Synthesis and Antibacterial Activities of 2-(1-Aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-oxadiazole Derivatives

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Eighteen novel 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-oxadiazole derivatives and two acylhydrazone intermediate compounds were synthesized by various pathways starting from 1-aryl-5-methyl-1,2,3-triazol-4-formhydrazide (**1**). All products were identified by spectroscopic analysis, and 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-benzalthio-1,3,4-oxadiazole was further validated by X-ray crystallography. Results from primary antibacterial activity tests indicated that most of the compounds were effective against *E. coli*, *P. aeruginosa*, *B. subtilis* and *S. aureus*.

INTRODUCTION

1,3,4-Oxadiazole derivatives are becoming an important member in the heterocyclic family not only because of their wide usage as dyes, photosensitive and electrical material,[1] but also because of their broad spectrum in biological activities such as HIV-activity, antibacterial and antifungal activities.[2] 1,2,3-Triazole and related compounds have attracted much attention in more and more reports due to their indispensable roles in both agriculture and industry. In recent years, incorporation of 1-substituted benzyl-1,2,3-triazole moiety with 1,3,4-oxadiazoles in the same molecule yielded promising results.[3-4] Combining 1-aryl-5-methyl-1,2,3-triazole with substituted 1,3,4-oxadiazole is expected to give new compounds with better biological activities. In this report, synthesis of 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-1,3,4-oxadiazole (**2**) was accomplished starting from 1-aryl-5-methyl-1,2,3-triazol-4-formhydrazide (**1**). Some reactions of **2** were studied, such as Mannich reaction, methylated reaction, as well as the reactions with halide and aldehyde for the production of new compounds **3**-**11**.

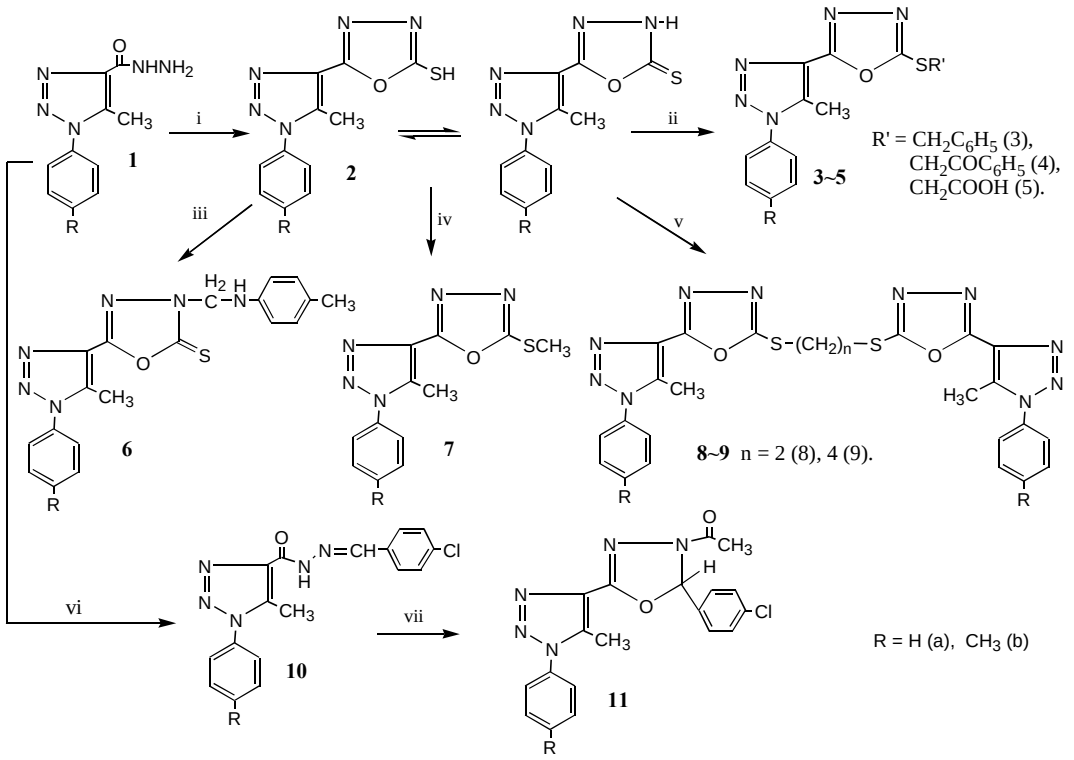
RESULTS AND DISCUSSION

2,5-Substituted-1,3,4-oxadiazole derivatives can be prepared from intermediate $RCONHNHCOR_2$ or $RCONHN=CHR_2$ via dehydration or oxidantion.[3-7] Alternatively, they can also be obtained by reactions of $RCONHNH_2$ with either R_2COOH or CS_2 directly.[8-9] We synthesized 2-(1-aryl-5-methyl-1,2,3-triazole-4-yl)-5-mercapto-1,3,4-oxadiazole (**2**) by the latter pathway in order to avoid corrosive reagents such as $POCl_3$, PbO_2 and $Pb(OAC)_4$. Our synthetic procedure of compounds **3**~**5** and **7**~**9** were completed mostly in water without PTC, which differs from previous literature reports.[10]

Products **2**~**11** formed distinct crystals, and their structures were confirmed by elemental analysis and spectral data (Table 1 and 2). In IR spectra, the two absorption bands at 1617~1640 cm^{-1} and 1255~1299 cm^{-1} are assigned to C=N and N-N=C functional groups, whereas the absorption bands at 1066~1083 cm^{-1} and 965~987 cm^{-1} are characteristic of C-O-C and N-N=N according to the literature.[11-12] The molecular ions of **6** can be detected by FAB-MS, but not by EI-MS due to the weak $N-CH_2-N$ bond. The ^1H NMR spectra of **2** in DMSO-d_6 displayed singlets at δ 14.51~14.80 ppm for NH, indicating that the compounds existed mainly in thione-form. According to previous results, protons of $S-CH_2-$ in **3**~**5** to **8**~**9** appeared at δ 4.23~4.51 ppm and δ 3.21~3.82 ppm, respectively. The difference in chemical shift is caused by functional groups attached to the $S-CH_2-$, which are either strong electron withdrawing substituents (phenyl and carbonyl) or weak electron withdrawing (methylene).[10,13]

Compound **3a** was dissolved in hot ethyl acetate-petroleum and filtrated. Evaporation of the solvent after 18 h gave colorless crystals suitable for X-ray crystallography.

Scheme I



i: CS_2/KOH/C_2H_5OH/reflux; HCl; ii: H_2O/NaOH $ClCH_2C6H_5$/r.t.(3) or $BrCH_2COC_6H_5$/EtOH/reflux (4) or $ClCH_2COOH$(5)/reflux; iii: C_2H_5OH/HCHO/*p*-$CH_3C_6H_4NH_2$, r.t.; iv: H_2O/NaOH/$(CH_3O)_2SO_2$, r.t.; v: H_2O/NaOH, $ClCH_2CH_2Cl$(8) or $Br(CH_2)_4Br$(9), reflux; vi: EtOH/*p*-ClC_6H_4CHO/TsOH, reflux; vii: Ac_2O, reflux.

Table 1. Physical Properties and Elemental Analysis of Compounds **2-11**

No.	Crystals	m.p. (ºC)	yield	Formula	Elemental anal. Found (Calcd.)/%		
					N %	C %	H %
2a	White plates	205-207	78	$C_{11}H_9N_5OS$	26.73 (27.01)	50.63 (50.96)	3.74 (3.40)
2b	White plates	224-226	83	$C_{12}H_{11}N_5OS$	25.48 (25.62)	52.55 (52.74)	4.31 (4.06)
3a	Colorless crystals	62-64	82	$C_{18}H_{15}N_5OS$	19.96 (20.04)	61.72 (61.88)	4.56 (4.33)
3b	White needles	112-114	86	$C_{19}H_{17}N_5OS$	18.97 (19.27)	62.61 (62.79)	4.31 (4.71)
4a	White plates	136-138	85	$C_{19}H_{15}N_5O_2S$	18.57 (18.56)	60.05 (60.47)	4.22 (4.06)
4b	White plates	177-179	90	$C_{20}H_{17}N_5O_2S$	17.47 (17.89)	61.32 (61.36)	4.69 (4.38)
5a	Pale brown plates	175-177	80	$C_{13}H_{11}N_5O_3S$	21.80 (22.07)	49.29 (49.21)	3.52 (3.49)
5b	White plates	162-164	82	$C_{14}H_{13}N_5O_3S$	21.24 (21.14)	50.71 (50.75)	3.96 (3.95)
6a	Pale yellow needles	145-147	85	$C_{19}H_{18}N_5O_2S$	22.25 (22.21)	60.17 (60.30)	4.98 (4.77)
6b	White plates	156-158	88	$C_{20}H_{20}N_5O_2S$	21.11 (21.41)	61.17 (61.21)	5.28 (5.14)
7a	White powder	94-96	72	$C_{12}H_{11}N_5OS$	25.37 (25.62)	52.46 (52.74)	4.19 (4.06)
7b	Pale yellow needles	143-145	76	$C_{13}H_{13}N_5OS$	24.48 (24.37)	54.42 (54.34)	4.66 (4.56)
8a	White granules	197-199	83	$C_{24}H_{20}N_{10}O_2S_2$	25.53 (25.72)	52.68 (52.93)	3.91 (3.70)
8b	White needles	202-204	84	$C_{26}H_{24}N_{10}O_2S_2$	23.99 (24.46)	54.32 (54.53)	4.35 (4.22)
9a	White plates	152-154	85	$C_{26}H_{24}N_{10}O_2S_2$	23.86 (24.46)	54.11 (54.53)	4.55 (4.22)
9b	White powder	194-196	90	$C_{28}H_{28}N_{10}O_2S_2$	23.17 (23.32)	55.76 (55.98)	5.04 (4.70)
10a	White plates	228-230	94	$C_{17}H_{14}N_5ClO$	20.82 (20.61)	60.40 (60.09)	4.36 (4.15)
10b	Long white needles	238-240	95	$C_{18}H_{16}N_5ClO$	19.62 (19.79)	61.29 (61.11)	4.63 (4.56)
11a	White plate	225-227	76	$C_{19}H_{16}N_5ClO_2$	18.60 (18.34)	59.44 (59.77)	4.29 (4.22)
11b	White needles	236-237	79	$C_{20}H_{18}N_5ClO_2$	18.02 (17.69)	60.33 (60.69)	4.82 (4.58)

Table 2. IR, MS and ^{1}H NMR Data of Compounds **2-11**

No.	IR υ_{max}/cm^{-1}	EI-MS (%)	^{1}H NMR
2a	3101, 1631, 1279, 1067, 983	259 (M^+, 28), 230 (25), 170 (100), 130 (32), 103 (10), 77 (69)	14.80 (s, 1H, NH), 7.67 (s, 5H, ArH), 2.53 (s, 3H, CH_3)
2b	3101, 1633, 1278, 1067, 987	273 (M^+, 15), 245 (19), 184 (44), 170 (78), 91 (100)	14.51 (s, 1H, NH), 7.63 (broad, 4H, ArH), 2.51, 2.43 (2s, 6H, $2CH_3$)
3a	3028, 1617, 1278, 1071, 973	----	7.50~7.58 (m, 10H, ArH), 4.58 (s, 2H, CH_2), 2.72 (s, 3H, CH_3)
3b	3062, 1617, 1270, 1068, 976	363 (M^+, 4), 262 (7), 172 (7), 132 (8), 115 (10), 91 (100), 65 (23)	7.52~7.29 (m, 9H, ArH), 4.57 (s, 2H, CH_2), 2.68, 2.49 (2s, 6H, $2CH_3$)
4a	3048, 1676, 1624, 1290, 1071, 971	377 (M^+, 11), 349 (4), 179 (10), 156 (23), 118 (27), 105 (100), 77 (57)	8.12~7.57 (m, 10H, ArH), 5.21 (s, 2H, CH_2), 2.57 (s, 3H, CH_3)
4b	3063, 1686, 1626, 1296, 1070, 977	391 (M^+, 26), 363 (29), 273 (2), 170 (46), 105 (100), 91 (44), 65 (14)	8.13~7.50 (m, 9H, ArH), 5.20 (s, 2H, CH_2), 2.54, 2.43 (2s, 6H, $2CH_3$)
5a	2936, 1718, 1624, 1267, 1073, 978	317 (M^+, 82), 289 (7), 158 (100), 156 (33), 130 (56), 118 (84), 77 (65)	13.19 (s, 1H, OH), 7.67 (s, 5H, ArH), 4.23 (s, 2H, CH_2), 2.58 (s, 3H, CH_3)
5b	2937, 1720, 1624, 1261, 1075, 980	----	13.31 (s, 1H, OH), 7.53~7.50 (m, 4H, ArH), 4.23 (s, 2H, CH_2), 2.56, 2.43 (2s, 6H, $2CH_3$)
6a	3328, 1635, 1272, 1082, 975	273 (2), 260 (15), 259 (100), 170 (13), 155 (21), 91 (17), 77 (16), 379 (M+1, FAB)	7.65~7.68 (m, 9H, ArH), 6.10 (s, 2H, CH_2), 5.54 (s, 1H, NH), 2.54, 2.31 (2s, 6H, $2CH_3$)
6b	3324, 1640, 1271, 1082, 976	317 (3), 273 (100), 198 (10), 184 (19), 169 (44), 91 (21), 65 (13), 393 (M+1, FAB)	7.47~6.89 (m, 9H, ArH), 6.08 (s, 2H, CH_2), 5.53 (s, 1H, NH), 2.51, 2.42, 2.22 (3s, 9H, $3CH_3$)
7a	3029, 1622, 1257, 1072, 977	----	7.58 (s, 5H, ArH), 2.81 (s, 3H, SCH_3), 2.70 (s, 3H, CH_3)
7b	3043, 1620, 1255, 1072, 980	287 (M^+, 27), 212 (22), 172 (48), 132 (48), 115 (52), 91 (100), 65 (80)	7.60 (broad, 4H, ArH), 2.82 (s, 3H, SCH_3), 2.72, 2.65 (2s, 6H, $2CH_3$)
8a	3044, 1620, 1265, 1066, 974	----	7.65 (s, 10H, ArH), 3.82 (s, 4H, S-CH_2-CH_2-S), 2.58 (s, 6H, $2CH_3$)
8b	3044, 1623, 1271, 1070, 973	572 (M^+, 17), 484 (3), 332 (11), 300 (36), 188 (22), 170 (100), 91 (30)	7.48 (br, 8H, ArH), 3.81 (s, 4H, S-CH_2-CH_2-S), 2.56, 2.43 (2s, 12H, 2*$2CH_3$)
9a	3041, 1623, 1278, 1070, 970	572 (M^+, 26), 445 (37), 314 (100), 226 (30), 158 (45), 156 (76), 77 (42)	7.67 (s, 10H, ArH), 3.40~3.31 (m, 4H, $2SCH_2$), 2.58 (s, 6H, $2CH_3$), 1.97 (m, 4H, $2SCH_2\underline{CH_2}$)
9b	3038, 1623, 1270, 1070, 973	----	7.51~7.49 (s, 8H, ArH), 3.39~3.31 (m, 4H, 2S CH_2), 2.56, 2.43, 1.97 (m, 4H, $2SCH_2\underline{CH_2}$)
10a	3297, 1674, 1574, 1287, 966	339 (M^+, 82), 337 (93), 309 (100), 280 (52), 138 (77), 111 (34), 77 (55)	12.22 (s, 1H, NH), 8.58 (s, 1H, CH), 7.80~7.46 (m, 9H, ArH), 2.57 (s, 3H, CH_3)
10b	3317, 1680, 1595, 1277, 979	353 (M^+, 19), 323 (100), 294 (29), 172 (29), 141 (13), 139 (29), 91 (5)	12.20 (s, 1H, NH), 8.57 (s, 1H, CH), 7.79~7.50 (m, 8H, ArH), 2.55, 2.43 (2s, 6H, $2CH_3$)
11a	3297, 1674, 1575, 1282, 1069, 965	----	8.24 (s, 1H, CH), 7.84~7.36 (m, 9H, ArH), 2.67, 2.50 (2s, 6H, $2CH_3$)
11b	3332, 1687, 1578, 1273, 1067, 981	395 (M^+, 21), 353 (100), 268 (32), 216 (52), 172 (83), 144 (62), 91 (42)	8.24 (s, 1H, CH), 7.83~7.39 (m, 8H, ArH), 2.65, 2.55, 2.43 (3s, 9H, $3CH_3$)

The crystal 0.42*0.38*0.38 mm was mounted with graphic monochromated MoKα (λ = 0.71073 Å), and data was collected in the range 1.97º - 25.00º. Details of the intensity collection are given in Table 3.

Compounds **2-11** were screened for their antibacterial activities against *E. coli, P. Aeruginosa*, *B. Subtilis* and *S. aureus* employing the cup-plate method at the concentration

Scheme II

Ortep 3 scheme of compound **3a**

Table 3. X-ray Crystallography Data of **3a**

Chemical formula	$C_{18}H_{15}N_5OS$
M	349.41
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	8.3530 (10)
b (Å)	10.331 (2)
c (Å)	10.843 (2)
α (°)	97.99 (2)
β (°)	101.610 (10)
γ (°)	111.170 (10)
V (Å^3)	831.4 (2)
F (000)	364
Z	2
Dc (g. cm^{-3})	1.396
Reflections collected	3221
Independent reflections	2896 (R_{int} = 0.0103)
T (K)	293 (2)
Final R indics [I > 2ó (I)]	R_1: 0.0343, wR_2: 0.0842
R indics	R_1: 0.0467, wR_2: 0.0882
Extinction cofficient	0.029 (3)
Largest diff. Peak and hole (eÅ^{-3})	0.191 and -0.204

of 100 μg/mL in the nutrient agar media (41 g nutrient agar/ 1000 mL water).[14] The investigation results are listed in Table 4. The results showed that all compounds were active except for **4b**, **5a** and **8-9a**. It is worthwhile to note that compounds **2-3a**, **7a-b**, **8-9b** and **11a-b** express significant antibacterial activity. The investigation on the structure-activity relationship shows that a thiadiazole ring enhances the antibacterial action of most of the title compounds.

Table 4. Inhibition Effect of Compounds **2-11**

No.	E. *coli*	P. *aeruginosa*	B. *subtilis*	S. *aureus*
2a	++	+++	++	+
2b	+	+	+	++
3a	++	++	+	+
3b	++	+++	-	+
4a	+	-	+	+
4b	++	-	-	-
5a	+++	-	-	-
5b	+++	++	+	++
6a	++	++	+	+
6b	++	+++	-	+
7a	++	+	++	++
7b	+	+++	++	+
8a	-	-	+	++
8b	++	++	++	+++
9a	-	-	++	+
9b	++	++	++	++
10a	-	++	+	++
10b	++	+++	++	-
11a	++	++	++	+
11b	+	++	++	+

Zone diameter of growth inhibition: < 10 mm (-), 10-13 mm (+) and 14-17 mm (++). Diameter of the cup = 8 mm.

EXPERIMENTAL

All reagents of laboratory grade were used without purification. The melting points are uncorrected and were taken on an X-4 microscopic melting point apparatus. IR spectra were recorded on a Nicolet AVATAR 360 FT-IR spectrometer in KBr disc. ^{1}H NMR was recorded on a Bruker AC-80 instrument in DMSO-d_6 with TMS as internal standard. Mass spectra were performed on a ZAB-HS (EI) and VG ZAB-HS (FAB) instruments. And the elemental analysis was performed on an Elementar Vario EL apparatus.

Compound 1-aryl-5-methyl-1,2,3-triazol-4-form hydrazide (1) was prepared from aryl amine by five steps according to the literature[15]

Preparation of 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-mercapto-1,3,4-oxadiazoles (2)

To an ethanol (100 mL) solution of KOH (75 mmol), hydrazide **1** (50 mmol) and carbon disulfide (100 mmol) were added and the mixture was refluxed for 36 h. It was concentrated to a small volume, poured into ice water and filtered. The filtrate on acidification gave a percipitate which was collected and recrystallized from ethanol.

General preparation of 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-alkylthio-1,3,4-oxadiazoles (3)-(5)

A mixture of thione **2** (1 mmol), sodium hydroxide (1 mmol for **3**-**4**, 2 mmol for **5**) and the appropriate halide (1 mmol) was stirred in 25 mL of water (ω-bromo-ω-acetophenone was dissolved in 5 mL of ethanol and then added dropwise). Compound **3** was formed after stirring for 8 h at room temperature, but **4**-**5** were successfully synthesized by refluxing for only 4 h. The resulting thioether (**5** appeared after being neutralized by 1N HCl) was collected by filtration, washed with water and recrystallized from a suitable solvent.

Preparation of 5-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-3-N-*p*-methylphenylaminomethyl-1,3,4-oxadiazolin-5-thiones (6)

A solution of **2** (1 mmol) in ethanol containing formaldehyde (0.15 mL) was stirred for 0.5 h under cooling by ice-water bath. *p*-Toluidine (1 mmol) was added and the reac-

tion mixture was stirred for 8 h at room temperature. The excessive EtOH was removed and the resulting solid was washed with petroleum (5 mL) and recrystallized from ethanol to yield **6**.

Synthesis of 2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-5-methylthio-1,3,4-oxadiazoles (7)

Dimethylsulfate (0.06 mmol) was added dropwise to the mixture of **2** (1 mmol) and sodium hydraoxide (1 mmol) and stirred overnight at room temperature to pricipate a white solid. The crude product was collected by filtration, washed with water and recrystallized from ethyl acetate-petroleum to get **7**.

General preparation of 1,2/1,4-bis[2-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-1,3,4-oxadiazolin-5-thio]ethanane/butanane (8)-(9)

Appropriate 1,2-dichloroethanane/1,4-dibromobutane (1/2 mmol) was added dropwise to the solution of **2** (1 mmol) and equivalent NaOH in 30 mL of water and stirred for 0.5 h. Then the mixture was refluxed for 2 h. The precipitation was purified as **3**-**4** and **7** to get **8**-**9**.

Synthesis of 3-N-acetyl-5-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-2-*p*-chlorophenyl-Δ_2-1,3,4-oxadiazoline (11)

A solution of **2** (2 mmol), equivalent *p*-chlorophenylaldehyde was refluxed in 20 mL of ethanol for 4 h catalyzed by *p*-toluene sulfonic acid. Intermediate *p*-chlorophenylaldehyde-(1-aryl-5-methyl-1,2,3-triazol-4-yl)-formhydrazone **10** was precipitated in high yield. It was collected, dried and refluxed in anhydrous acetic acid (5 mL) for 2 h. After removal of excessive solvent, the residue was poured into crushed ice to get a white powder. The crude product was recrystallized from ethanol-ethyl acetate to afford **11**.

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Key Words

1,2,3-Triazole; 1,3,4-Oxadiazole; X-ray crystallography; Antibacterial test.

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