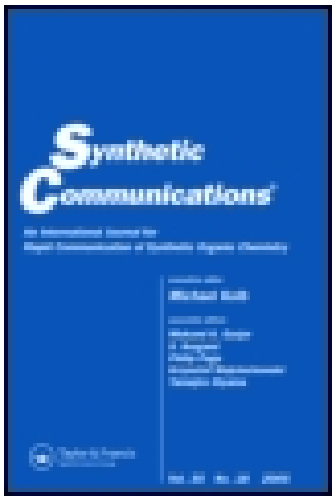

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MAGNESIUM IN METHANOL MEDIATED DEOXYGENATION OF THE CYCLIC THIONOCARBONATES OF AROMATIC 2,3-DIHYDROXY ESTERS

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MAGNESIUM IN METHANOL MEDIATED DEOXYGENATION OF THE CYCLIC THIONOCARBONATES OF AROMATIC 2,3-DIHYDROXY ESTERS

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ABSTRACT

The cyclic thionocarbonates of aromatic 2,3-dihydroxy esters, which have an electron-withdrawing group, undergo deoxygenation with magnesium in methanol to form α-keto esters or α-hydroxy esters, depending on the type of electron-withdrawing group.

α-Hydroxy ester functionality is frequently found in natural products and is valuable as a synthetic intermediate (1–3). They are usually prepared by the hydrolysis of α-halo esters (4), rearrangement of α-keto acetals (5), oxidation of ketene silyl acetals (6), reduction of α-keto esters (7,8), ring opening of epoxy esters, and subsequent reduction of the resulting iodohydrins (9,10). Recently, we have reported that the cyclic thionocarbonates of 2,3-dihydroxy esters are good

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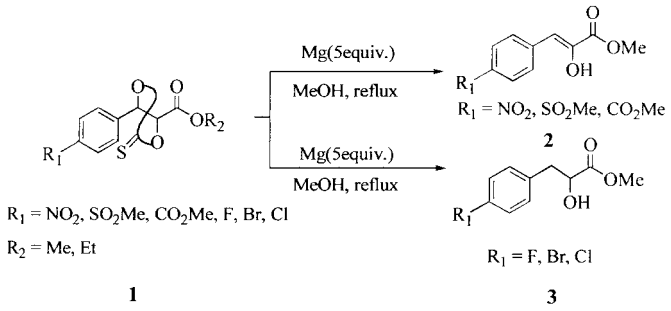

Scheme 1.

precursors for α-hydroxy esters *via* regioselective deoxygenation process induced by magnesium in methanol (11). Here, we wish to report deoxygenation of the cyclic thionocarbonates of aromatic 2,3-dihydroxy esters that have an electron-withdrawing substituent (Scheme 1).

The results of deoxygenation of cyclic thionocarbonates are summarized in Table 1. The diols were transformed to the cyclic thionocarbonates by treating with thiophosgene. The *para* nitro substituted cyclic thionocarbonates **1a** reacted with magnesium (5 equiv.) in refluxing dry methanol for 30 min to afford methyl (2*Z*)-2-hydroxy-3-(4-nitrophenyl) prop-2-enoate (**2a**) (19,20) in 75% yield (entry 1 in Table 1). This unexpected conversion is due to the presence of an electron-withdrawing substituent on the aromatic ring. A plausible mechanism for this conversion is outlined in Figure 1.

The deoxygenation occurs exclusively at the β-position of the carbonyl group (8). The chelation of the magnesium cation has an effect on the selectivity of deoxygenation. Electron-withdrawing substituents destabilize the deoxygenated radical intermediate at the benzylic position. The radical intermediate is subsequently converted into the enol form by abstraction of α-hydrogen. The destabilizing effect of the nitro group is the key factor to yield the α-keto ester product. The enol structure was established by 300 MHz ^{1}H NMR spectroscopy. For the methyl sulfone-substituted cyclic thionocarbonate **1b** and **1c** under the same conditions, α-keto ester **2b** was obtained in 81% and 78% yields as the sole

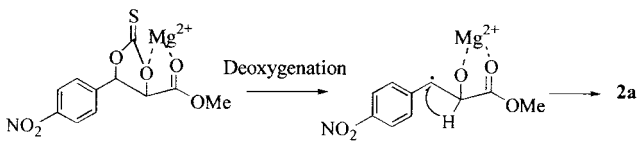

Figure 1.

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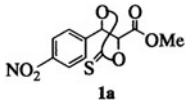
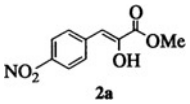
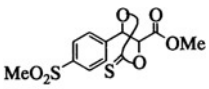
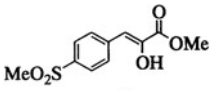
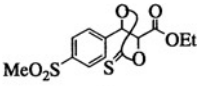
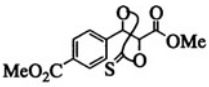
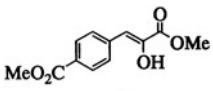
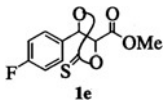
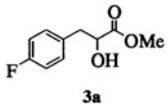
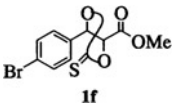
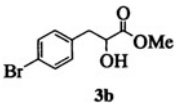
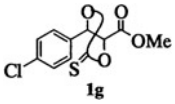
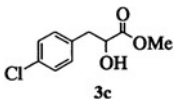
Table 1. Magnesium in Methanol Induced Deoxygenation of the Cyclic Thionocarbonate of Aromatic 2,3-dihydroxy Esters[a]

Entry	Substrate	Time (min)	Product	Yield (%)[b]
1	 **1a**	30	 **2a**	75
2	 **1b**	35	 **2b**	81
3	 **1c**	40	**2b**	78
4	 **1d**	45	 **2c**	65
5	 **1e**	25	 **3a**	72
6	 **1f**	30	 **3b**	69
7	 **1g**	30	 **3c**	70

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

product (entry 2 and 3). The ethyl ester was transformed into the methyl ester by transesterification. In the case of ester-substituted compound **1d**, α-keto ester **2c** was obtained together with a trace amount of α-hydroxy ester (entry 4). However, we could not obtain pure product.

In contrast to the above cases, when the fluorosubstituted cyclic thionocarbonate **1e** was reacted with magnesium in methanol, methyl 2-hydroxy-3-(4-fluorophenyl) propanoate **3a** was obtained in 72% yield (entry 5). This result apparantly indicates that the fluoro group does not destabilize the radical intermediate. The protonation of the radical intermediate must be faster than elimination in this case. The bromo-substituted cyclic thionocarbonate **1f** was also used to

prepare α-hydroxy ester **3b** (entry 6). Finally, the chloro-substituted cyclic thionocarbonate **1g** with magnesium in methanol produced α-hydroxy ester **3c** in 70% yield without formation of α-keto ester (entry 7). Deoxygenation did not occur when magnesium in absolute ethanol was used. Anhydrous reaction conditions are important to reduce the formation of deprotected diol as side product.

In summary, α-keto esters or α-hydroxy esters were synthesized by magnesium in methanol-induced deoxygenation of the cyclic thionocarbonates of aromatic 2,3-dihydroxy esters containing an electron-withdrawing substituent.

EXPERIMENTAL

Typical Procedure

Methyl (2*Z*)-2-hydroxy-3-(4-nitrophenyl) Prop-2-enoate (2a)

To a stirred solution of the cyclic thionocarbonate **1a** (200 mg, 0.70 mmol) in dry MeOH (10 mL) under nitrogen atmosphere was added magnesium turning (85 mg, 3.53 mmol) and the reaction mixture was heated at reflux for 30 min. To the gray solution was added diethyl ether (30 mL) and 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, $R_f = 0.55$) to give **2a** (118 mg, 75%). Mp 150°–151°C. IR (neat) 3451, 3010, 1732 cm^{-1}. ^1H NMR ($CDC1_3$, 300 MHz) δ 8.21 (d, 2H, $J = 9.6$ Hz), 7.89 (d, 2H, $J = 8.7$ Hz), 6.81 (s, 1H), 6.55 (s, 1H), 3.97 (s, 3H). MS (m/e) 223 (M^+), 163 (base peak), 136. Anal. calcd for $C_{10}H_9O_5N$: C, 53.82; H, 4.06; N, 6.27. Found: C, 53.75; H, 3.99; N, 6.23.

Methyl (2*Z*)-2-hydroxy-3-[4-(methylsulfonyl)phenyl]
Prop-2-enoate (2b)

TLC, SiO_2, EtOAc/hexanes 1 : 1, $R_f = 0.27$. Mp 157°–158°C. IR (neat) 3453, 3011, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92 (s, 4H), 6.73 (s, 1H), 6.54 (s, 1H), 3.96 (s, 3H), 3.06 (s, 3H). MS (m/e) 256 (M^+), 196, 169, 107 (base peak). Anal. calcd for $C_{11}H_{12}O_5S$: C, 51.55; H, 4.72; S, 12.51. Found: C, 51.47; H, 4.78; S, 12.46.

Methyl (2*Z*)-2-hydroxy-3-[4-(methoxycarbonyl)phenyl]
Prop-2-enoate (2c)

TLC, SiO_2, EtOAc/hexanes 1 : 1, $R_f = 0.60$. Mp 117–119°C. IR (neat) 3450, 3015, 1733 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03 (d, 2H, $J = 8.4$ Hz), 7.81

(d, 2H, $J = 8.4$ Hz), 6.64 (s, 1H), 6.54 (s, 1H), 3.93 (s, 3H), 3.91 (s, 3H). MS (m/e) 236 (M^+), 176 (base peak), 149. Anal. calcd for $C_{12}H_{12}O_5$: C, 60.01; H, 5.12. Found: C, 59.94; H, 5.10.

Methyl 2-hydroxy-(4-fluorophenyl) Propanoate (3a)

TLC, SiO_2, EtOAc/hexanes 1:1, $R_f = 0.50$. IR (neat) 3451, 3010, 1732 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26 (m, 2H), 7.08 (m, 2H), 4.42 (m, 1H), 3.77 (s, 3H), 3.12 (dd, 1H, $J = 13.8$, 4.2 Hz), 2.92 (dd, 1H, $J = 13.8$, 8.1 Hz), 2.76 (bs, 1H). MS (m/e) 198 (M^+), 180, 109 (base peak). Anal. calcd for $C_{10}H_{11}O_3F$: C, 66.60; H, 5.59. Found: C, 66.71; H, 5.67.

Methyl 2-hydroxy-(4-bromophenyl) Propanoate (3b)

TLC, SiO_2, EtOAc/hexanes 1:1, $R_f = 0.52$. IR (neat) 3450, 3015, 1733 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41 (d, 2H, $J = 8.1$ Hz), 7.08 (d, 2H, $J = 8.1$ Hz), 4.43 (m, 1H), 3.77 (s, 3H), 3.01 (dd, 1H, $J = 13.8, 4.2$ Hz), 2,89 (dd, 1H, $J = 13.8$, 6.9 Hz). 2.73 (bs, 1H) MS (m/e) 261 (M^{2+}), 259 (M^+), 241, 170 (base peak). Anal. calcd for $C_{10}H_{11}O_3Br$: C, 46.35; H, 4.28. Found: C, 46.20; H, 4.30.

Methyl 2-hydroxy-(4-chlorophenyl) Propanoate (3c)

TLC, SiO_2, EtOAc/hexanes 1 : 1, $R_f = 0.52$. Mp 117–119°C. IR (neat) 3451, 3010, 1732 cm^{-1}. ^1H NMR (DMSO, 300 MHz) δ 7.30 (d, 2H, $J = 8.1$ Hz), 7.22 (d, 2H, $J = 8.1$ Hz), 5.58 (bs, 1H), 4.22 (m, 1H), 3.61 (s, 3H), 2.95 (dd, 1H, $J = 13.8$, 4.2 Hz), 2.82 (dd, 1H, $J = 13.8$, 6.6 Hz). MS (m/e) 216 (M^{2+}), 214 (M^+), 196, 125 (base peak). Anal. calcd for $C_{10}H_{11}O_3Cl$: C, 55.96; H, 5.16. Found: C, 55.88; H, 5.09.

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