New Preparations of Ethyl 3,3-Diethoxypropionate and (Ethoxycarbonyl)malondialdehyde. Cu(I)-Catalyzed Acetal Formation from a Conjugated Triple Bond[1a]

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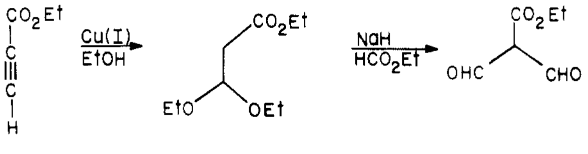
Prelog and co-workers[2] prepared (ethoxycarbonyl)-malondialdehyde (1) by the method of Panizzi[3] (formylation of ethyl 3,3-diethoxypropionate, 2) as part of a study of the preparation of phenols from diethyl 3-oxoglutarate and malondialdehydes. In conjunction with a study of the condensation of dimethyl 3-oxoglutarate and malondialdehydes under physiological conditions, where bicyclo-[3.3.1]nonane derivatives are sometimes produced,[4] we had the opportunity to repeat this preparation and to make some improvements in it. These include a change from Na to NaH in the preparation of 1 and a greatly improved preparation of 2 by a new route, viz., the copper(I) triflate catalyzed addition of ethanol to ethyl propiolate (3).



3 2 1

McElvain and Clarke[5] prepared 2 in 34% yield from the sodium enolate of ethyl formylacetate by the addition of ethanol and dry HCl. The low yield was attributed to the poor quality of the product obtained from the crossed ester condensation of ethyl formate and ethyl acetate. The actual yield of this reaction was determined to be 40%, as opposed to the 63% reported by Cogan.[6] The ester 2 also has been prepared in 40% yield by a modified Reformatsky reaction,[7] in 62% yield by the AIBN initiated addition of carbon tetrachloride to ethyl vinyl ether (followed by treatment with ethanol),[8] and in 50% yield by the reaction of acetylene and ethyl carbonate in the presence of alcohol-free sodium ethoxide (followed by treatment with 1% NaOEt/ethanol).[9] The treatment of ethyl 3-ethoxyacrylate (4) in ethanol with boron trifluoride etherate, sulfuric acid, or sodium bisulfate gave 2 in 72%, 41%, and 84% yield, respectively;[10] however, 4 is not commercially available. It is a side product in some of the above preparations of 2.[7,9] Ingold showed that the action of alcoholic sodium ethoxide on 3 gives 2, but no yield was reported.[11] Finally, Strauss and Voss[12] converted propiolic acid into 2 in 20% yield with anhydrous cupric sulfate in refluxing ethanol. Decarboxylation of the propiolic acid was responsible for the poor yield.

Results and Discussion

We have replaced the propiolic acid with 3 in order to avoid decarboxylation and have used a more active catalyst, copper(I) triflate (10 mol %), so that the reaction proceeds at room temperature. In this way an 86% yield of 2 is obtained, after treatment of the reaction mixture with sodium ethoxide to convert 4 into 2. When only 1 mol % of copper(I) triflate is used, the reaction yields 85% of 2 along with 9% of 4 after the mixture is stirred for 43 days at room temperature. Anhydrous cupric sulfate (10 mol %) in refluxing ethanol followed by an aqueous workup afforded 67% of 2, which was free of 4. No reaction was observed when the copper sulfate experiment was carried out at room temperature, nor was any observed with triflic acid or a mixture of cupric sulfate and triflic acid (all 10 mol %) at 23 °C. Boron trifluoride etherate, sulfuric acid, and potassium hydrogen sulfate all failed to catalyze the conversion of 3 to 2 in refluxing ethanol.

The formylation of 2 was carried out in dry ether with 1.2 equiv of NaH and 10 equiv of ethyl formate to yield 75% of 1. When carried out with 1.2 equiv of ethyl formate and sodium hydride, sodium dispersion, or potassium hydride, the condensation produced 49%, 39%, and 38% yields of 1, respectively. When 3 and ethyl formate (1–3 equiv) were added to a suspension of sodium ethoxide (1–2 equiv) in dry ether in an attempt to execute both steps (3 to 2 and 2 to 1) in the same flask, only 2 and 3 were detected. Panizzi[4] reported a 67% yield of 1 from 2 using sodium wire and 1.1 equiv of ethyl formate. Dyer reported an unspecified yield of the sodium salt of 1 from 2, ethyl formate, and powdered sodium from which 1 could not be purified completely, and that upon mild acid hydrolysis it "gave a mixture of unidentified oils".[13] The crude product from our procedure contains no impurities detected by ^{1}H NMR. The distillation of this compound is accompanied by substantial resinification and is not recommended for routine preparation. We have done it in order to be able to provide definitive spectral data.

Experimental Section

^{1}H NMR spectra were measured with a Varian T-60 spectrometer, UV spectra with a Perkin-Elmer 330 spectrometer, and IR spectra with a Perkin Elmer 597 spectrophotometer. GLC analyses were carrier out on a Hewlett-Packard 5880A chromatograph (using a 10 ft × $^{1}/_{8}$ in., 5% OV-101 on Chromosorb W-HP column) operated on a single ramp program of 10 °C/min from 45 to 155 °C.

Ethyl 3,3-Diethoxypropionate (2). A flame-dried, nitrogen-purged, 200-mL recovery flask containing a magnetic stirbar was charged with copper(I) triflate–benzene complex (4.50 g, 9.0 mmol; Strem) under argon in a drybox. Absolute ethanol (150 mL, sparged with argon for 1 h) was added by cannula to the septum-sealed flask. The resulting greenish-brown suspension was treated with 17.7 g (180 mmol; Aldrich) of ethyl propiolate, added dropwise by syringe over 1 h. The bright-yellow suspension was stirred under nitrogen at ambient temperature. Analysis of the reaction by GLC indicated that the starting ester was depleted after 4 days and approximately equal amounts of 2 and 4 were present. After another day there was no change; therefore the reaction was worked up. First it was treated with 55 mL of 0.4 M sodium ethoxide/ethanol and stirred for 10 min. Then 150 mL of water was added and the mixture was extracted with two 150-mL portions of dichloromethane. The combined organic phase was back-extracted with 50 mL of water and dried over anhydrous

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(1) (a) Part 3 of a series on New Copper Chemistry. For part 2, see Bertz, S. H. *Tetrahedron Lett.*, 21, 3151 (1980). (b) High School Summer Science Program of the Affirmative Action Center.

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sodium sulfate. The mixture was filtered through Celite and centrifuged to remove colloidal copper. The dichloromethane was removed under reduced pressure to yield 29.4 g (86%), which contained no impurities detected by GLC or ^1H NMR. Anal. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54. Found: C, 56.79; H, 9.72. Distillation of 28.1 g at 0.35 torr gave fractions of 14.7 g (bp 49-52 °C) and 9.1 g (bp 52-53 °C) for an 85% recovery. Anal. Found: C, 56.66; H, 9.53. **2**: IR (neat) 2982, 2937, 2900, 1735, 1445, 1373, 1310, 1190, 1110, 1060 cm^{-1}, ^1H NMR ($CDCl_3/Me_4Si$) δ 1.18 (t, J = 7 Hz, 6 H), 1.25 (t, J = 7 Hz, 3 H), 2.63 (d, J = 6 Hz, 2 H), 3.59 (q, J = 7 Hz, 2 H), 3.63 (q, J = 7 Hz, 2 H), 4.15 (q, J = 7 Hz, 2 H), 4.95 (t, J = 6 Hz, 1 H).

(Ethoxycarbonyl)malondialdehyde (1). To a flame-dried, 200-mL recovery flask was added 2.70 g (56 mmol; Aldrich) of 50% sodium hydride/oil dispersion. After the flask was purged with nitrogen, the oil was rinsed off with three 15-mL portions of ether; then 50 mL of fresh ether was added. A condenser was fitted to the flask under nitrogen, and the magnetically stirred slurry was cooled in an ice bath. Ethyl formate (34.8 g, 470 mmol; Aldrich) was added by syringe, followed by 8.84 g (46.5 mmol) of **2** dissolved in 25 mL of ether, added dropwise by syringe over 2 h. The reaction mixture was stirred for 1 day at 0 °C and then for 1 day at room temperature. (^1H NMR showed no improvement at the higher temperature.) It was poured into 100 mL of ice water and extracted with three 50-mL portions of ether, which were discarded. Acidification to pH 3 with 4.5 mL of concentrated HCl and extraction with three 50-mL portions of dichloromethane afforded (after drying the combined organic phase over anhydrous sodium sulfate and removal of solvent at reduced pressure) 5.10 g (75%) of **1**. Anal. Calcd for $C_6H_8O_4$: C, 50.00; H, 5.60. Found: C, 50.30; H, 5.72. The ^1H NMR spectrum was the same as that of distilled material. Distillation gave a 59% recovery, bp 30-32 °C (0.35 torr). Anal. Found: C, 49.70; H, 5.73. **1**: IR (neat) 3700-2500, 2986, 1700, 1645, 1580, 1240, 1103, 1015, 938, 763, 750 cm^{-1}; ^1H NMR ($CDCl_3/Me_4Si$) δ 1.30 (t, J = 7 Hz, 3 H), 4.30 (q, J = 7 Hz, 2 H), 9.13 (s, 2 H), 12.4 (br s, 1 H); UV (EtOH) λ_{max} 212 nm (ϵ 3500), 245 (6200), 263 (5400, sh).

Registry No. 1, 80370-42-9; 2, 10601-80-6; 3, 623-47-2; 4, 1001-26-9; copper(I) triflate, 42152-44-3.

Formaldehyde Semicarbazone

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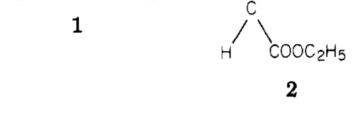
Our recent interest in the reactions of diazo compounds with azodicarbonamide (**1**)[2] has prompted us to examine the reaction between diazomethane and azodicarbonamide (**1**). Our initial studies of ethyl diazoacetate and **1** provided the *Z* isomer of the semicarbazone of glyoxylic acid (**2**; eq 1). We examined the reaction of diazomethane with **1** in order to initiate studies of the generality and ultimately the mechanism of this intriguing reaction. We now report that the product is formaldehyde semicarbazone and that this is the first time this derivative of formaldehyde has actually been prepared.

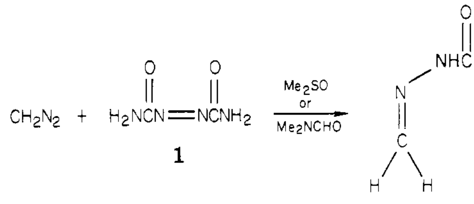


$$C_2H_5OC(=O)CHN_2 + H_2NC(=O)N{=}NC(=O)NH_2 \longrightarrow (H)(COOC_2H_5)C{=}NNHC(=O)NH_2 \qquad (1)$$

1 2

Results and Discussion

When a solution of diazomethane (substantial excess) is added to azodicarbonamide (**1**) in either Me_2SO or Me_2NCHO and the reaction mixture is allowed to stand overnight, a substance, mp 120-121 °C, is obtained after silica gel chromatography and recrystallization from ethanol. The properties of this substance, as described below, in addition to its formation in a reaction known to provide the semicarbazone skeleton, leave no doubt that it is the heretofore unknown formaldehyde semicarbazone (**3**; eq 2).



$$CH_2N_2 + H_2NC(=O)N{=}NC(=O)NH_2 \xrightarrow[Me_2NCHO]{Me_2SO\ \text{or}} H_2C{=}NNHC(=O)NH_2 \qquad (2)$$

1 3

The analyses and mass spectrum (M^+ at m/e 87) are consistent with the formula $C_2H_5N_3O$. Major peaks at m/e 43 and 44 represent cleavage of the molecule at the central C-N bond, and a peak at 60 represents loss of HCN, all consistent with the assigned semicarbazone structure.[3] The ^1H NMR spectrum (Me_2SO-d_6) shows an AB double doublet (CH_2) at δ 6.8 and 6.1 with $^2J_{HH}$ = 12 Hz, a broad singlet (NH_2) at δ 6.2 which overlaps one of the peaks centered at δ 6.1, and a broad singlet at δ 10.0 (NH). The ^{13}C NMR spectrum shows two peaks at 156.7 ppm ($>C{=}O$) and 130.4 ppm ($CH_2{=}$; relative to Me_4Si). These NMR resonances and assignments are completely consistent with those of semicarbazones previously reported.[2,4,5] For example, acetaldehyde semicarbazone shows the CH resonances (^1H NMR spectrum) at δ 7.00 and 6.47 (for the cis and trans isomers), ethyl glyoxylate semicarbazone shows the NH_2 protons at δ 6.55 and the NH proton at δ 10.95, and isobutyraldehyde and ethyl glyoxylate semicarbazones show the $>C{=}O$ carbon (^{13}C NMR spectrum) at 150-156 ppm and the Shiff base carbon ($>C{=}N-$) at 130 ppm for the latter and 159 ppm for the former. This apparent large difference between a $CH_2{=}N$ carbon and a monosubstituted *i*-PrCH=N carbon is reasonable, since it is known that terminal CH_2 vinyl carbon atoms absorb 10-40 ppm to higher field than substituted vinyl carbon atoms.[6]

The UV spectrum of **3** [λ_{max} (CH_3CN) 227 nm (log ϵ 3.73)] is consistent with those of other semicarbazones,[7] such as acetone semicarbazone [λ_{max} (CH_3CN) 223 nm (log ϵ 4.11)]. Finally, the infrared spectrum (KBr disk) [$\bar{\nu}$ 3310, 3260, 3200, 3090, 1660, and 1581 cm^{-1}] is also consistent with the assigned structure.[8]

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