A new approach towards thieno[2,3-h][1,6]naphthyridines

Maria P. Goykalova (Averyasova)[1], Victor V. Dotsenko[1,2]*, Elena A. Chigorina[3], Nikolay A. Aksenov[4], Inna V. Aksenova[4], Vladimir D. Strelkov[1,5]

[1]Kuban State University, 149 Stavropolskaya str, Krasnodar, 350040 Russia
e-mail: victor_dotsenko@bigmir.net
[2]ChemEx Lab, Vladimir Dal' Lugansk National University, 20A/7 Molodezhny, Lugansk, 91034 Russia
[3]The Federal State Unitary Enterprise «Institute of Chemical Reagents and High Purity Chemical Substances of National Research Centre «Kurchatov Institute», 3 Bogorodsky val, Moscow, 107076 Russia
[4]Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., 355009 Stavropol, Russia
[5]All-Russian Research Institute of Biological Plant Protection, Laboratory of plant growth regulators, 350039 Krasnodar, Russia

Abstract

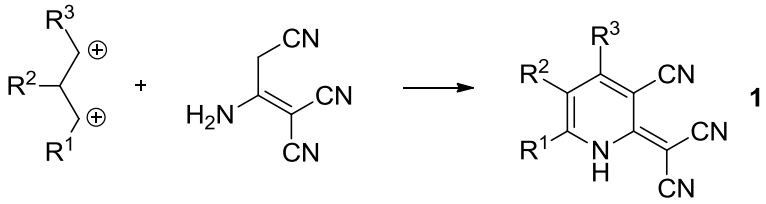
Triethylammonium salts of (4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)malononitriles were prepared by reaction of aldehydes with Meldrum's acid and 2-amino-1,1,3-tricyanopropene (malononitrile dimer) in the presence of triethylamine. Upon treatment with alpha-mercaptocarbonyl compounds in the presence of alkali, new thieno[2,3-h][1,6]naphthyridines were prepared in good yields.

Keywords

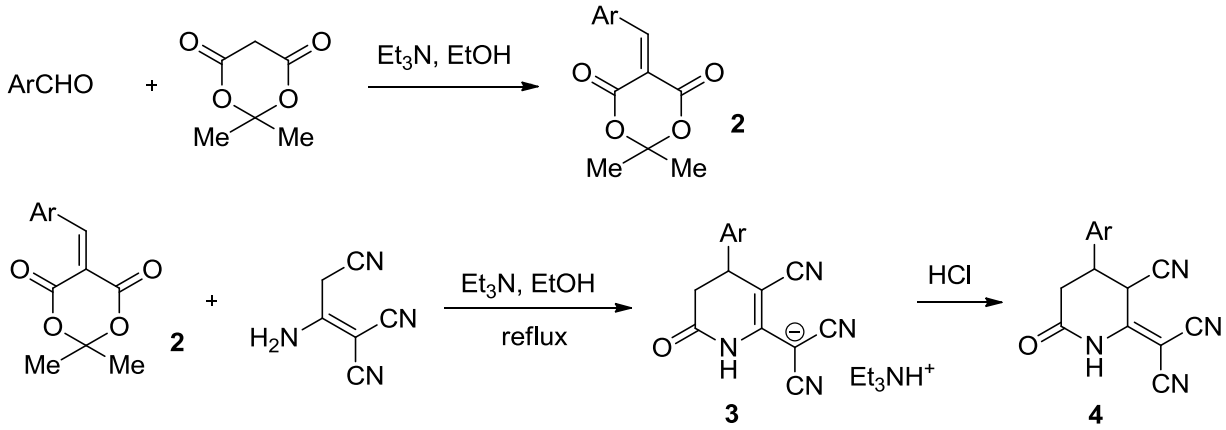
Meldrum's acid, 2-amino-1,1,3-tricyanopropene, malononitrile dimer, thieno[2,3-h][1,6]naphthyridines

(3-Cyanopyridin-2(1H)-ylidene)malononitriles **1** have been recognized as convenient reagents for various cascade transformations and are quite often used for the synthesis of heterocyclic compounds, especially 1,6-naphthyridines. (3-Cyanopyridin-2(1H)-ylidene)malononitriles **1** can be easily prepared by reaction of various 1,3-biselectrophilic reagents with 2-aminoprop-1-ene-1,1,3-tricarbonitrile (malononitrile dimer) (the chemistry

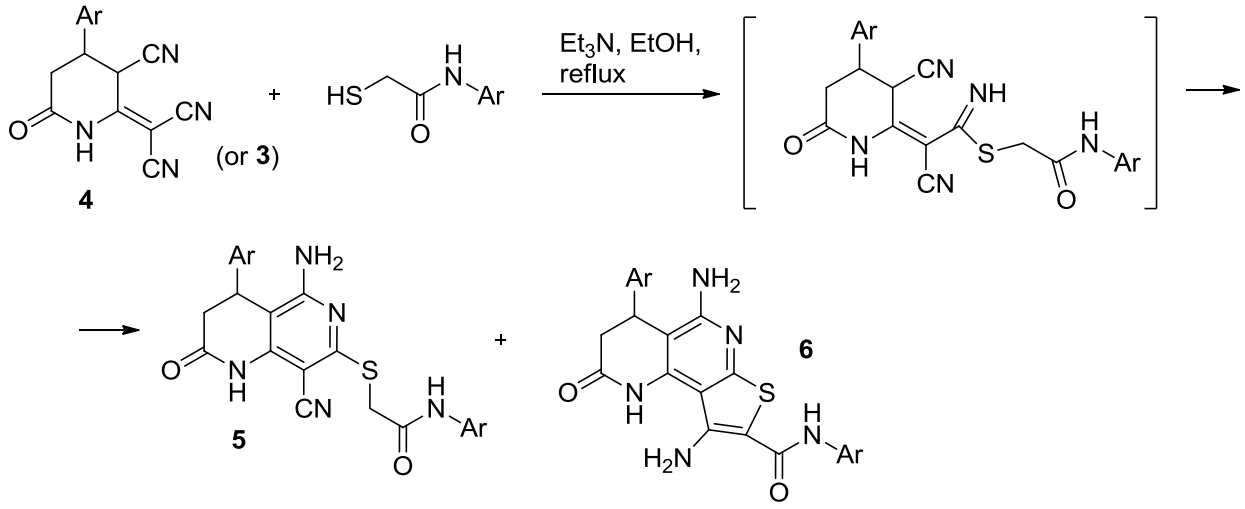
of 2-aminoprop-1-ene-1,1,3-tricarbonitrile has been covered in reviews [1-3]).



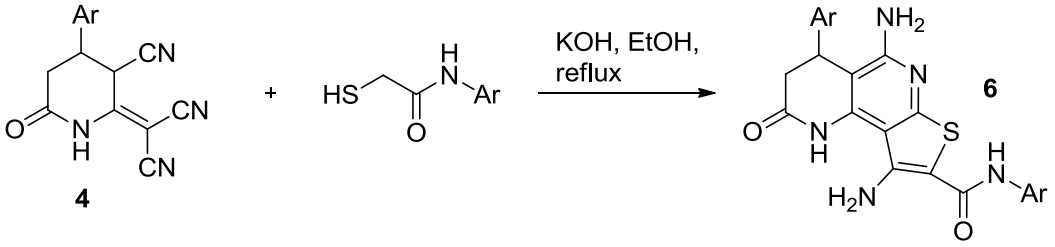
While continuing research in the chemistry of malononitrile dimer, we decided to study the reactivity of malononitrile dimer with 5-arylmethylene 2,2-dimethyl-1,3-dioxane-4,6-diones **2**, generated *in situ* from aldehydes and Meldrum's acid. We found that the reaction easily proceeds in the presence of Et_3N in boiling EtOH to give dicyanomethylide salts **3**, or, after treatment with an acid – corresponding piperidines **4**:



The structures of compounds **3** and **4** were studied by IR spectroscopy, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, HPLC-MS and elemental analysis. Noteworthy that preparation of analogs of compounds **4** was reported before [4], though by a quite different method. The reaction of (3-cyanopiperidin-2-ylidene)malononitriles **4** or salts **3** with thioglycolic acid anilides in hot EtOH in the presence of an excess of Et_3N proceeded through an attack by $ArNHC(O)CH_2S^-$ anion at one of the nitrile groups of the $=C(CN)_2$ moiety. The products were identified as a mixture of 1,6-naphthyridines **5** and their Thorpe–Ziegler cyclization products, isomeric thieno[2,3-h][1,6]naphthyridines **6**.



When KOH was taken instead an organic base, the yields of thieno[2,3-h][1,6]naphthyridines were increased up to 84% to give only **6** in pure form. In addition, when the mixtures **5+6** were treated with an excess of 10% aq. KOH, thieno[2,3-h][1,6]naphthyridines **6** were obtained in quantitative yields.



Experimental

*Preparation of (4-aryl-3-cyano-6-oxo-1,4,5,6-tetrahydropyridin-2-yl)malononitrile triethylammonium salts **3** and (4-aryl-3-cyano-6-oxopiperidin-2-ylidene)malononitriles **4** (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 (5-arylmethylene 2,2-dimethyl-1,3-dioxane-4,6-diones **2**) 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). The crystalline precipitate of salt **3** 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, to give compounds **4**. When no formation of salts **3** was observed, 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 **4**.

Synthesis of thieno[2,3-h][1,6]naphthyridines **6**

A mixture of trinitriles **4** (1.90 mmol) or salts **3** (1.90 mmol) and thioglycolic acid anilides (1.90-2.00 mmol) 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. 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 dried at 100°C. Thienonaphthyridines **6** 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.

Yield 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), ^{2}J = 15.7, 3-CH(cis)); 3.21 (1H, dd, ^{2}J = 15.7, ^{3}J = 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, ^{3}J = 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, probably due to partial protonation after treatment with AcOH. ^{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).

^{1}H and ^{13}C NMR spectra of 5,9-diamino-2-oxo-N,4-diphenyl-1,2,3,4-tetrahydrothieno[2,3-h][1,6]naphthyridine-8-carboxamide are shown in the Figures 1-3.

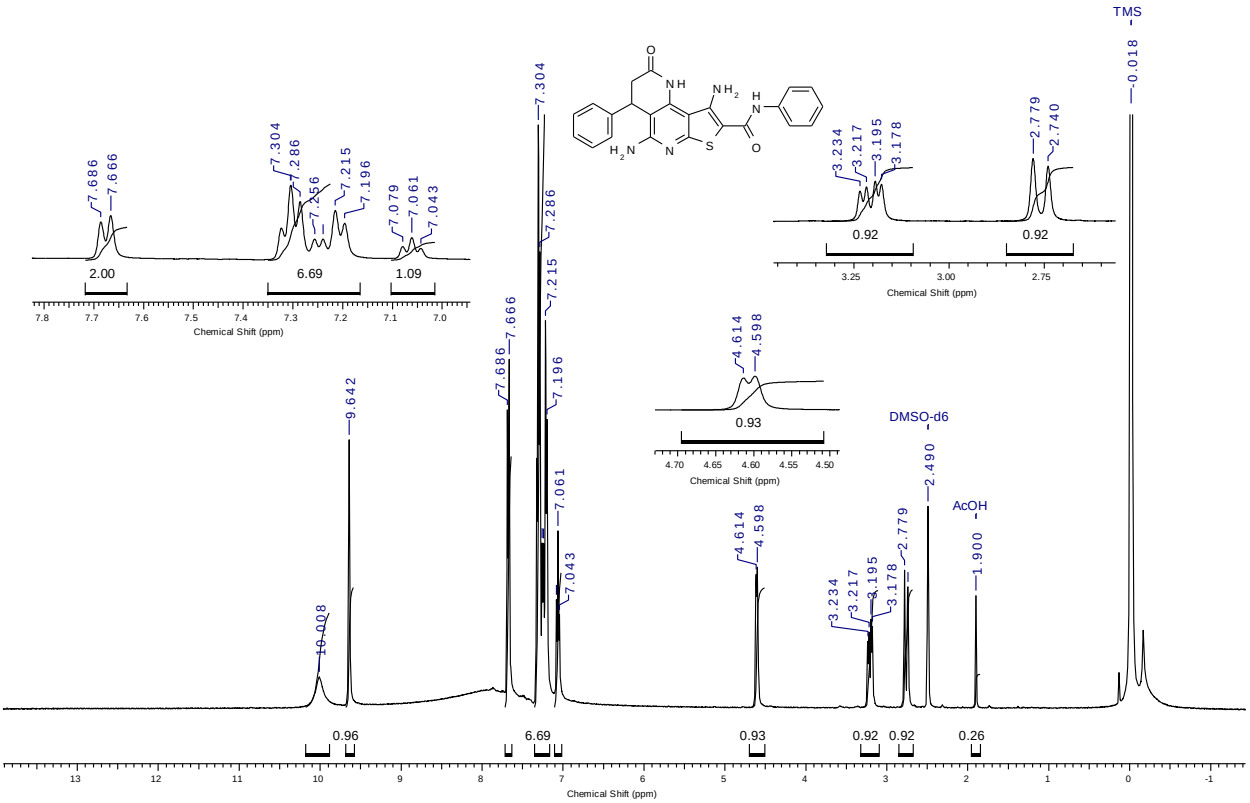


Fig. 1. ^{1}H NMR spectrum (400 MHz) of 5,9-diamino-2-oxo-N,4-diphenyl-1,2,3,4-tetrahydrothieno[2,3-h][1,6]naphthyridine-8-carboxamide

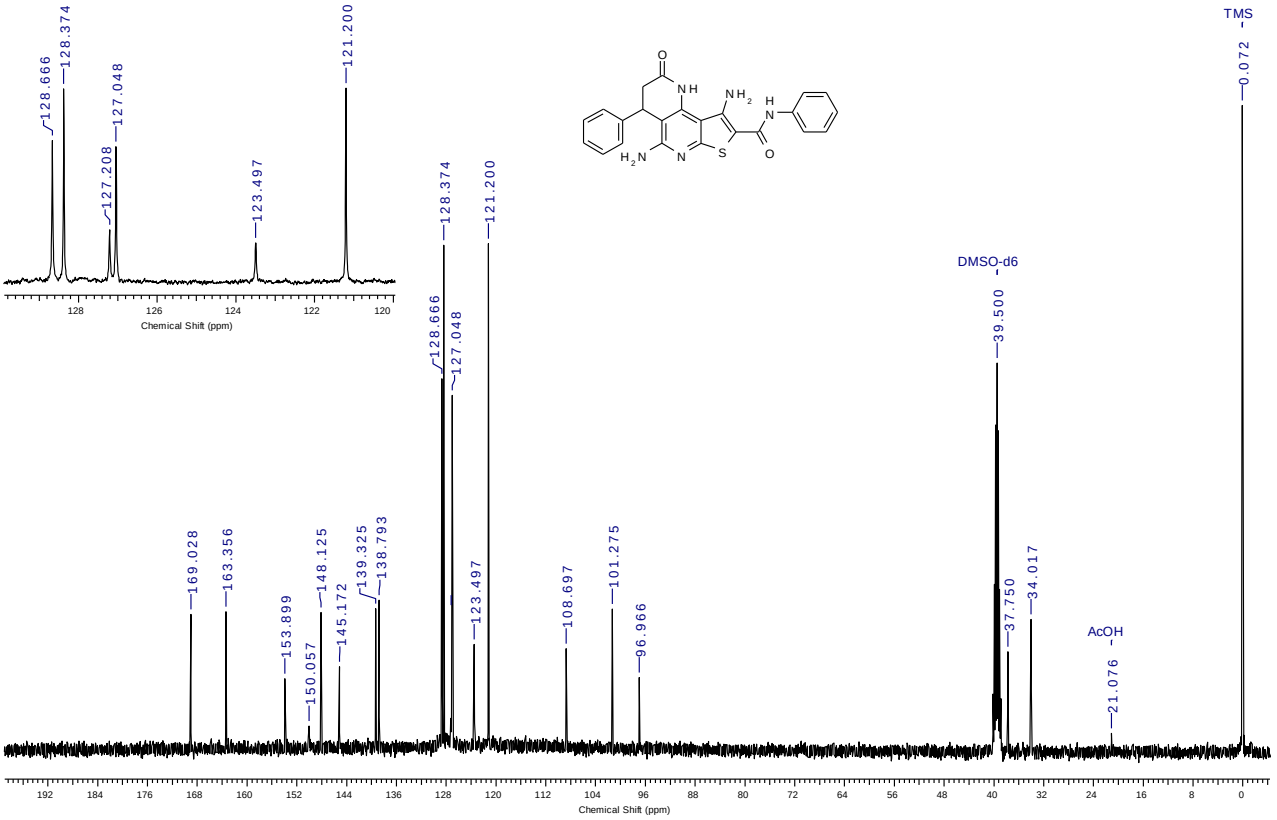


Fig. 2. ^{13}C NMR spectrum (101 MHz) of 5,9-diamino-2-oxo-N,4-diphenyl-1,2,3,4-tetrahydrothieno[2,3-h][1,6]naphthyridine-8-carboxamide

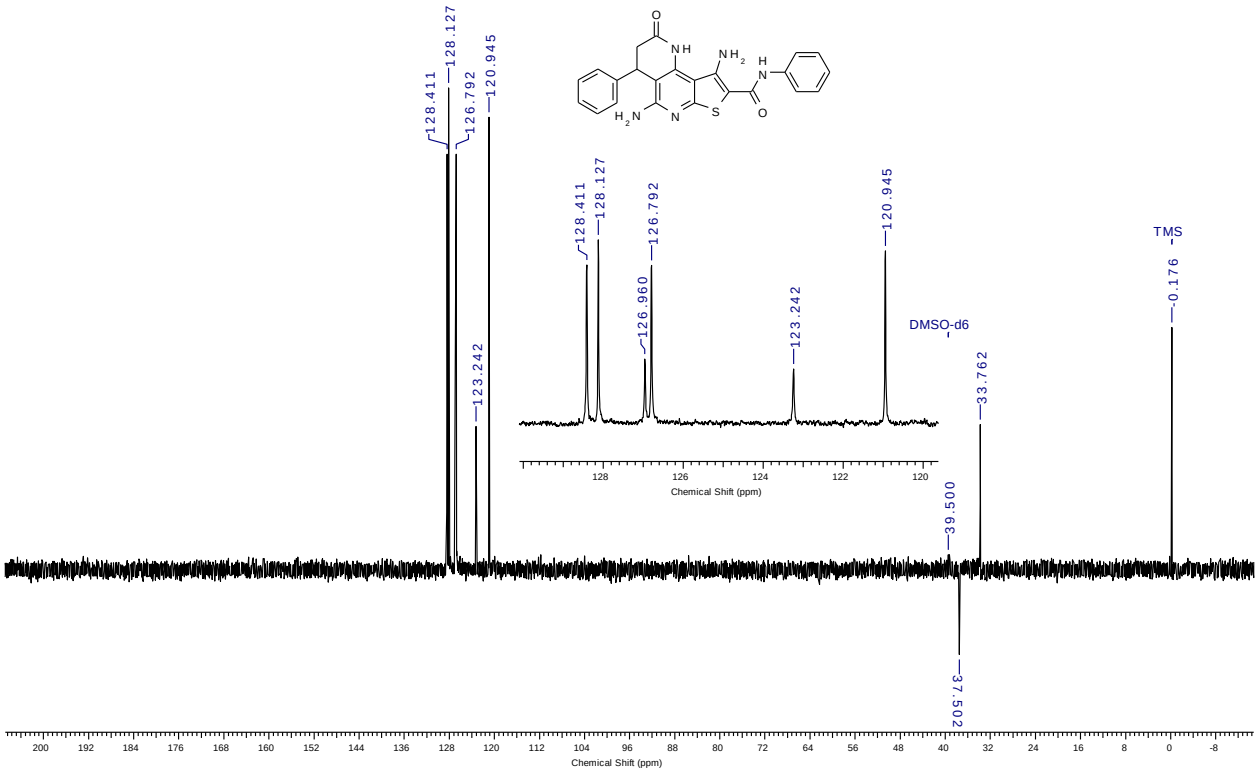


Fig. 3. ^{13}C NMR DEPT-135 spectrum (101 MHz) of 5,9-diamino-2-oxo-N,4-diphenyl-1,2,3,4-tetrahydrothieno[2,3-h][1,6]naphthyridine-8-carboxamide

References

1. Freeman, F. // Chem. Rev. 1969, 69, 591.

2. Fatiadi, A. J. // Synthesis 1978, 165.

3. Sharanin, Yu. A.; Promonenkov, V. K.; Litvinov, V. P. in *Results of Science and Technology. Organic Chemistry*, Shvekhgeimer, M.-G. A., Ed.; VINITI: Moscow, 1991, *Vol. 20 (Part 2)*, p. 59 (in Russian).

4. Victory, P. J.; Teixidó, J.; Borrell, J. I. // Heterocycles 1992, 34, 1905.