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SYNTHESIS OF NOVEL FIVE-MEMBERED NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS FROM DERIVATIVES OF ARYLSULFONYL- AND ARYLTHIOACETIC AND -PROPIONIC ACIDS

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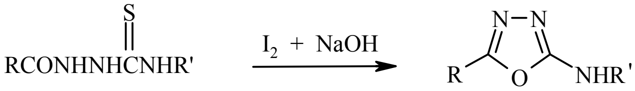
A series of novel substituted 1,3,4-oxa(thia)diazoles and triazoline-3-thiones has been synthesized from thiosemicarbazides and nitriles of arylthio-, arylsulfonylacetic and -propionic acids. A mechanism is proposed for the preparation of 2-amino-5-substituted 1,3,4-thiadiazoles from carboxylic acids in polyphosphoric acid medium.

Keywords: oxadiazole, thiadiazole, thiosemicarbazide, triazoline-3-thione, PPA, cyclization

Amongst derivatives of 1,3,4-oxa(thia)diazoles and 1,2,4-triazoles there are substances which possess anti-inflammatory, analgesic, antiviral, antibacterial, and other biological activity [1-5]. Based on these, a large number of medicinal preparations, polymers, dyes, etc. have been obtained. Since there is limited information in the literature regarding the methods of synthesis and the starting materials for compounds of this type [6] it was of interest to develop novel, efficient routes for their preparation thus increasing the range and establishing methods for their practical usage.

In this work we report the preparation of several novel substituted 1,3,4-oxa(thia)diazoles and triazoline-3-thiones, starting from the previously synthesized arylsulfonyl-, arylthioacetic and -propionic acids and also their derivatives which show clearly expressed biological activity [7, 8]. 1-Substituted and 1,4-disubstituted thiosemicarbazides **1**, **2** were prepared on this basis by two routes: the reaction of arylsulfonyl-, arylthioacetic and -propionic acid hydrazides with potassium thiocyanate or with phenyl isothiocyanate [9] and the acylation of thiosemicarbazide with arylthio-, arylsulfonylacetic and -propionic acid chlorides [10].

1,3,4-Oxadiazole derivatives **3** were prepared by the oxidative cyclization of 1-substituted and 1,4-disubstituted thiosemicarbazides **1** and **2** in the presence of sodium hydroxide and iodine in ethanol medium at 90°C. The yields of the target compounds achieved were 60-70%. Some parameters for the products obtained are given in Table 1.



1a–d, **2a–d** → **3a–h**

1a-d, **3a-d** R' = H; **2a-d**, **3e-h** R' = C_6H_5; **3a,e** R = 4-$ClC_6H_4SO_2CH_2CH_2$; **3b,f** R = $BrC_6H_4SO_2CH_2$; **3c,g** R = 4-$CH_3C_6H_4SCH_2CH_2$; **3d,h** R = 4-$BrC_6H_4SCH_2$

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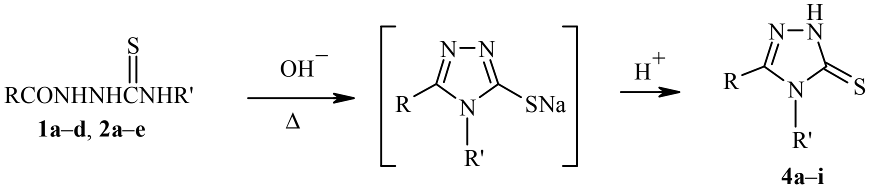
The IR spectra of oxadiazoles **3a-h** show bands corresponding to the deformation (970 cm^{-1}) and stretching (1000 cm^{-1}) vibrations of the C–O–C group. The intense doublet band in the region of 3450 cm^{-1} is assigned to the stretching vibrations of the C=N group at 1650 cm^{-1}.

Cyclodehydration of thiosemicarbazides **1** and **2** in alkaline medium brought about the synthesis of 5-substituted 1,2,4-triazoline-3-thiones **4**.



4a–d R' = H; **4e–i** R' = C_6H_5; **4a,e** R = 4-$ClC_6H_4SO_2CH_2CH_2$; **4b,f** R = $BrC_6H_4SO_2CH_2$; **4c,g** R = 4-$CH_3C_6H_4SCH_2CH_2$; **4d,h** R = 4-$BrC_6H_4SCH_2$; **2e**, **4i** R = C_6H_5

The basic cyclization agent used was sodium ethylate in ethanol or an aqueous solution of sodium hydroxide. It should also be mentioned that sodium hydroxide is more active cyclization agent for thiosemicarbazides (the reaction time is shortened from 12 to 2 h) and this allows one to suggest an ionic mechanism for the reaction.

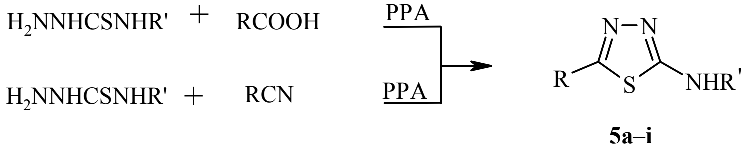
With the aim of exploring the optimum conditions for the synthesis we have examined the effect of the concentration of sodium hydroxide and of temperature on the yield of 1,2,4-triazoline-3-thione **4i**. It was found that the maximum yield (85-90%) was achieved at reaction temperature of 60°C and sodium hydroxide concentration of 10%.

The characteristics of the synthesized compounds **3** and **4** are given in Table 1.

In the IR spectra of compounds **4a-i** there are two absorption maxima at 1350-1340 and 1325-1320 cm^{-1}, typical of the vibrations of C=S group in 1,2,4-triazoline-3-thiones, an intense absorption band at 1525-1520 cm^{-1} for NH(C=S)NR group vibrations, and the absence of absorption bands for SH or CSH groups, all of which indicate that the given compound has 1,2,4-triazoline-3-thione structure rather than the tautomeric 3-mercapto-1,2,4-triazole structure.

There are a large number of methods for the synthesis of 2-amino-5-substituted 1,3,4-thiadiazoles [6] with different variations amongst them. The most usual is a two stage method consisting of acylation of thiosemicarbazide using carboxylic acid chlorides and subsequent cyclization of the intermediate acylthiosemicarbazides [9]. In the known methods various dehydrating agents are used to achieve this. The most widely applicable of these reagents are sulfuric acid, phosphorus oxychloride, benzoyl chloride, and acetyl chloride. Not all of these substances are readily available and convenient to use, moreover they often take part in side reactions which significantly lower the yield of the products and complicate their separation.

We have for the first time attempted to prepare 2-amino-5-substituted 1,3,4-thiadiazoles **5** in a single stage by the reaction of arylthio-, arylsulfonylacetic and -propionic acids or their nitriles with thiosemicarbazide in polyphosphoric acid (PPA) medium.



5a–d, **i** R' = H; **5e–h** R' = C_6H_5; **5a,e** R = 4-$ClC_6H_4SO_2CH_2CH_2$; **5b,f** R = $BrC_6H_4SO_2CH_2$; **5c,g** R = 4-$CH_3C_6H_4SCH_2CH_2$; **5d,h** R = 4-$BrC_6H_4SCH_2$; **5i** R = $C_6H_5CH_2$

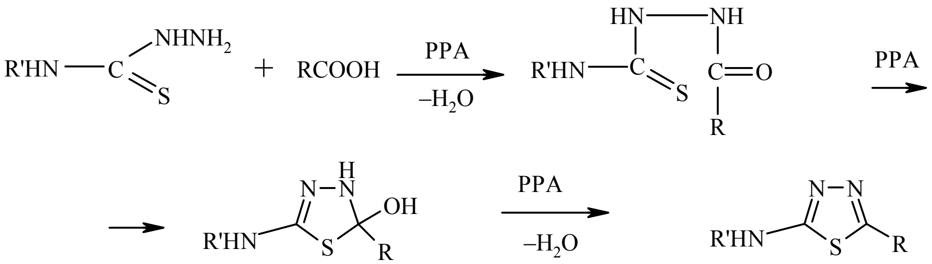
TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % Calculated, %			mp, °C	Yield, %
		C	H	S		
3a	$C_{10}H_{10}ClN_3O_3S$	42.27 41.74	3.5 3.5	10.82 11.14	176-180	40
3b	$C_9H_8BrN_3O_3S$	32.76 33.96	2.2 2.52	9.86 10.06	194-197	48
3c	$C_{11}H_{13}N_3OS$	53.57 56.15	5.67 5.57	14.15 13.65	156-159	40
3d	$C_9H_8BrN_3OS$	39.11 37.76	2.44 2.8	11.31 11.19	158-161	45
3e	$C_{16}H_{14}ClN_3O_3S$	54.11 52.82	4.04 3.88	8.84 8.81	230-233	42
3f	$C_{15}H_{12}BrN_3O_3S$	44.07 45.69	2.8 3.05	8.47 8.12	254-256	45
3g	$C_{17}H_{17}N_3OS$	67.78 65.57	5.28 5.5	9.87 10.3	200-202	43
3h	$C_{15}H_{12}BrN_3OS$	51.52 49.72	3.17 3.31	8.79 8.84	220-225	42
4a	$C_{10}H_{10}ClN_3O_2S_2$	37.58 39.54	3.46 3.32	20.64 21.11	234-235	86
4b	$C_9H_8BrN_3O_2S_2$	32.9 32.34	2.1 2.4	18.71 19.16	210-212	87
4c	$C_{11}H_{13}N_3S_2$	54.00 52.56	5.44 5.21	26.01 25.51	208-210	84
4d	$C_9H_8BrN_3S_2$	35.02 35.76	2.24 2.65	20.82 21.19	224-225	82
4e	$C_{16}H_{14}ClN_3O_2S_2$	49.03 50.59	3.56 3.71	16.94 16.88	267-268	89
4f	$C_{15}H_{12}BrN_3O_2S_2$	44.44 43.9	2.69 2.93	15.57 15.61	242-243	90
4g	$C_{17}H_{17}N_3S_2$	65.3 62.35	5.41 5.23	19.31 19.58	236-237	88
4h	$C_{15}H_{12}BrN_3S_2$	47.42 47.62	2.98 3.17	16.39 16.93	267-268	93
4i	$C_{14}H_{11}N_3S$	66.03 66.40	4.22 4.35	12.55 12.65	234-236	89
5a	$C_{10}H_{10}ClN_3O_2S_2$	37.84 39.54	3.47 3.32	20.99 21.11	277-278	89
5b	$C_9H_8BrN_3O_2S_2$	32.83 32.34	2.03 2.4	18.97 19.16	289-291	78
5c	$C_{11}H_{13}N_3S_2$	53.07 52.56	5.08 5.21	25.23 25.51	268-270	88
5d	$C_9H_8BrN_3S_2$	35.54 35.76	2.43 2.65	21.82 21.19	272-273	76
5e	$C_{16}H_{14}ClN_3O_2S_2$	50.87 50.59	3.56 3.71	17.7 16.88	315-316	95
5f	$C_{15}H_{12}BrN_3O_2S_2$	42.9 43.9	2.67 2.93	16.39 15.61	302-304	84
5g	$C_{17}H_{17}N_3S_2$	60.26 60.35	5.47 5.23	19.78 19.58	257-258	89
5h	$C_{15}H_{12}BrN_3S_2$	47.73 47.62	2.81 3.17	17.44 16.93	284-286	86
5i	$C_9H_9N_3S$	56.78 56.54	4.23 4.71	16.33 16.75	202-204	87

PPA possesses good solvent properties and contains anhydride groups by means of which water in the dehydration reaction is taken up. Moreover, its effective acidity is unchanged. In contrast to sulfuric acid, PPA is not an oxidant, does not take part in an aromatic substitution reaction, and is less likely to initiate rearrangements [11].

The investigation of the effect of temperature and duration of reaction of carboxylic acids with thiosemicarbazide on the yield of the target products permitted the determination of the optimum conditions for the reaction. These were: temperature of 130-140°C, reaction time of 3-4 h, and molar ratio of reagents of 1:1. The yields of the target products in this case reaches 40%.

It is likely that the following process occurs:



If nitriles are used as the starting compounds it is possible to increase the yield of the products **5a-i** significantly and the maximum yield (70-80%) is achieved at 100-110°C. It should also be mentioned that the reaction takes place within a rather narrow temperature range. At temperature below 90°C the reaction does not take place and, above the optimum, strong tarring of the desired compounds is observed.

In most cases the target compounds do not need extensive purification and are obtained quite pure after first recrystallization from ethanol or DMF. The structure of the synthesized compounds has been identified using IR and ^{1}H NMR spectroscopy. Their purity was monitored by TLC and nonaqueous potentiometric titration.

The absence of depression of melting point for samples prepared by the different methods points to their identity. This is also confirmed by ^{1}H NMR data and by TLC. The parameters for the compounds **5a-i** are given in Table 1.

The IR spectra of 2-amino-5-substituted 1,3,4-thiadiazoles **5** show absorption bands in the regions of 1520, 1490, 1385, 1235, 1040, and 865 cm^{-1} which are typical of the vibrations of 1,3,4-thiadiazole ring [12] and also absorption bands at 1320-1300 cm^{-1} assigned to the stretching vibrations of the C–N bond in aromatic amines.

EXPERIMENTAL

2-Amino- and 2-Phenylamino-5-substituted 1,3,4-Oxadiazoles (3a-h). Solution of NaOH (4 N, 5 ml) was added with cooling and stirring to suspension of the corresponding thiosemicarbazide **1** or **2** (0.01 mol) in ethanol (150 ml) and then treated dropwise with solution of iodine in aqueous KI solution (5%) at room temperature until the reaction product retained the iodine color. The mixture obtained was heated to reflux and solution of iodine was carefully added until a permanent coloration remained. The product was cooled to 20°C, poured onto ice, and the precipitated product was filtered, washed with warm water, dried, and recrystallized from aqueous acetone.

5-Substituted 1,2,4-Triazoline-3-thiones (4a-i). A. Mixture of thiosemicarbazide **1** or **2** (0.01 mol) and sodium (0.03 mol) in absolute ethanol (30 ml) was refluxed with stirring for 12 h. The reaction mixture was evaporated to dryness at reduced pressure and the residue was extracted with hot water (3 × 30 ml). The aqueous extract was cooled to 5°C and acidified using acetic acid to pH 5.5. The precipitated product **4** was then filtered, washed with water, and dried. Average yield 87%.

B. Suspension of thiosemicarbazide **1** or **2** (0.01 mol) in solution of sodium hydroxide (5%, 100 ml) was refluxed for 2 h and then held at room temperature for 12 h. The precipitate was filtered off, suspended with stirring in water (200 ml), and solution of HCl (5%) was added to pH 4.5-5.0. The precipitated product **4** formed was filtered off, washed with water, dried, and recrystallized from ethanol. Average yield 85%.

2-Amino-5-substituted 1,3,4-Thiadiazoles (5a-i). A 100 ml round-bottomed flask was fitted with a reflux condenser, thermometer, mechanical stirrer, and dropping funnel and polyphosphoric acid (25 ml) was poured in. Thiosemicarbazide (0.01 mol) was added and the mixture obtained was heated on an oil bath at 50°C under constant stirring. The flask was then charged with the corresponding acid or nitrile (0.01 mole) and the product was held strictly at 100-110°C for 3 h. The reaction mixture was then poured into water, cooled to room temperature, and aqueous ammonia (25%) was added to pH 9-10. The precipitate was filtered off and dried at 60°C. The obtained product **5** was recrystallized from mixture of DMF and ethanol (3:7).

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