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# Monohydroxylation of cyclic and acyclic β-keto esters with molecular oxygen catalyzed by cobalt(II) chloride in neutral conditions†

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**Abstract**

Cyclic and acyclic α-alkyl-α-hydroxy-β-keto esters **2** were obtained with 50–100% isolated yields from the corresponding β-keto esters **1** by oxidation with molecular oxygen in a mixture of $CH_3CN$/*i*-PrOH and in the presence of cobalt(II) chloride. 

*Keywords:* oxygen; hydroxylation; catalysis; keto esters.

The α-hydroxy-β-keto ester moiety **2** is used as a starting material or an intermediate for the synthesis of natural products.[1,2] It is also present in the structure of biologically active molecules such as indolic alkaloids.[3]

The shortest way for the preparation of compounds **2** is the oxidation of the corresponding β-dicarbonyl compounds **1** in basic conditions or via the enol derivatives. Various oxidants were already used, including $Pb(OAc)_4$,[4] $H_2O_2$,[3b] *m*-CPBA,[5] singlet oxygen,[6] molecular oxygen,[7] dimethyldioxirane[8] or oxaziridine derivatives.[2a,c]

Iqbal et al.[9] have described catalytic oxidation of alcohols and epoxidation of olefins by oxygen, using ethyl 2-oxocyclopentane carboxylate as reductant. During this reaction, the β-keto ester is converted into the corresponding α-hydroxylated derivative.

In order to achieve a general synthesis of α-hydroxy-β-keto esters **2** by aerobic oxidation, we studied the monohydroxylation reaction in the presence of isopropanol as a reductant. We report herein a very simple method that uses a catalytic amount of $CoCl_2$ in a mixture of acetonitrile/isopropanol (Scheme 1).

This procedure was applied to various cyclic β-keto esters or to a lactone derivative (Table 1, entries 1–4) to afford the corresponding α-hydroxy-β-keto esters **3**–**6** in 60–100% isolated yields. The above

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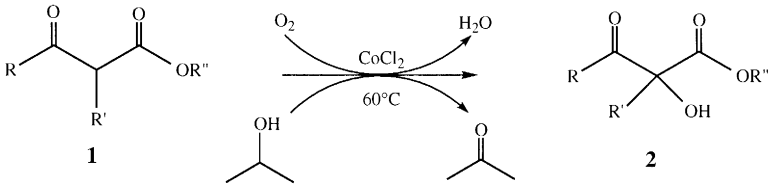
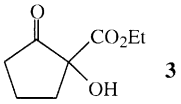
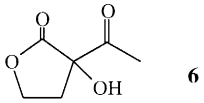
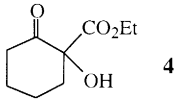
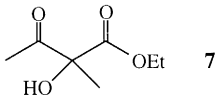
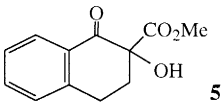
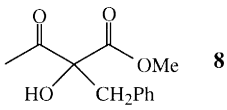



Scheme 1.

reaction conditions were also successful in the case of the less reactive acyclic β-keto esters (entries 5 and 6).[10]

Table 1
α-Hydroxylated β-keto esters

| Entry | Product | Yield(time) | Entry | Product | Yield(time) |
|---|---|---|---|---|---|
| 1 |  **3** | 83% (2h) | 4 |  **6** | 60% (20h) |
| 2 |  **4** | 60% (4h) | 5 |  **7** | 50% (24h) |
| 3 |  **5** | 100% (0.5h) | 6 |  **8** | 65% (24h) |

In conclusion, in this paper we propose a simple and efficient method of aerobic monohydroxylation in neutral conditions, leading to various α-hydroxy-β-keto esters, which can be obtained in an enantiopure form by kinetic resolution by using baker's yeast.[11]

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10. Typical procedure: Anhydrous cobalt(II) chloride (0.35 mmol) was heated at 60°C in acetonitrile (44 mL) and isopropanol (26 mL) under 1 atmosphere of oxygen. The β-keto ester **1** (7 mmol) was then added in the reaction mixture. At the end of the reaction (monitored by TLC) the solvent was evaporated in vacuo and the residue was purified by flash chromatography

on silica gel. Compound **3**:[7c,8] IR: 3471, 2981, 1757, 1725, 1260; $^1$H NMR (250 MHz, $CDCl_3$): $\delta$ 4.05 (2H, q, *J*=6.9), 3.95 (1H, s), 2.28 (3H, m), 1.93 (3H, m), 1.11 (3H, t, *J*=6.9); $^{13}$C NMR (62.9 MHz, $CDCl_3$): $\delta$ 213.4, 171.5, 79.6, 62.2, 35.7, 34.7, 18.2, 13.8; HRMS calcd for $C_8H_{12}O_4$: 172.0735; found: 172.0727; anal. calcd: C, 55.81; H, 6.98; found: C, 55.73; H, 6.96. Compound **4**:[5,7c] IR: 3455, 2945, 1721, 1253; $^1$H NMR ($CDCl_3$): $\delta$ 4.24 (1H, s), 4.19 (2H, q, *J*=7.2), 2.65–2.40 (3H, m), 1.95 (1H, m), 1.80–1.50 (4H, m), 1.21 (3H, t, *J*=7.2); $^{13}$C NMR ($CDCl_3$): $\delta$ 207.3, 170.0, 80.6, 62.0, 38.8, 37.6, 27.0, 21.9, 14.0; HRMS calcd for $C_9H_{14}O_4$: 186.0892; found: 186.0901; anal. calcd: C, 58.06; H, 7.53; found: C, 58.21; H, 7.61. Compound **5**:[6] mp 68°C; IR: 3464, 1737, 1678, 1269; $^1$H NMR ($CDCl_3$): $\delta$ 8.10 (1H, dd, *J*=7.8, 1.5), 7.57 (1H, td, *J*=7.5, 1.5), 7.38 (1H, t, *J*=7.5), 7.31 (1H, d, *J*=7.5), 4.26 (1H, s), 3.68 (3H, s), 3.07 (2H, m), 2.66 (1H, dt, *J*=13.6, 5.0), 2.20 (1H, ddd, *J*=13.6, 8.8, 6.5); $^{13}$C NMR ($CDCl_3$): $\delta$ 194.6, 171.2, 144.1, 134.5, 130.2, 129.0, 128.3, 127.1, 77.7, 53.1, 32.8, 25.6; HRMS calcd for $C_{12}H_{13}O_4$: 221.0813; found: 221.0807; anal. calcd: C, 65.45; H, 5.49; found: C, 65.03; H, 5.50. Compound **6**:[8] IR: 3427, 1771, 1716; $^1$H NMR ($CDCl_3$): $\delta$ 4.50–4.35 (2H, m), 4.21 (1H, s), 2.64 (1H, ddd, *J*=13.5, 7.2, 4.7), 2.34 (1H, ddd, *J*=13.5, 8.1, 7.5), 2.29 (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ 205.9, 175.1, 81.5, 66.3, 34.1, 24.8; HRMS calcd for $C_6H_9O_4$: 145.0501; found: 145.0498. Compound **7**:[12] IR: 3459, 1724, 1263; $^1$H NMR ($CDCl_3$): $\delta$ 4.17 (2H, q, *J*=7.2), 4.13 (1H, s), 2.21 (3H, s), 1.53 (3H, s), 1.22 (3H, t, *J*=7.2); $^{13}$C NMR ($CDCl_3$): $\delta$ 205.1, 171.2, 80.8, 63.7, 24, 21.6, 13.7; HRMS calcd for $C_7H_{13}O_4$: 161.0814; found: 161.0814. Compound **8**: IR: 3472, 3031, 1722, 1272; $^1$H NMR ($CDCl_3$): $\delta$ 7.3–7.2 (5H, m), 4.07 (1H, s), 3.79 (3H, s), 3.43 (1H, d, *J*= 14.7), 3.18 (1H, d, *J*=14.7), 2.3 (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ 204.4, 171.3, 134.9, 130.5, 128.7, 126.6, 84.8, 53.8, 41.4, 21.7; HRMS calcd for $C_{12}H_{14}O_4$: 223.0970; found: 223.0965.

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