Cyclocarbonylation of Bicyclic Vinylcyclopropanes – Selective Generation of Seven-Membered Enones

Matthias M. Schulze* and Ulrich Gockel

Institut für Organische Chemie und Biochemie der Universität Bonn,
Gerhard-Domagk-Straße 1, D-53121 Bonn, Germany
Fax: (internat.) +49(0)228/735388
E-mail: mmschulze@compuserve.com

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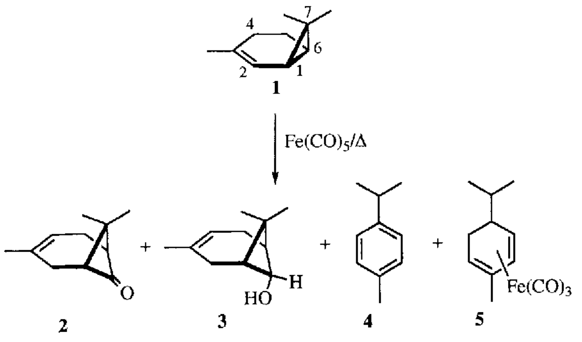
The cyclic vinylcyclopropane **6a** reacts at elevated temperatures with iron pentacarbonyl to selectively give the enone **7a** in 52% yield. Reducing the reaction time provided the isomeric ketones **7a–b**. Partial chromatographic separation of this mixture allowed the complete spectroscopic identification of **7b** by ^{1}H NMR. The structure of **7c** was determined from selected spectral data of the mixture of **7a** and **7c**. For comparison, the methyl substituted derivative **6b** was subjected to a carbonylation under the above conditions exclusively providing **8** in 42% yield. A mechanistic rationale for the two different modes of ring opening is presented.

The carbonylation of various unsaturated hydrocarbons using metal carbonyls has attracted considerable attention during recent decades[1]. Owing to its low cost and ready availability, many studies have been carried out using pentacarbonyl iron[2]. Sarel and coworkers[3] employed vinylcyclopropanes in their studies and obtained enones or dienes under thermal or photolytic conditions. Early mechanistic investigations for these reactions by the isolation and characterization of labile intermediates were carried out by Aumann[4]. Cyclic dienes were also converted to carbonyl compounds, but these procedures usually require high pressure and a carbon monoxide atmosphere[5]. Therefore our efforts were aimed at reactions using vinylcyclopropanes as starting materials. The insertion of CO into these readily available precursors can be performed without special means.

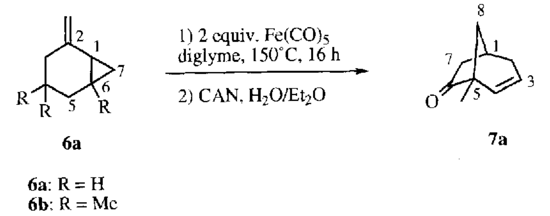
Structurally interesting carbonylation products were provided by the reaction of 2-carene (**1**) (Scheme 1) with $Fe(CO)_5$ at elevated temperatures[6]. Enone **2** and its reduction product **3** were isolated along with the hydrocarbon **4** and the diene complex **5**. The major compound, however, was unreacted starting material **1**. Recently, more comprehensive investigations[7] have been carried out concerning the reactivity of **1** under a variety of conditions with $Fe(CO)_5$ and these reactions resulted in even more complex reaction mixtures. These experiments also revealed important mechanistic details through the isolation and spectroscopic identification of key intermediates, which were obtained by the use of other reagents for the smooth generation of carbonyl complexes. Moreover, this report concluded that the species which undergoes the aforementioned carbonylation under vigorous conditions is not 2-carene (**1**) but the isomerized 3-carene.

Scheme 1



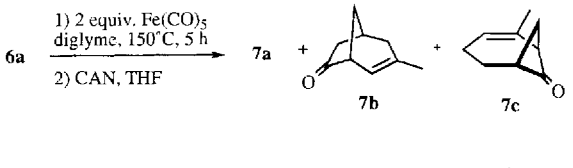
Our initial experiments with **1** furnished a product consisting mainly of starting material along with several unidentified isomers, as indicated by GC-MS. The amount of carbonylation products never reached 5%. Earlier findings that vinylcyclopropanes without alkyl substituents at the β-position show an enhanced degree of reactivity[8] led us to use **6a** for further studies (Scheme 2). Reaction conditions comparable to those reported for the CO-insertion of **1** (150°C, 16 h, diglyme as solvent) followed by oxidative work-up (ceric ammonium nitrate (CAN) in H_2O/Et_2O) gave **7a** in 52% yield. Complete consumption of the starting material **6a** was accomplished by this procedure. We excluded the possibility of conversion of isomerized starting material by heating the hydrocarbons **6a, b** in the absence of $Fe(CO)_5$. In both cases only partial decomposition or no transformation of the substrates was observed. The structure of the previously unknown ketone **7a** was elucidated by ^{1}H-COSY and selective decoupled ^{13}C-NMR spectroscopy. A particularly useful technique for the unambiguous assignment of all signals was to record the ^{1}H-NMR spectra in a solvent mixture of $CDCl_3$ and C_6D_6. While the methylene bridge of **7a** exhibited a broad singlet in $CDCl_3$ at $\delta = 1.74$, addition of C_6D_6 (40% in the sample) modified this signal to a complex multiplet centered at $\delta = 1.44$. The left part of the peak showed a *W* coupling ($J = 3$ Hz) to 7-H_{endo} ($\delta = 1.95$). Surprisingly, 7-H_{endo} did not show the expected vicinal coupling to the bridgehead proton (1-H). The Dreiding model, as well as molecular modeling, revealed a perpendicular orientation of 7-H_{endo} and 1-H. Instead, the usual vicinal coupling of 7-H_{exo} ($J = 8$ Hz) to 1-H was observed. Furthermore, comparison with ^{13}C-NMR data from the nor-derivative[9] confirmed the proposed structure.

Scheme 2



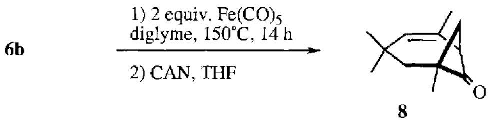
Shortening of the reaction time (5 h) and minor changes in the work-up procedure with **6a** (Scheme 3) led to a mixture comprising of **7c**, **7a**, and **7b** (ratio 4:3:2 respectively) in 42% yield. Flash chromatography (FC) allowed the isolation of pure **7b** whereas **7a** and **7c** were obtained as an inseparable mixture. The identification of **7b** was greatly simplified by the information previously gained about **7a**. On the basis of ^1H-COSY spectra, the presence of a bicyclo[3.2.1]octenone skeleton, as in **7a**, was assumed. In this case the methyl group ($\delta = 1.64$) had to be positioned at C-3, since the only olefinic proton (4-H) appeared as doublet ($\delta = 5.42$, $J = 7$ Hz). All other spectral data supported this arrangement. The NMR signals of the previously identified **7a** could be subtracted from the ^{13}C-NMR spectrum of **7a** and **7c**. Thus the remaining peaks were entirely in agreement with the cyclobutenone **7c**. A characteristic singlet ($\delta = 218.2$) together with an olefinic singlet and doublet ($\delta = 141.0$ and 118.1 respectively) left **7c** as the only reasonable product. The typical IR absorption (1756 cm^{-1}) for a four-membered ketone verified the proposed structure.

Scheme 3



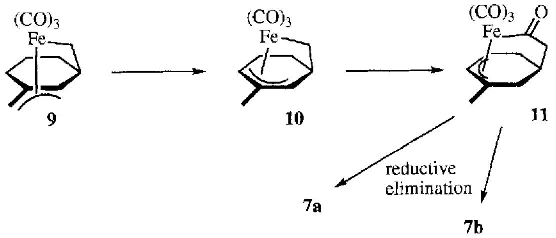
In order to examine the impact of methyl substituents in the cyclohexyl ring we chose **6b** (Scheme 4) as an appropriate starting point. Treatment of **6b** with $Fe(CO)_5$ (14 h) followed by work-up (CAN in THF) gave **8** as the sole product[10] in moderate yield (42%). Combined IR (1754 cm^{-1}) and ^{13}C-NMR (s, $\delta = 219.1$) data showed that this product is related to the strained cyclobutenone **7c**. In addition, complete ^1H-spin decoupling made the assignment of **8** unequivocal.

Scheme 4



The experimental results describved above differ substantially from those obtained in carbonylation studies of the related 2-carene (**1**)[6,7]. Cleavage of the C-1/C-7 bond occurs exclusively in **6a** with prolonged reaction time, whereas insertion of CO into the C-1/C-6 bond dominates the product pattern with reduced reaction times. A thermally promoted rearrangement of **7c** to **7a** or **7b** does not seem to be a suitable explanation. The complete disappearance of **7c** after 16 hours is presumably the result of a reversible cyclopropane ring opening[11] in the second reaction mode. The initially formed reactive intermediate **9** (Scheme 5) could undergo a rearrangement to give the π-allyl species **10**. Allyl shifts during the carbonylation of open-chain vinylcyclopropanes may well occur, as has been noted recently[12]. A further shift to **11** set the stage for the final reductive elimination leading to **7a** and **7b**. Apparently, the selectivity of this process depends heavily upon the exposure time. Several experiments with different work-up procedures did not lead to a significantly altered product mixture. The nature of the oxidation step did not affect the integrity of the ketones **7a–c** either. The reproducibly different outcomes of these reaction has to be attributed totally to the exposure time. Subjection of isolated **7b, c** to the reaction conditions showed no indication of structural changes.

Scheme 5



On preventing the possibility of such allyl shifts by the introduction of a geminal dimethyl group, as in **6b**, the reaction gave only the ketone **8**. It seems most likely that steric factors govern the ring opening of systems like **1** and **6**. Breaking of the C-1/C-7 bond in **1** is a minor reaction pathway because of the methyl substituent at C-7. Treatment of **1** with $Fe(CO)_5$ under mild conditions accounts for this hypothesis. The other reaction pathway, involving cleavage of C-1/C-6, dominates in the carene system. Regarding **6a** as a similar molecular framework, cleavage of C-1/C-7 proceeds easily and selectively, which is in contrast to **1**. Clearly the substitution pattern plays a pivotal role in bicyclic vinylcyclopropanes. Further investigations addressing this issue, as well as the effect of ring size and functional group tolerance, are currently being undertaken in this laboratory.

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Experimental Section

All reactions were carried out under argon. Solvents were purified and dried using literature methods. Reagents were employed as purchased from Aldrich. The yields refer to analytically pure compounds and are not optimized. – IR: Perkin-Elmer 1600 FT-IR. – ^{1}H and ^{13}C NMR: Bruker AM 400 with DEPT-135. If not specifically mentioned, chemical shifts refer to $\delta_{TMS} = 0.00$ according to the chemical shifts of residual solvent signals. – GC–MS: Finnigan ITD 800 (10 m SE 30 column), combined with Carlo Erba GC 6000, carrier gas He. – Thin-layer chromatography (TLC): Silica gel 60F (Merck 5735). The plates were inspected by UV light prior to development with iodine vapor. Column chromatography (FC): Silica gel 60 (Merck 9385, 0.040–0.063 mm), elution with light petroleum ether (PE) and ether.

5-Methylbicyclo[3.2.1]oct-3-ene-6-one (**7a**): To a solution of **6a** (140 mg, 1.30 mmol) in diglyme (15 ml) was added Fe(CO)$_5$ (0.30 ml, 2.30 mmol). The solution was stirred at 150°C for 16 h in the dark. The cooled reaction mixture was then filtered through Celite followed by washing with ether (100 ml). After vigorous stirring of the filtrate with CAN (10 g, 18 mmol) in water (80 ml) for 48 h at ambient temp. the mixture was poured into water (200 ml), extracted with Et$_2$O (3 × 200 ml) and the combined organic phases were washed repeatedly with water (5 × 200 ml). This solution was dried (MgSO$_4$) and concentrated under reduced pressure to leave a yellow oil, which was purified by FC with PE/Et$_2$O (8:2) as eluent to yield **7a** (92 mg, 52%) as colorless liquid. – IR (film): $\tilde{\nu}$ = 3026 cm^{-1}, 2928, 1742 (CO), 1628, 1452. – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.19 (s, 5-Me), 1.74 (s, br., 8-H$_2$), 1.99 (d, br., *J* = 19 Hz, 2-H$_{endo}$), 2.22 (d, br., *J* = 19 Hz, 7-H$_{endo}$), 2.42 (dd, *J* = 18, 3 Hz, 7-H$_{exo}$), 2.50 (m$_c$, 2-H$_{exo}$), 2.51 (m$_c$, 1-H), 5.35 (d, *J* = 9 Hz, 4-H), 5.72 (m, 3-H). – ^{13}C NMR (100.1 MHz, CDCl$_3$): δ = 17.8 (q, 5-Me), 28.4 (d, C-1), 33.9 (t, C-2), 39.2 (t, C-8), 43.9 (t, C-7), 48.4 (s, C-5), 128.1 (d, C-3), 132.1 (d, C-4), 213.8 (s, C-6). – GC-MS: *m/z* (%) = 136 (76) [M$^+$], 108 (58), 93 (100), 79 (48), 65 (13), 55 (30). – C$_9$H$_{12}$O (136.2): calcd. C 79.37, H 8.88; found C 79.19, H 8.90.

Oxidative Work-up after Five Hours Heating of **6a** *with Fe(CO)$_5$:* Exposure of **6a** (216 mg, 2.0 mmol) in diglyme (15 ml) to Fe(CO)$_5$ (0.4 ml, 3.0 mmol) according to the above procedure for 5 h and oxidative treatment of the filtrate with CAN (11 g, 20 mmol) in THF (200 ml) for 3 h at 0°C gave a yellow oil after extractive work-up and evaporation of the solvent. Purification by FC with PE/Et$_2$O (8:2) as eluent afforded pure **7b** (25 mg, 9%) and a mixture of **7a** and **7c** (90 mg, 33%, ratio 3:4) as yellow liquids.

3-Methylbicyclo[3.2.1]oct-3-ene-6-one (**7b**): IR (film): $\tilde{\nu}$ = 3020 cm^{-1}, 2922, 1740 (CO), 1626, 1458. – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.64 (s, 3-Me), 1.66 (dd, *J* = 11, 3 Hz, 8-H$_{endo}$), 1.82 (m, 2-H$_{endo}$), 1.86 (m, 8-H$_{exo}$), 2.11 (dd, *J* = 18, 3.5 Hz, 7-H$_{endo}$), 2.31 (dd, *J* = 18, 7 Hz, 7-H$_{exo}$), 2.49 (d, br., *J* = 18 Hz, 2-H$_{exo}$), 2.58 (m$_c$, 1-H), 2.75 (dd, *J* = 7, 5 Hz, 5-H), 5.42 (d, br., *J* = 7 Hz, 4-H). – ^{13}C NMR (100.1 MHz, CDCl$_3$): δ = 22.9 (q, 3-Me), 30.2 (d, C-1), 32.4 (t, C-2), 38.8 (t, C-8), 43.6 (t, C-7), 46.5 (d, C-5), 120.0 (d, C-4), 136.2 (s, C-3), 213.0 (s, C-6). – GC-MS: *m/z* (%) = 136 (79) [M$^+$], 105 (10), 92 (27), 65 (12), 53 (11). – C$_9$H$_{12}$O (136.2): calcd. C 79.37, H 8.88; found C 79.12, H 8.95.

2-Methylbicyclo[4.1.1]oct-2-ene-7-one (**7c**): Spectral data derived from the mixture of **7a** and **7c**. – IR (film): $\tilde{\nu}$ = 3028 cm^{-1}, 2926, 1756 (CO), 1628. – ^{13}C NMR (100.1 MHz, CDCl$_3$): δ = 22.1 (q, 2-Me), 25.6 (t, C-5), 29.1 (t, C-4), 41.0 (t, C-8), 41.6 (d, C-6), 49.7 (d, C-1), 118.1 (d, C-3), 141.0 (s, C-2), 218.2 (s, C-7). – GC-MS: *m/z* (%) = 136 (57) [M$^+$], 118 (6), 105 (11), 92 (100), 79 (31), 65 (13).

2,4,4,6-Tetramethylbicyclo[4.1.1]oct-2-ene-7-one (**8**): To a solution of **6b** (300 mg, 2.00 mmol) in diglyme (20 ml) was added Fe(CO)$_5$ (0.40 ml, 3.00 mmol). The solution was stirred at 150°C for 14 h in the dark. The cooled reaction mixture was then filtered through Celite followed by washing with ether (100 ml). After stirring the filtrate with CAN (11 g, 20 mmol) in THF (200 ml) for 3 h at 0°C the mixture was poured into water (200 ml), extracted with Et$_2$O (3 × 200 ml) and the combined organic phases were washed repeatedly with water (5 × 200 ml). This solution was dried (MgSO$_4$) and concentrated under reduced pressure to leave a yellow oil, which was purified by FC with PE/Et$_2$O (8:2) as eluent to yield **8** (150 mg, 42%) as colorless liquid. – IR (film): $\tilde{\nu}$ = 3025 cm^{-1}, 2930, 1754 (CO), 1680, 1452. – ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.92 (s, 6-Me), 1.03, 1.13 (2 s, 4-Me$_2$), 1.48 (d, br., *J* = 13 Hz, 8-H$_{endo}$), 1.70 (dd, *J* = 4, 2 Hz, 2-Me), 1.79 (d, br., *J* = 13 Hz, 6-H$_{exo}$), 1.99 (s, 1-H), 2.35 (s, br., 5-H$_2$), 5.28 (qd, *J* = 3.5, 1.5 Hz, 3-H). – ^{13}C NMR (100.1 MHz, CDCl$_3$): δ = 20.0 (q, 4-Me), 24.1 (q, 2-Me), 25.0 (q, 4-Me'), 30.1 (q, 6-Me), 40.1 (s, C-4), 46.6 (s, C-6), 48.9 (t, C-5), 50.3 (t, C-8), 62.8 (d, C-1), 120.0 (d, C-3), 138.5 (s, C-2), 219.1 (s, C-7). – GC-MS: *m/z* (%) = 178 (46) [M$^+$], 163 (5), 135 (11), 123 (100), 107 (24), 95 (28), 79 (40), 67 (21). – C$_{12}$H$_{18}$O (178.3): calcd. C 80.85, H 10.18; found C 80.97, H 10.11.

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