*Chemistry of Heterocyclic Compounds, Vol. 38, No. 9, 2002*

# INTERACTION OF 5-ARYL-1,3,4-OXADIAZOLINE-2(3H)-THIONES WITH N-SUBSTITUTED CHLOROACETAMIDES

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*The reactions of some 5-aryl-1,3,4-oxadiazoline-2(3H)-thiones (aryl = phenyl, 4-bromophenyl, 4-methylphenyl, 2,4-dichlorophenyl) with N-alkyl- and N-arylchloroacetamides has been studied. The nature of the substituents in the molecules of the thiones and the chloroacetamides does not affect the direction of the reaction but does affect the yield of the desired products.*

**Keywords:** S-alkyl derivatives, 5-aryl-1,3,4-oxadiazoline-2(3H)-thiones, N-substituted chloroacetamides, direction of reaction.

We have described previously the alkylation of 5-aryl-1,3,4-oxadiazoline-2(3H)-thiones with various alkylating agents: methyl iodide, dimethyl sulfate, butyl chlorides of various structures, allyl bromide and benzyl chloride, α-chloromethyl alkyl ethers [1-4]. In most of the reaction studied we obtained and characterized S-alkylated derivatives, although under definite conditions we successfully observed and isolated N-substituted thiones.

The objective of the present work was to investigate the reaction of 5-aryl-1,3,4-oxadiazoline-2(3H)-thiones with N-substituted chloroacetamides, containing substituents of different nature.

Some reactions of 5-aryl-1,3,4-oxadiazoline-2(3H)-thiones with N-substituted chloroacetamides are described in the literature.

For example, the authors [5] reported that high yields 5-(*p*-chlorophenyl)-2-[N-aryl- or N-hetaryl]-carbamoylmethylthio-1,3,4-oxadiazoles were obtained from the reaction of 5-(*p*-chlorophenyl-1,3,4-oxadiazoline-2(3H)-thiones with N-aryl and N-hetaryl-2-chloroacetamides in 10% ethanolic alkali solutions (60°C, 2 h).

Similarly [6] the synthesis of 5-substituted phenoxymethyl-2-[N-alkyl-(1,3,4-thiadiazol-5-yl)carbamoylmethylthio]-1,3,4-oxadiazoles in high yields was reported, although in contrast to the previous paper, the reactions required multihour boiling of the 5-substituted phenoxymethyl-1,3,4-oxadiazoline-2-thiones with a variety of 5-chloroacetamino-2-alkyl-1,3,4-thiadiazoles in ethanolic NaOH solutions.

We have used 5-aryl-substituted 1,3,4-oxadiazoline-2(3H)-thiones with various substituents in the aromatic ring (4-methyl-, 4-bromo-, 2,4-dichloro-) as substrates. Similarly we have chosen N-substituted chloroacetamides with alkyl and aryl substituents in order to discover the dependence of the direction of the reaction and the yields of the desired products on the nature of the substituents in both the thiones and the chloroacetamides.

In contrast to [5, 6] we initially studied the reactions of thiones **1-4** with N-substituted chloroacetamides **5** under conditions which we had used previously for the alkylation of 5-aryl substituted 1,3,4-oxadiazoline-

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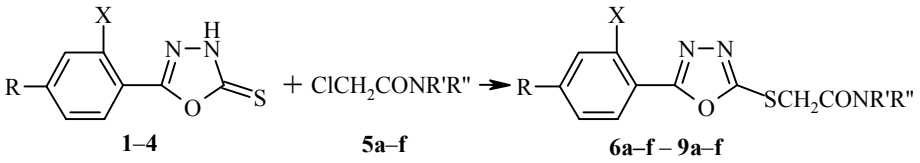
Institute of Phytochemistry, Uzbekistan Academy of Sciences, Tashkent 700170, Uzbekistan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, 1261-1267, September, 2002. Original article submitted January 20, 2000.

 0009-3122/02/3809-1104$27.00

2(3H)-thiones with alkyl, allyl, and benzyl halides [1-4], namely boiling equimolar amounts of the thiones **1-4**, the chloroacetamides **5**, and potassium carbonate in acetone (Table 1). It should be noted first of all that all of these reaction gave the S-substituted derivatives exclusively.




**1–4** **5a–f** **6a–f – 9a–f**

**1, 6** R = H, **2**, **7** R = Me, **3**, **8** R = Br, **4**, **9** R = Cl; **1-3**, **6-8** X = H, **4**, **9** X = Cl;
**5-9 a** R' = Et, **b** R' = Bu, **c-f** R' = H; **a** R" = Et, **b** R" = Bu, **c** R" = *cyclo*-$C_6H_{11}$, **d** R" = Bu, **e** R" = Ph,
**f** R" = 2,5-$Cl_2C_6H_3$

According to Table 1, the reaction of thiones **1-4** occurred successfully under these conditions with N,N-dialkyl- (**5a,b**), N-cyclohexyl- (**5c**) and N-benzylchloroacetamides (**5d**) (in the last case only with thiones **1-3**), with N-aryl-substituted chloroacetamides (**5e,f**) the products were obtained in relatively low yields only after prolonged heating and only in the case of chloroacetamide **5e**.

The nature of the substituent in the aromatic ring of the thione (see Table 1) under these conditions had almost no effect on the yield of the reaction products, only in the case of thione **4** influence of two chlorine atoms decreased the yield significantly in the reaction with the chloroacetamides **5d-f**.

In order to increase the yield of compounds **6d,e-9d,e** and with the hope of preparing compounds **6f-9f** we decided to carry out the reactions under more vigorous conditions – using alcoholic sodium hydroxide solution as recommended in papers [5, 6] in place of potassium carbonate. However with the conditions used in [5] (heating of the reagent mixture for 2 h at 60°C) the reactions of thiones **1-4** with the chloroacetamides **5e,f** did not give notable yields in our hands. This raises doubts about the high yields of products (not less than 75%) claimed by the authors cited, since they used reagents analogous to ours – 5-(*p*-chlorophenyl)-1,3,4-oxadiazoline-2-thione and N-arylchloroacetamides, where aryl is phenyl, *p*-Cl, Br, $CH_3$, $CH_3O$-phenyl, etc.

We obtained positive results only on prolonged boiling (15-30 h) of thiones **1-4** with chloroacetamides **5e,f** in 10% ethanolic sodium hydroxide, and under these conditions the yield of the reaction product is noticeable affected by substituents in both the thione and the chloroacetamide (Table 1). For example, with thione **2** the yields of reactions products with chloroacetamides **5e,f** were noticeably higher than in reactions with thione **3**. As for the relative reactivity of the N-substituted chloroacetamides, the influence of the nature of the substituents on the yields of reaction products showed up markedly: with N-phenylchloroacetamide (**5e**) the yields were considerably higher than with N-2,5-dichlorophenylchloroacetamide (**5f**).

The following conclusions can be drawn from the results obtained.

The yields of compounds **6a-f**–**9a-f** depend directly on the nature of the substituent in the chloroacetamide: the N-substituted chloroacetamides which we studied can be placed in the following order of decreasing reactivity:

N,N-dialkyl- ≥ N-cycloalkyl- > N-benzyl- > N-arylchloroacetamides.

The nature of the substituent in the thione molecule has no noticeable effect on the product yields in the case of the reactive chloroacetamides **5a-d**, whereas with compounds **5e,f** the effect is shown clearly.

Products **6-9** were isolated as pure substances and were characterized *via* their UV and $^1$H NMR spectra. Formation of S-substituted 5-aryl-1,3,4-oxadiazolinethiones is indicated by the presence of $\lambda_{max}$ in the 272-280 nm range in the UV spectrum, which is characteristic of S-derivatives [7]. N-Substituted products were neither isolated nor even observed by TLC. This provides a basis for the conclusion that, while the nature of the substituents in the molecules of both reagents determines the yields of the products, it has absolutely no effect on the direction of the reaction.

TABLE 1. Reaction Conditions and Yields of Desired Products in the Reactions of 5-Aryl-1,3,4-oxadiazoline-2(3H)-thiones with N-Substituted Chloracetamides **5a-f***

| Aryl | HCl Acceptor | Solvent | Time, h | Yields of compounds **6a-d–9a-d** ,%, based on thione used | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | **5a** | **5b** | **5c** | **5d** | **5e** | **5g** |
| Ph | $K_2CO_3$ | Acetone | 8 | 94 | 65 | 88 | 62 | 39 | 26 |
| Ph | KOH | Ethanol | 30 | | | | | 49 | 26 |
| 4-$MeC_6H_4$ | $K_2CO_3$ | Acetone | 8 | 91 | 76 | 88 | 70 | 60 | Traces |
| 4-$MeC_6H_4$ | KOH | Ethanol | 30 | | | | 85 | | 35 |
| 4-$BrC_6H_4$ | $K_2CO_3$ | Acetone | 8 | 88 | 61 | 78 | 68 | 7 | Traces |
| 4-$BrC_6H_4$ | $K_2CO_3$ | Acetone | 16 | | | | | 14 | Traces |
| 4-$BrC_6H_4$ | $K_2CO_3$ | Acetone | 30 | | | | | 38 | Traces |
| 4-$BrC_6H_4$ | KOH | Ethanol | 30 | | | | 78 | 65 | 20 |
| 2,4-$Cl_2C_6H_3$ | $K_2CO_3$ | Acetone | 8 | 93 | 61 | 87 | 10 | Traces | Traces |
| 2,4-$Cl_2C_6H_3$ | KOH | Ethanol | 30 | | | | 46 | 67 | 27 |

* Ratio of thione:chloroacetamide:HCl acceptor = 1:1:1.

TABLE 2. Characteristics of the Compounds Synthesized, **6-9**

| Compound | Empirical formula | Found, % / Calculated, % | | | mp, °C | UV spectrum, $\lambda_{max}$, nm (lg ε) | $^1$H NMR spectrum, δ, ppm |
|---|---|---|---|---|---|---|---|
| | | C | H | N | | | |
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| **6a** | $C_{14}H_{17}N_3O_2S$ | 57.98 / 57.71 | 5.46 / 5.88 | 14.17 / 14.42 | 114-115 | 273 (4.08) | 1.05-1.30 (6H, m, $CH_3$); 3.30-3.55 (4H, q, N–$CH_2$); 4.35 (2H, s, S–$CH_2$); 7.40-8.11 (5H, m, Ar–H) |
| **6b** | $C_{18}H_{25}N_3O_2S$ | 63.00 / 62.22 | 7.05 / 7.25 | 11.78 / 12.09 | Oil | 272 (4.07) | 0.90-1.40 (14H, m, $CH_2CH_2CH_3$); 3.25-3.72 (4H, m, N–$CH_2$); 4.35 (2H, s, S–$CH_2$); 7.20-8.00 (5H, m, Ar–H) |
| **6c** | $C_{16}H_{19}N_3O_2S$ | 59.71 / 60.55 | 5.62 / 6.03 | 13.06 / 13.24 | 136-137 | 278 (4.10) | 1.20-2.00 (10H, m, H-*cyclo*); 3.70 (1H, m, N–CH-*cyclo*); 3.80 (2H, s, S–$CH_2$); 6.80-6.90 (1H, br. d, NH); 7.30-8.00 (5H, m, Ar–H) |
| **6d** | $C_{17}H_{15}N_3O_2S$ | 62.98 / 62.75 | 4.49 / 4.65 | 12.64 / 12.91 | 170-172 | 268 (4.12) | 3.75 (2H, s, N–$CH_2$–Ph); 4.90 (2H, s, S–$CH_2$); 7.25-7.82 (10H, m, Ar–H); 8.64 (1H, not resolved m, NH) |
| **6e** | $C_{16}H_{13}N_3O_2S$ | 60.98 / 61.72 | 3.74 / 4.21 | 12.94 / 13.50 | 220-222 | 275 (3.99) | 4.97 (2H, s, S–$CH_2$); 7.25-7.55 (5H, m, Ar–H); 7.95-8.25 (5H, m, Ar–H); 10.2 (1H, s, NH) |
| **6f** | $C_{16}H_{11}Cl_2N_3O_2S$ | 50.25 / 50.54 | 2.64 / 2.92 | 10.78 / 11.05 | 133-135 | 271 (4.06) | 4.05 (2H, s, S–$CH_2$); 6.95-7.50 (5H, m, Ar–H); 7.96-8.05 (2H, 2d, Ar–H); 8.45 (1H, s, Ar–H) |
| **7a** | $C_{15}H_{19}N_3O_2S$ | 58.64 / 59.00 | 6.58 / 6.27 | 14.04 / 13.76 | 125 | 272 (4.10) | 1.08-1.40 (6H, m, $CH_3$); 2.15 (3H, s, Ar–$CH_3$); 3.25-3.70 (4H, q, N–$CH_2$); 4.50 (2H, s, S–$CH_2$); 7.05-7.35 (4H, 2d, Ar–H) |
| **7b** | $C_{19}H_{27}N_3O_2S$ | 62.78 / 63.13 | 7.15 / 7.53 | 11.21 / 11.62 | 85-87 | 276 (3.98) | 1.10-1.35 (14H, m, $CH_2CH_2CH_3$); 2.15 (3H, s, Ar–$CH_3$); 3.30-3.70 (4H, q, N–$CH_2$); 4.50 (2H, s, S–$CH_2$); 7.05-7.40 (4H, 2d, Ar–H) |
| **7c** | $C_{17}H_{21}N_3O_2S$ | 62.08 / 61.61 | 6.01 / 6.39 | 13.04 / 12.68 | 155-157 | 276 (3.96) | 1.30-2.10 (10H, m, CH-); 2.15 (3H, s, Ar–$CH_3$); 3.7 (1H, N–CH-*cyclo*); 4.0 (2H, s, S–$CH_2$); 6.80-6.90 (1H, br. d, NH); 7.15-7.45 (4H, 2d, ArH) |
| **7d** | $C_{18}H_{17}N_3O_2S$ | 64.08 / 63.70 | 5.42 / 5.05 | 12.02 / 12.38 | 168-169 | 272 (4.13) | 2.38 (3H, s, Ar–$CH_3$); 3.98 (2H, s, N–$CH_2$Ar); 4.90 (2H, s, S–$CH_2$); 7.25-7.75 (9H, m, Ar–H); 8.72 (1H, not resolved m, NH) |

TABLE 2 (continued)

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| **7e** | $C_{17}H_{15}N_3O_2S$ | 63.01<br>62.75 | 4.18<br>4.65 | 13.03<br>12.91 | 185-187 | 278 (4.08) | 2.38 (3H, s, Ar–$CH_3$); 4.92 (2H, s, S–$CH_2$);<br>7.05-7.60 (5H, m, Ar–H); 7.80-8.15 (4H, m, Ar–H);<br>10.35 (1H, s, NH) |
| **7f** | $C_{17}H_{13}Cl_2N_3O_2S$ | 52.08<br>51.79 | 3.01<br>3.32 | 11.02<br>10.66 | 170-175 | 274 (3.99) | 2.35 (3H, s, Ar–$CH_3$); 3.85 (2H, s, S–$CH_2$);<br>7.05-7.80 (7H, m, Ar–H); 10.20 (1H, s, N–H) |
| **8a** | $C_{14}H_{16}BrN_3O_2S$ | 44.98<br>45.41 | 4.71<br>4.36 | 11.63<br>11.35 | 125 | 271 (4.01) | 1.12-1.33 (6H, m, $CH_3$); 3.15-3.60 (4H, q, N–$CH_2$);<br>4.35 (2H, s, S–$CH_2$); 7.00-7.50 (4H, 2d, Ar–H) |
| **8b** | $C_{18}H_{24}BrN_3O_2S$ | 51,08<br>50.71 | 5.24<br>5.67 | 10.01<br>9.86 | 120 | 278 (4.03) | 0.85-1.35 (14H, m, $CH_2CH_2CH_3$);<br>3.15-3.72 (4H, m, N–$CH_2$); 4.45 (2H, s, S–$CH_2$);<br>7.05-7.45 (4H, 2d, Ar–H) |
| **8c** | $C_{16}H_{18}BrN_3O_2S$ | 49.84<br>48.49 | 5.01<br>4.58 | 10.97<br>10.60 | 185 | 275 (3.97) | 1.05-2.05 (10H, m, CH-*cyclo*); 3.65 (1H, m, N–CH-*cyclo*);<br>4.05 (2H, s, S–$CH_2$); 6.80-6.95 (1H, br. d, NH);<br>7.05-7.45 (4H, 2d, Ar–H) |
| **8d** | $C_{17}H_{14}BrN_3O_2S$ | 51.02<br>50.51 | 3.82<br>3.49 | 10.71<br>10.39 | 197 | 271 (4.00) | 3.85 (2H, s, HN–$CH_2$Ar); 4.95 (2H, s, S–$CH_2$);<br>7.25-7.91 (9H, m, Ar–H); 8.73 (1H, not resolved m, NH) |
| **8e** | $C_{16}H_{12}BrN_3O_2S$ | 48.89<br>49.24 | 3.35<br>3.10 | 11.06<br>10.77 | 225 | 276 (4.14) | 4.85 (2H, s, S–$CH_2$); 7.00-7.95 (9H, m, Ar–H);<br>10.20 (1H, s, NH) |
| **8f** | $C_{16}H_{10}BrCl_2N_3O_2S$ | 42.28<br>41.86 | 1.73<br>2.20 | 8.74<br>9.15 | >240 | 273 (4.13) | 3.92 (2H, s, S–$CH_2$); 7.10-7.75 (7H, m, Ar–H);<br>9.64 (1H, s, NH) |
| **9a** | $C_{14}H_{15}Cl_2N_3O_2S$ | 47.02<br>46.67 | 4.44<br>4.20 | 12.02<br>11.66 | 116-117 | 274 (4.12) | 1.08-1.28 (6H, m, $CH_3$); 3.20-3.55 (4H, q, N–$CH_2$);<br>4.42 (2H, s, S–$CH_2$); 7.25-7.85 (3H, m, Ar–H) |
| **9b** | $C_{18}H_{23}Cl_2N_3O_2S$ | 52.21<br>51.92 | 5.18<br>5.57 | 9.74<br>10.09 | 66-67 | 278 (3.99) | 1.10-1.40 (14H, m, $CH_2CH_2CH_3$); 3.20-3.60 (4H, q, N–$CH_2$);<br>4.35 (2H, s, S–$CH_2$); 7.25-7.85 (3H, m, Ar–H) |
| **9c** | $C_{16}H_{17}Cl_2N_3O_2S$ | 49.41<br>49.75 | 4.73<br>4.44 | 11.15<br>10.88 | 174-175 | 277 (4.10) | 1.35-2.05 (10H, m, CH-*cyclo*); 3.70 (1H, N–CH-*cyclo*);<br>3.85 (2H, s, S–$CH_2$); 6.70-6.87 (1H, br. d, NH);<br>7.25-7.82 (3H, m, Ar–H) |
| **9d** | $C_{17}H_{13}Cl_2N_3O_2S$ | 52.09<br>51.79 | 3.64<br>3.32 | 11.02<br>10.66 | 144-146 | 280 (4.04) | 3.82 (2H, s, N–$CH_2$Ar); 4.85 (2H, s, S–$CH_2$);<br>7.15-7.82 (8H, m, Ar–H); 10.35 (1H, not resolved m, NH) |
| **9e** | $C_{16}H_{11}Cl_2N_3O_2S$ | 50.88<br>50.54 | 2.53<br>2.92 | 10.87<br>11.05 | 173-174 | 276 (4.08) | 4.00 (2H, s, S–$CH_2$); 7.25-7.97 (8H, m, Ar–H);<br>10.45 (1H, s, NH) |
| **9f** | $C_{16}H_9Cl_4N_3O_2S$ | 43.01<br>42.79 | 1.79<br>2.02 | 9.05<br>9.36 | 204-205 | 275 (4.11) | 3.98 (2H, s, S–$CH_2$); 7.20-7.85 (6H, m, Ar–H);<br>9.85 (1H, s, NH) |

## EXPERIMENTAL

UV spectra of ethanol solutions were recorded on a Hitachi EPS-3T spectrometer. $^1$H NMR spectra of $CDCl_3$ solutions (Py-$d_5$ solution for **6e** and **9f**) with HMDS internal standard were recorded with a Tesla BS-567 machine (100 MHz). The progress of reactions and purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates with 1:24 ethanol–chloroform eluent and development with iodine vapour.

5-Aryl-1,3,4-oxadiazoline-2(3H)-thiones were prepared by a known method [8].

**1. General Method for Experiments Carried out in the Presence of Potassium Carbonate.** A mixture of a thione **1-4**, and N-substituted chloroacetamide **5** and potassium carbonate (0.05 mol of each) in acetone (25 ml) was boiled for 8 h. The progress of the reaction was monitored by TLC. The reaction was continued until the thione had completely disappeared from the reaction mixture or until it ceased to be consumed. The solvent was then evaporated, the residue was washed with 10% sodium hydroxide solution and water. It was then recrystallized from ethanol or aqueous ethanol.

**2. General Method for Experiments Carried out in the Presence of Potassium Hydroxide.** A thione (0.05 mol) was dissolved with stirring and gentle heating in the minimum amount of 10% ethanolic potassium hydroxide, then a solution of the corresponding chloroacetamide (0.05 mol) in ethanol was added, and the heating and work up were carried out analogously to method 1.

The characteristics of compounds **6-9** are cited in Table 2.

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