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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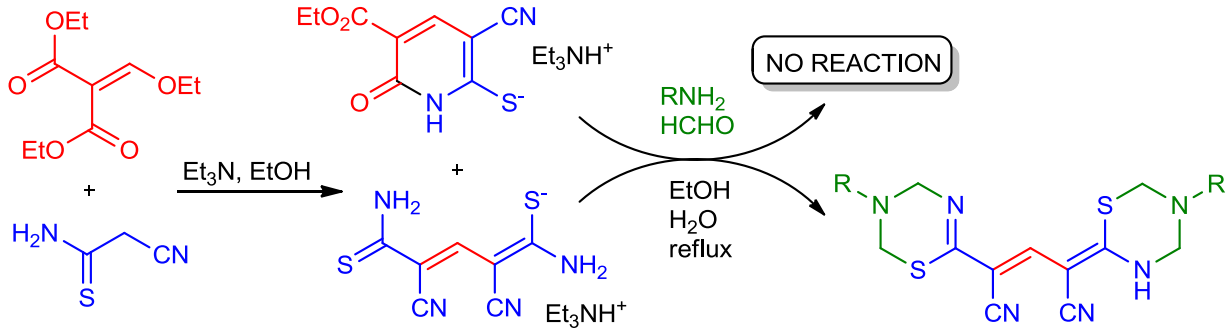
Graphical abstract



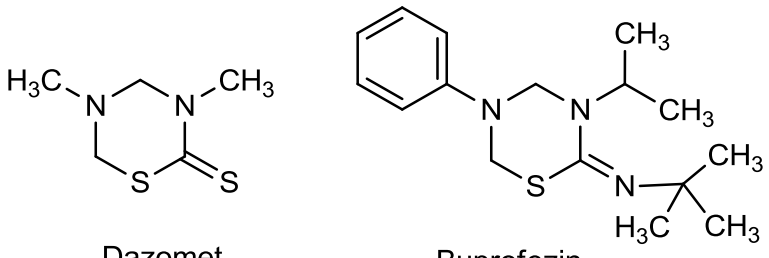
Abstract

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 the 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

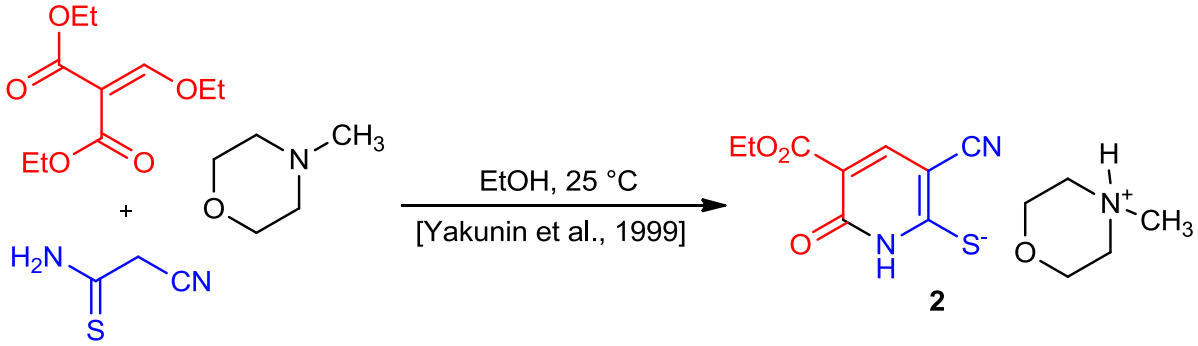
The Mannich reaction is an effective tool to build C – C – N and X – C – N bonds (where X = the N, O, S, Se, P, etc.), and therefore is often used in the synthesis of a wide variety of heterocyclic compounds (for the reviews on the various modifications of the Mannich reaction, see: Akhmetova et al., 2009; Akhmetova and Rakhimova, 2014; Arend et al., 1998; Bur & Martin, 2001; Keglevich & Bálint, 2012; Roselló et al., 2016; Subramaniapillai, 2013; Tramontini, 1973; Tramontini and Angiolini, 1990). 1,3,5-Thiadiazines belong to the important class of heterocyclic compounds. The synthesis of 1,3,5-thiadiazines is successfully realized on the basis of Mannich-type aminomethylation (Akhmetova et al., 2012; Bermello, 2011; Dotsenko et al., 2015; Rodríguez, 2012). 1,3,5-Thiadiazines are also of interest due a wide range of biological activity and practically important properties (Dotsenko et al., 2015; Kanno, 1987; De Cock and Degheele, 1998); among the most important representatives of this class, the fungicide Dazomet and the highly effective insecticide Buprofezin are worth to be mentioned (Fig. 1):



Dazomet Buprofezin

Our interest in the synthesis of condensed 1,3,5-thiadiazines through the aminomethylation of cyclic thioamides (Bibik et al., 2017; Chigorina et al., 2016; Dotsenko et al., 2015; Dotsenko et al., 2016) 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

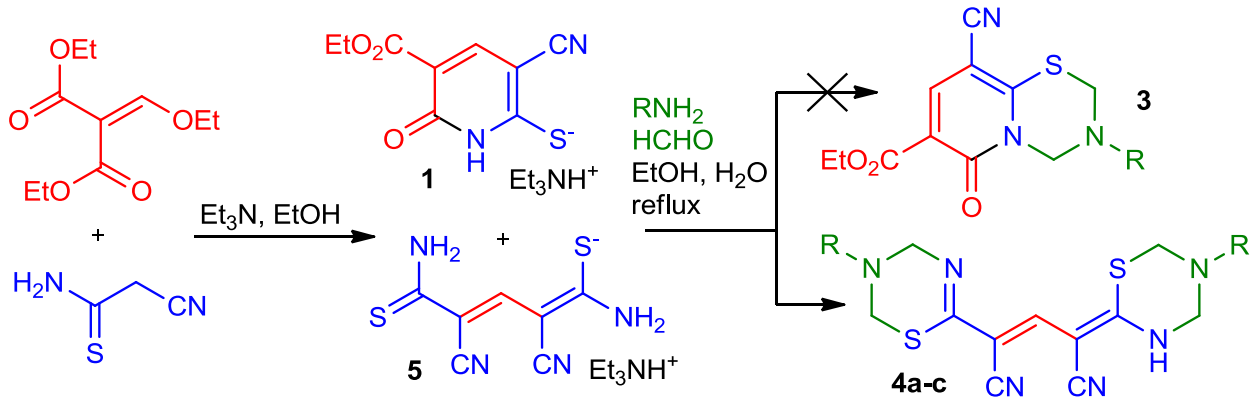
yield (52%) was described in Yakunin, Dyachenko, and Litvinova (Yakunin et al., 1999) (Scheme 1).



Due to the presence of 2 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 (Bibik et al. , 2017; Dotsenko et al., 2015). In the aminomethylation reactions, the nature of 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 (Rayer et al., 2014) 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 and 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 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 (Yakunin et al., 1999), 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.

These results can be explained by the mechanism presented in Scheme 3. First, S_NVin vinyl nucleophilic substitution reaction takes place (Dyachenko and Tkachev, 2003, 757; Dyachenko and Tkachev, 2006; Kudyakova et al., 2014) 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 (Dyachenko and Tkachev, 2003, 1174; Dyachenko et al., 2005; Schmidt and Junek, 1977; Tkachev et al. , 2007; Tkachova et al., 2010). Next, presumably 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 (Tkachova et al., 2010). 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 (Yakunin et al., 1999), pentadiethiolates **5** were not isolated; 2) replacement of N-

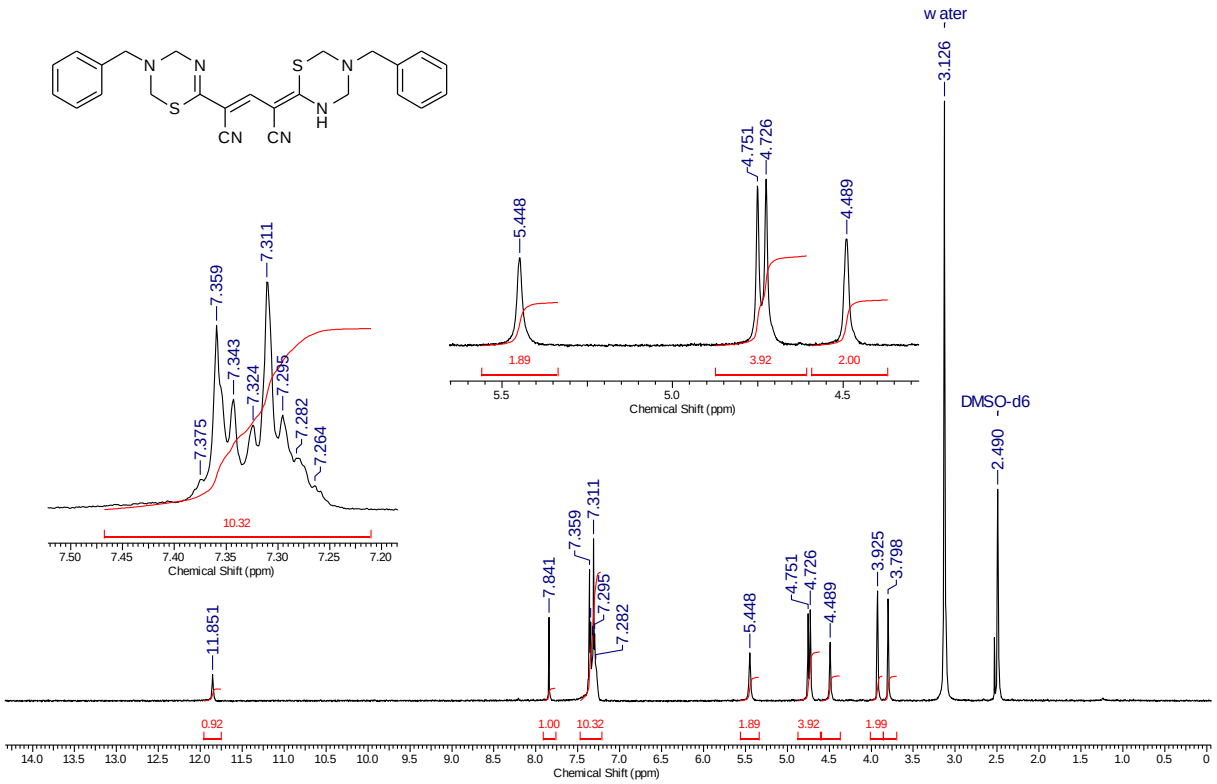
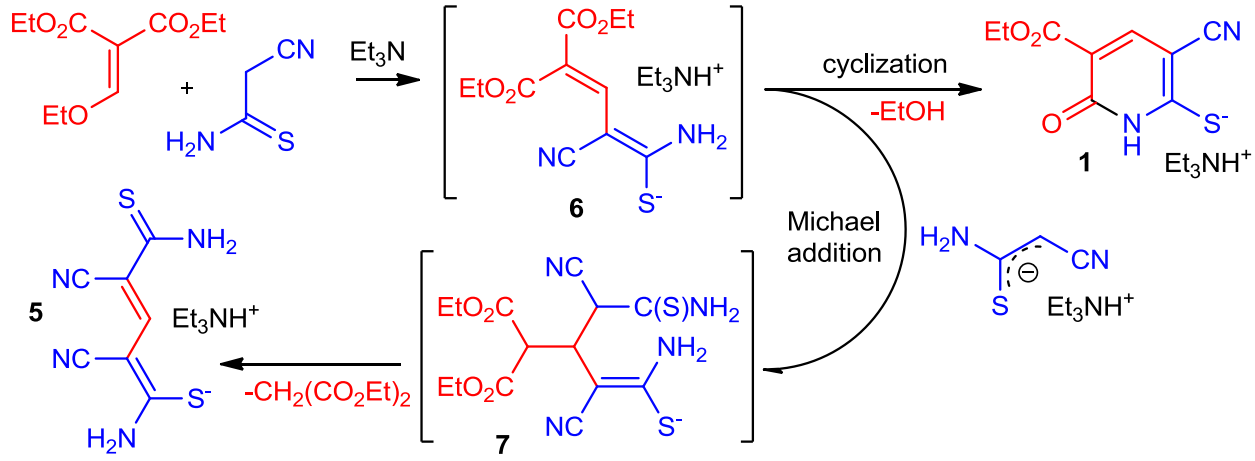


Figure 2. ^{1}H NMR spectrum (400 MHz, DMSO-d_6) of 4-(5-benzyl-1,3,5-thiadiazin-2-ylidene)-2-(3-benzyl-3,4-dihydro-2H-1, 3,5-thiadiazin-6-yl) pent-2-endinitrile **4a**

Scheme 3



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 ^{1}H 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 increase in the yields of thiolates **1** or **2**, but leads to a noticeable resinification

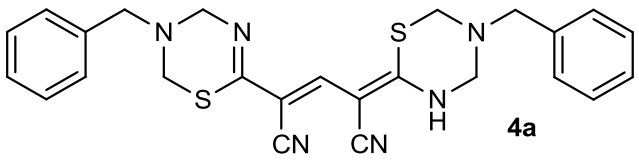
of reaction mixture, possibly due to further intramolecular cyclizations of compounds **5** or **7**, or self-condensation of cyanothioacetamide, which occurs under basic conditions (Fahmy and Mohareb, 1986; Mohareb & Fahmy, 1986). It should also be noted that, contrary to expectations, neither pure thiolate **1** nor thiolate **2** does not 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 pyridine ring.

Experimental

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, atmospheric pressure electrospray ionization. Selected experimental procedures are given. Cyanothioacetamide was synthesized by passing hydrogen sulfide through a solution of malononitrile in EtOH according to a known procedure (Brunskill et al., 1978). 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 resulted solution was filtered through a paper filter, the filtrate was added to a solution of benzylamine (3 mmol), an excess of formalin (5 ml) in 5 ml of EtOH. The mixture was boiled with stirring for 1-2 minutes, during which a crystalline precipitate is formed. The product was filtered off, 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<u>H</u>$_2$Ph); 3.93 (br s, 2 H, NC<u>H</u>$_2$Ph); 4.49 (br s, 2 H, NC<u>H</u>$_2$NH); 4.73 (br s, 2 H, NC<u>H</u>$_2$S); 4.75 (br s, 2 H, NC<u>H</u>$_2$S); 5.45 (br s, 2 H, NC<u>H</u>$_2$N); 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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