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Chemistry of Heterocyclic Compounds **2016**, *52*(7), 473–483

Synthesis, structure, and reactions of (4-aryl-3-cyano-6-oxopiperidin-2-ylidene)malononitriles

Victor V. Dotsenko[1]*, Arif I. Ismiev[2], Anastasiya N. Khrustaleva[1], Konstantin A. Frolov[1], Sergey G. Krivokolysko[1], Elena A. Chigorina[3], Aleksey P. Snizhko[1], Vladimir M. Gromenko[1], Ivan S. Bushmarinov[4], Rizvan K. Askerov[2], Tatyana M. Pekhtereva[5], Sergey Yu. Suykov[6], Elena S. Papayanina[7], Aleksandr V. Mazepa[8], Abel M. Magerramov[2]

[1] *Kuban State University, 149 Stavropol'skaya St., Krasnodar 350040, Russia; e-mail: victor_dotsenko@bigmir.net*

[2] *Baku State University, 23 Academic Zahid Khalilov St., AZ 1148 Baku, AZ-1073/1, Azerbaijan; e-mail: arif_ismiev@mail.ru*

[3] *Federal State Unitary Enterprise "State Scientific Research Institute of Chemical Reagents and High Purity Chemical Substances" (FSUE "IREA"), 3 Bogorodsky Val, Moscow 107076, Russia; e-mail: echigorina@mail.ru*

[4] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 Vavilova St., Moscow 119991 V-334, Russia; e-mail: ib@ineos.ac.ru*

[5] *L. M. Litvinenko Institute of Physico-Organic Chemistry and Coal Chemistry, 70 R. Luxemburg St., Donetsk 83114, Ukraine; e-mail: infou_nmr@bigmir.net*

[6] *Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmanska St., Kyiv 02660, Ukraine; e-mail: sergel@ua.fm*

[7] *University of Erlangen-Nuremberg, Institute of Organic Chemistry II, 42 Henkestr., Erlangen 91054, Germany; e-mail: infou_nmr@bigmir.net*

[8] *A. V. Bogatsky Physico-Chemical Institute, National Academy of Sciences of Ukraine, 86 Lustdorfskaya Rd., Odessa 65080, Ukraine; e-mail: almazepa@rambler.ru*

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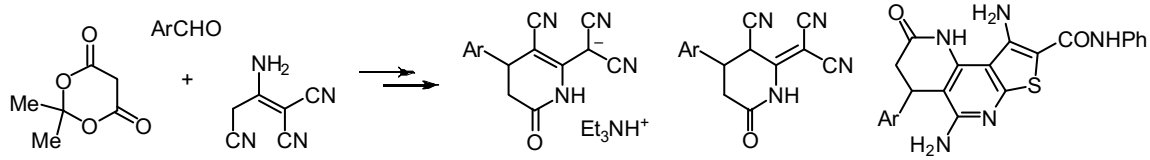


The reaction of aromatic aldehydes with Meldrum's acid and malononitrile dimer in the presence of triethylamine led to the formation of (4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)malononitrile triethylammonium salts, which were converted upon acidification to (4-aryl-3-cyano-6-oxopiperidin-2-ylidene)malononitriles. The reaction of these compounds with thioglycolic acid anilide was observed to produce derivatives of 1,6-naphthyridine or thieno[2,3-*h*][1,6]naphthyridine, depending on the conditions. Structures of (3-cyano-6-oxo-4-phenylpiperidin-2-ylidene)malononitrile and its triethylammonium salt were studied by X-ray structural analysis.

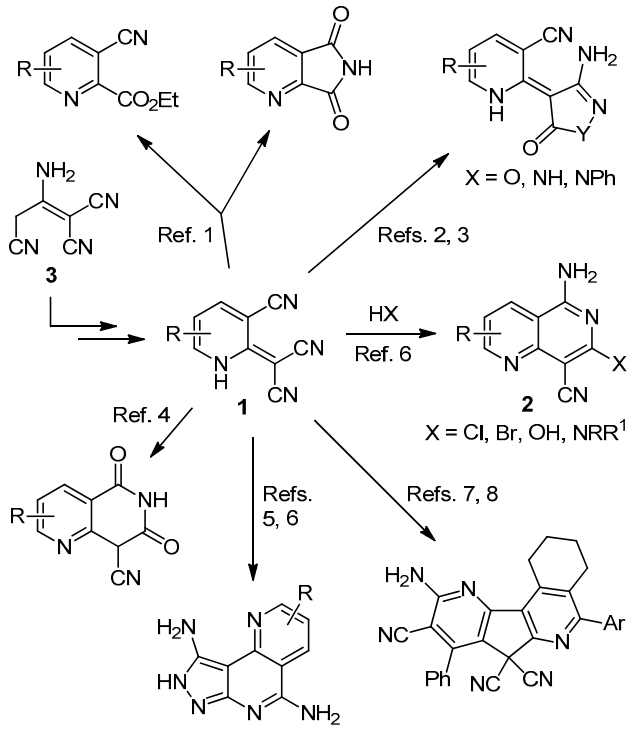
Keywords: 2-aminoprop-1-ene-1,1,3-tricarbonitrile, Meldrum's acid, 1,6-naphthyridines, thieno[2,3-*h*][1,6]naphthyridines, cascade heterocyclization, X-ray structural analysis.

Due to the presence of three electrophilic reactive sites, (3-cyanopyridin-2(1*H*)-ylidene)malononitrile derivatives **1** have gained recognition as convenient reagents for various cascade transformations and are quite often used for the synthesis of heterocyclic compounds,[1–8] especially derivatives of 1,6-naphthyridine **2**[6,9–15] (Scheme 1).

(3-Cyanopyridin-2(1*H*)-ylidene)malononitriles **1** can be easily synthesized[16–28] by cyclocondensation of various 1,3-biselectrophilic reagents with 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**3**) (malononitrile dimer) (the chemistry of 2-aminoprop-1-ene-1,1,3-tricarbonitrile has been covered in review articles[29–31]).

Previously, we developed an original method for the preparation of functionalized 1,2,3,4-tetrahydropyridin-2-ones **4**, based on a multicomponent reaction of aldehydes with Meldrum's acid and chalcogenamides with activated methylene groups, followed by cyclization of Michael adducts **5** (Scheme 2).[32–43]

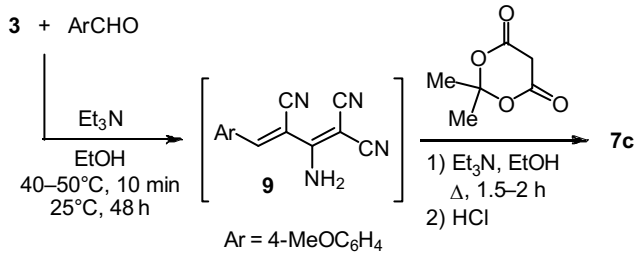
Scheme 1



While continuing research in this direction, we decided to study the reactivity of malononitrile dimer **3** under these conditions. It was established that the reaction sequence of Meldrum's acid with aromatic aldehydes and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**3**) in the presence of Et_3N in alcohol, followed by refluxing, led to the formation of salts **6a**,**b**, or else, after acidification of the reaction mixture, provided (4-aryl-3-cyano-6-oxopiperidin-2-ylidene)malononitriles **7c**,**d** (Scheme 3). Salts **6a**,**b** were quantitatively converted upon acidification to pyridines **7a**,**b**. In contrast to the reactions with chalcogenamides of cyanoacetic acid, none of the experiments with malononitrile dimer **3** resulted in isolation and characterization of intermediates, the respective Michael adducts **8a**–**d**.

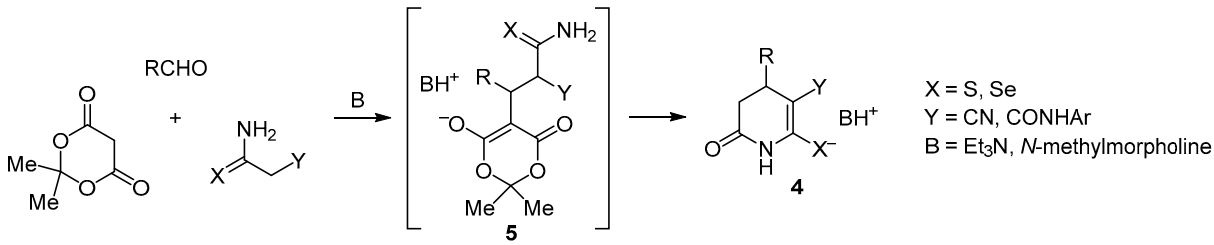
The sequence of reagent addition played a substantial role in successful outcome of these reactions. Thus, the tricyanobutadiene **9**, separately prepared by *in situ* condensation of dimer **3** with anisaldehyde, also gave pyridine **7c** in reaction with Meldrum's acid, but the product yield (29%) was significantly lower than in the case of the aforementioned method with a preliminary step of aldehyde condensation with Meldrum's acid (Scheme 4). A possible reason for the observed differences was the lower electrophilicity of dienes **9** in Michael addition reactions, compared to arylmethylidene derivatives of Meldrum's acid.

Scheme 4

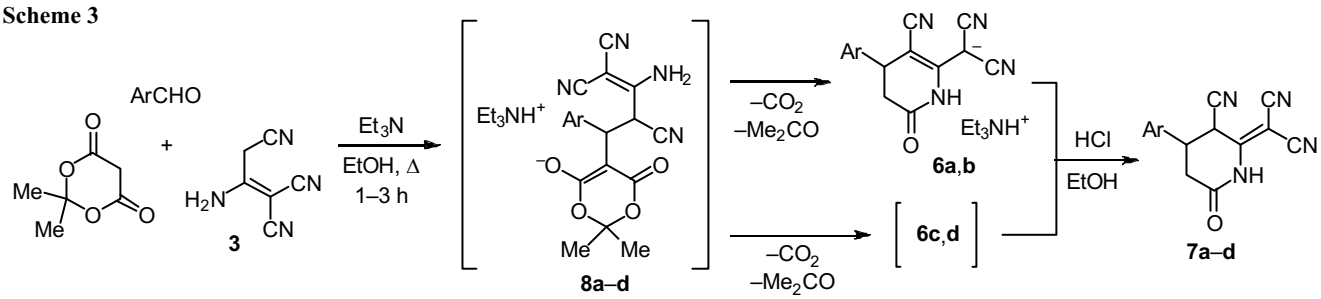


The structures of compounds **6a**,**b** and **7a**–**d** were studied by IR spectroscopy, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, HPLC-MS and elemental analysis, and X-ray structural analysis. ^1H NMR spectra of salts **6a**,**b** contained characteristic proton signals of the ABX system: a pair of double doublets (or multiplets) of 5-CH_2 group at 2.43–2.53 ppm (*cis* protons) and 2.88–2.96 ppm (*trans* protons), as well as an unresolved double doublet of the 4-CH group at 3.69–4.04 ppm. The structure of compounds **6a**,**b** was confirmed by X-ray structural analysis of (3-cyano-6-oxo-4-phenyl-1,4,5,6-tetrahydro-pyridin-2-yl)-malononitrile triethylammonium salt (**6a**) (Fig. 1).

Scheme 2



Scheme 3



a Ar = Ph, **b** Ar = 2-ClC_6H_4, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 3,4-$(MeO)_2C_6H_4$

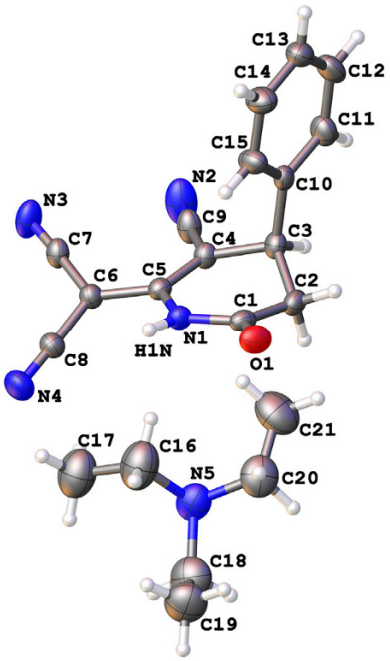


Figure 1. The molecular structure of salt **6a** with atoms represented by thermal vibration ellipsoids of 50% probability.

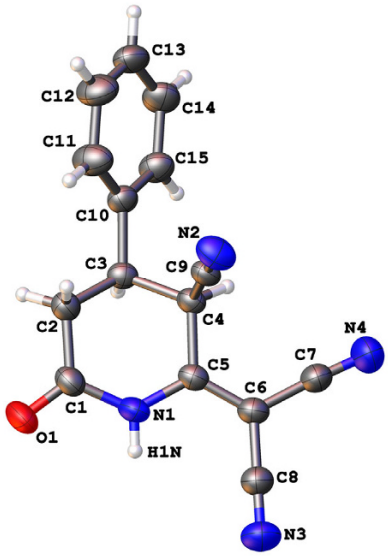


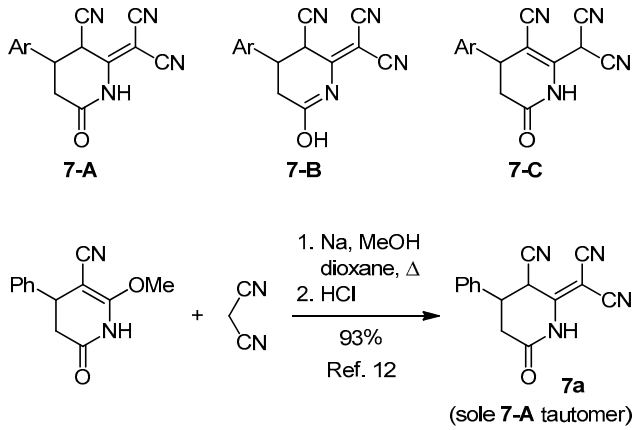
Figure 2. The molecular structure of (3-cyano-6-oxo-4-phenylpiperidin-2-ylidene)malononitrile **7a** with atoms represented by thermal vibration ellipsoids of 50% probability.

The structural features of compounds **7a**,**b** were more interesting. X-ray structural analysis data obtained for monocrystal of compound **7a** indicated a structure corresponding to (3-cyanopiperidin-2-ylidene)malononitrile in crystalline state (Fig. 2). Powder X-ray diffraction analysis of compound **7a** also confirmed that the main product was the dicyanomethylidene tautomer. The main peaks observed in the powder diffractogram agreed with the monocrystal diffraction data. The Rietveld refinement performed for the monocrystal structure of compound **7a** by using powder diffraction data showed that the sample was monophasic, with the main phase content of 99±1%.

At the same time, according to ^{1}H and ^{13}C NMR data, compounds **7** existed in solution phase as a mixture of prototropic tautomers **7-A** and **7-B** (Scheme 5), while no signals of the possible dicyanomethyl tautomer **7-C** were observed. It should be noted that compound **7a**, previously obtained[12] by a reaction of 5-cyano-6-methoxy-3,4-dihydropyridin-2(1*H*)-one with malononitrile, has been reported to exist exclusively in the form of tautomer **7-A** (Scheme 5). Besides the data of monocrystal X-ray structural analysis and powder X-ray diffraction, the structure of compounds **7a**–**d** was confirmed by IR spectroscopy, elemental analysis, HPLC-MS analysis, as well as NMR dataset (APT and DEPT-135 ^{13}C, COSY, NOESY, EXSY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC).

In our case, the existence of compounds **7a**–**d** in solution phase as tautomers **7-A** and **7-B** was confirmed by doubling of the characteristic pattern of proton signals, pointing to the same spin system topology (Fig. 3), as well as dynamic equilibrium between two forms, as established by EXSY NMR experiment (Fig. 4, with matching phases of diagonal peaks and cross peaks).

Scheme 5



The ratio of lactam **7-A** and lactim **7-B** tautomers in the mixtures varied from ~4:1 to ~2:1 and mainly depended on the solvent and structure of compound **7**. The tautomer ratio could be determined from the integrated intensities of ^{1}H NMR signals, where the signals were assigned to specific tautomers based on the analysis of NH and OH proton signals. The spectrum of compound **7a** (see the Supplementary information file) contained two proton signals in the interval of 8.81–9.07 ppm with combined integral corresponding to ~1H. According to ^{1}H–^{13}C HSQC and EXSY NMR data, these signals belonged to heteronuclear protons and were involved in a dynamic equilibrium. The signal at 8.81 ppm was narrower, probably belonging to amide NH proton of the main tautomer **7a-A**, while a very broad signal with a maximum at 9.07 ppm was assigned to OH proton of the minor tautomer **7a-B**. The assignment of NMR signals for

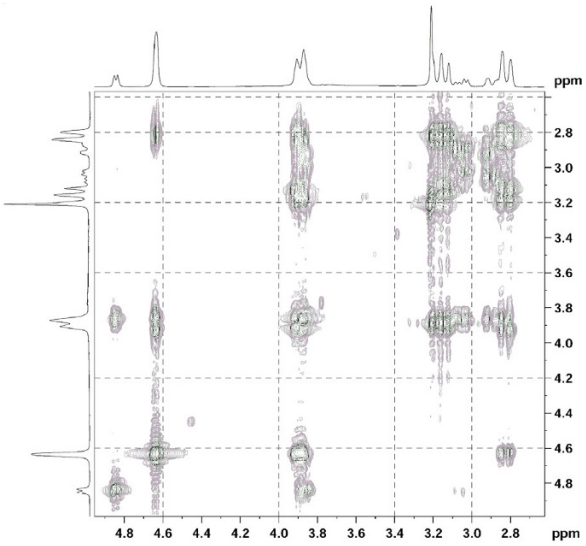


Figure 3. Part of ^{1}H–^{1}H COSY NMR spectrum of (3-cyano-6-oxo-4-phenylpiperidin-2-ylidene)malononitrile (**7a**).

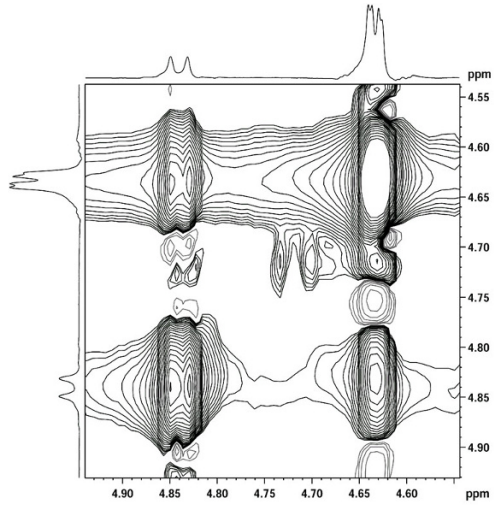


Figure 4. Part of EXSY NMR spectrum of compound **7a**, with signals of protons at the C-3 atom shown. The antiphase components are plotted with gray lines, main peaks and cross peaks having a matching phase are plotted with black lines.

compound **7a** was based on the analysis of NMR dataset including APT and DEPT-135 ^{13}C, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC experiments (Fig. 5, Table 1).

An interesting NMR spectral feature of compounds **7c**,**d** in DMSO-d_6 solution was the altered character and doubling of the number of aromatic proton signals, while the integrated intensity of these signals still corresponded to one set of H Ar protons. The probable reason for this was the rotation of aromatic substituent to various conformations. The same samples in CCl_4–DMSO-d_6 solution gave the usual NMR spectral features.

Some properties of the obtained compounds were studied, such as the reaction with thioglycolic acid anilide (**10**) (Scheme 6). The reaction of (3-cyanopiperidin-2-ylidene)malononitriles **7a**,**c**,**d** with anilide **10** in refluxing alcohol in the presence of ~2.7 equiv of Et_3N proceeded through an attack by RS^- anion at one of the nitrile groups of the $=C(CN)_2$ moiety. The initial cascade cyclization products were 1,6-naphthyridines **11a**,**c**,**d**, which under the reaction conditions partially underwent intramolecular Thorpe–Ziegler cyclization, forming the expected thieno-[2,3-*h*][1,6]naphthyridines **12a**,**c**,**d**.

The extent of the cascade process and the ratio of naphthyridines **11a**,**c**,**d** and thienonaphthyridines **12a**,**c**,**d** in the mixture under these conditions obviously depended on the structure of aryl substituent and the solubility of products (Table 2).

Thieno[2,3-*h*][1,6]naphthyridines are a relatively new type of polyheterocyclic compounds, with only a few examples of synthesis reported.[44–46] It should also be noted that our proposed approach of using cascade reactions has not been previously applied to the synthesis of analogous thienoazines[47–50] or sulfur-containing naphthyridine derivatives.[51–55]

In order to optimize and increase the yield of the target 1,2,3,4-tetrahydrothieno[2,3-*h*][1,6]naphthyridines **12a**–**c**, various options of basic catalysis were examined. For

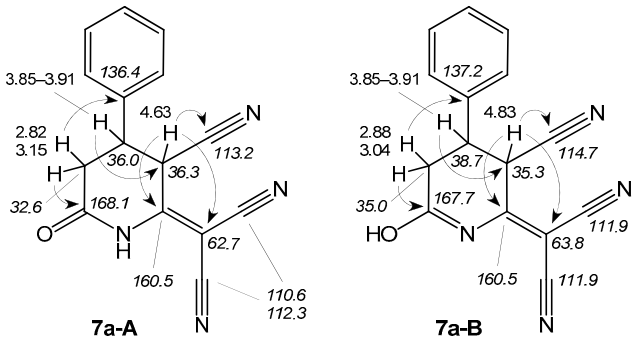
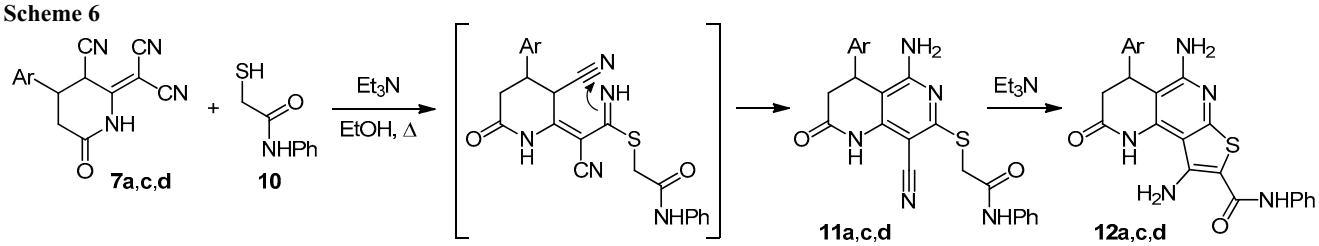


Figure 5. ^{1}H–^{13}C HMBC correlations for the tautomers of compound **7a**.

Table 1. The main ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC correlations observed for tautomers of compound **7a**

^{1}H NMR chemical shifts, δ, ppm	2D NMR correlations, δ, ppm	
	^{1}H–^{13}C HSQC	^{1}H–^{13}C HMBC
***7a-A** (major tautomer)*		
2.82 (dd, 5-CH(*cis*)); 3.15 (dd, 5-CH(*trans*))	32.6	36.0 (C-4); 36.3 (C-3); 136.4 (C-1 Ph); 168.1 (C=O)
3.85–3.91 (m, 4-CH)	36.0	32.6 (C-5); 36.3 (C-3); 113.2 (CN); 127.4 (C Ph); 136.4 (C-1 Ph); 160.5 (C-2); 168.1 (C=O)
4.63 (d, 3-CH)	36.3	32.6 (C-5); 36.0 (C-4); 62.7 (C=C(CN)$_2$); 113.2 (C≡N); 136.4 (C-1 Ph); 160.5 (C-2)
***7a-B** (minor tautomer)*		
2.88 (dd, 5-CH(*cis*)); 3.04 (dd, 5-CH(*trans*))	35.0	35.3 (C-3); 38.7 (C-4); 137.2 (C-1 Ph); 167.7 (C-6)
3.85–3.91 (m, 4-CH)	38.7	35.0 (C-5); 35.3 (C-3); 114.7 (CN); 137.2 (C-1 Ph); 160.5 (C-2); 167.7 (C-6)
4.83 (d, 3-CH)	35.3	35.0 (C-5); 38.7 (C-4); 63.8 (C=C(CN)$_2$); 114.7 (C≡N); 137.2 (C-1 Ph); 160.5 (C-2)

Scheme 6



a Ar = Ph, **c** Ar = 4-$MeOC_6H_4$, **d** Ar = 3,4-$(MeO)_2C_6H_4$

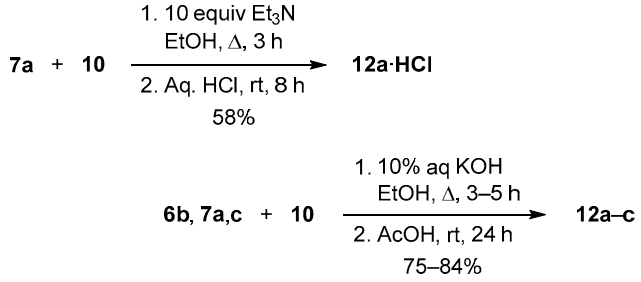
Table 2. The products of reactions between (3-cyanopiperidin-2-ylidene)malononitriles **7a**,**c**,**d** and thioglycolic acid anilide **10**

Starting material	Ar	Reaction time, h	Total yield **11**+**12**, %	Ratio of reaction products **11** : **12** (method)
7a	Ph	4.5	68	~2:5 (^{1}H NMR,) ~1:4 (HPLC)
7c	4-$MeOC_6H_4$	5	57	~5:2 (^{1}H NMR) ~2:1 (HPLC)
7d	3,4-$(MeO)_2C_6H_3$	4	64	>95:traces (^{1}H NMR) 100:0 (HPLC)

example, refluxing the trinitrile **7a** with thioglycolic acid anilide (**10**) in the presence of a large excess of Et_3N (10 equiv), followed by treatment with an excess of HCl gave thienonaphthyridine hydrochloride **12a** in 58% yield (Scheme 7). Substitution of the organic base with 10% aqueous KOH solution gave good results, increasing the yields of thieno[2,3-*h*][1,6]naphthyridines **12a**–**c** from trinitriles **7a**,**c** or from salt **6b** to 75–84%. The mixtures of compounds **11a**,**c** and **12a**,**c** described above were converted nearly quantitatively to compounds **12a**,**c** upon heating with KOH in EtOH.

Thus, we have investigated the reaction of malononitrile dimer with aromatic aldehydes and Meldrum's acid, developed methods for the preparation of triethylammonium salts of (4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)malononitriles and (4-aryl-3-cyano-6-oxopiperidin-2-ylidene)malononitriles, performed detailed characterization of product structure, including X-ray crystallography studies. The obtained dicyanomethylidene derivatives participated in a previously unreported cascade reaction with thioglycolic acid anilide, leading to the formation of relatively little known thieno[2,3-*h*][1,6]naphthyridine derivatives.

Scheme 7



Experimental

IR spectra of compounds **6a**,**b**, **7a** were recorded on an Infraspek FSM-1201 FT-IR spectrophotometer in KBr pellets, the spectra of other compounds were recorded on an IKS-29 spectrometer in Nujol. ^{1}H, ^{13}C and APT ^{13}C NMR spectra of compounds **6a**,**b**, **7a**,**c**,**d**, **11d** were acquired on a Bruker DRX-500 instrument (500 and 125 MHz, respectively) in DMSO-d_6, with TMS as internal standard. ^{1}H, ^{13}C, and DEPT-135 ^{13}C NMR spectra of compounds **7a**–**c**, **12a**·HCl, **12a**–**c**, as well as the NOESY, ^{1}H–^{13}C COSY, ^{1}H–^{13}C HSQC, and ^{1}H–^{13}C HMBC NMR experiments for compound **7a** were acquired on a Bruker Avance II 400 instrument (400 MHz for ^{1}H nuclei, 100 MHz for ^{13}C nuclei) in DMSO-d_6 (compounds **12a**,**c**) or in ~1:2 CCl_4–DMSO-d_6 (the rest of the compounds), with TMS as internal standard. Signals of the major tautomer are denoted with one asterisk (*) in ^{1}H and ^{13}C NMR spectra, while the signals of the minor tautomer are denoted with two asterisks (**). Those ^{13}C NMR signals observed in antiphase are labeled in italics. Mass spectra were recorded on an MX1321 spectrometer by using a system for direct introduction of samples at 200°C ionization chamber temperature and EI ionization (70 eV). HPLC-MS analysis was performed on an Agilent 1100 Series chromatograph with diode matrix (215, 254, and 265 nm) and mass selective (Aligent LC/MSD SL) detectors, ionization by atmospheric pressure electrospray (ES-API). Elemental analysis was performed on a Carlo-Erba 1106 Analyzer. Melting points were determined on a Kofler bench and were not corrected. Powder X-ray diffractogram of compound **7a** was recorded on a DRON-4-07 diffractometer. Purity of the obtained compounds was controlled by TLC on Silufol UV-254 plates, eluent 1:1 acetone–hexane, visualization with iodine vapor or under UV light.

2-Aminoprop-1-ene-1,1,3-tricarbonitrile (**3**) was obtained by dimerization of malononitrile in the presence of KOH in EtOH according to the procedure described by Mittelbach.[56] 2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) was obtained by a published procedure.[57] Thioglycolic acid anilide (**10**) is a commercially available reagent.

Preparation of (4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)malononitrile triethylammonium salts 6a,b and (4-aryl-3-cyano-6-oxopiperidin-2-ylidene)-malononitriles 7a–d (General method). A 250-ml round bottom flask was charged with Meldrum's acid (6.0 g,

41.6 mmol), EtOH (50 ml), aromatic aldehyde (42 mmol), and 6 drops of Et_3N. The mixture was stirred until complete dissolution of the starting reagents (5–10 min). Precipitation of condensation product may occur during this time. The mixture was treated with additional EtOH (20 ml), malononitrile dimer **3** (5.5 g, 41.6 mmol), and Et_3N (8.7 ml, 62.4 mmol, 1.5 equiv). The obtained solution was refluxed for 1–3 h, evaporated to a syrup consistency, cooled, treated with acetone (20 ml) and EtOH (5 ml). In the case of Ar = Ph and 2-ClC_6H_4, the crystalline precipitate of salt **6a**,**b** was filtered off after 48 h, washed with cold acetone and petroleum ether. The filtrate obtained after separation of the salt was vigorously stirred and cooled while adding a mixture of alcohol and concd. HCl to pH 2. The yellow precipitated product was filtered off after 4 h, washed with EtOH and petroleum ether, giving compounds **7a**,**b**.

In the rest of the cases the obtained acetone-alcohol solution was treated by dropwise addition of an excess of 1:1 concd. HCl solution in EtOH to pH 2. The obtained suspension was stirred for 3–4 h, the product was filtered off, washed with EtOH and petroleum ether, giving compounds **7c**,**d**.

(3-Cyano-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridin-2-yl)malononitrile triethylammonium salt (6a). Yield 9.75 g (64%), pale-yellow crystals, mp 130–132°C. IR spectrum, ν, cm^{-1}: 3411, 3220, 3155 (N–H), 2187, 2165, 2133 (C≡N), 1707 (C=O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.16 (9H, t, ^3J = 7.1, $N(CH_2C\underline{H}_3)_3$); 2.49–2.53 (1H, m, 5-CH(*cis*)) (partial overlap with the DMSO signal); 2.88 (1H, dd, ^2J = 16.2, ^3J = 6.9, 5-CH(*trans*)); 3.08 (6H, q, ^3J = 7.1, $(C\underline{H}_2CH_3)_3$); 3.69–3.71 (1H, m (unresolved dd), 4-CH); 7.18–7.23 (3H, m, H Ph); 7.29–7.32 (2H, m, H Ph); 8.81–8.82 (2H, m, NH, NH^+). APT ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.6 ($N(CH_2\underline{C}H_3)_3$); *30.7* ($(NC)_2\underline{C}^-$); 39.1 (C-5); 39.1 (C-4); *45.8* ($N(\underline{C}H_2CH_3)_3$); *68.0* (C-3); *120.9* (3-CN); *121.3* ($(N\underline{C})_2C^-$); 126.7 (C-3,4,5 Ph); 128.4 (C-2,6 Ph); *142.5* (C-1 Ph); *150.4* (C-2); 168.9 (C=O). Mass spectrum, *m*/*z* (ES-API): 102.2 $[Et_3NH]^+$, 261.1 $[M–Et_3NH]^-$. Found, %: C 69.20; H 7.07; N 19.32. $C_{21}H_{25}N_5O$. Calculated, %: C 69.40; H 6.93; N 19.27.

[4-(2-chlorophenyl)-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-yl]malononitrile triethylammonium salt (6b). Yield 12.10 g (73%), pale-yellow fine crystalline powder, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3434, 3390, 3201, 3143 (N–H), 2190, 2165, 2144 (C≡N), 1711 (C=O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.16 (9H, t, ^3J = 7.1, $N(CH_2C\underline{H}_3)_3$); 2.43–2.49 (1H, m, 5-CH(*cis*)) (partial overlap with the DMSO signal); 2.96 (1H, dd, ^2J = 16.2, ^3J = 6.9, 5-CH(*trans*)); 3.08 (6H, q, ^3J = 7.1, $N(C\underline{H}_2CH_3)_3$); 4.02–4.04 (1H, m (unresolved dd), 4-CH); 7.18 (1H, d, ^3J = 7.1, H Ar); 7.27–7.30 (1H, m, H Ar); 7.33–7.36 (1H, m, H Ar); 7.45 (1H, d, ^3J = 7.7, H Ar); 8.83 (1H, very br. s, NH^+); 9.00 (1H, s, NH). APT ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm (*J*, Hz): *8.6* ($N(CH_2\underline{C}H_3)_3$); 31.2 ($(NC)_2\underline{C}^-$); *36.7* (C-4); 37.6 (C-5); 47.8 ($N(\underline{C}H_2CH_3)_3$); 66.1 (C-3); 120.5 (3-CN); 121.1 ($(N\equiv\underline{C})_2C^-$); *127.5* (C Ar); *128.1* (C Ar); *128.8* (C Ar); *129.7* (C Ar); 132.3 (C Ar); 138.7 (C Ar); 151.6 (C-2); 168.4 (C=O). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 296 $[M–Et_3N]^+$ (17), 254 $[M–Et_3N–CH_2CO]^+$ (21), 219 (14), 165 (65), 139 (13), 137 (12), 101 $[Et_3N]^+$ (32), 86 $[Et_3N–CH_3]^+$ (100), 58 (37), 45 (16). Mass spectrum, *m*/*z* (ES-API): 102.2 $[Et_3NH^+]$, 295.0, 297.0 $[M–Et_3NH]^-$. Found, %: C 63.34; H 6.22; N 17.72. $C_{21}H_{24}ClN_5O$. Calculated, %: C 63.39; H 6.08; N 17.60.

(3-Cyano-6-oxo-4-phenylpiperidin-2-ylidene)malononitrile (7a). Yield 1.20 g (11%, when filtrate was acidified after separation of salt **6a**) or 4.97 g (46%, when salt **6a** was not isolated prior to acidification), yellow crystals, mp 212–214°C (MeOH) (mp 251–253°C[12]). IR spectrum, ν, cm^{-1}: 3420, 3216, 3137 (N–H), 2250, 2225, 2167 (C≡N), 1717 (C=O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz) (~3:1 ratio of tautomers **7a-A** and **7a-B**): 2.83–2.90 (1H, m, 5-CH(*cis*)); 3.04** (0.25H, dd, ^2J = 16.5, ^3J = 9.3, 5-CH(*trans*)); 3.19–3.25* (0.75H, m (unresolved dd), 5-CH(*trans*)); 3.91–3.93 (1H, m, 4-CH); 4.79–4.81* (0.75H, m, 3-CH); 4.97** (0.25H, d, ^3J = 7.8, 3-CH); 7.19–7.44 (5H, m, H Ph); 8.81* (0.75H, s, NH); 9.07** (0.25H, very br. s, OH). ^{1}H NMR spectrum (400 MHz, CCl_4–DMSO-d_6), δ, ppm (*J*, Hz) (~4:1 ratio of tautomers **7a-A** and **7a-B**): 2.82* (0.8H, br. dd, ^2J = 17.1, ^3J = 3.0, 5-CH(*cis*)); 2.88** (0.2H, dd, ^2J = 17.1, ^3J = 4.4, 5-CH(*cis*)); 3.04** (0.2H, br. dd, ^2J = 17.1, ^3J = 8.1, 5-CH(*trans*)); 3.15* (0.8H, br. dd, ^2J = 17.1, ^3J = 14.2, 5-CH(*trans*)); 3.85–3.91 (1H, m, 4-CH); 4.63* (0.8H, br. d, ^3J = 4.0, 3-CH); 4.83** (0.2H, d, ^3J = 7.1, 3-CH); 7.32–7.44 (5H, m, H Ph). Signals of protons bonded to heteroatoms were not observed due to deuterium exchange. APT ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 32.6 (C-5); 35.3 (CH); *35.7* (CH); *36.3* (CH); 68.0 (=$\underline{C}(CN)_2$); 111.1 (CN); 111.3 (CN); 112.9 (CN); 113.8 (CN); 120.9 (CN); 121.3 (CN); *126.8* (CH Ph); *127.2* (CH Ph); *127.6* (CH Ph); *128.2* (CH Ph); *128.5* (CH Ph); *128.8* (CH Ph); *129.0* (CH Ph); 136.7 (C-1 Ph); 161.2 (C-2); 161.5 (C-2); 168.4 (C-6); 168.9 (C-6). ^{13}C NMR spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: 32.9* (C-5); 35.0** (C-5); 35.3** (C-3); 36.0* (C-4); 36.3* (C-3); 38.7** (C-4); 62.7* (=$\underline{C}(CN)_2$); 63.8** (=$\underline{C}(CN)_2$); 110.6* (=$C(\underline{C}N)_2$); 111.9** (=$C(\underline{C}N)_2$); 112.3* (=$C(\underline{C}N)_2$); 113.2* (3-CN); 114.7** (3-CN); 127.0** (C-2,6 Ph); 127.4* (C-2,6 Ph); 128.0** (C-4 Ph); 128.1* (C-4 Ph); 128.6* (C-3,5 Ph); 128.8** (C-3,5 Ph); 136.4* (C-1 Ph); 137.2** (C-1 Ph); 160.5* (C-2); 167.7** (C-6); 168.1* (C-6). ^{13}C NMR DEPT-135 spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: *32.4*; *34.6*; 34.9; 35.6; 35.8; 38.2; 126.5; 127.0; 127.5; 127.6; 128.1; 128.3. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 262 $[M]^+$ (27), 220 $[M–CH_2C(O)]^+$ (67), 131 $[PhCHCHC(O)]^+$ (100), 105 (33), 103 (35), 77 (22), 52 (15). Mass spectrum, *m*/*z* (ES-API): 261.0 $[M–H]^-$. Found, %: C 68.64; H 3.92; N 21.38. $C_{15}H_{10}N_4O$. Calculated, %: C 68.69; H 3.84; N 21.36.

[4-(2-Chlorophenyl)-3-cyano-6-oxopiperidin-2-ylidene]-malononitrile (7b). Yield 0.70 g (6%, when filtrate was acidified after separation of salt **6b**) or 8.65 g (70%, when salt **6b** was not isolated prior to acidification), pale-yellow powder, mp 284–286°C (EtOH). IR spectrum, ν, cm^{-1}: 3447, 3228 (N–H), 2265, 2235 (C≡N), 1722 (C=O).

^{1}H NMR spectrum (400 MHz, CCl_4–DMSO-d_6), δ, ppm (*J*, Hz) (~4:1 ratio of tautomers **7b-A** and **7b-B**): 2.80* (0.8H, br. d (unresolved dd), ^2J = 15.3, 5-CH(*cis*)); 2.96** (0.2H, dd, ^2J = 14.4, ^3J = 4.5, 5-CH(*cis*)); 3.32* (0.8H, pseudo t (unresolved dd), ^2J = 15.3, 5-CH(*trans*)); 3.44** (0.2H, br. dd, ^2J = 14.4, ^3J = 7.3, 5-CH(*trans*)); 4.21–4.24 (1H, m, 4-CH); 4.50* (0.8H, m, 3-CH); 4.94** (0.2H, d, ^3J = 7.6, 3-CH); 7.21–7.49 (4H, m, H Ar); 8.36* (0.6H, br. s, NH). The NH proton signal had lower intensity due to partial deuterium exchange, the OH proton signal was not observed. ^{13}C NMR spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: 32.6* (C-5); 33.7* (C-3); 34.2* (C-4); 35.0** (C-5); 36.2** (C-3); 36.9** (C-4); 62.9* (=<u>C</u>$(CN)_2$); 65.6* (=<u>C</u>$(CN)_2$); 110.4* (CN); 110.9** (CN); 111.9** (CN); 112.2* (CN); 112.7* (CN); 112.8** (CN); 127.6* (C Ar); 127.9** (C Ar); 128.2** (C Ar); 128.4* (C Ar); 129.1** (C Ar); 129.6** (C Ar); 129.7* (C Ar); 129.9* (C Ar); 132.6** (C Ar); 133.2* (C Ar); 133.4* (C Ar); 134.8** (C Ar); 159.6* (C-2); 160.6** (C-2); 167.5** (C-6); 167.9* (C-6). ^{13}C NMR DEPT-135 spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: *32.0*; 33.2; 33.7; *35.0*; 35.7; 36.5; 126.9; 127.2; 127.4; 127.9; 128.9; 129.1; 129.2; 129.4. Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 296 $[M]^+$ (21), 254 $[M–CH_2CO]^+$ (36), 219 (24), 165 $[ArCHCHCO]^+$ (100), 139 $[ArCHCH_2]^+$ (18), 103 (17), 101 (15), 77 (11), 52 (11). Found, %: C 60.54; H 3.18; N 18.78. $C_{15}H_9ClN_4O$. Calculated, %: C 60.72; H 3.06; N 18.88.

[3-Cyano-4-(4-methoxyphenyl)-6-oxopiperidin-2-ylidene]-malononitrile (7c). Yield 10.26 g (84%), pale-yellow fine crystalline powder, mp 246–248°C (acetone). IR spectrum, ν, cm^{-1}: 3375, 3222 (N–H), 2265, 2229 (C≡N), 1730 (C=O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz) (~3:1 ratio of tautomers **7c-A** and **7c-B**): 2.79–2.82 (1H, m, 5-CH(*cis*)); 3.00** (0.25H, dd, ^2J = 16.5, ^3J = 8.8, 5-CH(*trans*)); 3.15–3.21* (0.75H, m (unresolved dd), 5-CH (*trans*)); 3.64–3.85 (4H, m, 4-CH, OCH_3); 4.72–4.75* (0.75H, m, 3-CH); 4.90** (0.25H, d, ^3J = 7.7, 3-CH); 6.86* (0.75H, d, ^3J = 7.1, H Ar); 6.95–7.00 (1.25H, m, H Ar); 7.09* (0.75H, d, ^3J = 7.1, H Ar); 7.28** (0.25H, d, ^3J = 6.6, H Ar); 7.50–7.40 (1H, m, H Ar); 8.77* (0.50H, br. s, NH). The NH proton signal had lower intensity due to partial deuterium exchange, the OH proton signal was not observed. ^{1}H NMR spectrum (400 MHz, CCl_4–DMSO-d_6), δ, ppm (*J*, Hz) (~4:1 ratio of tautomers **7c-A** and **7c-B**): 2.77* (0.8H, br. d, ^2J = 16.6, 5-CH(*cis*)); 2.85** (0.2H, dd, ^2J = 17.2, ^3J = 4.1, 5-CH(*cis*)); 3.01** (0.2H, br. dd, ^2J = 17.2, ^3J = 8.1, 5-CH(*trans*)); 3.08–3.16* (0.8H, m (unresolved dd), 5-CH(*trans*)); 3.77** (0.6H, s, OCH_3); 3.78* (2.4H, s, OCH_3); 3.82–3.84 (1H, m, 4-CH); 4.57–4.59* (0.8H, m, 3-CH); 4.79** (0.2H, d, ^3J = 7.1, 3-CH); 6.88–6.92 (2H, m, H Ar); 7.25** (0.4H, d, ^3J = 8.1, H Ar); 7.33* (1.6H, d, ^3J = 8.1, H Ar); 12.26 (0.6H, very br. s, OH, NH). Signals of protons bonded to heteroatoms were not observed due to deuterium exchange. ^{13}C NMR spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: 33.0* (C-5); 35.1** (C-5); 35.3* (C-3); 35.5** (C-3); 36.5* (C-4); 37.9** (C-4); 54.8* (MeO); 62.4* (=<u>C</u>$(CN)_2$); 110.5* (CN); 111.9** (CN); 112.4* (CN); 113.2* (CN); 113.8* (C-3,5 Ar); 114.0** (C-3,5 Ar); 114.6** (CN); 114.8** (CN); 128.0** (C-2,6 Ar); 128.1* (C-1 Ar); 128.5* (C-2,6 Ar); 128.8** (C-1 Ar); 158.9** (C-4 Ar); 159.0* (C-4 Ar); 160.6* (C-2); 167.8** (C-6); 168.2* (C-6). ^{13}C NMR DEPT-135 spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: *32.6** (C-5); *34.8*** (C-5); 34.9* (C-3); 35.1** (C-3); 36.1* (C-4); 37.5** (C-4); 54.4* (OCH_3); 113.5* (C-3,5 Ar); 113.7** (C-3,5 Ar); 127.7* (C-2,6 Ar); 128.1** (C-2,6 Ar). Mass spectrum, *m*/*z* (ES-API): 293.2 $[M+H]^+$, 310.2 $[M+NH_3]^+$, 315.0 $[M+Na]^+$, 291.2 $[M–H]^-$. Found, %: C 65.63; H 4.28; N 19.22. $C_{16}H_{12}N_4O_2$. Calculated, %: C 65.75; H 4.14; N 19.17.

[3-Cyano-4-(3,4-dimethoxyphenyl)-6-oxopiperidin-2-ylidene]malononitrile (7d). Yield 11.82 g (88%), pale-yellow fine crystalline powder, mp 238–240°C (acetone). IR spectrum, ν, cm^{-1}: 3451, 3208 (N–H), 2265, 2218 (C≡N), 1722 (C=O). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz) (~2:1 ratio of tautomers **7d-A** and **7d-B**): 2.78–2.83 (1H, m, 5-CH(*cis*)); 3.02–3.09** (0.33H, m, 5-CH(*trans*)); 3.19–3.25* (0.66H, m, 5-CH (*trans*)); 3.63–3.83 (7H, m, 4-CH, $2OCH_3$); 4.77–4.78* (0.66H, m, 3-CH); 4.97** (0.33H, d, ^3J = 6.6, 3-CH); 6.66 (0.5H, d, ^3J = 7.7, H Ar); 6.80 (0.5H, br. s, H Ar); 6.86 (0.5H, d, ^3J = 7.7, H Ar); 6.94–7.01 (1H, m, H Ar); 7.06 (0.5H, br. s, H Ar); 8.82* (0.5H, br. s, NH); 12.29** (0.2H, very br. s, OH). Signals of protons bonded to heteroatoms were not observed due to deuterium exchange. APT ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 32.9* (C-5); 35.3** (C-5); *35.5** (C-3); *36.5** (C-4); *38.4*** (C-3); *38.8*** (C-4); *55.54** (OCH_3); *55.57** (OCH_3); *55.62*** (OCH_3); *55.63*** (OCH_3); 61.88* (=<u>C</u>$(CN)_2$); 61.92** (=<u>C</u>$(CN)_2$); 111.2* (CN); *111.4*** (CH Ar); *111.8** (CH Ar); 112.2** (CN); 113.0* (CN); 113.9* (CN); 114.0** (CN); *118.6*** (CH Ar); *119.2*** (CH Ar); *119.5** (CH Ar); *120.7** (CH Ar); 129.0* (C-1 Ar); 129.6** (C-1 Ar); *148.3*** (C Ar); 148.7* (C Ar); 149.7* (C Ar); 150.3* (C Ar); 161.3* (C-2); 168.6** (C-6); 169.1* (C-6). Mass spectrum, *m*/*z* (ES-API): 340.2 $[M+NH_4]^+$, 321.2 $[M–H]^-$. Found, %: C 63.30; H 4.51; N 17.32. $C_{17}H_{14}N_4O_3$. Calculated, %: C 63.35; H 4.38; N 17.38.

Reaction of 2-amino-4-(4-methoxyphenyl)buta-1,3-diene-1,1,3-tricarbonitrile (9) with Meldrum's acid. A mixture of malononitrile dimer **3** (1.00 g, 7.57 mmol), anisaldehyde (0.92 ml, 7.57 mmol), and EtOH (15 ml) was treated with Et_3N (0.20 ml, 1.44 mmol) and heated at 40–50°C until homogeneous. The obtained solution was stirred at this temperature for 10 min and left for 48 h at 25°C. The obtained suspension, containing yellow crystalline precipitate of butadiene **9**, was treated with Meldrum's acid (1.15 g, 8.00 mmol) and Et_3N (1.40 ml, 10.00 mmol). The obtained solution was refluxed for 1.5–2 h, cooled, and treated with an excess of 1:1 concd. HCl in EtOH to pH 2. The obtained suspension was stirred for 3–4 h, the yellow product was filtered off, washed with EtOH and petroleum ether, and recrystallized from a 1:1 mixture of MeOH–Me_2CO, giving compound **7c**. Yield 0.70 g (29%), creme-colored fine crystalline powder. The spectral characteristics of the product were identical to those given above.

Reactions of (3-cyanopiperidin-2-ylidene)malononitriles 7a,c,d with thioglycolic acid anilide (10) in the

presence of Et_3N. A mixture of trinitrile **7a**,**c**,**d** (2.70 mmol) and anilide **10** (0.68 g, 4.05 mmol, 1.5 equiv) in 96% EtOH (10–12 ml) was treated with Et_3N (1.0 ml, 7.20 mmol). The obtained solution was stirred and refluxed for the duration indicated in Table 2. Rapid precipitation started after 1.5–2.5 h, the mixture was cooled, the precipitate was filtered off after 2–3 h, washed with EtOH and petroleum ether. The product was naphthyridine **11d**, or mixtures of naphthyridines and thienonaphthyridines **11a**+**12a** and **11c**+**12c**. The product yields and ratios are indicated in Table 2. Mixtures of compounds **11** and **12** are separable by silica gel column chromatography, eluting with acetone.

2-[(5-Amino-8-cyano-2-oxo-4-phenyl-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl)sulfanyl]-*N*-phenylacetamide (11a) and 5,9-diamino-2-oxo-*N*,4-diphenyl-1,2,3,4-tetrahydrothieno[2,3-*h*][1,6]naphthyridine-8-carboxamide (12a). Total yield 0.78 g (68%), pale-yellow fine crystalline powder. Ratio of **11a**:**12a** ~2:5 (^{1}H NMR) or ~1:4 (HPLC). ^{1}H, APT ^{13}C NMR and HPLC-MS data for the mixture are provided in the Supplementary information file.

2-{[5-Amino-8-cyano-4-(4-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]sulfanyl}-*N*-phenylacetamide (11c) and 5,9-diamino-4-(4-methoxyphenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydrothieno[2,3-*h*]-[1,6]naphthyridine-8-carboxamide (12c). Total yield 0.72 g (57%), pale-yellow fine crystalline powder. Ratio of **11c**:**12c** was ~5:2 (^{1}H NMR) or ~2:1 (HPLC). ^{1}H NMR, APT ^{13}C NMR spectra, and HPLC-MS analysis data for the mixture are provided in the Supplementary information file.

2-{[5-Amino-8-cyano-4-(3,4-dimethoxyphenyl)-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-7-yl]sulfanyl}-*N*-phenylacetamide (11d). Yield 839 mg (64%), beige fine crystalline powder, readily soluble in acetone. The purity according to HPLC-MS data was ~100%. The product contained ~5% impurity of the isomeric thienonaphthyridine **12d** according to ^{1}H NMR data. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.61 (1H, br. d (unresolved dd), ^2J = 15.9, 3-CH(*cis*)); 3.04 (1H, dd, ^2J = 15.9, ^3J = 6.6, 3-CH(*trans*)); 3.67 (3H, s, OCH_3); 3.69 (3H, s, OCH_3); 4.05 (2H, AB system, ^2J = 14.3, SCH_2); 4.19–4.20 (1H, m, 4-CH); 6.45 (1H, d, ^3J = 7.7, H Ar); 6.79 (1H, d, ^3J = 7.7, H Ar); 6.83 (1H, s, H Ar); 6.92 (2H, br. s, NH_2); 7.02–7.06 (1H, m, H Ph); 7.27–7.30 (2H, m, H Ph); 7.55 (2H, d, ^3J = 7.1, H Ph); 10.04 (1H, br. s, NH); 10.20 (1H, br. s, NH). APT ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 33.9 (C-3); *34.1* (C-4); 38.5 (SCH_2); *55.4* (OCH_3); *55.5* (OCH_3); 82.0 (C-8); 98.9 (C-4a); *111.5* (CH Ar); *111.8* (CH Ar); 114.8 (CN); *118.0* (CH Ar); *119.2* (C-2,6 Ph); *123.5* (C-4 Ph); *128.7* (C-3,5 Ph); 132.7 (C-Ar); 138.8 (C-1 Ph); 147.7 (C–OMe); 147.9 (C–OMe); 148.8 (C-8a); 157.7 (C-5(7)); 160.0 (C-7(5)); 166.5 (CONH); 169.3 (CONH). Mass spectrum (ES-API), *m*/*z*: 490.2 $[M+H]^+$, 488.0 $[M–H]^-$. Found, %: C 61.28; H 4.84; N 14.29. $C_{25}H_{23}N_5O_4S$. Calculated, %: C 61.34; H 4.74; N 14.31.

5,9-Diamino-2-oxo-*N*,4-diphenyl-1,2,3,4-tetrahydrothieno[2,3-*h*][1,6]naphthyridine-8-carboxamide hydrochloride (12a·HCl). A mixture of trinitrile **7a** (500 mg, 1.90 mmol) and thioglycolic acid anilide **10** (320 mg, 1.91 mmol) in 96% EtOH (10 ml) was treated with an excess of Et_3N (2.6 ml, 19 mmol). The obtained yellow solution was stirred and refluxed. Precipitation of a crystalline product started after approximately 1 h. The mixture was refluxed for 3 h, cooled, and treated with an excess of concd. HCl to pH 2. The reaction mixture was maintained for 8 h, the precipitated product was filtered off, washed with cold acetone, and dried. Yield 515 mg (58%), pinkish-colored powder, decomp. temp. >300°C. The product gave positive tests for chloride ion (Beilstein test, $AgNO_3$), while the mass spectral signals at *m*/*z* 36–38 were characteristic of hydrochlorides. IR spectrum, ν, cm^{-1}: 3345 (N–H), 1695 sh., 1682 (C=O). ^{1}H NMR spectrum (400 MHz, CCl_4–DMSO-d_6), δ, ppm (*J*, Hz): 2.75 (1H, br. d (unresolved dd), ^2J = 15.7, 3-CH(*cis*)); 3.19 (1H, dd, ^2J = 15.7, ^3J = 6.3, 3-CH(*trans*)); 4.53–4.54 (1H, m, 4-CH); 7.05–7.08 (1H, m, H Ph); 7.18–7.31 (7H, m, H Ph); 7.66 (2H, d, ^3J = 7.6, H Ph); 9.53 (1H, br. s, NH); 9.92 (1H, very br. s, NH). The signals of protonated 5-NH_2 and 9-NH_2 amino groups were identified as a very broad signal at 7.00–7.70 ppm. ^{13}C NMR spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: 33.8 (C-3); 37.5 (C-4); 97.8 (C-4a); 100.6 (C Ar); 108.8 (C Ar); 120.7 (C Ph); 122.8 (C Ph); 126.7 (C Ph); 126.9 (C Ph); 127.7 (C Ph); 128.3 (C Ph); 138.7 (C-1 Ph); 138.9 (C-1 Ph); 145.6 (C Ar); 147.2 (C Ar); 147.7 (C Ar); 152.9 (C Ar); 162.7 (CONH); 168.0 (CONH). ^{13}C NMR DEPT-135 spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: *33.9* (C-3); 37.6 (C-4); 120.9 (CH Ph); 123.2 (CH Ph); 126.8 (CH Ph); 126.9 (CH Ph); 128.1 (CH Ph); 128.4 (CH Ph). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 429 $[M–HCl]^+$ (9), 336 $[M–HCl–PhNH_2]^+$ (15), 220 (8), 131 (11), 93 (22), 77 $[Ph]^+$ (9), 56 (14), 39 (39), 38 (58), 37 $[HCl]^+$ (100), 36 (38). Found, %: C 59.42; H 4.54; N 15.09. $C_{23}H_{19}N_5O_2S·HCl$. Calculated, %: C 59.29; H 4.33; N 15.03.

Reaction of compounds 6b and 7a,c with thioglycolic acid anilide (10) in the presence of KOH. A mixture of trinitrile **7a**,**c** (1.90 mmol) or salt **6b** (500 mg, 1.26 mmol) and an equimolar amount of anilide **10** in 96% EtOH (10 ml) was treated with an excess of 10% aqueous KOH solution (1.0 ml, 1.95 mmol, ~1.5 equiv). The obtained yellow solution was stirred and refluxed for 3–5 h, possibly accompanied by the formation of precipitate. The mixture was treated with excess of AcOH, maintained for 24 h, the precipitate was filtered off and washed with EtOH. The reaction products were purified by refluxing with AcOH, cooled, the precipitate was filtered off and and dried at 100°C. Thienonaphthyridines **12a**–**c** were obtained as beige or yellow powders.

5,9-Diamino-2-oxo-*N*,4-diphenyl-1,2,3,4-tetrahydrothieno[2,3-*h*][1,6]naphthyridine-8-carboxamide (12a). Yield 610 mg (75%), beige powder, decomp. temp. >300°C. IR spectrum, ν, cm^{-1}: 3311, 3151 (N–H), 1695 (C=O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.76 (1H, br. d (unresolved dd), ^2J = 15.7, 3-CH(*cis*)); 3.21 (1H, dd, ^2J = 15.7, ^3J = 6.7, 3-CH(*trans*)); 4.60–4.61 (1H, m, 4-CH); 7.04–7.08 (1H, m, H Ph); 7.20–7.32 (7H, m, H Ph); 7.68 (2H, d, ^3J = 8.1, H Ph); 9.64 (1H, br. s, NH); 10.01 (1H, very br. s, NH). The signals of 5-NH_2 and

9-NH_2 amino groups were observed as a very broad peak at 7.20–8.70 ppm. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 34.0 (C-3); 37.8 (C-4); 97.0 (C-4a); 101.3 (C-Ar); 108.7 (C-Ar); 120.2 (C Ph); 123.5 (C Ph); 127.1 (C Ph); 127.2 (C Ph); 128.4 (C Ph); 128.7 (C Ph); 138.8 (C-1 Ph); 139.3 (C-1 Ph); 145.2 (C Ar); 148.1 (C Ar); 150.1 (C Ar); 153.9 (C Ar); 163.4 (CONH); 169.0 (CONH). ^{13}C NMR DEPT-135 spectrum (100 MHz, DMSO-d_6), δ, ppm: 33.8 (C-4); *37.5* (C-3); 121.0 (CH Ph); 123.2 (CH Ph); 126.8 (CH Ph); 127.0 (CH Ph); 128.1 (CH Ph); 128.4 (CH Ph). Found, %: C 64.08; H 4.59; N 16.10. $C_{23}H_{19}N_5O_2S$. Calculated, %: C 64.32; H 4.46; N 16.31.

5,9-Diamino-4-(2-chlorophenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydrothieno[2,3-*h*][1,6]naphthyridine-8-carboxamide (12b). Yield 485 mg (80%), light-yellow powder, decomp. temp. >300°C. IR spectrum, ν, cm^{-1}: 3413, 2290 (N–H), 1712 (C=O). ^{1}H NMR spectrum (400 MHz, CCl_4–DMSO-d_6), δ, ppm (*J*, Hz): 2.75 (1H, br. d (unresolved dd), ^2J = 15.4, 3-CH(*cis*)); 3.06 (1H, dd, ^2J = 15.4, ^3J = 6.1, 3-CH(*trans*)); 4.57–4.59 (1H, m, 4-CH); 6.78–6.79 (1H, m, H Ar); 6.98–7.00 (1H, m, H Ar); 7.16–7.24 (4H, m, H Ar); 7.45–7.46 (1H, m, H Ar); 7.64–7.65 (2H, m, H Ar); 9.08 (1H, br. s, CONH); 9.65 (1H, very br. s, CONH). The signals of 5-NH_2 and 9-NH_2 amino groups were observed as a very broad peak at 5.20–6.20 ppm. ^{13}C NMR spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: 33.2 (C-4); 36.2 (C-3); 99.0 (C-4a); 107.8 (C-8); 121.0 (CH Ph); 122.9 (C Ar); 127.4 (C Ar); 127.7 (C Ar); 128.1 (CH Ph); 129.0 (C Ar); 130.1 (C Ar); 133.3 (C Ar); 136.6 (C Ar); 139.1 (C Ar); 143.3 (C Ar); 148.5 (C Ar); 157.2 (C Ar); 159.6 (C Ar); 163.9 (CONH); 168.3 (CONH). ^{13}C NMR DEPT-135 spectrum (100 MHz, CCl_4–DMSO-d_6), δ, ppm: 33.0 (C-4); 35.9 (C-3); 120.7 (CH Ph); 122.7 (CH Ar); 127.1 (CH Ar); 127.5 (CH Ar); 127.8 (CH Ph); 128.7 (CH Ar); 129.9 (CH Ar). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 465 [M(^{37}Cl)]$^+$ (22), 463 [M(^{35}Cl)]$^+$ (53), 373 [M(^{37}Cl)–$PhNH_2$]$^+$ (33), 371 [M(^{35}Cl)–PhNH]$^+$ (100), 93 [$PhNH_2$]$^+$ (12), 46 (31), 44 (28). Found, %: C 59.40; H 4.02; N 15.12. $C_{23}H_{18}ClN_5O_2S$. Calculated, %: C 59.54; H 3.91; N 15.10.

5,9-Diamino-4-(4-methoxyphenyl)-2-oxo-*N*-phenyl-1,2,3,4-tetrahydrothieno[2,3-*h*][1,6]naphthyridine-8-carboxamide (12c). Yield 735 mg (84%), yellow powder, decomp. temp. >300°C. IR spectrum, ν, cm^{-1}: 3348, 3162 (N–H), 1709 (C=O). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.72 (1H, br. d (unresolved dd), ^2J = 15.7, 3-CH(*cis*)); 3.16 (1H, dd, ^2J = 15.7, ^3J = 6.3, 3-CH(*trans*)); 3.69 (3H, s, OCH_3); 4.52–4.53 (1H, m, 4-CH); 6.85 (2H, d, ^3J = 8.1, H Ar); 7.05–7.12 (3H, m, H Ph); 7.29–7.33 (2H, m, H Ph); 7.66 (2H, d, ^3J = 8.1, H Ar); 9.69 (1H, br. s, CONH); 9.99 (1H, very br. s, CONH). The signals of 5-NH_2 and 9-NH_2 amino groups were observed as a very broad peak at 5.50–6.50 ppm. ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ, ppm: 33.3 (C-4); 37.9 (C-3); 55.1 (OCH_3); 97.1 (C-4a); 101.8 (C Ar); 108.8 (C-8); 114.1 (CH Ar); 121.3 (CH Ph); 123.6 (CH Ar); 128.2 (CH Ar); 128.5 (CH Ar); 131.0 (C Ar); 138.8 (C Ar); 145.2 (C Ar); 148.1 (C Ar); 149.4 (C Ar); 153.6 (C Ar); 158.5 (C Ar); 163.3 (CONH); 169.2 (CONH). ^{13}C NMR DEPT-135 spectrum (100 MHz, DMSO-d_6), δ, ppm: 33.0 (C-4); *37.7* (C-3); 54.9 (OCH_3); 113.8 (CH Ar); 121.0 (CH Ph); 123.4 (CH Ph); 127.9 (CH Ar); 128.2 (CH Ph). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 459 [M]$^+$ (48), 367 [M–PhNH]$^+$ (100), 340 (10), 161 (12), 119 (12), 93 [$PhNH_2$]$^+$ (30). Found, %: C 62.51; H 4.78; N 15.20. $C_{24}H_{21}N_5O_3S$. Calculated, %: C 62.73; H 4.61; N 15.24.

X-ray structural analysis of compounds 6a and 7a. Crystals of compound **6a** ($C_{21}H_{25}N_5O$, *M* 363.46) were monoclinic, space group $P2_1/n$; at *T* 296 K: *a* 15.4817(5), *b* 8.1208(3), *c* 16.1815(5) Å; β 3.7160(10)°; *V* 2030.12(12) Å^3; *Z* 4; d_{calc} 1.189 g/cm^3; *F*(000) 776; μ 0.076 mm^{-1}. The unit cell parameters and intensities of 20804 reflections (4443 independent reflections, R_{int} 0.0211) were measured on a Bruker APEX II CCD automated three-circle diffractometer (λMoKα radiation, graphite monochromator, ω- and φ-scanning, $2\theta_{max}$ 54°). The structure was solved by direct methods and refined with full matrix method of least squares by F^2 in anisotropic approximation for non-hydrogen atoms. The position of H atom involved in hydrogen bonding was found from differential synthesis of electron density and refined in isotropic approximation. The coordinates of other hydrogen atoms were calculated geometrically and refined according to the "rider" model. The final probability factors were R_1 0.0737 for 3458 independent reflections with $I > 2\sigma(I)$ and wR_2 0.2224 for all independent reflections. All calculations were performed by using the SHELXTL software suite.[58] The complete crystallographic dataset for compound **6a** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 978371).

Crystals of compound **7a** ($C_{15}H_{10}N_4O$, *M* 262.27) were monoclinic, space group $P2_1/c$; at *T* 296 K: *a* 11.2643(5), *b* 16.6323(7), *c* 6.9332(3) Å; β 96.9710(10)°; *V* 1289.34(10) Å^3; *Z* 4; d_{calc} 1.351 g/cm^3; *F*(000) 544; μ 0.090 mm^{-1}. The unit cell parameters and intensities of 14501 reflections (3112 independent reflections, R_{int} 0.0200) were measured on a Bruker APEX II CCD automated three-circle diffractometer (λMoKα radiation, graphite monochromator, ω- and φ-scanning, $2\theta_{max}$ 56°). The structure was solved by direct methods and refined with full matrix method of least squares by F^2 in anisotropic approximation for non-hydrogen atoms. The position of H atom involved in hydrogen bonding was found from differential synthesis of electron density and refined in isotropic approximation. The coordinates of other hydrogen atoms were calculated geometrically and refined according to the "rider" model. The final probability factors were R_1 0.0438 for 2544 independent reflections with $I > 2\sigma(I)$ and wR_2 0.1182 for all independent reflections. All calculations were performed by using the SHELXTL software suite.[58] The complete crystallographic dataset for compound **7a** was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 978217).

The Supplementary Iiformation file containing spectra of compounds, as well as the X-ray crystallographic data for compounds **6a**, **7a**, is available at http://link.springer.com/journal/10593.

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