SHORT PAPER

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Studies on isocyanides and related compounds. *N,N′*-disubstituted 2-cyanoacetoxy-2-cyanomethylmalondiamides from an unusual reaction between isocyanides and cyanoacetic acid†

Stefano Marcaccini,*[a] Roberto Pepino,[a] Paola Paoli,[b] Patrizia Rossi[b] and Tomás Torroba[c]

[a]*Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, via Gino Capponi 9, I-50121 Firenze, Italy*

[b]*Dipartimento di Energetica "Sergio Stecco", Università di Firenze, via S. Marta 3, I-50139 Firenze, Italy*

[c]*Departamento de Química, Facultad de Ciencias, Universidad de Burgos, E-09001 Burgos, Spain*

The reaction between cyanoacetic acid **1** and isocyanides **2** afforded the unexpected *N,N′*-disubstituted 2-cyanoacetoxy-2-cyanomethylmalondiamides **3** which were easily cleaved in very mild conditions to the corresponding 2-hydroxy derivatives **4**. The structure of compound **4a** was confirmed by X-ray analysis. A hypothesis for the mechanism of formation of compounds **3** is presented.

Keywords: isocyanides, cyanoacetic acid

The activating effect of isocyanides in the esterification and amidation of carboxylic acids is well-documented.[1] In some cases protic or Lewis acids can promote α-addition reactions on isocyanides.[2] With regard to the reactivity of isocyanides towards acids without additional reagents, only a small number of interesting reactions are known.[3]

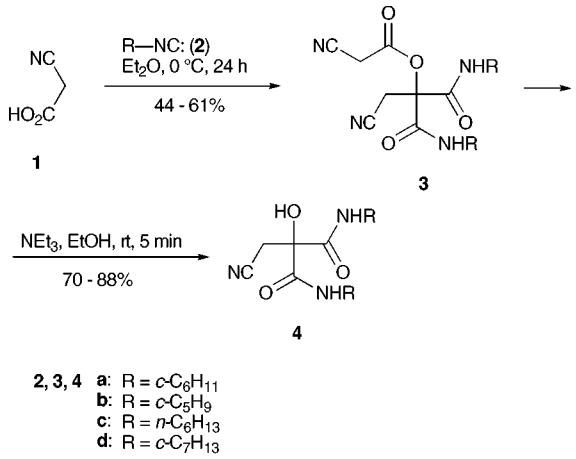
In our continuing studies on the reactivity of isocyanides,[4] we reported that arylglyoxals[5] and arylglyoxal anils[6] react with cyanoacetic acid and isocyanides to give the expected three- and four-component condensation products. Now we have found that cyanoacetic acid reacts with isocyanides even in the absence of carbonyl compounds.

The reaction between cyanoacetic acid **1** and cyclohexyl isocyanide **2a** in Et_2O afforded a crystalline product with m.p. 162–164°C which was recognised as *N,N′*-dicyclohexyl-2-cyanoacethoxy-2-cyanomethylmalonic acid diamide **3a** on the basis of its analytical, IR, ^{1}H NMR, and mass spectral data. Upon treatment with ethanolic NEt_3, compound **3a** underwent a quick cleavage, to give *N,N′*-dicyclohexyl-2-cyanomethyl-2-hydroxymalonic acid diamide **4a**.[1] Evidence for the assigned structure **4a** was provided by IR, ^{1}H NMR, and X-ray analysis. An analogous behaviour was found by reacting **1** with cyclopentyl isocyanide **2b**, *n*-hexyl isocyanide **2c**, and cycloheptyl isocyanide **2d** (Scheme 1).

A possible reaction pathway is reported in Scheme 2.

The key step is the formation of cyanoketene **5**, which appears to be reasonable on the basis of the known "dehydrating" character of isocyanides.[1] The formation of the adduct **7** is in agreement with the high electrophilic character of ketenes. The step **7** → **8** is an usual Passerini reaction. The elimination of cyanoketene from the adduct **8** leads to the formation of the final product **3** and ensures the cyclic continuation of the reaction.

Although the yields are only fair, the reactivity of isocyanides towards cyanoacetic acid seems to be noteworthy, since it provides, by an experimentally simple procedure, a series of compounds which appear not to be easily available from other synthetic routes. Furthermore, the variety of the functional groups in **3** and **4** allows us to consider these compounds as useful for synthetic purposes.



Scheme 1

Experimental

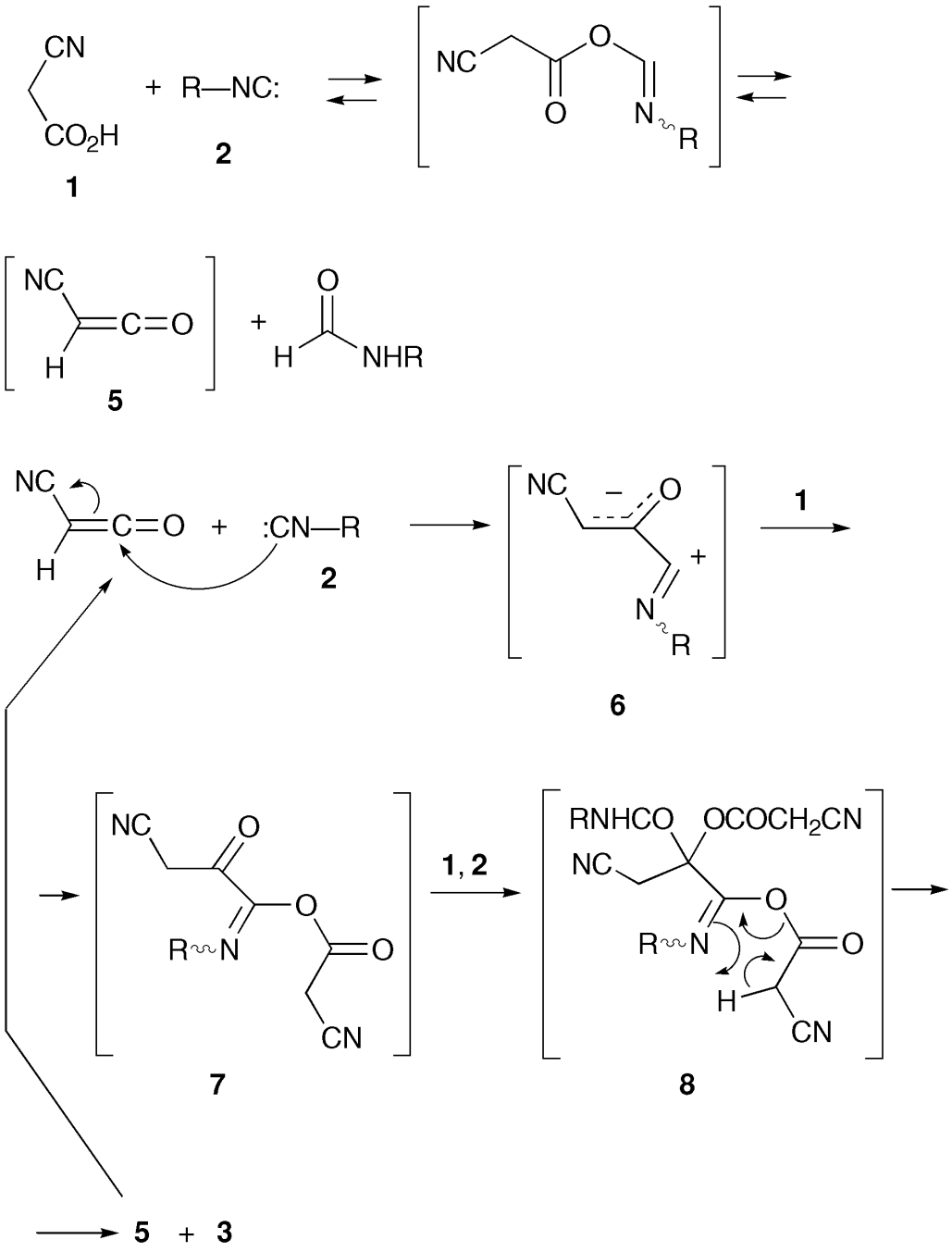
Cyanoacetic acid **1** and cyclohexyl isocyanide (**2a**) were purchased from Aldrich. Cyclopentyl isocyanide **2b**,[5] *n*-hexyl isocyanide **2c**,[7] and cycloheptyl isocyanide **2d**[8] were prepared according to literature procedures. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer, and ^{1}H NMR spectra on a Varian Gemini 200 spectrometer. The mass spectrum of compound **3a** was measured on a Carlo Erba QMD 1000 apparatus, operating with electron impact at 70 eV. Elemental analyses were performed with a Perkin-Elmer 240 Elemental Analyzer.

Reaction between cyanoacetic acid **1** *and isocyanides* **2**: Isocyanide **2** (49 mmol) was added to a well-stirred saturated solution of cyanoacetic acid **1** (4.34 g, 51 mmol) in Et_2O at 0°C. The resulting mixture was allowed to stand at 0°C for 24 h and then filtered to give the crude **3**.

2-Cyanoacetoxy-2-cyanomethyl-N,N′-dicyclohexylmalondiamide **3a**: Colourless crystals (5.80 g, 61%); m.p. 162–164°C (from EtOH); IR (KBr/cm^{-1}): 3318 (NH), 2266 (CN), 1778 (CO), 1672 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.08–1.96 (m, 20 H cyclohexane), 3.41 (s, 2 H, CH_2CN), 3.62–3.84 (m, 2 H, 1-H cyclohexane), 4.24 (s, 2 H, $COCH_2CN$), 7.07 (d, *J* = 7.3 Hz, 2 H, NH); *m/z* 389 (M^++1, 5%), 322

* To receive any correspondence. E-mail:marc@chimorg.unifi.it

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M)*.



Scheme 2

(8), 307 (10), 196 (100), 113 (71), 98 (40), 83 (48). $C_{20}H_{28}N_4O_4$ calcd: C, 61.84; H, 7.27; N, 14.42; found: C, 62.12; H, 7.37; N, 14.31.

2-Cyanoacetoxy-2-cyanomethyl-N,N′-dicyclopentylmalondiamide **3b**: Colourless crystals (4.51 g, 51%); m.p. 181–182°C (from EtOH); IR (KBr/cm^{-1}): 3303 (NH), 2265 (CN), 1773 (CO), 1666 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.24–2.10 (m, 16 H cyclopentane), 3.39 (s, 2 H, CH_2CN), 3.76 (s, 2 H, $COCH_2CN$), 4.04–4.25 (m, 2 H, 1-H cyclopentane), 7.21 (d, J = 7.1 Hz, 2 H, NH). $C_{18}H_{24}N_4O_4$ calcd: C, 59.99; H, 6.71; N, 15.55; found: C, 59.79; H, 6.78; N, 15.69.

2-Cyanoacetoxy-2-cyanomethyl-N,N′-di-n-hexylmalondiamide **3c**: Colourless crystals (4.23 g, 44%); m.p. 114–115°C (from *i*-PrOH); IR (KBr/cm^{-1}): 3300 (NH), 2255 (CN), 1780 (CO), 1672 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.75–1.92 (m, 22 H hexane), 3.12–3.40 (m, 4 H, NCH_2), 3.37 (s, 2 H, CH_2CN), 3.77 (s, 2 H, $COCH_2CN$); 7.38 (t, J = 5.6 Hz, 2 H, NH). $C_{20}H_{32}N_4O_4$ calcd: C, 61.20; H, 8.22; N, 14.27; found: C, 61.07; H, 8.15; N, 14.23.

2-Cyanoacetoxy-2-cyanomethyl-N,N′-dicycloheptylmalondiamide **3d**: Colourless crystals (5.82 g, 57%); m.p. 162–163°C (from EtOH); IR (KBr/cm^{-1}): 3318 (NH), 2266 (CN), 1778 (CO), 1672 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.08–1.96 (m, 24 H cycloheptane), 3.41 (s, 2 H, CH_2CN), 3.62–3.84 (m, 2 H, 1-H cycloheptane), 4.24 (s, 2 H, $COCH_2CN$), 7.07 (d, J = 7.3 Hz, 2 H, NH). $C_{22}H_{32}N_4O_4$ calcd: C, 63.44; H, 7.74; N, 13.45; found: C, 63.70; H, 7.60; N, 13.51.

Cleavage of compounds **3a,b,d**: A well-stirred suspension of **3** (5.9 mmol) in EtOH (8 cm^3) was treated dropwise with NEt_3 until a clear solution was obtained. The reaction mixture was stirred for an additional 5 min and then treated with water (30 cm^3). The resulting suspension was filtered to give **4**.

2-Cyanomethyl-N,N′-dicyclohexyl-2-hydroxymalondiamide **4a**: Colourless crystals (1.67 g, 88%); m.p. 130–131°C (from *i*-PrOH); IR (KBr/cm^{-1}): 3385 (OH), 3317 (NH), 2255 (CN), 1682 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.04–2.01 (m, 20 H cyclohexane), 2.93 (s, 2 H, CH_2), 3.62–3.82 (m, 2 H, 1-H cyclohexane), 5.22 (s, 1 H, OH), 7.25 (d, J = 7.0 Hz, 2 H, NH). $C_{17}H_{27}N_3O_3$ calcd: C, 63.53; H, 8.47; N, 13.07; found: C, 63.84; H, 8.31; N, 13.30.

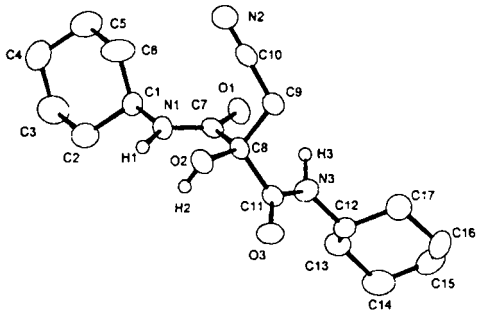


Fig. 1 X-ray crystal structure of **4a**.

2-Cyanomethyl-N,N′-dicyclopentyl-2-hydroxymalondiamide **4b**: Colourless crystals (1.30 g, 75%); m.p. 88°C (from *i*-PrOH), the product resolidified and melted again at 104–105°C; IR (KBr/cm^{-1}): 3396 (OH), 3316 (NH), 2268 (CN), 1666 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.23–2.12 (m, 16 H cyclopentane), 2.92 (s, 2 H, CH_2), 3.98–4.26 (m, 2 H, 1-H cyclopentane), 5.23 (s, 1 H, OH), 7.34 (d, *J* = 6.9 Hz, 2 H, NH). $C_{15}H_{23}N_3O_3$ calcd: C, 61.41; H, 7.90; N, 14.32; found: C, 61.31; H, 8.19; N, 14.11.

2-Cyanomethyl-N,N′-dicyloheptyl-2-hydroxymalondiamide **4d**: Colourless crystals (1.47 g, 71%); m.p. 101–102°C (from *i*-PrOH); IR (KBr/cm^{-1}): 3318 (NH), 2266 (CN), 1778 (CO), 1672 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.23–1.98 (m, 24 H cycloheptane), 2.88 (s, 2 H, CH_2), 3.75–3.95 (m, 2 H, 1-H cycloheptane), 5.22 (s, 1 H, OH), 7.30 (d, *J* = 7.4 Hz, 2 H, NH). $C_{19}H_{31}N_3O_3$ calcd: C, 65.30; H, 8.94; N, 12.02; found: C, 65.57; H, 9.21; N, 11.80.

2-Cyanomethyl-N,N′-di-n-hexyl-2-hydroxymalondiamide **4c**: a well-stirred suspension of **3c** (2.32 g, 5.9 mmol) in EtOH (8 cm^3) was treated dropwise with NEt_3 until a clear solution was obtained. The reaction mixture was evaporated to dryness and the residue stirred with $CHCl_3$ (50 cm^3) and water (50 cm^3). The organic layer was separated, washed again with water (50 cm^3), dried with anhydrous Na_2SO_4, and then evaporated to dryness. The residue was chromatographed on silica gel (benzene) to give **4c** as a viscous oil (1.34 g, 70%), alternatively a mixture of hexanes/toluene (1:4 v/v) gave **4c** in 59% yield; IR (neat/cm^{-1}): 3340 (OH + NH), 2257 (CN), 1679 (CO); ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.88–1.88 (m, 22 H hexane), 2.93 (s, 2 H, CH_2CN), 3.19–3.32 (m, 4 H, NCH_2), 5.31 (s, 1 H, OH), 7.37 (t, *J* = 5.3 Hz, 2 H, NH). $C_{17}H_{31}N_3O_3$ calcd: C, 62.74; H, 9.60; N, 12.91; found: C, 62.99; H, 9.31; N, 13.27.

Crystal data of **4a**: $C_{17}H_{27}N_3O_3$ (321.42), triclinic, space group *P1*, *a* = 6.112(8), *b* = 10.590(4), *c* = 14.790(8) Å, β = 94.30(9)°, *V* = 895.4(13) Å^3, *Z* = 2, *Dc* = 1.192 g/cm^3, μ(MoK$_\alpha$) = 0.082 mm^{-1}, *F(000)* = 348.

Cell parameters and reflection intensities were measured at room temperature on a Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo-Ka radiation. Intensity data were corrected for Lorentz polarisation and absorption effects.[9] The structure was solved by direct methods[10] and refined on F^2 by full-matrix least-squares techniques.[11] Reflections collected: 1741; final *R* indices [$I>2\sigma(I)$]: R_1 = 0.0835, wR_2 = 0.2171; *R* indices (all data): R_1 = 0.1405, wR_2 = 0.3097; largest diff. peak/hole: 0.430/-0.349 e/Å^3. The hydrogen atoms were introduced in calculated positions. All non-hydrogen atoms were refined with anisotropic temperature factors, whereas for the hydrogen atoms an overall isotropic temperature factor was assigned. Analytical expressions of neutral-atom scattering factors were employed, and anomalous dispersion corrections were incorporated.

The cyclohexane rings have the most stable chair conformation. The two amide groups are of *trans*-type, with C(1)–N(1)–C(7)–C(8) and C(12)–N(3)–C(11)–C(8) dihedral angles of 171.3(5)° and 174.6(5)°, respectively. The other dihedral angles in the main chain, *i.e.* N(1)–C(7)–C(8)–C(11) and N(3)–C(11)–C(8)–C(7) have values of 119.4(6)° and 52.3(7)°, respectively. The structural conformation is determined by some short intramolecular hydrogen bonds as provided by the following donor-acceptor distances: N(3)....O(1) = 2.838(8) Å, N(1)....O(2) = 2.614(7) Å, O(2)....O(3) = 2.644(7) Å. Finally an intermolecular hydrogen bond probably exists between O(2) and O(3) (-x, -y, -z+1), their distance apart being equal to 2.870(7) Å. A selection of bond lengths and angles is reported in Table 1. The data have been deposited at the Cambridge Structural Database and registered under the reference CCDC164734.

Table 1 Selected bond lengths [Å] and angles [deg]

O(1)–C(7)	1.238(7)
O(2)–C(8)	1.415(6)
O(3)–C(11)	1.227(7)
N(1)–C(7)	1.308(7)
N(1)–C(1)	1.444(8)
N(2)–C(10)	1.131(8)
N(3)–C(11)	1.342(7)
N(3)–C(12)	1.447(7)
C(7)–C(8)	1.556(9)
C(8)–C(11)	1.522(8)
C(8)–C(9)	1.526(8)
C(9)–C(10)	1.457(10)
C(7)–N(1)–C(1)	123.2(5)
C(11)–N(3)–C(12)	125.0(5)
O(1)–C(7)–N(1)	124.3(6)
O(1)–C(7)–C(8)	118.0(5)
N(1)–C(7)–C(8)	117.6(5)
O(2)–C(8)–C(11)	110.0(4)
C(11)–C(8)–C(9)	109.1(5)
O(2)–C(8)–C(7)	108.3(4)
C(9)–C(8)–C(7)	108.3(5)
C(10)–C(9)–C(8)	113.1(5)
O(3)–C(11)–N(3)	123.9(5)
O(3)–C(11)–C(8)	119.9(5)
N(3)–C(11)–C(8)	116.0(5)

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