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Selective Deprotection of Alkyl Esters Using Magnesium Methoxide

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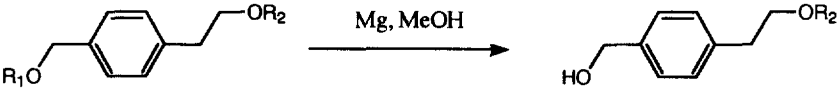
Abstract: The use of magnesium methoxide for the deprotection of alkyl esters is described. This mild reagent provides a good method to cleave esters efficiently and more importantly, allows for effective differentiation between two different esters. The order of the reactivity of this reagent towards acyl cleavages was found to be: *p*-nitrobenzoate > acetate > benzoate > pivaloate >> acetamide.

Selective deprotection of a functional group in the presence of others is still one of the most important manipulations in modern organic synthesis.[1] This common practice in the chemistry laboratory becomes very challenging when these protecting groups are similar in nature. A typical example among many others is the ester functionality such as acetate, benzoate and pivaloate, which are frequently used for hydroxyl protection.

A great deal of effort has been devoted to develop selective ester deprotection reagents. Herzig et al has reported that KCN slowly hydrolyzes 1,2-diol diacetates until the first acetate is removed.[2] Danishefsky has used $BF_3 \cdot Et_2O$ in wet CH_3CN to cleave anomeric acetate in the presence of other acetates.[3] There were many other selective ester deprotection reagents reported,[1] including DBU,[4] Bu_3SnOMe,[5] 50% NH_3 in MeOH,[6] guanidine,[7] *Candida Cylindracea*,[8] and NH_2NH_2 in AcOH and pyridine.[9] Recently, we also reported that a protocol utilizing magnesium metal and anhydrous methanol (Mg/MeOH) can selectively cleave different esters.[10] All the esters shown in Scheme 1 can be efficiently hydrolyzed using this protocol. Amides are not cleaved under these conditions. Excellent selectivity for cleaving one in the presence of other less reactive esters can be achieved simply by adjusting the equivalents of magnesium.

Scheme 1



1 2

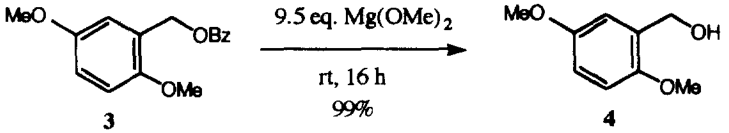
R_1 = PNB; R_2= Ac, Bz, Pv 68-99%
R_1 = Ac; R_2 = Bz, Pv 76-92%
R_1 = Bz; R_2 = Pv 94%

Although this is a practically useful method for selective deprotection of esters, a significant drawback is the high reactivity of this reagent towards a variety of functional groups. It has been reported that compounds containing functional groups of alkyl and aryl halides,[11] conjugated ketones,[12] esters,[13] nitriles,[14] amides,[15] triple and double bond conjugated to aromatics[16] all react with Mg/MeOH to yield different products. Therefore, the usefulness of this method is limited to the substrates without these aforementioned functional groups. This confinement prompted us to explore new reagents with improved applicability.

Magnesium slowly reacts with methanol to generate $Mg(OMe)_2$ and H_2 gas. This was observed to occur first during the ester deprotection process. It was postulated that $Mg(OMe)_2$ is the active reagent for ester hydrolysis, while Mg^0, which is a known reductant,[11-16] could be the cause of other side reactions. Therefore, a study of $Mg(OMe)_2$ as a new reagent for selective ester hydrolysis was initiated.

We first began to investigate the effectiveness of $Mg(OMe)_2$ in ester hydrolysis. As indicated in Scheme 2, benzoate **3** was converted to its corresponding alcohol **4** in almost quantitative yield, indicating that $Mg(OMe)_2$ is indeed a very effective reagent for ester cleavage.

Scheme 2

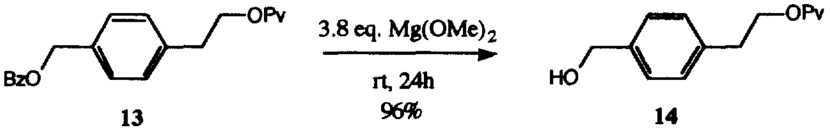


3 **4**

We then systematically investigated the selectivity of this reagent towards a variety of esters employing competitive deprotection strategy. The results are summarized in Table 1. All the competitive reactions were carried out with two different esters, and the progress of the reaction was monitored by TLC. The reactions were intercepted by quenching with 0.2 N HCl solution when one of the two esters was completely consumed. The product alcohol **12** and the recovered starting materials, the less reactive esters, were isolated by flash column chromatography.[17] As shown in the entries 1, 2, 3 of Table 1, *p*-nitrobenzoate (PNB) is the most sensitive group among the esters investigated. Compound **7** can be selectively hydrolyzed using 0.1 to 0.3 equivalents of $Mg(OMe)_2$ in the presence of acetate **8**, benzoate **9**, and pivaloate **10**. The selectivity is moderate with acetate (entry 1), and excellent with benzoate and pivaloate (entry 2, 3). As seen in entries 4 and 5, the acetate of compound **8** can be cleanly removed using approximately 0.6 equivalents of $Mg(OMe)_2$, while benzoate **9** and pivaloate **10** were stable under these conditions. The competitive study in entry 6 indicates that benzoate **9** can be selectively hydrolyzed in the presence of pivaloate **10**. Finally, the reaction of pivaloate **10** and acetamide **11** with $Mg(OMe)_2$ gave only alcohol **12**; the acetamide was recovered in 95% yield after purification by flash chromatography. It was further found that acetamide **11** remains intact even with 18 equivalents of the reagent at room temperature for two days. From the data in Table 1, it is clear that the selectivity among the compounds with PNB, acetate, benzoate, pivaloate and acetamide groups can be very well controlled by adjusting the amount of $Mg(OMe)_2$ reagent.

We also tested the competitive reaction with NaOMe, a commonly used reagent for selective ester cleavage. Treatment of a equal molar mixture of **8** and **9** with NaOMe (0.6 eq) at room temperature for 6 h gave rise to benzoate **9** in only 41% yield, and alcohol **12** in 144%. The selectivity is obviously deteriorated compared with the same reaction using $Mg(OMe)_2$ shown in entry 4 of Table 1.

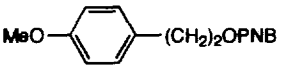
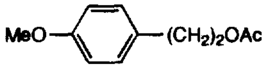
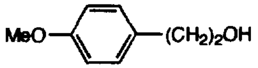
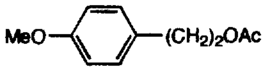
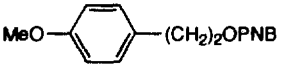
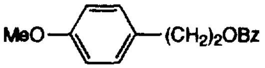
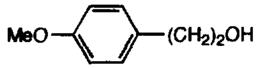
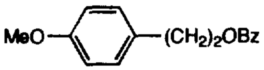
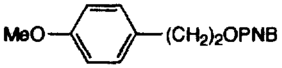
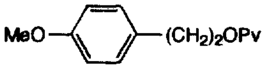
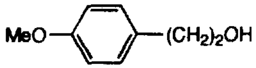
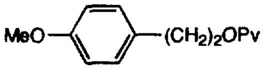
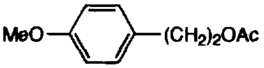
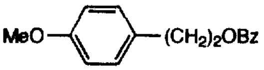
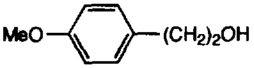
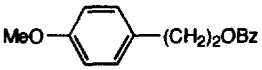
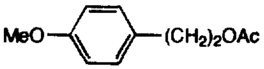
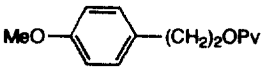
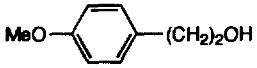
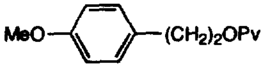
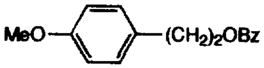
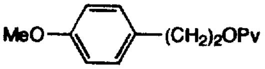
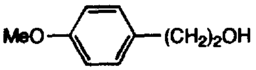
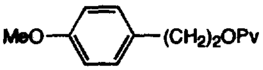
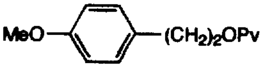
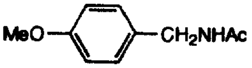
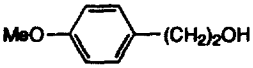
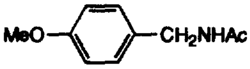
Scheme 3



13 **14**

To further demonstrate the selectivity, compound **13** bearing both benzoate and pivaloate functional groups was prepared.[10] As indicated in Scheme 3, treatment of compound **13** with $Mg(OMe)_2$ gave pivaloate alcohol **14** in 96% yield. No diol was observed.

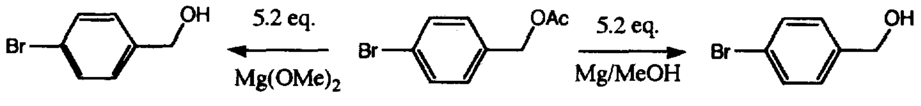
Table 1: Selective Deprotection of Esters with Magnesium Methoxide

Entry	Starting Materials	Conditions[a]	Products and Unreacted Esters[b] (isolated yields[c])
1	 **7**  **8**	0.12 eq. $Mg(OMe)_2$ MeOH/THF (19:1) rt, 6h	 **12** (91%)  **8** (71%)
2	 **7**  **9**	0.24 eq. $Mg(OMe)_2$ MeOH/THF (19:1) rt, 24h	 **12** (95%)  **9** (93%)
3	 **7**  **10**	0.26 eq. $Mg(OMe)_2$ MeOH/THF (19:1) rt, 14h	 **12** (95%)  **10** (93%)
4	 **8**  **9**	0.61 eq. $Mg(OMe)_2$ MeOH 6h	 **12** (92%)  **9** (90%)
5	 **8**  **10**	0.58 eq. $Mg(OMe)_2$ MeOH 48h	 **12** (89%)  **10** (90%)
6	 **9**  **10**	3.6 eq. $Mg(OMe)_2$ MeOH 24h	 **12** (94%)  **10** (89%)
7	 **10**  **11**	8.8 eq. $Mg(OMe)_2$ MeOH 27h	 **12** (93%)  **11** (95%)

a) The concentration of reactant is about 0.05M. b) Satisfactory spectral data were obtained for all products. c) Isolated yield.

In order to compare $Mg(OMe)_2$ with Mg/MeOH, 4-bromobenzyl acetate **15** was subjected to both conditions. As indicated in Scheme 4, almost quantitative yield of 4-bromobenzyl alcohol **16** was obtained with $Mg(OMe)_2$. In sharp contrast to that, treatment of **15** with Mg/MeOH did not give any desired product **16**, only a complicated mixture was obtained. This clearly suggests the superiority of $Mg(OMe)_2$ over Mg/MeOH for ester deprotection with more functionalized substrates.

Scheme 4



16 96% **15** 0% **16**

In summary, $Mg(OMe)_2$ provides a new and useful method that allows for effective and selective ester deprotection. From a limited number of esters studied, the order of reactivity towards this reagent was found to be as follows: PNB > acetate > benzoate > pivaloate >> acetamide. By adjusting the equivalents of $Mg(OMe)_2$, it is possible to effectively differentiate among these esters. Due to its economy, high yield and selectivity, $Mg(OMe)_2$ will find many application in organic synthesis.

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17. All compounds were characterized by ^1H NMR, mass spectrum, and some by elemental analysis.

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