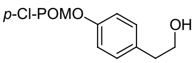
Table 1



Entry	Substrate	Temp (°C)	Reaction time (h)	Product	Yield (%)
1		rt	8		76
2					
	(A) R = H	rt	7		85
	(B) R = OMOM	rt	26		94
3		rt	9.25		70
4		rt	24		71
5		rt	8.5		99
6		rt	48		96
7		rt	8.5		61
8					
	(A) R = MOM	50	34		94
	(B) R = SEM	50	10		95
	(C) R = MEM	50	48		96
	(D) R = MTM	50	3.5		96
	(E) R = *p*-Cl-POM	50	34	 + 	36 41

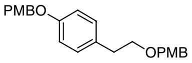
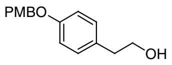
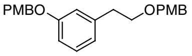
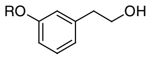
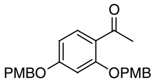
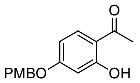
MOM = CH_3OCH_2; SEM = $(CH_3)_3SiCH_2CH_2OCH_2$; MEM = $CH_3OCH_2CH_2OCH_2$; MTM = CH_3SCH_2; *p*-Cl-POM = *p*-Cl-$C_6H_4OCH_2$.

with the adjacent MOM ether under the reaction conditions, to give the corresponding 2-hydroxy-4-(α-methoxymethoxy)benzoic acid in good yield (entry 2B). Even a tris-MOM ether of 2,4,6-trihydroxyacetophenone could be selectively bis-deprotected at the 2- and 6-positions in 71% yield. The same was not true for entries 5 and 6 where complete deprotection was observed. This is likely a result of electronic factors and neighboring group effects. In the case of entry 7, formation of the tertiary ether was the major reaction pathway.

Also of interest was the degree of selectivity between aliphatic versus phenolic deprotections.[12] To examine these issues, the bis-alkoxymethyl derivatives of 2-(4-hydroxyphenyl)ethanol were prepared and subjected to several different reaction conditions. We found that alcoholic alkoxymethyl groups were cleaved faster than phenolic alkoxymethyl groups, but not fast enough to give synthetically useful yields of mono-deprotected product. Entry 8 (Table 1) lists the conditions required for complete deprotection of the substrate. Methylthio-

Table 2

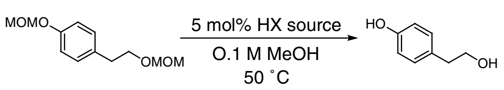
$$\text{R–OPMB} \xrightarrow{\text{1 wt\% } I_2 \text{ / MeOH}} \text{R–OH}$$

Substrate	Reaction temp (°C)	Reaction time (h)	Product	Yield (%)
	60	9		61
				
	rt	7 d	R = PMB	51
	50	48	R = H	Quant
	50	1.3		71

methyl (MTM) ethers (8D) were removed very quickly, though this is likely a redox process (at sulfur) as the iodine is completely decolorized. Aryloxylmethyl ethers were found to be the most stable of the protecting groups examined, with no observed reaction occurring at room temperature after 2.5 h. At 50 °C, selective removal of the aliphatic acetal was achieved, but transacetalization compromised the utility of the reaction. Based on the derivatives examined, the order of stability for these derivatives to these reaction conditions can be summarized as follows: *p*-Cl-POM > MEM > MOM > SEM > MTM.

Extending our studies to include *p*-methoxybenzyl (PMB) groups uncovered that hydroxyphenylethanol derivatives demonstrated greater selectivity than alkoxymethyl ethers. Reaction conditions varied (due to solubility differences) and selectivity was modest (Table 2). The reaction at room temperature was particularly slow (Table 2, entry 2). In contrast, a useful yield of a mono-deprotected 2,4-dihydroxyacetophenone derivative was attainable. Such compounds are useful precursors to flavanone natural products (Table 1, entries 1 and 4).

Table 3



Catalysts giving clean reaction	Reaction time (h)	Catalysts giving no reaction[a]
$AlCl_3$	50	$CrCl_3$
$BiCl_3$	48	$CuCl_2$
$FeCl_3$	37	$InCl_3$
$HfCl_4$	23	$NiCl_2$
$PdCl_2$	48	$YbCl_3$
$ScCl_3$	48	YCl_3
$SnCl_4$[c]	58	
$TiCl_4$[c]	10	
$(CH_3)_3SiCl$[b]	6.3	
VCl_3	30	
$Yb(OTf)_3$	50% conv. after 4 d	
$ZrCl_4$	13	
Dowex 50wx2-200	30	
TsOH	24	

[a] No detectable conversion of starting material after 48 h.
[b] One drop (approx. 25 mol%) TMSCl used.
[c] 1.0 M solution in CH_2Cl_2 used.

In addition to I_2, other potential catalysts were screened for their ability to remove alcoholic and phenolic MOM ethers and are summarized in Table 3. The deprotection process is fairly general even though the mechanisms of acid generation and deprotection may vary.[13] A large number of agents were effective at removing both alcoholic and phenolic MOM groups at a loading of only 5 mol%.[14] Early high-valent transition metals and main-group metals were among the most reactive. The practicality of these catalysts varies considerably. For example, the least expensive is $FeCl_3$, while DOWEX 50wx2-200 affords the most convenient workup. The screen for new catalysts was not exhaustive and there are likely many other agents[15] that would afford similar results.

In conclusion, we have discovered novel and mild conditions for the removal of both alcoholic and phenolic alkoxymethyl ethers and esters. Additionally, we have uncovered conditions for the selective removal of MOM and PMB groups from 2,4-dihydroxyacetophenone and 2,4,6-trihydroxyacetophenone as well as their carboxylic acid derivatives. These mono-protected compounds are useful building blocks for natural product syntheses.

Acknowledgements

I would like to thank Jiejun Wu for NMR work on this project.

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8. Standard procedure: The substrate is dissolved in methanol (0.1 M) and then treated with 1 wt % iodine (10 mg I_2/mL MeOH). The resultant mixture is then stirred at the desired temperature with monitoring by TLC. Once the desired degree of deprotection has been achieved, the reaction is quenched with aqueous $Na_2S_2O_3$ and the product extracted with ethyl ether or methylene chloride. The organic layer is washed with satd $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and evaporated to dryness to give the crude product. The products can be purified chromatographically or by recrystallization (acids).
9. Phenol protons adjacent to a carbonyl appear considerably downfield (12–13 ppm) by ^{1}H NMR. NOE analysis further confirmed the assigned structures.
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13. We suspect most of the metal halides are undergoing methanolysis with liberation of HCl, and that $PdCl_2$, undergoes reduction to Pd(0) (palladium mirror was evident) leading to the generation of HCl.
14. Reaction rates can be improved by increasing the catalyst loading, but for the sake of this study, were kept constant to afford meaningful comparisons between catalysts.
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