

Synthesis and Silica Gel Promoted Rearrangement of 5-Methylthio-3-carbo-*t*-butoxy-pent-3-en-2-one

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Knoevenagel Condensation,
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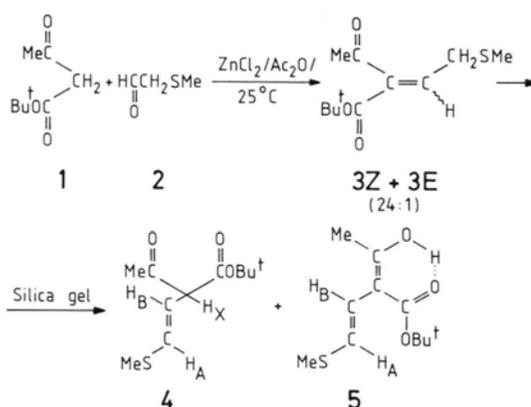
The title compound **3** obtained by the Knoevenagel condensation of *t*-butyl acetoacetate (**1**) with methylthioethanal (**2**) in the presence of zinc chloride was found to undergo an easy isomerization on silica gel to its β,γ -isomer which exists as a mixture of the keto (**4**) and enol (**5**) forms.

Since the discovery by Knoevenagel [1] that doubly activated carbonic acids (CH-acids) react with carbonyl compounds to give the corresponding conjugated olefins, this reaction has been widely used in organic synthesis as an important method for carbon-carbon bond formation [2, 3]. The condensation of 1,3-dicarbonyl compounds with monocarbonyl compounds usually leads to α,β -unsaturated products [4]. However, it has recently been described that the reaction of alkoxyethanal with methyl or ethyl acetoacetate gives a mixture of α,β - and β,γ -unsaturated carbonyl compounds [5] or results in the formation of a β,γ -unsaturated carbonyl compound and 2,3,5-trisubstituted-4,5-dihydrofuran [6]. In both cases β,γ -unsaturated carbonyl condensation products were enolized to some extent (15–45%) [5, 6].

In the course of our studies on the synthesis of methylenomycin A and other cyclopentanoid antibiotics we selected 5-methylthio-3-carbo-*t*-butoxy-pent-3-en-2-one (**3**) as a potential Michael reaction acceptor which should allow us to construct the 1,4-dicarbonyl skeleton according to the Umpolung concept. In this paper we would like to report the synthesis of **3** from commercially available *t*-butyl acetoacetate (**1**) and methylthioethanal (**2**) as well as its isomerization to the corresponding β,γ -isomer. Although the synthesis of **2** has been described in our recent paper [7] dealing with the synthesis of methyl-

enomycin B, we wish to disclose here a modified procedure for hydrolysis of 1,1-diethoxy-2-methylthioethane leading to **2** which is practically uncontaminated with the starting acetal.

We found that the desired compound **3** is formed in high yield when the reaction of **1** and **2** is carried out in acetic anhydride at room temperature in the presence of zinc chloride. The use of zinc chloride as a catalyst in this condensation is crucial because our attempts to obtain **3** under the typical Knoevenagel reaction conditions [4–6, 8] were unsuccessful. The ^1H NMR (300 MHz) spectrum of the crude reaction products revealed only the presence of **3** as a mixture of Z and E isomers in a 2.4:1 ratio. No β,γ -unsaturated isomers of **3** or the corresponding cyclic product were detected even when the reaction mixture was refluxed in carbon tetrachloride for a few hours in the presence of acetic acid. Moreover, distillation, by which **3** was isolated in a pure state, did not change the E/Z ratio nor cause isomerization of the double bond.



NOE experiments involving irradiation of the methylene doublets in **3** allowed the assigning of the Z-geometry to the major isomer present in the mixture. Irradiation of the vinylic triplets was not conclusive in this case.

Generally, 2-alkylidene substituted 1,3-dicarbonyl compounds are unstable [8]. For example, methyl methylideneacetoacetate is stable for a short time at -78 °C. The presence of the *t*-butyl group in a molecule of such compounds greatly increases their stability, for example di-*t*-butyl methylidenemalonate is stable for four weeks at 25 °C [9]. For this reason, our compound **3** shows also quite a satisfactory stability and may be kept at room temperature for a relatively long time.

However, all attempts to separate the E and Z isomers of **3** by preparative thin layer chromatog-

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raphy, column chromatography under normal pressure of flash chromatography on silica gel caused rapid isomerization of **3** to 1-methylthio-3-carbo-*t*-butoxy-pent-1-en-4-one (**4**) and 1-methylthio-3-carbo-*t*-butoxy-4-hydroxy-pentadi-1,3-ene (**5**). The latter compounds formed in a 1:1–6.5 ratio were obtained together with small amounts of **3** (Z+E) and pure Z-**3** after chromatography. The ^1H NMR (300 MHz) spectra of **4** (keto-form) and **5** (enol-form) clearly showed that in both compounds the olefinic protons H_A and H_B have a *trans* spatial relation.

It is interesting to note that the above described isomerization of **3** to **4** and **5** was very slow in the absence of silica gel. Thus, in a chloroform solution of **3** kept at room temperature for two weeks only 10% of the isomerized products **4** and **5** was detected; in a pentane-acetone (40:1) solution samples of **3** could be stored at 0 °C for several weeks without significant isomerization.

Unfortunately, our attempts to obtain the 1,4-adducts of 1-potassio-1-nitropropane and 1-lithio-1-ethylsulfenyl-1-ethylsulfanylpropane to **3** were unsuccessful most probably due to a protonation of the carbanions by **3**. The typical work-up led to recovery of the reaction substrates.

In conclusion, we have described herein: a) the improved synthesis of methylthioethanal (**2**), b) the conversion of *t*-butyl acetoacetate into its vinylogous derivative **3** and c) silica gel catalyzed isomerization of **3** to β , γ -isomers **4** and **5**.

Experimental

Acetic acid anhydride was distilled before use. Anhydrous zinc chloride (Fluka A.G.) and *t*-butyl acetoacetate (Merck) were used without purification. ^1H NMR spectra were recorded with a Bruker MSL spectrometer at 300.13 MHz. Column chromatography and flash chromatography were done using Merck silica gel (70–230 mesh and 230–400 mesh). Preparative thin layer chromatography was done on 20×20 cm silica gel plates (Merck, 60 F_{254s}) with 4×20 cm concentrated zone. *n*-Pentane-acetone solution (50:1) was used as an eluent.

Methylthioethanal (**2**). An improved procedure

Crude 1,1-diethoxy-2-methylthioethane obtained in 90% yield from 1,1-diethoxy-2-bromoethane (85.6 g, 0.43 mole) and sodium mercaptide according to ref. [10], is dissolved in methylene chloride (200 ml) and added to a solution of *p*-toluenesulfonic acid monohydrate (76.0 g, 0.4 mole) in water (200 ml). After 1.5–2 h of vigorous stirring under

argon, the organic phase and aqueous solution are separated. A fresh portion of *p*-toluenesulfonic acid monohydrate (76.0 g, 0.4 mole) in water (200 ml) is added to the methylene chloride solution and the resulting two-phase solution is stirred under argon for 2 h. The above acid treatment of the organic phase is repeated twice. Then, the methylene chloride solution is washed with brine (100 ml), sodium bicarbonate (100 ml), brine (2×100 ml) and dried over anhydrous magnesium sulfate. After removal of the solvent the crude **2** (26.4 g, 75%) is distilled under argon to afford 20 g (57%) of methylthioethanal (**2**); b.p. 60°/60 mbar, $n_{\text{D}}^{20} = 1.4820$.

5-Methylthio-3-carbo-*t*-butoxy-pent-3-en-2-one (**3**)

Methylthioethanal (**2**) (1.8 g, 20 mmole) and acetic anhydride (1.74 g, 17 mmole) are added to *t*-butyl acetoacetate (**1**) (2.13 g, 13.5 mmole) with stirring at 20 °C (water bath). Anhydrous zinc chloride (0.276 g, 2 mmole) is added in portions to this mixture and stirring is continued for 24 h at room temperature. Methylene chloride (100 ml) is then added to the reaction mixture and the organic solution is washed with water (2×60 ml), sodium bicarbonate solution (60 ml) and water (2×60 ml), dried over anhydrous magnesium sulfate and evaporated to give the crude product **3** (Z/E mixture in a 2.4:1 ratio). Its distillation gave a pure **3** with the same Z/E ratio; b.p. 108–110 °C/0.2 mbar (140–150 °C, oil bath); $n_{\text{D}}^{20} = 1.4945$; yield: 2.64 g (85%) based on **1**.

Analysis for C₁₁H₁₈O₃S (230.32)

Found C 57.36 H 7.88,

Calcd C 56.98 H 7.89.

M.S. 70 eV (*rel.int.* %) = 230(0.2), 174(28), 157(22), 156(48), 132(14), 130(20), 114(70), 109(68), 87(32), 85(16), 83(14), 59(30), 57(99), 53(13), 47(11), 45(30), 43(100), 39(30), 29(29), 27(13). – ^1H NMR (CDCl₃/TMS): Z-**3** (major): $\delta = 1.43$ (s, 9H, Bu'), 1.95 (s, 3H, MeS), 2.22 (s, 3H, MeCO), 3.21 (d, 2H, CH₂, $^3J_{\text{H-H}} = 8.2$), 6.58 (t, 1H, CH, $^3J_{\text{H-H}} = 8.2$); E-**3** (minor): $\delta = 1.40$ (s, 9H, Bu'), 1.96 (s, 3H, MeS), 2.24 (s, 3H, MeCO), 3.13 (d, 2H, CH₂, $^3J_{\text{H-H}} = 8.2$), 6.67 (t, 1H, CH, $^3J_{\text{H-H}} = 8.2$).

Isomerization of **3** on silica gel

When **3** (1.15 g, 5 mmol) was flash chromatographed ($\varnothing = 50$, $l = 250$, nitrogen pressure driven, Merck silica gel 230–400 mesh, *n*-pentane-acetone solution as an eluent in a 50:1 ratio), a mixture (0.96 g, 82%) of **4** and **5** (70%, in a 1:6.5 ratio) together with **3** (12%; Z/E = 5.3:1) and pure Z-**3** (0.12 g, 10%, $n_{\text{D}}^{20} = 1.4910$) was obtained. Similar

isomerization leading to the mixture of **4** and **5** and the starting material **3** was observed using preparative thin layer chromatography or column chromatography under normal pressure.

1-Methylthio-3-carbo-t-butoxy-pent-1-en-4-one (4)

$^1\text{H NMR}$ (CDCl_3/TMS): $\delta = 1.35$ (s, 9H, Bu^t); 2.11 (s, 3H, MeS); 2.17 (s, 3H, MeCO); 3.97 (d, 1H, $^3J_{\text{H-H}} = 9.1$ Hz, H_X); 5.38 and 5.41 (dd, 1H,

$^3J_{\text{H-H}} = 9.1$ Hz; 15.1 Hz, H_B); 6.18 ppm (d, 1H, $^3J_{\text{H-H}} = 15.1$ Hz, H_A).

1-Methylthio-3-carbo-t-butoxy-4-hydroxy-pentadi-1,3-ene (5)

$^1\text{H NMR}$ (CDCl_3/TMS): $\delta = 1.41$ (s, 9H, Bu^t); 1.98 (d, 3H, $^5J_{\text{H-H}} = 0.6$ Hz, MeC=); 2.16 (s, 3H, MeS); 5.79 and 6.11 (AB system, 2H, $J_{\text{AB}} = 15.4$ Hz); 13.21 ppm (s, 1H, OH).

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