

Reactions of diethyl 2-(ethoxymethylene)malonate with 2-cyanoacetanilides: unexpected transfer of the ethoxymethylene moiety

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Abstract

A sodium ethoxide catalyzed reaction of *N*-substituted cyanoacetanilides **1a-f** with diethyl 2-(ethoxymethylene)malonate **2** unexpectedly leads to the corresponding 2-amino-5-cyano-6-oxo-*N*,1-diaryl-1,6-dihydropyridine-3-carboxamides **3a-f**, while the expected 5-cyano-2-hydroxy-6-oxo-1-aryl-1,6-dihydropyridine-3-carboxylates **4a-f** were observed only as minor products.

Keywords: Cyanoacetanilides, 2-pyridone derivatives, ethoxymethylene derivatives, diethyl 2-(ethoxymethylene)malonate

Introduction

The synthesis of 2-pyridone derivatives is of a continued interest in the field of heterocyclic chemistry. Several topical reviews have appeared in the literature over the last years about the synthesis of the 2-pyridone ring.¹ These heterocycles attracted attention because of their applications as bioactive compounds for example as a promising class of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs),² as antibacterial,³ antifungal⁴ and cardiogenic agents.⁵ Moreover, such derivatives have recently become important due to their structural similarity to nucleosides.⁶ Also, 2-pyridones were used as ligands for the late 3d-metals.⁷ Thus, the development of novel methods for the synthesis of the 2-pyridone ring is of topical interest.

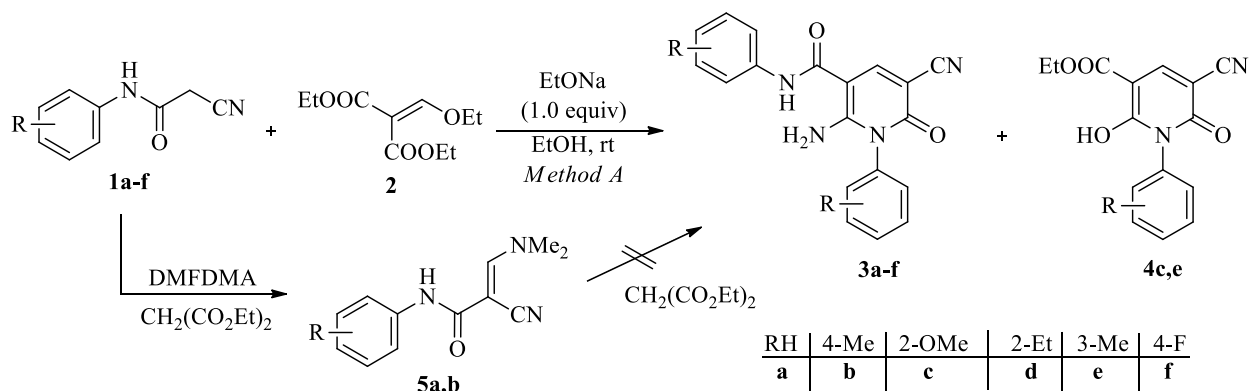
Our efforts in this area are focused on the synthetic routes where the 2-pyridone ring is assembled from a C-1 synthon and two methylene active components.⁸ Application of *N*-substituted cyanoacetamides as CH-acids⁹ in such schemes allows introduction of an

additional diversity point into the final 2-pyridone molecule via the amide group¹⁰ or, depending on the reaction conditions, leads to *N*-1-substituted 3-cyano-2-pyridones.¹¹

In this work we aimed to investigate a novel interaction of *N*-substituted cyanoacetamides **1a-f** with diethyl 2-(ethoxymethylene)malonate¹² (DEEMM) **2**.

Results and Discussion

Reactions of *N*-substituted cyanoacetamides **1a-f** with DEEMM **2** in EtOH in the presence of 1.0 equiv of EtONa at room temperature resulted in the isolation of diaryl derivatives **3a-f** as major products instead of the expected ethyl carboxylates **4a-f** (Scheme 1). The compounds **3a-f** were isolated upon filtration in moderate to good yields after recrystallization (Table 1, Method A), however, the formation of the expected products **4a-f** was also detected by LC/MS of the crude products **3a-f**.



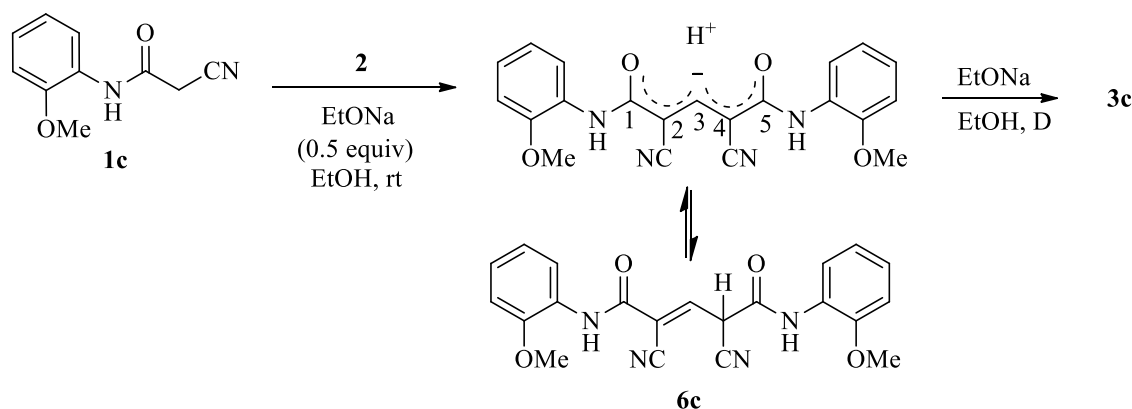
Scheme 1

Table 1. Isolated yields of the synthesized compounds **3a-f**, **4c,e** and **6c**

Product	R	Isolated yields, % Method A (B)
3a	H	40 (93)
3b	4-Me	71 (91)
3c	2-OMe	25 (81)
3d	2-Et	24
3e	3-Me	35
3f	4-F	25
4c	2-OMe	7
4e	3-Me	8
6c	2-OMe	71

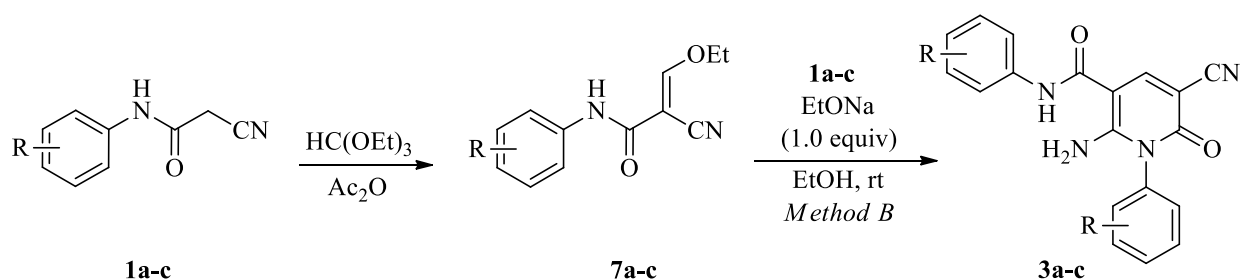
Application of weaker bases (*N*-methylmorpholine, Et₃N in EtOH or DMF) at room or elevated temperatures resulted in recovery of the starting materials. The use of DEEMM **2** taken in excess did not increase the yield of the minor products **4a-f**, however, excess of sodium ethoxide allowed isolation of two representatives of the minor ester derivatives **4c,e** in small yields from the mother solutions (Table 1). To obtain the desired products **4a,b** we also attempted to use dimethylformamide dimethylacetal (DMFDMA) as C-1-synthon in three-component or one-pot step-by-step reaction format (with initial interaction between diethyl malonate and DMFDMA). All these attempts resulted in the isolation of the known adducts **5a,b**¹³ which did not react with diethyl malonate.

The application of smaller amounts of sodium ethoxide (0.5 equiv) led to the isolation of open chain products **6** (Scheme 2) in the mixture with their isomers of type **3**. One representative of such isomeric compounds bearing an *ortho*-methoxy group **6c** was successfully isolated. This compound is stable enough in DMSO-*d*₆ during NMR measurements and could be purified by recrystallization. Heating of **6c** in EtOH in the presence of sodium ethoxide resulted in the formation of 2-pyridone **3c** in 80% yield.



Scheme 2

We found in the literature only a single instance¹⁴ where a representative of the heterocyclic class **3** was obtained. Thus, to examine a possible alternative synthetic route to such molecules, and also to model one of the possible reaction stages of their formation from cyanoacetamides **1a-f** and DEEMM **2** (Scheme 1) we utilized ethoxymethylene derivatives **7a-c** (Scheme 3). Thus, their reaction with cyanoacetamides **1a-c** under the same conditions resulted in formation of the desired derivatives **3a-c** in very high yields (Table 1, Method B) without additional purification.



Scheme 3

Comparing Methods A and B one should take into account that the Method B required the initial synthesis of ethoxymethylene compounds **7a-c** which were obtained in 65-90% isolated yields (see Experimental Section for details).

Structural elucidation

The structure of the representative **3a** (Schemes 1 and 3) is undoubtedly determined by single crystal X-ray analysis (Figure 1). Spectral data for **3a** (^1H NMR, MS and IR spectra) are in accordance with this structure. It was interesting to compare the cyclic compound **3c** with its open chain isomer **6c** (Scheme 2). These compounds give the same mass of their molecular ions ($m/z = 391,2$ $[\text{M}+1]^+$), but differ in their IR characteristic bands, thus, a slightly split band of CN-group in the acyclic compound **6c** lies at 2195 cm^{-1} , whereas the CN-group of compound **3c** appears at 2224 cm^{-1} . The absorption of carbamide C=O groups for compound **6c** is found at 1626 cm^{-1} , and at 1678 cm^{-1} for **3c**.

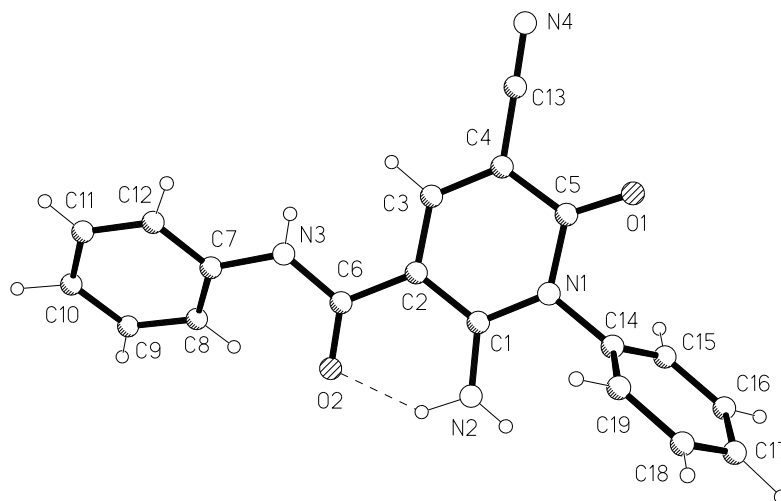
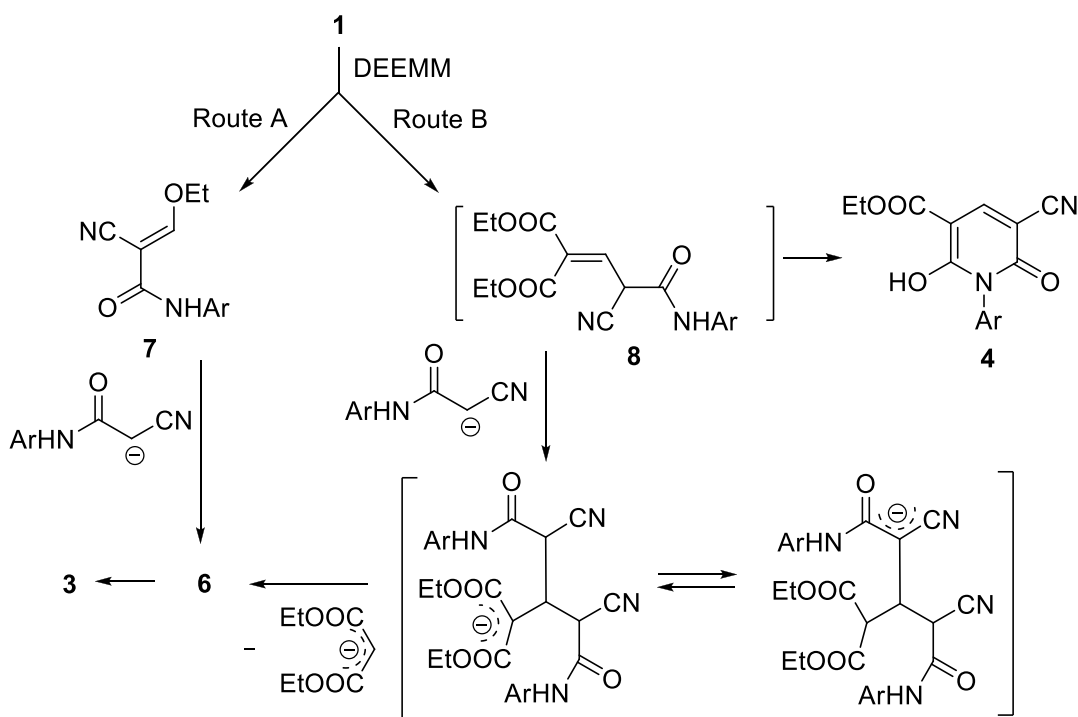


Figure 1. The molecular structure of compound **3a**. Selected bond lengths (Å) and valence angles (°) in the molecule **3a**: C¹-N¹ 1.370(2), C⁵-N¹ 1.416(2), C¹-C² 1.419(2), C²-C³ 1.392(2), C³-C⁴ 1.367(2), C⁴-C⁵ 1.434(3), C²-C⁶ 1.472(2), C¹-N² 1.321(2), C⁵-O¹ 1.216(2), C⁶-N³ 1.350(2); N¹-C¹-C² 119.47(14), C⁴-C³-C² 122.95(16), C³-C⁴-C⁵ 121.46(15), N¹-C⁵-C⁴ 114.17(15), C¹-N¹-C⁵ 124.48(14).

The ^1H NMR spectrum of compound **6c** shows 3-CH proton signals at 8.28 ppm (compared to **3c**, the corresponding singlet of 4-CH proton is at 7.94 ppm) and it contains also one range of proton signals of two equivalent aromatic substituents with a double integral intensity, whereas two aromatic rings of **3c** differ in their proton chemical shifts. The amide protons of this compound appear in the usual area for them (8.66, 9.45 ppm), for the open chain isomer **6c** one broad signal of its amide groups is located at 8.20 ppm probably due to the efficient conjugation and distribution of the charge in the anion form. The signal of 2-/4-CH proton is absent in the ^1H NMR spectrum of **6c** in $\text{DMSO}-d_6$ probably due to fast deuterium exchange. However in the ^{13}C NMR spectrum, a signal at 75.13 ppm can be obviously assigned to the 2-/4-CH carbons. This signal does not appear in the DEPT also demonstrating the mobility of this CH proton.

Possible reaction mechanisms

In view of the chemical behavior of DEEMM in the reactions with 2-cyanoacetanilides and the determined structures of the products **3**, **4** and **6** one can consider two possible reaction pathways to the diaryl derivatives **3** (Scheme 4). The first suggests initial transfer of the ethoxymethylene moiety from DEEMM onto the active cyanomethylene compound **1** giving ethoxymethylene derivative **7** (analogous behavior was previously observed for DMFDMA adducts,¹⁰ see also Schemes 1 and 3), which then reacts with another molecule **1** giving an open chain kinetic product **6** which after base catalyzed cyclization gives pyridone **3** (Route A).



Scheme 4

On the other hand, the formation of the minor product **4** proceeds via conjugate addition of the methylene active nitrile **1** to DEEMM. Intermediate **8** that meanwhile may undergo a Michael addition of the second molecule of **1**, as showed on the Scheme 4, and after elimination of diethylmalonate finally results in formation of pyridone **3** (Route B).

Conclusions

Interaction of *N*-substituted cyanoacetamides **1a-f** with DEEMM **2** in the presence of sodium ethoxide (1.0 equiv) at room temperature proceeds via two competing reaction pathways resulting in formation of diaryl derivatives **3a-f** and admixtures of ethyl carboxylates **4a-f**. Application of lower amounts of sodium ethanolate was favorable for isolation of acyclic intermediate **6c** which was transformed into the corresponding pyridone **3c**.

Experimental Section

General. The IR spectra were recorded on a FIR «Spectrum One» (PerkinElmer) in KBr. Melting points were determined on a Koeffler apparatus. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury VX-200 and Bruker Avance DRX 500 spectrometers in DMSO- d_6 with TMS as an external standard. LC/MS data were recorded using chromatography/mass spectrometric system “Agilent 1100 Series” equipped with a diode-matrix and massselective detector “Agilent LC/MSD SL” with Zorbax SB-C18, 1.8 μm , 4.6 mm $\times$ 15 mm column using eluents: A, acetonitrile/water (95:5), 0.1% TFA; B, water (0.1% of TFA) and eluent flow: 3 mL/sec. Volume of the injected sample was 1 μL . UV detectors were operated at 215, 254, and 265 nm. Chemical ionization under atmospheric pressure was used in MS detector. Ionization mode: simultaneous scanning of positive and negative ions in the mass range of 80–1000 m/z . Elemental analysis was carried out on an EuroVector EA-3000 instrument. TLC was performed on Silufol UV-254 plates with eluent system: acetone-hexane (3:5), visualization: UV light, iodine vapors.

X-Ray structure determination for (3a)

Crystal data: $\text{C}_{19}\text{H}_{14}\text{N}_4\text{O}_2$, M 330.34, monoclinic, space group $P2_1$, $a = 9.2159(14)$, $b = 8.2387(12)$, $c = 10.8726(17)\text{\AA}$, $\beta = 93.054(5)^\circ$, $V = 824.4(2)\text{\AA}^3$, $Z = 2$, $d_c = 1.331\text{ g}\cdot\text{cm}^{-3}$, μ 0.090 mm^{-1} , $F(000)$ 344 crystal size ca. 0.40 $\times$ 0.28 $\times$ 0.13 mm. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer operating in the ω and ϕ scans mode. The cell parameters were obtained from the least-squares treatment of 1918 reflections in the θ range of 2.82–26.55°. The intensity data were collected within the range of $2.82 \leq \theta \leq 29.49^\circ$ using Mo- $\text{K}\alpha$ radiation ($\lambda = 0.71078\text{\AA}$). The intensities of 5873 reflections were collected (3856 unique reflections, $R_{\text{merg}} = 0.0217$). Data were corrected for Lorentz and polarization effects. The SADABS absorption correction (the ratio of minimum

to maximum apparent transmission is 0.653252) was applied. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the SHELXS97 and SHELXL97 programs.^{16,17} All hydrogen atoms were refined isotropically. In the refinement 3856 independent reflections (3026 reflections with $I \geq 2\sigma(I)$) were used. Convergence was obtained at $R1 = 0.0597$ and $wR2 = 0.0962$, $GOF = 1.003$ for all reflection and $R1 = 0.0420$ and $wR2 = 0.0867$, $GOF = 1.003$ for observed (282 parameters; observed/variable ratio 10.7; the largest and minimal peaks in the final difference map 0.13 and $-0.31 \text{ e}/\text{\AA}^3$, weighting scheme is as follows: $\omega = 1/[\sigma^2(\text{Fo}^2) + (0.0442P)^2 + 0.0316P]$, where $P = (\text{Fo}^2 + 2\text{Fc}^2)/3$), Flack parameter 0.0(12), thus absolute configuration was not determined because of absence of heavy atoms. Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 784198.

Preparation of compounds (3a-f, 4c,e) and (6c). Method A

Sodium (0.005 mol) was dissolved in 2 mL of abs. EtOH. To this solution the appropriate CH-acid **1a-f** (0.005 mol) was added and stirred for 5 min at rt. DEEMM **2** (0.005 mol) was added to the mixture and stirred for 1 h at rt. The precipitate **3** was filtered off and washed with ethanol and hexane, crystallized from DMF (for **3a-c,f**) or butanol-1 (for **3d,e**).

Compounds **4c,e** were isolated following this procedure with a use of 0.01 mol of EtONa. To the filtrate from precipitation of **3** 1 mL of 10% KOH aqueous solution was added and the precipitates **4c,e** was left overnight was filtered off and washed with ethanol and hexane. Recrystallisation was performed from butanol-1 **4c** or DMF **4e**.

Compound **6c** was obtained in 71% yield following method A using 2.5 mmol sodium ethanolate. The product was recrystallized from acetone.

Preparation of compounds (3a-f). Method B

Initial compounds **7a-c** were obtained by slightly modified procedure described previously.¹⁵ A mixture of 0.02 mol of the appropriate CH-acid **1a-c** and triethylorthoformate (0.04 mol) was refluxed in 0.06 mL of acetic anhydride. Then volatile waste-products were slowly distilled off at atmosphere pressure until temperature reached 82 °C. The precipitate of **7a-c** formed on cooling was filtered off, washed with dry cold methanol and after drying was used for the next step without additional purification. Yields: 81% **7a**, 78% **7b**, 60% **7c**.

Sodium (0.005 mol) was dissolved in 2 mL of abs. EtOH. To this solution the appropriate CH-acid **1a-c** (0.005 mol) was added and stirred for 5 min at rt. The appropriate ethoxymethylene derivative **7a-c** (0.005 mol) was added to the mixture and stirred for 1 h at rt. The precipitate **3a-c** was filtered off and washed with ethanol and hexane.

2-Amino-5-cyano-6-oxo-N,1-diphenyl-1,6-dihydropyridine-3-carboxamide (3a). Yellow crystals (from DMF); mp 295-296 °C. IR (KBr) cm^{-1} : 3320 (NH_2 , NH), 2218 ($\text{C}\equiv\text{N}$), 1682 ($\text{C}=\text{O}$), 1538, 1588 (δNH_2 , NH). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.09 (t, $J = 6.7 \text{ Hz}$, 1H, H_{Ar}),

7.33 (m, 4H, H_{Ar}), 7.57 (m, 5H, H_{Ar}), 8.69 (s, 1H, C⁴H), 9.91 (s, 1H, NHAr), no NH₂ signals was observed, presumably due to fast deuteroexchange. LC/MS, *m/z* (%): 331.2 (100) [M+1]⁺. ¹³C NMR (50 MHz, DMSO-*d*₆) δ 85.54, 93.74, 118.27, 121.44, 124.16, 129.15, 130.22, 130.73, 134.32, 139.05, 145.64, 157.56, 160.11, 165.24. Anal. Calcd for C₁₉H₁₄N₄O₂: C, 69.1; H, 4.3; N, 16.9. Found: C, 69.3; H, 4.1; N, 16.8.

2-Amino-5-cyano-6-oxo-*N*,1-di-(*p*-tolyl)-1,6-dihydropyridine-3-carboxamide (3b). Pale yellow powder (from DMF); mp 287-288 °C. IR (KBr) cm⁻¹: 3397 (NH₂, NH), 2224 (C≡N), 1678 (C=O), 1581, 1539 (δ NH₂, NH). ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.29 (s, 3H, CH₃), 2.43 (s, 3H, CH₃), 7.16 (d, *J* = 8.15 Hz, 2H, H_{Ar}), 7.25 (d, *J* = 7.89 Hz, 2H, H_{Ar}), 7.43 (d, *J* = 7.84 Hz, 2H, H_{Ar}), 7.51 (d, *J* = 8.24 Hz, 2H, H_{Ar}), 8.69 (s, 1H, C⁴H), 9.87 (s, 1H, NHAr), no NH₂ signal was observed, presumably due to fast deuteroexchange. LC/MS, *m/z* (%): 359.0 (100) [M+1]⁺. ¹³C NMR (50 MHz, DMSO-*d*₆) δ 20.39, 20.89, 74.43, 119.68, 120.99, 128.26, 128.79, 128.92, 131.10, 132.64, 136.17, 137.39, 139.08, 145.82, 147.56, 157.20, 164.54. Anal. Calcd for C₂₁H₁₈N₄O₂: C, 70.4; H, 5.1; N, 15.6. Found: C, 70.1; H, 4.9; N, 15.3.

2-Amino-5-cyano-*N*,1-di-(2-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (3c). Red crystals (from DMF); mp 260-261 °C. IR (KBr) cm⁻¹: 3397 (NH₂, NH), 2224 (C≡N), 1678 (C=O), 1581 (δ NH₂, NH). ¹H NMR (500 MHz, DMSO-*d*₆) δ 3.76 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 6.93 (t, *J* = 7.52 Hz, 1H, H_{Ar}), 7.07 (d, *J* = 8.17 Hz, 1H, H_{Ar}), 7.13 (t, *J* = 7.54 Hz, 1H, H_{Ar}), 7.19 (t, *J* = 7.82 Hz, 1H, H_{Ar}), 7.28 (t, *J* = 9.11 Hz, 2H, H_{Ar}), 7.40 (d, *J* = 7.66 Hz, 1H, H_{Ar}), 7.54 (t, *J* = 7.48 Hz, 1H, H_{Ar}), 7.94 (s, 1H, NH), 8.66 (s, 1H, C⁴H), 9.45 (s, NH₂), signal of NH₂ group has decreased intensity. ¹³C NMR (50 MHz, DMSO-*d*₆) δ 56.47, 56.56, 77.77, 101.84, 111.87, 113.83, 120.64, 121.08, 121.94, 122.12, 122.42, 130.48, 130.99, 132.04, 145.34, 149.58, 156.76, 158.26, 164.18. LC/MS, *m/z* (%): 388.8 [M-1]⁺ (100). Anal. Calcd for C₂₁H₁₇N₄O₄: C, 64.6; H, 4.7; N, 14.4. Found: C, 56.4; H, 5.1; N, 12.5.

2-Amino-5-cyano-*N*,1-di-(2-ethylphenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (3d). Pale yellow powder (from BuOH); mp 238-239 °C. IR (KBr) cm⁻¹: 3454, 3327 (NH₂, NH), 2213 (C≡N), 1666 (C=O), 1516 (δ NH₂, NH). ¹H NMR (500 MHz, DMSO-*d*₆) δ 1.10 (t, *J* = 7.63 Hz, 3H, CH₃), 1.13 (t, *J* = 7.58 Hz, 3H, CH₃), 2.32 (dd, *J* = 7.43, 4.2 Hz, 2H, CH₂), 2.59 (q, *J* = 7.41, 4.2 Hz, 2H, CH₂), 7.20 (d, *J* = 7.18 Hz, 2H, H_{Ar}), 7.22 (d, *J* = 7.16 Hz, 1H, H_{Ar}), 7.27 (m, 2H, H_{Ar}), 7.42 (m, 1H, H_{Ar}), 7.52 (d, *J* = 4.18 Hz, 2H, H_{Ar}), 8.72 (s, 1H, C⁴H), 9.69 (s, 1H, NHAr), no NH₂ signal was observed, presumably due to fast deuteron-exchange. ¹³C NMR, DEPT (50 MHz, DMSO-*d*₆) δ 19.1(CH₃), 19.6(CH₃), 28.5(CH₂), 29.3(CH₂), 131.4(CH), 132.1(CH), 133.2(CH), 133.4(CH), 133.8(CH), 134.2(CH), 135.3(CH), 135.7(CH), 151.8(CH). LC/MS, *m/z* (%): 387.2 (100) [M+1]⁺, 99.2 (5). Anal. Calcd for C₂₃H₂₂N₄O₂: C, 71.5; H, 5.7; N, 14.5. Found: C, 71.4; H, 6.0; N, 14.4.

2-Amino-5-cyano-6-oxo-*N*,1-di-(*m*-tolyl)-1,6-dihydropyridine-3-carboxamide (3e). Yellow powder (from BuOH); mp 330-331 °C. IR (KBr) cm⁻¹: 3409, 3294 (NH₂, NH), 2212 (C≡N), 1662 (C=O), 1557 (δ NH₂, NH). ¹H NMR (500 MHz, DMSO-*d*₆) δ 2.29 (s, 3H, CH₃), 2.37 (s, 3H, CH₃), 6.91 (s, 1H, H_{Ar}), 7.18 (m, 3H, H_{Ar}), 7.41 (m, 2H, H_{Ar}), 7.46 (m, 2H, H_{Ar}), 8.67 (s, 1H, C⁴H), 9.84 (s, 1H, NHAr), no NH₂ signal was observed, presumably due to fast deuteron-

exchange. LC/MS, m/z (%): 359.0 (100) $[M+1]^+$. ^{13}C NMR (50 MHz, $\text{DMSO}-d_6$) δ 21.35, 21.66, 118.38, 118.44, 118.50, 121.90, 124.87, 126.04, 128.88, 129.45, 130.64, 130.95, 134.36, 138.21, 139.07, 140.47, 146.61, 157.67, 160.14, 165.24. Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_2$: C, 70.4; H, 5.1; N, 15.6. Found: C, 70.0; H, 4.9; N, 15.0.

2-Amino-5-cyano-*N*,1-di-(4-fluorophenyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (3f).

Yellow powder (from DMF); mp 322-324 °C. IR (KBr) cm^{-1} : 3439 (NH_2 , NH), 2224 ($\text{C}\equiv\text{N}$), 1668 ($\text{C}=\text{O}$), 1596, 1537 (δ NH_2 , NH). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 7.17 (t, J = 8.61 Hz, 2H, H_{Ar}), 7.44 (d, J = 6.48 Hz, 4H, H_{Ar}), 7.61 (m, 2H, H_{Ar}), 8.65 (s, 1H, C^4H), 9.96 (br s, 1H, NH), no NH_2 signal was observed, presumably due to fast deuteron-exchange with water present in the solvent. ^{13}C NMR (50 MHz, $\text{DMSO}-d_6$) δ 85.99, 93.99, 115.52, 115.96, 117.72, 118.18, 123.69, 123.84, 130.81, 131.88, 135.55, 146.86, 156.87, 158.15, 160.24, 161.65, 165.56, 165.80. LC/MS, m/z (%): 367.0 $[M+1]^+$ (100), 124.2 (10). Anal. Calcd for $\text{C}_{19}\text{H}_{12}\text{F}_2\text{N}_4\text{O}_2$: C, 62.3; H, 3.3; N, 15.3. Found: C, 62.0; H, 2.9; N, 14.9. M = 366.32.

Ethyl 5-cyano-2-hydroxy-1-(2-methoxyphenyl)-6-oxo-1,6-dihydropyridine-3-carboxylate (4c).

Yellow powder (from BuOH); mp 180-183 °C. IR (KBr) cm^{-1} : 3400 (NH_2 , NH), 2216 ($\text{C}\equiv\text{N}$), 1672 ($\text{C}=\text{O}$). ^1H NMR (200 MHz, $\text{DMSO}-d_6$) δ 1.18 (t, J = 6.90 Hz, 3H, CH_2CH_3), 3.85 (s, 3H, OCH_3), 4.06 (q, J = 6.90 Hz, 2H, CH_2CH_3), 6.88 (t, J = 7.38 Hz, 1H, H_{Ar}), 6.96 (t, J = 7.72 Hz, 1H, H_{Ar}), 7.02 (d, J = 7.85 Hz, 1H, H_{Ar}), 8.13 (s, 1H, C^4H), 8.21 (br s, 1H, OH), 8.25 (d, J = 7.77 Hz, 1H, H_{Ar}). ^{13}C NMR (50 MHz, $\text{DMSO}-d_6$) δ 15.10, 56.53, 59.58, 72.78, 75.14, 111.12, 118.89, 118.99, 120.16, 121.07, 123.05, 128.82, 148.09, 149.22, 163.65, 167.22. LC/MS, m/z (%): 315.0 (100) $[M+1]^+$, 287.0 (10). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_5$: C, 61.1; H, 4.5; N, 8.9. Found: C, 61.4; H, 4.3; N, 8.5. M = 314.29.

Ethyl 5-cyano-2-hydroxy-6-oxo-1-*m*-tolyl-1,6-dihydropyridine-3-carboxylate (4e).

Yellow powder (from DMF); mp 184 °C. IR (KBr) cm^{-1} : 2213 ($\text{C}\equiv\text{N}$), 1722, 1693 ($\text{C}=\text{O}$). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 1.28 (t, J = 7.1 Hz, 3H, CH_2CH_3), 2.35 (s, 3H, ArCH_3), 4.21 (q, 2H, CH_2CH_3), 6.82 (d, J = 7.7 Hz, 1H, H_{Ar}), 6.89 (s, 1H, H_{Ar}), 7.12 (d, J = 7.7 Hz, 1H, H_{Ar}), 7.26 (t, J = 7.7 Hz, 1H, H_{Ar}), 8.12 (s, 1H, C^4H), no OH signal was observed, presumably due to fast deuteron-exchange. ^{13}C NMR (50 MHz, $\text{DMSO}-d_6$) δ 10.91, 14.94, 26.12, 59.00, 62.97, 79.87, 98.66, 120.47, 126.78, 128.00, 128.69, 130.28, 138.11, 148.40, 162.41, 164.97. LC/MS, m/z (%): 298.8 (100) $[M+1]^+$, 252.8 (25). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.0; H, 4.9; N, 9.7.

2,4-Dicyano-*N*1,*N*5-di-(2-methoxyphenyl)pent-2-enediamide (6c).

Yellow needles (from acetone); mp 255-256 °C. IR (KBr) cm^{-1} : 3379 (NH), 2195 ($\text{C}\equiv\text{N}$), 1626 ($\text{C}=\text{O}$), 1595, 1531 (δ NH). ^1H NMR (200 MHz, $\text{DMSO}-d_6$) δ 3.85 (s, 6H, 2OCH_3), 6.88 (t, J = 6.96 Hz, 2H, H_{Ar}), 6.96 (t, J = 6.96 Hz, 2H, H_{Ar}), 7.01 (d, J = 7.32 Hz, 2H), 8.19 (d, 2H, C^{3-4}), 8.22 (s, 1H, NH), 8.25 (d, J = 6.75 Hz, 2H, H_{Ar}), no NH signal was observed, presumably due to fast deuteron-exchange. ^{13}C NMR, DEPT (50 MHz, $\text{DMSO}-d_6$) δ 152.9 (CH), 127.8 (CH), 126.05 (CH), 124.1 (CH), 116.2 (CH), 61.55 (CH_3). LC/MS, m/z (%): 391.2 $[M+1]^+$ (100), 124.2 (25). Anal. Calcd for $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}_4$: C, 64.6; H, 4.7; N, 14.4. Found: C, 64.4; H, 4.5; N, 14.5.

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