# SYNTHESIS OF 5-(4,6-DIMETHYL-2-PYRIMIDINYL)-1,3,4-OXADIAZOLE-2-THIONE AND ITS ALKYLATION, AMINOMETHYLATION, AND ACYLATION

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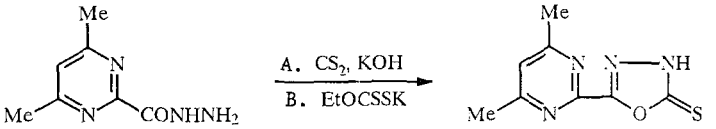
*The reaction of the hydrazide of 4,6-dimethyl-2-pyrimidinecarboxylic acid with potassium ethylxanthate gave 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione. The alkylation of this product in an alkaline medium proceeds at the sulfur atom, while the aminomethylation and acylation proceed at the nitrogen atom. The major criterion for the structure of the S- and N-derivatives is the chemical shift of $C_{(2)}$ in the 1,3,4-oxadiazole ring in the $^{13}C$ NMR spectra.*

Derivatives of 1,3,4-oxadiazole-2-thione display various types of biological activity, including bactericidal [1-13], antimicotic [4], anti-inflammatory [5], hypotensive [5], and anticonvulsant activity [6]. A number of 1,3,4-oxadiazole-2-thione derivatives have fungicidal activity [7-9]. 5-Substituted 1,3,4-oxadiazole-2-thiones are also interesting since they may exist as ambident anions in alkaline medium and display dual reactivity, which has not been studied sufficiently.

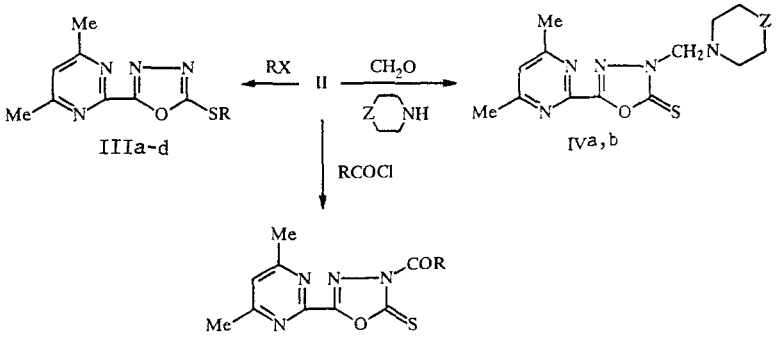
In a continuation of a study of 5-pyrimidinyl-1,3,4-oxadiazoles [10, 11], we have developed a convenient synthesis for 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) and investigated its alkylation, aminomethylation, and acylation.

5-(4,6-Dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) was obtained by two procedures: by the reaction of the hydrazide of 4,6-dimethyl-2-pyrimidinylcarboxylic acid (I) with carbon disulfide in the presence of KOH (method A, usually employed in the synthesis of 5-substituted 1,3,4-oxadiazole-2-thiones [12]) and with potassium ethylxanthate (method B). Method B gives a higher yield than method A (87% vs. 64%). Furthermore, there is no need to work with dangerous carbon disulfide in method B.




I II

Product II in the solid state exists as the thione form as indicated by its IR spectrum, displaying bands for NH (3192) and C=S groups (1332) but lacking a band at 2600-2500 $cm^{-1}$ (SH stretching vibrations). The finding of these bands is in accord with the data of Ainswort [12] for various 5-substituted 1,3,4-oxadiazole-2-thiones.




IIIa-d IVa,b

V a,b

III, V a R = Me; III/b R = $C_6H_5CH_2$, c R = $CH_3OCOCH_2$, d R = $C_6H_5COCH_2$;
IV a Z = $CH_2$, b Z = O; V b R = Ph

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TABLE 1. Alkylation of 5-(4,6-Dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) by Methyl Bromoacetate

| Reaction conditions (reflux, h) | Yield of IIIc, % |
|---|---|
| $K_2CO_3$, acetone (15) | 14 |
| $K_2CO_3$, DMFA* (1) | 43 |
| $C_2H_5ONa$, ethanol (12) | 43 |
| $(C_2H_5)_3N$, ethanol (1) | 85 |

*18-20°C.

TABLE 2. Indices of Products II-V

| Compound | mp, °C | IR spectrum, ν, $cm^{-1}$ | | | | Yield, % |
|---|---|---|---|---|---|---|
| | | C–O–C | C=S | C=N | C=O | |
| II* | 244...245 | 1160 | 1312 | 1592 | | 64 (A)<br>87 (B) |
| IIIa | 160...161,5 | 1156 | | 1596 | | 67 |
| IIIb | 129...131,5 | 1152 | | 1592 | | 79 |
| IIIc | 149...150 | 1156 | | 1594 | 1750 | 85 |
| IIId | 158...160 | 1156 | | 1596 | 1680 | 45 |
| IVa | 139...141 | 1180 | 1325 | 1590 | | 40 |
| IVb | 176...177 | 1165 | 1324 | 1586 | | 49 |
| Va | 213...216 | 1160 | 1328 | 1592 | 1766 | 58 |
| Vb | 164...167 | 1186 | 1334 | 1592 | 1726 | 57 |

*$\nu_{NH}$ in the IR spectrum is at 3192 $cm^{-1}$.

The selection of the best base and solvent was checked for the alkylation of II by methyl bromoacetate. Table 1 shows that the best yield was obtained in ethanol using triethylamine as the base. The low yields when stronger bases are used probably result from side reactions accompanying the alkylation [13]. Under the conditions found, the alkylation of II using other alkylating agents proceeded with satisfactory yields.

Oxadiazolethione II undergoes aminomethylation upon reaction with formaldehyde and piperidine or morpholine in ethanol at room temperature.

The highest yields in the acylation of II by acetyl or benzoyl chloride were obtained in acetonitrile in the presence of triethylamine.

Only one isomer was isolated in all the cases of alkylation, aminomethylation, and acylation of II examined.

The available information in the literature [1-9, 14-16] on the structure of the products of alkylation [1-3, 8, 9, 15, 16], aminomethylation [3, 4, 6-8, 14], and acylation [16] of 5-substituted 1,3,4-oxadiazole-2-thiones is contradictory in nature and the assigned structures are questionable in some cases. Thus, the products of the alkylation and acylation of 5-aryl-1,3,4-oxadiazole-2-thiones were identified as S-derivatives [16], while the products of the alkylation and aminomethylation of 5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thione were identified as N-derivatives [8]. However, no proof for these assignments was given.

Comparison of the IR spectra of III and IV (Table 2) shows a strong band at 1324-1334 $cm^{-1}$, which was assigned, in accord with starting 1,3,4-oxadiazole-2-thione II, to C=S stretching vibrations and is characteristic for nitrogen-substituted derivatives IV and V.

The chemical shifts of the methylene group signals are most important in establishing the structure of III and IV using PMR spectroscopy. The $SCH_2$ group signal for IIIb and IIIc appears at 4.12-4.93 ppm, while the position of the $NCH_2$ group signal for IVa and IVb is shifted somewhat downfield (Table 3). However, the major information permitting us unequivocally to establish the structure of the S-derivatives III and N-derivatives IV and V is provided by $^{13}C$ NMR spectroscopy (Table 4).

TABLE 3. PMR Spectra of II-V

| Compound | Chemical shifts, δ, ppm, in $CDCl_3$* | | | |
|---|---|---|---|---|
| | pyrimidine ring | | 1,3,4-oxadiazole ring | |
| | 4,6-$CH_3$ (6H, s) | 5-H (1H, s) | $SCH_2$ (2H, s) | other signals |
| II | 2,65 | 7,53 | | |
| IIIa | 2,5 | 7,03 | | 2,7 (3H, s, $SCH_3$) |
| IIIb | 2,5 | 7,4 | 4,13 | 6,65...7,00 (5H, m, $C_6H_5$) |
| IIIc | 2,5 | 7,05 | 4,12 | 3,8 (3H, s, $OCH_3$) |
| IIId | 2,45 | 7,00 | 4,93 | 7,13...8,00 (5H, m, $C_6H_5$) |
| IVa | 2,43 | 6,95 | 4,95** | 1,25...1,75 (6H, m, $CH_2$); 2,55...2,8 (4H, m, $N(CH_2)_2$) |
| IVb | 2,54 | 7,13 | 5,06** | 2,66...2,9 (4H, m., $N(CH_2)_2$); 3,5...3,7 (4H, m, $O(CH_2)_2$) |
| Va | 2,43 | 7,3 | | 1,83 (3H, s, $CH_3$) |
| Vb | 2,57 | 7,16 | | 7,23...8,05 (5H, m, $C_6H_5$) |

*The spectra of II and Va were taken in DMSO-$d_6$, while the spectrum of IIIb was taken in $CF_3CO_2H$.

**Signal for the $NCH_2$ group (2H, s).

TABLE 4. $^{13}C$ NMR Spectra of II-V

| Compound | Chemical shifts, δ, ppm, in $CDCl_3$ | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | pyrimidine ring | | | | 1,3,4-oxadiazole ring | | | | | |
| | $C_{(2)}$ | $C_{(4,6)}$ | $C_{(5)}$ | 4,6-$CH_3$ | $C_{(2)}$ | $C_{(5)}$ | $SCH_2$ | $NCH_2$ | CO | other signals |
| II | 151,8 | 167,6 | 121,6 | 23,3 | 178,1 | 159,6 | | | | |
| IIIa | 151,8 | 167,7 | 121,0 | 23,7 | 166,9 | 163,8 | | | | 14,33 ($SCH_3$) |
| IIIb | 151,5 | 167,6 | 121,4 | 23,3 | 164,9 | 163,7 | 35,9 | | | 127,8; 128,5; 129,0; 136,1 ($C_6H_5$) |
| IIIc | 150,6 | 167,8 | 121,2 | 23,7 | 165,6 | 161,4 | 33,9 | | 173,4 | 52,8 ($OCH_3$) |
| IIId | 152,4 | 167,9 | 121,2 | 23,7 | 165,6 | 162,6 | 41,5 | | 191,8 | 128,3; 128,6; 133,9; 134,4 ($C_6H_5$) |
| IVa | 151,5 | 167,8 | 121,3 | 23,7 | 179,1 | 157,2 | | 71,5 | | 23,3 ($CH_2$); 25,6 ($2CH_2$); 51,3 ($N(CH_2)_2$) |
| IVb | 151,2 | 167,9 | 121,5 | 23,7 | 178,8 | 157,2 | | 70,3 | | 50,4 ($N(CH_2)_2$); 66,5 ($O(CH_2)_2$) |
| Va | 151,2 | 167,9 | 121,7 | 23,3 | 177,0 | 156,0 | | | 171,8 | 20,9 ($CH_3$) |
| Vb | 151,8 | 168,2 | 122,2 | 23,6 | 178,8 | 156,6 | | | 170,6 | 128,3; 129,9; 130,8; 133,9 ($C_6H_5$) |

*The spectra of II, IIIb, and Va were taken in DMSO-$d_6$.

The characteristic signals used for distinguishing between these compounds are the signals of the carbon atom of the C–S group ($C_{(2)}$), which are found in two narrow ranges: 164.9-166.9 and 177.0-179.1 ppm. The former group of signals corresponds to $C_{(2)}$ of S-derivatives IIIa-IIId, while the latter group corresponds to $C_{(2)}$ thione carbon of the N-derivatives. The chemical shift for $C_{(2)}$ of starting compound II is also found at 177.0-179.1 ppm, which indicates that it exists in solution in the thione form. Furthermore, a significant difference in the chemical shifts of the methylene carbon in the side chain is observed in the $^{13}C$ NMR spectra of IIIb-IIId vs. IVa and IVb. Thus, the $SCH_2$ signal in the spectra of S-derivatives IIIb-IIId appears at 33.9-41.5 ppm, while the $NCH_2$ signal in the spectra of N-derivatives IVa and IVb is seen at 70.3-71.5 ppm.

Hence, the alkylation of 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) proceeds at the sulfur atom, while aminomethylation and acylation proceed at the nitrogen atom. These findings may be explained in the framework of the theory of hard and soft acids and bases [17]. The alkyl halide is a relatively soft (readily polarizable) electrophile and, thus, attacks

the softer nucleophilic site, namely, the sulfur atom. On the other hand, formaldehyde in the first step of the Mannich reaction and acyl halide are harder electrophiles than alkyl halides and attack the harder reaction site, namely, the nitrogen atom.

Comparison of the chemical shifts for the methylene group in the PMR spectra of the aminomethylated (4.9-5.9 ppm) and alkylated derivatives (2.9-4.2 ppm) of 5-(2,4-dichlorophenyl)-1,3,4-oxadiazole-2-thione [8] with our present data (Table 3) indicates that Goswami et al. [8] incorrectly identified these alkylation products as N-derivatives.

The compounds synthesized were tested as anti-inflammatory agents by Dr. P. Gaidyalis at the Laboratory for Drug Synthesis and Testing Laboratory of Vilnius University. Products IIIa and IIIc displayed weak anti-inflammatory activity.

## EXPERIMENTAL

The reaction course and purity of the compounds were monitored on Silufol plates. The IR spectra were taken on a Karl Zeiss (Jena) Specord M80 spectrometer for KBr pellets. The $^1$H NMR spectra were taken on a Tesla BS 487C spectrometer at 80 MHz using HMDS as the internal standard, while the $^{13}$C NMR spectra were taken on a Tesla 587A spectrometer at 20 MHz.

The elemental analysis data for C, H, and N corresponded to the calculated values.

Hydrazide I was synthesized according to our previous procedure [18].

**5-(4,6-Dimethyl-2-pyrimidinyl)1,3,4-oxadiazole-2-thione (II, $C_8H_8N_4OS$). A.** A solution of 1.17 g (30 mmoles) potassium hydroxide in 6 ml water and 2.66 g (2.0 ml, 35 mmoles) carbon disulfide were added to a solution of 5 g (30 mmoles) hydrazide of 4,6-dimethyl-2-pyrimidinecarboxylic acid (I) in 100 ml ethanol and the mixture was heated at reflux for 6 h. Then 50 ml solvent was distilled off and 200 ml water was added. The mixture was acidified to pH 4 by the addition of concentrated hydrochloric acid. The precipitate was filtered off, washed with water, dried, and crystallized from ethanol. The yield of II was 4.0 g (64%).

**B.** A sample of 4.95 g (30 mmoles) potassium ethylxanthate was added to a solution of 5 g (30 mmoles) hydrazide I in 100 ml ethanol and heated at reflux for 6 h. The product was isolated according to procedure A. The yield of II was 5.45 g (87%).

**5-(4,6-Dimethyl-2-pyrimidinyl)-2-(methoxycarbonylmethylthio)-1,3,4-oxadiazole (IIIc, $C_{11}H_{12}N_4O_3S$). A.** A reaction mixture consisting of 1.04 g (5 mmoles) 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II), 0.69 g (5 mmoles) freshly roasted potassium carbonate, 50 ml dry acetone, and 0.76 g (0.46 ml, 5 mmoles) methyl bromoacetate was heated at reflux for 15 h on a steam bath and cooled. The precipitate was filtered off and recrystallized from ethanol. The yield of IIIc was 0.2 g (14%).

**B.** A sample of 0.76 g (0.46 ml, 5 mmoles) methyl bromoacetate was added dropwise to a solution of 1.04 g (5 mmoles) 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) and 0.69 g (5 mmoles) freshly roasted potassium carbonate in 30 ml absolute dimethylformamide. The mixture was stirred at room temperature for 1 h. Dimethylformamide was distilled off in vacuum to leave a dry residue, which was washed with diethyl ether and crystallized from ethanol. The yield of IIIc was 0.6 g (43%).

**C.** A sample of 1.1 g (5.2 mmoles) 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) was dissolved in absolute ethanol at reflux. Then a sodium ethylate solution prepared by adding 0.12 g (5.2 mmoles) metallic sodium to 4 ml absolute ethanol was added to the solution. A sample of 0.95 g (0.58 ml, 6.3 mmoles) methyl bromoacetate was added dropwise to the reaction mixture, which was then heated at reflux for 12 h and cooled. The precipitate was filtered off and crystallized from ethanol. The yield of IIIc was 0.6 g (43%).

**General Method for the Alkylation of 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II).** A sample of 1.0 g (4.8 mmoles) 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) was dissolved in 22 ml absolute ethanol. A sample of 0.49 g (0.67 ml, 4.8 mmoles) dry triethylamine and 5.8 mmoles of the corresponding alkyl halide were added to the cooled solution. The mixture was heated at reflux for 1 h (in the case of alkylation using ω-bromoacetophenone, 9 h) and cooled. The crystalline precipitate was filtered off. Product IIIa ($C_9H_{10}N_4OS$) was crystallized from ethyl acetate. Product IIIb ($C_{15}H_{14}N_4OS$) was crystallized from ethanol. Product IIId ($C_{16}H_{14}N_4O_2S$) was crystallized from methanol.

**3-Aminomethyl-5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thiones (IVa, $C_{14}H_{19}N_5OS$ and IVb, $C_{13}H_{17}N_5O_2S$).** A sample of 1.0 g (4.8 mmoles) 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) was dissolved in 50 ml hot ethanol. Then 0.54 ml (7.2 mmoles) 40% formalin and 4.8 mmoles of the corresponding amine (0.47 ml piperidine or 0.42 ml morpholine) were added to the cooled solution. The mixture was stirred at room temperature for 3 h.

The residue was filtered off and crystallized. The yield of IVa was 0.6 g (40%) (from 2-propanol). The yield of IVb was 0.72 g (49%) (ethanol).

**3-Acyl-5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thiones (Va, $C_{10}H_{10}N_4O_2S$ and Vb, $C_{15}H_{12}N_4O_2S$).** A sample of 1.0 g (4.8 mmoles) 5-(4,6-dimethyl-2-pyrimidinyl)-1,3,4-oxadiazole-2-thione (II) was dissolved in 150 ml hot absolute acetonitrile. A sample of 0.49 g (0.67 ml, 4.8 mmoles) dry triethylamine and 5.8 mmoles acyl halide (0.41 ml acetyl chloride or 0.67 ml benzoyl chloride) were added to the cooled solution. The mixture was stirred with a magnetic stirrer at room temperature for 2 h. The solvent was distilled off on a rotary evaporator to leave a dry residue. In the case of Va, the residue was washed with acetonitrile and crystallized from acetonitrile. The yield of Va was 0.7 g (58%). In the case of Vb, the residue was extracted with acetone. The extract was evaporated to dryness on a rotary evaporator and the residue was crystallized from chloroform–ether to give 0.85 g Vb (57%).

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