Chemistry of Heterocyclic Compounds, Vol. 48, No. 3, June, 2012 (Russian Original Vol. 48, No. 3, March, 2012)

5-ARYL-1,3,4-OXADIAZOLINE-2(3*H*)-THIONES IN REACTIONS WITH ALKYL HALOACETATES

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The reaction of 5-aryl-1,3,4-oxadiazoline-2(3H)-thiones with alkyl haloacetates has been studied. It was shown that the reaction proceeds to give S-substituted products. The effect of the nature of the substituents in the molecules of both the thiones and the haloacetates on the reaction route and yields has been examined.

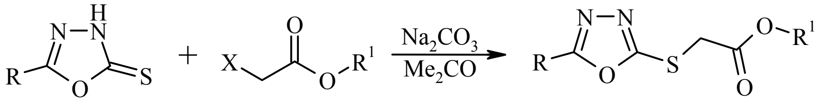
Keywords: alkylating agent, 5-aryl-1,3,4-oxadiazoline-2(3*H*)-thiones, haloacetic acids, *S*- and *N*-substituted products, alkylation, orientation.

The alkylation of 5-aryl-1,3,4-oxadiazoline-2(3*H*)-thiones by alkylating agents of various types (alkyl-, allyl-, and benzyl halides, α-chloromethylalkyl esters etc.) has been studied previously [1-4]. Now we have examined the reaction of 5-aryl-1,3,4-oxadiazoline-2(3*H*)-thiones with alkyl haloacetates in order to establish the factors influencing the reaction route and product yields.

Literature data regarding the reactions of alkyl α-haloalkanoates with oxadiazoline thiones is very contradictory. The reaction of 5-aryl-1,3,4-oxadiazoline-2(3*H*)-thiones with chloroacetic acid in the presence of NaOH (K_2CO_3) in DMF or alcohol [5, 6] and with its methyl and ethyl esters in the presence of KOH in different solvents has been reported [7]. It was shown that the *S*-derivatives were formed exclusively. At the same time, the authors of [8, 9] have studied the reactions of 5-(2,4-dichlorophenyl)-1,3,4-oxadiazoline-2-thione with ethyl chloroacetate and have characterized the products obtained as *N*-alkyl derivatives.

The occurrence of this reaction at the *N*-center was taken without convincing evidence (more often from IR spectroscopic data or simply by assigning this structure to the compound).

Scheme 1



1–4 **5a–f** **6a–d, 7a,b, 8a–f, 9a–d**

1, **6a–d** R = Ph; **2**, **7a**,**b** R = 4-MeC_6H_4; **3**, **8a–f** R = 2-pyridyl; **4**, **9a–d** R = 2,4-$Cl_2C_6H_3$;
5**a**, **6a**, **7a**, **8a**, **9a** R^1 = Me; 5**b**, **6b**, **7b**, **8b**, **9b** R^1 = Et; 5**c**, **8c** R^1 = Pr; 5**d**, **8d** R^1 = Bu;
5**e**, **6c**, **8e**, **9c** R^1 = *i*-Pr; 5**f**, **6d**, **8f**, **9d** R^1 = $PhCH_2$; **5a–e** X= Cl, **f** X = Br

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 520-523, March 2012. Original article submitted February 8, 2011. Revision submitted September 9, 2011.

TABLE 1. Physicochemical Characteristics of Compounds **6-9**

Compound	Empirical formula	Found N, % Calculated N, %	Mp, °C	Yield, %
6a	$C_{11}H_{10}N_2O_3S$	10.41 11.19	83-84	97
6b	$C_{12}H_{12}N_2O_3S$	10.38 10.60	82-83	91
6c	$C_{13}H_{14}N_2O_3S$	10.34 10.06	76-77	92
6d	$C_{17}H_{14}N_2O_3S$	8.82 8.58	93-94	88
7a	$C_{12}H_{12}N_2O_3S$	10.39 10.60	77-79	96
7b	$C_{13}H_{14}N_2O_3S$	10.26 10.06	68-70	92
8a	$C_{10}H_9N_3O_3S$	17.03 16.72	78-80	88
8b	$C_{11}H_{11}N_3O_3S$	16.21 15.84	37-39	81
8c	$C_{12}H_{13}N_3O_3S$	14.78 15.04	38-40	79
8d	$C_{13}H_{15}N_3O_3S$	13.98 14.32	Oil	80
8e	$C_{12}H_{13}N_3O_3S$	15.28 15.04	66-68	82
8f	$C_{16}H_{13}N_3O_3S$	13.17 12.84	82-84	90
9a	$C_{11}H_8Cl_2N_2O_3S$	8.98 8.78	85-86	94
9b	$C_{12}H_{10}Cl_2N_2O_3S$	8.12 8.41	66-67	84
9c	$C_{13}H_{12}Cl_2N_2O_3S$	7.76 8.07	96-98	86
9d	$C_{17}H_{12}Cl_2N_2O_3S$	7.34 7.09	106-107	92

We have thoroughly investigated the reaction of the 5-aryl-1,3,4-oxadiazoline-2(3*H*)-thiones **1-4** (aryl = phenyl, 2,4-dichlorophenyl, 4-methylphenyl, and α-pyridyl) with the alkyl haloacetates **5a-f**. The reaction studied in most detail was that with C_1 to C_4 alkyl chloroacetates (Scheme 1).

The reactions were carried out by refluxing equimolar amounts of the thione, the haloacetate, and potassium carbonate in acetone and the course of the reaction was monitored by TLC. The results obtained are given in Tables 1 and 2.

Analysis of the products by ^{1}H NMR and UV spectroscopy showed that the *S*-derivatives are formed in all of the reactions (absorption bands at 270-286 nm in the UV spectra, absence of N–CH_2 protons signals and presence of S–CH_2 protons signals in the ^{1}H NMR spectra).

As is evident from Table 1, the reactions occur in good yields and the main part of the thione is consumed over 7-10 h. Comparison of the results of the reaction of different thiones with the same ester has shown that the thione aromatic ring substituents are not proven to have a marked effect on the yield of products.

Several reactions of the benzyl bromoacetate **5f** with thiones **1, 3, 4** also yielded the *S*-derivatives with comparable yields under the same conditions.

Hence the reaction of 5-aryl-1,3,4-oxadiazoline-2(3*H*)-thiones with alkyl haloacetates occurs with exclusive formation of *S*-derivatives. The nature of the halogen in these reactions does not have a significant effect on the product yields.

TABLE 2. Spectroscopic Properties of Compounds **6-9**

Compound	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	UV spectrum, λ_{max}, nm (log ε)
6a	7.94 (2H, dt, *J* = 7.9, *J* = 1.4, H-2',6'); 7.40-7.50 (3H, m, H-3',4',5'); 4.06 (2H, s, SCH_2); 3.75 (3H, s, OCH_3)	273 (4.00)
6b	7.94 (2H, dt, *J* = 7.9, *J* = 1.4, H-2',6'); 7.40-7.50 (3H, m, H-3',4',5'); 4.05 (2H, s, SCH_2); 4.20 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 1.24 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$)	278 (3.86)
6c	7.94 (2H, dt, *J* = 7.9, *J* = 1.4, H-2',6'); 7.40-7.50 (3H, m, H-3',4',5'); 5.03 (1H, septet, *J* = 6.3, $C\underline{H}(CH_3)_2$); 4.02 (2H, s, SCH_2); 1.21 (6H, d, *J* = 6.3, $CH(C\underline{H}_3)_2$)	276 (3.42)
6d	7.91 (2H, dt, *J* = 8.1, *J* = 1.6, H-2',6'); 7.40-7.48 (3H, m, H-3',4',5'); 7.23-7.29 (5H, m, H Ph); 5.16 (2H, s, CH_2Ph); 4.09 (2H, s, SCH_2)	280 (3.88)
7a	7.30 (2H, dt, *J* = 8.0, *J* = 2.0, H-2',6'); 7.10 (2H, dt, *J* = 8.0, *J* = 2.0, H-3',5'); 4.10 (2H, s, SCH_2); 3.74 (3H, s, $COOCH_3$); 2.31 (3H, s, $C_6H_4C\underline{H}_3$)	274 (3.94)
7b	7.30 (2H, dt, *J* = 8.1, *J* = 2.1, H-2',6'); 7.12 (2H, dt, *J* = 8.1, *J* = 2.1, H-3',5'); 4.16 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 4.08 (2H, s, SCH_2); 2.31 (3H, s, $C_6H_4C\underline{H}_3$); 1.21 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$)	280 (3.86)
8a	8.62 (1H, ddd, *J* = 4.8, *J* = 1.8, *J* = 1.0, H-6'); 8.13 (1H, dt, *J* = 7.9, *J* = 1.0, H-3'); 7.78 (1H, td, *J* = 7.9, *J* = 1.8, H-4'); 7.33 (1H, ddd, *J* = 7.9, *J* = 4.8, *J* = 1.0, H-5'); 4.07 (2H, s, SCH_2); 3.741 (3H, s, $COOCH_3$)	286 (3.70)
8b	8.70 (1H, ddd, *J* = 4.8, *J* = 1.9, *J* = 1.1, H-6'); 8.13 (1H, dt, *J* = 7.7, *J* = 1.1, H-3'); 7.82 (H, td, *J* = 7.7, *J* = 1.9, H-4'); 7.40 (1H, ddd, *J* = 7.7, *J* = 4.8, *J* = 1.1, H-5'); 4.20 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 4.09 (2H, s, SCH_2); 1.24 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$)	286 (3.84)
8c	8.62 (1H, ddd, *J* = 4.8, *J* = 1.8, *J* = 1.0, H-6'); 8.13 (1H, dt, *J* = 7.9, *J* = 1.0, H-3'); 7.78 (1H, td, *J* = 7.9, *J* = 1.8, H-4'); 7.33 (H, ddd, *J* = 7.9, *J* = 4.8, *J* = 1.0, H-5'); 4.08 (2H, t, *J* = 6.6, OCH_2); 4.06 (2H, s, SCH_2); 1.65 (2H, sextet, *J* = 7.3, $CH_2C\underline{H}_2CH_3$); 0.92 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$)	286 (3.74)
8d	8.70 (1H, ddd, *J* = 4.8, *J* = 1.9, *J* = 1.1, H-6'); 8.13 (1H, dt, *J* = 7.7, *J* = 1.1, H-3'); 7.83 (1H, td, *J* = 7.7, *J* = 1.9, H-4'); 7.40 (1H, ddd, *J* = 7.7, *J* = 4.8, *J* = 1.1, H-5'); 4.14 (2H, t, *J* = 6.6, $COOCH_2$); 4.10 (2H, s, SCH_2); 1.58 (2H, quin, *J* = 7.7, $CH_2C\underline{H}_2CH_2$); 1.31 (2H, sextet, *J* = 7.4, $CH_2C\underline{H}_2CH_3$); 0.85 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$)	286 (3.77)
8e	8.69 (1H, ddd, *J* = 4.8, *J* = 1.7, *J* = 1.0, H-6'); 8.12 (1H, dt, *J* = 7.8, *J* = 1.0, H-3'); 7.80 (1H, td, *J* = 7.8, *J* = 1.7, H-4'); 7.38 (1H, ddd, *J* = 7.7, *J* = 4.8, *J* = 1.0, H-5'); 5.02 (1H, septet, *J* = 6.2, $C\underline{H}(CH_3)_2$); 4.05 (2H, s, SCH_2); 1.20 (6H, d, *J* = 6.2, $CH(C\underline{H}_3)_2$)	286 (4.21)
8f	8.70 (1H, ddd, *J* = 4.8, *J* = 1.8, *J* = 1.1, H-6'); 8.12 (1H, dt, *J* = 7.7, *J* = 1.1, H-3'); 7.82 (1H, td, *J* = 7.7, *J* = 1.8, H-4'); 7.40 (1H, ddd, *J* = 7.7, *J* = 4.8, *J* = 1.1, H-5'); 7.22-7.32 (5H, m, $CH_2C_6H_5$); 5.16 (2H, s, $COOCH_2$); 4.13 (2H, s, SCH_2)	286 (4.07)
9a	7.83 (1H, d, *J* = 8.3, H-6'); 7.50 (1H, d, *J* = 2.0, H-3'); 7.32 (1H, dd, *J* = 8.3, *J* = 2.0, H-5'); 4.05 (2H, s, SCH_2); 3.74 (3H, s, $COOCH_3$)	280 (3.64)
9b	7.83 (1H, d, *J* = 8.3, H-6'); 7.50 (1H, d, *J* = 2.0, H-3'); 7.32 (1H, dd, (*J* = 8.3, *J* = 2.0, H-5'); 4.20 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 4.05 (2H, s, SCH_2); 1.24 (3H, t, *J* = 7.2, CH_2CH_3)	280 (3.48)
9c	7.84 (1H, d, *J* = 8.3, H-6'); 7.50 (1H, d, *J* = 2.0, H-3'); 7.32 (1H, dd, *J* = 8.3, *J* = 2.0, H-5'); 4.15-4.25 (1H, septet, *J* = 6.3, $C\underline{H}(CH_3)_2$); 4.02 (2H, s, SCH_2); 1.21 (6H, d, *J* = 6.3, $CH(C\underline{H}_3)_2$)	276 (3.53)
9d	7.80 (1H, d, *J* = 8.6, H-6'); 7.50 (1H, d, *J* = 2.0, H-3'); 7.31 (1H, dd, *J* = 8.6, *J* = 2.0, H-5'); 7.23-7.29 (5H, m, H Ph); 5.16 (2H, s, CH_2Ph); 4.09 (2H, s, SCH_2)	274 (3.84)

EXPERIMENTAL

UV spectra were recorded on a Hitachi EPS-3T spectrometer using ethanol. ^{1}H NMR spectra were recorded on a Tesla BS-567 (100 MHz) (compounds **7a,b**) or a Unity +400 instrument (400 MHz) (remaining compounds) at 20-25°C using $CDCl_3$ with HMDS (δ 0.05 ppm) as internal standard. Monitoring of the reaction course and the purity of the compounds synthesized was carried out by TLC on Silufol UV-254 plates in the system $CHCl_3$–EtOH (20:1) and revealed using iodine vapor.

Alkyl (5-aryl-1,3,4-oxadiazolylsulfanyl)acetates (6-9) (General Method). A mixture of 5-aryl-1,3,4-oxadiazoline-2(3*H*)-thione **1-4** (5 mmol), the alkyl haloacetate **5a-f** (5 mmol), and potassium carbonate (5 mmol) in dry acetone (20 ml) was refluxed for 7-10 h. After removal of the solvent, the residual crystals were washed with NaOH solution to remove the unreacted thione and then with cold water to neutral reaction. In the case of the oily products they were extracted with chloroform and also washed with alkali solution and water. The crystalline compounds obtained were recrystallized from EtOH (compounds **6a-d, 7a,b**), aqueous EtOH (compounds **9a-d**) or cyclohexane (compounds **8a-f**).

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