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Ho-Sik Rho [a] & Byoung-Seob Ko [b]

[a] Pharmaceutical & Health Science Research Institute, Pacific Corporation , Yongin-Si, Kyounggi-do, 449-900, Korea

[b] Korea Institute of Oriental Medicine , Chongdam-dong, Kangnam-ku, Seoul, 135-100, Korea

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REGIOSELECTIVE DEOXYGENATION OF THE CYCLIC THIONOCARBONATES OF 2,3-DIHYDROXY ESTERS WITH MAGNESIUM IN METHANOL

Ho-Sik Rho*, Byoung-Seob Ko†

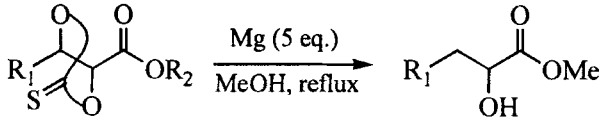
Pharmaceutical & Health Science Research Institute, Pacific Corporation, Yongin-Si, Kyounggi-do 449-900, Korea
†Korea Institute of Oriental Medicine, Chongdam-dong, Kangnam-ku, Seoul 135-100, Korea

Abstract: Deoxygenation of the cyclic thionocarbonates of 2,3-dihydroxy esters was mediated with magnesium in methanol, which provided a facile method for the synthesis of α-hydroxy esters

Magnesium in methanol is able to reduce various funtional groups.[1] Reductive cleavage[2] of C-O and C-N bond, intramolecular cyclization[3] and hydrodimerization[4] with magnesium in methanol have been described. It seems to be simple in comparison with other electron transfer reagent such as SmI_2.[5] Recently, we have reported[6] the synthesis of β-hydroxy esters and ketones by tri-butyltin hydride induced free radical deoxygenation of the cyclic thionocarbonates.

*To whom the correspondence should be addressed.

To find new and different deoxygenation process which could not be achieved with tributyltin hydride, we have explored the deoxygenation of the cyclic thionocarbonates with magnesium in methanol as electron transfer reagent. Now we have found that α-hydroxy esters can be prepared from the cyclic thionocarbonate esters based on regioselective deoxygenation by using magnesium in methanol (Scheme 1).



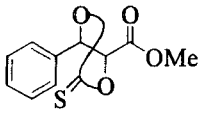
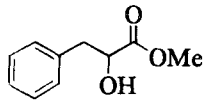
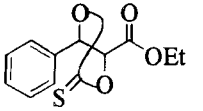
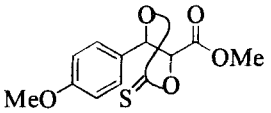
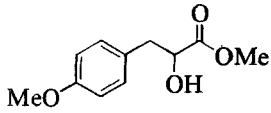
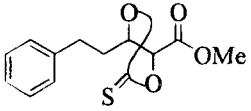
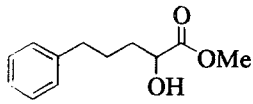
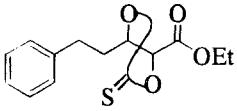
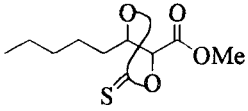
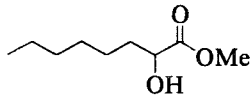
R_2 = Me, Et

1 **2**

Scheme 1

The results of deoxygenation of cyclic thionocarbonates are summarized in Table 1. The cyclic thionocarbonates were synthesized from the corresponding diols by treating with thiocarbonyldiimidazole.[7] The cyclic thionocarbonate **1a** reacted with magnesium (5 equiv.) in refluxing dry methanol for 30 min to afford methyl 2-hydroxy-3-phenyl propanoate (**2a**)[6] in 79% yield (entry 1 in Table 1). The deoxygenation of the cyclic thionocarbonate occurred exclusively at position C(β) of carbonyl. This is in contrast to the deoxygenation of the cyclic thionocarbonate with tributyltin hydride.[6] Although the reason has not been clarified, the chelating effect of magnesium cation seems to interrupt the deoxygenation of the C(α) position. When the cyclic thionocarbonate of ethyl ester **1b** was treated with magnesium in methanol, α-hydroxy methyl ester **2a** was obtained as the sole product (entry 2). The deoxygenation was accompanied by complete transesterification. Treatment of the cyclic thionocarbonate **1c** with magnesium (5 equiv.) in methanol afforded methyl 2-hydroxy-3-(4-methoxy

Table 1. Magnesium in methanol induced deoxygenation of the cyclic thionocarbonate of 2,3-dihydroxy esters[a]

Entry	Substrate	Time (min)	Rroduct	Yield(%)[b]
1	 **1a**	30	 **2a**	79
2	 **1b**	40	**2a**	74
3	 **1c**	35	 **2b**	72
4	 **1d**	30	 **2c**	70
5	 **1e**	40	**2c**	68
6	 **1f**	50	 **2d**	65

[a]All the reactions were run with magnesium (5 equiv.) in refluxing dry MeOH.
[b]The yields are for isolated compouds.

phenyl) propanoate (**2b**)[8] in 72% yield (entry 3). *p*-Methoxy group of benzene ring has no effect on the regioselectivity of deoxygenation process. For the cyclic thionocarbonate **1d** and **1e** in the same condition, α-hydroxy methyl ester **2c** was obtained without formation of β-hydroxy ester in 70 and 68 % yield (entry 4 and 5). Finally, the reaction of magnesium in methanol with the cyclic thionocarbonate **1f** produced methyl 2-hydroxy octanoate (**2d**),[9] where deoxygenation had occured exclusively at position C(β) in 65 % yield (entry 6). Above all reactions were carried out in anhydrous condition. In the presence of water in this reaction, deprotected diol was obtained as major product.

In summary, magnesium in methanol induced deoxygenation of the cyclic thionocarbonates of 2,3-dihydroxy esters afforded α-hydroxy esters with high regioselectivity.

Experimental Section

Typical Procedure

Methyl 2-hydroxy-3-phenyl propanoate (2a)

To a stirred solution of the cyclic thionocarbonate **1a** (200 mg, 0.84 mmol) in dry MeOH (5ml) under nitrogen atmosphere was added magnesium turning (100 mg, 4.20 mmol) and the reaction mixture was heated at reflux for 30 min. To the gray solution was added diethyl ether (20ml), the whole mixture was filtered through a celite pad and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography (EtOAc/hexanes 1 : 1, R_f = 0.35) to give **2a** (120 mg, 79%). IR(neat) 3451, 3010, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20(m, 5H), 4.40(m, 1H), 3.69(s, 3H), 3.15(dd, 1H, J = 13.8, 4.2 Hz), 2.99(dd, 1H, J = 13.8, 6.6 Hz), 2.75(bs, 1H). MS(m/e) 180(M^+), 162, 91(base peak). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65 ; H, 6.71. Found : C, 66.72 ; H, 6.68.

Methyl 2-hydroxy-3-(4-methoxyphenyl) propanoate (2b)

TLC, SiO_2, EtOAc/hexanes 1: 2, R_f = 0.30. IR(neat) 3450, 3015, 1733 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14(d, 2H, J = 9.0 Hz), 6.84(d, 2H, J = 9.0 Hz), 4.41(m, 1H), 3.78(s, 3H), 3.76(s, 3H), 3.04(dd, 1H, J = 14.1, 4.5 Hz), 2.93(dd, 1H, J = 14.1, 6.6 Hz), 2.71(bs, 1H). MS(m/e) 210(M^+), 192, 151, 121(base peak). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85 ; H, 6.71. Found : C, 62.80 ; H, 6.65.

Methyl 2-hydroxy-5-phenyl pentanoate (2c)

TLC, SiO_2, EtOAc/hexanes 1: 2, R_f = 0.45. IR(neat) 3453, 3011, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20(m, 5H), 4.20(m, 1H), 3.70(s, 3H), 2.74(bs, 1H), 2.64(m, 2H), 1.62 - 1.84(m, 4H). MS(m/e) 208(M^+), 190, 131, 91(base peak). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21 ; H, 7.74. Found : C, 69.24 ; H, 7.73.

Methyl 2-hydroxy octanoate (2d)

TLC, SiO_2, EtOAc/hexanes 1: 2, R_f = 0.55. IR(neat) 3451, 2928, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 4.20(m, 1H), 3.79(s, 3H), 2.71(bs, 1H), 1.78(m, 2H), 1.21 - 1.70(m, 8H), 0.87(t, 3H, J = 6.6 Hz). MS(m/e) 174(M^+), 115, 97(base peak).

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