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The Knoevenagel Condensation of O,S- and S,S-Diethyl Malonates and Ethyl Pyruvate

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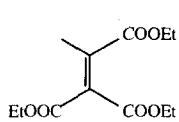
In Memory of Professor Paul Dowd

Abstract: *The Knoevenagel condensation of O,O-, O,S- and S,S-diethyl malonates with ethyl pyruvate is described. The elimination sequence in* **2** *and* **6** *is suppressed by the presence of* $ZnCl_2$.

The Knoevenagel condensation is an important method for the preparation of α,β-unsaturated dicarbonyl compounds.[1] The course of the reaction depends upon employed substrates and catalysts, and several mechanisms may operate. Malonic esters and aldehydes easily undergo the Knoevenagel reaction in the presence of secondary amines or their salts.[2] Ketones usually require the use of Lewis acids such as titanium tetrachloride,[3] zinc chloride[4] or zinc acetate.[5] Some is known about the Knoevenagel condensation of thiomalonates.[6] In the condensation of benzaldehyde with S,S-diethyl dithiomalonate, the thiomalonate is about four times more reactive than diethyl malonate.[6a]

Unsaturated tricarboxylates (*vide infra*) are important synthetic intermediates[7] possessing an electron deficient double bond and a malonic ester functionality. These compounds have found use in several enzyme model studies, including the mechanism of action of vitamin B_{12}.[8]

The reaction of diethyl malonate (1.0 eq.) and ethyl pyruvate (1.1 eq.) in the presence of acetic anhydride (4.9 eq.) and zinc chloride (1.6 eq.) at 100 °C yields triethyl prop-1-ene-1,1,2-tricarboxylate, **1** (70%).[4a] Replacing diethyl malonate with S,S-diethyl dithiomalonate[9] resulted in nearly quantitative isolation of **2**; no elimination product **3** was observed. When acetic anhydride was omitted from the procedure, no



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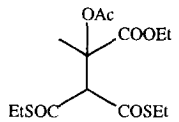

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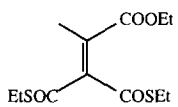

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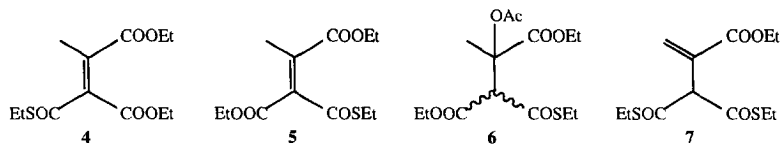
reaction took place and S,S-diethyl dithiomalonate was recovered. Omitting zinc chloride from the reaction mixture resulted in an isolation of the two products **2** (34%) and **3** (4%) and recovery of the dithiomalonate (50%).

From condensation of O,S-diethyl thiomalonate[6b] with ethyl pyruvate in the presence of acetic anhydride and zinc chloride, two isomers were isolated,[10] the unsaturated triesters **4** and **5** (62% by GC-MS; 10:1 ratio respectively) and the stereoisomers of the acetate adduct **6** (38% by GC-MS; 1:1.5 ratio).



Tetraester **2** undergoes elimination in the presence of various bases yielding **3** and/or **7** (Table). Even the weak base sodium acetate promotes elimination, yielding **3** and **7**. As expected, addition of an equimolar amount of zinc chloride to sodium acetate resulted in the recovery of **2**.

Table. Distribution of products in base-catalyzed elimination of **2**.

Base	Time [hr]	3[a]	7[a]
tert-BuOK/THF	0.3	0	92
K_2CO_3/DMF	12[b]	0	87
Na_2CO_3/py	4	24	73
AcONa/THF/rfx	21	77	19

[a]Isolated yields. [b]After 35 min. TLC indicates the absence of the substrate and the presence of the two products **3** and **7**.

In the thiomalonate Knoevenagel reaction the condensation step occurs according to the Hann-Lapworth mechanism through a β-hydroxy intermediate.[11] The hydroxyl group is then acetylated with acetic anhydride in the presence of zinc chloride. Thiomalonates are more acidic[12] than ordinary malonates due to poor 2p-3p overlap of sulfur with the carbonyl group of the thioester.[13] This might be expected to enhance the elimination step. However, the elimination step is suppressed by the presence of $ZnCl_2$, possibly because of stabilization of the OAc-zinc complex[14] with the available electrons of the sulfur atom(s).

EXPERIMENTAL

General Methods. ^1H and ^{13}C NMR spectra were determined on a Bruker IBM-AF 300 (300.13 and 75.46 MHz, respectively) spectrometer. Infrared spectra (IR) were obtained as thin films on an IBM 132 FT-IR spectrometer. Low-resolution mass spectra (MS) were recorded on a VG 70-SE spectrometer with peaks as units of mass charge (m/e). High-resolution mass spectra (HRMS) were recorded on a Varian Mat CH5DH spectrometer and were calibrated by peak matching. Gas chromatography-mass spectroscopy (GC-MS) was performed on a Hewlett Packard 5890 using a 12 m x 0.2 mm I. D. fused silica HP-1 capillary column. Flash chromatography was carried out on Merck 230-400 mesh silica gel with 5% ethyl acetate in hexane.

Materials. Distilled reagent grade solvents were used for all chromatographic separations. Ethyl pyruvate and 1M zinc chloride in ether were purchased from Aldrich. Zinc chloride solution was evaporated prior to the reaction.

Triethyl prop-1-ene-1,1,2-tricarboxylate **1** was prepared in 66% yield according to the procedure of Malachowski and Czornodola.[4a] All of the other condensations followed this procedure.

Ethyl (2-carbothioethoxy-3-acetoxy-3-carboethoxy)thiobutanoate **2** (t_r 3.64 in GC-MS) was prepared in 99% yield. ^1H-NMR 4.82 (s, 1H), 4.19 (q, J=7.1, 2H), 3.01-2.84 (m, 4H), 2.07 (s, 3H), 1.87 (s, 3H), 1.27 (t, J=7.2, 3H), 1.25 (t, J=7.2, 6H). ^{13}C-NMR 189.8 (s), 189.0 (s), 169.8 (s), 169.6 (s), 80.4 (s), 68.3 (d,

J=137), 62.0 (t, J=147), 24.4 (t, J=141), 24.2 (t, J=145), 21.0 (q, J=130), 20.1 (q, J=128), 14.2 (q, J=125), 14.1 (q, J=125), 13.8 (q, J=127). IR 2978, 2934, 1748 (vs), 1705 (vs), 1451, 1416, 1372, 1238, 1186, 1130, 1017, 934. MS 289 (25, M^+-SEt), 245 (11, M^++H-SEt-OEt), 229 (100, M^+-SEt-AcOH), 201 (62, M^++H-SEt-COSEt), 139 (80). HRMS calc'd for $C_{12}H_{17}O_6S$ 289.0746; found 289.0746.

Triethyl prop-1-ene-1,1-dithio-2-tricarboxylate **3** (t_r 3.20 in GC-MS). ^{1}H-NMR 4.24 (q, J=7.1, 2H), 3.03 (q, J=7.3), 2.97 (q, J=7.4, total of 4H), 2.07 (s, 3H), 1.33 (t, J=7.5), 1.29 (t, J=7.1), 1.28 (t, J=7.4, all triplets 9H). ^{13}C-NMR 190.3 (s), 188.2 (s), 167.4 (s), 142.1 (s), 138.0 (s), 61.9 (t, J=145), 24.4 (t, J=143), 24.3 (t, J=143), 17.1 (q, J=130), 14.3 (q, J=131), 14.1 (q, J=131), 13.8 (q, J=128). IR 2964, 2924, 1735 (vs), 1663 (vs), 1452, 1371, 1274, 1193, 1106, 1020, 957. MS 245 (8, M^+-OEt), 229 (60, M^+-SEt), 201 (52, M^+-COSEt) 183 (6, M^++H-OEt-SEt), 167 (4, M^++H-2SEt), 139 (100, M^++H-SEt-COSEt). HRMS calc'd for $C_{10}H_{13}O_3S_2$ 245.0306; found 245.0306. Compound **3** matches its spectral characteristics with that of authentic sample prepared in 19% yield with β-alanine as the catalyst.[15] From this reaction 58% of S,S-diethyl dithiomalonate was recovered and none of **2** was observed.

Triethyl prop-1-ene-1-thio-1,2-tricarboxylate **4** (t_r 2.41 in GC-MS) was separated by flash chromatography from the mixture of **4** and **5**. ^{1}H-NMR 4.27 (q, J=7.1), 4.24 (q, J=7.1, total of 4H), 3.01 (q, J=7.5, 2H), 2.09 (s, 3H), 1.32 (t, J=7.4, 6H), 1.28 (t, J=7.1, 3H). ^{13}C-NMR 190.4 (s), 167.8 (s), 162.9 (s), 142.2 (s), 134.1 (s), 61.9 (t, J=149), 61.8 (t, J=149), 24.1 (t, J=142), 17.3 (q, J=132), 14.4 (q, J=128), 13.9 (q, J=128). IR 2982, 2936, 1732 (vs), 1672, 1449, 1368, 1250, 1186, 1055, 1018. MS 229 (12, M^+-OEt), 213 (50, M^+-SEt) 201 (11, M^+-COOEt), 185 (42, M^+-COSEt), 157 (88), 139 (100, M^+-COSEt-EtOH). The ^{1}H-NMR spectrum of isomer **5** (t_r 2.38 in GC-MS) differs from **4** having signals of the Me group at 2.20 (s) and -CH_2- of the thioester group at 2.97 (q, J=7.4).[10] In the ^{13}C-NMR spectrum, singlets of **5** in the lower field were assigned as 189.5, 167.5, 163.8, 142.2, 135.7. HRMS of the mixture of **4** and **5** calc'd for $C_{10}H_{13}O_4S$ 229.0535; found 229.0535.

Ethyl (2,3-carboethoxy-3-acetoxy)thiobutanoate **6** was obtained as 1:1.5 mixture of the two stereoisomers. The major isomer was isolated by flash chromatography. ^{1}H-NMR 4.57 (s, 1H), 4.28-4.14 (m, 4H), 2.91 (q, J=7.4, 2H), 2.05 (s, 3H), 1.87 (s, 3H), 1.28 (t, J=7.5, 3H), 1.26 (t, J=7.5, 6H). ^{13}C-NMR 190.2 (s), 169.4 (s), 165.1 (s), 80.1 (s), 62.0 (d, J=137), 61.9 (t, J=149), 24.0 (t, J=143), 20.8 (q, J=130), 19.6 (q, J=132), 14.3 (q, J=129), 14.0 (q, J=129), 13.8 (q, J=127). IR 2980, 2353, 1746 (vs), 1694, 1651, 1634, 1454, 1370, 1238, 1190, 1127, 1020. MS 273 (11, M^+-SEt), 229 (23, M^+-OEt-AcOH), 213 (60, M^+-SEt-AcOH), 203 (98), 185 (50, M^+-AcOH-COSEt), 157 (100), 139 (48, M^+-AcOH-COSEt-EtOH). HRMS calc'd for $C_{12}H_{17}O_7$ 273.0974; found 273.0974.

Base-catalyzed elimination of **2** was achieved by using an excess of the base, *i.e. tert*-BuOK (2.0 eq.), K_2CO_3 (1.2 eq.), Na_2CO_3 (1.2 eq.) and CH_3CO_2Na (1.2 eq.). From these reactions triethyl prop-2-ene-1,1-dithio-2-tricarboxylate **7** (t_r 3.10 in GC-MS) was isolated (Table). ^{1}H-NMR 6.57 (s, 1H), 6.11 (s, 1H), 5.11 (s, 1H), 4.24 (q, J=7.1, 2H), 2.93 (q, J=7.4, 4H), 1.30 (t, J=7.1, 3H), 1.26 (t, J=7.4, 6H). ^{13}C-NMR 192.0 (s), 165.3 (s), 132.1 (s), 130.5 (t, J=162), 66.7 (d, J=134), 61.7 (t, J=145), 24.4 (t, J=142), 14.3 (q, J=129), 14.2 (q, J=129). IR 2976, 2932, 1701 (vs), 1626, 1559, 1456, 1412, 1373, 1248, 1144, 1024, 968. MS 245 (4, M^+-OEt), 229 (32, M^+-SEt), 201 (100, M^+-COSEt), 183 (29, M^++H-OEt-SEt), 167 (71, M^++H-2SEt), 139 (43, M^++H-SEt-COSEt). HRMS calc'd for $C_{10}H_{13}O_3S_2$ 245.0306; found 245.0306.

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