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REACTION OF 5-ARYL-1,3,4-OXADIAZOLE-2(3H)-THIONES WITH CHLOROMETHYL ALKYL ETHERS

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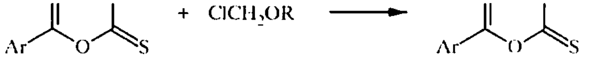
3-Alkoxymethyl-5-aryl-1,3,4-oxadiazole-2(3H)-thiones were synthesized. The direction of alkylation of 5-aryl-1,3,4-oxadiazoline-2-thiones and their potassium salts was studied relative to the substrate, alkylating agent, solvent, and reaction conditions.

We have previously studied alkylation of 5-substituted 1,3,4-oxadiazole-2(3H)-thiones by various alkyl halides in solvents differing in polarity such as acetone, ethanol, acetonitrile, DMF, and HMPTA at 56-81°C. Our results showed that the S-alkyl derivatives were the predominant if not exclusive products in all the cases [1, 2] although the literature data on these reactions are very contradictory [3, 4].

In continuation of these studies, we investigated the previously unexamined reaction of 5-aryl-1,3,4-oxadiazole-2(3H)-thiones with some chloromethyl alkyl ethers. The extremely labile halogen atom in α-halodialkyl ethers is the most important feature of these compounds. Strong polarization of the C–Cl bond in the α-halo ether molecule occurs under the influence of the alkoxy group [6], leading to the increase of the positive charge on the carbon atom and to the decrease of its polarizability. According to Pearson's theory of hard and soft acids and bases [6], such a carbon atom becomes a more hard electrophile. An increase in the hardness of the electrophilic site of the alkylating agent facilitates the proceeding of reaction at the atom of the ambident anion, which possesses the greatest electron density [7]. Such a site in the ambifunctional NH–C=S group in 5-aryl-1,3,4-oxadiazole-2(3H)-thione molecule is the nitrogen atom.

Hence, we would expect that the reaction of these thiones with chloromethyl alkyl ethers should lead to N-substituted oxadiazolinethiones, whose analogs could not be obtained in the course of alkylation of these thiones by alkyl halides. The reactions of oxadiazolinethiones with chloromethyl alkyl ethers were carried out under the conditions of the alkylation of the same thiones by haloalkanes, namely, by heating a mixture of the reagents in dry acetone or acetonitrile in the presence of K_2CO_3 [1, 2]. 5-Aryl-1,3,4-oxadiazole-2(3H)-thiones (aryl = phenyl, 2-chlorophenyl, 2,4-dichlorophenyl, and 2-methoxyphenyl) were taken as the thiones. Chloromethyl methyl, chloromethyl ethyl, and chloromethyl 1-butyl ethers were used as the halo ethers. The reaction conditions were varied principally in the case of chloromethyl methyl ether (Table 1).



I–IVa–c

I–IV Ar = Ph (I): 2-ClC$_6$H$_4$ (II): 2,4-Cl$_2$C$_6$H$_3$ (III): 2-MeOC$_6$H$_4$ (IV): R = Me (a). C$_2$H$_5$ (b). *n*-C$_4$H$_9$ (c)

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TABLE 1. Alkylation of 5-Aryl-1,3,4-oxadiazole-2(3H)-thiones by Chloromethyl Methyl Ether*

Aryl	Solvent	Temperature, °C	Thione:halo ether ratio	Time, h	Reaction product	Yields of N-methoxymethyl derivatives Ia-IVa, % (rel. to thione taken)
Ph	Acetone	56	1:2	5	Ia	17
"	"	56	1:3	11	Ia	19
"	"	56	1:4	5	Ia	24
"	Acetonitrile	56	1:4	5	Ia	36
"	"	81	1:4	5	Ia	57
"	"	81	1:4	18	Ia	74
2-ClC_6H_4	Acetone	56	1:4	5	IIa	21
"	Acetonitrile	81	1:4	18	IIa	92
2,4-$Cl_2C_6H_3$	"	81	1:4	5	IIIa	32
"	"	81	1:4	18	IIIa	94
2$MeOC_6H_4$	"	81	1:4	18	IVa	92

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* Acceptor HCl–K_2CO_3.

Table 1 shows that the alkylation product yields depend mainly on the reaction conditions. The use of a more polar solvent – acetonitrile, the increase of temperature, or increase of reaction time leads to a sharp increase in the yield of the desired product. The nature of substituent in the benzene ring of 5-aryl-1,3,4-oxadiazole-2(3H)-thione also has some influence on the product yield. The yield in the absence of substituent is 74%, while the yield in the case of occurence 2-chloro and 2-methoxy groups in the phenyl substituent is 20% higher. The results of the reaction of

TABLE 2. Physicochemical Characteristics of 3-Alkoxy-5-aryl-1,3,4-oxadiazoline-2-thiones

Compound	Empirical formula	Found, % Calculated, % C	 H	 N	mp*, °C	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, δ, ppm
Ia	$C_{10}H_{10}N_2O_2S$	54.31 54.05	4.32 4.50	12.82 12.61	100-102	296 (3.75)	3.45 (3H, s, CH_3) 5.42 (2H, s, N–CH_2) 7.21-7.96 (5H, m, Ar)
IIa	$C_{10}H_9ClN_2O_2S$	46.57 46.78	3.72 3.51	11.18 10.92	95-96	297 (3.90)	3.50 (3H, s, CH_3) 5.47 (2H, s, N–CH_2) 7.25-8.00 (4H, m, Ar)
IIIa	$C_{10}H_8Cl_2N_2O_2S$	41.43 41.24	2.56 2.75	9.79 9.62	125-126	309 (3.95)	3.50 (3H, s, CH_3) 5.40 (2H, s, N–CH_2) 7.25-7.80 (3H, m, Ar)
IVa	$C_{11}H_{12}N_2O_3S$	52.60 52.38	4.95 4.76	11.40 11.11	156-158	314 (3.78)	3.49 (3H, s, CH_3) 3.76 (3H, s, Ar–OCH_3) 5.40 (2H, s, N–CH_2) 6.90-7.90 (4H, m, Ar)
Ib	$C_{11}H_{12}N_2O_2S$	56.13 55.93	5.76 5.08	11.72 11.86	Oil	295 (3.81)	1.20 (3H, t, CH_3) 3.78 (2H, q, CH_2) 5.52 (2H, s, N–CH_2) 7.45-8.18 (5H, m, Ar)
Ic	$C_{13}H_{16}N_2O_2S$	58.89 59.09	6.37 6.06	10.34 10.61	70-71	297 (3.72)	0.91 (3H, m, CH_3) 1.42 (4H, m, 2CH_2) 5.48 (2H, s, N–CH_2) 7.48-8.12 (5H, m, Ar)

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* Ia-IVa (from ethanol), Ic (from hexane).

5-phenyl-1,3,4-oxadiazole-2(3H)-thione with three different halo ethers show some tendency to the higher product yield in going from chloromethyl methyl ether (17% yield) to chloromethyl ethyl ether (44% yield) and chloromethyl butyl ether (33% yield).

The UV and PMR spectra are usually employed to identify the products as S- or N-alkyl derivatives. Our products have a UV absorption band at 296-314 nm, while the protons of the N–CH_2 group give PMR signals at 5.33-5.54 ppm in the PMR spectra (Table 2), which is characteristic of the N-derivatives [1, 2]. These results suggest that alkoxymethylation of the studied thiones, as expected, proceeds exclusively at the atom with greatest electron density, i.e., at the nitrogen atom, to give only 3-alkoxymethyl-5-aryl-1,3,4-oxadiazole-2(3H)-thiones in contrast to alkylation by alkyl halides, which proceeds predominantly at the sulfur atom. The S-alkyl derivatives could not be detected by either UV or PMR spectroscopy.

Similar results were obtained in the reaction of the potassium salts of oxadiazolinethiones with chloromethyl methyl ether. S-Derivatives were also not detected in the reaction products, while the yields of N-derivatives were somewhat lower than in the analogous reactions with free thione.

Thus, N-alkyl derivatives were obtained exclusively in the reaction of 5-aryl-1,3,4-oxadiazole-2(3H)-thiones with chloromethyl alkyl ethers in polar solvents. Replacing the thione by its potassium salt under analogous conditions does not alter the direction of the reaction.

EXPERIMENTAL

The UV spectra were taken on a Hitachi EPS-3T spectrometer, while the PMR spectra were taken on a Tesla BS-567 spectrometer at 100 MHz at 20-25°C in $CDCl_3$ with HMDS as the internal standard. The thin-layer chromatographic analysis was carried out on Silufol UV-254 plates using 24:1 chloroform–ethanol as the eluent and iodine vapors as the developer.

Samples of chloromethyl alkyl ethers were obtained according to the Henri–Litterscheid procedure [5].

General Alkylation Procedure. Mixture of 5-aryl-1,3,4-oxadiazole-2(3H)-thione (5 mmol), chloromethyl methyl ether (20 mmol; 10 mmol in the case of chloromethyl ethyl ether and chloromethyl butyl ether), and potassium carbonate (5 mmol) in dry acetone or acetonitrile (20-25 ml) was heated for 5-18 h (Table 1). The solvent was then removed from the reaction mixture and the residue was extracted with chloroform. The extract was washed with 10% aqueous NaOH to remove the unreacted thione and, then, with cold water until the wash water was neutral. The washed extract was dried over $CaCl_2$. The reaction products obtained after removal of chloroform were purified by recrystallization from ethanol or hexane.

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