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Addition of Lithiated Acetonitrile to β-Substituted Methylenemalonates. Revision and Correction

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Summary. In the context of an attempt to prepare the 2-cyanoethylenemalonates **1** and **3**, the addition of lithiated acetonitrile to the β-substituted methylenemalonates **2**, **4**, **6**, and **8** was performed. Starting with **2** and **4**, the dimers **5** and **10** were obtained instead of the expected addition products **1** and **3**. The dimer **5** was formed exclusively from the adducts **7** and **9**, obtained by addition of lithioacetonitrile to **6** and **8**, upon elimination.

Keywords. Lithiated acetonitrile; β-Substituted methylenemalonates; Dimerization of 2-cyanoethylenemalonates.

Addition von lithiiertem Acetonitril an β-substituierte Methylenmalonate. Neubearbeitung und Korrektur

Zusammenfassung. In der Absicht, die 2-Cyanoethylenmalonate **1** und **3** herzustellen, wurde die Addition von Acetonitril an die β-substituierten Methylenmalonate **2**, **4**, **6** und **8** durchgeführt. Im Fall von **2** und **4** bildeten sich an Stelle der gewünschten Verbindungen **1** bzw. **3** deren Dimere **5** bzw. **10**. Bei der Reaktion von **6** und **8** konnten die Additionsprodukte **7** und **9** isoliert werden; beim Versuch der Eliminierung wurde jedoch ausschließlich das Dimere **5** gebildet.

Introduction

In the course of a research program focusing on the synthesis of functionalized decahydro isoquinolines, we were interested in dimethyl 2-cyanoethylenemalonate **1** as a potential dienophile for *Diels-Alder* reactions. The preparation of **1** has already been described by *Demir et al*. in 1991 *via* addition of deprotonated acetonitrile to dimethyl phenylmethylaminomethylenemalonate **2** (Fig. 1) [1].

In our attempts to use this procedure for the synthesis of the homologous diethyl 2-cyanoethylenemalonate **3**, we started from diethyl phenylmethylaminomethylenemalonate **4** which was available in our laboratory. Instead of the addition product **3**, however, we isolated the dimer **5**.

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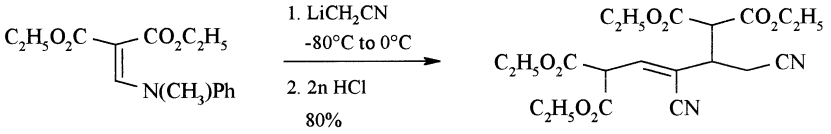
1 R = CH_3 **2** R = CH_3

3 R = C_2H_5 **4** R = C_2H_5 **Fig. 1**

Results and Discussion

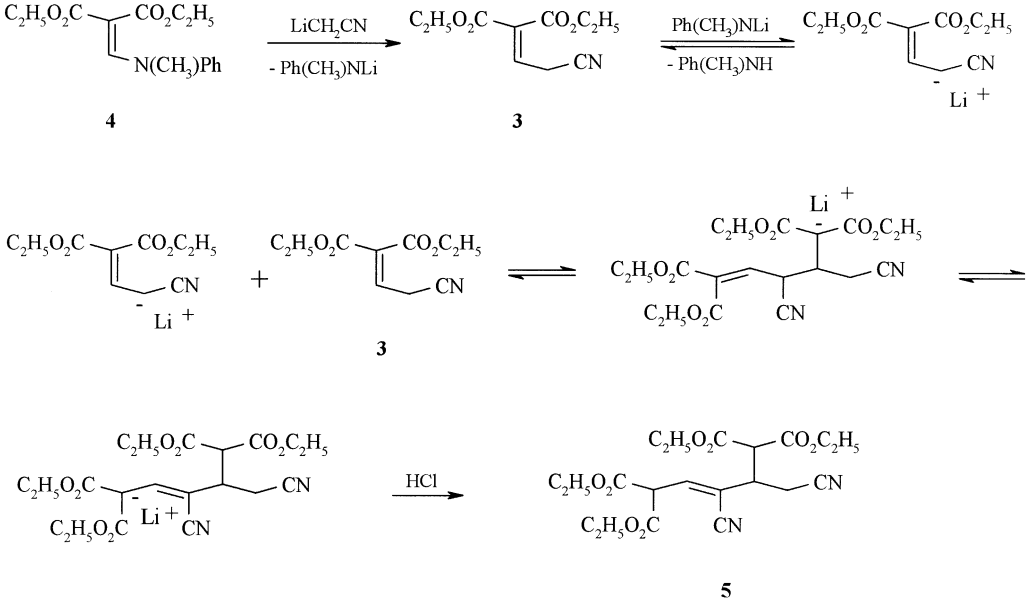
Following the literature, we tried to deprotonate acetonitrile with sodium hydride in *THF* at room temperature [1]. However, no evolution of hydrogen could be detected and no reaction with **4** occured. Modifying the procedure, we used *n*-BuLi for the deprotonation at −80°C [2], but after addition of **4** not the expected product **3** but the dimer **5** was obtained in good yield (Scheme 1).



4 **5**

Scheme 1

The formation of **5** can be explained by a base induced dimerization (*e.g.* with lithium N-methylanilide) of the primary product **3** as outlined in Scheme 2.



Scheme 2

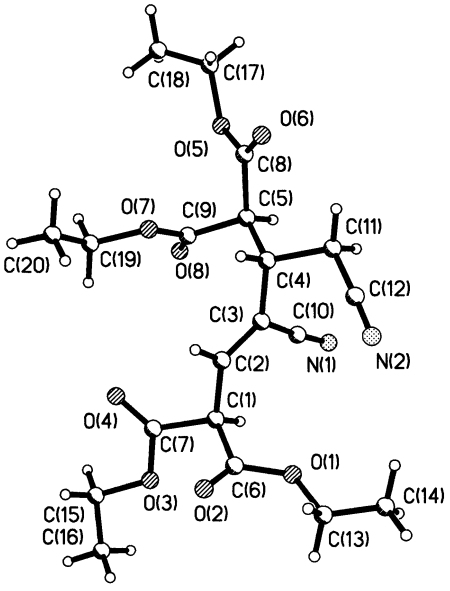
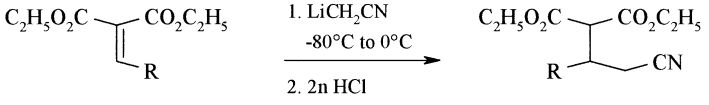


Fig. 2

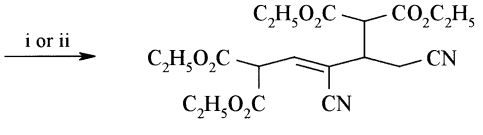
Although we had some evidence for the proposed structure from NMR spectroscopy, the constitution as well as the stereochemistry of **5** was finally confirmed by X-ray diffraction analysis (Fig. 2) [3]. It is interesting to note that the double bond is conjugated to the nitrile group and not to the two ester functionalities. An attempt to shift the double bond with sodium ethanolate in ethanol failed, showing that the given constitution is in fact the thermodynamic more stable one.

As a consequence of these observations we tried to avoid elimination under basic conditions. Thus, we added acetonitrile to the commercially available diethyl ethoxymethylenemalonate **6**, and the stable adduct **7** was isolated in good yield. However, our attempt to obtain **3** by acid catalyzed elimination of ethanol was not successful: again the dimer **5** was formed instead of **3** (Scheme 3).



6 R = OC_2H_5 **7** R = OC_2H_5 82%

8 R = SPh **9** R = SPh 72%



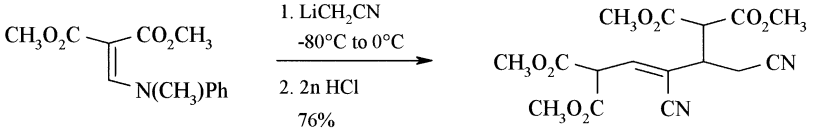
5

i: 7 and CH_3SO_3H, RT 7h, 70%; ii: **9** and 1.0 eq. m-CPBA, 84%

Scheme 3

Addition of acetonitrile to diethyl phenylthiomethylenemalonate **8** [4] yielded **9** which after oxidation with peracids should be able to eliminate phenylsulfinic acid under very mild conditions. However, after oxidation of **9** with one equivalent of *m-CPBA*, the dimer **5** was formed already during the chromatographic purification of the intermediate (Scheme 3).

In a last attempt we tried now to reproduce exactly the published procedure [1] for the preparation of **1** starting with the originally used dimethyl malonate **2** [5]. As already expected, only the dimeric product **10** was again isolated (Scheme 4).



2 **10**

Scheme 4

As a consequence, we have shown that **1** respectively **3** are unstable under basic as well as under acidic conditions. It therefore seems very unlikely that **1** was really isolated by *Demir et al.* [1].

Experimental

Melting points were determined on a Kofler apparatus and are not corrected. All column chromatographic purifications were accomplished on silica gel 60 (Merck).

NMR spectra were recorded on a Bruker AC 200 FT-NMR spectrometer and are expressed in δ values (ppm) downfield to *TMS* which was used as an internal standard. Significant ^{1}H NMR data are tabulated in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; b, broad), coupling constant(s) in Hz, number of protons, and assignments.

General procedure for the addition of acetonitrile

Under nitrogen, a solution of 7.21 mmol of *n*-BuLi in hexane was added to 7 ml of dry *THF* cooled below -40°C by a syringe. Then, a solution of 7.21 mmol of dry acetonitrile in 4 ml of dry *THF* was added over a period of 5 minutes, keeping the temperature between -80 and -70°C. A white suspension was formed. After the addition, the temperature was allowed to rise to -60°C. The suspension was cooled again to -80°C, and a solution of 7.21 mmol of methylenemalonate **2**, **4**, **6**, or **8** in 7 ml of dry *THF* was added quickly. The temperature of the homogeneous solution was allowed to rise to 0°C and the mixture was quenched with 2 *N* HCl and extracted twice with diethyl ether. The combined organic phases were washed with sat. $NaHCO_3$, dried over Na_2SO_4, evaporated *in vacuo*, and the crude product was further purified by recrystallization, destillation, or chromatography.

Diethyl E-4-cyano-5-cyanomethyl-2,6-bis(ethoxycarbonyl)-3-heptendioic acid (**5**)

5 was recrystallized from ethanol to afford 1.22 g (80%) colorless crystals.

M.p.: 70–72°C; ^{1}H NMR ($CDCl_3$): $\delta = 1.20$–1.35 (m, 12H, OCH_2CH_3), 2.72 (dd, $J = 17$ Hz, $J = 9.5$ Hz, 1H, CH_2CN), 2.92 (dd, $J = 17$ Hz, $J = 4$ Hz, 1H, CH_2CN), 3.45 (ddd, $J = 9.5$ Hz, $J = 9.5$ Hz, $J = 4$ Hz, 1H, H-5), 3.63 (d, $J = 9.5$ Hz, 1H, H-6), 4.15–4.30 (m, 8H, OCH_2CH_3), 4.55 (d, $J = 10$

Hz, 1H, H-2), 6.78 (d, $J = 10$ Hz, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.5$ (q, OCH_2CH_3), 13.6 (q, OCH_2CH_3), 19.8 (t, CH_2CN), 40.1 (d, C-5), 53.6 (d, C-2*), 54.1 (d, C-6*), 62.2 (t, OCH_2CH_3), 62.3 (t, OCH_2CH_3), 62.4 (t, OCH_2CH_3), 62.5 (t, OCH_2CH_3), 113.5 (s, C-4*), 115.9 (s, CN*), 116.7 (s, CN*), 142.3 (d, C-3), 164.9 (s, CO), 165.0 (s, CO), 165.6 (s, CO), 166.0 (s, CO) ppm; $C_{20}H_{26}N_2O_8$ (422.43); calcd.: C 56.87, H 6.20, N 6.63; found: C 56.97, H 6.19, N 6.56.

Diethyl (1-ethoxy-2-cyanoethyl)propandioic acid (**7**)

7 was destilled bulb to bulb (Büchi GKR-51 apparatus, 150°C, 0.02 mbar) to obtain 82% of a colorless liquid.

^{1}H NMR ($CDCl_3$): $\delta = 1.12$–1.35 (m, 9H, OCH_2CH_3), 2.70–2.92 (m, 2H, CH_2CN), 3.50–3.85 (m, 3H, OCH_2CH_3 + CHCOOEt), 4.10–4.30 (m, 5H, $COOCH_2CH_3$ + CHOEt) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.8$ (q, $COOCH_2CH_3$), 13.9 (q, $COOCH_2CH_3$), 15.0 (q, OCH_2CH_3), 21.5 (t, CH_2CN), 55.6 (d, CHCOOEt), 61.7 (t, $COOCH_2CH_3$), 61.8 (t, $COOCH_2CH_3$), 66.6 (t, OCH_2CH_3), 73.3 (d, EtOCH), 116.9 (s, CN), 166.4 (s, CO), 166.5 (s, CO) ppm; $C_{12}H_{19}NO_8$ (257.29); calcd.: C 56.02, H 7.44, N 5.44; found: C 56.20, H 7.50, N 5.15.

Diethyl (1-phenylthio-2-cyanoethyl)propandioic acid (**9**)

9 was destilled bulb to bulb (Büchi GKR-51 apparatus, 215°C, 0.02 mbar) to obtain 72% of a pale yellow liquid.

^{1}H NMR ($CDCl_3$): $\delta = 1.25$–1.38 (m, 6H, OCH_2CH_3), 2.72–2.98 (m, 2H, CH_2CN), 3.68–3.85 (m, 2H, PhSCH + CHCOOEt), 4.20–4.35 (m, 4H, OCH_2CH_3), 7.30–7.42 (m, 3H, H-2/6 + H-4), 7.52–7.65 (m, 2H, H-3/5) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 13.8$ (q, OCH_2CH_3), 21.9 (t, CH_2CN), 44.4 (d, PhSCH), 55.1 (d, CHCOOEt), 62.0 (t, OCH_2CH_3), 116.8 (s, CN), 128.9 (d, C-4), 129.3 (d, C-3/5*), 131.2 (s, C-1), 134.2 (d, C-2/6*), 166.4 (s, CO) ppm; $C_{16}H_{19}NO_4S$ (321.40); calcd.: C 59.79, H 5.96, N 4.36; found: C 59.67, H 6.02, N 4.35.

Dimethyl E-4-cyano-5-cyanomethyl-2,6-bis(methoxycarbonyl)-3-heptendioic acid (**10**)

10 was chromatographed on 25 g of silica gel using light petroleum and ethyl acetate (2:1) yielding 76% of a colorless oil.

^{1}H NMR ($CDCl_3$): $\delta = 2.75$ (dd, $J = 17$ Hz, $J = 9.5$ Hz, 1H, CH_2CN), 2.95 (dd, $J = 17$ Hz, $J = 4$ Hz, 1H, CH_2CN), 3.51 (ddd, $J = 9.5$ Hz, $J = 9.5$ Hz, $J = 4$ Hz, 1H, H-5), 3.70–3.85 (m, 13H), 4.58 (d, $J = 10$ Hz, 1H, H-2), 6.70. (d, $J = 10$ Hz, 1H, H-3) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 19.7$ (t, CH_2CN), 40.1 (d, C-5) 52.8, 52.9, 53.0, 53.1, 53.3, 53.5, 113.3 (s, C-4*), 115.9 (s, CN*), 116.7 (s, CN*), 142.1 (d, C-3), 165.3 (s, CO), 165.4 (s, CO), 166.0 (s, CO), 166.4 (s, CO) ppm; $C_{16}H_{18}N_2O_8$ (366.33); calcd.: C 52.46, H 4.95, N 7.65; found: C 52.73, H 4.84, N 7.61.

Elimination of ethanol from **7**

A solution of 0.50 g (1.94 mmol) **7** in 2 ml methanesulfonic acid was stirred for 7 h at room temperature. The mixture was diluted with diethyl ether and washed with sat. $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was recrystallized from ethanol to afford 0.29 g (70%) of **5**; m.p.: 70–72°C.

Oxidation of **9** *with m-CPBA*

A solution of 0.36 g (1.24 mmol) *m-CPBA* in 5 ml CH_2Cl_2 was added slowly to an ice-cooled solution of 0.40 g (1.24 mmol) **9** in 4 ml of CH_2Cl_2. After 30 min the mixture was diluted with 20 ml

of CH_2Cl_2 and washed twice with sat. $NaHCO_3$ solution. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was chromatographed on 12 g of silica gel using light petroleum and ethyl acetate (2:1) giving 0.22 g (84%) of **5** as colorless crystals; m.p.: 70–72°C.

X-Ray structure determination for **5**

Crystal data: $C_{20}H_{26}N_2O_8$, $M = 422.43$, monoclinic, space group $P2_1/c$ (No. 14), $a = 9.184(3)$, $b = 15.150(4)$, $c = 18.084(5)$ Å, $\beta = 98.51(4)°$, $V = 2324.2(12)$ Å^3, $Z = 4$, $D_X = 1.207$ g · cm^{-3}. Data were measured on a Philips PW 1100 diffractometer with graphite monochromated MoK_α radiation. A total of 3083 reflexions (830 with $I > 2\sigma(I)$) were collected using the ω-2θ scan technique to a maximum ω value of 22°. The structure was solved by direct methods and refined by full-matrix least squares on F^2 with all non-hydrogen atoms anisotropic [6]. Final R_1 for 791 $F > 4\sigma(F) = 0.092$, wR_2 for all data (2828 reflexions) = 0.186. The final ΔF synthesis showed no peaks outside the range of + 0.24 to −0.20 eÅ^{-3}.

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