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Extended Abstract

Synthesis of 4-(1,3,5-Thiadiazinan-2-ylidene)-2-(3,4-dihydro-2H-1,3,5-thiadiazin-6-yl)pent-2-enedinitriles †

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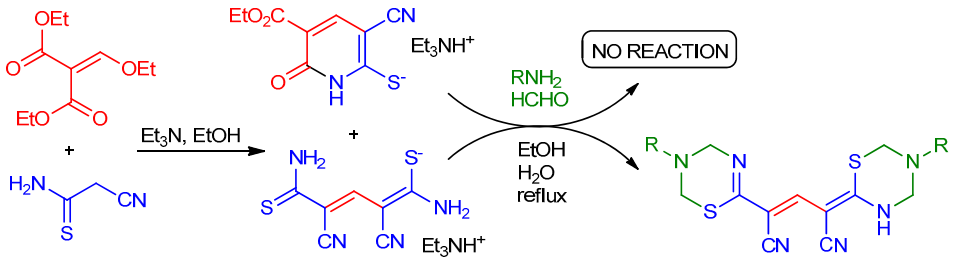
Abstract: The reaction of cyanothioacetamide with diethyl ethoxymethylenemalonate in the presence of triethylamine in hot EtOH proceeds non-selectively and leads to the formation of a mixture of triethylammonium 1,5-diamino-2,4-dicyano-5-thioxopenta-1,3-diene-1-thiolate (minor) and triethylammonium 3-cyano-5-ethoxycarbonyl-6-oxo-1H-pyridine-2-thiolate (major). Upon treatment with primary amines and 37% aqueous HCHO in boiling aqueous ethanol, the reaction product affords only 4-(1,3,5-thiadiazinan-2-ylidene)-2-(3,4-dihydro-2H-1,3,5-thiadiazin-6-yl)pent-2-enedinitrile derivatives, instead of the expected pyrido[2,1-b][1,3,5]thiadiazines. Triethylammonium 3-cyano-5-ethoxycarbonyl-6-oxo-1H-pyridine-2-thiolate does not react under these conditions. The structure of the resulted products was confirmed by means of NMR, IR spectroscopy, and LCMS. The mechanism of the formation of the products is discussed.

Keywords: cyanothioacetamide; diethyl ethoxymethylenemalonate; aminomethylation; Mannich reaction; 1,3,5-thiadiazines

1. Graphical Abstract



The Mannich reaction is an effective tool to build C–C–N and X–C–N bonds (where X = N, O, S, Se, P, etc.), and therefore it is often used in the synthesis of a wide variety of heterocyclic compounds (for the reviews on the various modifications of the Mannich reaction, see [1–9]. 1,3,5-Thiadiazines belong to an important class of heterocyclic compounds. The synthesis of 1,3,5-thiadiazines is successfully realized on the basis of Mannich-type aminomethylation [10–13]. 1,3,5-Thiadiazines are also of interest due a wide range of biological activity and practically important properties [12,14,15];

among the most important representatives of this class, the fungicide Dazomet and the highly effective insecticide Buprofezin, are worth mentioning (Figure 1).

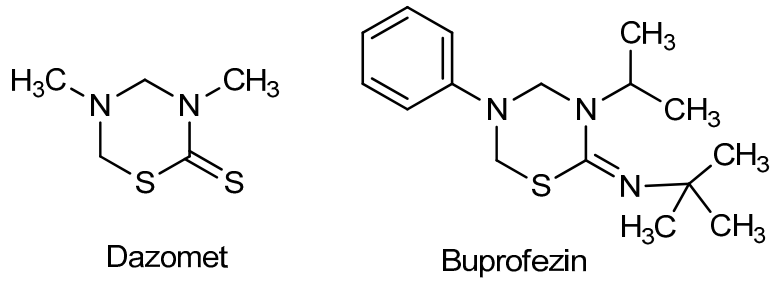
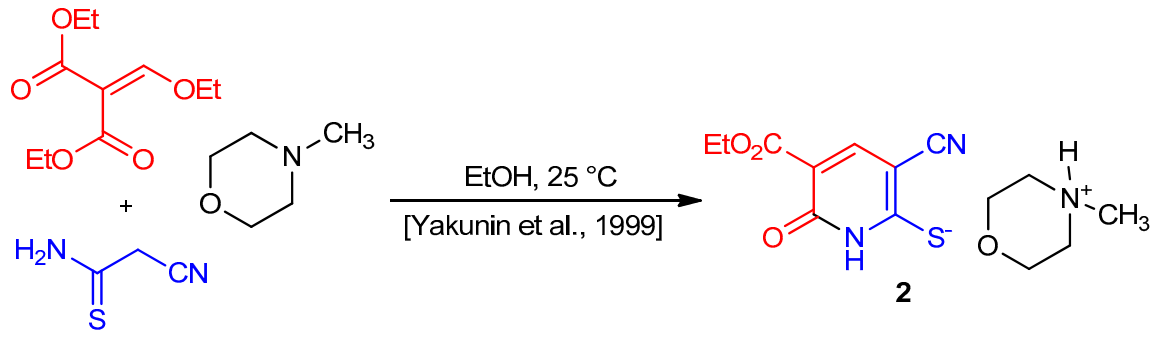


Figure 1. Bioactive 1,3,5-thiadiazines.

Our interest in the synthesis of condensed 1,3,5-thiadiazines through the aminomethylation of cyclic thioamides [12,16–18] prompted us to study the behavior of new cyclic cyanothioacetamide derivatives in the reaction with primary amines and formaldehyde. Triethylammonium 3-cyano-5-ethoxycarbonyl-6-oxo-1H-pyridine-2-thiolate **1** was chosen as a starting compound. The synthesis of N-methylmorpholinium analogue **2** in moderate yield (52%) was described in Yakunin, Dyachenko, and Litvinov [19] (Scheme 1).

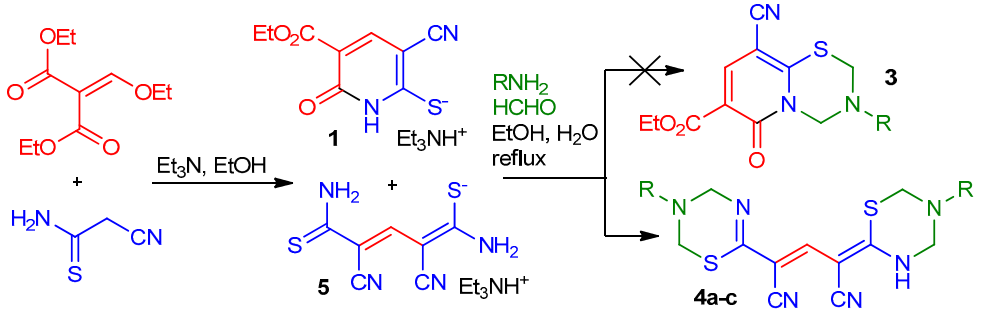


Scheme 1. Synthesis of thiolate **2.**

Due to the presence of two nucleophilic centers (endocyclic nitrogen atom and sulfur atom), thiolate **1** seemed to be a promising substrate for aminomethylation leading to pyrido[2,1-b][1,3,5]thiadiazines with potential biological activity [12,16]. In the aminomethylation reactions, the nature of the trialkylammonium cation, as a rule, does not affect significantly the yields and the direction of a process. Therefore, in order to increase the yield of the starting thiolate, we decided to replace N-methylmorpholine with a more basic [20] triethylamine.

To prepare thiolate **1**, cyanothioacetamide was reacted with ethoxymethylene malonate in the presence of a 1.5-fold excess of Et_3N while slowly heating the reaction mixture to boiling point. The reaction product was put into reaction with primary amines with an excess of 37% without further purification. The aminomethylation products were precipitated from a boiling solution during the reaction. To our surprise, the IR spectra of the supposed pyrido[2,1-b][1,3,5] thiadiazines **3** revealed the absence of stretching vibration bands of the ester C=O group, while the bands corresponding to the stretching vibrations of the conjugated cyano group (~ 2215–2220 cm^{-1}) and N–H bonds (ν ~ 3350–3400 cm^{-1}) were observed. In the ^1H NMR spectra of the synthesized compounds, there are a broadened NH proton singlet (δ 11.86–12.06 ppm), two sets of signals from primary amines, and four non-equivalent signals of the X–CH_2–N protons in the expected region (δ 4.5 ... 6.0 ppm), as well as a narrow singlet at δ 7.63–7.85 ppm (Figure 2). Moreover, the characteristic signals of the ethoxycarbonyl group were absent in the NMR spectrum. Analysis of spectral data, the results of elemental analysis, as well as HPLC-MS data allowed us to conclude that the products actually have a structure of 4-(1,3,5-thiadiazin-2-ylidene)-2-(3,4-dihydro-2H-1,3,5-thiadiazin-6-yl)pent-2-endinitriles **4** (Scheme 2). A detailed analysis of the spectral data of the starting thiolate **1** revealed that, unlike the

thiolate **2** obtained by a known method [19], the sample we synthesized is actually a mixture of triethylammonium 1,5-diamino-2,4-dicyano-5-thioxopenta-1,3-diene-1-thiolate **5** (minor product) and triethylammonium 3-cyano-5-ethoxycarbonyl-6-oxo-1H-pyridine-2-thiolate **1** (main product) (Scheme 2).



4 a: R = CH_2Ph; **b:** R = 4-$EtOC_6H_4$; **c**: R = 4-EtC_6H_4.

Scheme 2. Synthesis of compounds **4a–c.**

These results can be explained by the mechanism presented in Scheme 3. First, an S_NVin vinyl nucleophilic substitution reaction takes place [21–23] leading to the formation of an intermediate - diene **6**. The formation of such diene species in the reactions of vinyl ethers with active methylene compounds is well documented [24–28]. Next, presumably, the activated double bond of intermediate **6** was attacked by cyanothioacetamide anion, followed by decomposition of the Michael adduct **7**, which is accompanied by elimination of malonic ester and formation of pentadiene thiolate **5**. The formation of such structures was previously observed in the reaction of cyanoacetanilides with ethoxymethylenemalonate [28]. At the same time, an alternative and preferential pathway for the transformation of intermediate **6** is intramolecular *6-exo-trig*-cyclization with the formation of pyridine-2-thiolate **1**.

Further investigation of the reaction of cyanothioacetamide with ethoxymethylene malonate in the presence of triethylamine and N-methylmorpholine allowed us to conclude that: (1) in the case of N-methylmorpholine under the conditions described earlier [19]; pentadiethiolates **5** were not isolated; (2) replacement of N-methylmorpholine to triethylamine favors the formation of compound **5** under short-term heating of a mixture; (3) the content of product **5** in the mixture does not exceed 10–15 mol% (according to ^1H NMR); (4) analytically pure triethylammonium 3-cyano-5-ethoxycarbonyl-6-oxo-1H-pyridine-2-thiolate **1** can be prepared by reaction of cyanothioacetamide and ethoxymethylene malonate in acetonic solution at the room temperature; (5) a longer heating neither favors the formation of compound **5**, nor leads to an increase in the yields of thiolates **1** or **2**, but leads to a noticeable resinification of the reaction mixture, possibly due to further intramolecular cyclizations of compounds **5** or **7**, or self-condensation of cyanothioacetamide, which occurs under basic conditions [29,30].

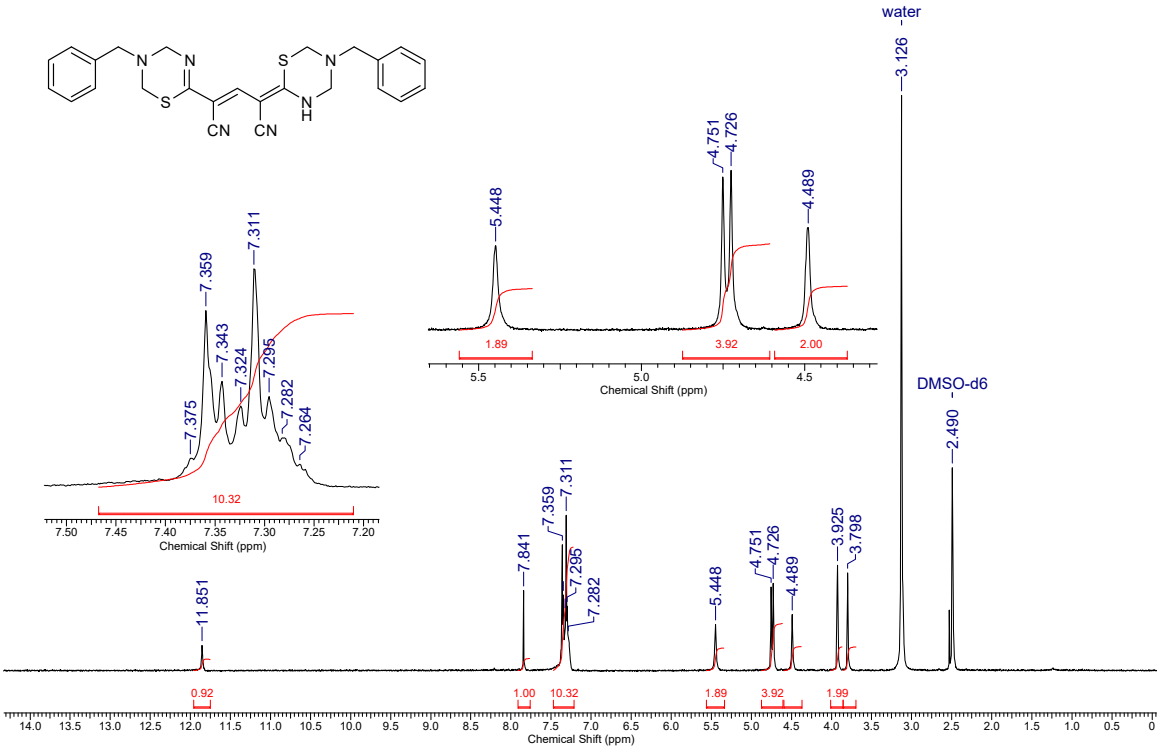
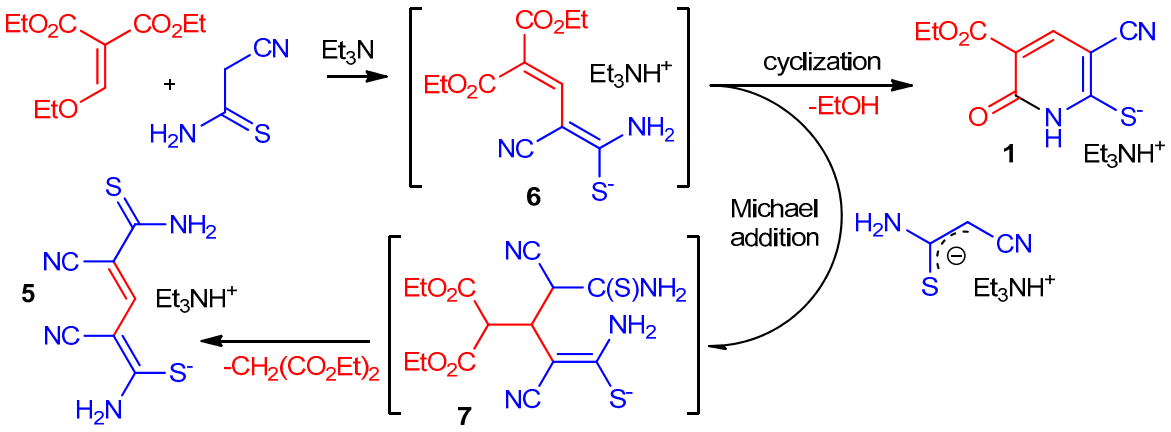


Figure 2. ^{1}H NMR spectrum (400 MHz, DMSO-d$_6$) of 4-(5-benzyl-1,3,5-thiadiazin-2-ylidene)-2-(3-benzyl-3,4-dihydro-2H-1, 3,5-thiadiazin-6-yl)pent-2-endinitrile **4a.**



Scheme 3. The possible mechanism of the formation of compounds **1** and **5**

It should also be noted that, contrary to expectations, neither pure thiolate **1** nor thiolate **2** give any Mannich-type products under the conditions stated; a noticeable resinification of reaction mass was observed during the synthesis. The TLC and NMR data of a gummy residue after removal of the solvent showed the presence of starting thiolate, along with a complex mixture of the reaction products between amines, HCHO, and solvent. In our opinion, this can be explained by the reduced N-/S-nucleophilicity of the substrate due to the presence of two strong electron-withdrawing groups (CN, COOEt) in the pyridine ring.

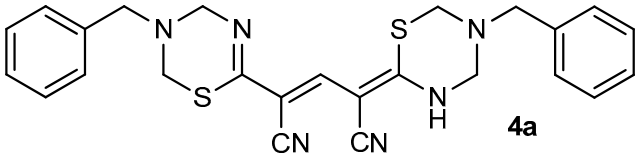
2. Experiment

IR spectra were recorded on an IKS-29 spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker DPX-400 spectrometer (400 MHz) in DMSO-d$_6$ using TMS as an internal standard. HPLC-MS analysis was performed on a Shimadzu LC-10AD LC with a Shimadzu SP D-10A UV–Vis (254 nm) detector and Sedex 75 ELSD, combined with a PE SCIEX API 150EX mass spectrometer and atmospheric pressure electrospray ionization. Selected experimental procedures

will now be described. Cyanothioacetamide was synthesized by passing hydrogen sulfide through a solution of malononitrile in EtOH according to a known procedure [31]. Ethoxymethylenemalonic ester is a commercially available reagent (Acros).

4-(5-Benzyl-1,3,5-thiadiazin-2-ylidene)-2-(3-benzyl-3,4-dihydro-2H-1,3,5-thiadiazin-6-yl)-pent-2-endinitrile **4a**.

A mixture of thiolates **1** and **5** (1.0 g) (prepared by reaction of cyanothioacetamide with ethoxymethylene malonate in the presence of Et_3N in boiling EtOH), was dissolved in hot 80% EtOH (10 mL). The resulting solution was filtered through a paper filter, then the filtrate was added to a solution of benzylamine (3 mmol) and an excess of formalin (5 mL) in 5 mL of EtOH. The mixture was boiled with stirring for 1–2 min, during which time a crystalline precipitate formed. The product was filtered off and washed with EtOH to afford 1,3,5-thiadiazine **4a** in analytically pure form.



4a

Yellow cryastalline solid, yield was 0.18 g. IR (nujol), ν, cm^{-1}: 3360 (N–H); 2217 (CN). NMR ^1H (400 MHz, DMSO-d_6), δ, ppm: 3.80 (br s, 2 H, $NC\underline{H}_2Ph$); 3.93 (br s, 2 H, $NC\underline{H}_2Ph$); 4.49 (br s, 2 H, $NC\underline{H}_2NH$); 4.73 (br s, 2 H, $NC\underline{H}_2S$); 4.75 (br s, 2 H, $NC\underline{H}_2S$); 5.45 (br s, 2 H, $NC\underline{H}_2N$); 7.26-7.38 (m, 10 H, 2 Ph); 7.84 (s, 1 H, –CH=); 11.85 (br s, 1 H, NH). LC-MS (ESI), m/z: 947.0 $[2M+H]^+$, 826.5 $[2M+H-PhCH_2N=CH_2]^+$, 473.5 $[M+H]^+$, 354.5 $[M-PhCH_2N=CH_2+H]^+$, 235.1 $[M-2PhCH_2N=CH_2+H]^+$. Found, %: C 63.64; H 5.22; N 17.72. $C_{25}H_{24}N_6S_2$ (M = 472.63). Calculated, %: C 63.53; H 5.12; N 17.78.

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