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SYNTHESIS AND PROPERTIES OF 4,6-DIMETHYLPYRIMIDINE-2-YL ESTERS OF AROMATIC THIOSULFOACIDS

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Methods for the synthesis of thiosulfoesters with a pyrimidine moiety were investigated by the interaction of sulfinic acids with 4,6-dimethylpyrimidine-2-yl sulfenamide. The interaction of 4,6-dimethylpyrimidin-2-yl esters of aromatic thiosulfoacids with amines (benzylamine, morpholine, ammonia) was investigated. It is established that the interaction of synthesized 4,6-dimethylpyrimidin-2-yl thiosulfoacid esters with different amines is interesting not only in terms of studying the properties of thiosulfoesters, but also as an interaction with significant practical value, since it can be proposed for use as a new method of synthesis pyrimidine sulfenamides. The structure and individuality of the synthesized compounds were confirmed by IR, ¹H NMR spectroscopy, elemental analysis and TLC method.

Keywords: aromatic thiosulphoacid salts, thiosulphonates, alkylation, thiosulphoesters with pyrimidine moiety.

Introduction

Increased attention of researchers working in the field of medical chemistry attracts pyrimidine derivatives. However, despite the rich history of searching for potential biologically active agents among the substances containing the heterocyclic moiety, their potential is still not exhausted. It was confirmed by the large number of pyrimidine-containing medicines with diversified activity, in particular, antiviral (idoxuridine, tenofovir, peciclovir), antimetabolite (ralitrexel), diuretic (triamterene), etc. [1]. Among pyrimidine derivatives it was found vasodilators, antidiabetic, antibacterial, antimalarial substances [2]. Also, barbituric acid derivatives are widely used as hypnotics and anticonvulsants [3]. Substances containing the pyrimidine cycle are widespread in nature, since they are involved in plenty important biological processes, in particular, are included in nucleotides. In addition, pyrimidine cycle is a fragment of some B vitamins, namely B₁, coenzymes and antibiotics. The study of the properties of new derivatives of condensed nitrogen-containing compounds with a pyrimidine moiety is important in order to create effective antimicrobial

agents for prevention and treatment of infectious complications [4, 5].

Pyrimidine derivatives have been introduced into medical practice for the treatment of cancer, as the active substances of the drugs dopanum, nimustine, fluorouracil, cytarabine, ftorafur [2].

The heterocyclic pyrimidine system is the structural basis of many naturally occurring physiologically active substances that are fundamental for cell life (purine alkaloids, nucleic acids, DNA, RNA, etc.).

Particularly important as biologically active substances are sulfur-containing pyrimidine derivatives (sulfides, sulfoacid salts, sulfonamides, sulfenamides, disulfides). Among them it was found plant growth regulators [6, 7], herbicides, insecticides and acaricides, fungicides and bactericides [8, 9], herbicide antidotes and others. Also, pyrimidine derivatives serve as intermediates for the synthesis of a number of active organophosphorus insecticides and derivatives of carbamic acid and urea derivatives. Pyrimidine derivatives have been used as hardness stabilizers of vulcanized rubber compositions [10], as building blocks in polymer

chemistry for the introduction of functional end groups into polymers [11], in color photography as a new type of against foggy compounds [12], and also as nitrogen-containing chemical reagents.

Sulfur-containing compounds – thiosulfonates, are important as effective sulfenilation and sulfonilation chemical reagents that can react with a nucleophile, electrophile and radicals [11,13,14], as well as practically valuable compounds, that exhibit a wide range of biological effects [15,16,17,18,19]. Nevertheless in literature, there is limited data on the synthesis of pyrimidine sulfur-containing derivatives, particular thiosulfoacid esters with pyrimidine moiety.

Therefore, the aim of this work is the development of method for synthesis and research of chemical properties of pyrimidine esters of thio-sulfoacids.

Materials and methods of study

IR spectra were taken on a spectrophotometer SPECORD M 80 (KBr pellets); ¹H NMR spectra were recorded on a spectrometer Varian VXR-300, (¹H chemical shifts are expressed in δ – a scale relative to tetramethylsilane, solvent – DMSO-D₆, and the integral intensities correspond to the attributions that were made); purity of the synthesized compounds were monitored by TLC and elemental analysis performed on standard microanalysis equipment.

Methodology 1. S-(4,6-dimethylpyrimidin-2-yl)thiohydroxylamine 2

At a temperature of -3÷-4 °C to 240 ml of cooled 5 % ammonia solution in small quantities with constant stirring was added 80 ml sodium hypochlorite solution. The resulting solution of chloramine was quickly poured into a solution of 8.4 g (0.06 mol) chlorohydrate of 4,6-dimethyl-2-mercaptopyrimidine in 60 ml of 2 N potassium hydroxide solution. After an hour at room temperature, the precipitate was filtered off and washed with ice water on the filter and was dried.

The yield of S-(4,6-dimethylpyrimidin-2-yl)thiohydroxylamine with T_{mp} = 100 °C was 6.2 g (84 %).

Methodology 2. S-(4,6-dimethylpyrimidin-2-yl)benzenesulfonylthioate 4a

To a solution of 23.8 g (0.16 mol) of benzenesulfinic acid **3a** in 51 ml of ethanol and 19.5 ml of water was added a solution of 12.9 g (0.08 mol) of S-(4,6-dimethylpyrimidin-2-yl)thiohydroxylamine in 140 ml of ethanol and 86 ml of water. After one hour at 20 °C, the precipitate was filtered off, washed several times with water and 30 % ethanol, recrystallized from ethanol. The yield of thiosulfoester **4a** with T_{mp} = 114–115 °C was 17.8 g (76,39 %).

Methodology 3. S-(4,6-dimethylpyrimidin-2-yl)4-((methoxycarbonyl)amino)benzenesulfonylthioate 4b.

To a solution of 17.5 g (0.08 mol) of 4-[(methoxycarbonyl)amino]benzenesulfoacid **3b** in 110 ml of ethanol and 67 ml of water was added a solution of 6.2 g (0.04 mol) of S-(4,6-dimethylpyrimidin-2-yl)thiohydroxylamine **2** in 55 ml of ethanol and 16 ml of water.

After one hour at 20 °C, the precipitate was filtered off, washed several times with water, recrystallized from ethanol. The yield of thiosulfoester **4b** with T_{mp} = 182 °C was 5.8 g (41.08 %).

Methodology 4. S-(4,6-dimethylpyrimidin-2-yl)ethanesulfonylthioate 4c.

Solution of 4.6 g (0.048 mol) of the sodium ethanesulfinate in mixture of 20 ml of ethanol and 10 ml of water was acidified with concentrated hydrochloric acid to pH = 2. To the resulting solution was added a solution of 3.08 g (0,022 mol) 4,6-dimethylpyrimidin-2-yl sulfenamide of **3c**. After hour at 20 °C, the solution was cooled, by water ester **4c** was sedimented, then filtered. The purification was carried out by recrystallization from aqueous ethanol (1:1). The yield of product **4c** T_{mp} = 63–65 °C was 1 g (21.5 %).

Methodology 5. S-(4,6-dimethylpyrimidin-2-yl)benzenesulfonylthioate 4a with benzylamine.

To a suspension of 5 g (0.018 mol) of pyrimidine ester **4a** in 70 ml of absolute ether, 4.18 g (0.039 mol) of benzylamine was added. After 7-hour exposure at 20 °C the precipitate of benzylamino salt of benzenesulfinic acid **6a** was filtered. From the

filtrate, ether was removed by a stream of dry air, and N-benzyl-1-(4,6-dimethylpyrimidin-2-yl)4-sulfanimine **5a** was purified by recrystallization from ethanol. The yield of sulfenamide **5a** with $T_{mp} = 51-52$ °C was 1.9 g (42.60 %).

Purification of salt **6a** was performed by recrystallization from ethanol. The yield of salt **6a** with $T_{mp} = 160-162$ °C was 1.8 g (41,14 %).

Methodology 6. S-(4,6-dimethylpyrimidin-2-yl)benzenesulfothioate 4a with morpholine.

2.5 g (0.028 mol) of freshly distilled morpholine was added to a solution of 3.9 g (0.014 mol) of pyrimidine ester **4a** in 30 ml of anhydrous chloroform. After 48 hours exposure of reaction mass, chloroform was distilled off in vacuo. The insoluble morpholinamide of 4,6-dimethylpyrimidin-2-ylsulfenic acid **5b** was filtered off, purified by recrystallization from ethanol. The yield of sulfenamide **5b** with $T_{mp} = 96-97$ °C was 0.9 g (28.2 %).

In vacuum from the aqueous solution water was evacuated. The yield of the benzenesulfenic salt of morpholine **6b** was 1,04g (68.4 %). The obtained salt of morpholine **6b** was a viscous syrupy liquid that does not crystallize at -5 °C. Purification was carried out by re-precipitation from the alcohol-ether mixture.

Methodology 7. S-(4,6-dimethylpyrimidin-2-yl)4-((methoxycarbonyl)amino)benzenesulfothioate 4b with gaseous ammonia.

Through a suspension of 4 g (0.012 mol) of ester **4b** in 80 ml of anhydrous chloroform at a temperature of 0÷4 °C was passed gaseous ammonia for 1 hour. The completion of the reaction was determined by the complete solubility in water of the sediment sample from the reaction mass. After 1 hour exposure, the ammonium salt of 4-[(methoxy-carbonyl)amino]benzenesulfenic acid **3c** was filtered off, washed with chloroform, recrystallized from ethanol.

The yield of thiosulfoester **6** is 1.7 g (64.4 %), $T_{mp} = 150$ °C.

The chloroform filtrate was distilled off in vacuo, the residue was washed with water and cold ethanol. The yield of 4,6-dimethyl-2-sulfenamide of pyrimidine **2** 1.7 g (96.52 %), $T_{mp} = 99-100$ °C . A

sample of mixing the obtained sulfenamide with the product obtained by counter-synthesis by a known method, the depression of the melting point was not given.

Methodology 8. S-(4,6-dimethylpyrimidin-2-yl)benzenesulfothioate 4a with KOH solution in ethyl alcohol

To a suspension of 5 g (0.018 mol) of ester **4a** solution of potassium hydroxide (1 g KOH in 20 ml of ethanol) was added in 100 ml of ethanol . After exposure for 20 hours at 20 °C, from the reaction mass the solvent was removed in vacuo, the residue was treated with water, the insoluble precipitate was recrystallized twice from ethanol.

Yield of disulfide **7** was 1.3 g (26.2 %), $T_{mp} = 157-160$ °C.

The aqueous solution was evaporated to dryness to obtain potassium benzene-sulfinate **8a** after purification by recrystallization from ethanol in 1 g (33.3 %). Potassium benzenesulfinate **8a** was identified by conversion to benzenesulfenic acid, the temperature of melting point of which corresponds to the literature ($T_{mp} = 84-85$ °C).

Methodology 9. S-(4,6-dimethylpyrimidin-2-yl)4-((methoxycarbonyl)amino)benzenesulfothioate 4b with KOH solution in ethyl alcohol

To a suspension of 5 g (0.015 mol) of S- ester **4b** in 90 ml of ethanol, solution of potassium hydroxide (0.83 g of KOH in 20 ml of the same alcohol) was added. After exposure for 20 h at 20 °C from the reaction mass, the solvent was removed in vacuo, and the residue was treated twice with a small amount of water, the insoluble precipitate was recrystallized from ethanol.

Yield of disulfide **7** was 2.9 g (73.6 %), $T_{mp} = 160$ °C . lit. $T_{mp} = 155$ °C sample mixing with known disulfide $T_{mp} = 157-160$ °C .

The aqueous solution was evaporated to dryness to obtain the potassium salt of 4-methoxycarbonylaminobenzenesulfenic acid **8b** to yield 0.9 g (25.14 %). Salt was identified by its conversion to 4-[(methoxycarbonyl)amino]benzenesulfenic acid, which was isolated by treatment with hydrochloric acid. $T_{mp} = 150-155$ °C. lit. $T_{mp} = 145-150$ °C. Sample mixing of the obtained 4-[(methoxy-carbonyl)amino]benzenesulfenic acid with product

that was obtained by known methods, the depression of the melting point did not give.

Results of the studies and discussion

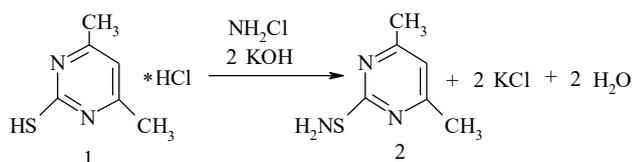
In continuation of our research on the synthesis of thiosulfoesters with the pyrimidine moiety from thiol sulfur side [20] it was carried out the reaction of sulfinic acids with 4,6-dimethylpyrimidin-2-yl sulphenamide.

With this aim, two ways to obtain 4,6-dimethylpyrimidin-2-yl sulphenamide were investigated, directly from free base of 4,6-dimethylpyrimidine-2-thiol and from its chlorohydrate.

While obtaining of 4,6-dimethylpyrimidin-2-yl sulphenamide directly from the free base of 4,6-dimethyl-2-mercaptopyrimidine, the chlorohydrate of the latter was pre-treated with a dilute (13 %) solution of ammonia. The desired sulfanilamide **2** was obtained with the yield of 46.1 %, based on the starting chlorohydrate of 4,6-dimethyl-2-mercaptopyrimidine. The low yield of 4,6-dimethylpyrimidin-2-yl sulphenamide can obviously be explained by the significant losses in the free base step of 4,6-dimethyl-2-mercaptopyrimidine, since the latter is partially soluble in water.

In view of this, sulfanilamide **2** is more appropriate to be obtained directly from mercaptopyrimidine chlorohydrate **1** by the action of chloramine in an aqueous alkaline medium.

Scheme 1



Using such method of synthesis, the yield of the target product **3** is higher (84.93 %) and the process time is significantly reduced.

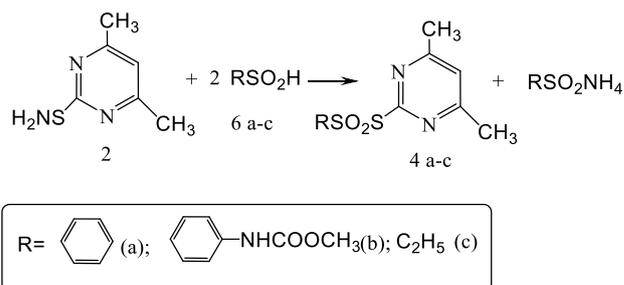
Sulfinic acids **3 a-c** were pre-synthesized by reduction of the corresponding sulfochlorides with sodium sulfite in an alkaline medium or by zinc in an alcoholic medium, depending on the structure of the sulfinic acid.

The interaction of 4,6-dimethylpyrimidin-2-yl sulfenamide **2** with aromatic and aliphatic sulfinic

acids **3 a-c** has been investigated in different solvents under different temperature conditions.

It was found that it is reasonable to carry out the reaction in an alcohol-aqueous medium at room temperature. The target 4,6-dimethylpyrimidin-2-yl S-esters of the corresponding thiosulfonic acids **4 a-c** were obtained in yields of 22-76 %.

Scheme 2



The physicochemical characteristics of compounds **7 a-c** are shown in Table 1.

Table 1

Characteristics of the synthesized compounds 4a-c

№	Yield, %	T _{mp} , °C	Found, %			
			Calculated, %			
			C	H	N	S
4a	76	114–115	<u>51,03</u>	<u>4,25</u>	<u>9,88</u>	<u>22,69</u>
			51,43	4,29	10,00	22,86
4b	41	182–183	<u>47,13</u>	<u>4,21</u>	<u>11,78</u>	<u>18,01</u>
			47,59	4,25	11,90	18,13
4c	21	63–64	<u>41,02</u>	<u>5,12</u>	<u>12,48</u>	<u>27,42</u>
			41,38	5,17	12,07	27,59

The structure and individuality of the first synthesized thiosulfoesters **4 a-c** were confirmed by IR data, ¹H NMR spectroscopy (Table 2), elemental analysis (Table 1) and TLC method.

In the IR spectrum of 4,6-dimethylpyrimidin-2-S-ester of ethanethiosulfoacid **4 c** it is observed intense absorption band at 1145_{γs} and 1312_{γas} cm⁻¹ characteristic of symmetric and asymmetric stretching vibration of SO₂ group. In addition, the IR spectra exhibit less intense absorption bands at 1452, 1518, 1512, and 1582, 1590 cm⁻¹, which are characteristic of the valence vibrations of the pyrimidine cycle [11].

Table 2

IR data and ¹H NMR spectroscopy of compounds 4 a-c

№ сп	IR spectrum, absorption frequency ν, cm ⁻¹	¹ H NMR spectrum, chemical shift δ, ppm
4a	1588, 1522-1482 1460, (pyrimidine cycle); 1580 (Ar); 1320 _{γas} , 1135 _{γs} , (SO ₂);	2.54 (6H, s, CH ₃), 7.13 (1 H, s, CH-Het) 7.70 – 7.84 (3 H, m, CH-Ar) 8.04 (2 H, d, J = 6.60 Hz, CH-Ar)
4b	3338 (NH); 1670, 1626, (C = O); 1588 (Ar); 1586, 1544, 1458, (pyrimidine cycle); 1315 _{γas} , 1132 _{γs} (SO ₂);	2.52 (6 H, s, CH ₃), 3.28 (3 H, s, CH ₃), 7.08 (1 H, s, CH-Het) 7.36 (2 H, d, J = 9.60 Hz, CH-Ar) 8.19 (2 H, d, J = 9.60 Hz, CH-Ar), 9.98 (1H, c, NH)
4c	1590, 1582, 1518, 1512, 1452 (pyrimidine cycle); 1312 _{γas} 1145 _{γs} , (SO ₂);	1.34 (3 H, t, J = 7.53 Hz, CH ₃) 2.36 (6H, s, CH ₃), 3.86 (2 H, q, J = 7.70 Hz, CH ₂), 7.17 (1 H, s, CH-Het)

In the IR spectra of such pyrimidine esters benzene- and carbmethoxyaminobenzenethiosulfoacid **4 a,b** represent absorption bands due to stretching vibrations of pyrimidine core at 1460, 1482–1522, 1588 cm⁻¹ for compound **4 a** and according to compound **4 b** strip – 1458, 1544, 1586 cm⁻¹. Absorption of the SO₂ group in these compounds is shown by sufficiently intense bands of symmetric valence vibrations of 1135 cm⁻¹ for **4a** and 1132 cm⁻¹ for **4b**, asymmetric valence oscillations are expressed less clearly at 1320 cm⁻¹ in the benzenethiosulfonic acid ester and 1315 cm⁻¹ for **4b**, 4-carb-methoxyaminobenzene-thiosulfoacid. In addition, in compounds **4 a,b** there are bands, respectively, at 1580 and 1588 cm⁻¹ characteristic of aromatics. In the IR spectrum of the thioester **4b** there are absorption bands 1670 cm⁻¹ characteristic of C = O and 1626, 3338 cm⁻¹ characteristic of the NH group.

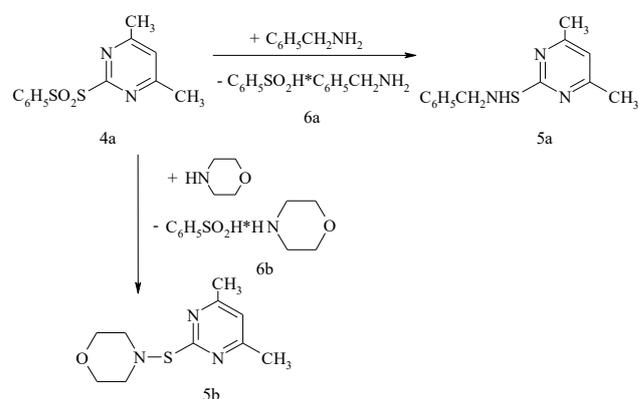
Taking into account the considerable chemical potential of esters of thiosulfoacid, it was investigated some chemical properties of thiosulfoesters with a pyrimidine moiety. Particularly important among the reactions characteristic of the above-mentioned

compounds are nucleophilic substitution reactions. Esters of thiosulfoacids easily interact with nucleophilic agents like thiols, organometallic compounds, amines, alkalis. This ability of thiosulfoacid esters is due to the presence of a partial positive charge on the divalent sulfur atom.

The interaction of 4,6-dimethylpyrimidine-2-yl esters of aromatic thiosulfoacids with amines (benzylamine, morpholine, ammonia) was investigated in anhydrous solvents (diethyl ether, chloroform) at room temperature and at a molar ratio of reagents 1:2.

Under these conditions, the 4,6-dimethylpyrimidin-2-yl ester of benzenethiosulfo acid **4 a** with benzylamine and morpholine formed respectively benzylamine **6 a** and morpholine **6 b** salt of benzenesulfonic acid and benzylamide **5 a** and morpholinamide **5 b** 4,6-dimethylpyrimidine-2-ylsulfenic acid.

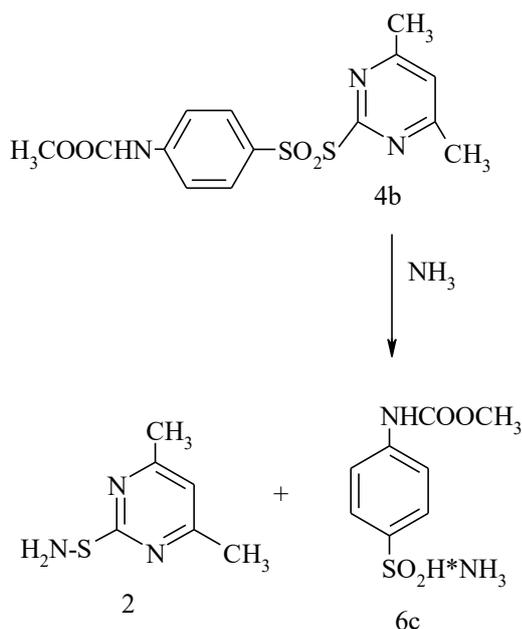
Scheme 3



In the study of the interaction of S-(4,6-dimethylpyrimidin-2-yl) ester of 4-carb-methoxyaminobenzene-thiosulfoacid **4 b** with benzylamine it was found that under similar conditions and also while heating, the specified thiosulfoester does not react with benzylamine.

By action of gaseous ammonia on suspension of S-(4,6-dimethylpyrimidin-2-yl) ester of 4-carb-methoxyaminobenzene-thiosulfoacid **4 b** in chloroform at 0–4 °C was obtained ammonium salt of 4-carb-methoxyaminobenzenesulfenic acid **6 c** and 4,6-methylpyrimidin-2-ylsulfenamide **2**.

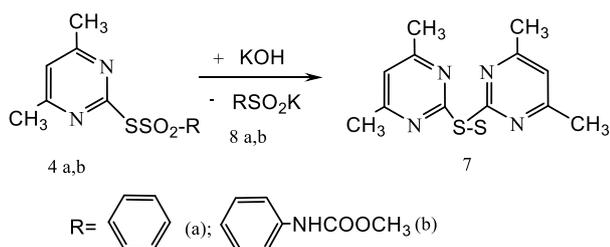
Scheme 4



The ammonium salt **6c** was identified by converting it into 4-carbomethoxyaminobenzene-sulfonic acid with a melting point of 150–151 °C (in literature – 145–150 °C), and sulfenamide **2** by the melting point and mixing test with known sulfenamide obtained by counter-synthesis (their mixing dispersion of the melting point did not give).

Analyzing the results we can conclude that the interaction of synthesized 4,6-dimethyl-pyrimidin-2-yl thiosulfonic acid esters with different amines is interesting not only in terms of studying the properties of thiosulfoesters, but also as an interaction with significant practical value, since it can be used as a practical new method for the synthesis of pyrimidine sulfenamides. The usual route of synthesis of such compounds – the interaction of sulfonyl chlorides with amines – in this case is not suitable because of the instability and inability to obtain the majority of sulfonyl chlorides of pyrimidine.

Scheme 5



Also there were investigated the interaction of 4,6-dimethylpyrimidin-2-yl thiosulfoesters **4 a,b** with potassium hydroxide.

While carrying out interaction in ethanol at room temperature and 20 h exposure as reaction products were isolated potassium salts of corresponding sulfenic acids **8 a,b** and pyrimidine disulfide **7**.

Conclusions

A new method for the synthesis of nitrogen-containing heterocyclic thiosulfoesters was proposed.

For the first time, thiosulfoesters with a pyrimidine core from the thiol sulfur moiety were obtained by reacting 4,6-dimethyl-2-sulfenamide pyrimidine with aromatic and aliphatic sulfenic acids in an alcohol-aqueous medium.

The interaction of 4,6-dimethyl-2-pyrimidine esters of thiosulfoacids with nucleophilic reagents (amines, potassium hydroxide) was investigated. It is shown that in an anhydrous solvent medium (diethyl ether, chloroform) at room temperature, thiosulfoesters form sulfenic acid salts and corresponding sulfenic acid derivatives, and in case of instability of the latter, sulfenic acid salts and disulfides were isolated as reaction products. Reactions of pyrimidine thiosulfoesters with amines can be proposed as a new method of synthesis of pyrimidine sulfenamides.

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СИНТЕЗ ТА ВЛАСТИВОСТІ 4,6-ДИМЕТИЛПІРИМІДИН-2-ІЛОВИХ ЕСТЕРІВ АРОМАТИЧНИХ ТІОСУЛЬФОКИСЛОТ

Досліджено методи синтезу тіосульфоестерів із піримідиновим фрагментом взаємодією сульфінкових кислот з 4,6-диметилпіримідин-2-іл сульфенамідом. Досліджено взаємодію 4,6-диметилпіримідин-2-ілових естерів ароматичних тіосульфокислот з амінами (бензиламін, морфолін, амоніак). Встановлено, що взаємодія синтезованих 4,6-диметилпіримідин-2-ілових естерів тіосульфокислот із різними амінами є цікавою не лише в плані вивчення властивостей тіосульфоестерів, а також як взаємодія з вагомим практичним значенням, оскільки може бути запропонована до використання як новий метод синтезу сульфенамідів піримідину. Будову та індивідуальність синтезованих сполук підтверджено даними ІЧ, ¹Н ЯМР спектроскопії, елементним аналізом та методом ТШХ.

Ключові слова: солі ароматичних тіосульфокислот, тіосульфонати, алкілування, тіосульфоестери з піримідиновим фрагментом.