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Selective Deprotection of Esters Using Magnesium and Methanol

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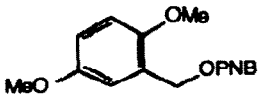
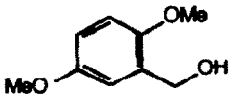
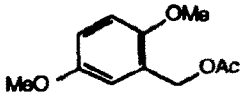
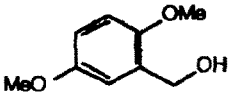
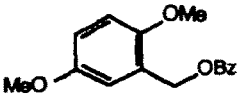
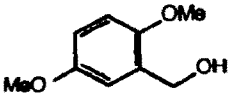
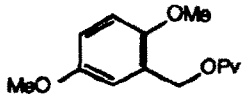
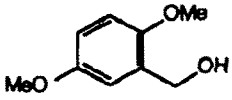
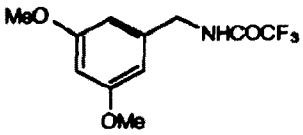
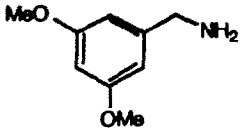
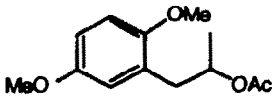
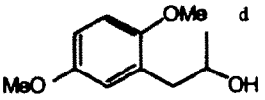
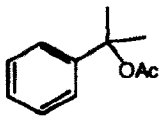
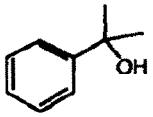
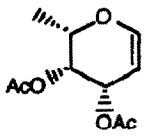
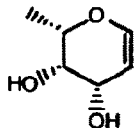
Abstract: The use of magnesium metal in methanol for the deprotection of alkyl esters is described. This mild reagent also provides good to excellent selectivity to cleave different esters. The order of the reactivity of this reagent towards acyl cleavages was found to be: *p*-nitrobenzoate > acetate > benzoate > pivaloate >> trifluroacetamide.

Of the many methods available to protect a free hydroxy group,[1] esters such as acetate, benzoate, pivaloate, etc. are still regarded as some of the most useful protecting groups. Parallel with that, numerous deprotection methods have since been developed to liberate hydroxy functionality from esters.[1] As organic chemists challenge themselves to synthesize more and more complicated structures, the need of developing new and more effective deprotective reagents, especially those with high selectivity to deprotect one in the presence of others, are becoming more and more desirable. Herein, we wish to report an effective and selective regent for the cleavage of different esters to their alcohols.

In anhydrous conditions, magnesium metal slowly reacts with methanol to generate magnesium methoxide and hydrogen gas. The usefulness of this reagent has previously been explored, and these include the selective reduction of the double bonds conjugated to ketones,[2] esters,[3] nitriles,[4] and amides.[5] Triple and double bonds conjugated to an aromatic system have also been reduced using Mg/MeOH.[6] Reductive cleavage of γ-functionalized α, β-unsaturated ester can also be effected by Mg/MeOH.[7] Recently, magnesium methoxide has been found to selectively cleave lactam-carbamates.[8] In connection to our recent effort directed towards the synthesis of anthracycline antibiotics,[9] we were intrigued by an unexpected acetyl cleavage when a molecule, containing both an α, β-unsaturated ketone and an acetate functionality, was subjected to Mg/MeOH conditions. In light of this new result, we set forth to exploit the potential application of Mg/MeOH to effect ester cleavage. The results are summarized in Table I. We found that Mg/MeOH is an effective reagent for unmasking the alcohols from their esters and is generally applicable to various esters. As indicated in Table I, aromatic substrates were chosen for studying this deprotection reaction because of easy TLC detection and product isolation. As shown in Table I, *p*-nitrobenzoate (PNB), acetate and benzoate were cleaved to give their corresponding alcohols in excellent yields. Cleavage of the pivaloate was also very efficient with more reagent (entry 4), while trifluoroacetamide is totally inert to Mg/MeOH condition (entry 5). The acetate of secondary and tertiary alcohols could also be effectively removed (entries 6 &7).

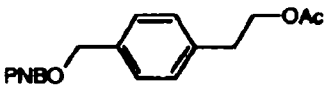
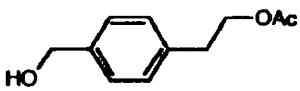
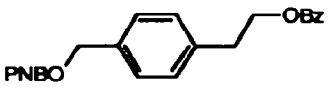
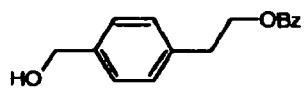
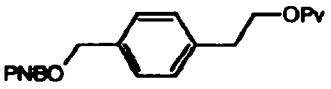
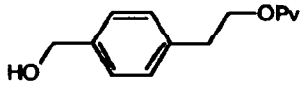
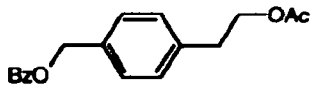
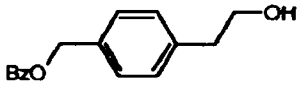
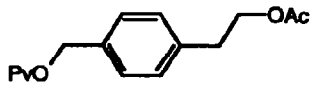
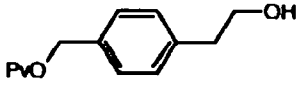
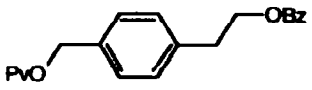
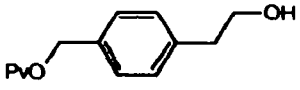
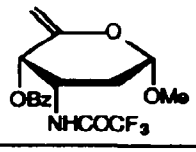
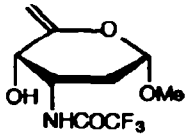
During these experiments, we observed that, from *p*-nitrobenzoate, acetate, benzoate to pivaloate, more and more magnesium metal was required to effect the ester hydrolysis. Having noted the different reactivities of these esters towards Mg/MeOH reagent, we decided to investigate systematically the selective cleavage among these esters. The results were presented in Table II. The *p*-nitrobenzoate was selectively removed in the

Table I: Deprotection of Esters with Magnesium in Methanol

Entry	Reactant	Conditions[a]	Product[b]	Yield (%)
1		Mg, 1.0 eq, MeOH rt, 2.5 h		99
2		Mg, 1.0 eq, MeOH rt, 2.5 h		98
3		Mg, 5.0 eq, MeOH rt, 6h		95
4		Mg, 12 eq. MeOH rt, 24h		85
5		Mg, excess, MeOH rt, 24h		0[c]
6		Mg, 4.0 eq, MeOH rt, 6h	 [d]	98
7		Mg, 10.0 eq, MeOH rt, 12h		93
8		Mg, 3.0 eq, MeOH rt, 4h		95

a) The concentration of reactant is 0.05 M for all reactions. b) Unless otherwise indicated, all products were compared with authentic samples from commercial suppliers. c) Recovered starting material. d)Satisfactory spectral data were obtained for this product.

Table II: Selective Deprotection of Esters with Magnesium in Methanol

Entry	Reactant	Conditions[a]	Product[b]	Yield (%)
1		Mg, 1.0 eq, MeOH/THF (10:1), 0^0C, 2.5 h		68[c]
2		Mg, 1.0 eq, MeOH/THF (10:1), rt, 2.5 h		90[d]
3		Mg, 1.0 eq, MeOH/THF (10:1), rt, 2.5 h		99[e]
4		Mg, 1.5 eq. MeOH rt, 3h		76[f]
5		Mg, 2 eq, MeOH rt, 6h		92[e]
6		Mg, 6.0 eq, MeOH rt, 10h		94[e]
7		Mg, 3.0 eq, MeOH rt, 13h		91

a) The concentration of reactant is 0.05 M for all reactions. b) Satisfactory spectral data were obtained for all the products. c) A 29% yield of the diol resulting from the removal of both ester groups was isolated. d) The corresponding diol was isolated in 5% yield. e) No corresponding diol was observed in ^{1}H NMR. f) The diol was isolated in 18%.

presence of acetate. Although the selectivity was moderate (68:29), a synthetically useful yield (68%) of monoalcohol could be obtained (entry 1). The selectivity of removing PNB in the presence of benzoate increased significantly (90:5). Complete control of selectively removing PNB with respect to pivaloate could be realized (entry 3). Of particular interest is the selective deprotection of acetate in the presence of benzoate (entry 4), a system known to be difficult to achieve selectivity.[10] Excellent selectivity was observed between acetate and pivaloate (entry 5). Effective cleavage of benzoate was also successful using Mg/MeOH without affecting pivaloate and trifluoroacetamide functionalities (entries 6 & 7).

In conclusion, Mg/MeOH provides an alternative method suitable for effective, selective ester deprotection. Due to its economy, ease of use, and higher yields and selectivity, Mg/MeOH will find many applications in organic synthesis.

A typical procedure is as follows: To a stirred solution of 2, 5-dimethoxybenzyl benzoate (431.0 mg, 1.58 mmol) in 32 mL of anhydrous methanol was added magnesium turnings (192.0 mg, 7.90 mmol) under nitrogen. After 15 to 30 min induction period, a mild exothermic reaction started with evolving hydrogen gas. (In the case of alkyl *p*-nitrobenzoate where the reactant is not soluble in methanol, a solution of reactant in a minimum of THF was added to a solution of magnesium in methanol after the induction period.) Stirring was continued for 6 h to dissolve all magnesium metal while maintaining the pot at room temperature in a water bath. After 10 mL of 1N HCl solution was added, the mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic phases were dried, filtered, and concentrated. Flash chromatography of the residue using hexanes and EtOAc gave 2, 5-dimethoxybenzyl alcohol (251.8 mg, 95%), which is identical to the authentic compound purchased from Aldrich.

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