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SYNTHESIS OF PYRIDO[1,2-*a*][1,3,5]TRIAZINE DERIVATIVES BY AMINOMETHYLATION OF 6-AMINO-4-ARYL-2-OXO-1,2-DIHYDROPYRIDINE-3,5-DICARBONITRILES

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The aminomethylation of 6-amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles by treatment with primary amines and an excess of formaldehyde resulted in the formation of 3-R-8-aryl-6-oxo-1,3,4,6-tetrahydro-2H-pyrido[1,2-a][1,3,5]triazine-7,9-dicarbonitriles. The structure of 6-oxo-3,8-diphenyl-1,3,4,6-tetrahydro-2H-pyrido[1,2-a][1,3,5]triazine-7,9-dicarbonitrile was investigated by X-ray structural analysis.

Keywords: 6-amino-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles, pyrido[1,2-*a*][1,3,5]triazines, multicomponent cyclocondensation, Mannich reaction, X-ray structural analysis.

3-Cyanopyridine-2(1*H*)-chalcogenones are important starting reagents for the preparation of various heterocyclic systems, many of which exhibit biological activity [1-7]. Our research group is currently engaged in the study of aminomethylation reactions of 3-cyanopyridine-2(1*H*)-thione and -selenone [8-29]. At the same time, the literature contains only isolated reports of reactions involving their oxygen-containing analogs [1, 3]. We decided to continue our research program in this direction by studying the reactivity of the 6-amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles **1a**,**b** under the conditions of the Mannich reaction.

It was established that the starting pyridones **1a**,**b** readily reacted with primary amines and an excess of formaldehyde, forming the 3-R-8-aryl-6-oxo-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitriles **2a**-**h** in 23-77% yields (Scheme 1).

The substantial difference in the yields was likely due to the different solubility of the reaction products. The reaction presumably involved the non-isolating intermediate **3**, which underwent an intramolecular cyclocondensation upon interacting with a second molecule of formaldehyde, resulting in compounds **2a**-**h**. Remarkably, the direction of Mannich reaction with analogous sulfur-containing pyridines

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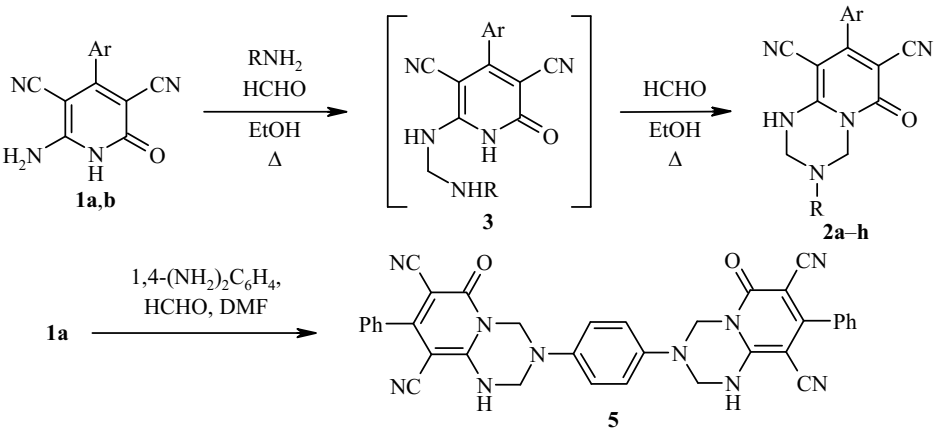
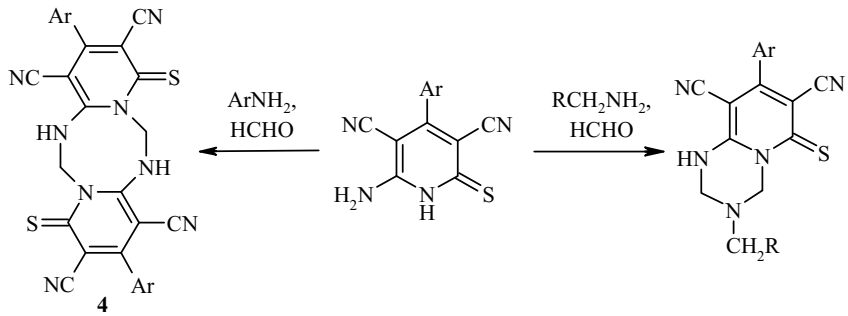
Scheme 1



1a, **2a**–**e** Ar = Ph; **1b**, **2f**–**h** Ar = 4-$MeOC_6H_4$;
2 a,**f** R = Me, **b**,**g** R = CH_2Ph, **c** R = Ph, **d**,**h** R = 4-MeC_6H_4, **e** R = 4-FC_6H_4

depended on the nature of the amine. Thus, using highly nucleophilic aliphatic amines led to pyrido[1,2-*a*]-[1,3,5]triazine derivatives, while in the case of aromatic amines only the dipyridotetrazocines **4** were formed or mixtures of the latter with pyrido[1,2-*a*][1,3,5]triazines [28] (Scheme 2).

Scheme 2



It was established that aminomethylation of the oxygen-containing substrates **1a**,**b** led to the formation of pyrido[1,2-*a*][1,3,5]triazines regardless of the nature of the amine component. The attempts under similar conditions to perform a reaction of compounds **1a**,**b** with secondary amines (morpholine) and HCHO were not successful, and the starting pyridones were isolated in 51 and 70% yields, respectively. The reaction of the pyridone **1a** with *p*-phenylenediamine in a 2:1 stoichiometry in the presence of excess HCHO gave 3,3'-(1,4-phenylene)bis(6-oxo-8-phenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile) (**5**) in 65% yield (Scheme 1).

The obtained compounds **2a**-**h** were fine crystalline powders, poorly soluble in EtOH and ether, and moderately soluble in acetone and DMSO. Compound **5** was insoluble in EtOH and acetone, poorly soluble in DMF and DMSO. The structures of compounds **2a**-**h** and **5** were confirmed by spectral data. The IR spectra contained stretching bands of C=O groups at 1710-1725 cm^{-1}, conjugated nitrile groups at 2200-2232 cm^{-1}, and N–H bonds at 3167-3480 cm^{-1}. The ^1H NMR spectra of these compounds exhibited signals due to the two methylene groups 2-CH_2 and 4-CH_2 (resolved as broadened singlets at 4.33-5.07 ppm and 4.89-5.63 ppm, respectively) and NH proton signals as broadened singlets at 8.91-9.31 ppm.

The structure of 6-oxo-3,8-diphenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbo-nitrile (**2c**) was confirmed by X-ray structural analysis (Fig. 1). The central fused ring system in the molecule **2c** was essentially planar (the mean least square deviation of atoms from the plane was 0.05 Å), except for the N(3) atom, which deviated from the plane by 0.726(2) Å. This atom had a pronounced pyramidal configuration (with the substituents deviating from the plane by 0.353(2) Å) and its lone electron pair was not conjugated to the phenyl ring, as evidenced by the pseudo torsion angle (*lone pair*)–N(3)–C(10)–C(11) equal to 60°.

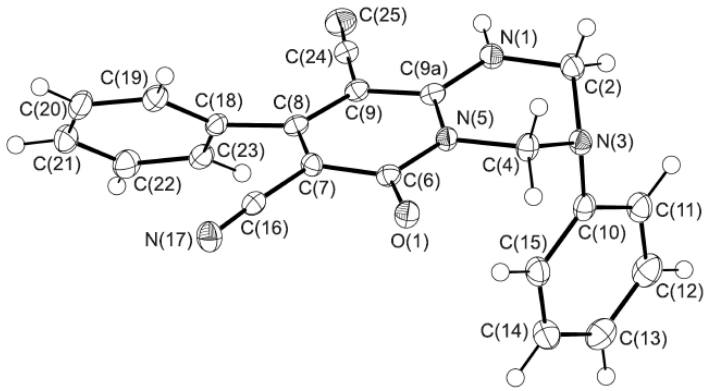


Fig. 1. The molecular structure of compound **2c** with atoms represented by thermal vibration ellipsoids of 50% probability.

At the same time, the pseudo torsion angles (*lone pair*)–N(3)–C(2)–N(1) and (*lone pair*)–N(3)–C(4)–N(5) were optimal for the stereoelectronic interactions $n_N \rightarrow \sigma^*_{C-N}$, with the values of 167.7 and 171.9°, respectively. Indeed, the bond N(5)–C(4) (1.493(2) Å) was lengthened by 0.059(4) Å, compared to the bond C(4)–N(3) (1.434(2) Å), while the bond N(1)–C(2) (1.478(2) Å) was longer by 0.035(4) Å than the bond N(3)–C(2) (1.443(2) Å). This meant that there were both (*lone pair*)–N(3)–C(2)–N(1) and (*lone pair*)–N(3)–C(4)–N(5) stereoelectronic interactions observed in the crystal, and the N(5) atom of the amide was a stronger electron acceptor than the N(1) atom of the enamine, as it was expected.

The phenyl ring C(18)–C(23) was rotated by 61.78(5)° relative to the central fused ring system, and was not involved in conjugation with the double bond system. The diene fragment C(7)–C(8)–C(9)–C(9a) was strongly conjugated: the formal single bond C(8)–C(9) (1.405(2) Å) was shorter than the formal double bond C(9)–C(9a) (1.415(2) Å). This could be explained by the significant resonance contribution of canonical structures with charge transfer from the N(1) and N(5) atoms to the C(7) or C(9) atoms, where the negative charge may be stabilized by the cyano groups.

Compound **2c** in crystalline state formed chains of intramolecular N(1)–H(1)···O(11) hydrogen bonds along the axis *a* (N···O 2.931(3) Å, N–H···O 155(2)°). The links between these chains consisted of weak C–H···π interactions.

Thus, the aminomethylation of 6-amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles could be successfully used for the synthesis of new pyrido[1,2-*a*][1,3,5]triazine derivatives.

EXPERIMENTAL

IR spectra were recorded in Nujol on an IKS-29 spectrometer. ^{1}H NMR spectra were acquired on Bruker DRX-500 (500 MHz) and Varian Unity Plus (400 MHz) instruments in DMSO-d_6, ^{13}C NMR spectra were recorded on a Bruker DRX-500 (125 MHz) instrument in DMSO-d_6, with TMS as internal standard. HPLC/MS analysis was performed on an Agilent 1100 liquid chromatograph with DAD and ELSD Sedex 75 detectors, fitted with an Agilent LC/MSD VL mass spectrometer, using electrospray ionization at the ambient pressure. Elemental analysis was performed on a Carlo-Erba 1106 Elemental Analyzer. Melting points were determined on a Kofler bench and were not corrected. The purity of the obtained compounds was controlled by TLC on Silufol UV-254 plates, the eluent was 1:1 acetone–hexane, visualization by iodine vapor or under UV light.

Preparation of 6-Amino-4-aryl-2-oxo-1,2-dihydropyridine-3,5-dicarbonitriles 1a,b (General Method). Compounds **1a**,**b** were obtained by a modification of the literature method [30]. Sodium metal (0.69 g, 0.03 mol) was dissolved in absolute EtOH (30 ml), and a mixture of the corresponding aryl-methylidenemalononitrile (0.02 mol) and cyanoacetamide (1.68 g, 0.02 mol) was added. The reaction mixture was refluxed for 2 h (precipitation was observed) and left overnight at 20°C, then acidified with conc. HCl to pH 4-5. The mixture was maintained at 4°C for 48 h. The precipitate was filtered off and washed with cold EtOH. An additional crop of the product was obtained from the mother liquors after keeping for 72 h in a refrigerator. Compounds **1a**,**b** were used for further transformations without additional purification.

6-Amino-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile (1a). Yield 2.2 g (46%), yellow fine crystalline powder, mp 267-269°C (mp 270°C [30], 315-320°C [31]). IR spectrum, ν, cm^{-1}: 3320 (N–H), 2220 (C≡N), 1695 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm: 7.42-7.52 (5H, m, H Ph); 8.36 (2H, br. s, NH_2); 12.52 (1H, br. s, NH). Mass spectrum, *m*/*z*: 237 $[M+H]^+$. Mass spectrum, *m*/*z*: 235 $[M-H]^-$, 471 $[2M-H]^-$.

6-Amino-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (1b). Yield 2.5 g (46%), greenish-yellow fine crystalline powder, mp >250°C (mp 205-207°C [32], 290°C (decomp.) [33]). IR spectrum, ν, cm^{-1}: 3330, 3180 (N–H), 2235, 2220 (C≡N), 1665 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 3.82 (3H, s, OCH_3); 7.07 (2H, d, ^3J = 8.1, H Ar); 7.43 (2H, d, ^3J = 8.1, H Ar); 8.27 (2H, br. s, NH_2); 12.32 (1H, br. s, NH). Mass spectrum, *m*/*z*: 267 $[M+H]^+$. Mass spectrum, *m*/*z*: 265 $[M-H]^-$, 531 $[2M-H]^-$.

Preparation of 3-R-8-Aryl-6-oxo-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitriles 2a-h (General Method). A mixture of the pyridone **1a**,**b** (1.7 mmol) and the corresponding primary amine (3.7 mmol) was stirred in EtOH (30 ml) at 60°C until the dissolution of the starting reagents. Then 37% formalin (2.0 ml, 26.6 mmol, free of paraform impurity) was added. The obtained solution was refluxed for 2-3 min and quickly filtered through a folded paper filter. The reaction mixture was left at 20°C for 48-72 h. The precipitate formed was filtered off and washed with EtOH. Compounds **2c**,**d**,**e**,**g** were additionally purified by recrystallization from a 1:1 mixture of EtOH–acetone.

3-Methyl-6-oxo-8-phenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2a). Yield 150 mg (30%), light-yellow fine crystals, mp 236-238°C (decomp.). IR spectrum, ν, cm^{-1}: 3390, 3300 (N–H), 2220, 2200 (C≡N), 1723 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm: 2.48 (3H, s, CH_3); 4.34 (2H, br. s, 2-CH_2); 4.90 (2H, br. s, 4-CH_2); 7.45-7.56 (5H, m, H Ph); 8.98 (1H, br. s, NH). Mass spectrum, *m*/*z*: 292 $[M+H]^+$. Mass spectrum, *m*/*z*: 290 $[M-H]^-$. Found, %: C 65.81; H 4.60; N 24.13. $C_{16}H_{13}N_5O$. Calculated, %: C 65.97; H 4.50; N 24.04.

3-Benzyl-6-oxo-8-phenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2b). Yield 480 mg (77%), yellow fine crystals, mp 232-234°C (decomp.). IR spectrum, ν, cm^{-1}: 3480, 3302 (N–H), 2220 (C≡N), 1710 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm: 3.88 (2H, br. s, C$\underline{H}_2$Ph); 4.40 (2H, br. s, 2-CH_2); 4.97 (2H, br. s, 4-CH_2); 7.30-7.39 (5H, m, H Ph); 7.46-7.51 (2H, m, H Ph); 7.53-7.59 (3H, m, H Ph); 8.98 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 54.3 ($\underline{C}H_2$Ph); 59.5, 61.5 (C-2,4); 75.1 (C-9); 86.8 (C-7); 115.2 (C≡N); 116.3 (C≡N); 127.6 (C Ar); 127.9 (C Ar); 128.3 (C Ar); 128.6 (C Ar); 128.9 (C Ar); 130.2 (C Ar); 134.5 (C Ar); 136.9 (C Ar); 153.7 (C-8); 158.8 (C-9a); 160.2 (C-6). Mass spectrum, *m*/*z*: 368 $[M+H]^+$. Mass spectrum, *m*/*z*: 366 $[M-H]^-$. Found, %: C 71.83; H 4.78; N 18.88. $C_{22}H_{17}N_5O$. Calculated, %: C 71.92; H 4.66; N 19.06.

6-Oxo-3,8-diphenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2c). Yield 140 mg (23%), light-yellow fine crystals, mp 202-204°C (decomp.). IR spectrum, ν, cm^{-1}: 3292 (N–H), 2222 (C≡N), 1720 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm: 5.07 (2H, br. s, 2-CH_2); 5.63 (2H, br. s, 4-CH_2); 7.00-7.05 (1H, m, H Ph); 7.12-7.18 (2H, m, H Ph); 7.32-7.39 (2H, m, H Ph); 7.44-7.55 (5H, m, H Ph); 9.31 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 58.9, 59.9 (C-2,4); 75.2 (C-9); 87.0 (C-7); 114.9 (C≡N); 116.0 (C≡N); 117.8 (C Ar); 122.6 (C Ar); 127.9 (C Ar); 128.6 (C Ar); 129.7 (C Ar); 130.3 (C Ar); 134.2 (C Ar); 145.6 (C Ar); 153.8 (C-8); 158.5 (C-9a); 160.4 (C-6). Mass spectrum, *m*/*z*: 352.0 $[M-H]^-$. Found, %: C 71.41; H 4.39; N 19.77. $C_{21}H_{15}N_5O$. Calculated, %: C 71.38; H 4.28; N 19.82.

3-(4-Methylphenyl)-6-oxo-8-phenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2d). Yield 450 mg (72%), yellow fine crystals, mp 183-185°C (decomp.). IR spectrum, ν, cm^{-1}: 3342 (N–H), 2232, 2210 (C≡N), 1712 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.22 (3H, s, 4-CH_3); 5.02 (2H, br. s, 2-CH_2); 5.59 (2H, br. s, 4-CH_2); 7.03 (2H, d, ^3J = 8.2, H Ar); 7.14 (2H, d, ^3J = 8.2, H Ar); 7.45-7.55 (5H, m, H Ph); 9.29 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 20.1 (CH_3); 59.1, 60.2 (C-2,4); 75.1 (C-9); 87.0 (C-7); 114.9 (C≡N); 116.0 (C≡N); 117.8 (C Ar); 127.9 (C Ar); 128.6 (C Ar); 130.1 (C Ar); 130.3 (C Ar); 131.6 (C Ar); 134.2 (C Ar); 143.2 (C Ar); 153.8 (C-8); 158.5 (C-9a); 160.4 (C-6). Mass spectrum, *m*/*z*: 366.1 $[M-H]^-$. Found, %: C 71.84; H 4.75; N 18.97. $C_{22}H_{17}N_5O$. Calculated, %: C 71.92; H 4.66; N 19.06.

3-(4-Fluorophenyl)-6-oxo-8-phenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2e). Yield 190 mg (30%), light-yellow fine crystals, mp 172-174°C (decomp.). IR spectrum, ν, cm^{-1}: 3241 (N–H), 2222, 2200 (C≡N), 1711 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm: 5.01 (2H, br. s, 2-CH_2); 5.58 (2H, br. s, 4-CH_2); 7.18-7.22 (4H, m, H Ar); 7.47-7.58 (5H, m, H Ar); 9.27 (1H, br. s, NH). Mass spectrum, *m*/*z*: 370.0 $[M-H]^-$. Found, %: C 67.88; H 3.88; N 18.79. $C_{21}H_{14}FN_5O$. Calculated, %: C 67.92; H 3.80; N 18.86.

8-(4-Methoxyphenyl)-3-methyl-6-oxo-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2f). Yield 169 mg (31%), mustard yellow fine crystals, mp 252-254°C (decomp.). IR spectrum, ν, cm^{-1}: 3308 (N–H), 2206 (C≡N), 1710 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.47 (3H, s, CH_3); 3.83 (3H, s, OCH_3); 4.33 (2H, br. s, 2-CH_2); 4.89 (2H, br. s, 4-CH_2); 7.08 (2H, d, ^3J = 8.3, H Ar); 7.45 (2H, d, ^3J = 8.3, H Ar); 8.91 (1H, br. s, NH). Mass spectrum, *m*/*z*: 322.0 $[M+H]^+$. Mass spectrum, *m*/*z*: 320.1 $[M-H]^-$. Found, %: C 63.49; H 4.79; N 21.69. $C_{17}H_{15}N_5O_2$. Calculated, %: C 63.54; H 4.71; N 21.79.

3-Benzyl-8-(4-methoxyphenyl)-6-oxo-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2g). Yield 189 mg (28%), yellow-green fine crystals, mp 204-206°C (decomp.). IR spectrum, ν, cm^{-1}: 3451, 3272 (N–H), 2219, 2205 (C≡N), 1725 (C=O). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 3.83 (3H, s, OCH_3); 3.87 (2H, br. s, C$\underline{H_2}$Ph); 4.39 (2H, br. s, 2-CH_2); 4.95 (2H, br. s, 4-CH_2); 7.10 (2H, d, ^3J = 8.3, H Ar); 7.28-7.37 (5H, m, H Ph); 7.45 (2H, d, ^3J = 8.3, H Ar); 8.92 (1H, br. s, NH). Mass spectrum, *m*/*z*: 398.1 $[M+H]^+$. Mass spectrum, *m*/*z*: 396.1 $[M-H]^-$. Found, %: C 69.39; H 4.90; N 17.58. Calculated, %: C 69.51; H 4.82; N 17.62.

8-(4-Methoxyphenyl)-3-(4-methylphenyl)-6-oxo-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonitrile (2h). Yield 182 mg (27%), yellow-green fine crystals, mp 158-160°C (decomp.). ^{1}H NMR spectrum (500 MHz), δ, ppm (*J*, Hz): 2.22 (3H, s, CH_3); 3.81 (3H, s, OCH_3); 5.01 (2H, br. s, 2-CH_2); 5.57 (2H, br. s, 4-CH_2); 7.01 (2H, d, ^3J = 8.3, H Ar); 7.06 (2H, d, ^3J = 8.3, H Ar); 7.14 (2H, d, ^3J = 8.8, H Ar); 7.43 (2H, d, ^3J = 8.8, H Ar); 9.20 (1H, br. s, NH). Mass spectrum, *m*/*z*: 396.1 $[M-H]^-$. Found, %: C 69.37; H 4.84; N 17.55. $C_{23}H_{19}N_5O_2$. Calculated, %: C 69.51; H 4.82; N 17.62.

3,3'-(1,4-Phenylene)bis(6-oxo-8-phenyl-1,3,4,6-tetrahydro-2*H*-pyrido[1,2-*a*][1,3,5]triazine-7,9-dicarbonit-rile (5). A mixture of the pyridone **1a** (600 mg, 2.5 mmol) and *p*-phenylenediamine (140 mg, 1.3 mmol) in DMF (10 ml) was stirred at 60°C until the dissolution of the starting reagents, then 37% formalin (2.5 ml, 33.3 mmol, free of paraform impurity) was added. The obtained solution was refluxed for 5 min and quickly filtered through a folded paper filter. The reaction mixture was left for 24 h at 20°C. The precipitate formed was filtered off and washed with EtOH. Yield 510 mg (65%), light-yellow fine crystals, mp 237-239°C. IR spectrum, ν, cm^{-1}: 3342, 3167 (N–H), 2220 (C≡N), 1710 (C=O). ^{1}H NMR spectrum (500 MHz), δ, ppm: 5.01 (4H, br. s, 2,2'-CH_2); 5.57 (4H, br. s, 4,4'-CH_2); 7.14 (4H, br. s, H Ar); 7.40-7.57 (10H, m, H Ph); 9.01 (2H, br. s, 2NH). Compound **5** could not be characterized by HPLC/MS due to its low solubility. Found, %: C 68.69; H 3.97; N 22.22. Calculated, %: C 68.78; H 3.85; N 22.28.

X-ray Structural Investigation of Compound 2c. Monocrystals of compound **2c** ($C_{21}H_{15}N_5O$, *M* 353.38) were grown from a 1:1 mixture of EtOH and acetone and were rhombic, space group *Pbca* (No. 61). The unit cell parameters at 100 K: *a* 14.496(10), *b* 10.013(7), *c* 23.526(16) Å; *V* 3415(4) $Å^3$; *Z* 8; μ(Mo*K*α) 0.089 mm^{-1}; d_{calc} 1.375 g/cm^3. In the range of $3.462 \le 2\theta \le 66.454°$ there were 32742 reflections measured, of which 6343 were independent (R_{int} 0.1490, R_{sigma} 0.1255). The final probability factors: R_1 0.0610

(reflections with $I > 2\sigma(I)$), wR_2 0.1344 (all reflections). A suitable quality crystal was selected and positioned on a glass needle in a Bruker APEX II DUO instrument. The measurements were performed with the Olex2 software package [34], the structure was solved with the olex2.solve software by the "charge flipping" method and was refined by the method of least squares, using the ShelXLMP-2012 software [35]. The complete set of X-ray structural data for compound **2c** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 976616).

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