The Structure of the Product Formed by Condensation of Malononitrile with Dialkyl Acetone-1,3-dicarboxylates

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Dedicated to Professor Peter Stanetty, Vienna University of Technology, on the occasion of his 65th birthday

By the condensation of malononitrile (**1**) with dialkyl acetone-1,3-dicarboxylates **2a**, **b** alkyl (3-cyano-6-alkoxy-2-oxo-1,2-dihydropyridin-4-yl)acetates **6a**, **b** are formed in contrast to an earlier report according to which diethyl 3-(dicyanomethylene)glutarate **3b** was obtained in the reaction of **1** and **2a**. Compounds **6a**, **b** were transformed with DMFDMA into the corresponding (*E*)-alkyl 2-(3-cyano-6-alkoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoates **7a**, **b**. The structures of **6a** and **7a** were confirmed by X-ray structural analysis.

Key words: Enamino Esters, Malononitrile, Dialkyl Acetone-1,3-dicarboxylates, X-Ray Structures

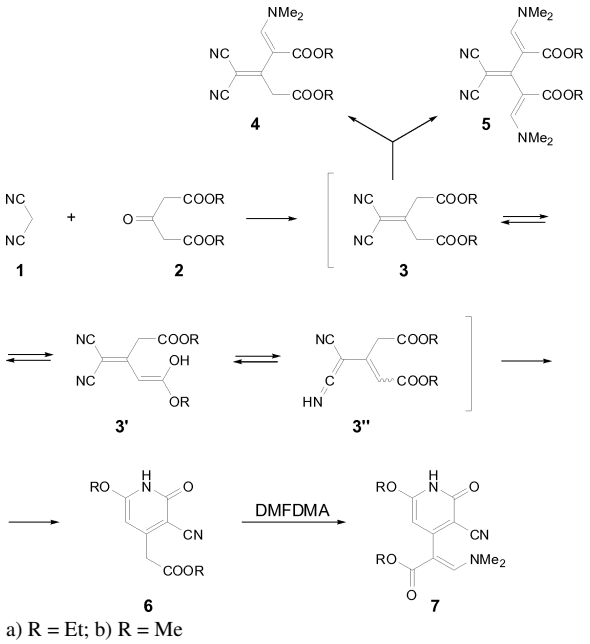
Introduction

It has been reported that the reaction of malononitrile (**1**) with diethyl acetone-1,3-dicarboxylate (**2a**) gave the corresponding 3-(dicyanomethylene)glutarate (**3a**) [1]. This seems to be an excellent starting compound for the preparation of diethyl 2-(dimethylaminomethylene)-3-(dicyanomethylene)glutarate (**4**) and diethyl 2,4-bis(dimethylaminomethylene)-3-(dicyanomethylene)glutarate (**5**) as polyfunctional enamino esters in connection with our interest in the synthesis of various heterocyclic systems [2, 3] and natural products [4].

Results and Discussion

When we repeated the above mentioned experiment, we isolated a compound showing identical melting point and giving the elemental analysis for C, H, and N corresponding to the molecular formula $C_{12}H_{14}N_2O_4$. No spectral data were given in the early report. The ^{1}H NMR spectrum of our product showed two different ethoxy groups: two triplets at δ = 1.31 and 1.49 ppm for two CH_3 groups and two overlapping quartets at δ = 4.26 ppm for two CH_2 groups, a singlet at δ = 3.75 ppm for another CH_2 group, and a singlet at δ = 5.88 ppm for a CH=C structural element. In the IR spectrum a single peak at ν = 2216 cm^{-1} for the CN group was observed. Similarly, the compound obtained from malononitrile (**1**) and dimethyl acetone-1,3-dicarboxylate (**2b**) gave a correct microanalysis for C, H, and N and a molecular ion peak in the HRMS corresponding to $C_{10}H_{10}N_2O_4$. The ^{1}H NMR spectrum showed two singlets at δ = 3.66 and 3.88 ppm for two CH_3O groups, a singlet at δ = 3.80 ppm for a CH_2 group, a singlet at δ = 6.35 ppm for a CH=C structural element, and a broad singlet at δ = 12.64 ppm for an exchangeable N*H* group. In the IR spectrum a single peak at ν = 2218 cm^{-1} for the CN group was observed. On the basis of this information one can conclude that the condensation product must exist in a non-symmetrical form. The isomer **3** is therefore excluded, and the non-symmetrical tautomeric forms **3′** and **3″** seem to be highly improbable due to their suspected reactivity (Scheme 1).

When the condensation product was treated with *N,N*-dimethylformamide dimethylacetal (DMFDMA) in dichloromethane at r. t. for 12 h, a compound was isolated in 76 % yield, for which the microanalysis and the HRMS correspond to the molecular formula $C_{15}H_{19}N_3O_4$. The ^{1}H NMR spectrum shows two triplets at δ = 1.14 and 1.31 ppm and two quartets at δ = 4.02 and 4.27 ppm for two OEt groups, a broad



a) R = Et; b) R = Me

Scheme 1.

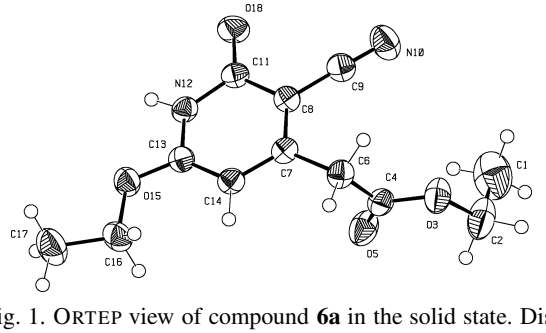


Fig. 1. ORTEP view of compound **6a** in the solid state. Displacement ellipsoids are drawn at the 50 % probability level; H atoms are drawn as spheres of arbitrary radii.

singlet at δ = 2.81 ppm for an NMe_2 group, two singlets at δ = 5.98 and 7.57 ppm for protons attached to the double bond CH=C, and a broad singlet at δ = 12.31 ppm for the NH group. These data suggest that by the condensation of malononitrile (**1**) with dialkyl acetone-1,3-dicarboxylates **2a**, **b** the corresponding dialkyl 2-(dicyanomethylene)glutarates **3** have not been formed, instead the cyclic alkyl (3-cyano-6-alkoxy)-2-oxo-1,2-dihydropyridin-4-yl)acetates **6a**, **b** were produced, which upon treatment with DMFDMA gave the corresponding alkyl (*E*)-2-(3-cyano-6-alkoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoates **7a**, **b**. The structures of compounds **6a** and **7a** were confirmed by X-ray analysis (Scheme 1, Figs. 1 and 2, Table 1).

Table 1. Crystal data and numbers pertinent to data collection and structure refinement for **6a** and **7a**.

	6a	**7a**
Formula	$C_{12}H_{14}N_2O_4$	$C_{15}H_{19}N_3O_4$
Formula weight	250.25	305.33
Color of crystal	colorless	yellowish
Shape of crystal	plate	plate
Dimensions, mm^3	0.40×0.25×0.025	0.38×0.20×0.08
Crystal system	orthorhombic	monoclinic
Space group	*Pnaa*	$P2_1/c$
a, Å	8.0028(2)	9.2577(2)
b, Å	14.3093(3)	14.9823(2)
c, Å	21.8945(5)	11.8187(2)
β, deg	90	97.0444(8)
V, $Å^3$	2507.24(10)	1626.90(5)
Z	8	4
ρ, Mg m^{-3}	1.33	1.25
μ, mm^{-1}	0.1	0.1
Temperature, K	293(1)	293(1)
Radiation; wavelength, Å	0.71073	0.71073
θ_{max}, deg	27.49	27.49
No. of integr. / indep. refl.	21154 / 3273	26914 / 3864
R_{int}	0.036	0.042
No. of obs. refl. [$I \geq 2.0\ \sigma(I)$]	2212	2741
No. of ref. param.	163	199
Final R and R_w	0.042 / 0.035	0.048 / 0.049
$(\Delta/\sigma)_{max}$	0.00118	0.00017
$\Delta\rho_{min\,/\,max}$, e $Å^{-3}$	−0.21 / 0.20	−0.30 / 0.30

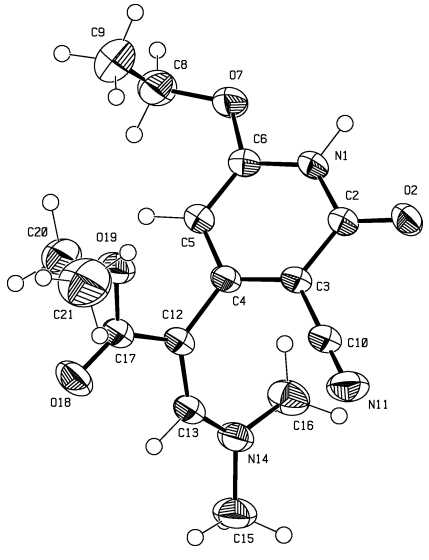


Fig. 2. ORTEP view of compound **7a** in the solid state. Displacement ellipsoids are drawn at the 50 % probability level; H atoms are drawn as spheres of arbitrary radii.

Conclusion

In the reaction of malononitrile (**1**) with dialkyl acetone-1,3-dicarboxylates **2a**, **b** alkyl (3-cyano-6-alkoxy-2-oxo-1,2-dihydropyridin-4-yl)acetates **6a**, **b**

are formed in contrast to an earlier report according to which diethyl 3-(dicyanomethylene)glutarate (**3a**) was produced in the reaction of **1** and **2a**. Compounds **6a**, **b** were transformed with DMFDMA into the corresponding alkyl 2-(3-cyano-6-alkoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoates **7a**, **b**. The structures of **6a** and **7a** have been confirmed by X-ray structural analysis.

Experimental Section

Melting points were determined on a Kofler micro hot stage. The ^{1}H NMR spectra were obtained on a Bruker Avance DPX 300 instrument at 300 MHz using [D$_6$]DMSO and $CDCl_3$ as solvents with TMS as the internal standard. Mass spectra were recorded on an AutoSpecQ spectrometer, IR spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN analyzer 2400 II.

*Ethyl (3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-acetate (**6a**)*

The preparation of this compound is essentially the same as described in the literature for preparation of diethyl 3-(dicyanomethylene)glutarate (**3a**) [1].

Malononitrile (**1**; 0.66 g, 0.01 mol) and diethyl acetone-1,3-dicarboxylate (**2a**; 2.02 g, 0.01 mol) were dissolved in ethanol (20 mL). Diethylamine (0.2 mL) was added, and the mixture was left at r. t. for 20 d. The volatile components were evaporated *in vacuo*. The oily residue crystallized by standing in a refrigerator for several hours. The crude product was recrystallized from toluene to give **6a**; 81 % yield (2.05 g). – M. p. 170 – 173 °C (ref. [1]: 166 °C). – IR (KBr): ν = 2216 cm^{-1} (CN). – ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.31 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.49 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.75 (s, 2H, CH_2COOEt), 4.26 (2 overlapped q, 4H, J = 7.2 Hz, 2 × OCH_2CH_3), 5.88 ppm (s, 1H, CH=C), NH exchanged. – HRMS ((+)-ESI): m/z = 250.0954 (calcd. $C_{12}H_{14}N_2O_4$ for 250.0954, [M]$^+$). – $C_{12}H_{14}N_2O_4$.(250.3): calcd. C 57.59, H 5.64, N 11.19; found C 57.75, H 5.69, N 11.16.

*Methyl (3-cyano-6-methoxy-2-oxo-1,2-dihydropyridin-4-yl)-acetate (**6b**)*

This compound was prepared from **1** (0.66 g, 0.01 mol) and **2b** (1.74 g, 0.01 mol), following the procedure described for **6a**; 87 % yield (1.95 g). – M. p. 203 – 205 °C (from MeOH/H_2O). – IR (KBr): ν = 2218 cm^{-1} (CN). – ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 3.66 (s, 3H, OCH_3), 3.80 (s, 2H, CH_2COOMe), 3.88 (s, 3H, OCH_3), 6.35 (br. s 1H, CH=C), 12.64 ppm (br. s, 1H, NH). – HRMS ((+)-ESI): m/z = 223.0719 (calcd. 223.0717 for $C_{10}H_{11}N_2O_4$, [M-H]$^+$). – $C_{10}H_{10}N_2O_4$.(222.2): calcd. C 54.05, H 4.54, N 12.61; found C 54.10, H 4.40, N 12.66.

*(E)-Ethyl 2-(3-cyano-6-ethoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoate (**7a**)*

To a solution of **6a** (3.0 g, 12 mmol) in dichloromethane (10 mL) *N,N*-dimethylformamide dimethylacetal (1.70 mL, 13.2 mmol) was added dropwise. The mixture was stirred overnight at r. t. The volatile components were evaporated *in vacuo*. The oily residue solidified by addition of toluene (10 mL). The crude product was collected by filtration and recrystallized from toluene to give **7a** as yellow crystals, 76 % yield (2.78 g). – M. p. 165 – 168 °C. – IR (KBr): ν = 2220 cm^{-1} (CN). – ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 1.14 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.31 (t, 3H, J = 6.9 Hz, OCH_2CH_3), 2.81 (br. s, 6H, NMe_2), 4.02 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 4.27 (2H, J = 6.9 Hz, OCH_2CH_3), 5.98 (br. s, 1H, CH=C), 7.57 (br. s, 1H, CH=C), 12.31 ppm (br. s, 1H, NH). – HRMS ((+)-ESI): m/z = 306.1380 (calcd. 305.1376 for $C_{15}H_{19}N_3O_4$, [M]$^+$). – $C_{15}H_{19}N_3O_4$.(305.3): calcd. C 59.01, H 6.27, N 13.76; found C 57.07, H 6.31, N 13.73.

*(E)-Methyl 2-(3-cyano-6-methoxy-2-oxo-1,2-dihydropyridin-4-yl)-3-(dimethylamino)propenoate (**7b**)*

This compound was prepared as described for **7a** from **6b** (2.44 g, 11 mmol) and DMFDMA (1.43 g, 12 mmol); yellow crystals; 52 % yield (1.60 g). – M. p. 216 – 220 °C (from EtOH/pyridine). – IR (KBr): ν = 2217 cm^{-1} (CN). – ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 2.81 (s, 6H, NMe_2), 3.54 (s, 3H, O*Me*), 3.87 (s, 3H, O*Me*), 6.05 (br. s, 1H, CH=C), 7.58 (s, 1H, CH=C), 12.41 ppm (br. s, 1H, NH). – HRMS ((+)-ESI): m/z = 300.0960 (calcd. 300.0960 for $C_{13}H_{15}N_3O_4Na$, [M+Na]$^+$).

*X-Ray structure analysis for compounds **6a** and **7a***

Single-crystal X-ray diffraction data of compounds **6a** and **7a** were collected at r. t. on a Nonius Kappa CCD diffractometer using the Nonius COLLECT Software [5]. DENZO and SCALEPACK [6] were used for indexing and scaling of the data, and the structures were solved by means of SIR97 [7]. Refinement was done using the XTAL3.4 [8] program package. The crystal structures were refined on F^2 using full-matrix least-squares procedures. The non-hydrogen atoms were refined anisotropically, while the positions of the hydrogen atoms were calculated geometrically, and their positional and isotropic atomic displacement parameters were not refined. Absorption correction was not necessary. Regina weighting scheme [9] was used in both cases. ORTEP-III [10] drawings of the content of the asymmetric unit showing the crystallographic atom labeling scheme for compounds **6** and **7** are presented in Figs. 1 and 2, respectively. Crystal

data and details concerning data collection and refinement for compounds **6a** and **7a** are summarized in Table 1.

CCDC 761671 (**6a**) and 761672 (**7a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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