Cerium-catalyzed α-Oxidation of β-Dicarbonyl Compounds with Molecular Oxygen

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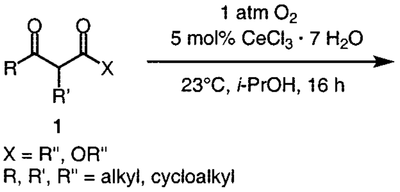
Abstract: β-Ketoesters and β-diketones are α-hydroxylated by molecular oxygen in the presence of 5 mol% $CeCl_3 \cdot 7\ H_2O$ in *i*-PrOH as solvent. The method is limited to substrates with an α-alkyl substituent. Optimal yields are achieved with cyclic starting materials.

Key words: catalysis, cerium, β-dicarbonyl compounds, oxidation, oxygen

Procedures for the selective oxidation of functional groups hold a central position in synthetic organic chemistry. α-Hydroxy-β-dicarbonyl compounds are prepared – apart from some other methods[1] – by oxidation of the parent β-dicarbonyl. Common electrophilic reagents for this transformation are $Pb(OAc)_4$,[2] MoOPH,[3] or peracids.[4] Besides, a sequence via the epoxide of the corresponding silyl enol ether known as Rubottom oxidation is established.[5] Moreover, dialkyldioxiranes have been reported for the selective oxidation of β-dicarbonyl compounds.[6]

With regard to ecological and economical concerns, molecular oxygen should be the oxidant of choice.[7] The manganese-, cobalt- or cesium-catalyzed oxidations of β-dicarbonyl compounds by O_2 have been published recently. However, procedures are either inefficient (Mn),[8] require toxic transition metals (Co),[9] or an over stoichiometric amount of Cs-salts.[10,11] Herein we wish to report on the oxidation of β-ketoesters and β-diketones with molecular oxygen catalyzed by $CeCl_3 \cdot 7\ H_2O$.[12] The advantages are the use of the inexpensive and non-toxic cerium salt and *i*-PrOH as the solvent.

Stirring of a 2–3 molar solution of starting materials **1** in *i*-PrOH containing 5 mol% $CeCl_3 \cdot 7\ H_2O$ under 1 atmosphere of O_2 for 10–20 hours afforded the hydroxylated products **2** (Scheme, Table). At least for the cyclic compounds **2a**–**d** the workup procedure was remarkably simple: Filtration through a small pad of SiO_2 removed all metal containing materials and gave analytically pure products.[13] In the case of cyclic oxoesters **2a**–**c** the yields were excellent and significantly improved compared to Mn- (89% for **2a**) and Co-catalysis (83% for **2a**). Compound **2b** bearing the enantiopure (–)-menthyl moiety was obtained as a 1:1 mixture of two diastereoisomers.[14] Products **2d**–**i** slowly decomposed under the reaction conditions. In the case of lactone **2d**, unidentified, polar by-products were removed by the mentioned simple filtration through SiO_2 (60%) or chromatography (78%), and the yield obtained was improved to that achieved with Co-catalysis. Main decomposition product of the ester **2e** was the acid **3**,[15] which was separable either by distillation, extraction, or by chromatography. The yields obtained depended on the workup procedure, but were about the same as for Co-catalysis. Yields of the compounds **2f**–**i** were not satisfying. The products **2g**–**i** had to be purified by chromatography. In the cases of **2e** and **2i** the chloro derivatives **4a**[16] and **4b** were identified as by-products.



Scheme Cerium-catalyzed α-hydroxylation of β-dicarbonyl compounds

Conversion of starting materials without an α-alkyl substituent resulted in complex product mixtures, which were only partly characterized and shall not be discussed in detail here. On the other hand, malonates showed no conversion under the reaction conditions.[17] From a mechanistic point of view, we presume formation of Ce(IV)-diketonate complexes in situ undergoing intramolecular electron transfer to give Ce(III) species and an oxidized dicarbonyl intermediate, whose nature could be a radical. The latter assumption is supported by the observation of halogenated by-products like **4a** and **4b**. Ce(III) species are reoxidized by O_2. Actually, the same catalytic activity is observed with $(NH_4)_2Ce(NO_3)_6$.

In summary, cyclic β-dicarbonyl compounds are chemoselectively α-hydroxylated by molecular oxygen. The catalyst $CeCl_3 \cdot 7\ H_2O$ is inexpensive and non-toxic, and the solvent applied is *i*-PrOH. The workup procedure can be as simple as filtration through some SiO_2 yielding analytically pure materials. We are presently working on enlarging the scope of this method by optimizing the yields of acyclic products.

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1437-2096,E;2002,0,01,0119,0121,ftx,en;G19201ST.pdf.

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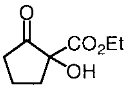
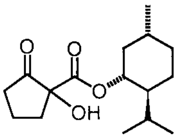
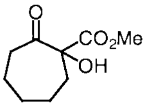
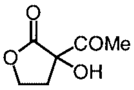
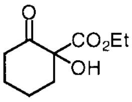
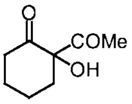
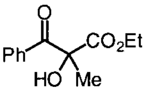
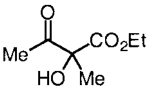
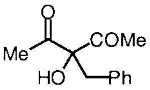
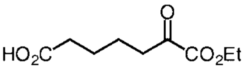
Table Products, Yields, and Workup Procedures

Product		Yield
	**2a**	99%[a]
	**2b**	99%[a,b]
	**2c**	96%[a]
	**2d**	78%,[c] 54%,[d] 53%[a]
	**2e**	59%,[d] 38%[c,e]
	**2f**	51%,[d] 46%[c]
	**2g**	30%[c,f]
	**2h**	29%[c]
	**2i**	44%[c,g]

[a] Filtration through 2 cm SiO_2.
[b] Mixture of two diastereoisomers, ratio 1:1 by ^1H NMR.
[c] Chromatography.
[d] Kugelrohr distillation.
[e] Acid **3** (28%) and chloro compound **4a** (4%) were isolated as by-products.
[f] Starting material was recovered (16%).
[g] By-product **4b** was isolated in 7% yield.



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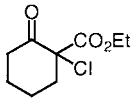
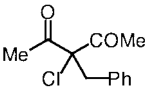


4a



4b

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References

(1) (a) Crout, D. H. G.; Rathbone, D. L. *J. Chem. Soc., Chem. Commun.* **1987**, 290. (b) Crout, D. H. G.; Rathbone, D. L. *Synthesis* **1989**, 40. (c) Tamaki, K.; Shotwell, J. B.; White, R. D.; Drutu, I.; Petsch, D. T.; Nheu, T. V.; He, H.; Hirokawa, Y.; Maruta, H.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1689.
(2) Demir, A. S.; Jeganathan, A. *Synthesis* **1992**, 235.
(3) MoO_5 · pyridine · HMPA: Vedejs, E.; Engler, A. D.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(4) Hubert, A. J.; Starcher, P. S. *J. Chem. Soc. C* **1968**, 2500.
(5) Andriamialisoa, R. Z.; Langois, N.; Langois, Y. *Tetrahedron Lett.* **1985**, *26*, 3563.
(6) (a) Adam, W.; Prechtl, F. *Chem. Ber.* **1991**, *124*, 2369. (b) Adam, W.; Smerz, A. K. *Tetrahedron* **1996**, *52*, 5799.
(7) (a) Döbler, C.; Mehltretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (c) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475.
(8) Christoffers, J. *J. Org. Chem.* **1999**, *64*, 7668.
(9) Baucherel, X.; Levoirier, E.; Uziel, J.; Juge, S. *Tetrahedron Lett.* **2000**, *41*, 1385.
(10) Watanabe, T.; Ishikawa, T. *Tetrahedron Lett.* **1999**, *40*, 7795.
(11) Use of catalytic (10 mol%) amounts of Cs-salts resulted in significantly lower yields.
(12) The combination of molecular oxygen and catalytic $CeCl_3$ is known for oxidation of benzyl alcohol to benzaldehyde in the presence of Pt/C and $Bi_2(SO_4)_3$: Oi, R.; Takenaka, S. *Chem. Lett.* **1988**, 1115.
(13) **Typical Procedure for 2c**: Ester **1c** (1.09 g, 6.40 mmol) was added to a suspension of $CeCl_3·7\ H_2O$ (119 mg, 0.32 mmol) in isopropanol (2.0 mL). The flask was evacuated twice to ca. 500 mbar, flushed with oxygen, and the mixture was then stirred for 16 h under 1 atm of O_2. After filtration through SiO_2 (2 cm, washing with ethyl acetate) and removal of all volatile materials from the filtrate in vacuo 1.14 g (96%, 6.12 mmol) of compound **2c** were obtained as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.24–1.32 (m, 1 H), 1.33–1.58 (m, 2 H), 1.67–1.90 (m, 2 H), 1.91–2.05 (m, 1 H), 2.07–2.15 (m, 1 H), 2.27 (dd, J = 14.9 Hz, J = 10.6 Hz, 1 H), 2.59 (ddd, J = 11.7 Hz, J = 7.0 Hz, J = 1.7 Hz, 1 H), 2.96 (td, J = 12.1 Hz, J = 2.9 Hz, 1 H), 3.67 (s, 3 H), 4.35 (s, 1 H) ppm. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.27; H, 7.33.
(14) Selected data for new compounds, **Menthyl Ester 2b**: ^1H NMR ($CDCl_3$, 300 MHz), diastereoisomer 1: δ = 0.71 (d, J = 6.8 Hz, 3 H), 0.86 (d, J = 7.4 Hz, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.95−1.13 (m, 2 H), 1.33−1.56 (m, 2 H), 1.63−1.74 (m, 3 H), 1.88−2.17 (m, 5 H), 2.40–2.52 (m, 3 H), 3.86 (s, 1 H), 4.77 (dt, J = 10.5 Hz, J = 7.3 Hz, 1 H) ppm; diastereoisomer 2: δ = 0.77 (d, J = 7.3 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.4 Hz, 3 H), 0.95−1.13 (m, 2 H), 1.33−1.56 (m, 2 H), 1.63−1.74 (m, 3 H), 1.88−2.17 (m, 5 H), 2.40−2.52 (m, 3 H), 3.86 (s, 1 H), 4.78 (dt, J = 10.9 Hz, J = 7.3 Hz, 1 H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 75 MHz), diastereoisomer 1: δ = 15.92 (CH_3), 18.46 (CH_2), 20.70 (CH_3), 21.94 (CH_3), 23.09 (CH_2), 26.06 (CH), 31.36 (CH), 34.06 (CH_2), 34.96 (CH_2), 36.00 (CH_2), 40.21 (CH_2), 47.02 (CH), 76.85 (CH), 79.71 (C), 171.33 (C=O), 213.38 (C=O) ppm; diastereoisomer 2: δ = 15.99 (CH_3), 18.48 (CH_2), 20.85 (CH_3), 21.89 (CH_3), 23.17 (CH_2), 26.26 (CH), 31.33 (CH), 34.03 (CH_2), 34.63 (CH_2), 35.80 (CH_2), 40.71 (CH_2), 46.95 (CH), 76.90 (CH), 79.70 (C), 171.27 (C=O), 213.43 (C=O) ppm. Mol. mass calcd for $C_{16}H_{26}O_4$: 282.1831. Found: 282.1831 [M^+]. Anal. Calcd: C, 68.06; H, 9.28.

Found: C, 67.97; H, 9.22. **Ethyl 2-benzoyl-2-hydroxypropanoate 2g**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.15 (t, *J* = 7.2 Hz, 3 H), 1.74 (s, 3 H), 4.23 (q, *J* = 7.1 Hz, 2 H), 4.51 (s, 1 H), 7.42−7.48 (m, 2 H), 7.55−7.60 (m, 1 H), 7.97−8.00 (m, 2 H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 75 MHz): δ = 13.81 (CH_3), 23.52 (CH_3), 62.51 (CH_2), 79.48 (C), 128.62 (CH), 129.47 (CH), 133.14 (C), 133.70 (CH), 172.31 (C=O), 195.94 (C=O) ppm. Mol. mass calcd for $C_{12}H_{14}O_4$: 222.0892. Found: 222.0876 [M^+]. **3-Benzyl-3-hydroxy-2,4-pentanedione 2i**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.23 (s, 6 H), 3.28 (s, 2 H), 4.69 (s, 1 H), 7.19–7.28 (m, 5 H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ = 25.66 (CH_3), 41.88 (CH_2), 91.06 (C), 127.58 (CH), 128.69 (CH), 130.05 (CH), 134.50 (C), 206.70 (C=O) ppm. Mol. mass calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0953 [M^+]. **3-Benzyl-3-chloro-2,4-pentanedione 4b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.15 (s, 6 H), 3.42 (s, 2 H), 7.19–7.22 (m, 2 H), 7.26–7.31 (m, 3 H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$, 125 MHz): δ = 27.39 (CH_3), 42.39 (CH_2), 80.22 (C), 127.55 (CH), 128.37 (CH), 130.69 (CH), 133.88 (C), 201.09 (C=O) ppm. Mol. mass calcd for $C_{12}H_{13}ClO_2$: 224.0604. Found: 224.0612 [M^+].

(15) Formation of by-product **3** was also observed with other procedures.[4,8]

(16) (a) Brenner, J. E. *J. Org. Chem.* **1961**, *26*, 22. (b) Hussey, C. W. T.; Pinder, A. R. *J. Chem. Soc.* **1962**, 1517. (c) Karrenbrock, F.; Schäfer, H. J. *Tetrahedron Lett.* **1978**, 1521.

(17) The oxidative dehydrodimerization of malonates with Ce(IV) or Mn(III) under ultrasonic conditions has been reported: Linker, T.; Linker, U. *Angew. Chem. Int. Ed.* **2000**, *39*, 902.