An Enone−Dienol Tautomerism and an Iron(III)-Catalyzed Dimerization of Cycloalkenone-2-carboxylates

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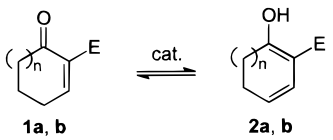
Cycloalkenone-2-carboxylates **1** can be accessed by various methods,[1] and they are valuable synthons in organic synthesis. For example, they are applied as acceptors in Michael reactions[2] and they readily undergo Diels−Alder reactions with donor-functionalized dienes.[3] In the course of our investigations on Fe(III)-catalyzed conversions of carbonyl compounds,[4] we found a so far unknown catalyzed tautomerization of **1** to the dienols **2**.[5] The equilibration shown in Scheme 1 can be achieved by applying either Brönstedt acids (TFA) or base (DMAP). It can be observed by NMR spectroscopy in $CDCl_3$ as solvent. Since mixtures of **1** and **2** in an ∼1:1 ratio are obtained in this catalyzed equilibration, isomers **2** bear reasonable thermodynamic stability. The latter is due to H-bonding and, however, is nothing unusual for β-keto esters [**2a**, δ(OH) ca. 12.5 ppm]. Interestingly, both tautomers show also extraordinary kinetic stability: They can, for example, be separated by chromatography, and no interconversion is observed in *neutral* media at room temperature over days. Complete characterization data were collected for a number of compounds; exemplary data are given for **1a** and **2a** in the Experimental Section.

Enone−dienol equilibration can also be achieved with a catalytic amount of iron(III) chloride hexahydrate in CH_2Cl_2 as solvent; however, these mixtures are not stable, but they convert at room temperature into unique

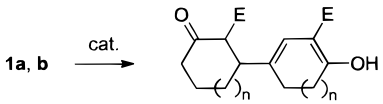
Scheme 1



1a, b **2a, b**

a n = 1, E = CO_2Et; **b** n = 2, E = CO_2Me;
cat. = TFA or DMAP in $CDCl_3$ as solvent

Scheme 2



3a, b

3a: n = 1, E = CO_2Et, cat. = 1 mol% $FeCl_3 \cdot 6\ H_2O$, 3 h, 81%;
3b: n = 2, E = CO_2Me, cat. = 4 mol% $FeCl_3 \cdot 6\ H_2O$, 12 h, 73%

products **3**, which can be subsequently isolated by chromatography (Scheme 2). Compound **3b** bears the constitution shown in Scheme 2, and we presume a relative trans configuration (on account of the coupling constant in the ^{1}H NMR spectrum). Compound **3a** is actually in rapid equilibrium with its enol tautomer **3c**, and therefore, both cannot be separated. Characterization data for **3a**−**c** are presented in the Experimental Section.

At first glance, products **3** are dimers of the starting materials **1**. Upon closer inspection, the constitution of **3** is formally that of a Michael reaction product of the acceptor **1** with the vinylogous donor **2**. Vinylogous reactivity of Michael donor molecules in their γ-position, which is well-known in aldol chemistry,[6] is a so far very rarely precedented principle in organic synthesis.[7] A mechanistic rationale for the formation of **3** involves−after enone−dienol tautomerization−formation of an iron(III)−dionato complex **4**, which should be planar and particularly stabilized by π-delocalization.[8] Complex **4** is postulated to undergo a [4 + 2]-cycloaddition with **1** to furnish the tricyclic intermediate **5**,[9] which bears an aldol constitution: a tertiary alcohol function adjacent to an acceptor group E. Due to the strained nature of compound **5**, a retro-aldol type C−C bond cleavage should occur to give **3**. Thus, the constitution of a formally vinylogous (with respect to the donor) Michael reaction product is generated by a sequence of enone−dienol tautomerization, Diels−Alder, and retro-aldol reaction.

In summary, the equilibrium of **1** and **2** can be catalyzed by either acid or base. Both tautomers are separable and exhibit extraordinary kinetic stability. Iron(III) as the catalyst drives the starting material to react as a donor in the γ-position to yield dimer **3** as the final product. In our eyes, this formally vinylogous reactivity of donors can be a valuable complement to the

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(1) (a) Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Para, K. S.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8849−8850. (b) Schultz, A. G.; Holoboski, M. A. *Tetrahedron Lett.* **1993**, *34*, 3021−3024. (c) Kato, M.; Kamat, V. P.; Yoshikoshi, A. *Synthesis* **1988**, 699−701. (d) Liotta, D.; Barnum, C.; Puelo, R.; Zima, G.; Bayer, C.; Kezar, H. S., III. *J. Org. Chem.* **1981**, *46*, 2920−2923. (e) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434−5447. (f) Brenner, J. E. *J. Org. Chem.* **1961**, *26*, 22−27.

(2) (a) Bernadi, A.; Karamfilova, K.; Sanguinetti, S.; Scolastico, C. *Tetrahedron* **1997**, *53*, 13009−13026. (b) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943−4946. (c) Marx, J. N.; Minaskanian, G. *J. Org. Chem.* **1982**, *47*, 3306−3310. (d) Bruhn, J.; Heimgartner, H.; Schmidt, H. *Helv. Chim. Acta* **1979**, *62*, 2630−2654. (e) Marx, J. N.; Minaskanian, G. *Tetrahedron Lett.* **1979**, 4175−4178.

(3) (a) Desimoni, G.; Faita, G.; Mella, M.; Ricci, M.; Righetti, P. *Tetrahedron* **1997**, *53*, 13495−13508. (b) Lavallee, J.-F.; Spino, C.; Ruel, R.; Hogan, K. T.; Deslongchamps, P. *Can. J. Chem.* **1992**, *70*, 1406−1426. (c) Spino, C.; Deslongchamps, P. *Tetrahedron Lett.* **1990**, *31*, 3969−3972. (d) Lavallee, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117−5118. (e) Orban, J.; Turner, J. V. *Tetrahedron Lett.* **1983**, *24*, 2697−2700.

(4) (a) Christoffers, J. *J. Chem. Soc., Chem. Commun.* **1997**, 943−944. (b) Christoffers, J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3141−3149.

(5) For a related photoinduced process see: Ricard, R. R.; Sauvage, P.; Wan, C. S. K.; Weedon, A. C.; Wong, D. F. *J. Org. Chem.* **1986**, *51*, 62−67.

(6) (a) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1988; p 831. (b) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813−814.

(7) Kraus, G. A.; Roth, B. *Tetrahedron Lett.* **1977**, 3129−3132.

(8) The complexation of an Fe(III) ion under formation of a species **4** is supported by the observation that after adding the catalyst to the starting materials the reaction mixture turns deeply blue. After the conversion is complete, this blue color is replaced by a brownish tone.

(9) There is a considerable analogy to Diels−Alder reactions of 1-alkoxy and 1-silyloxy dienes.

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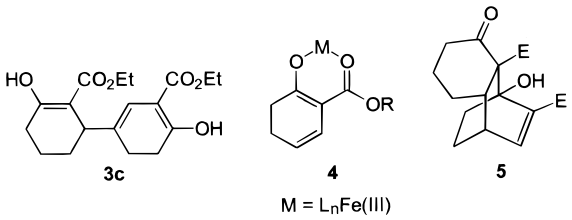

3c **4** **5**

M = $L_nFe(III)$

normal Michael reaction chemistry. The scope of this reaction is currently under investigation in our laboratory.

Experimental Section

General Methods. Column chromatography was accomplished with Merck silica gel (Type 60, 0.063−0.200 mm) using *tert*-butyl methyl ether (MTB). Multiplicity assignments of ^{13}C NMR resonances were made using DEPT experiments. All starting materials were commercially available, except **1a**[1c] and **1b**,[1b] which were prepared according to literature procedures.

Ethyl 3-oxocyclohexene-2-carboxylate (1a): ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.27 (t, J = 7.1 Hz, 3 H), 1.99−2.05 (m, 2 H), 2.46−2.51 (m, 4 H), 4.22 (q, J = 7.2 Hz, 2 H), 7.63 (t, J = 4.1 Hz, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 13.85 (CH_3), 21.86 (CH_2), 25.80 (CH_2), 38.42 (CH_2), 60.73 (CH_2), 132.9 (C), 155.7 (CH), 164.3 (C), 202.2 (C); IR (ATR) 1/λ 1730 (vs), 1692 (vs), 1620 (m) cm^{-1}.

Ethyl 1-Hydroxy-1,3-cyclohexadiene-2-carboxylate (2a). A suspension of **1a** (310 mg, 1.84 mmol) and ion-exchange resin (50 mg; DOWEX 50 W × 8, strongly acidic) was stirred in absolute EtOH (0.5 mL) for about 12 h at rt. After removal of all volatile materials in vacuo, chromatography on silica gel (hexane/MTB 1:1) yielded two fractions, the first containing dienol **2a** (167 mg, 1.00 mmol, 54%; R_f = 0.65; colorless oil) and the second containing the starting material **1a** (112 mg, 0.66 mmol, 36%; R_f = 0.30; colorless oil). ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (t, J = 7.2 Hz, 3 H), 2.25−2.31 (m, 2 H), 2.42−2.49 (m, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 5.43 (dt, J = 9.8 Hz, J = 4.2 Hz, 1 H), 6.23 (dt, J = 9.6 Hz, J = 1.4 Hz, 1 H), 12.50 (s, br, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 14.04 (CH_3), 21.94 (CH_2), 27.64 (CH_2), 60.20 (CH_2), 98.47 (C), 117.0 (CH), 120.1 (CH), 170.3 (C), 174.5 (C); IR (ATR) 1/λ 1737 (vs), 1685 (vs), 1619 (m) cm^{-1}; mol mass calcd 168.0786, found 168.0784 (M^+, HRMS). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.14.

2-(Ethoxycarbonyl)-4-[2-(ethoxycarbonyl)-3-hydroxy-2-cyclohexen-1-yl]-1,3-cyclohexadien-1-ol (3a). A mixture of **1a** (210 mg, 1.25 mmol), $FeCl_3$•$6H_2O$ (3.3 mg, 0.012 mmol), and CH_2Cl_2 (375 mg) was stirred for 3 h at rt. Subsequently, all volatile materials were removed in vacuo, and the residue was chromatographed on silica gel (hexanes/MTB 2:1, R_f = 0.7−0.3)[10] to furnish the title compound **3a** (170 mg, 0.510 mmol, 81%) as a colorless oil, which consisted of two equilibrating tautomers: ^1H NMR ($CDCl_3$, 400 MHz) shows a mixture of two tautomers **3a** and **3c** (ratio 20/80) **3c** δ 1.18 (t, J = 7.1 Hz, 3 H), 1.28 (t, J = 7.3 Hz, 3 H), 1.56−1.72 (m, 4 H), 2.16−2.28 (m, 4 H), 2.33−2.50 (m, 2 H), 3.10−3.22 (m, 1 H), 4.13−4.40 (m, 4 H), 5.71 (s, 1 H), 12.41 (s, 1 H), 12.48 (s, 1 H) ppm; **3a** δ 3.44 (d, J = 12.1 Hz, 1 H), 6.04 (s, 1 H), all other signals are hidden by the signals of the major tautomer **3c**; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) **3c** δ 14.08 (CH_3), 14.24 (CH_3), 17.27 (CH_2), 26.26 (CH_2), 26.81 (CH_2), 28.76 (CH_2), 29.04 (CH_2), 38.60 (CH), 59.98 (CH_2), 60.28 (CH_2), 98.92 (C), 99.47 (C), 115.7 (CH), 133.5 (C), 170.6 (C), 172.5 (C), 172.9 (C), 173.2 (C); **3a** δ 13.96 (CH_3), 14.20 (CH_3), 23.50 (CH_2), 24.83 (CH_2), 28.53 (CH_2), 29.70 (CH_2), 40.91 (CH_2), 48.12 (CH), 60.42 (CH_2), 60.75 (CH_2), 61.60 (CH), 98.32 (C), 117.0 (CH), 129.6 (C), 169.1 (C), 170.3 (C), 173.6 (C), 203.4 (C); IR (ATR) 1/λ 1741 (s), 1729 (s), 1645 (vs), 1615 (s) cm^{-1}; mol mass calcd 336.1573, found 336.1575 (M^+, HRMS). Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.39; H, 7.18.

2-(Methoxycarbonyl)-4-[2-(methoxycarbonyl)-3-oxo-1-cycloheptyl]-1,3-cycloheptadien-1-ol (3b). A mixture of **1b** (411 mg, 2.44 mmol), $FeCl_3$•$6H_2O$ (24.0 mg, 0.0890 mmol), and CH_2Cl_2 (850 mg) was stirred for about 12 h at rt. Subsequently, all volatile materials were removed in vacuo, and the residue was chromatographed on silica gel (hexanes/MTB 2:1, R_f = 0.33) to furnish the title compound **3b** (300 mg, 0.890 mmol, 73%) as a colorless oil: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38−1.62 (m, 4 H), 1.84−2.02 (m, 2 H), 2.06 (t, J = 6.6 Hz, 2 H), 2.11−2.18 (m, 2 H), 2.31 (t, J = 6.8 Hz, 2 H), 2.46−2.50 (m, 1 H), 2.88−2.96 (m, 2 H), 3.51 (d, J = 11.3 Hz, 1 H), 3.63 (s, 3 H), 3.75 (s, 3 H), 5.99 (s, 1 H), 12.73 (s, 1 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz) δ 26.20 (CH_2), 27.43 (CH_2), 29.21 (CH_2), 32.06 (CH_2), 32.87 (CH_2), 34.38 (CH_2), 42.02 (CH_2), 49.15 (CH), 51.52 (CH_3), 52.14 (CH_3), 64.96 (CH), 99.56 (C), 119.6 (CH), 141.8 (C), 169.4 (C), 172.1 (C), 178.8 (C), 207.8 (C); IR (ATR) 1/λ 1736 (s), 1706 (vs), 1646 (s), 1597 (s) cm^{-1}; mol mass calcd 336.1573, found 336.1577 (M^+, HRMS). Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.17.

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Supporting Information Available: Full characterization data and NMR spectra assignments for **2a**,**b** and **3a**−**c** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(10) Since the two tautomers **3a** and **3c**, which bear significantly different polarity, are in equilibrium, there is no well-defined spot on the TLC.