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THE ROUTE OF ALKYLATION OF 5-SUBSTITUTED 1,3,4-THIADIAZOLINE-2-THIONES

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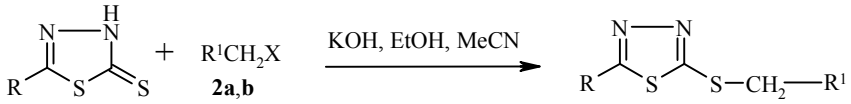
The reaction of 5-anilino(toluidino-, morpholino)-1,3,4-thiadiazoline-2-thiones at 80°C with allyl bromide and benzyl chloride in alcohol, acetonitrile or DMF in the presence of KOH and also with phenoxymethyloxirane in alcohol in the absence of base gives the corresponding novel allyl-, benzyl-, and 2-hydroxy-3-phenoxypropyl products substituted at the exocyclic S atom. Alkylation of the indicated thiones with benzyl chloride at 150-153°C in DMF in the presence of KOH occurs similarly. Under these conditions, allyl bromide forms alkylation products at the endocyclic $N_{(3)}$ atom as a result of an S→N thio-Claisen rearrangement of the initially formed product which is allyl substituted at the exocyclic S atom.

Keywords: allyl bromide, benzyl chloride, 5-substituted 1,3,4-thiadiazoline-2-thiones, phenoxy-2,3-epoxypropane, S- and N-alkylation, S→N thio-Claisen rearrangement.

It is known that 1,3,4-thiadiazoline-2-thiones are categorized as heterocyclic compounds capable to tautomeric conversion [1]. In alkylation reactions they can form products both at the exocyclic sulfur atom and at the endocyclic $N_{(3)}$ atom. The methylation of 5-substituted 1,3,4-thiadiazoline-2-thiones by diazomethane in ether gives a mixture of the isomeric alkylation products at the S and N atoms [2, 3] but the action of an equimolar amount of methyl iodide in alcoholic base solution gives only S-methylated products [4]. It is important to note that many S-substituted 1,3,4-thiadiazoline-2-thiones exhibit different kinds of biological activity [5, 6].

In order to study the route of reaction for the alkylation of 5-substituted 1,3,4-thiadiazoline-2-thiones using various alkylation agents and also the synthesis of novel, biologically active materials we have carried out, for the first time, in this work the alkylation of the 5-anilino-(*p*-toluidino-, morpholino)-1,3,4-thiadiazoline-2-thiones (**1a-c**) using allyl bromide (**2a**), benzyl chloride (**2b**), and phenoxymethyloxirane (**3**). The reaction of the thiones **1a-c** with compounds **2a,b** was carried out in the presence of potassium hydroxide at 78-80°C in alcohol, acetonitrile, and DMF, and also in DMF at 150-153°C. The corresponding S-alkylated derivatives **4a-f** were obtained at 78-80°C over 5 h in all cases independently of the nature of the reagents and the solvent parameters.



1a–c **2a**,**b** **4a–f**

1 a R = PhNH, **b** R = *p*-MeC_6H_4NH, **c** R = $O(CH_2CH_2)_2N$; **2 a** R^1 = CH_2=CH, X = Br, **b** R^1 = Ph, X = Cl; **4 a–c** R^1 = CH_2=CH, **d–f** R^1 = Ph, **a**, **d** R = PhNH, **b**, **e** R = *p*-MeC_6H_4NH, **c**, **f** R = $O(CH_2CH_2)_2N$

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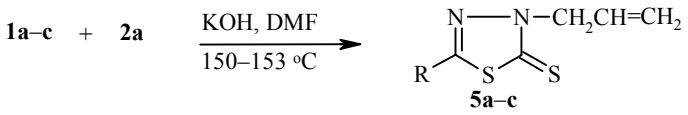
In DMF at the higher temperature (150-153°C) over 3 h the thiones **1a-c** and benzyl chloride **2b** also gave the S-benzyl derivatives **4d-f**. However, under the same conditions, the alkylation with allyl bromide **2a** gave as the basic product the N-allyl derivatives **5a-c** with trace amounts of the corresponding S-derivatives **4a-c**, as shown by TLC of the reaction mixtures.



5a–c

a R = PhNH, **b** R = *p*-MeC_6H_4NH, **c** R = $O(CH_2CH_2)_2N$

The formation of compounds **5a-c** is a result of a thio-Claisen rearrangement of the initially formed S-allyl derivatives **4a-c**. This was shown experimentally. Refluxing the individual compounds **4a-c** in DMF for 3 h gave compounds **5a-c**. A similar rearrangement has been observed in the case of the S-allyl derivatives of thioquinolines [7].

When the thiones **1a-c** are held with the oxirane **3** in ethanol for 5 h at 78°C the compounds **6a-c** are obtained in 68-76% yields (Table 1), and the structures are confirmed by their spectroscopic characteristics (Table 2).

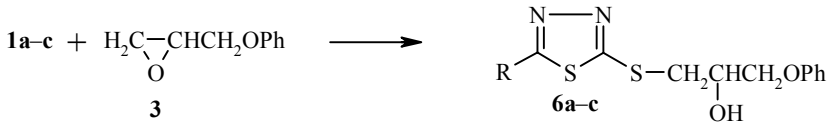
TABLE 1. Parameters for Compounds **4a-f**, **5a-c**, and **6a-c**

Compound	Empirical formula	Found, % / Calculated, %			mp*, °C	R_f (benzene–ethanol, 10:1)	Yield, %
		C	H	N			
4a	$C_{11}H_{11}N_3S_2$	53.28 / 53.54	0.52 / 0.44	17.01 / 16.87	96-98	0.47	72 (A), 64*[2]
4b	$C_{12}H_{13}N_3S_2$	54.89 / 54.75	5.11 / 4.94	15.80 / 15.96	101-103	0.53	68 (A), 62*[2]
4c	$C_9H_{13}N_3OS_2$	44.66 / 44.44	5.42 / 5.35	17.39 / 17.28	42-43	0.72	60 (A), 59*[2]
4d	$C_{15}H_{13}N_3S_2$	60.36 / 60.20	4.47 / 4.35	14.32 / 14.05	120-121	0.64	65 (A), 81*[2]
4e	$C_{16}H_{15}N_3S_2$	61.47 / 61.34	4.96 / 4.79	13.31 / 13.42	126-127	0.52	61 (A), 79*[2]
4f	$C_{13}H_{15}N_3OS_2$	53.39 / 53.24	0.66 / 0.51	14.48 / 14.33	108-109	0.66	54 (A), 52*[2]
5a	$C_{11}H_{11}N_3S_2$	53.23 / 53.01	0.60 / 0.44	17.10 / 16.87	142-143	0.71	78 (B)
5b	$C_{12}H_{13}N_3S_2$	54.91 / 54.75	5.14 / 4.94	16.14 / 15.96	149-150	0.45	73 (B)
5c	$C_9H_{13}N_3OS_2$	44.60 / 44.44	5.46 / 5.35	17.48 / 17.28	71-72	0.41	70 (B)
6a	$C_{17}H_{17}N_3O_2S_2$	57.10 / 56.82	5.05 / 4.73	11.92 / 11.70	148-150	0.35	76 (C), 79*[2]
6b	$C_{18}H_{19}N_3O_2S_2$	58.18 / 57.91	5.27 / 5.09	11.42 / 11.26	102-103	0.66	70 (C), 74*[2]
6c	$C_{15}H_{19}N_3O_3S_2$	51.22 / 50.99	5.28 / 5.10	12.17 / 11.90	68-70	0.26	68 (C)

* Solvent for crystallization: hexane–benzene, 10:1 (compound **4a**), hexane (**4b,c,f**, **5a,c**, **6a-c**), aqueous alcohol (**4d,e**), hexane–benzene, 2:1 (**5b**).
*[2] Refluxing for 5 h in acetonitrile.

TABLE 2. Spectroscopic Characteristics for Compounds **4a-f**, **5a-c** and **6a-c**

Compound	UV spectrum, λ_{max}, nm	IR spectrum, ν, cm^{-1}				^{1}H NMR spectrum, δ, ppm (*J*, Hz)
		CH_2=CH–	NH	OH	C–C arom.	
4a	310	1630	3200	—	1580, 1510	3.72 (2H, d, *J* = 5, SCH_2); 4.62 (2H, d, *J* = 5, $\underline{CH}$=CH_2); 5.12 (1H, m, *J* = 6, CH=CH_2); 5.87 (1H, m, *J* = 8, NH); 7.00-7.70 (5H, m, *J* = 6, H arom.)
4b	312	1635	3150	—	1590, 1520	2.25 (3H, s, *J* = 6.25, $\underline{CH_3}$–C_6H_4); 3.70 (2H, d, *J* = 6.25, SCH_2); 4.65 (2H, d, *J* = 5, CH=$\underline{CH_2}$); 5.12 (1H, m, *J* = 5, $\underline{CH}$=CH_2); 5.85 (1H, m, *J* = 6.25, NH); 7.00-7.50 (5H, m, *J* = 7.5, H arom.)
4c	305	1640	—	—	—	3.40 (4H, m, *J* = 3.7, NCH_2); 3.63 (6H, m, *J* = 5, $2OCH_2$, CH=$\underline{CH_2}$); 4.10 (2H, d, *J* = 5, SCH_2); 5.10 (1H, m, *J* = 3.75, $\underline{CH}$=CH_2)
4d	313	—	3180	—	1590, 1510	4.10 (2H, d, *J* = 6.25, SCH_2); 7.10-7.50 (11H, m, *J* = 5, NH, 10H arom.)
4e	312	—	3170	—	1585, 1520	2.27 (3H, s, *J* = 6, $\underline{CH_3}$–C_6H_4); 4.05 (2H, d, *J* = 5.5, SCH_2); 7.12-7.60 (10H, m, *J* = 7.6, NH, 9H arom.)
4f	295	—	—	—	1580	3.38 (4H, m, *J* = 5, $2NCH_2$); 3.70 (4H, m, *J* = 5, $2OCH_2$); 4.30 (2H, s, *J* = 3.75, SCH_2); 7.30 (5H, m, *J* = 5, H arom.)
5a	327	1630	3175	—	1580, 1520	4.24 (2H, s, *J* = 4, N_3CH_2); 4.85 (2H, d, *J* = 5.5, CH=$\underline{CH_2}$); 5.30 (1H, m, *J* = 7.5, $\underline{CH}$=CH_2); 5.85 (1H, m, NH); 7.10-7.50 (5H, m, H arom.)
5b	325	1630	3200	—	1590, 1510	2.30 (3H, s, *J* = 6, CH_3–C_6H_4); 4.25 (2H, s, *J* = 4, N_3CH_2); 4.80 (2H, d, *J* = 3.25, CH=$\underline{CH_2}$); 5.35 (1H, m, *J* = 7, $\underline{CH}$=CH_2); 5.80 (1H, m, *J* = 3.95, NH); 7.10-7.50 (5H, m, *J* = 7.3, H arom.)
5c	320	1640	—	—	—	3.90-4.20 (8H, m, *J* = 3, NCH_2, OCH_2); 4.70 (2H, s, *J* = 3, N_3–CH_2, CH=$\underline{CH_2}$); 5.80 (1H, m, *J* = 4, $\underline{CH}$=CH_2)
6a	307	—	3200	3300	1600, 1500	3.30 (2H, m, *J* = 5, SCH_2); 4.05 (2H, m, *J* = 3, $2OCH_2$); 4.75 (1H, m, *J* = 5, OCH); 6.78-7.40 (6H, m, *J* = 5, NH, 5H arom.)
6b	308	—	3170	3350	1600, 1520	2.20 (3H, s, *J* = 6.1, CH_3–C_6H_4); 3.32 (2H, m, *J* = 5, SCH_2); 4.10 (2H, m, *J* = 5, OCH_2); 4.70 (1H, m, *J* = 3.5, OCH); 6.78-7.40 (6H, m, *J* = 7.25, NH, 5H arom.)
6c	290	—	—	3250	1575	3.35 (4H, m, *J* = 3.75, $2NCH_2$); 3.75 (4H, m, *J* = 3.75, $2OCH_2$); 4.20 (5H, m, *J* = 2.5, SCH_2, OCH and OCH_2); 6.80-7.25 (5H, m, *J* = 5, H arom.)



6 a R = PhNH, **b** R = *p*-MeC_6H_4NH, **c** R = $O(CH_2CH_2)_2N$

We have found that UV spectroscopic data can be used to identify the S- or N-derivatives of the 5-R-1,3,4-thiadiazoline-2-thiones even though many authors have used only IR and ^{1}H NMR spectroscopy [8, 9]. Thus the presence of absorption maxima at 290-313 nm in the UV spectra of compounds **4a-f** and **6a-c** points to the formation of the S-alkylated derivatives. Absorption maxima at 320-327 nm in the spectra of compounds **5a-c** confirm their thione structures.

In the ^{1}H NMR spectra of compounds **4a-f** and **6a-c** the signals for the S–CH_2 group protons is observed at 3.30-4.30 ppm. The signals for the $N_{(3)}$–CH_2 group protons occur at lower field than for the S–CH_2 group and this is typical for compounds of the type **5a-c**.

Hence we have shown that the reaction of the thiones **1a-c** with allyl bromide **2a** and benzyl chloride **2b** occurs in the presence of an equimolar amount of potassium hydroxide at 80°C to give the corresponding S-alkyl derivatives **4a-f**. A similar reaction route is observed when treating the same thiones with phenoxymethyloxirane **3** in ethanol at 78°C in the absence of base. In the case of allyl bromide **2a** in refluxing DMF the products of allylation at the endocyclic $N_{(3)}$ atom are obtained as a result of the rearrangement of the initially formed S-allylation products.

EXPERIMENTAL

UV spectra were taken on a Hitachi EPS-3T spectrometer for solutions in ethanol. IR spectra were recorded on a UR-20 instrument for KBr tablets. ^{1}H NMR spectra were recorded on a Jeol C-60HL (60 MHz) instrument using $CDCl_3$ solvent and HMDS internal standard. The purity of the compounds prepared was controlled using TLC on Silufol UV-254 plates using benzene–alcohol (10:1) as eluent.

5-R-1,3,4-Thiadiazoline-2-thiones 1-3 were synthesized by a known method [10].

Method for the Alkylation of 5-R-1,3,4-thiadazoline-2-thiones 1a-c. A. A solution of compound **2a,b** (20 mmol) in DMF (10 ml) was added dropwise with stirring at 40-50°C over 30 min to a solution of the thione **1a-c** (5 mmol) and potassium hydroxide (5 mmol) in DMF (15 ml). The reaction mixture was stirred at 80°C for 5 h, diluted with water (100 ml), extracted with chloroform (3 × 20 ml), and the extract dried over calcium chloride, the solvent evaporated, and the residue recrystallized to give the products **4a-f**.

B. A solution of compound **2a** (20 mmol) in DMF (10 ml) was added dropwise with stirring at 40-50°C over 30 min to a solution of the thione **1a-c** (5 mmol) and potassium hydroxide (5 mmol) in DMF (15 ml) and then refluxed for 3 h. Solvent was distilled off at reduced pressure and the product was recrystallized to give compounds **5a-c**.

C. A solution of the oxirane **3** (1 mmol) in ethanol (10 ml) was added with stirring over 30 min to a solution of the thione **1a-c** (5 mmol) in ethanol (15 ml). The reaction mixture was refluxed for 5 h, ethanol was distilled off, and the residue was recrystallized to give compounds **6a-c**.

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