A CONVENIENT SYNTHESIS OF (*Z*)-3-(α-CYANO-α-ALKOXYCARBONYLMETHYLENE)-2-PIPERAZINONES AND THEIR DERIVATIVES

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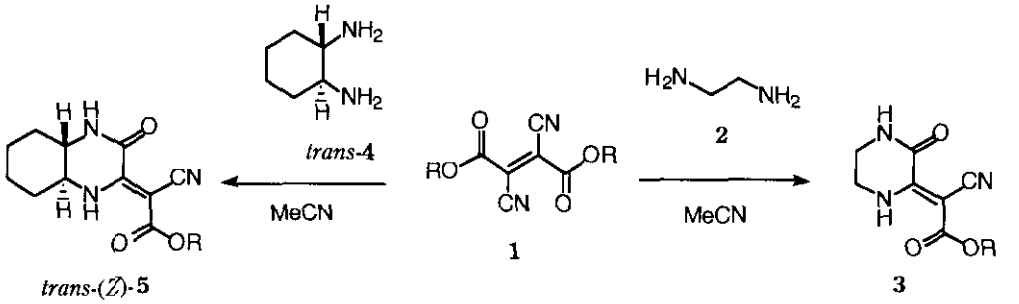
Abstract - (*Z*)-3-(α-Cyano-α-alkoxycarbonylmethylene)-2-piperazinone derivatives (**3**) and *trans*-(*Z*)-3-(α-cyano-α-alkoxycarbonylmethylene)-octahydro-2(1*H*)-quinoxalinone derivatives (**5**) possessing various alkoxycarbonyl groups are prepared directly from the reaction of dialkyl (*E*)-2,3-dicyanobutenedioates (**1**) with ethylenediamine (**2**) and with *trans*-1,2-diaminocyclohexane (**4**), respectively. Furthermore, *cis*-1,2-diaminocycloheptane (**6**) and *meso*-2,3-diaminobutane (**8**) were reacted with the diethyl ester **1b** to give *cis*-(*Z*)-3-(α-cyano-α-ethoxycarbonylmethylene)decahydro-2*H*-cycloheptapyrazin-2-one (**7**) and *cis*-(*Z*)-3-(α-cyano-α-ethoxycarbonylmethylene)-5,6-dimethyl-2-piperazinone (**9**), respectively. The structural studies of **3**, **5**, **7**, and **9** were carried out by NMR experiments in some details.

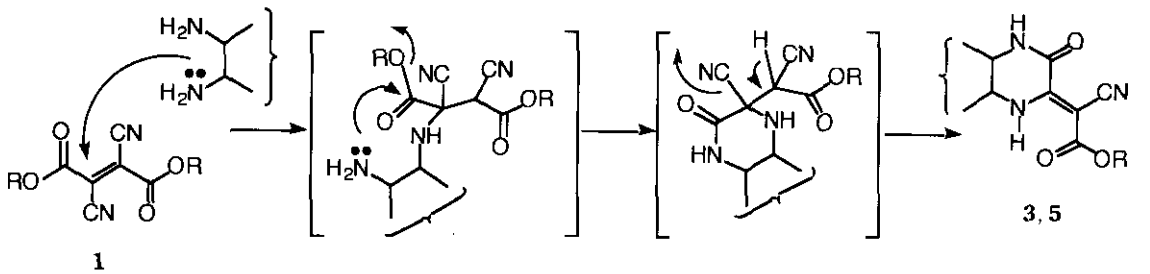
It is known that the piperazine ring is an important moiety of various biologically active compounds.[1-3] Continuing with our research on the reaction of dialkyl (*E*)-2,3-dicyanobutenedioates (**1**) with the nucleophiles having two reactive functional groups,[4-6] we have designed a simple synthesis for several new 2-piperazinones having a 3-(α-cyano-α-alkoxycarbonyl)methylene group *via* the reaction of aliphatic 1,2-diamines, such as ethylenediamine (**2**) or *trans*-1,2-diaminocyclohexane (**4**), with **1** bearing alkyl groups such as methyl, ethyl, propyl, butyl, and benzyl, respectively. We now wish to report a convenient method for one-step synthesis of (*Z*)-3-(α-cyano-α-alkoxycarbonylmethylene)-2-piperazinones (**3**) from **1** and **2**, and *trans*-(*Z*)-3-(α-cyano-α-alkoxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinones (**5**) from **1** and *trans*-**4**, respectively (Scheme 1). This method consists of the reaction of **1** with the small excess amount of *vic*-diamine (**2**) or (**4**) (in a 1:1.3 molar ratio), carried out in acetonitrile at room temperature for thirty minutes.

A possible reaction process is illustrated in Scheme 2. Presumably, a Michael addition by an amino group of the diamine to the ethylenic double bond leads to open-chain adduct, which cyclizes by intramolecular nucleophilic attack at the ester group to form the piperazine ring.



R=Me, Et, Pr, *i*-Pr, Bu, *i*-Bu, *s*-Bu, Bn

Scheme 1

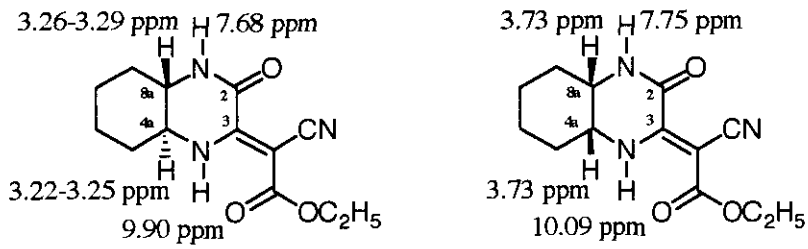


Scheme 2

The IR spectra of **3** and **5** showed absorption bands due to the lactam NH stretching vibration of the 1-position in the 3292-3198 cm^{-1} region and the enamine NH stretching vibration of the 4-position in the 3208-3082 cm^{-1} region, an α,β-unsaturated nitrile C≡N at 2208-2198 cm^{-1}, and an ester and an amide C=O groups at 1688-1705 cm^{-1} and 1664-1654 cm^{-1}, respectively. Furthermore, ^1H NMR spectra (DMSO-d_6) of **3** and **5** revealed signals at δ 9.83-10.18 and at δ 8.58-9.01 each corresponding to one proton. These were assigned to the 4- and 1-protons, respectively. Appearance of the IR absorption band at 1675-1705 cm^{-1} and ^1H NMR signal at δ 9.83-10.18 would indicate the formation of an intramolecular hydrogen-bond between the 3-unsaturated ester C=O and 4-proton.

In view of NMR spectroscopy, (*Z*)-3-(α-cyano-α-alkoxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinones (**5**) are of interest because of their *cis*/*trans* isomerization of 4a- and 8a-positions on the octahydro-2(1*H*)-quinoxalinone ring. The *trans*-isomer (*trans*-**5b**) was

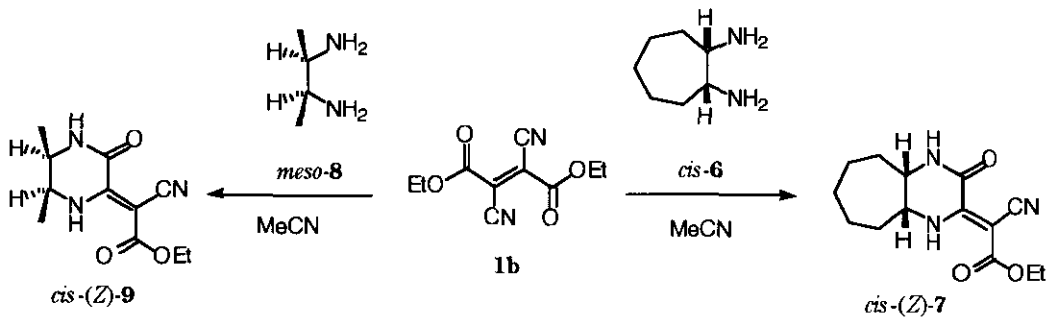
isolated selectively *via* the reaction of **1b** with *trans*-1,2-diaminocyclohxane (**4**). We observed ^{1}H- and ^{13}C-NMR (Table 3), and ^{1}H-detected multiple-bond heteronuclear multiple-quantum coherence (HMBC) spectra of **5b** in chloroform-*d* to avoid overlapping of broad signal (3.2-3.4 ppm) caused by water. An HMBC experiment of *trans*-**5b** indicated long-range (^{2}J) coupling interactions between 4a-H (3.22-3.25 ppm) and C8a (55.8 ppm), and between 8a-H (3.22-3.25 ppm) and C4a (54.9 ppm). Similarly, long-range (^{2}J) coupling interactions between both 1-H (7.68 ppm) with C8a, and 4-H (9.90 ppm) with C4a were observed. Furthermore, long-range (^{3}J) coupling interactions were also showed between 1-H and C3 (155.9 ppm), and between 4-H and C2 (158.4 ppm), respectively.



trans-**5b** *cis*-**5b**

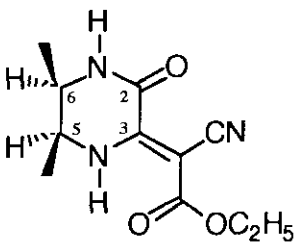
Scheme 3. ^{1}H NMR Data of *trans*- and *cis*-**5b** ($CDCl_3$)

On the other hand, the mixture of *trans*- and *cis*-**5b** (*trans*/*cis* = 7:3) was obtained from the reaction of **1b** with the geometrical mixture of **4** (*trans*/*cis* = 7:3). In the comparison of ^{1}H NMR data in chloroform-*d* (Scheme 3), 4a-H and 8a-H on *cis*-**5b** revealed a merged signal (3.73 ppm, br s, 2H), shifted to lower field than the 4a-H (3.22-3.25 ppm, m, 1H) and 8a-H (3.26-3.29 ppm, m, 1H) on *trans*-**5b**. Similarly, both the lactam proton 1-H (7.75 ppm) and the hydrogen-bonded enamine proton 4-H (10.09 ppm) on *cis*-**5b** shifted to lower field than 1-H (7.68 ppm) and 4-H (9.90 ppm) protons on *trans*-**5b**.



Scheme 4

Furthermore, *cis*-form piperazinones, such as *cis*-(*Z*)-3-(α-cyano-α-ethoxycarbonylmethylene)-decahydro-2*H*-cycloheptapyrazin-2-one (**7**) and *cis*-(*Z*)-3-(α-cyano-α-ethoxycarbonylmethylene)-5,6-dimethyl-2-piperazinone (**9**), were also prepared from the reaction of **1b** with *cis*-1,2-diaminocycloheptane (**6**) and *meso*-2,3-diaminobutane (**8**),[7-9] respectively.



Irradiated Proton	Observed NOE (%)
6-CH_3 (1.05 ppm)	6-H (16.3), 1-H (4.1)
5-CH_3 (1.09 ppm)	5-H (14.4)
5- and 6-H (3.76 ppm)	6-CH_3 (8.3), 5-CH_3 (5.1), 1-H (3.7), 4-H (2.3)

Scheme 5 Difference NOE Data of *cis*- (*Z*)-**9** (DMSO-d_6)

The molecular formula of obtained compounds (**3**, **5**, **7**, and **9**) was confirmed by the elemental analysis and MS spectral data. The structure of **3**, **5**, **7**, and **9** was also confirmed by DEPT (determination of CH_3, CH_2, CH, or quaternary carbon), and ^{1}H-detected heteronuclear multiple-quantum coherence (HMQC, $^1J_{CH}$ correlation) data.

The principal advantages of the method described here are that the time of reaction is short, the work up is convenient, and the reaction is easily carried out and proceeds under mild conditions to give, in general, high yields of 2-piperazinones having a 3-(α-cyano-α-alkoxycarbonyl)methylene group.

Table 1 ^{1}H-NMR Data of Compounds (**3**, **5**, **7**, and **9**)

Product	^{1}H-NMR (DMSO-d_6): δ (ppm), *J* (Hz)
3a	3.31-3.37 (m, 2H, NCH_2), 3.46-3.52 (m, 2H, NCH_2), 3.70 (s, 3H, OCH_3), 8.86 (br s, 1H, NH), 10.14 (br s, 1H, NH)
3b	1.23 (t, 3H, *J* =7.1, CH_3), 3.31-3.37 (m, 2H, NCH_2), 3.46-3.52 (m, 2H, NCH_2), 4.17 (q, 2H, *J* =7.1, OCH_2), 8.58 (br s, 1H, NH), 10.16 (br s, 1H, NH)
3c	0.91 (t, 3H, *J* =7.4, CH_3), 1.62 (sextet, 2H, *J* =7.1, CH_2CH_3), 3.31-3.36 (m, 2H, NCH_2), 3.45-3.50 (m, 2H, NCH_2), 4.08 (t, 2H, *J* =6.6, OCH_2), 8.85 (br s, 1H, NH), 10.15 (br s, 1H, NH)
3d	1.23 (d, 6H, *J* =6.2, $2CH_3$), 3.31-3.37 (m, 2H, NCH_2), 3.45-3.51 (m, 2H, NCH_2), 4.98 (septet, 1H, *J* =6.2, OCH), 8.84 (br s, 1H, NH), 10.18 (br s, 1H, NH)
3e	0.91 (t, 3H, *J* =7.4, CH_3), 1.36 (sextet, 2H, *J* =7.4, CH_2CH_3), 1.60 (quintet, 2H, *J* =6.5, OCH_2CH_2), 3.31-3.36 (m, 2H, $NHCH_2$), 3.45-3.50 (m, 2H, NCH_2), 4.13 (t, 2H, *J* =6.5, OCH_2), 8.85 (br s, 1H, NH), 10.15 (br s, 1H, NH)

Table 1 (Continued)

Product	^{1}H-NMR (DMSO-d_6): δ (ppm), J (Hz)
3f	0.92 (d, 6H, J=6.7, 2CH_3), 1.92 (nonet, 1H, J=6.7, CH), 3.31-3.36 (m, 2H, NCH_2), 3.46-3.51 (m, 2H, NCH_2), 3.91 (d, 2H, J=6.5, OCH_2), 8.85 (br s, 1H, NH), 10.14 (br s, 1H, NH)
3g	0.87 (t, 3H, J=7.4, CH_2CH_3), 1.21 (d, 3H, J=6.3, $CHCH_3$), 1.57 (quintet, 2H, J=6.9, CH_2CH_3), 3.31-3.36 (m, 2H, NCH_2), 3.45-3.50 (m, 2H, CH_2), 4.82 (sextet, 1H, J=6.2, OCH), 8.83 (br s, 1H, NH), 10.17 (br s, 1H, NH)
3h	3.31-3.35 (m, 2H, NCH_2), 3.46-3.50 (m, 2H, NCH_2), 5.22 (s, 2H, OCH_2), 7.33-7.41 (m, 5H, C_6H_5), 8.87 (br s, 1H, NH), 10.18 (br s, 1H, NH)
trans-**5a**	1.20-1.36 (m, 4H), 1.65-1.75 (m, 2H), 1.86-1.92 (m, 1H), 2.05-2.09 (m, 1H), 3.24-3.29 (m, 2H), 3.71 (s, 3H, OCH_3), 9.00 (br s, 1H, NH), 9.83 (br s, 1H, NH)
trans-**5b**	1.23 (t, 3H, J=7.1, CH_3), 1.23-1.31 (m, 4H), 1.67-1.72 (m, 2H), 1.87-1.90 (m, 1H), 2.05-2.08 (m, 1H), 3.24-3.26 (m, 2H), 4.18 (q, 2H, J=7.1, OCH_2), 8.99 (br s, 1H, NH), 9.86 (br s, 1H, NH)
trans-**5c**	0.91 (t, 3H, J=7.4, CH_3), 1.23-1.31 (m, 4H), 1.63 (q, 2H, J=6.9, OCH_2CH_2), 1.66-1.72 (m, 2H), 1.86-1.90 (m, 1H), 2.05-2.09 (m, 1H), 3.24-3.26 (m, 2H), 4.09 (t, 2H, J=6.4, OCH_2), 9.00 (br s, 1H, NH), 9.87 (br s, 1H, NH)
trans-**5d**	1.21-1.31 (m, 4H), 1.23 (d, 3H, J=6.2, CH_3), 1.24 (d, 3H, J=6.2, CH_3), 1.66-1.70 (m, 2H), 1.86-1.90 (m, 1H), 2.05-2.09 (m, 1H), 3.23-3.25(m, 2H), 4.99 (septet, 1H, J=6.2, OCH), 9.00 (br s, 1H, NH), 9.92 (br s, 1H, NH)
trans-**5e**	0.90 (t, 3H, J=7.3, CH_3), 1.23-1.32 (m, 4H), 1.33 (sextet, 2H, J=7.0, CH_2CH_3), 1.60 (quintet, 2H, J=7.3, OCH_2CH_2), 1.67-1.70 (m, 2H), 1.87-1.90 (m, 1H), 2.05-2.07 (m, 1H), 3.24-3.26 (m, 2H), 4.14 (t, 2H, J=6.2, OCH_2), 8.98 (br s, 1H, NH), 9.84 (br s, 1H, NH)
trans-**5f**	0.91 (d, 6H, J=6.7, 2CH_3), 1.24-1.32 (m, 4H), 1.67-1.70 (m, 2H), 1.87-1.90 (m, 1H), 1.92 (nonet, 1H, J=6.65, OCH_2CH), 2.06-2.08 (m, 1H), 3.24-3.26 (m, 2H), 3.93 (d, 2H, J=6.6, OCH_2), 8.99 (br s, 1H, NH), 9.83 (br s, 1H, NH)
trans-**5g**	0.87 (dt, 3H, J=7.4,CH_2CH_3), 1.21 (dd, 3H, J=6.2, 2.4, $OCHCH_3$), 1.24-1.31 (m, 4H), 1.57 (quintet, 2H, J=6.9, CH_2CH_3), 1.67-1.73 (m, 2H), 1.87-1.90 (m, 1H), 2.05-2.08 (m, 1H), 3.23-3.25 (m, 2H), 4.83 (d, sextet, J=6.2, 3.8, OCH), 8.97 (br s, 1H, NH), 9.87 (br s, 1H, NH)
trans-**5h**	1.24-1.33 (m, 4H), 1.68-1.73 (m, 2H), 1.87-1.91 (m, 1H), 2.07-2.09 (m, 1H), 3.24-3.27 (m, 2H), 5.23 (s, 2H, OCH_2), 7.39 (s, 5H, C_6H_5), 9.01 (br s, 1H, NH), 9.83 (br s, 1H, NH)
cis-**7**	1.23 (t, 3H, J=7.1, CH_3), 1.30-1.99 (m, 10H, 5CH_2), 3.76-3.84 (m, 2H, 2CH), 4.17 (q, 2H, J=7.1, OCH_2), 8.81 (br s, 1H, NH), 10.17 (br s, 1H, NH)
cis-**9**	1.05 (d, 3H, J=6.5, 6-CH_3), 1.09 (d, 3H, J=6.5, 5-CH_3), 1.23 (t, 3H, J=7.1, CH_2CH_3), 3.73-3.78 (m, 2H, 2CH), 4.17 (q, 2H, J=7.1, OCH_2), 8.82 (br s, 1H, NH), 10.19 (br s, 1H, NH)

Table 2 Typical ^{13}C-NMR Data of Compounds (ethyl esters **3b**, **5b**, **7**, and **9**)

Product	^{13}C-NMR (DMSO-d_6): δ (ppm)
3b	14.2 (CH_3), 38.1 (NCH_2), 39.8 (NCH_2), 60.1 (OCH_2), 69.7 (*C*-CN), 116.9 (CN), 156.8 (C3), 156.9 (COO), 167.9 (C2)
trans-**5b**	14.1 (CH_3), 22.7, 23.2, 28.1, 28.5 ($4CH_2$, cyclohexane ring), 53.4, 55.0 (2NCH), 60.4 (OCH_2), 70.2 (*C*-CN), 116.4 (CN), 156.8 (C3), 156.8 (COO), 168.3 (C2)
cis-**7**	14.2 (CH_3), 21.3, 22.3, 27.5, 28.5, 29.2 ($5CH_2$, cycloheptane ring), 51.7, 53.3 (2NCH), 60.3 (OCH_2), 69.5 (*C*-CN), 116.7 (CN), 155.2 (C3), 156.3 (COO), 168.2 (C2)
cis-**9**	13.9 (CH_3), 14.2 (CH_3), 15.1 (CH_3), 47.8, 49.0 (2NCH), 60.2 (OCH_2), 69.8 (*C*-CN), 116.7 (CN), 155.6 (C3), 156.6 (COO), 168.0 (C2)

Table 3 NMR Data of two isomers (*trans*- and *cis*-**5b**), in $CDCl_3$

Compound	^{1}H NMR ($CDCl_3$): δ (ppm), *J* (Hz)	^{13}C NMR ($CDCl_3$): δ (ppm)
trans-**5b**	1.34 (t, 3H, *J*=7.1, CH_3), 1.39-1.45 (m, 4H, cyclohexane ring), 1.84-1.88 (m, 2H, cyclohexane ring), 2.04-2.08 (m, 2H, cyclohexane ring), 3.22-325 (m, 1H), 3.26-3.29 (m, 1H), 4.25 (q, 2H, *J*=7.1, OCH_2), 7.65 (br s, 1H, NH), 9.89 (br s, 1H, NH)	14.3 (CH_3), 23.3, 23.8, 29.1, 29.2 ($4CH_2$ cyclohexane ring), 54.9 (C4a), 55.8 (C8a), 61.3 (OCH_2), 73.3 (*C*-CN), 116.6 (CN), 155.9 (C3), 158.4 (COO), 169.0 (C2)
cis-**5b**	1.34 (t, 3H, *J*=7.1, CH_3), 1.39-1.45 (m, 4H, cyclohexane ring), 1.58-1.62 (m, 2H, cyclohexane ring), 1.77-1.81 (m, 2H, cyclohexane ring), 3.71-3.75 (m, 2H, two methine protons), 4.25 (q, 2H, *J*=7.1, OCH_2), 7.75 (br s, 1H, NH), 10.09 (br s, 1H, NH)	14.3 (CH_3), 21.0, 21.2, 28.8, 28.8 ($4CH_2$ cyclohexane ring), 49.7, (C4a), 50.2 (C8a), 61.3 (OCH_2), 73.0 (*C*-CN), 116.7 (CN), 155.4 (C3), 158.2 (COO), 169.2 (C2)

EXPERIMENTAL

Melting points were determined on a Yamato MP-21 apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR 1000 PC spectrophotometer (in potassium bromide). The ^{1}H NMR spectra were recorded on either a JEOL EX-400 (400 MHz) or a Varian VXR-300 (300MHz) instrument. The ^{13}C NMR spectra were taken on a JEOL EX-400 (100 MHz) instrument. The DEPT spectra were run in a standard manner, using θ=135° pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively. Moreover, the signals caused by quaternary carbons were identified by the comparison

between ^{13}C NMR and DEPT spectra. The difference-NOE, HMQC (using C-H spin-spin coupling constant $^{1}J_{CH}$=140Hz), and HMBC (using C-H long range coupling constant $^{n}J_{CH}$=8Hz) experiments were also carried out with a JEOL EX-400 instrument. MS spectra were obtained with a JEOL AX-500 spectrometer (EI: 70 eV). *trans*-1,2-diaminocyclohexane (**4**) was purchased from Tokyo Kasei Co. *cis*-1,2-Diaminocycloheptane (**6**) and *meso*-2,3-diaminobutane (**8**) were obtained according to literature.[7-9]

General Procedure for the Preparation of (*Z*)-3-(α-Cyano-α-alkoxycarbonylmethylene)-2-piperazinones (3).

To a magnetically stirred solution of 4.5 mmol of dialkyl (*E*)-2,3-dicyanobutenedioate (**1**) in acetonitrile (10 mL) was added a solution of 0.35 g (5.9 mmol) of ethylenediamine (**2**) in acetonitrile (5 mL) at rt. The solution was further stirred at rt for 30 min. Evaporation of the solvent *in vacuo* gave the colorless or yellowish solid, which was washed with cold ether / ethanol (1:1), and was filtered. The collected crystalline solid was recrystallized from suitable solvent to give **3**.

(*Z*)-3-(α-Cyano-α-methoxycarbonylmethylene)-2-piperazinone (3a).
This compound was obtained as colorless needles (pyridine / ethanol), 86% yield, mp 253.5-254°C (decomp); IR: ν 3248, 3162 (NH), 2202 (CN), 1690 (COO), 1656 (N-C=O); MS: *m/z*: 195 (M^+), 163, 135, 107, 70; *Anal.* Calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.15; H, 4.37; N, 21.24.
(*Z*)-3-(α-Cyano-α-ethoxycarbonylmethylene)-2-piperazinone (3b).
This compound was obtained as colorless needles (ethanol), 57% yield, mp 187-188.5°C; IR: ν 3264, 3120 (NH), 2200 (CN), 1690 (COO), 1655 (N-C=O); MS: *m/z*: 209 (M^+), 163, 137, 110, 70; *Anal.* Calcd for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.54; H, 5.21; N, 20.24.
(*Z*)-3-(α-Cyano-α-propoxycarbonylmethylene)-2-piperazinone (3c).
This compound was obtained as colorless needles (ethanol), 50% yield, mp 165-166.5°C; IR: ν 3280, 3122 (NH), 2202 (CN), 1690 (COO), 1654 (N-C=O); MS: *m/z*: 223 (M^+), 181, 164, 137, 70; *Anal.* Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.55; H, 5.85; N, 18.69.
(*Z*)-3-(α-Cyano-α-isopropyloxycarbonylmethylene)-2-piperazinone (3d).
This compound was obtained as colorless needles (ethanol), 41% yield, mp 212-213°C decomp; IR: ν 3198, 3082 (NH), 2202 (CN), 1701 (COO), 1663 (N-C=O); MS: *m/z*: 223 (M^+), 181, 164, 137, 70; *Anal.* Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.87; H, 5.70; N, 18.88.
(*Z*)-3-(α-Cyano-α-butoxycarbonylmethylene)-2-piperazinone (3e).
This compound was obtained as colorless needles (ethanol), 38% yield, mp 173.5-174°C; IR: ν

3204, 3098 (NH), 2204 (CN), 1693 (COO), 1657 (N-C=O); MS: *m/z*: 237 (M^+), 181, 164, 137, 70; *Anal.* Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.74; H, 6.46; N, 17.67.

(*Z*)-3-(α-Cyano-α-isobutyloxycarbonylmethylene)-2-piperazinone (3f).

This compound was obtained as colorless needles (ethanol), 58% yield, mp 192-193°C; IR: ν 3224, 3124 (NH), 2204 (CN), 1688 (COO), 1658 (N-C=O); MS: *m/z*: 237 (M^+), 181, 164, 137, 70; *Anal.* Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.79; H, 6.40; N, 17.82.

(*Z*)-3-(α-Cyano-α-*sec*-butyloxycarbonylmethylene)-2-piperazinone (3g).

This compound was obtained as colorless needles (ethanol), 29% yield, mp 224-225°C (decomp); IR: ν 3245, 3115 (NH), 2208 (CN), 1689 (COO), 1657 (N-C=O); MS: *m/z*: 237 (M^+), 181, 164, 137, 114, 70; *Anal.* Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.63; H, 6.31; N, 17.77.

(*Z*)-3-(α-Cyano-α-benzyloxycarbonylmethylene)-2-piperazinone (3h).

This compound was obtained as colorless needles (ethanol), 68% yield, mp 224.5-225.5°C; IR: ν 3292, 3208 (NH), 2198 (CN), 1700 (COO), 1659 (N-C=O); MS: *m/z*: 271 (M^+), 227, 137, 91, 70; *Anal.* Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.83; H, 4.86; N, 15.64.

General Procedure for the Preparation of *trans*-(*Z*)-3-(α-Cyano-α-alkoxycarbonylmethylene)-3,4,4a,5,6,7,8,8a-octahydro-2(1*H*)-quinoxalinones (5).

To a magnetically stirred solution of 4.5 mmoles of dialkyl (*E*)-2,3-dicyanobutenedioate (**1**) in acetonitrile (10 mL) was added a solution of 0.67 g (5.9 mmoles) of (*E*)-1,2-diaminocyclohexane (**4**) in acetonitrile (5 mL) at rt. The solution was further stirred at rt. After 2-5 min, a colorless or yellowish precipitate was observed. After 30 min, the crystalline solid was filtered, washed with cold ether / ethanol (1:1), and recrystallized from suitable solvent to give **5**.

***trans*-(*Z*)-3-(α-Cyano-α-methoxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinone (5a).**

This compound was obtained as colorless needles (dioxane / ethanol), 74% yield, mp 285.5-286°C (decomp); IR: ν 3202, 3102 (NH), 2200 (CN), 1702 (COO), 1664 (N-C=O); MS: *m/z*: 249 (M^+), 217, 189, 125, 81; *Anal.* Calcd for $C_{12}H_{15}N_3O_3$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.62; H, 5.95; N, 16.68.

***trans*-(*Z*)-3-(α-Cyano-α-ethoxycarbonylmethylene)octahydro--2(1*H*)-quinoxalinone (5b).**

This compound was obtained as colorless needles (ethanol / water), 61% yield, mp 242-242.5°C; IR: ν 3200, 3092 (NH), 2198 (CN), 1701 (COO), 1659 (N-C=O); MS: *m/z*: 263 (M^+), 217, 191, 148, 81; *Anal.* Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.23; H,

6.46; N, 15.98.

***trans*-(*Z*)-3-(α-Cyano-α-propoxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinone (5c).**

This compound was obtained as colorless needles (ethanol / water), 81% yield, mp 219-222°C; IR: ν 3204, 3102 (NH), 2200 (CN), 1702 (COO), 1663 (N-C=O); MS: *m/z*: 277 (M^+), 235, 218, 191, 148, 81; *Anal.* Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.38; H, 7.19; N, 15.05.

***trans*-(*Z*)-3-(α-Cyano-α-isopropyloxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinone (5d).**

This compound was obtained as colorless needles (ethanol / water), 61% yield, mp 267-268°C (decomp); IR: ν 3200, 3102 (NH), 2202 (CN), 1705 (COO), 1661 (N-C=O); MS: *m/z*: 277 (M^+), 235, 218, 191, 148, 81; *Anal.* Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.42; H, 6.93; N, 14.98.

***trans*-(*Z*)-3-(α-Cyano-α-butoxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinone (5e).**

This compound was obtained as colorless needles (acetonitrile), 34% yield, mp 220.5-221°C; IR: ν 3206, 3098 (NH), 2200 (CN), 1702 (COO), 1663 (N-C=O); MS: *m/z*: 291 (M^+), 235, 218, 191, 148, 81; *Anal.* Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.73; H, 7.46; N, 14.70.

***trans*-(*Z*)-3-(α-Cyano-α-*i*-butyloxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinone (5f).**

This compound was obtained as colorless needles (ethanol / water), 70% yield, mp 239-242°C (decomp); IR: ν 3202, 3096 (NH), 2202 (CN), 1705 (COO), 1664 (N-C=O); MS: *m/z*: 291 (M^+), 235, 218, 191, 148, 81; *Anal.* Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.78; H, 7.39; N, 14.37.

***trans*-(*Z*)-3-(α-Cyano-α-*s*-butyloxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinone (5g).**

This compound was obtained as colorless needles (ethanol / water), 48% yield, mp 269.5-270°C (decomp); IR: ν 3198, 3100 (NH), 2200 (CN), 1704 (COO), 1662 (N-C=O); MS: *m/z*: 291 (M^+), 235, 218, 191, 148, 81; *Anal.* Calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.66; H, 6.99; N, 14.60.

***trans*-(*Z*)-3-(α-Cyano-α-benzyloxycarbonylmethylene)octahydro-2(1*H*)-quinoxalinone (5h).**

This compound was obtained as colorless needles (dioxane / ethanol), 83% yield, mp 229.5-230.5°C (decomp); IR: ν 3200, 3096 (NH), 2200 (CN), 1700(COO), 1659 (N-C=O); MS: *m/z*: 325 (M^+), 281, 219, 191, 156, 91; *Anal.* Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.88; N, 12.91. Found: C, 66.29; H, 6.07; N, 12.90.

***cis*-(*Z*)-3-(α-Cyano-α-ethoxycarbonylmethylene)-1,3,4,4a,5,6,7,8,9,9a-decahydro-2*H*-cycloheptapyrazin-2-one (7).**

To a magnetically stirred solution of 200 mg (0.89 mmol) of diethyl (*E*)-2,3-dicyanobutenedioate (**1b**) in acetonitrile (1 mL) was added a solution of 150 mg (1.15 mmol) of *cis*-1,2-diaminocycloheptane (**6**) in acetonitrile (1 mL) at rt. The solution was further

stirred at rt. After 1 h, the reaction mixture was concentrated to dryness under reduced pressure, and then ether (2 mL) was added to the residue and the suspension thus obtained was set aside in a refrigerator. The deposited solid was filtered, washed with cold ether, and recrystallized from ethanol to give **7** (76 mg, 32 %) as colorless needles, mp 289-289.5°C (decomp); IR: ν 3300, 3200 (NH), 2200 (CN), 1695 (COO), 1655 (N-C=O); MS: *m/z*: 277 (M^+), 231, 205; *Anal.* Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.90; N, 15.15. Found: C, 60.67; H, 6.85; N, 15.35.

***cis*-(*Z*)-3-(α-Cyano-α-ethoxycarbonylmethylene)-5,6-dimethyl-2-piperazinone (9).**

To a magnetically stirred solution of 200 mg (0.89 mmol) of diethyl (*E*)-2,3-dicyanobutenedioate (**1**) in acetonitrile (1 mL) was added a solution of 102 mg (1.15 mmol) of *meso*-2,3-diaminobutane (**8**) in acetonitrile (1 mL) at rt. The solution was further stirred at rt. After 30 min, the mixture was concentrated to dryness under reduced pressure, and then ether (2 mL) was added to the resulting viscous oil and the suspension thus obtained was set aside in a refrigerator. The deposited solid was isolated by filtration, and recrystallized from ethanol to give **9** (130 mg, 58%) as yellowish needles, mp 179-181°C (decomp); IR: ν 3300, 3195 (NH), 2200 (CN), 1695 (COO), 1655 (N-C=O); MS: *m/z*: 237 (M^+), 191, 165; *Anal.* Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.45; H, 6.58; N, 17.49.

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