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# On the Mechanism of the Mander Carbomethoxylation of Ketone Enolates with Methyl Cyanoformate

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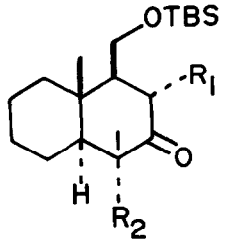
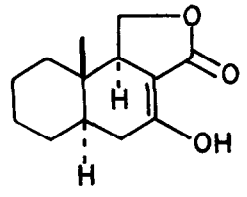
**Summary:** The acylation of lithium enolates of ketones with methyl cyanoformate has been shown to proceed through an aldol-type intermediate that can be trapped at low temperature.

In conjunction with an ongoing synthetic problem, we required the β-ketoester **1b**, or its enol, to be formed by carbomethoxylation of decalone **1a**.[1] Although acylation occurred successfully at $C_2$ using potassium tert-butoxide (dimethylcarbonate, THF, reflux), the vigorous reaction conditions also effected desilylation and lactonization to form **2**.




**1a**, $R_1 = R_2 = H$
**b**, $R_1 = CO_2Me$, $R_2 = H$
**c**, $R_1 = H$, $R_2 = CO_2Me$
**d**, $R_1 = R_2 = CO_2Me$
**e**, $R_1 = H$, $R_2 = C(OTMS)(OMe)CN$

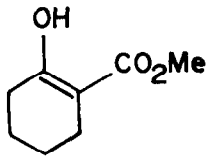
**2**

Mander[2] has recently reported the successful, high yield carbomethoxylation of lithium enolates of ketones with 1.2 equiv. of methyl cyanoformate in the presence of 1.0 equiv. of hexamethylphosphoramide (HMPA) (-78°C --> 0°C, THF). When these conditions were applied to decalone **1a** (LDA/THF, -78°C --> 0°C --> -78°C), a mixture of four compounds was obtained in a 6:2:1:1 ratio. The structures of the first three of these compounds were assigned as β-ketoesters **1c** and **1b**, and ketodiester **1d**, respectively.[3] The formation of ketodiesters in this reaction has not been previously observed. One explanation for the formation of ketodiester **1d** requires γ-deprotonation of β-ketoester **1b** or **1c** (enolate exchange or slight excess LDA) without α-deprotonation, a requirement that must be met because the β-ketoester tautomers are isolated, and not their enolic forms. This mechanism is unlikely because the β-ketoesters are readily converted to their enols with LDA or t-BuOK in THF. An alternative hypothesis suggests that an aldol-type intermediate, which collapses to the β-ketoester upon warming, or may undergo further γ-enolization during the acylation and give ketodiester **1d**, is responsible for the observed behavior.

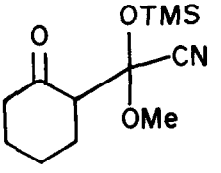
Deprotonation of decalone **1a** (1.1 equiv. LDA, -78°C, THF), followed by the successive addition of methyl cyanoformate (1.5 equiv., -78°C, THF, with or without HMPA), and chlorotrimethylsilane (17 equiv., -78°C, THF, freshly distilled) afforded four products, which were isolated by analytical hplc, in a 10:10:3:1 ratio. High-field NMR spectroscopy

identified the last three of these substances as the previously observed ketoesters **1c** and **1b**, and ketodiester **1d**, respectively. The other product was characterized as a single diastereomer of the trimethylsilylcyanohydrin **1e** resulting from O-silylation of the intermediate aldol product. Exposure of the masked cyanohydrin to tetra-n-butylammonium fluoride/THF afforded the ketoester **1c**.

When a similar experiment was conducted on cyclohexanone, three products were formed in a 4.5:1:4.5 ratio (hplc, ratio and isolation). One of the major components proved to be methyl 2-hydroxycyclohex-1-enecarboxylate (**3**), while the other two products were the α-methoxy trimethylsilylcyanohydrins **4**.[4] Treatment of the latter, separated diastereomers with tetra-n-butylammonium fluoride/THF gave rise to ester **3**.




**3**




**4**

**Acknowledgments:**

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**References and Notes:**

1. Details of the preparation of **1a** will appear in J. Am. Chem. Soc., **107**, 0000 (1985).

2. L. N. Mander and S. P. Sethi, Tetrahedron Lett., **24**, 5425 (1983).

3. **1b**: mp 81-82°C (pentane); IR 1748, 1716 $cm^{-1}$; $^1H$ NMR δ 3.85 (dd, J=10.9, 2.5 Hz, 1H), 3.76 (d, J=12.3 Hz, $C_8$-H), 3.74 (s, $CO_2CH_3$), 3.56 (dd, J=10.9, 4.4 Hz, 1H), 2.27 (dd, J=13.3, 12.9 Hz, $C_{1\beta}$-H), 2.19 (dd, J=13.3, 4.3 Hz, $C_{1\alpha}$-H), 2.02 (ddd, J=12.3, 4.4, 2.5 Hz, $C_4$-H), 1.89 (dt, J=12.5, 3.0 Hz, $C_{5\beta}$-H), 1.75 (br.d, J=12.5 Hz, 1H), 1.66-1.45 (m, 3H), 1.40-1.20 (m, 3H), 1.06 (td, J=12.5, 4.5 Hz, $C_{5\alpha}$-H), 1.06 (s, angular $CH_3$), 0.88 (s, 9H), 0.02 (s, 3H), -0.02 (s, 3H); $^{13}C$ NMR 205.9, 170.3, 59.6, 56.7, 52.5, 51.4, 45.3, 44.6, 38.6, 35.7, 28.3, 26.0, 25.6, (x3), 21.4, 18.0, 12.7, -5.9, -6.2 ppm; Anal: C, H; **1c**: $^1H$ NMR (250 MHz) δ 3.76 (s, $CO_2CH_3$), 3.74 (dd, J=10.0, 4.0 Hz, 1H), 3.54 (dd, J=10.0, 7.0 Hz, 1H), 3.17 (d, J=13.0 Hz, $C_1$-H), 2.61 (dd, J=15.5, 4.5 Hz, $C_{3\alpha}$-H), 2.38 (dd, J=15.5, 13.0 Hz, $C_{3\beta}$-H), 1.96-1.85 (m, 2H), 1.80-1.70 (m, 2H), 1.60-1.25 (m, 5H), 1.15 (td, J=13.0, 4.0 Hz, $C_{5\alpha}$-H), 1.01 (angular $CH_3$), 0.88 (s, 9H), 0.034 (s, 3H), 0.03 (s, 3H). **1d**: NMR (250 MHz) δ 0.05 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 0.87 (3H, s, angular Me), 2.74 (1H, d, J=12.0 Hz, $C_1$-H), 2.98 (1H, d, J=10.0 Hz, $C_3$-H), 3.48 (1H, dd, J=10.0, 6.5 Hz, ABX), 3.77 (1H, dd, J=10.0, 3.5 Hz, ABX), 3.76 (3H, s, $CO_2Me$), and 3.82 (3H, s, $CO_2Me$); **1e**: IR[4] 1745 $cm^{-1}$; NMR (250 MHz), δ 3.73 (3H, $OCH_3$), 0.90 (9H, OSi-t-$BuMe_2$), 0.23 (9H, OTMS), 0.06 (3H, OSi-t-$BuMe_2$). and 0.05 (3H, OSi-t-$BuMe_2$); **4**: [major: NMR (250 MHz) δ 2.53 (1H, dd, J=13.2, 3.7 Hz), 3.74 (3H, s), and 0.23 (9H, s), IR[4] 1739 $cm^{-1}$, MS (70 eV) m/z 240 (21%, $M^+$-15); minor: NMR (250 MHz) δ 2.76 (1H, t, J=6.5 Hz), 3.73 (3H, s), and 0.24 (9H, s); IR 1738 $cm^{-1}$, MS (70 eV) m/z 240 (30%, $M^+$-15)].

4. The high ketone frequencies in this series of compounds is probably due to the inductive effect of the three electronegative groups. No nitrile absorption is observed because of the electronegativity of the methoxy and trimethylsilyloxy group.

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