Articles

A Reagent for Selective Deprotection of Alkyl Acetates

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The use of magnesium methoxide for selective deprotection of alkyl esters is described. By adjusting the equivalents of the magnesium methoxide reagent, it is possible to selectively cleave primary acetate in the presence of secondary and tertiary acetate and to cleave secondary acetate in the presence of tertiary acetate. A high selectivity can also be obtained for the same primary acetates if the β-positions of the acetates render a different steric bulkiness. This mild reagent has been successfully applied to the selective deprotection of many natural-occurring molecules including hydroxycitronnellol diacetate, *trans*-sobrerol diacetate, betulin diacetate, and baccatin III.

Introduction

Of the many methods available for hydroxy group protection, esters have still retained a position of prominence due to their ease of formation and cleavage as well as their rich choices of a whole array of different esters such as acetate, benzoate, pivaloate, etc.[1] The acetate esters are among the most popular protecting groups for hydroxy functions in synthetic chemistry as they are readily introduced and removed by a variety of reaction conditions.

One of the common practices encountered in the organic chemistry laboratory is the use of a reagent to selectively remove a protecting group. Selective deprotecting agents are particularly important and beneficial in complex synthetic sequences in which two protected functional groups must be unmasked at different stages of a synthesis. A great deal of effort has been devoted to develop deprotection conditions to remove one ester in the presence of other esters. DBU in benzene,[2] for example, has been reported to cleave acetates only, without affecting benzoates. Guanidine in ethanol and dichloromethane has also been found to selectively remove acetates in the presence of benzoates, pivaloates, and acetamides.[3] There are many other deprotection protocols reported, including 50% NH_3 in methanol,[4] NH_2-NH_2 in acetic acid and pyridine,[5] and Mg metal in methanol.[6] Recently, magnesium methoxide in methanol has been reported to be a selective ester deprotection agent and allows for an effective differentiation among *p*-nitrobenzoates, acetates, benzoates, pivaloates, and acetamides.[7]

The other important aspect of selective ester deprotection is to differentiate the same type of esters, for example, primary acetates vs secondary acetates, etc. Deprotection agents with such selectivity are more practically useful because initial protection can be carried out in a single step. Several agents with moderate selectivity have been reported. $BF_3{\cdot}Et_2O$ in wet acetonitrile[8] and Bu_3SnOMe in $ClCH_2CH_2Cl$[9] have been found to cleave anomeric acetates in the presence of alkyl acetates. Lipase from *Candida cylindracea*[10] and Al_2O_3 in benzene[11] are also reported to be effective agents for deacylation of primary acetates. Other conditions for selectively removing primary acetates include KCN in EtOH,[12] 5% KOH in methanol,[13] and K_2CO_3 in methanol and water.[14] It should be noted that most of these conditions can work only for a specific set of substrates. There is no single agent reported that can effectively differentiate among primary, secondary, and tertiary acetates. In connection with our recent interest in selective deprotection agents,[7] we report our new findings that magnesium methoxide is a selective agent for effective differentiation of various acetates and it is widely applicable to many organic substrates.

Results and Discussion

During our recent studies of selective deprotection of different esters using magnesium methoxide in methanol,[7] it was found that the amount of the reagent is essential to obtain a high selectivity. It was our expectation that the steric unlikeness of various acetates resulting from primary, secondary, and tertiary alcohols could also be differentiated by controlling the amount of magnesium methoxide reagent. For this purpose, a competitive deacylation reaction from a primary acetate and a tertiary acetate was set out to test this hypothesis.

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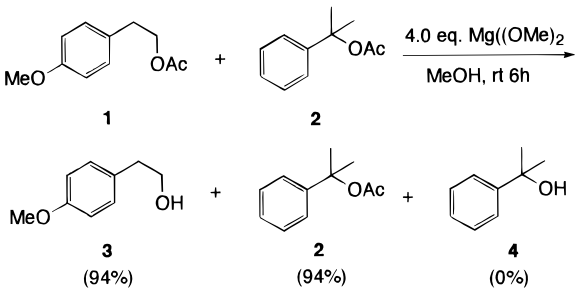
Scheme 1



As shown in Scheme 1, a mixture of primary acetate **1** (1.0 mmol) and tertiary acetate **2** (1.0 mmol) in methanol was treated with 4.0 equiv of magnesium methoxide under nitrogen at rt. The reaction was worked up after 6 h when acetate **1** was all consumed. A primary alcohol **3**, resulting from deacylation of **1**, was isolated in 94% yield. Tertiary alcohol **4** was not detected from the reaction mixture; instead, the tertiary acetate **2** was recovered in 94% yield. Treatment of **2** with 15 equiv of magnesium methoxide afforded **4** in 95% yield. These experiments clearly indicate that it is possible to control the rate of cleavage of primary acetate **1** and tertiary acetate **2** by adjusting the amount of magnesium methoxide.

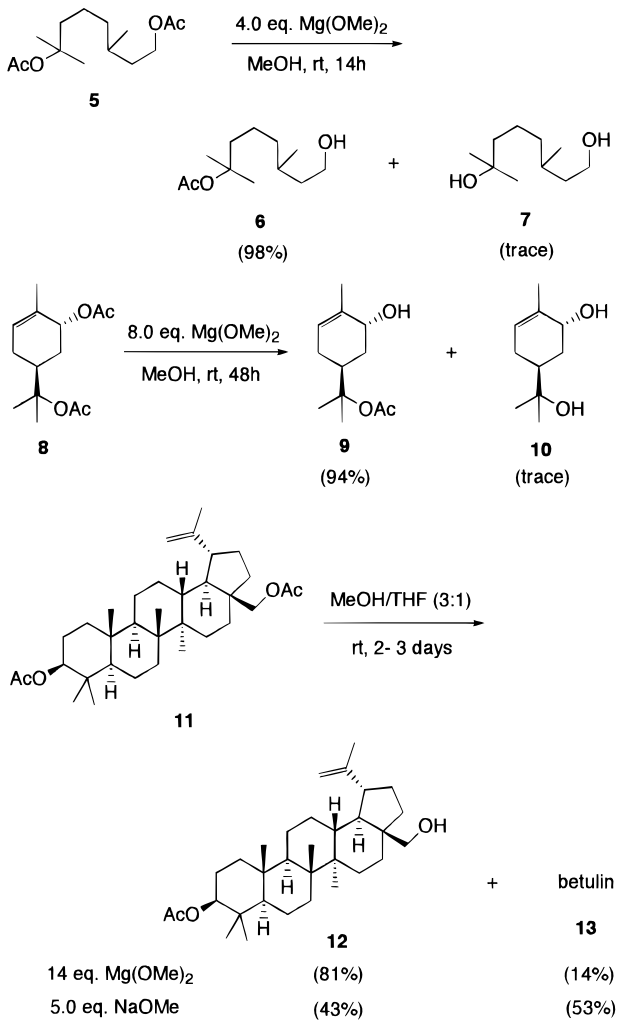
Encouraged by this data, we decided to study systematically the selective deacylation reaction on a set of substrates bearing two sterically different acetate functionalities. Therefore, a series of diacetates **5**, **8**, and **11** was prepared from their corresponding diols **7** (hydroxycitronnellol), **10** (*trans*-sobrerol), and **13** (betulin), respectively. The choice to prepare these diacetates for the selective deacylation study is mainly due to the commercial availability of the starting diols.

As indicated in Scheme 2, treatment of hydroxycitronnellol diacetate **5** with 4.0 equiv of magnesium methoxide in methanol at rt for 14 h resulted in the formation of monoacetate product **6** in 98% isolated yield. Only a trace amount of hydroxycitronnellol (**7**) was observed on TLC but could not be isolated due to the small quantity of the material. The reaction is very selective with deacylation occurring predominantly at the primary acetate.

We next examined the selective deacylation reaction on (±)-*trans*-sobrerol diacetate (**8**), which bears two acetates resulting from secondary and tertiary alcohols. Upon treatment of compound **8** with 8.0 equiv of magnesium methoxide at rt for 48h, sobrerol monoacetate (**9**) was isolated in 94% yield. Diol **10** was only detected by TLC and could not be isolated. In comparison with the previous deacylation reaction (substrate **5**), it has been noted that more equivalents of reagents were required for the substrate **8**. The selective deacylation of **8** with only 4 equiv of magnesium methoxide is too slow to be practically useful. Although the steric difference between the secondary acetate and the tertiary acetate in structure **8** is less than that of the primary acetate and the tertiary acetate in structure **5**, a very good selectivity for diacetate **8** was still obtained.

We then examined the selectivity among a primary acetate and a secondary acetate for betulin diacetate (**11**). It should be noted that both the primary acetate and the secondary acetate in compound **11** have a similar quaternary carbon residing next to them. This, however, is not expected to influence the absolute difference between

Scheme 2

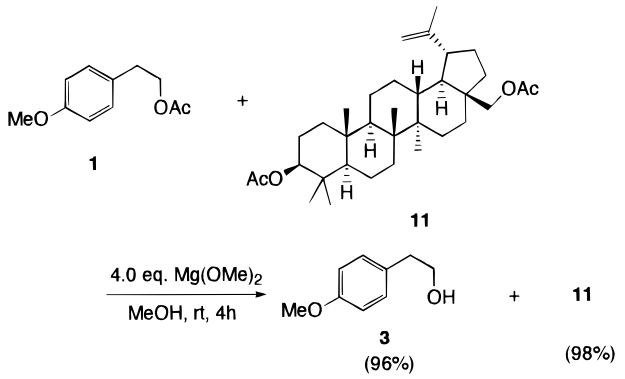


these acetates. There was very little reaction observed after compound **11** was treated with 4.0 equiv of magnesium methoxide in methanol for 14 h. The deacylation reaction began to proceed when 14.0 equiv of magnesium methoxide was employed. The reaction mixture was stirred at rt for 3 days before it was worked up, affording 81% yield of betulin monoacetate (**12**) along with only 14% of betulin (**13**). Although the selectivity has dropped in comparison with the previous two cases, a synthetically useful yield of monoacetate **12** was obtained.

In order to compare magnesium methoxide with other commonly used reagents for selective ester cleavage, we tested the selective ester hydrolysis of betulin diacetate (**11**) with sodium methoxide in methanol and THF. The reaction progressed very slowly with up to 3.0 equiv of sodium methoxide. With 5.0 equiv of the reagent, the starting material was consumed in 2 days and betulin monoacetate (**12**) and betulin (**13**) were isolated in 43% and 53% yield, respectively. The selectivity is clearly deteriorated in comparison with the previous reaction using magnesium methoxide.

The requirement of 14.0 equiv of magnesium methoxide to cleave the primary acetate from compound **11** was a little surprising because primary acetates of both compounds **1** and **5** were removed cleanly with only 4.0 equiv of the reagent. Looking into the structure differences of these compounds, it was noted that compound **11** possesses a quaternary carbon α to the primary acetate. In light of the changes of the reactivity (4.0

Scheme 3

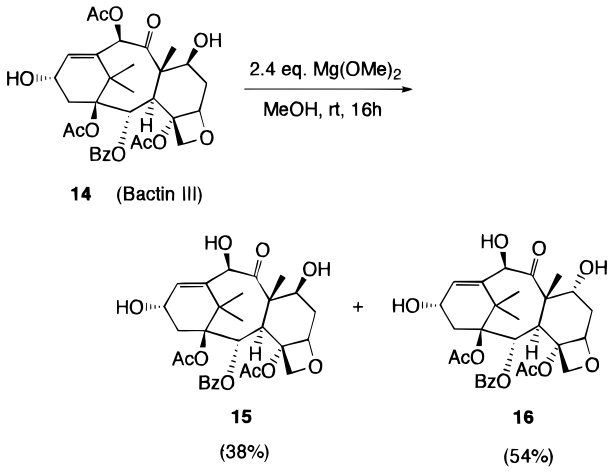


equiv vs 14.0 equiv) reflected by this steric difference, it is envisioned that it might be possible to differentiate two primary acetates by magnesium methoxide if β-positions of the primary acetates render a steric difference. In order to test this hypothesis, a competitive deacylation reaction of primary acetate **1** and primary acetate **11** was carried out (Scheme 3). Upon treatment of the mixture of compound **1** (0.5 mmol) and betulin diacetate (**11**) (0.5 mmol) with 4.0 equiv of magnesium methoxide at rt for 4 h, a primary alcohol **3**, resulting from acetate **1**, was isolated in 96% yield. Betulin diacetate (**11**), intact under these conditions, was almost fully recovered (98%).

In order to demonstrate the synthetic utility of magnesium methoxide as a reagent for selective deacylation reaction, a selective cleavage of an acetate for baccatin III was investigated. There are two major reasons for us to study baccatin III. First, there is a great deal of interest in taxol analogs for developing potent anticancer agents.[15] Baccatin III, being a late stage intermediate, has been used for the synthesis of taxol and taxol analogs.[16] Secondly, baccatin III, possessing three acetates and one benzoate, is an ideal substrate to test the selectivity of magnesium methoxide in the ester hydrolysis reaction.

As shown in Scheme 4, the reaction of **14** with 2.4 equiv of magnesium methoxide in methanol at rt for 16 h afforded a mixture of 10-deacetylbaccatin III (**15**) and 10-deacetylbaccatin V (**16**) in 92% overall yield. The deacylation occurred exclusively at the C-10 secondary acetate. The tertiary acetates as well as the benzoate were not impacted under these conditions. Compound **16** was derived from product **15** by the epimerization at the C-7 position through a retro-aldol reaction. Such an epimerization process under basic and acidic conditions has been reported in the literature.[17] 10-Deacetylbaccatin III (**15**) has been converted to taxol analogs of 10-deacetoxytaxol and 10-deoxytaxotere, which are more cytotoxic than taxol.[16e]

Scheme 4



Conclusions

From this study, it has been demonstrated that magnesium methoxide is an effective and selective reagent for deprotection of a variety of acetates. By adjusting the equivalents of the reagent, it is possible to effectively differentiate among a primary acetate, a secondary acetate, and a tertiary acetate. It is also possible to selectively hydrolyze a primary acetate in the presence of other primary acetates if the α-positions of these acetates have different steric environments. Due to its high selectivity in ester deprotection, magnesium methoxide will find many applications in organic synthesis.

Experimental Section

All experiments were run under a positive pressure of dry nitrogen. Unless otherwise indicated all common reagents and anhydrous solvents were used as obtained from commercial suppliers without further purification. Magnesium methoxide was purchased from Aldrich and stored under nitrogen. Melting points were determined in open capillary tubes using a capillary melting point apparatus and are uncorrected. Routine ^{1}H NMR spectra were recorded on a 300 MHz spectrometer. Infrared spectra were recorded on a FT-IR spectrometer. Field desorption mass spectroscopy (FDMS) and elemental analysis were carried out by Physical Chemistry Laboratory at Lilly Corporate Center.

Competitive Deprotection Reaction of Primary Acetate 1 and Tertiary Acetate 2 with Magnesium Methoxide. To a stirred solution of 4-methoxyphenethyl acetate (**1**) (194.0 mg, 1.0 mmol) and 2-phenyl-2-propyl acetate (**2**) (187.0 mg, 1.0 mmol) in 20 mL of anhydrous methanol was added dropwise 4.1 mL of 10.3% magnesium methoxide solution in methanol (0.973 N, 4.0 mmol) under nitrogen at rt. The progress of the reaction was monitored by TLC. After the mixture was stirred at rt for 6 h, starting material **1** was all consumed. HCl solution (0.2 N) was added until the pH of the mixture equaled 4 to 5. Part of the methanol was removed by reduced pressure. The product was extracted with dichloromethane (30 mL × 5). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the crude residue using hexanes and ethyl acetate (7:3) gave 4-methoxyphenethyl alcohol (**3**) (144.0 mg, 0.94 mmol) in 94% yield along with recovered starting material **3** (176.0 mg, 0.94 mmol) in 94% yield. No 2-phenyl-2-propanol was detected. Compound **3** has spectral data identical to that of the commercially available authentic sample from Aldrich. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.00; H, 7.76.

Selective Deacylation Reaction of Hydroxycitronellol Diacetate (5) with Magnesium Methoxide. To a stirred solution of diacetate **5** (327.3 mg, 1.27 mmol) in 12 mL of anhydrous methanol was added dropwise 5.2 mL of 10.3%

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magnesium methoxide solution in methanol (0.973 N, 5.06 mmol) under nitrogen at rt. The resulting mixture was stirred at rt for 10 h. At this point, all starting material was consumed. Besides major product **6**, there was a faint spot on TLC from the mixture corresponding to hydroxycitronellol (**7**). Workup as described in the first experiment followed by flash chromatography of the crude residue using hexanes and ethyl acetate (6:4) gave 7-acetoxy-3,7-dimethyl-1-octanol (**6**) (269.8 mg, 1.25 mmol) in 98% yield as a clear oil. No hydroxycitronellol (**7**) was isolated. Compound **6**: ^{1}H NMR ($CDCl_3$) δ 0.95 (d, 3H, J = 7.2 Hz), 1.10−1.40 (m, 5H), 1.42 (s, 6H), 1.59 (m, 2H), 1.71 (t, 2H, J = 7.3 Hz), 1.99 (s, 3H), 3.71 (pseudo q, 2H, J = 7.2 Hz); HRMS for $C_{12}H_{25}O_3$ calcd 217.1804, found 217.1798. Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.20; H, 10.79.

Selective Deacylation Reaction of (±)-*trans*-Sobrerol Diacetate (8) with Magnesium Methoxide. To a stirred solution of diacetate **8** (344.7 mg, 1.35 mmol) in 14 mL of anhydrous methanol was added dropwise 11.0 mL of 10.3% magnesium methoxide solution in methanol (0.973 N, 10.70 mmol) under nitrogen at rt. The resulting mixture was stirred at rt for 48 h. At this point, all starting material was consumed. Besides major product **9**, there was a very faint spot on TLC from the mixture corresponding to (±)-*trans*-sobrerol (**10**). Workup as described in the first experiment followed by flash chromatography of the crude residue using hexanes and ethyl acetate (6:4) gave (±)-*trans*-8-acetoxy-*p*-menth-6-en-2-ol (**9**) (270.4 mg, 1.27 mmol) in 94% yield as a clear oil. No (±)-*trans*-sobrerol (**10**) was isolated. (±)-*trans*-8-Acetoxy-*p*-menth-6-en-2-ol (**9**): ^{1}H NMR ($CDCl_3$) δ 1.39−1.50 (m, 2H), 1.42 (s, 3H), 1.43 (s, 3H), 1.72−2.00 (m, 2H), 1.79 (br s, 3H), 1.98 (s, 3H), 2.00−2.12 (m, 1H), 2.13−2.25 (m, 1H), 4.01 (m, 1H), 5.58 (m, 1H); FDMS 213.1 (M + H). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.89; H, 9.66.

Selective Deacylation Reaction of Betulin Diacetate (11) with Magnesium Methoxide. To a stirred solution of diacetate **11** (228.0 mg, 0.43 mmol) in 20 mL of anhydrous methanol and 6 mL of anhydrous THF was added dropwise 6.4 mL of 10.3% magnesium methoxide solution in methanol (0.973 N, 6.23 mmol) under nitrogen at rt. The resulting mixture was stirred at rt for 3 days. At this point, all starting material was consumed. Workup as described in the first experiment followed by flash chromatography of the crude residue using hexanes and ethyl acetate (4:1) gave betulin monoacetate (**12**) (169.1 mg, 0.35 mmol) in 81% yield as a white solid, along with the isolation of betulin (**13**) (27.4 mg, 0.06 mmol) in 14% yield as a white solid. Betulin monoacetate (**12**): mp 256−258 °C; ^{1}H NMR ($CDCl_3$) δ 0.75−2.00 (m, 25H), 0.83 (s, 3H), 0.84 (s, 6H), 0.97 (s, 3H), 1.02 (s, 3H), 1.68 (br s, 3H), 2.04 (s, 3H), 2.31−2.42 (m, 1H), 3.32 (d, 1H, J = 12.8 Hz), 3.80 (d, 1H, J = 12.8 Hz), 4.41−4.51 (m, 1H), 4.58 (br s, 1H), 4.69 (br s, 1H); IR (neat) 3400 s, 2943 s, 1732 s, 1246 s, 1027 s cm^{-1}; FDMS 484.3 (M^+). Anal. Calcd for $C_{32}H_{52}O_3$: C, 79.29; H, 10.81. Found: C, 79.33; H, 10.85. Betulin (**13**) has spectral data identical to that of the commercially available authentic sample from Aldrich: mp 254−256 °C (256−257 °C was listed in Aldrich catalog).

Selective Deacylation Reaction of Betulin Diacetate (11) with Sodium Methoxide. To a stirred solution of diacetate **11** (129.5 mg, 0.255 mmol) in 12 mL of anhydrous methanol and 4 mL of anhydrous THF was added sodium methoxide solid (13.5 mg, 0.25 mmol) under nitrogen at rt. Very little progress of the reaction was observed after 2 h. Additional portions of sodium methoxide were added (13.5 mg, 28 mg, 12 mg), with a total of 5.0 equiv of the reagent. The resulting mixture was stirred at rt until the starting material was consumed (2 days). Workup as described in the first experiment followed by flash chromatography of the crude residue using hexanes and ethyl acetate (4:1) gave betulin monoacetate (**12**) (53.6 mg, 0.11 mmol) in 43.4% yield as a white solid, along with the isolation of betulin (**13**) (59.9 mg, 0.135 mmol) in 53.1% yield as a white solid.

Competitive Deprotection Reaction of Primary Acetate 1 and Betulin Diacetate (11) with Magnesium Methoxide. To a stirred solution of 4-methoxyphenethyl acetate (**1**) (97.0 mg, 0.5 mmol) and betulin diacetate (**11**) (263.4 mg, 0.5 mmol) in 25 mL of anhydrous methanol was added dropwise 2.0 mL of 10.3% magnesium methoxide solution in methanol (0.973 N, 1.95 mmol) under nitrogen at rt. The progress of the reaction was monitored by TLC. After the mixture was stirred at rt for 4 h, starting material **1** was all consumed. Workup as described in the first experiment followed by flash chromatography of the crude residue using hexanes and ethyl acetate (7:3) gave 4-methoxyphenethyl alcohol (**3**) (73.1 mg, 0.48 mmol) in 96% yield along with recovered betulin diacetate (**11**) (258.5 mg, 0.49 mmol) in 98% yield. No betulin (**13**) was detected. Compound **3** has spectral data identical to that of the commercially available authentic sample from Aldrich. Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.75; H, 8.09.

Selective Deacylation Reaction of Baccatin III (14) with Magnesium Methoxide. To a stirred solution of baccatin III (**14**) (9.4 mg, 16.0 μmol) in 2 mL of anhydrous methanol was added 40 μL of 10.3% magnesium methoxide solution in methanol (0.973 N, 39.0 μmol) under nitrogen at rt. The resulting mixture was stirred at rt for 16 h. At this point, all starting material was consumed. Workup as described in the first experiment followed by flash chromatography of the crude residue using 10% methanol in dichloromethane gave a fast-running product **16** (4.7 mg, 8.6 μmol) in 54% yield, along with a slow-running product **15** (3.3 mg, 6.1 μmol) in 38% yield. The fast-running compound has spectral data identical to that of the structure **16** reported in the literature.[18] Compound **16**: FDMS 544 (M^+, 100). The slow-running compound has spectral data identical to the structure **15** reported in the literature. Compound **15**: FDMS 544 (M^+, 100).

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