A Michael Addition-Induced Favorskii Rearrangement

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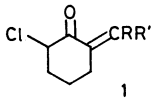
Synopsis. Reaction of 6-chloro-2-vinylidenecyclohexanone with sodium methoxide gave methyl 2-vinylidene-1-cyclopentanecarboxylate and methyl *trans*-2-(1-methoxyalkyl)-1-cyclopentanecarboxylate along with 6-methoxy-2-vinylidenecyclohexanone via a Michael addition-induced Favorskii rearrangement.

The Favorskii rearrangement is the skeletal rearrangement of α-halogenated ketones in the presence of base to give carboxylic acid derivatives.[1] It is useful for organic synthesis, especially for the preparation of highly branched acyclic carboxylic acids.[1] Since the first description of this rearrangement by Favorskii in 1894,[2] various types of the rearrangement have been still reported.[3] In connection with our previous study of Favorskii rearrangement of vinylogs of α-halo ketones,[4] we investigated reactions of 6-chloro-2-vinylidenecyclohexanones (**1**) with sodium methoxide.



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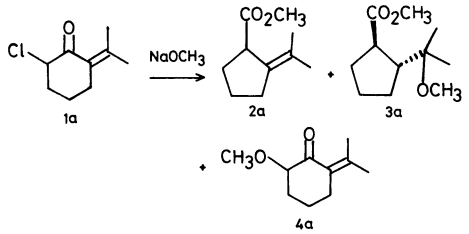
Treatment of 6-chloro-2-isopropylidenecyclohexanone (**1a**) with five equivalents of sodium methoxide at 25—50 °C gave a mixture of methyl 2-isopropylidenecyclopentanecarboxylate (**2a**), methyl *trans*-2-(1-methoxy-1-methylethyl)cyclopentanecarboxylate (**3a**),[5] and 2-isopropylidene-6-methoxycyclohexanone (**4a**).

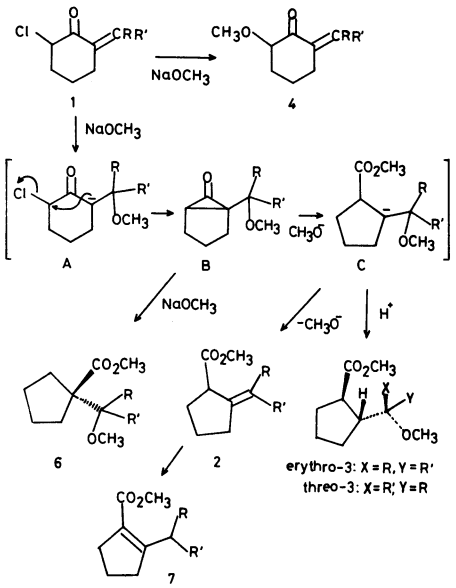


These products were separated by preparative GLC and identified by spectral analysis. To get further support for the structural elucidation, chemical transformations of **2a** were carried out. Hydrogenolysis of **2a** in the presence of palladium-charcoal yielded methyl 2-isopropylcyclopentanecarboxylate (**5**) in 54% yield and oxidation of **2a** with potassium permanganate gave adipic acid which was seemed to be derived from methyl 2-oxocyclopentanecarboxylate.

The formation of **2** and **3** can be explained by Favorskii rearrangement induced by the Michael addition of sodium methoxide to **1**, as shown in Scheme 1. In accordance with the generally accepted mechanism of the Favorskii rearrangement,[1] we suggest three intermediates **A**, **B**, and **C** to account for our results. The elimination of methoxide anion from the intermediate **C** will give vinylidene carboxylate **2** and the protonation of **C** will afford methoxy carboxylate **3**.

Table 1. Reaction of 6-Chloro-2-vinylidenecyclohexanone **1** with $NaOCH_3$

No.	1		Yield/% of Products				
	R	R′	**2**	**3** (erythro/threo)	**4**	**6**	**7**
a	CH_3	CH_3	52	9	4	0	0
b	H	CH_3	0	38 (20/18)	0	24	0
c	H	C_6H_5	0	62 (33/29)	0	0	8



Scheme 1.

We further investigated the reaction of other readily available 6-chloro-2-vinylidenecyclohexanones with sodium methoxide and the results are summarized in Table 1. Treatment of 6-chloro-2-ethylidenecyclohexanone (**1b**) with five equivalents of sodium methoxide at 25—50 °C afforded a mixture of three Favorskii rearrangement product, methyl 1-(1-methoxyethyl)cyclopentanecarboxylate (**6**) (24%) and methyl *trans*-2-(1-methoxyethyl)cyclopentanecarboxylate (**3b**) (erythro/threo, 20:18) (38%). Formation of ester **6** can be explained to be derived from the intermediate B, as shown in Scheme 1. Similar treatment of 6-chloro-2-benzylidenecyclohexanone (**1c**) with sodium methoxide gave methyl *trans*-2-(α-methoxybenzyl)methylcyclopentanecarboxylate (**3c**) in 62% yield as a mixture of two stereoisomers (erythro/threo, 33:29) and methyl 2-benzyl-1-cyclopentenecarboxylate (**7c**) in 8% yield. The trans geometry of **3b** and **3c** was determined by comparison of ^{13}C NMR data with those of similar

compounds[6] on the basis of the steric effect.[7] Assignment of erythro and threo between C-2 and C-1′ was made by analyzing the ^{1}H NMR spectra with reference of the literature data.[8] In ^{1}H NMR spectra of *threo*-**3b** and **3c**, signals due to C-2 protons (3.15 and 3.82 ppm) appeared at higher fields than those of erythro-isomers (3.34 and 4.06 ppm, respectively). In the ^{13}C NMR spectrum of *erythro*-**3b**, all signals except those of methyl carbon appeared at higher fields as compared with those of *threo*-**3b**.[9] Similarly, in the spectrum of *erythro*-**3c**, signals due to C-1 (50.6), C-2 (46.5), C=O (176.9), and $\underline{C}HOCH_3$ (86.0) appeared at higher fields than those of *threo*-**3c** (50.8, 47.9, 177.1, and 87.5, respectively).

To our knowledge, the present reaction is a new type of Favorskii rearrangement which includes initiation by the Michael addition of alkoxide and it will be useful for the synthesis of substituted cyclopentane derivatives.

Experimental

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Eiichiro Amano in our laboratory. Analytical determinations by GLC were performed on a Hitachi Model K-53 gas chromatograph fitted with 10% Apiezone Grease L on Chromosorb W column (3 mm o.d.×1 m). Preparative isolations by GLC were performed on a Yanagimoto Model GCG-550T gas chromatograph (3 mm o.d.×1 m, Apiezone Grease L on Chromosorb W).

2-Isopropylidenecyclohexanone (**10**) was prepared from 2-ethoxycarbonylcyclohexanone by the method described in the literature:[10] bp 65 °C/3 Torr (1 Torr=133.322 Pa) (lit,[10] 94—98 °C/14 Torr); 32% yield. 2-Ethylidenecyclohexanone (**11**) was prepared by the reaction of 2-formylcyclohexanone with methylmagnesium iodide:[11] bp 59—61 °C/3 Torr; 55% yield. 2-Benzylidenecyclohexanone (**12**) was obtained by the reaction of *N*-(1-cyclohexenyl)morpholine with benzaldehyde:[12] bp 147 °C/4 Torr (lit,[12] 123—126 °C/0.2 Torr); 52% yield.

6-Chloro-2-isopropylidenecyclohexanone (1a) was prepared by the reaction of **10** with 1.2 equiv of *N*-chlorosuccinimide (NCS) in CCl_4 at the reflux temperature for 20 min:[13] 83% yield; IR (neat) 1680, 1610 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.81 (s, 3H), 1.89 (s, 3H), 2.20 (m, 6H), 4.22 (dd, J=4 and 5 Hz, 1H); MS (70 eV) m/z (rel intensity) 172 (48, 1 Cl, M$^+$), 157 (6), 149 (46), 110 (32), 109 (100), 95 (32), 93 (46), 82 (67), 67 (93). Found: C, 62.31; H, 7.42%. Calcd for $C_9H_{13}ClO$: C, 62.61; H, 7.59%.

6-Chloro-2-ethylidenecyclohexanone (1b) was prepared by the reaction of **11** with 1.2 equiv of NCS in CCl_4 at the reflux temperature:[13] 71% yield; bp 65—70 °C/2.5 Torr; IR (neat) 1700, 1625, 1130, 890, 750 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.75 (dt, J=7.5 and 1.0 Hz, 3), 4.27 (dd, J=4.5 and 6.0 Hz, 1), 6.64 (qt, J=7.5 and 2.5 Hz, 1); MS (70 eV) m/z (rel intensity) 158 (40, 1 Cl, M$^+$), 143 (6), 140 (5), 124 (23), 95 (100), 79 (47), 68 (48), 67 (77), 55 (72). Found: C, 60.63; H, 7.00%. Calcd for $C_8H_{11}OCl$: C, 60.58; H, 6.99%.

6-Chloro-2-benzylidenecyclohexanone (1c) was prepared by the reaction of **12** with 1.2 equiv of NCS in CCl_4 at the reflux temperature:[13] 80% yield; mp 60—62 °C (from hexane); IR (neat) 1680, 1598, 1130, 790 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.5—3.0 (m, 6H), 4.50 (apparent dd, J=5 Hz, 1H), 7.26 (br. s, 6H). It was too labile for elemental analysis.

Reaction of 1a with Sodium Methoxide. To a solution of sodium methoxide (1.76 g, 32.6 mmol) in 20 ml of absolute methanol was added 1.12 g (6.50 mmol) of **1a** at room temperature with stirring. The mixture was stirred for 20 min at 50 °C, and then cooled. It was poured into cold water and acidified with 10% HCl. The organic materials were extracted with ether, washed with water, dried over $MgSO_4$ and concentrated. The resulting residue was purified by short column chromatography (SiO_2, hexane/ethyl acetate (10 : 1)) to give 0.725 g of an oil, which was analyzed by GLC (column: 130 °C, carrier gas: N_2, 0.5 kg cm^{-2}). Peaks, retention times (min), and integrated percentages are as follows: 1, 3.0, 78; 2, 4.5, 6; 3, 6.4, 16. Each component was separated by preparative GLC and identified.

Peak 1: **Methyl 2-Isopropyldenecyclopentanecarboxylate (2a);** 52% yield; IR (neat) 1732, 1430, 1160 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.65 (s, 6H), 1.6—2.5 (m, 6H), 3.3 (m, 1H), 3.59 (s, 3H); MS (70 eV) m/z (rel intensity) 168 (36, M$^+$), 109 (100), 108 (53), 93 (40), 67 (73), 55 (33). Found: C, 71.05; H, 9.44%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

Peak 2: **2-Isopropylidene-6-methoxycyclohexanone (4a);** 4% yield; IR (neat) 1695, 1630, 1450, 1130, 1096 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.78 (s, 3H), 1.88 (s, 3H), 1.5—2.6 (m, 6H), 3.32 (s, 3H), 3.56 (m, 1H). Found: C, 71.25; H, 9.41%. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%.

Peak 3: **Methyl trans-2-(1-Methoxy-1-methylethyl)cyclopentanecarboxylate (3a);** 8.9% yield; IR (neat) 1740, 1450, 1200, 1162 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.06 (s, 6H), 1.4—2.8 (m, 8H), 3,10 (s, 3H), 3.59 (s, 3H). Found: C, 65.82; H, 9.96%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%.

Methyl 2-Isopropylcyclopentanecarboxylate (5).[14] A mixture of **2a** (0.79 g, 4.70 mmol), 7 ml of methanol and palladium-carbon (4 mg) was stirred for 12 h under an atmosphere of hydrogen. Preparative TLC (SiO_2, hexane/ethyl acetate (3 : 1)) of the crude product gave 0.431 g (54%) of **5**:[14]) IR (neat) 1735, 1435, 1367, 1195, 1155 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.88 (d, J=7 Hz, 6H), 1.74 (m, 8H) 2.30 (m, 1H), 3.60 (s, 3H).

Oxidation of 2a with $KMnO_4$. To a mixture of **2a** (0.447 g, 2.66 mmol), $NaHCO_3$ (0.083 g, 1 mmol), and acetone (3 ml) was added powdered $KMnO_4$ (1.46 g, 9.24 mmol) below 7 °C over 1.5 h. The mixture was stirred for 1 h, and then dilute H_2SO_4 and a small amount of $NaHSO_3$ were added alternately until it becomes clear. The mixture was concentrated, washed with ether and acidified with dilute HCl. The organic materials were extracted with ether three times, washed with brine and dried over $MgSO_4$. Removal of the solvent gave 200 mg (52%) of adipic acid: mp 151—152 °C (from benzene)(lit,[15] 151—152 °C).

Reaction of 1b with Sodium Methoxide. To a stirred solution of sodium methoxide (1.51 g, 28 mmol) in 20 ml of absolute methanol was added dropwise 0.888 g (5.60 mmol) of **1b** at 25 °C. The mixture was stirred for 20 min at 50 °C and then cooled, acidified with 10% HCl. The organic layer was extracted with ether and combined extracts were washed with aqueous $NaHCO_3$, brine and water, and then dried over $MgSO_4$. After concentration, the residual oil was distilled with balb-to-balb tube oven to give 0.850 g of a clean oil, which was analyzed by GLC (column, 120 °C; carrier gas, N_2, 0.5 kg cm^{-2}). Peaks, retention times (min), and integrated percentages are as follows: 1, 1.3, 5.0; 2, 2.4, 19; 3, 3.4, 30; 4, 4.3, 24; 5, 4.8, 22. Each component was separated by preparative GLC. Peaks 1 and 2 were not identified. Peaks 3, 4, and 5 were identified as a stereoisomer of **3b**, respectively: total yield, 62%.

Peak 3: **Methyl 1-(1-Methoxyethyl)cyclopentanecarboxylate (6);** 24% yield; IR (neat) 1735, 1165, 1140, 1104, 1006 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.98 (d, J=6 Hz, 3H), 1.3—2.2 (m, 8H), 3.2 (m, 1H), 3.23 (s, 3H), 3.59 (s, 3H); MS (70 eV) m/z (rel intensity) 186 (1, M$^+$), 172 (2), 154 (5), 139 (13), 128 (76), 95 (46), 67 (34), 59 (100); ^{13}C NMR ($CDCl_3$) δ=17.0 (q, $CH\underline{C}H_3$),

25.2 (t, C-4), 27.0 (t, C-3), 31.0 (t, C-5), 45.9 (d, C-2), 49.3 (d, C-1), 51.5 (q, OCH_3), 56.5 (q, $CO_2\underline{C}H_3$), 80.3 (d, $\underline{C}HOCH_3$), 177.2 (s, C=O). Found: C, 64.25; H, 9.80%. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%.

Peak 4: **Methyl *trans-erythro*-2-(1-Methoxyethyl)cyclopentanecarboxylate (3b);** 20% yield; IR (neat) 1735, 1195, 1160, 1090 cm^{-1}; ^1H NMR (CCl_4) δ=1.06 (d, J=6 Hz, 3H), 1.5—2.8 (m, 8H), 3.31 (s, 3H), 3.34 (dq, J=4 and 7 Hz, 1H), 3.68 (s, 3H); MS (70 eV) m/z (rel intensity) 186 (1, M^+), 171 (6), 155 (4), 149 (11), 111 (33), 95 (50), 67 (34), 59 (100); ^{13}C NMR ($CDCl_3$) δ=17.0 (q, $CH\underline{C}H_3$), 25.3 (t, C-4), 27.1 (t, C-3), 31.1 (t, C-5), 46.1 (d, C-2), 49.4 (d, C-1), 51.5 (q, OCH_3), 56.6 (q, ester CH_3), 78.0 (d, C-1′), 177.1 (s, C=O). Found: C, 64.43; H, 9.73%. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%.

Peak 5: **Methyl *trans-threo*-2-(1-Methoxyethyl)cyclopentanecarboxylate (3b);** 18% yield; IR (neat) 1736, 1196, 1158, 1092 cm^{-1}; ^1H NMR (CCl_4) δ=1.10 (d, J=6 Hz, 3H), 1.5—2.7 (m, 8H), 3.15 (m, 1H), 3.27 (s, 3H), 3.65 (s, 3H); MS (70 eV) m/z (rel intensity) 186 (3, M^+), 171 (7), 156 (4), 155 (4), 139 (5), 126 (12), 123 (7), 111 (30), 95 (53), 59 (100); ^{13}C NMR ($CDCl_3$) δ=17.0 (q, $CH\underline{C}H_3$), 25.3 (t, C-4), 29.1 (t, C-3), 31.2 (t, C-5), 47.6 (d, C-2), 50.2 (d, C-1), 51.5 (q, OCH_3), 56.3 (q, ester C=O), 80.4 (d, C-1′), 177.4 (s, C=O). Found: C, 64.68; H, 9.75%. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%.

Reaction of 1c with Sodium Methoxide. To a stirred solution of sodium methoxide (2.35 g, 43.5 mmol) in 30 ml of absolute methanol was added dropwise 1.94 g (8.80 mmol) of **1c** at room temperature. The mixture was stirred for 30 min at 50 °C, cooled, and acidified with 10% HCl. The organic materials were extracted with ether and the combined extracts were washed with aqueous $NaHCO_3$, brine and water, and then dried over $MgSO_4$. After concentration, the residual oil (1.68 g) was analyzed by GLC (column, 180 °C; carrier gas, N_2, 0.5 kg cm^{-2}). Peaks, retention times (min), and integrated percentages are as follows: 1, 7.5, 5; 2, 9.3, 43; 3, 10.5, 37; 4, 27.0, 6; 5, 30.0, 9. Each component was separated by preparative GLC (column, Apiezone Grease L, 185 °C; carrier gas, H_2, 27 ml min^{-1}). Components 1 and 5 were not identified. Components 2 and 3 were identified as a stereoisomer of **3c**, respectively: total yield, 67%.

Peak 2: **Methyl *trans-erythro*-2-Methoxyphenylmethylcyclopentanecarboxylate (3c);** 33% yield: bp 98 °C/0.15 Torr; IR (neat) 1735, 1605, 1494, 768, 705 cm^{-1}; ^1H NMR (CCl_4) δ=1.3—2.15 (m, 6H), 2.2—2.8 (m, 2H), 3.18 (s, 3H), 3.45 (s, 3H), 4.06 (d, J=5 Hz, 1H), 7.20 (s, 5H); MS (70 eV) m/z (rel intensity) 248 (1, M^+), 233 (2), 184 (2), 157 (14), 121 (100), 115 (15), 105 (24), 91 (51). ^{13}C NMR ($CDCl_3$) δ=25.0 (t, C-3), 28.2 (t, C-4), 31.1 (t, C-5), 46.5 (d, C-2), 50.6 (d, C-1), 51.5 (q, OCH_3), 57.1 (q, $CO_2\underline{C}H_3$), 86.0 (d, $\underline{C}HOCH_3$), 127.4, 127.6, and 128.3 (d, phenyl), 140.9 (s, phenyl), 176.9 (s, C=O). Found: C, 72.39; H, 7.91%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

Peak 3: **Methyl *trans-threo*-2-Methoxyphenylmethylcyclopentanecarboxylate (3c);** 29% yield; bp 98 °C/0.15 Torr; IR (neat) 1735, 1605, 1494, 768, 705 cm^{-1}; ^1H NMR (CCl_4) δ=1.1—2.13 (m, 6H), 2.2—2.9 (m, 2H), 3.10 (s, 3H), 3.52 (s, 3H), 3.82 (d, J=8 Hz, 1H), 7.20 (s, 5H); MS (70 eV) m/z (rel intensity) 248 (1, M^+), 233 (2), 184 (2), 157 (14), 121 (100). ^{13}C NMR ($CDCl_3$) δ=24.7 (t, C-3), 29.1 (t, C-4), 31.1 (t, C-5), 47.9 (d, C-2), 50.8 (d, C-1), 51.4 (q, OCH_3), 56.9 (q, $CO_2\underline{C}H_3$), 87.5 (d, $\underline{C}HOCH_3$), 127.2, 127.6, and 128.1 (d, phenyl), 140.9 (s, phenyl), 177.1 (s, C=O). Found: C, 72.77; H, 8.18%. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12%.

Peak 4: **Methyl 2-Benzyl-1-cyclopentenecarboxylate (7c):** 8.0% yield; IR (neat) 1670, 1630, 1600, 1493, 700 cm^{-1}; ^1H NMR (CCl_4) δ=1.5—2.1 (m, 2H), 2.1—2.6 (m, 4H), 3.56 (s, 2H), 3.70 (s, 3H), 7.17 (s, 5H); MS (70 eV) m/z (rel intensity) 216 (86, M^+), 185 (6), 155 (42), 129 (39), 121 (45), 115 (46), 91 (100). Found: C, 77.62; H, 7.51%. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46%.

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