A Vinylogous Donor in an Iron(III)-Catalysed Michael Reaction and an Enone–Dienol Tautomerism

Jens Christoffers

Technische Universität Berlin, Institut für Organische Chemie, Sekretariat C 3,
Straße des 17. Juni 135, D-10623 Berlin, Germany
Fax: (internat.) + 49(0)30/723-1233
E-mail: jchr@wap0105.chem.tu-berlin.de

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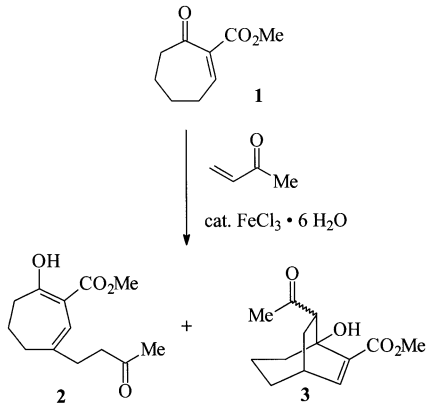
A double acceptor-activated cycloalkene **1** reacts in an $FeCl_3 \cdot 6\ H_2O$ catalysed Michael reaction surprisingly as a donor. The constitution of the product **2** results from a reaction of **1** in the γ-position, thus the Michael reaction is vinylogous with respect to the donor. A tautomerism between the enone **1** and the dienol **4** is found to be a precondition for this reactivity.

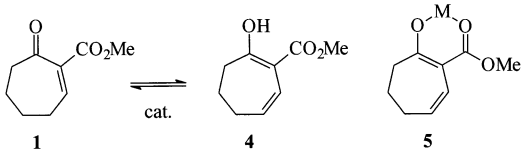
The Michael reaction is generally understood as the conjugate addition of a carbon nucleophile (Michael donor) to an acceptor-activated double bond.[1] If α,β-unsaturated carbonyl compounds are employed as Michael acceptors and enolates as nucleophiles, the Michael reaction is a vinylogous (with respect to the acceptor) aldol addition. Double acceptor-activated cycloalkenes[2] like **1**[3] are known to serve as Michael acceptors in conjugate additions of carbon nucleophiles.[4] In the course of our studies of iron(III)-catalysed Michael reactions[5] we wished to perform tandem reactions,[6] in which in the first step a nucleophile adds to the acceptor **1** to produce an Fe^{III}-stabilised enolate. Subsequently, this enolate of a β-oxo ester should undergo an Fe^{III}-mediated Michael addition with methyl vinyl ketone (MVK). To our surprise there was never an indication for our proposed tandem Michael addition sequence. However, in the reaction mixtures always 1:1 adducts of **1** and MVK were detectable by GCMS, and after chromatographic workup two products **2** and **3** were obtained (Scheme 1), the constitutions of which were clearly elucidated by NMR.[7]

Obviously, compound **3** was formed under the reaction conditions from the tautomeric keto structure of **2** in a subsequent intramolecular aldol addition. The constitution of the primary product results from a reaction of **1** with MVK at the γ-position. In order to explain this surprising result a tautomeric equilibrium of **1** with dienol **4** can be postulated (Scheme 2). Under the reaction conditions tautomer **4** should form a dionatoiron(III) chelate complex **5**. The chelating dionato moiety in a complex **5** would be planar and particularly stabilised by π-electron delocalisation. Complexation of an Fe^{III} ion by either species **1** or **4** is supported by the observation that after addition of the catalyst to the starting materials the reaction mixture turns deeply blue. After the conversion is complete, this blue colour is replaced by a brownish tone.

Scheme 1. Iron(III)-catalysed conversion of **1** with MVK; conditions: **1** (1 equiv.) + MVK (1.5 equiv.) + $FeCl_3 \cdot 6\ H_2O$ (0.04 equiv.), CH_2Cl_2, 5 h at room temp.; yields: 24% of **2** and 51% of **3**



Scheme 2. Catalysed tautomerisation of **1**; cat. = TFA, DMAP, or $FeCl_3 \cdot 6\ H_2O$; M = 1/3 Fe^{III}



Experimental evidence for the tautomeric equilibrium was readily found: Under acidic (1 equiv. TFA in $CDCl_3$) as well as under basic [0.5 equiv. 4-(dimethylamino)pyridine (DMAP) in $CDCl_3$] conditions the equilibration of **1** and **4** takes place within minutes and is detectable by NMR.[8] Herein the dienol **4** has immense thermodynamic stability,[9] which is, however, not unusual for β-dicarbonyl compounds. More interestingly, both tautomers exhibit remarkable and extraordinary kinetic stability under neutral conditions. They are for example separable by column chro-

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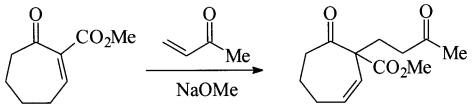
matography,[10] can be fully characterised, and do not interconvert over a period of at least a week (at room temp.). Importantly, the equilibration of **1** with **4** can also be achieved by a catalytic amount of $FeCl_3 \cdot 6\ H_2O$. But the role of Fe^{III} can not only be to catalyse equilibration. Its coordination to **4** also mediates the reaction with MVK, because we did never observe Brönsted acid mediated conversion (not even with up to 5 equiv. TFA) of **1** or **4** with MVK. Possibly, iron(III) does not only activate the π-system of the Michael donor **4**, but does also coordinate the acceptor MVK at the same time.

The distinct effect of the iron(III) catalysis becomes particularly clear in comparison with the base-catalysed conversion of **1** with MVK, which yields product **6** (Scheme 3). The latter can be understood as the classic Michael reaction product, whereas Fe^{III} forces **1** to react as a vinylogous Michael donor, a result, which is to the best of our knowledge unprecedented.

Scheme 3. Base-catalysed conversion of **1** with MVK; conditions: **1** (1 equiv.) + MVK (1.8 equiv.) + NaH (0.04 equiv.), MeOH, ca. 12 h at room temp.; yield: 85% of **6**



1 **6**

In summary, the equilibrium of **1** and **4** can be catalysed by either acid, base, or iron(III). Both tautomers are separable and exhibit extraordinary kinetic stability. Whereas base-catalysed conversion of **1** with MVK yields a Michael reaction product in the classical sense, Fe^{III} catalysis drives the Michael donor **1** to react in a vinylogous fashion to yield **2**. This unprecedented behaviour is another example for novel selectivities, which can be achieved by the application of transition metals as catalysts. Because of the particular mild reaction conditions and the ecologically and economically friendly nature of the catalyst $FeCl_3 \cdot 6\ H_2O$ this novel vinylogous (with respect to the donor) Michael reaction is an enrichment of the classic Michael-type C−C-bond forming reactions.

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Experimental Section

General: Column chromatography was accomplished with Merck silica gel (Type 60, 0.063−0.200 mm) using *tert*-butyl methyl ether (MTB). − ^{1}H NMR: Bruker AM 400 (400 MHz). − ^{13}C NMR: Bruker AC 200 (50 MHz), assignments were made using DEPT experiments. − MS: Varian MAT 711 and MAT 955Q (high resolution). − IR: Nicolet Magna IR 750. − Elemental analysis: Analytik Jena Vario EL. − All reagents used were commercially available. − Compound **1** was prepared according to an improved literature procedure.[3]

Methyl 3-Oxocycloheptene-2-carboxylate (**1**): A solution of methyl 2-oxocycloheptanecarboxylate (2.84 g, 16.7 mmol) and $Cu(OAc)_2 \cdot H_2O$ (83 mg, 0.42 mmol) in CH_2Cl_2 (50 ml) was stirred for 30 min at room temperature. $Pb(OAc)_4$ (8.87 g, 20.0 mmol) was added, and the resulting mixture was stirred for 3 d at room temp. Finally, ethylene glycol (10 ml) was added, and after stirring for 30 min at room temp., the mixture was filtered through SiO_2 (10 cm, washed with CH_2Cl_2). After rotary evaporation of the solvent, the residue was chromatographed on SiO_2 (hexane/MTB, 1:1; R_f = 0.24) to yield 2.21 g (13.1 mmol, 79%) of the title compound as a colourless oil. − ^{1}H NMR ($CDCl_3$): δ = 1.64−1.70 (m, 2 H), 1.72−1.78 (m, 2 H), 2.41 (q, J = 5.9 Hz, 2 H, 7-CH_2), 2.57 (t, J = 6.7 Hz, 2 H, 4-CH_2), 3.65 (s, 3 H, OMe), 7.30 (t, J = 5.8 Hz, 1 H, 1-CH). − ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 22.32 (CH_2), 24.08 (CH_2), 28.64 (CH_2), 43.39 (CH_2), 51.90 (OMe), 136.23 (=C), 148.94 (=CH), 165.26 (C=O), 202.03 (C=O).

Iron(III)-Catalysed Conversion of **1** *with Methyl Vinyl Ketone (MVK):* A mixture of enone ester **1** (585 mg, 3.47 mmol), MVK (366 mg, 5.22 mmol), $FeCl_3 \cdot 6\ H_2O$ (40 mg, 0.15 mmol), and CH_2Cl_2 (300 mg) was stirred for 5 h at room temp.; then all volatile materials were removed in vacuo, and the residue chromatographed on SiO_2 (hexane/MTB, 1:1) to yield two fractions the first containing compound **2** (195 mg, 0.89 mmol, 24%; R_f = 0.35) and the second compound **3** (425 mg, 1.78 mmol, 51%; R_f = 0.20), both as colourless oils.

Methyl 1-Hydroxy-4-(3-oxobutyl)-1,3-cycloheptadiene-2-carboxylate (**2**): ^{1}H NMR ($CDCl_3$): δ = 2.06−2.15 (m, 4 H), 2.17 (s, 3 H, CH_3), 2.34−2.42 (m, 4 H), 2.60 (t, J = 7.6 Hz, 2 H, 7-CH_2), 2.77 (s, 3 H, OMe), 5.94 (s, 1 H, 3-CH), 12.80 (s, 1 H, OH). − ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 29.82 (CH_3), 29.86 (CH_2), 31.35 (CH_2), 33.39 (CH_2), 33.61 (CH_2), 42.90 (CH_2), 51.56 (OMe), 99.55 (=C), 118.07 (=CH), 138.93 (=C), 172.33 (=C), 178.51 (C=O), 208.20 (C=O). − IR (ATR): 1/λ = 3411 (s, br.), 2952 (m), 2937 (m), 2867 (w), 1715 (vs), 1644 (s), 1599 (s), 1442 (s), 1358 (s), 1304 (m), 1246 (vs), 1215 (m), 1200 (m), 1177 (m), 1076 (m), 1046 (m) cm^{-1}. − MS (EI, 70 eV); *m/z* (%): 238 (4) [M^+], 236 (6) [M^+ − 2 H], 206 (26) [M^+ − MeOH], 196 (48) [M + H^+ − COMe], 168 (50) [M^+ − CH_2=CHCOMe], 164 (32) [M^+ − COMe − OMe], 136 (100) [M^+ − COMe − COOMe]. − $C_{13}H_{18}O_4$ (238.3): calcd. C 65.53, H 7.61; found C 65.31, H 7.68. − Mol. mass: calcd. 238.1205, found 238.1208 (HRMS).

Methyl 8-Acetyl-1-hydroxybicyclo[3.2.2]non-6-ene-7-carboxylate (**3**): ^{1}H NMR ($CDCl_3$,): δ = 1.43−1.50 (m, 2 H, 3-CH_2), 1.75−1.88 (m, 5 H), 2.15 (s, 3 H, CH_3), 2.43−2.49 (m, 1 H), 2.66−2.73 (m, 1 H, 5-CH), 3.39 (dd, J = 10.0 Hz, J = 5.5 Hz, 1 H, 8-CH), 3.74 (s, 3 H, OMe), 5.76 (s, br., 1 H, OH), 7.24 (d, J = 12.1 Hz, 1 H, 6-CH). − ^{13}C{^{1}H} NMR ($CDCl_3$): δ = 21.54 (CH_2), 26.58 (CH_2), 27.80 (CH_2), 31.76 (CH_3), 31.97 (CH), 41.31 (CH_2), 51.83 (OMe), 56.29 (CH), 73.85 (1-C), 134.41 (7-C), 145.35 (6-CH), 167.53 (C=O), 211.36 (C=O). − IR (ATR): 1/λ = 3417 (s, br.), 2998 (w), 2934 (s), 2858 (m), 1711 (vs), 1685 (vs), 1632 (m), 1438 (s), 1372 (m), 1356 (s), 1324 (m), 1291 (m), 1268 (s), 1251 (vs), 1198 (m), 1169 (s), 1123 (m), 1101 (s), 1088 (s), 1054 (m), 1035 (m), 759 (m) cm^{-1}. − MS (EI, 70 eV); *m/z* (%): 238 (4) [M^+], 206 (28) [M^+ − MeOH], 196 (46) [M + H^+ − COMe], 168 (30) [M^+ − CH_2=CHCOMe], 164 (48) [M^+ − COMe − OMe], 136 (100) [M^+ − COMe − COOMe]. − $C_{13}H_{18}O_4$ (238.3): calcd. C 65.53, H 7.61; found C 65.43, H 7.66. − Mol. mass: calcd. 238.1205, found 238.1207 (HRMS).

Methyl 1-Hydroxy-1,3-cycloheptadiene-2-carboxylate (**4**): A suspension of **1** (310 mg, 1.84 mmol) and ion exchange resin (50 mg; DOWEX 50 W X 8, strongly acidic) was stirred in absolute MeOH (0.5 ml) for about 12 h at room temp. After evaporation of the solvent in vacuo, chromatography on SiO_2 (hexane/MTB, 1:1)

yielded two fractions the first containing dienol **4** (167 mg, 1.00 mmol, 54%; R_f = 0.65; colourless oil), and the second containing starting material **1** (112 mg, 0.66 mmol, 36%). – ^{1}H NMR ($CDCl_3$): δ = 1.94–2.01 (m, 2 H, 6-CH_2), 2.22–2.27 (m, 2 H, 5-CH_2), 2.48–2.50 (m, 2 H, 7-CH_2), 3.78 (s, 3 H, OMe), 5.64 (dt, *J* = 12.1 Hz, *J* = 5.0 Hz, 1 H, 4-CH), 6.18 (dt, *J* = 12.1 Hz, *J* = 1.9 Hz, 1 H, 3-CH), 13.04 (s, br., 1 H, OH). – $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 26.32 (CH_2), 29.76 (CH_2), 34.69 (CH_2), 51.56 (OMe), 99.09 (=C), 121.10 (=CH), 126.68 (=CH), 172.65 (=C), 179.02 (C=O). – IR (ATR): 1/λ = 3429 (br., s), 2954 (s), 2873 (m), 1727 (vs), 1640 (m), 1438 (s), 1345 (m), 1254 (vs), 1175 (m), 1071 (s), 1029 (m), 937 (m), 784 (m) cm^{-1}. – MS (EI, 70 eV); *m/z* (%): 168 (36) [M^+], 136 (100) [M^+ – MeOH], 81 (30) [$C_6H_9^+$]. – $C_9H_{12}O_3$ (168.2): calcd. C 64.27, H 7.19; found C 64.21, H 7.17. – Mol. mass: calcd. 168.0786, found 168.0785 (HRMS).

Methyl 4-Oxo-3-(2-oxobutyl)cycloheptene-3-carboxylate (**6**): To a solution of enone ester **1** (397 mg, 2.36 mmol) and MVK (300 mg, 4.28 mmol) in absolute MeOH (500 mg) was added a catalytic amount of NaH (80% dispersion in mineral oil; ca. 3 mg, ca. 0.1 mmol). The mixture was stirred at room temp. for about 12 h; then all volatile materials were removed in vacuo, and the residue was chromatographed on SiO_2 (hexane/MTB, 1:1; R_f = 0.32) to yield **6** (477 mg, 2.00 mmol, 85%) as a colourless oil. – ^{1}H NMR ($CDCl_3$,): δ = 1.68–1.78 (m, 2 H, 6-CH_2), 2.04 (s, 3 H, CH_3), 1.99–2.16 (m, 3 H), 2.26–2.32 (m, 1 H), 2.37–2.47 (m, 3 H), 2.82 (dt, *J* = 15.3 Hz, *J* = 5.6 Hz, 1 H), 3.65 (s, 3 H, OMe), 5.36 (dt, *J* = 11.6 Hz, *J* = 1.8 Hz, 1 H, 2-CH), 5.82 (ddd, *J* = 11.6 Hz, *J* = 6.1 Hz, *J* = 4.4 Hz, 1 H, 1-CH). – $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 21.18 (CH_2), 27.59 (CH_2), 29.38 (CH_2), 29.73 (CH_3), 38.68 (CH_2), 41.52 (CH_2), 52.49 (OMe), 62.72 (3-C), 126.61 (CH), 132.54 (CH), 172.26 (C=O), 204.91 (C=O), 207.35 (C=O). – IR (ATR): 1/λ = 2951 (m), 1739 (s), 1708 (vs), 1433 (m), 1367 (m), 1354 (m), 1233 (s), 1195 (s), 1167 (s), 1088 (m), 1042 (m), 1002 (m), 934 (m), 788 (m), 670 (m) cm^{-1}. – MS (EI, 70 eV); *m/z* (%): 238 (1) [M^+], 206 (64) [M^+ – MeOH], 163 (100) [M^+ – MeOH – MeCO – H], 108 (32) [M^+ – $CH_2CHCOMe$ – CO_2Me – H]. – $C_{13}H_{18}O_4$ (238.28): calcd. C 65.53, H 7.61; found C 64.96, H 7.64. – Mol. mass: calcd. 238.1205, found 238.1207 (HRMS).

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[7] In compound **3**, which was obtained as a single diastereomer, the relative configuration of C-8 could not be determined, not even when applying 2D/NOE experiments.
[8] It is surprising that this is the first report on this equilibrium, although systems like **1** have been intensively studied in the literature.
[9] The equilibrium is somewhat dependent from the solvent and additives, but always in the range of about 1:1.
[10] A significant amount (ca. 60%) of dienol **4** was also obtained in the preparation of **1**,[3] if the crude product of the latter, which contained acetic acid, was allowed to stand for about 12 h at room temp. before it was chromatographed [SiO_2; hexane/*tert*-butyl methyl ether, 1:1; R_f = 0.24 (**1**); R_f = 0.65 (**4**)].

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