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Targeted synthesis and in vitro bactericidal and fungicidal activities of 2-alkylthio-5-(p-aminophenyl)-1,3,4-oxadiazoles

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5-(p-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione, selective alkylation, S-alkyl derivatives, fungicidal and bactericidal activity, spectral characterization

Abstract: Selective alkylation of 5-(p-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione with alkyl halides have been studied. It was revealed that alkylation goes on more polarized thiogroup in position 2 and corresponding 2-alkylthio-1,3,4-oxadiazoles were obtained in high yields. Structure of novel synthesized compounds confirmed by physical methods of research as UV-, IR- and ^{1}H NMR-spectroscopy. Primary in vitro biological activity have been studied and it was found that all obtained S-alkyl derivatives have weak activity against bacteria *Xanthomonas malvacearum* and fungicidal activity against fungi *Fusarium oxysporum*.

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INTRODUCTION

A wide variety of structures with different properties, including biological activity are very attractive for researchers, who studied a chemistry of substituted 1,3,4-oxadiazol-2-thiones [Kishore et al., 2010; Macaev et al., 2011; Sahu et al., 2011; Husain and Ajmal, 2009] and their six- membered analogues [Levkovich et al., 2016; Khodjaniyazov et al., 2016]. The structural features of 5-aryl-1,3,4-oxadiazol-2-thiones are possibility of them in the difference tautomeric forms in the presence of SH- or NH- group; it makes possible to produce derivatives of one or the other nucleophilic centers depending on the condition of interaction and a nature of the reacting electrophilic agents. As is known, aminobenzoic acid derivatives (alkyl ester and hydrazide) are convenient and available substances for the synthesis of various classes of compounds, including 5-substituted-1,3,4-oxadiazol-2-thiones [Zhakina et al., 2007].

The aim of this work is to study the alkylation of 5-(p-aminophenyl)-1,3,4-oxadiazol-2 (3H)-thione with alkyl halides in C_1-C_9 homological series, the influence of the nature of the alkylating agent (length, branched alkyl radical) on the yield and interaction directions, establishing physic-chemical properties and structure, as well as in vitro primary biological screening of synthesized S-alkyl derivatives.

MATERIALS AND METHODS

^{1}H NMR spectra was recorded in DMSO-d6 and $CDCl_3$, on Varian 400-MR spectrometer operating accordingly at 400 MHz. Hexamethyldisiloxane (HMDSO) was used as internal standard, chemical shift δ of ^{1}H was recorded in ppm.

Mps were measured on a Boetius and were uncorrected. IR spectra were recorded on IR Fury System 2000 (Perkin-Elmer) as KBr pellets, UV spectra were recorded on a Lambda-16 spectrometer Perkin Elmer in ethanol.

The reactionary process was monitored by TLC on Whatman UV-254 precoated aluminum plates and Merck silicagel 60F254 using $CHCl_3$ - EtOH, 24: 1 system and developed plates were visualized under UV lamp and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 and concentrated with a RVO-64 ROT VAC Evaporator at reduced pressure.

Synthesis of 5-(p-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione (1)

A mixture of 50 mmol of p-aminobenzoic acid hydrazide and 50 mmol of potassium ethyl xanthate was dissolved in 150 ml of ethanol and refluxed 10 hours. Solvent was distilled off, the residue was diluted with water, acidified with hydrochloric acid up to pH=5-6. The resulting residue was filtered, washed with water and dried in air. After recrystallization from ethanol the reaction product **1** has been obtained in high yield.

Yield: 92 %, mp 242-243^{0}C, R_f=0.49. H^1 NMR (DMSO-d_6): 4.36 (2H, bs, NH_2), 6.67 (2H, d, H_{Ar}-3,5), 7.51 (2H, d, H_{Ar}-2,6), 14.42 (1H, bs, NH). IR (KBr) cm^{-1}: 3063 (ν_{NH}), 1348 ($\nu_{C=S}$), 1170 (ν_{C-O-C}). UV (λmax, nm): 261, 318.

Alkylation of 5-(p-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione (1) with alkyl halides (General procedure).

The equmolar mixture of 5 mmol oxadiazolthione (**1**), alkyl halide and K_2CO_3 (in the case of methyl iodide, 10 mmol) was heated in 15 ml dry acetone

for 4-5 hours. The solvent was removed; the residue was placed in a funnel with glass filter and washed with NaOH solution to remove of unreacted thione (**1**), washed with water until neutral medium, dried and the desired S-alkyl products have been obtained.

2-Methylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (2)

Yield: 90%, mp 114-115°C, R_f=0.33. ^{1}H NMR ($CDCl_3$): 2.67 (3H, t, CH_3), 4.11 (2H, bs, NH_2), 6.64 (2H, d, H_{Ar}-3,5), 7.72 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3313 (ν_{NH2}), 1178 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 314.

2-Ethylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (3)

Yield: 90%, mp 101-102°C, R_f=0.57. ^{1}H NMR ($CDCl_3$): 1.43 (3H, t, CH_3), 3.22 (2H, q, S-CH_2CH_3), 3.99 (2H, bs, NH_2), 6.65 (2H, d, H_{Ar}-3,5), 7.72 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3312 (ν_{NH2}), 1174 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 311.

2-Propylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (4)

Yield: 98%, mp 111-112°C, R_f=0.38. ^{1}H NMR ($CDCl_3$): 1.00 (3H, t, CH_3), 1.79 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.17 (2H, t, S-CH_2), 4.06 (2H, brs , NH_2), 6.65 (2H, d, H_{Ar}-3,5), 7.71 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3324 (ν_{NH2}), 1172 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 312.

2-Butylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (5)

Yield: 97%, mp 119-120°C, R_f=0.51. ^{1}H NMR ($CDCl_3$): 0.89 (3H, t, CH_3), 1.42 (2H, m, $CH_2CH_2C\underline{H}_2CH_3$), 1.74 (2H, m, $CH_2C\underline{H}_2CH_2CH_3$), 3.20 (2H, t, S-$CH_2$), 4.03 (2H, bs, NH_2), 6.65 (2H, d, H_{Ar}-3,5), 7.72 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3345 (ν_{NH2}), 1177 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 311.

2-Pentylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (6)

Yield: 90%, mp 98-99°C, R_f=0.53. ^{1}H NMR ($CDCl_3$): 0.84 (3H, t, CH_3), 1.37 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.76 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 3.18 (2H, t, S-$C\underline{H}_2CH_2CH_2CH_2CH_3$), 4.05 (2H, bs, NH_2), 6.65 (2H, d, H_{Ar}-3,5), 7.71 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3342 (ν_{NH2}), 1176 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 311.

2-Isopentylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (7)

Yield: 94%, mp 86-87°C, R_f=0.53. ^{1}H NMR ($CDCl_3$): 0.88 (6H, d, $2CH_3$), 1.66 (3H, m, $C\underline{H}_2C\underline{H}(CH_3)_2$), 3.20 (2H, m, S-$C\underline{H}_2CH_2CH(CH_3)_2$), 4.07 (2H, bs, NH_2), 6.64 (2H, d, H_{Ar}-3,5), 7.71 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3330 (ν_{NH2}), 1180 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 312.

2-Hexylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (8)

Yield: 97%, mp 97-98°C, R_f=0.68. ^{1}H NMR ($CDCl_3$): 0.82 (3H, t, CH_3), 1.24 (4H, m, $C\underline{H}_2C\underline{H}_2CH_3$), 1.39 (2H, m, $C\underline{H}_2CH_2CH_2CH_3$), 1.75 (2H, m, $C\underline{H}_2(CH_2)_3CH_3$), 3.19 (2H, t, S-$C\underline{H}_2(CH_2)_4CH_3$), 3.72 (2H, bs, NH_2), 6.65 (2H, d, H_{Ar}-3,5), 7.71 (2H, d, H_{Ar}-2.6). IR (KBr) cm^{-1}: 3309 (ν_{NH2}), 1170 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 311.

2-Heptylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (9)

Yield: 96%, mp 79-80°C, R_f=0.63. ^{1}H NMR ($CDCl_3$): 0.81 (3H, t, CH_3), 1.22 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 1.37 (2H, m, $C\underline{H}_2(CH_2)_3CH_3$), 1.75 (2H, m, $C\underline{H}_2(CH_2)_4CH_3$), 3.19 (2H, t, S-$C\underline{H}_2(CH_2)_5CH_3$), 4.04 (2H, bs, NH_2), 6.64 (2H, d, H_{Ar}-3,5), 7.71 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3353 (ν_{NH2}), 1176 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 313.

2-Octylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (10)

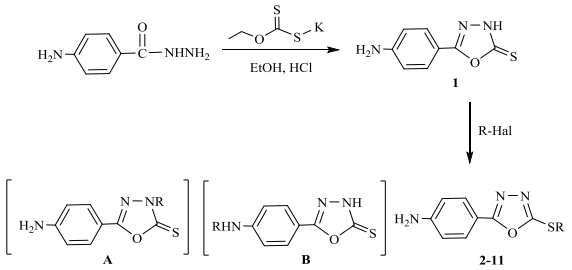
Yield: 97%, mp 72-73°C, R_f=0.63. ^{1}H NMR ($CDCl_3$): 0.81 (3H, t, CH_3), 1.21 (8H, m, $C\underline{H}_2(CH_2)_3CH_3$), 1.38 (2H, $C\underline{H}_2(CH_2)_4CH_3$), 1.75 (2H, m, $C\underline{H}_2(CH_2)_5CH_3$), 3.19 (2H, t, S-$C\underline{H}_2(CH_2)_6CH_3$), 4.04 (2H, bs, NH_2), 6.64 (2H, d, H_{Ar}-3,5), 7.71 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3318 (ν_{NH2}), 1182 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 310.

2-Nonylthio-5-(p-aminophenyl)-1,3,4-oxadiazole (11)

Yield: 98%, mp 83-84°C, R_f=0.58. ^{1}H NMR ($CDCl_3$): 0.81 (3H, t, CH_3), 1.19 (10H, m, $C\underline{H}_2(C\underline{H}_2)_4CH_3$), 1.38 (2H, m, $C\underline{H}_2(CH_2)_5CH_3$), 1.75 (2H, m, $C\underline{H}_2(CH_2)_6CH_3$), 3.19 (2H, t, S-$C\underline{H}_2(CH_2)_7CH_3$), 4.02 (2H, bs, NH_2), 6.64 (2H, d, H_{Ar}-3,5), 7.71 (2H, d, H_{Ar}-2,6). IR (KBr) cm^{-1}: 3317 (ν_{NH2}), 1182 ($\nu_{C\text{-}O\text{-}C}$). UV (λmax, nm): 312.

RESULTS AND DISCUSSION

Cyclization of p-amino benzoic acid hydrazide and potassium ethyl xanthate 5-(p-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione (**1**) was synthesized in high (92%) yield. Alkylation of thione **1** with alkyl halides carried out by reflux in acetone (in the presence of K_2CO_3) in a ratio of reactants - thione: alkyl halide: K_2CO_3 - 1:1:1 (in the case of CH_3I - 1:2:1):



It should be noted that the alkylation products of the nitrogen atom in position 3 (**A**) or exocyclic amino group (**B**) are not formed.

The reactions occur in high yields (90-98%) of the corresponding desired products. Relatively smaller yield (90%) observed in the cases of methyl iodide, ethyl iodide and pentyl bromide. Studying of IR- and ^{1}H NMR - spectra of the products showed that the reaction proceeds only at the S-center to give 2-alkylthio-5-(p-aminophenyl)-1,3,4-oxadiazoles **2-**

Table 1. Yields and R in compounds **2-11**

№	Starting compounds		R	Product	Empiric formula	Yield, %
	Thione	**Alkyl halide**				
1	**1**	Methyl iodide	CH_3	**2**	$C_9H_9N_3OS$	90
1	**1**	Ethyl iodide	C_2H_5	**3**	$C_{10}H_{11}N_3OS$	90
2	**1**	Propyl iodide	C_3H_7	**4**	$C_{11}H_{13}N_3OS$	98
3	**1**	Butyl iodide	C_4H_9	**5**	$C_{12}H_{15}N_3OS$	97
4	**1**	Pentyl bromide	C_5H_{11}	**6**	$C_{13}H_{17}N_3OS$	90
5	**1**	i-Pentyl iodide	i-C_5H_{11}	**7**	$C_{13}H_{17}N_3OS$	94
6	**1**	Hexyl iodide	C_6H_{13}	**8**	$C_{14}H_{19}N_3OS$	97
7	**1**	Heptyl iodide	C_7H_{15}	**9**	$C_{15}H_{21}N_3OS$	96
8	**1**	Octyl iodide	C_8H_{17}	**10**	$C_{16}H_{23}N_3OS$	97
9	**1**	Nonyl iodide	C_9H_{19}	**11**	$C_{17}H_{25}N_3OS$	98

11; so in the IR-spectra there is no band corresponding to C=S (1345-1380 cm^{-1}) [Vijayaraghavan et al., 2009; Ebtehal et al., 2014], and in the ^1H NMR spectra are observed the presence of S-CH_2 proton signals as singlets in the field of 2.67-3.20 ppm and absence of N-CH_2 group signals [Ziyaev et al., 2012]. There are in ^1H NMR-spectra of all synthesized compounds **2-11** the aromatic proton signals with chemical shift in the range of 6.34-7.71 ppm, NH_2- group signals (br s) are in the range of 3.72-4.10 ppm which also confirmed the structure of the obtained substances. The absorption maximum of the synthesized compounds in the UV spectra corresponds to the literature data for the S- alkyl derivatives [Sandstrom et al., 1966; Rozhkova et al., 1983].

All synthesized compounds were tested for fungicidal activity in vitro. The primary action of the substances on the growth, development of bacterial blight *Xanthomonas malvacearum* (*Smith*) *Dawson* and fungi *Fusarium oxysporum Schr f. vasinfectum Bilai* have been studied. Assessment of the action of tested substances on the fungicidal activity was carried out by the Krasilnikov paper discs (diameter 10mm disc) [Krasilnikov et al., 1958]. The inhibitory effects of commercial available Vitavax and Bronapol are served as the standard.

The obtained primary screening results showed that all the S-alkyl oxadiazole derivatives have weak activity against bacteria *Xanthomonas malvacearum* and fungicidal activity against fungi *Fusarium oxysporum*.

CONCLUSIONS

Thus, by reacting of 5-(p-aminophenyl)-1,3,4-oxadiazol-2(3H)-thione with alkyl halides with the C_1-C_9 homologous series are obtained exclusively S-alkyl derivatives, but possible N-alkyl isomers were not detected. The nature of alkylating agent (alkyl chain length and branching of alkyl halides) has little effect on yields of the desired products, whereas the direction of the reaction is influenced not observed. We studied the structure, physic-chemical data and fungicidal and bactericidal activity of the synthesized 2-alkylthio-5-(p-aminophenyl)-1,3,4-oxadiazoles.

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