DIRECTION OF ALKYLATION OF 5-ARYL-1,3,4-OXADIAZOLINE-2-THIONES

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The reaction of potassium salt of 5-(2,4-dichlorophenyl)-1,3,4-oxadiazoline-2-thione with dimethyl sulfate was carried out in water and HMPT. It was shown that the nature of the solvent affects the ratio of the formed products of S- and N-methylation. The alkylation of 5-aryl-1,3,4-oxadiazoline-2-thiones with isomeric butyl chlorides showed that the reaction takes place only with n-butyl chloride with the formation of the corresponding S-butyl-substituted derivative.

Methylation of a series of 5-aryl-1,3,4-oxadiazoline-2-thiones with various methylating agents has been described [1-4]. Radha Vakula and Srinivasan [1] carried out the methylation of the indicated thiones with dimethyl sulfate in an alkaline medium and thus obtained S-methyl derivatives exclusively. We studied the alkylation of thiones with methyl iodide and other alkyl halides under various conditions [3, 4]. Continuing these studies, we investigated the reaction of the potassium salt of 5-(2,4-dichlorophenyl)-1,3,4-oxadiazoline-2-thione (I) with dimethyl sulfate in a protic (water) and aprotic (HMPT) solvent. When the reaction was carried out in the HMPT medium (equimolar ratio of reactants, 60-80°C, 5 h) a mixture of products of S- (IIa) and N-methylation (IIIa) was obtained in a high yield (86% based on the thione used); the ratio IIa : IIIa (according to ESR data) was 85:15.



IIa, IIIa R = Me; Ar = $2,4-Cl_2C_6H_3$

When water was used, the total yield of the methyl-substituted derivatives IIa and IIIa was 89%, and the ratio IIa : IIIa was 95 : 5. The structure of the components of the mixture of S- or N-methylation products was determined by analyzing the data of ESR and UV spectra [3] of the pure compounds, isolated from the reaction mixture by column chromatography.

Thus the results obtained on silica gel show that in both variants studied, the total yield of the products was approximately the same, but the amount of the N-alkylation product when HMPT was used was three times that of the product used in the case of water. This is consistent with the known concept that an aprotic solvent promotes alkylation at the center of the highest electron density (rigid center) [5], which is the nitrogen atom in the ambidentate group NH-C=S. Such a course of the reaction was also observed in the case of methylation of salt I with methyl iodide in DMF or HMPT: under these conditions, formation of an appreciable amount of N-substituted product was also noted [3].

We also showed that the direction of the reaction depends on both the nature of the solvent and the character of the alkylating agent. In the case of methylation of salt I with methyl iodide or dimethyl sulfate in HMPT under identical conditions, the fraction of the product of N-alkylation is greater when dimethyl sulfate is used, this being due to its higher reactivity.

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To further elucidate the influence of the nature of the alkylating agent (character of the departing group, branching of the alkyl) on the direction of the reaction, we studied the reaction of 5-aryl-1,3,4-oxadiazoline-2-thiones (IVa-c) with methyl tosylate (MeOTs) and isomeric butyl chlorides.

It is well known that the lower the polarizability and higher the electronegativity of the departing group of the alkylating agent, the more product is formed at the rigid center of the ambidentate group [5]. Thus, in the case of methylation of benzothiazoline-2-thione with agents MeX (X = Cl, Br, I, OTs) in the presence of sodium hydride in THF, Halasa and Smith [6] showed that the yield of N-methylbenzthiazoline-2-thione increases in the series MeI < MeBr < MeCl < MeOTs. On the basis of the above, we assumed that in the reaction of 5-(2,4-dichlorophenyl)-1,3,4-oxadiazoline-2-thione (IVa) with methyl tosylate (5-hour boiling in dry acetone in the presence of K_2CO_3), an appreciable amount of N-methylation product IIIa should be formed. Indeed, the alkylation product which we obtained in a practically quantitative yield (96%) contained 90-92% of compound IIa and 10-8% of compound IIIa, this being several times the amount of the latter formed by methylation of the same thione with methyl iodide under analogous conditions (1-2%) [4].

Alkylation of 5-aryl-1,3,4-oxadiazoline-2-thione IVa-c with isomeric butyl chlorides (Va-c) takes place with much more difficulty.



IV a Ar = 2,4-Cl₂C₆H₃, b Ar = 2-ClC₆H₄, c Ar = Ph; V a R = n-Bu, b R = sec - Bu, c R = tert-Bu; II, III, b-d R = n-Bu, b Ar = 2,4-Cl₂C₆H₃, c Ar = 2-ClC₆H₄, d Ar = Ph; IIe IIIe R = sec-Bu, Ar = Ph

Thus under conditions analogous to those of methylation with methyl tosylate, the reaction takes place only in the case of n-butyl chloride. The yields of the products in this case are 21-37%, and the alkylation takes place mainly at the sulfur atom (based on the ESR and UV spectra), while the N-butyl derivative was detected in trace amounts (TLC) [4]. In attempts to carry out the reaction with secondary and tertiary butyl chloride, the product was sometimes observed in the form of a faint spot under TLC conditions, but it could not be separated from the reaction mixture. Only for thione IIIc of sec-butyl chloride in acetonitrile was it possible to obtain in a 10% yield a product in the form of an oil which, according to TLC data (24:1 chloroform – ethanol), consisted of two compounds with $R_f 0.83$ and 0.92. According to the data of ESR and UV spectra, the main product of alkylation at the sulfur atom is 2-(sec-butylthio)-5-phenyl-1,3,4-oxadiazoline Vc.

Certain conclusions can thus be drawn from the results obtained: in the case of methylation of oxadiazolinethiones with dimethyl sulfate, the reaction takes place primarily at the sulfur atom; the amount of N-methyl-substituted product increases with decreasing polarity of the solvent, and when a harsher alkylating agent, methyl tosylate, is used.

EXPERIMENTAL

The UV spectra were recorded on an EPS-3T Hitachi spectrometer in ethanol, the ESR spectra were recorded on a Tesla BS-567 instrument (100 MHz) at 20-25°C, the solvent was $CDCl_3$, and the internal standard was HMDS. The TLC analysis was carried out on Silufol UV-254 wafers, the eluent was 24:1 chloroform—ethanol, and the developer was iodine vapor. Separation of the products from the reaction mixture was carried out on a column packed with Chemapol 100/250 μ m silica gel to the ratio of silica gel to the mixture being separated was 60:1), with 10:1 hexane—chloroform as the eluent. Thiones IVa-c were synthesized as described in [7], and salt I was obtained by the usual method [3].

Reaction of K Salt of 5-(2,4-Dichlorophenyl)-1,3,4-oxadiazoline-2-thione with Dimethyl Sulfate. A mixture of 0.71 g (2.5 mmole) of potassium salt I and 0.23 g (2.5 mmole) of dimethyl sulfate in 20 ml of HMPT or water is agitated on a water bath agitated on a water bath (60-80°C) for 5 h. When HMPT is used, the reaction mixture is then poured into a beaker containing ice, and the precipitate formed is filtered off and extracted with chloroform. The extract obtained is washed several times with 10% aqueous NaOH (to remove the unreacted salt I), then with cold water to a neutral reaction, dried on CaCl₂,

and evaporated. A mixture of products IIa and IIIa is obtained in an amount of 0.56 g (86%). When water is used, the reaction mixture at the end of the reaction is cooled, the precipitate formed is filtered off, and the subsequent treatment is carried out as described above. There is obtained 0.58 g (89%) of a mixture of compounds IIa and IIIa. UV spectrum, λ_{max} : 281 (S-Me), 310 nm (N-Me). ESR spectrum: 2.74 and 3.75 (3H, s.s, SMe and NMe); 7.25-7.91 ppm (3H, m, H_{arom}).

Reaction of 5-Aryl-1,3,4-oxadiazoline-2-thiones IVa-c with Methyl Tosylate and Isomeric Butyl Chlorides. A mixture of 5 mmole of thione IVa-c, 5 mmole of methyl tosylate or 10 mmole of chloride Va-c, and 5 mmole of K_2CO_3 is boiled for 5 h in 20 ml of dry acetone. After the acetone is removed, the residue is treated as described above. In the case of alkylation with methyl tosylate from 1.23 g (5 mmole) of thione IVa, there is obtained 1.24 g (96%) of a mixture of products IIa and IIIa (IIa:IIIa ~9:1). UV spectrum, λ_{max} : 280 nm. ESR spectrum: 2.75 (3H, s, Me); 7.24-7.9 ppm (3H, m, H_{arom}).

From 0.89 g (5 mmole) of thione IVc and 1.1 ml (10 mmole) of sec-butyl fluoride Vb there is obtained 0.1 g (10%) of product IIe. UV spectrum, λ_{max} : 273 nm. ESR spectrum: 0.98 (6H, m, 2Me); 1.9 (2H, m, CH₂); 3.16 (1H, m, SCH); 7.45-7.9 ppm (5H, m, H_{arom}).

The preparation of products IIb-d and IIIb-d is described elsewhere [4].

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