HETEROCYCLES, Vol. 86, No. 1, 2012, pp. 343 - 356. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 14th May, 2012, Accepted, 15th June, 2012, Published online, 18th June, 2012
DOI: 10.3987/COM-12-S(N)16

REACTIONS OF AMINES AND HYDRAZIDES DERIVED FROM L-PROLINE WITH DIALKYL DICYANOFUMARATES

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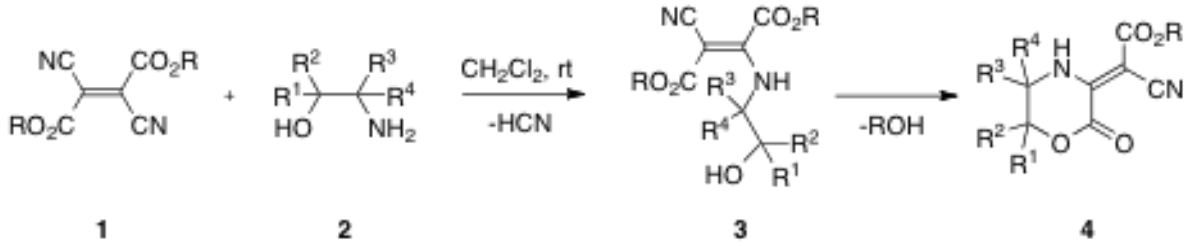
Dedicated to Professor Dr. Ei-ichi Negishi on the occasion of his 77th birthday

Abstract – The reaction of prolinamine derivatives (**8a**,**b**) and dialkyl dicyanofumarates (**1**) in dichloromethane at room temperature leads to the optically active enamines (**10**). Whereas products (**10**) in the case of 1-benzyl prolinamine (**8a**) are stable compounds, the corresponding enamines obtained from the non-protected prolinamine (**8b**) smoothly undergo a cyclocondensation at room temperature to give perhydropyrrolo[1,2-*a*]pyrazine derivatives (**11**). The molecular structure of **11a** was established by X-Ray crystallography. In analogy to **8a**, 1-benzyl prolinehydrazide (**9a**) and **1b** in dichloromethane react to yield the enehydrazine (**12b**). On the other hand, the reaction of **9a** and **1** in methanol at room temperature leads to the corresponding dialkyl 3-amino-1*H*-pyrazole-4,5-dicarboxylates (**13**) and methyl 1-benzylprolinate (**14b**) via a stepwise mechanism. The analogous reaction was observed between a 3-oxidoimidazole-4-carbohydrazide (**15**) and **1b**.

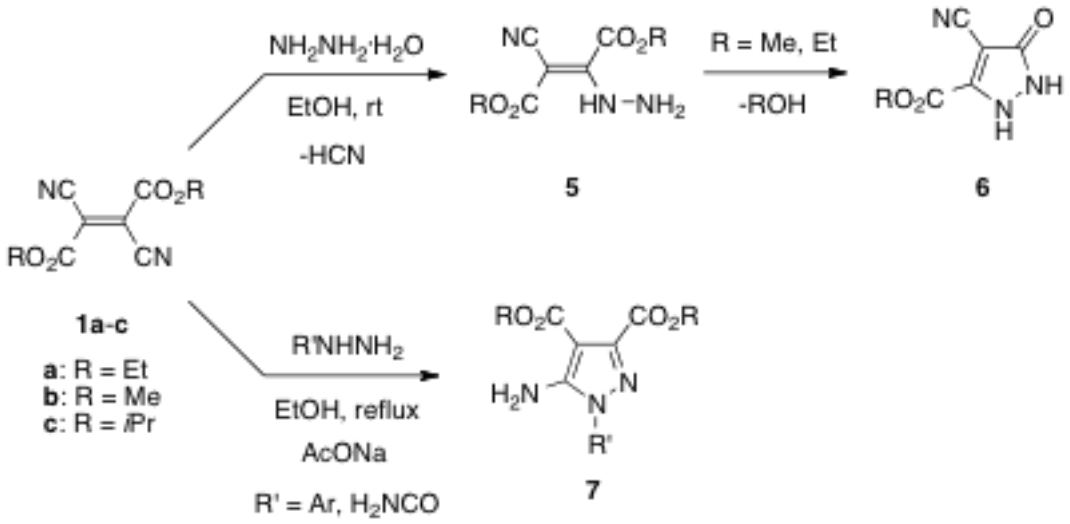
INTRODUCTION

In a series of our recent papers, reactions of electron-deficient dicyanofumarates (**1**) with N- and O-nucleophiles were reported.[3–6] For example, in the case of β-amino alcohols (**2**), the reaction occurs stepwise and, after initial formation of the β-hydroxyalkylenamine (**3**), subsequent cyclocondensation affords morpholinone derivatives (**4**)[6] (Scheme 1).



Scheme 1

Similarly, reactions of diethyl dicyanofumarate (**1a**) with 1,2-diamines open a convenient access to 2-oxopiperazine derivatives.[7] Unexpectedly, hydrazine hydrate reacts with **1a** (R = Et) and **1b** (R = Me) to give the pyrazol-3(2*H*)-one derivatives (**6**)[6] (Scheme 2).



Scheme 2

The intermediate (**5**) was isolated as a stable compound in the case of the sterically congested isopropyl ester (**1c**, R = iPr) and did not cyclize even after prolonged heating. In contrast to hydrazine, arylhydrazines as well as semicarbazide react with **1** in boiling ethanol in the presence of sodium acetate yielding 5-aminopyrazole derivatives (**7**) as the final products.[8]

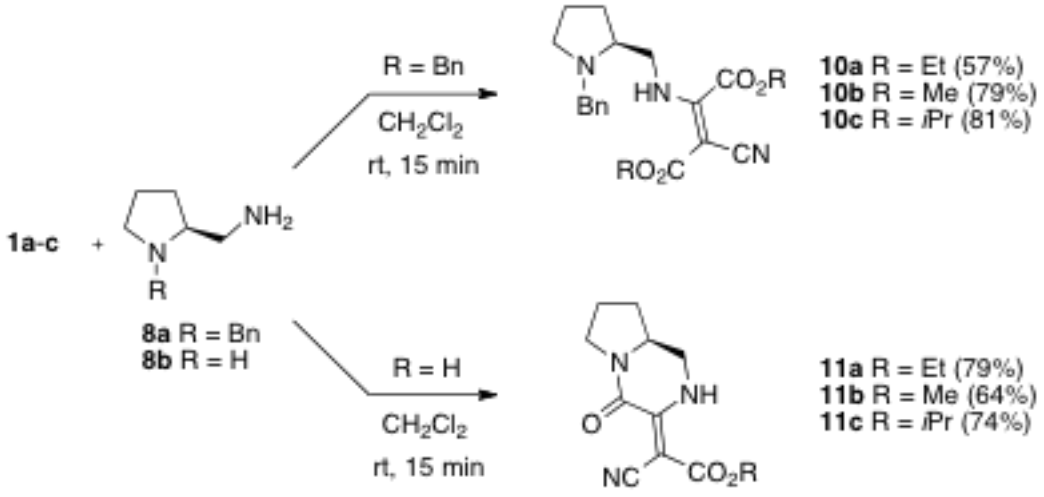
In two recent publications, reactions of **1a** with aromatic carbohydrazides were described, and in both cases two types of products were isolated.[9] One of them was identified as a 1-substituted pyrazol-5-one derivative of type **6**, and the second one was described as a 1,3,4-oxadiazin-6-one derivative in the first paper but then as a 1,3,4-oxadiazole derivative in the second one.

Due to our ongoing interest in the preparation of enantiomerically pure bis-heterocycles derived from L-proline,[10] we became interested in reactions of dicyanofumarates (**1**) with [(2*S*)-pyrrolidin-2-yl]-

methylamines (**8a**,**b**, 'prolinamines') and proline hydrazides (**9a**, **b)**, respectively.

RESULTS AND DISCUSSION

The reaction of *N*-benzyl prolinamine (**8a**) with dimethyl dicyanofumarate (**1b**) in dichloromethane occurred smoothly at room temperature, and the expected enamine (**10b**) was isolated after chromatography in good yield (79%) as a pale yellow oil (Scheme 3). Its structure was confirmed by spectroscopic data which fitted well with those of earlier reported 'push-pull' enamines of this type.[4] The proposed (*Z*)-configuration of **10b** is supported by ^{1}H- and ^{13}C-NMR data. Firstly, the NH-absorption at 9.80 ppm indicates an intramolecular hydrogen bond with the ester group. Secondly, three characteristic signals for sp^{2}-C atoms, attributed to two C=O groups and to C(3) of the but-2-enedioate, appear at 168.2, 161.9, and 161.3 ppm. The signal of C(2) was characteristically shifted to high field and was found at 70.8 ppm. The analogous products **10a** and **10c** were obtained in good yields starting with diethyl and diisopropyl dicyanofumarate, respectively.



Scheme 3

The corresponding experiment with non-protected prolinamine (**8b**) and **1b** was also carried out at room temperature, and the ^{1}H-NMR spectrum of the crude reaction mixture, registered after 10 min, evidenced the presence of **11b** as the sole product. The analogous reaction was observed with **8b** and **1a**, and even in the case of the bulky diisopropyl dicyanofumarate (**1c**), no intermediate enamine of type **10** could be detected after 10 min at room temperature. Fractional crystallization of the crude mixtures gave analytically pure products, which were identified as the bicyclic 2-oxopiperazine derivatives (**11**) (Scheme 3). The structure of **11a** was unambiguously confirmed by X-Ray crystallography (Figure 1).

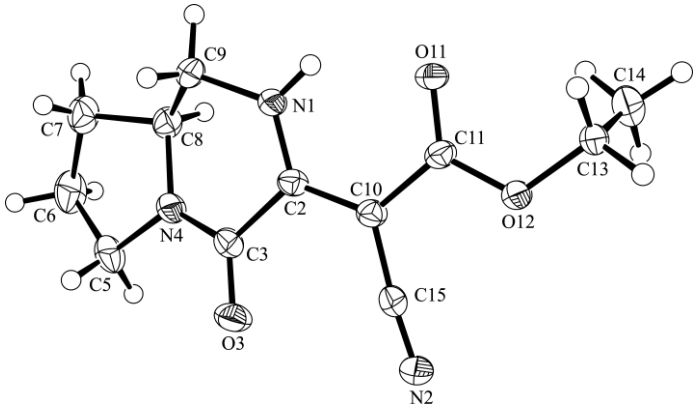


Figure 1. ORTEP plot[11] of the molecular structure of one of the symmetry-independent molecules in the crystal structure of **11a** (arbitrary numbering of the atoms; 50% probability ellipsoids)

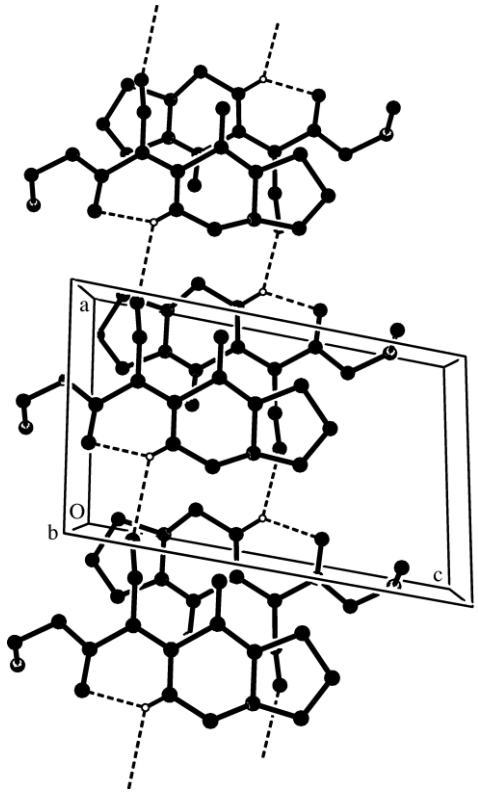


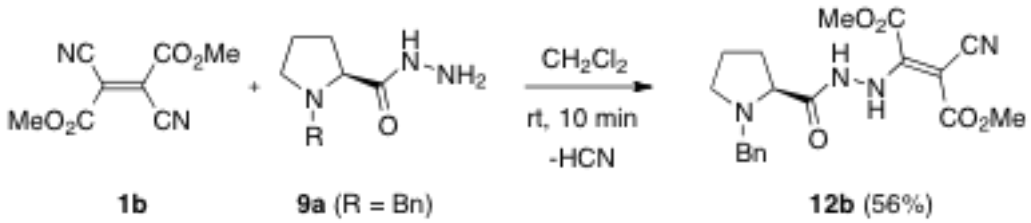
Figure 2. Packing diagram of **11a** showing the hydrogen bonding interactions (uninvolved hydrogen atoms omitted for clarity)

There are two of the enantiomerically pure molecules in the asymmetric unit whose conformations differ by slightly different puckering of the six-membered ring and a significantly different orientation of the terminal ester methyl group (ca. 165° rotation about the ester O–C bond). The amine group forms bifurcated hydrogen bonds. One is an intramolecular interaction with the ester carbonyl O atom [N(1)–H···O(11) and N(21)–H···O(31)] which can be described by a graph set[12] motif of S(10). The

other is an intermolecular interaction with the cyano group [N(1)–H···N(2') and N(21)–H···N(22')] which links the independent molecules into separate extended chains which run parallel to the [100] direction (Figure 2). This interaction can be described by a graph set motif of C(6).

The mechanistic pathway leading to the bicyclic products (**11**) leads via the initially formed enamine type (**10**), which results from the preferred nucleophilic addition of the primary amino group.[4,6] In the second step, a cyclocondesation occurs with the secondary amino group. The latter reaction takes place in a selective manner with the ester group leading to the six-membered lactam.[7]

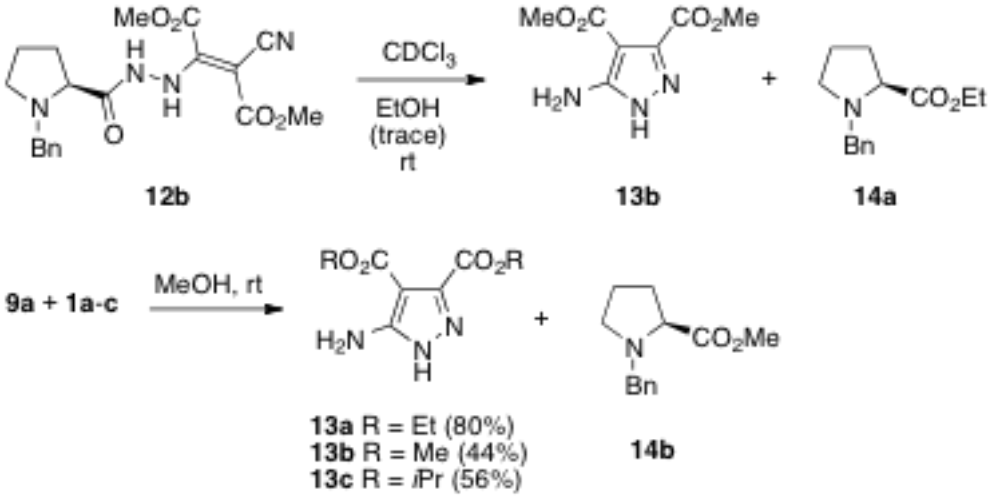
Along with prolinamines (**8**), the *N*-benzyl protected L-proline hydrazide (**9a**) was reacted with dicyanofumarates (**1**). The first experiment was performed in dichloromethane at room temperature with **9a** and **1b**. After 10 min, the solvent was evaporated and a colorless solid was obtained. On the basis of the spectroscopic data, the structure of this product was elucidated as the enehydrazine derivative (**12b**) (Scheme 4). For example, the IR spectrum (KBr) shows strong absorptions of a C≡N and three C=O groups at 2202, 1752, 1667, and ca. 1660 cm^{-1}. In addition, a very intense absorption at 1559 cm^{-1} is attributed to the C=C bond of the 'push-pull' enehydrazine structure.[4] The ^{1}H-NMR spectrum indicates the presence of two MeO groups, with absorptions at 3.95 and 3.81 ppm, and the *N*-benzylpyrrolidine moiety.



Scheme 4

In order to examine cyclization reaction of compound **12b**, a sample of **12b** was dissolved in commercial $CDCl_3$ (for the NMR usage) and was periodically controlled by ^{1}H-NMR spectroscopy. Unexpectedly, after 24 h, the starting compound (**12b**) was converted into new products, which subsequently were separated by preparative TLC. The more polar fraction was obtained as colorless crystals, which showed only three signals in the ^{1}H-NMR spectrum at 3.83 and 3.94 ppm (2 MeO), and 6.10 ppm. The latter disappeared after addition of D_2O. In the IR spectrum (KBr), a prominent absorption at 3281 cm^{-1} indicated the presence of amino groups. The HR-ESI-MS (MeCN + NaI) showed the $[M+Na]^+$ peak at *m/z* 222.04834 corresponding with the molecular formula $C_7H_9N_3O_4$. In addition, the ^{13}C-NMR spectrum revealed the presence of two methyl ester groups (51.1/52.6 and 152.9/163.9 ppm) and only three additional signals at 93.5, 142.5, and 164.6 ppm. Based on these data, the structure of the isolated product was formulated as dimethyl 5-aminopyrazole-3,4-dicarboxylate (**13b**), *i.e.* the *N*-unsubstituted analogue

of the earlier reported products of the reactions of arylhydrazines with dicyanofumarates[8] (Scheme 5). The less polar fraction was also isolated and identified as ethyl *N*-benzylprolinate (**14a**).[13]

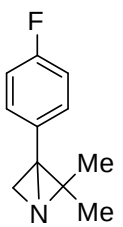


Scheme 5

The formation of products **13b** and **14a** results from the ethanolysis of **12b** by traces of ethanol in the used $CDCl_3$. Prompted by this observation, a sample of **12b** was dissolved in methanol and, after 1 h at room temperature, the ^{1}H-NMR spectrum confirmed the presence of **13b** and methyl *N*-benzylprolinate (**14b**). Moreover, when equimolar amounts of diethyl dicyanofumarate (**1a)** and hydrazide (**9a**) were dissolved in methanol at room temperature, already after 5 min a colorless solid was formed. After 30 min, again a clear solution was observed, and after evaporation of the solvent and chromatographic workup, the two products (**13a**) and (**14b**) were obtained in ca. 1:1 ratio. The same protocol was used in reactions of **9a** with **1b** and **1c** leading to the expected **13b** and **13c**, respectively, in addition to **14b**.

Two other experiments were performed in order to evaluate the reactivity of proline hydrazides (**9**) towards dicyanofumarates (**1**). In one case, proline hydrazide (**9b**, R = H) was reacted with an equimolar amount of **1b** in methanolic solution. After 1 h, the reaction was complete, and the ^{1}H-NMR analysis of the reaction mixture again confirmed the presence of **13b** side by side with methyl prolinate. This result points out that the NH_2 group of the hydrazide reacts faster with **1b** than the proline NH group.

In analogy to our previous study,[5] a three-component reaction of equimolar amounts of **9a**, **1b**, and 3-(4-fluorophenyl)-2,2-dimethyl-1-azabicyclo[1.1.0]butane (**15**) was carried out in methanol at room temperature. The ^{1}H-NMR analysis of the reaction mixture performed after 1 h confirmed the presence of unconverted azabicyclobutane along with **13b** and **14b**. Thus, the nucleophilicity of the hydrazide exceeds that of the 1-azabicylo[1.1.0]butane derivative.



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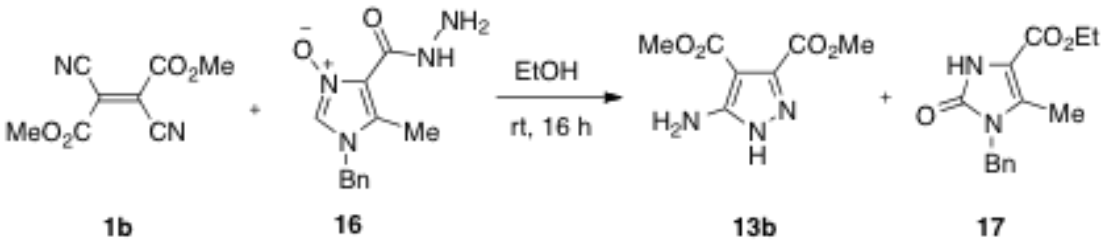
In an extension of the study with proline hydrazides (**9**), the hydrazide (**16**), derived from imidazole *N*-oxide, was reacted with **1b** in ethanol. After 16 h at room temperature, two major products were formed and by comparison with original samples identified as **13b** and ethyl 2-oxoimidazole-4-carboxylate (**17**) (Scheme 6).[14] The latter is formed via the known thermal isomerization of the corresponding 3-oxidoimidazole-4-carboxylate formed *in situ* via ethanolysis of the initially formed enehydrazine like **12**.



Scheme 6

It is worth mentioning that in all experiments carried out with hydrazides (**9a**) and (**16**), no formation of pyrazolones, 1,3,4-oxadiazinones, or 1,3,4-oxadiazoles, suggested as isolated products in earlier reports,[9] was observed. Therefore, the reactions of **1b** with **9a** and **16** were performed also in boiling ethyl acetate. In both cases, after heating for 4 h, complex mixtures of non-identified products were obtained, and the attempted chromatographic separation was unsuccessful.

CONCLUSIONS

The present study shows that prolinamines (**8a**,**b**) smoothly react with the electron-deficient dicyanofumarates (**1a**-**c**) leading, in the initial step, after elimination of HCN, to enamines of type **10**. In the case of the non-protected prolinamine (**8b**), subsequent cyclocondensation leads smoothly to enantiomerically pure bicyclic oxopiperazine derivatives (**11**) in a selective manner. Compounds of that type are of potential interest as building blocks for the preparation of biologically active, bicyclic heterocycles.[15] Proline derived hydrazides undergo the reaction with **1** via addition of the NH_2 group onto the C,C-double bond. The enhydrazines (**12**) obtained thereafter, display remarkable reactivity toward alcohols and are easily cleaved to the corresponding ester and the non-substituted enehydrazines. The latter undergo selective cyclization with the C≡N group forming 3-aminopyrazoles (**13**). The formation of these products deserves a brief comment. As described in our previous paper,[5] the enehydrazines obtained from dicyanofumarates and hydrazine hydrate, which are believed to posses the (*Z*)-configuration, undergo selectively the alternative cyclocondensation, *i.e.* lactamization. A plausible explanation for the observed discrepancy in the cyclization step, e.g. the presence of differently configured enehydrazines, is not available yet.

EXPERIMENTAL

General remarks. Melting points were determined in a capillary using a Melt-Temp. II (Aldrich) or STUART SMP30 apparatus and they are uncorrected. The IR Spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr; absorptions (υ) in cm^{-1}. The ^{1}H- and $^{13}C[^{1}H]$-NMR spectra were measured on a Bruker Avance III (600 and 150 MHz, resp.) instrument using solvent signals as reference. Chemical shifts (δ) are given in ppm and coupling constants *J* in Hz. Assignments of signals in ^{13}C-NMR spectra were made on the basis of HMQC experiments. HR-ESI-MS: Bruker maXis spectrometer. Optical rotations were determined on a PERKIN-ELMER 241 MC polarimeter for λ = 589 nm.

Starting materials. All solvents are commercially available and used as received. Dimethyl-, diethyl-, and diisopropyl dicyanofumarates (**1a**–**1c**) were prepared from the corresponding cyanoacetates by treatment with thionyl chloride according to the published general procedure.[16] [(2*S*)-Pyrrolidin-2-yl]-methylamines (**8a**,**b**),[17a,b] proline hydrazides (**9a**,**b**),[10,18] and 3-oxidoimidazole-4-carbohydrazide (**16**)[19] were prepared according to known procedures.

General procedure for the preparation of compounds 10 and 11. To a magnetically stirred solution of the corresponding dialkyl dicyanofumarate (**1**, 1 mmol) in CH_2Cl_2 (2 mL) at rt, a solution of **8a** or **8b** (1 mmol) in CH_2Cl_2 (2 mL) was added dropwise. When the addition was complete, stirring was continued for 15 min, and then the solvent was evaporated to dryness. The crude product was purified by PLC (SiO_2).

Diethyl (2*Z*)-2-({[(2*S*)-1-benzylpyrrolidin-2-yl]methyl}amino)-3-cyanobut-2-enedioate (**10a**). Yield: 220 mg (57%). Pale yellow oil. $[\alpha]_D^{20}$ –135 (*c* 0.4, CH_2Cl_2). IR (film): *v* 3226*m*, 2978*m*, 2211*s* (CN), 1746*s* (C=O), 1674*s*, 1588*s*, 1274*m*, 1044*m*, 785*m*. ^{1}H-NMR ($CDCl_3$): *δ* 9.81 (*s*, 1H, NH); 7.38–7.22 (*m*, 5 arom. H); 4.42 (*q*, $J_{H,H}$ = 7.2 Hz, 2H, MeCH_2); 4.31–4.23 (*m*, 2H, MeCH_2); 3.87 (*d*, $J_{H,H}$ = 13.2 Hz, 1H, PhCH_2); 3.47 (*d*, $J_{H,H}$ = 13.2 Hz, 1H, PhCH_2); 3.31–3.25 (*m*, 1H, HC(6')); 3.18–3.12 (*m*, 1H, HC(6')); 3.09–3.04 (*m*, 1H, HC(5')); 2.84–2.78 (*m*, 1H, HC(2')); 2.32–2.26 (*m*, 1H, HC(5')); 2.01–1.93 (*m*, 1H, HC(3')); 1.76–1.69 (*m*, 2H, H_2C(4')); 1.68–1.61 (*m*, 1H, HC(3')); 1.40 (*t*, $J_{H,H}$ = 7.2 Hz, 3H, *Me*CH_2); 1.33 (*t*, $J_{H,H}$ = 7.2 Hz, 3H, *Me*CH_2). ^{13}C-NMR ($CDCl_3$): *δ* 167.91 (*C*(2)=C); 161.57, 161.41 (2 C=O); 139.22 (arom. C); 128.81, 128.56, 127.35 (5 arom. CH); 117.15 (CN); 70.93 (C=*C*(3)); 63.70 (Me*C*H_2); 62.05 (C(2')); 61.10 (Me*C*H_2); 58.89 (Ph*C*H_2); 54.76 (C(5')); 48.21 (C(6')); 28.66 (C(3')); 23.44 (C(4')); 14.03, 14.55 (2 *Me*CH_2). ESI-HRMS (MeOH+0.1% HCOOH): 386.20757(calcd.386.20743 for $C_{21}H_{27}N_3O_4$, $[M+1]^+$).

Dimethyl (2*Z*)-2-({[(2*S*)-1-benzylpyrrolidin-2-yl]methyl}amino)-3-cyanobut-2-enedioate (**10b**).

Yield: 283 mg (79%). Pale yellow oil. $[\alpha]_D^{20}$ –133 (*c* 1.0 CH_2Cl_2). IR (film): *v* 3228*m*, 2954*m*, 2211*s* (CN), 1748*s* (C=O), 1680*s*, 1589*s*, 1281*m*, 1045*m*, 796*m*. ^{1}H-NMR ($CDCl_3$): δ 9.80 (*s*, 1H, NH); 7.38–7.23 (*m*, 5 arom. H); 3.94 (*s*, 3H, MeO); 3.86 (*d*, $J_{H,H}$ = 13.21 Hz, 1H, PhC*H*$_2$); 3.81 (*s*, 3H, MeO); 3.48 (*d*, $J_{H,H}$ = 13.21 Hz, 1H, PhC*H*$_2$); 3.30–3.26 (*m*, 1H, HC(6')); 3.16–3.11 (*m*, 1H, HC(6')); 3.09–3.05 (*m*, 1H, HC(5')); 2.84–2.79 (*m*, 1H, HC(2')); 2.32–2.27 (*m*, 1H, HC(5')); 2.01–1.93 (*m*, 1H, HC(3')); 1.75–1.69 (*m*, 2H, H_2C(4')); 1.66–1.59 (*m*, 1H, HC(3')). ^{13}C-NMR ($CDCl_3$): δ 168.19 (*C*(2)=C); 161.93, 161.30 (2 C=O); 139.16 (arom. C); 128.81, 128.59, 127.37 (5 arom. CH); 117.17 (CN); 70.81 (C=*C*(3)); 61.99 (C(2')); 58.88 (Ph*C*H$_2$); 54.78 (C(5')); 53.87, 52.11 (2 Me); 48.32 (C(6')); 28.65 (C(3')); 23.47 (C(2')). ESI-HRMS (MeOH+0.1% HCOOH): 358.17619 (calcd. 358.17613 for $C_{19}H_{23}N_3O_4$, $[M+1]^+$).

Diisopropyl (2*Z*)-2-({[(2*S*)-1-benzylpyrrolidin-2-yl]methyl}amino)-3-cyanobut-2-enedioate (10c). Yield: 333 mg (81%). Pale yellow oil. $[\alpha]_D^{20}$ –135 (*c* 0.4 CH_2Cl_2). IR (film): *v* 3223*m*, 2980*m*, 2211*s* (CN), 1743*s* (C=O), 1668*s*, 1588*s*, 1277*m*, 1100*m*, 700*m*. ^{1}H-NMR ($CDCl_3$): δ 9.80 (*s*, 1H, NH); 7.38–7.35 (*m*, 2 arom. H); 7.32–7.28 (*m*, 2 arom. H); 7.25–7.22 (*m*, 1 arom. H); 5.29–5.23 (*m*, 1H, Me$_2$C*H*); 5.13–5.08 (*m*, 1H, Me$_2$C*H*); 3.88 (*d*, $J_{H,H}$ = 13.21 Hz, 1H, PhC*H*$_2$); 3.36 (*d*, $J_{H,H}$ = 13.21 Hz, 1H, PhC*H*$_2$); 3.30–3.25 (*m*, 1H, HC(6')); 3.18–3.12 (*m*, 1H, HC(6')); 3.08–3.03 (*m*, 1H, HC(5')); 2.83–2.78 (*m*, 1H, HC(2')); 2.31–2.26 (*m*, 1H, HC(5')); 2.00–1.92 (*m*, 1H, HC(3')); 1.76–1.69 (*m*, 2H, HC(4')); 1.68–1.62 (*m*, 1H, HC(3')); 1.39, 1.38 (2*d*, $J_{H,H}$ = 6.24 Hz, 6H, 2 *Me*$_2$CH); 1.31, 1.30 (2*d*, $J_{H,H}$ = 6.60, 6.54 Hz, 6H, 2 *Me*$_2$CH). ^{13}C-NMR ($CDCl_3$): δ 167.55 (*C*(2)=C); 161.52, 161.18 (2 C=O); 139.27 (arom. C); 128.82, 128.55, 127.33 (5 arom. CH); 117.13 (CN); 72.29 (Me$_2$*C*H); 71.05 (C=*C*(3)); 68.68 (Me$_2$*C*H); 62.10 (C(2')); 58.90 (Ph*C*H$_2$); 54.76 (C(5')); 48.07 (C(6')); 28.65 (C(3')); 23.43 (C(4')); 22.09, 22.08, 21.71, 21.68 (2 *Me*$_2$CH). ESI-HRMS (MeOH+0.1% HCOOH): 414.23874 (calcd. 414.23873 for $C_{23}H_{32}N_3O_4$, $[M+1]^+$).

Ethyl (2*Z*)-2-[(8a*S*)-4-oxo-1,2,6,7,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-3-ylidene]-2-cyanoacetate (11a). Yield: 198 mg (79%). Pale yellow crystals, mp 213–214 °C (CH_2Cl_2/hexane). $[\alpha]_D^{20}$ +534 (*c* 1.0 CH_2Cl_2). IR (KBr): *v* 3443*m*, 3208*m*, 2204*s* (CN), 1664*s* (C=O), 1585*s*, 1243*s*, 1174*s*, 796*m*. ^{1}H-NMR ($CDCl_3$): δ 10.06 (*s*, 1H, NH); 4.29–4.22 (*m*, 2H, MeC*H*$_2$); 3.91–3.85 (*m*, 1H, HC(8a')); 3.75–3.62 (*m*, 3H, HC(6'), H_2C(1')); 3.24–3.19 (*m*, 1H, HC(6')); 2.28–2.22 (*m*, 1H, HC(8')); 2.14–2.09 (*m*, 1H, HC(7')); 1.96–1.88 (*m*, 1H, HC(7')); 1.69–1.61 (*m*, 1H, HC(8')); 1.33 (*t*, $J_{H,H}$ = 7.20 Hz, *Me*CH$_2$). ^{13}C-NMR ($CDCl_3$): δ 169.4, 156.7 (2 C=O); 155.2 (*C*(3')=C); 116.7 (CN); 73.9 (C=*C*(2)); 61.5 (Me*C*H$_2$); 55.9 (C(8a')); 45.9 (C(1')); 45.7 (C(6')); 30.7 (C(8')); 23.1 (C(7')); 14.4 (*Me*CH$_2$). ESI-HRMS (MeOH+NaI): 272.10049 (calcd. 272.10056 for $C_{12}H_{15}N_3NaO_3$, $[M+Na]^+$).

Methyl (2*Z*)-2-[(8a*S*)-4-oxo-1,2,6,7,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-3-ylidene]-2-cyanoacetate (**11b**). Yield: 152 mg (64%). Pale yellow crystals, mp 240–242 °C (decomp., CH_2Cl_2/hexane). $[\alpha]_D^{20}$ +294 (*c* 1.0 CH_2Cl_2). IR (KBr): *v* 3439*m*, 3211*m*, 2210*s* (CN), 1663*s* (C=O), 1592*s*, 1252*s*, 1194*s*, 797*m*. ^{1}H-NMR ($CDCl_3$): δ 10.03 (*s*, 1H, NH); 3.92–3.85 (*m*, 1H, HC(8a')); 3.81 (*s*, 3H, MeO); 3.75–3.62 (*m*, 3H, HC(6'), H_2C(1')); 3.25–3.19 (*m*, 1H, HC(6')); 2.29–2.23 (*m*, 1H, HC(8')); 2.15–2.08 (*m*, 1H, HC(7')); 1.96–1.87 (*m*, 1H, HC(7')); 1.69–1.61 (*m*, 1H, HC(8')). ^{13}C-NMR ($CDCl_3$): δ 169.5, 156.7 (2 C=O); 155.3 (*C*(3')=C); 116.7 (CN); 73.3 (C=*C*(2)); 55.9 (C(8a')); 52.4 (MeO); 46.0 (C(1')); 45.7 (C(6')); 30.7 (C(8')); 23.1 (C(7')). ESI-HRMS (MeOH+NaI): 258.08485 (calcd. 258.08491 for $C_{11}H_{13}N_3NaO_3$, $[M+Na]^+$).

Isopropyl (2*Z*)-2-[(8a*S*)-4-oxo-1,2,6,7,8,8a-hexahydropyrrolo[1,2-*a*]pyrazin-3-ylidene]-2-cyano-acetate (**11c**). Yield: 196 mg (74%). Pale yellow crystals, mp 200–202 °C (CH_2Cl_2/hexane). $[\alpha]_D^{20}$ +507 (*c* 1.0 CH_2Cl_2). IR (KBr): *v* 3442*m*, 2983*m*, 2209*s* (CN), 1675*s* (C=O), 1601*s*, 1253*s*, 1110*s*, 770*m*. ^{1}H-NMR ($CDCl_3$): δ 10.08 (*s*, 1H, NH); 5.09–5.01 (*m*, 1H, Me_2CH); 3.93–3.84 (*m*, 1H, HC(8a')); 3.75–3.61 (*m*, 3H, HC(6'), H_2C(1')); 3.24–3.18 (*m*, 1H, HC(6')); 2.27–2.21 (*m*, 1H, HC(8')); 2.13–2.02 (*m*, 1H, HC(7')); 1.95–1.86 (*m*, 1H, HC(7')); 1.68–1.60 (m, 1H, HC(8')); 1.31, 1.30 (2*d*, $J_{H,H}$ = 6.00 Hz, Me_2CH). ^{13}C-NMR ($CDCl_3$): δ 168.9, 156.6 (2 C=O); 155.5 (*C*(3')=C); 116.7 (CN); 74.2 (C=*C*(2)); 69.3 (Me_2CH); 55.9 (C(8a')); 45.9 (C(1')); 45.7 (C(6')); 30.6 (C(8')); 23 (C(7')); 22.0, 21.9 (Me_2CH). ESI-HRMS (MeOH+NaI): 286.11607 (calcd. 286.11621 for $C_{13}H_{17}N_3NaO_3$, $[M+Na]^+$).

Preparation of dimethyl 2-{[N^2-(1-benzylpyrrolidin-2-yl)carbonyl]hydrazino}-3-cyanobut-2-ene-dioate (12b). To a solution of hydrazide (**9a**, 1 mmol) in 1 mL of CH_2Cl_2, 1 mmol of dicyanofumarate (**1b**) was added in portions. The mixture was stirred for 10 min at rt, and the solvent was removed under vacuum to give **12b** as yellowish solid. Yield: 200 mg (56%). Yellowish solid, mp 162–165 °C (EtOH). $[\alpha]_D^{20}$ –103 (*c* 1.0, CH_2Cl_2). IR (KBr): 3220*m* (NH), 2955*w*, 2202*s* (C≡N), 1752*vs* (C=O), 1667*vs* (C=O), 1559*s*, 1281*s*. ^{1}H-NMR ($CDCl_3$): 7.33–7.18 (*m*, 5 arom. H); 7.10 (br.*s*, NH); 4.42–4.40 (*m*, CH); 3.95 (*s*, MeO); 3.87 (*d*, *J* = 12.6 Hz, 1H, PhCH_2); 3.81 (*s*, MeO); 3.64 (*d*, *J* = 12.6 Hz, 1H, PhCH_2); 3.16–3.14 (*m*, 1H), 2.52–2.38 (*m*, 2H); 1.95–1.82 (*m*, 3H). ^{13}C-NMR ($CDCl_3$): 176.6, 92.3 (C=C); 163.1, 162.8, 153.9 (3 C=O); 146.3 (1 arom. C); 129.0, 128.1, 127.2 (5 arom. CH); 114.9 (C≡N); 64.4 (CH); 58.7 (PhCH_2); 52.7, 51.3 (2 MeO); 54.6, 30.1, 23.3 (3 proline CH_2). HR-ESI-MS (MeCN+HCOOH): 387.16658 (calcd. 387.16630 for $C_{19}H_{23}N_4O_5$, $[M+H]^+$).

Reactions of hydrazides (9a, b) and (16) with dicyanofumarates (1). – **General procedure**. To a solution of hydrazide **9** or **16** (1 mmol) in 1 mL of MeOH (or EtOH), 1 mmol of **1** was added and the

mixture was stirred at rt. In the case of the reactions with **9a** and **9b**, the conversion was complete after 1 h. The solvent was removed under vacuum, and the residue was purified on preparative TLC plates (SiO_2) using hexane/AcOEt (1:4) to give **13a** – **c** as more polar fractions ($R_f \sim 0.2$). In all cases, the less polar fraction (($R_f \sim 0.8$) was isolated and indetified as methyl prolinate (**14b**).

The reaction of **16** with **1b**, carried out in EtOH solution, was complete only after 16 h, and after evaporation of the solvent, crude products were separated on preparative TLC plates (SiO_2) using hexane/AcOEt (1:4). In this case, **13b** was isolated as a the less polar fraction and imidazolone (**17**) from a fraction located near the start line. After eluation and evaporation of the solvent, the isolated material was identified by comparison of its ^{1}H NMR with a literature sample.[14]

Diethyl 3-amino-1*H*-pyrazole-4,5-dicarboxylate (**13a**). Yield: 169 mg (80%). Colorless solid, mp 93–96 °C (MeOH). IR (KBr): 3363*m* (NH), 3290*s* (NH), 2983*m*, 1717*vs* (C=O), 1684*vs* (C=O), 1619*m*, 1520*m*, 1305*m*, 1254*m*, 1131*m*, 1050*m*. ^{1}H-NMR ($CDCl_3$): 6.13 (br.*s*, NH_2); 4.41, 4.29 (2*q*, J = 7.2 Hz, 2 MeCH_2); 1.39, 1.34 (2*t*, J = 7.2 Hz, *Me*CH_2). ^{13}C-NMR ($CDCl_3$): 164.5, 142.8, 93.5 (3 arom. C); 163.7, 153.0 (2 C=O); 61.9, 59.8 (2 Me*C*H_2); 14.4, 14.1 (2 *Me*CH_2). HR-ESI-MS (MeCN+NaI): 250.07958 (calcd. 250.07983 for $C_9H_{13}N_3NaO_4$, [*M*+Na]$^+$).

Dimethyl 3-amino-1*H*-pyrazole-4,5-dicarboxylate (**13b**). Yield: 81 mg (44%). Colorless solid, mp 163–166 °C (MeOH). IR (KBr): 3281*s* (NH), 2958*m*, 1730*vs* (C=O), 1697*vs* (C=O), 1625*m*, 1524*m*, 1254*m*, 1130*m*. ^{1}H-NMR ($CDCl_3$): 6.10 (br.*s*, NH_2); 3.94, 3.83 (2*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 164.6, 142.5, 93.5 (3 arom. C); 163.8, 152.9 (2 C=O); 52.6, 51.2 (2 MeO). HR-ESI-MS (MeCN+NaI): 222.04834 (calcd. 222.04853 for $C_7H_9N_3NaO_4$, [*M*+Na]$^+$).

Diisopropyl 3-amino-1*H*-pyrazole-4,5-dicarboxylate (**13c**). Yield: 132 mg (56%). Colorless solid, mp 182–185 °C (MeOH). IR (KBr): 3326*m* (NH), 3281*s* (NH), 2981*m*, 1713*vs* (C=O), 1680*vs* (C=O), 1625*m*, 1520*m*, 1300*m*, 1100*m*, 1032*m*. ^{1}H-NMR ($CDCl_3$): 6.10 (*br.s*, NH_2); 5.27–5.20 (*m*, 2 CH); 1.39, 1.34 (2*d*, J = 6.6, 4 Me). ^{13}C-NMR ($CDCl_3$): 164.2, 143.0, 93.7 (3 arom. C); 163.2, 152.9 (2 C=O); 70.1, 67.3 (2 CH); 22.2, 21.8 (4 Me). HR-ESI-MS (MeCN+NaI): 278.11129 (calcd. 278.11113 for $C_{11}H_{17}N_3NaO_4$, [*M*+Na]$^+$).

Ethyl 1-benzyl-2,3-dihydro-5-methyl-2-oxo-1*H*-imidazole-4-carboxylate (17). Yield: 0.143 g (55%). Colorless crystals, mp 195–198 °C (MeOH, lit.,[14] 194–198 °C, CH_2Cl_2/Et_2O). ^{1}H-NMR ($CDCl_3$): 9.70 (*br. s*, NH); 7.37–7.21 (*m*, 5 arom. H); 4.91 (*s*, PhCH_2); 4.28 (*q*, J = 7.1 Hz, MeCH_2); 2.29 (*s*, Me); 1.32 (*t*, J = 7.1 Hz, *Me*CH_2).

Three-component reaction of 9a, 1b and 3-(4-fluorophenyl)-2,2-dimethyl-1-azabicyclo[1.1.0]butane (15). To a solution of hydrazide (**9a**, 1 mmol) and **15**[20] (1 mmol) in 1 mL of MeOH, 1 mmol of dicyanofumarate (**1b**) was added. The mixture was stirred for 1 h at rt, the solvent was evaporated under vacuum, and the residue was purified on preparative TLC plates (SiO_2) using hexane/AcOEt mixture (1:4) to give **13b**. Yield: 138 mg (69%).

X-Ray Crystal-Structure Determination of 11a (Figures 1 and 2).[21] All measurements were made on a Agilent Technologies SuperNova area-detector diffractometer[22] using CuK_α radiation (λ = 1.54184 Å) from a micro-focus X-ray source and an Oxford Instruments Cryojet XL cooler. Data reduction was performed with CrysAlisPro.[22] The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction using spherical harmonics[22] was applied. The space group was determined from packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure. Equivalent reflections, other than Friedel pairs, were merged. The data collection and refinement parameters are given below. A view of the molecule is shown in Figure 1 and the packing diagram in Figure 2. The structure was solved by direct methods using SHELXS97,[23] which revealed the positions of all non-H-atoms. There are two molecules in the asymmetric unit whose conformations differ by slightly different puckering of the six-membered ring and a significantly different orientation of the terminal ester methyl group. The non-H-atoms were refined anisotropically. The amine H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the methyl group). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2–F_c^2)^2$. A correction for secondary extinction was applied. Neutral atom scattering factors for non-H-atoms were taken from ref.[24], and the scattering factors for H-atoms were taken from ref.[25] Anomalous dispersion effects were included in F_C;[26] the values for f' and f'' were those of ref.[27] The values of the mass attenuation coefficients are those of ref.[28] All calculations were performed using the SHELXL97 program.[23] Crystal data for **11a**: Crystallized from hexane/CH_2Cl_2, $C_{12}H_{15}N_3O_3$, M = 249.27, pale yellow, tablet, crystal dimensions 0.09 × 0.20 × 0.20 mm, triclinic, space group $P\bar{1}$, Z = 2, reflections for cell determination 5029, 2θ range for cell determination 12–153°, a = 7.3920(3) Å, b = 7.4342(3) Å, c = 11.7274(5) Å, α = 98.503(3), β = 98.135(3)°, γ = 103.850(4), V = 608.25(4) Å^3, D_X = 1.361 g·cm^{-3}, μ(CuK_α) = 0.830 mm^{-1}, T = 160(1) K, ω scans, 2θ_{max} = 153.2°, transmission factors (min; max) 0.738; 1.000, total reflections measured 6237, symmetry independent reflections 3907, reflections with $I > 2\sigma(I)$

3875, reflections used in refinement 3907, parameters refined 336, restraints 3, final $R(F)$ ($I > 2\sigma(I)$ reflections) = 0.0337, $wR(F^2)$ (all data) = 0.1048 ($w = [\sigma^2(F_o^2) + (0.0576P)^2 + 0.1927P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$, goodness of fit 1.128, final $\Delta_{max}/\sigma = 0.001$, $\Delta\rho$ (max; min) = 0.28; –0.19 e Å^{-3}.

ACKNOWLEDGEMENTS

We thank the analytical services of our institute for NMR spectra and PD Dr. L. Bigler, University of Zurich, for HR-ESI-MS. A. M. P. is grateful for financial support within the project *European Social Fund 'HUMAN – BEST INVESTMENT!'*, co-funded by the *European Union*. Skilful help by Mrs. Małgorzata Celeda in performing of some experiments is acknowledged.

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