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Optimal strategy of new 6*H*-1,3,4-thiadiazines synthesis in search of the promising antidiabetic agents

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Abstract

In this work, we report a convenient method for the preparation of new 2-hydroxyethylamino-substituted 6*H*-1,3,4-thiadiazine hydrobromides for the search of new agents with pleiotropic (antioxidant and antiglycating) activity. The synthesis is based on the cyclocondensation reaction of 4-substituted thiosemicarbazide with various α-haloketones. We compared approaches to the key intermediate for the synthesis of the 6*H*-1,3,4-thiadiazine system – 4-substituted thiosemicarbazide. The approach we proposed was modified to obtain the intermediate and is based on the reaction of a substituted carbamothioylthioacetate with hydrazine. This approach has a number of advantages, like fewer stages, atom economy, elimination of stages with the isolation of undesirable by-products, availability of starting materials and simplicity of the procedure. New 2-hydroxyethylamino-5-substituted 6*H*-1,3,4-thiadiazine hydrobromides were characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis.

Keywords

1,3,4-thiadiazine
antioxidant activity
cyclocondensation reaction
4-substituted thiosemicarbazide
antidiabetic agent

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Key findings

- The approach for obtaining 4-substituted thiosemicarbazide from monoethanolamine was proposed and modified.
- Under the proposed conditions, cyclocondensation of N-(2-hydroxyethyl)hydrazinecarbothioamide with various α-haloketones leads to the formation of 6*H*-1,3,4-thiadiazine hydrobromides without the formation of alternative isomeric heterocycles.
- The obtained new 6*H*-1,3,4-thiadiazine hydrobromides are stable and do not undergo ring transformation during storage and in aqueous solutions, but are capable of forming mercaptopyrazoles *in vivo*.

Supplementary materials

1. Introduction

For decades, the researchers, interest in 1,3,4-thiadiazine derivatives has not waned [1,2]. Many compounds of the 1,3,4-thiadiazine class have proven themselves as substances with antiplatelet [3], cardiovascular [4], cardiotonic [5] and hypotensive [6], enzyme-inhibiting [7–9], radioprotective [10], antioxidant [11, 12] and antiglycating [13] effects. Some of these compounds have combined activity and are promising for studying and searching for means of correcting pathochemical conditions, for example, in diabetes mellitus. To prevent late complications of diabetes mellitus (micro- and macroangiopathy, neuropathy), it is necessary not only to maintain normoglycemia, but also to conduct antioxidant therapy, which reduces lipid peroxidation processes. We showed that the compound 2-morpholino-5-phenyl-6*H*-1,3,4-thiadiazine hydrobromide **L-17** exhibits both antiglycating and antioxidant activity [14]; therefore, investigating its structural analogues looks promising (Figure 1). Introduction of amino alcohol fragment into position 2 of the thiadiazine cycle is aimed at enhancing antioxidant properties and increasing the water solubility and bioavailability of the compounds.

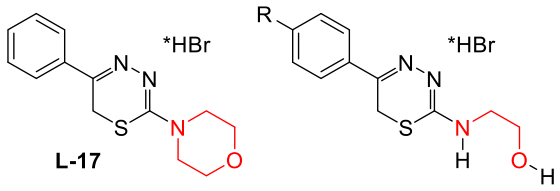


Figure 1 Compound **L-17** c with combined antiglycating and antioxidant activity and its new structural analogues.

The most common and simple method for constructing the thiadiazine system is the cyclocondensation of 4-substituted thiosemicarbazides and α-halocarbonyl compounds such as α-haloketones, α-halaldehydes or alkyl bromoacetates [15, 16]. This interaction is characterized as a reaction of nucleophilic substitution of halogen by sulfur and it is known that the mechanism is bimolecular (Scheme 1) [17, 18].

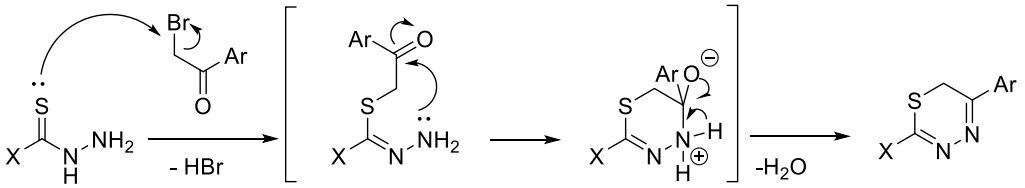
Often, preliminary activation of the nucleophilic center of 4-substituted thiosemicarbazide facilitates the interaction: for example, Et_3N can be added for this purpose. After the elimination of HBr, an intermediate is formed in which a nucleophilic attack on the carbonyl occurs, followed by the cyclization of the 1,3,4-thiadiazine ring with loss of water. In such reactions, thiosemicarbazides are considered to be N,S-dinucleophiles [19].

To create the desired 6*H*-1,3,4-thiadiazine systems, a specific approach to the construction of substituted thiosemicarbazide is required. We already possess well developed methods for the preparation of α-halocarbonyl compounds [11]. First of all, we were interested in the possibility of introducing an amino alcohol fragment into position 2 of the 1,3,4-thiadiazine system, to obtain 1,3,4-thiadiazine with a morpholine fragment analogue in position 2. To achieve this goal, it is necessary to carefully study the methods of obtaining 4-substituted thiosemicarbazides.

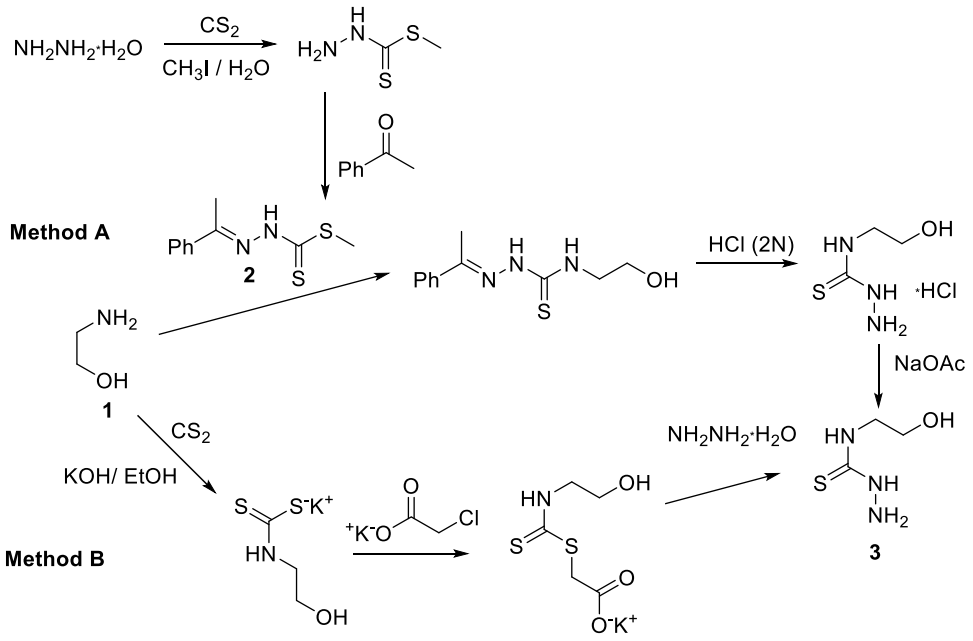
The most suitable existing method for obtaining 4-substituted thiosemicarbazides is the method [20] that allows the use of various amino derivatives, including amino alcohols. To obtain the desired 4-substituted thiosemicarbazide from aminoethanol **1** (Scheme 2, Method A) the condensation product, acetophenone methyldithiocarbazone **2**, is used. We obtained the target product **3** by this method [20], but a number of difficulties arose, requiring us to search for and develop an alternative synthetic approach to 4-substituted thiosemicarbazides. We developed this method for the preparation of cycloalkylamine derivatives and their structural analogues [21, 22] and modified it for the synthesis of N-(2-hydroxyethyl)hydrazinecarbothioamide **3**.

2. Experimental part

All reagents were purchased from commercial sources and used without further purification. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on a Bruker DRX-400 Avance spectrometer with DMSO-d$_6$ as a solvent at ambient temperature. Chemical shifts are reported in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *m*, multiplet; *br s*, broad signal), coupling constant (Hz), integration.



Scheme 1 Proposed 6*H*-1,3,4-thiadiazines formation mechanism.



Scheme 2 Preparation of N-(2-hydroxyethyl)hydrazinecarbothioamide **3**.

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TLC was used to monitor the reaction course and purity of the products on the Silufol UV-254 plates in a butanol — acetic acid — water (4:1:5) system of solvents. Elemental analyses were performed on a PE 2400 II CHN-analyzer (Perkin Elmer). The melting points were measured with a STUART SMP10 instrument. All solvents were dried and distilled before use. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Merck.

2.1. N-(2-hydroxyethyl)hydrazinecarbothioamide 3.

Potassium hydroxide (70 g, 1.25 mol) was dissolved in 150 ml aqueous ethanol. Monoethanolamine **1** (1 mol) was added at room temperature. Carbon disulfide (1 mol) was added dropwise, shaking the reaction mixture and cooling it to 0 °C. Then solution was held for 8 h (Scheme 2, Method B).

Then the solution of 95 g (1 mol) of chloroacetic acid in 150 ml of water and neutralized with potassium carbonate was added and left overnight. After that, we carried out a reaction with hydrazine hydrate (50%) at heating, carefully evaporated the solution to 2/3 of its volume, filtered off the precipitate that formed during cooling, N-(2-hydroxyethyl)hydrazinecarbothioamide **3**, and washed it with ice water. The total product **3** yield reaches 80%. The data on physicochemical properties and spectral characteristics correspond to the literature data [20].

2.2. New 2-hydroxyethylamino-5-substituted 6*H*-1,3,4-thiadiazine hydrobromides 5a-d.

2.2.1. General procedure

To a solution of 2.70 g (20 mmol) of N-(2-hydroxyethyl)hydrazinecarbothioamide **3** in 40 ml of absolute ethanol corresponding 4-substituted α-bromoacetophenone (20 mmol) **4** in absolute ethanol was added, and boiled for 30 min. After hot filtration and cooling, dry ether was added to the reaction solution and kept in ice. The resulting precipitate **5** was filtered off and crystallized from absolute ethanol.

2.2.2. 2-Hydroxyethylamino-5-phenyl-6*H*-1,3,4-thiadiazine, hydrobromide 5a

Pale yellow precipitate. Yield 3.57 g, 56 %. m.p. 175 °C, R_f = 0.56. Found (%):C 41.75; H 4.42; N 13.32 $C_{11}H_{14}N_3OSBr$ Calculated (%):C 41.78; H 4.46; N 13.29; ^{1}H NMR (400 MHz, DMSO-d6), δ 3.53 (*bs*, 1H, OH), 3.66–3.68 (*m*, 4H, $2CH_2$), 4.27 (*s*, 2H, 6-CH_2), 7.50–7.51 (*m*, 3H, Ph), 7.92–7.93 (*m*, 2H, Ph), 10.56 (*br s*, 1H, NH) 12.97 (*br s*, 1H, HBr). ^{13}C NMR (101 MHz, DMSO-d6) δ 161.12(C-5), 152.68(C-2), 133.50 (C, Ar), 131.94 (CH, Ar), 129.53 (2CH, Ar), 127.47 (2CH, Ar), 59.05 (CH_2), 47.45 (CH_2), 22.81 (C-6).

2.2.3. 2-Hydroxyethylamino-5-(4′-fluorophenyl)-6*H*-1,3,4-thiadiazine, hydrobromide 5b

Yellow precipitate Yield: 5.35 g, 80%. m.p. 105 °C, R_f = 0.48. Found (%):C 39.50; H 3.94; N 12.50 $C_{11}H_{13}N_3OSFBr$ Calculated (%):C 39.53; H 3.92; N 12.57; ^{1}H NMR (400 MHz, DMSO-d6), δ 3.53 (*br s*, 1H, OH), 3.65–3.67 (*m*, 4H, $2CH_2$), 4.32 (*s*, 2H, 6-CH_2), 7.37–7.42 (*m*, 2H, Ar), 7.97–8.01 (*m*, 2H, Ar), 10.53 (*br s*, 1H, NH) 13.00 (*br s*, 1H, HBr). ^{13}C NMR (101 MHz, DMSO-d6) δ 165.66(C-F), 162.98(C-5), 161.08(C-2), 151.77 (C, Ar), 130.24 (2CH, Ar), 116.50 (2CH, Ar), 59.39 (CH_2), 47.03 (CH_2), 22.90 (C-6).

2.2.4. 2-Hydroxyethylamino-5-(4′-chlorophenyl)-6*H*-1,3,4-thiadiazine, hydrobromide 5c

Pale orange precipitate Yield: 5.12g, 73%. m.p. 153 °C, R_f = 0.5. Found (%): C 37.60; H 3.70; N 11.89 $C_{11}H_{13}ClN_3OSBr$ Calculated (%): C 37.68; H 3.74; N 11.98; ^{1}H NMR (400 MHz, DMSO-d6), δ 3.52 (*br s*, 1H, OH), 3.55–3.66 (*m*, 4H, $2CH_2$), 4.32 (*s*, 2H, 6-CH_2), 7.51–7.53 (*d*, 2H, *J* = 8), 7.94–7.96 (*d*, 2H, *J*=8), 10.57 (*br s*, 1H, NH), 13.10 (*br s*, 1H, HBr). ^{13}C NMR (101 MHz, DMSO-d6) δ 161.11(C-5), 151.63(C-2), 136.73(C–Cl), 132.27 (C, Ar), 129.93 (2CH, Ar), 128.94 (2CH, Ar), 59.03 (CH_2), 47.36 (CH_2), 22.96 (C-6).

2.2.5. 2-Hydroxyethylamino-5-(4′-hydroxyphenyl)-6*H*-1,3,4-thiadiazine, hydrobromide 5d

Pale yellow precipitate. Yield 1.75 g, 26%. m.p. 191 °C, R_f = 0.49. Found (%):C 39.70; H 4.27; N 12.57; $C_{11}H_{14}N_3O_2SBr$ Calculated (%):C 39.77; H 4.25; N 12.65; ^{1}H NMR (400 MHz, DMSO-d6), δ 3.50 (*br s*, 1H, OH), 3.66–3.68 (*m*, 4H, $2CH_2$), 4.24 (*s*, 2H, 6-CH_2), 6.91–6.94 (*d*, 2H, *J* = 8.5 Hz), 7.77–7.80 (*d*, 2H, *J* = 8.7 Hz), 9.81 (*br s*, 1H, Ar-OH), 10.32 (*br s*, 1H, NH), 13.00 (*br s*, 1H, HBr). ^{13}C NMR (101 MHz, DMSO-d6) δ 161.22(C-5), 160.89(C–OH, Ar), 152.70(C-2), 129.45 (2CH, Ar), 123.82 (C, Ar), 116.35 (2CH, Ar), 59.07 (CH_2), 47.30 (CH_2), 22.59 (C-6).

3. Results and Discussions

Methods for constructing the 1,3,4-thiadiazine ring by different types of cyclization are known and well described. Previously, we successfully used the chosen cyclocondensation of 4-substituted thiosemicarbazides and α-halocarbonyl compounds, not least due to its preparative simplicity. The main advantage of this method is the possibility of obtaining compounds with various substituents needed in positions 2, 5 and 6 of the thiadiazine ring due to the initial compounds' diversity. We started our research with searching for a method for synthesizing 4-substituted thiosemicarbazide **3** from monoethanolamine **1**. Initially, Kazakov's method [20] seemed optimal. This method allows avoiding the decomposition during the exchange of the thioester group for the amino alcohol fragment. But, when obtaining the target product **3**, we encountered a number of significant disadvantages, which the authors did not point out. At the stage of methyldithiocarbazone acetophenonesynthesis, when preparing methyl ester of dithiocarbazic acid, the reactions are accompanied by the appearance of a strong disgusting smell of mercaptans. The overall yield of 4-substituted thiosemicarbazides is low: in particular, for the aminoethanol derivative the yield is 36%, which significantly increases the loss of matter in the multi-stage process. In addition, the risk of decomposition is significant for

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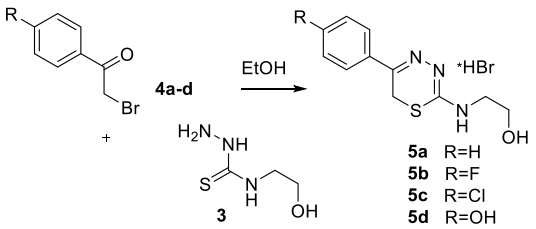
exchange reactions with derivatives of polyhydric alcohols, and for our derivative is more stable. The required 4-substituted thiosemicarbazide **3** can be obtained from aminoethanol more easily.

We decided to use the method we had previously developed, adapting it for amino alcohols (Scheme 2, Method B). This method is easier to carry out and more convenient, although it is necessary to observe safety precautions when working with carbon disulfide, ensuring that the reaction mass is cooled to room temperature. Difficulties arose in isolating the semi-products, since when working with cycloalkylamine derivatives, many semi-products precipitated, while for monoethanolamine derivatives the solubility is much higher, and heating during evaporation is undesirable.

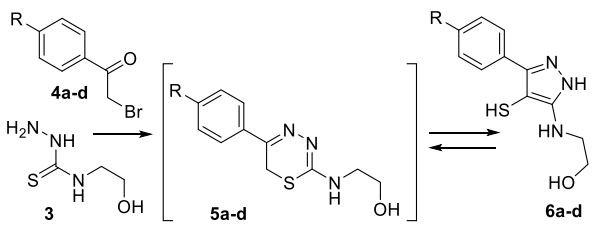
The synthesis of target products was carried out by the reaction of **3** with **4a–d** in high yield (Scheme 3), in accordance with the described procedure.

The cyclocondensation reaction was carried out by boiling in ethanol without adding additional HBr, while monitoring the progress of the reaction by TLC. To facilitate the isolation of highly soluble reaction products and purification from decomposition products, it is possible to add dry diethyl ether and cool the solution.

Depending on conditions, such as the concentration of H^+ ions, solvent polarity, reaction temperature, and the influence of substituents, the cyclocondensation reaction of 4-substituted thiosemicarbazides with α-haloketones leads to the production of thiazolo-2-hydrazones, thiazolone-2-imides or 1,3,4-thiadiazines [2, 23-25]. The reaction conditions determine whether the alternative heterocycle will be a by-product or an isomerization product of 1,3,4-thiadiazine [26]. A reliable way to obtain exclusively 1,3,4-thiadiazine is to carry out the reaction with 4,4-dialkyl-substituted thiosemicarbazides [27]. In addition, the 1,3,4-thiadiazine antiaromatic 8π-system may turn by valence isomerization to mercaptopyrazol **6a–d** (Scheme 4) and further, with extrusion of sulfur, into pyrazole [28, 29].



Scheme 3 Synthesis of 2-aminoethanol-5-substituted 6*H*-1,3,4-thiadiazines **5a–d**.



Scheme 4 Possible transformations of the thiadiazine system into mercaptopyrazol.

A mixture of heterocyclic isomers is often formed [30]. To selectively synthesize 6*H*-1,3,4-thiadiazines, it is necessary that the reaction proceed in a slightly acidic environment when heated. We planned to obtain 6*H*-1,3,4-thiadiazine hydrobromides, which are stable and can be stored for a long time in dry form, being easily water-soluble to facilitate activity testing and subject to transformation into thiols *in vivo*. This is why we performed cyclocondensation reactions with haloketones for our 4-hydroxyethylamino-substituted thiosemicarbazide **3** without additional amounts of HBr (which usually increased the yield of the product when using 4,4-dialkyl-substituted thiosemicarbazides). In addition, the dynamics of the reaction were monitored by TLC, and overheating of the reaction mass was avoided. This also allowed avoiding the appearance of decomposition products. The formation of 6*H*-1,3,4-thiadiazines was confirmed by NMR spectroscopy data. The presence of signals from the 6-CH_2 group protons confirms the formation of products **5a–d** in the form of 6*H*-1,3,4-thiadiazines. Even after long-term storage of compounds **5a–d**, their isomerization or decomposition did not occur.

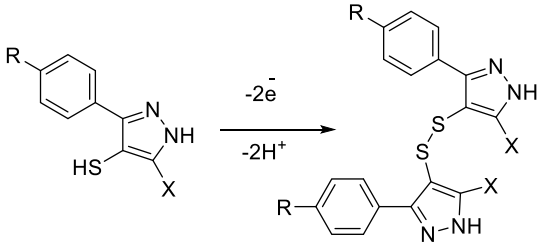
Substituents at positions 2, 5, 6 affect the stability of the system and the rate of desulfurization [31]. For example, presence of an electron-withdrawing group located at position 6 result in a destabilization of the 1,3,4-thiadiazine moiety and desulfurization. The aromatic substituent at position 5 stabilizes the 1,3,4-thiadiazine moiety.

The ability of 6*H*-1,3,4-thiadiazine derivatives to transform *in vivo* into mercaptopyrazoles (thiols) with the possibility of forming disulfides and donating electrons allows these compounds to be used as promising thiol antioxidants, the most important class of endogenous antioxidants in the regulation of cell proliferation and apoptosis, vascular endothelial function, and tissue sensitivity to insulin (Scheme 5).

Therefore, when creating thiadiazine systems, we set the task not only to avoid isomerization *in situ*, but also to preserve the possibility of transformation *in vivo*.

4. Limitations

There are significant limitations for the method we chose for the synthesis of 4-substituted thiosemicarbazides: compounds such as diethanolamine give intermediate products that are prone to destruction; therefore, such thiosemicarbazides cannot be obtained using this method.



Scheme 5 Thiol transformations providing antioxidant activity.

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Kazakov's method [20] is more universal in terms of the choice of starting amines; however, sufficiently basic amines are required (aromatic amines do not react), and this method is not suitable for obtaining significant quantities of compounds. In addition, it should be taken into account that by achieving good aqueous solubility of products, we complicate their isolation and purification, as well as sample storage.

Probably, when synthesizing 6*H*-1,3,4-thiadiazines with fragments of polyhydric alcohols, careful selection of conditions for the cyclocondensation reaction and the choice of methods for isolating and purifying the products will be required due to possible decomposition. It will complicate the preparation for subsequent tests of biological activity.

5. Conclusions

We reviewed existing methods for obtaining important synthons – 4-substituted thiosemicarbazides. The procedure was modified and N-(2-hydroxyethyl)hydrazinecarbothioamide was obtained, which was then included in the cyclocondensation reaction with α-haloketones. By choosing this synthetic strategy, we first obtained new 2-hydroxyethylamino-5-substituted 6*H*-1,3,4-thiadiazine hydrobromides for further testing of antioxidant and antiglycation activity in search of new antidiabetic drugs. The use of this method allowed us to easily introduce the required substituents into positions 2 and 5 of the thiadiazine ring. New 2-hydroxyethylamino-5-substituted 6*H*-1,3,4-thiadiazine hydrobromides were characterized by ^{1}H NMR, ^{13}C NMR and elemental analysis.

• Supplementary materials

This manuscript contains supplementary materials, which are available on the corresponding online page.

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• Conflict of interest

The authors declare no conflict of interest.

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