An Improved Synthesis of a Mixture of Diethyl (*Z*)- and (*E*)-3-Methylglutaconates from Ethyl Acetoacetate

Kaleria I. Kuchkova, Alla B. Morari, Pavel F. Vlad*

Institutul de chimie al Academiei de Ştiinţe a Republicii Moldova, strada Academiei 3, 277 028 Chişinău, Moldavia

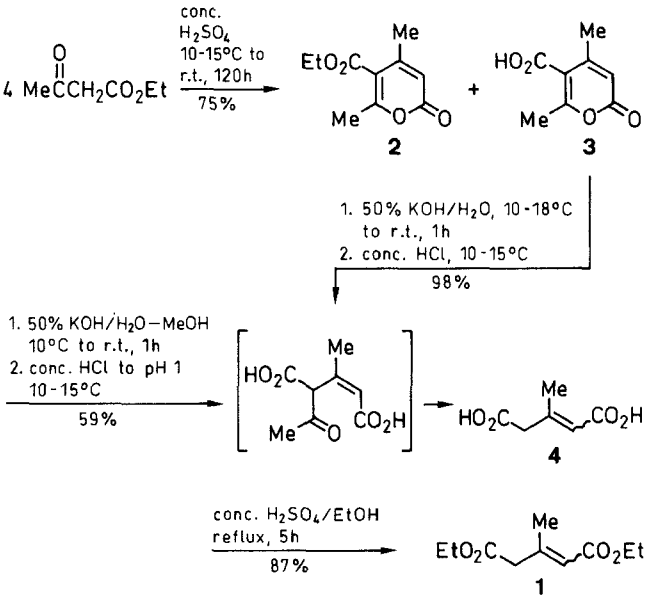
Received 23 April 1993

A simple, efficient two-step synthesis of a mixture of diethyl (*Z*)- and (*E*)-3-methylglutaconates from isodehydroacetic acid in 83% yield is described. On the basis of this synthesis an improved procedure for the preparation of a mixture of (*Z*)- and (*E*)-3-methylglutaconic acids from ethyl acetoacetate in 44% overall yield was elaborated.

Diethyl 3-methylglutaconate (**1**) is used in the syntheses of retinoids,[1] abscisic acid analogues,[2] juvenile hormones[3] and other biologically active compounds. Among the known procedures for the preparation of this compound,[4-6] the sodium ethylate catalyzed cleavage of ethyl isodehydroacetate (**2**) into **1** (50% yield)[4] is one of the most simple methods. Ester **2** is usually obtained by condensation of ethyl acetoacetate in the presence of concentrated sulfuric acid (26–32% yield).[7] Besides ester **2**, isodehydroacetic acid (**3**) is also formed in this reaction approximately in the same yield.[7] Acid **3** can then be esterified by treatment of its chloroanhydride with anhydrous ethanol (85% yield).[8] As a result of the above mentioned transformations, the overall yield of **1** reaches ca. 25%.

We now report a simple, efficient procedure for conversion of **3** into **1**, possessing a number of advantages in comparison with the above described method. The treatment of **3** with 50% aqueous potassium hydroxide results in the following one-pot successive transformations: hydrolysis of **3**, acid cleavage of the hydrolysis product, and partial isomerization of the initially formed (*Z*)-3-methylglutaconic acid into a mixture of (*Z*)- and (*E*)-acids **4** (ca. 1:1) in 98% overall yield. The conditions, given in the experimental section, are optimized. We point out, that the base concentration and the reaction temperature are crucial for the success of this process. The acid mixture **4** was then converted into ester mixture **1** (87% yield, the same isomer ratio) by refluxing with anhydrous ethanol in the presence of concentrated sulfuric acid. Based on this method of transformation of **3** into **1**, we elaborated an improved procedure for the preparation of **1** directly from ethyl acetoacetate in 38% overall yield. According to procedure,[7] ethyl acetoacetate was converted into the mixture of acid **3** and its ester **2** followed by treatment with 50% aqueous potassium hydroxide to give acid **4** (59% yield), which was esterified into the mixture (ca. 1:1) of (*Z*)- and (*E*)-esters **1**.

All reagents were of commercial quality. Ethyl acetoacetate was distilled under reduced pressure before use. Anhydrous ethanol was prepared by standard procedure and distilled from CaO. Other reagent quality solvents were used without purification. Melting points were measured on a Boetius melting point apparatus and are uncorrected. IR spectra were obtained on a Specord 75 spectrometer. ^{1}H NMR Spectra were recorded at 80 MHz on a Bruker AC 80 spectrometer with TMS as an internal standard in $(CD_3)_2CO$ solutions. Analytical TLC was performed using commercial aluminum-backed silica gel plates with luminescent indicator for UV 254 (Silufol UV 254). Visualization was accomplished by UV light, iodine.



Preparation of a Mixture of (*Z*)- and (*E*)-3-Methylglutaconic Acids (4) from Isodehydroacetic Acid (3):

To a stirred, cooled (10°C) solution of KOH (106 g, 1.892 mol) in water (100 mL), acid **3** (40 g, 238 mmol) was added in portions over 1 h. As a result, the reaction temperature rose to 18°C. Stirring was continued for an additional 1 h at 22–23°C, then the reaction mixture was re-cooled to 10°C and conc. HCl (144 mL) was added dropwise to pH 1 at 10–15°C over 1 h. The precipitate was filtered off and washed with EtOAc (3 × 100 mL). The filtrate was extracted with EtOAc (3 × 300 mL). The combined extracts and washings were dried (Na_2SO_4), filtered and concentrated in vacuo to give a white solid, which was recrystallized from MeCN to provide 33.5 g (98%) of **4** as a mixture of (*Z*)- and (*E*)-isomers (ca. 1:1, ^{1}H NMR data). Mp 111–118°C {Lit.[6] mp 111–115°C [a mixture, ca. 2:1, of (*Z*)- and (*E*)-isomers]}.

IR (Nujol): ν = 1705, 1685, 1640 cm^{-1}.

^{1}H NMR (80 MHz, CD_3COCD_3): δ = 2.04 and 2.27 (2 d, J = 1 Hz, 3 H), 3.27 (d, J = 1 Hz) and 3.81 (s) (2 H), 5.85–5.92 (m, 1 H), 9.63 (s, 2 H).

Preparation of a Mixture of (*Z*)- and (*E*)-3-Methylglutaconic Acids (4) from Ethyl Acetoacetate:

To stirred, cooled (ice bath) conc. H_2SO_4 (225 mL, 4.23 mol) was added dropwise ethyl acetoacetate (162.5 g, 1.25 mol) at 10–15°C. The resulting mixture was allowed to stand for a further 120 h at r.t., poured onto crushed ice (500 g), stirred and extracted with Et_2O (3 × 500 mL). The extract was washed with water (3 × 20 mL), dried (Na_2SO_4), filtered and the solvent was evaporated to provide 85.14 g (75%) of the mixture of acid **3** and its ester **2** (ratio ca. 1:1, determinated by TLC analysis).

To a stirred, cooled (ice bath) solution of a portion (10 g) of this mixture in MeOH (14 mL) was added dropwise a solution of KOH (24.7 g) in water (24.7 mL) over 30 min and the resulting mixture was allowed to stand for 1 h at r.t. Water (140 mL) was then added and the mixture was worked up as described above to give 4.72 g (44% overall yield) of acid **4** (a mixture of (*Z*)- and (*E*)-isomers, ca. 1:1, ^{1}H NMR data). Mp 109–114°C.

Preparation of a Mixture of Diethyl (*Z*)- and (*E*)-Glutaconates (1): To a solution of **4** [mixture of (*Z*)- and (*E*)-isomers, ca. 1:1] (20 g, 139 mmol) in anhydrous EtOH (80 mL) was added conc. H_2SO_4 (1.6 mL, 30 mmol) and the reaction mixture was refluxed for 5 h. EtOH was evaporated in vacuo and the residue was dissolved in EtOAc (100 mL). The solution was washed with sat. aq $NaHCO_3$ (15 mL) and water, dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was distilled in vacuo to afford 24.29 g (87%) of **1** [(*Z*)-and (*E*)-isomers, ca. 1:1, ^{1}H NMR data]. Bp 117–119°C /4 mmHg; n_D^{25} = 1.4480. {Lit.[6] Bp 65–66°C/1 mmHg; n_D^{25} 1.4488 [(*Z*)- and (*E*)-isomers mixture, ca. 1:1, ^{1}H NMR data]}.

IR (neat): ν = 1733, 1707, 1647 cm^{-1}.

^{1}H NMR (80 MHz, CD_3COCD_3): δ = 1.27 (t, 6 H), 2.02 and 2.24 (2 d, J = 2 Hz, 3 H), 3.26 (d, J = 1 Hz) and 3.80 (s) (2 H), 4.16 (q, 4 H), 5.81–5.88 (m, 1 H).

(1) Poliachenko, L.N.; Davydova, L.P.; Darskaya, E.N.; Filippova, T.M.; Samokhvalov, G.I. *Zh. Org. Khim.* **1985**, *21*, 756.
(2) Gramenitskaya, V.N.; Kozimina, E.A.; Golovkina, L.S.; Vulfson, N.S. *Zh. Org. Khim.* **1981**, *17*, 1892.
(3) Henrick, C.A.; Willy, W.E.; Baum, J.W.; Baer, T.A.; Garcia, B.A.; Mastre, T.A.; Chang, S.M. *J. Org. Chem.* **1975**, *40*, 1. Shekhter, O.V.; Sergovskaya, N.L.; Tsizin, Yu.S. *Zh. Org. Khim.* **1979**, *15*, 260; *Chem. Abstr.* **1979**, *91*, 19851.
(4) Bland, N.; Thorpe, I.F. *J. Chem. Soc.* **1912**, *101*, 1557.
(5) Krasnaya, Zh.A.; Kucherov, V.F. *Izv. Akad. Nauk SSSR. Ser. Khim.* 1965, 110; *Chem. Abstr.* **1965**, *62*, 11682.
(6) Payne, G.B. *J. Org. Chem.* **1968**, *33*, 1284.
(7) Wiley, R.H.; Smith, N.R. *J. Am. Chem. Soc.* **1951**, *73*, 3531.
(8) Wiley, R.H.; Smith, N.R. *J. Am. Chem. Soc.* **1953**, *75*, 244.