

Synthesis and Biological Activity of ω -(5-Aryl-1,3,4-oxadiazol-2-thio)- and ω -(5-Aryl-1,3,4-oxadiazol-2-thioacetoxyl)- ω -(1-*H*-1,2,4-triazol-1-yl)acetophenones

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Eighteen novel ω -(5-Aryl-1,3,4-oxadiazol-2-thio)- ω -(1-*H*-1,2,4-triazol-1-yl)acetophenones (**4a-4i**) and ω -(5-Aryl-1,3,4-oxadiazol-2-thioacetoxyl)- ω -(1-*H*-1,2,4-triazol-1-yl)acetophenones (**5a-5i**) were synthesized. All the compounds synthesized were confirmed by elemental analyses and spectral data. The biological activity of representative compounds was evaluated.

INTRODUCTION

In recent years, many chemists have paid much attention to compounds bearing 1*H*-1,2,4-triazole rings due to their broad spectrum of biological activities such as fungicidal, anti-inflammatory, antiparasitic, insecticidal, herbicidal, antiviral, antitumor and hypotensive effects.¹⁻⁷ Up to now, a great variety of these kinds of compounds have been synthesized, among which some commercially antifungal agents have been developed including triadimefon, triadimenol and diniconazole. Moreover, 1,3,4-oxadiazole derivatives have been reported to associate with antibacterial,

anti-inflammatory and insecticidal properties.⁸⁻¹⁰ It is well known that the synthesis of heterocyclic compounds tends to contain multi-structure in a molecule. The biological activity of a heterocyclic compound may be improved by the promotion of its combination with the microstructure of the cell and the accumulation of various biological activities resulting from the incorporation of different heterocyclic and non-heterocyclic nuclei in it. In view of the above mentioned facts and as a proceeding of our research for new and better biologically active agents, we wish to describe the synthesis of eighteen novel 1*H*-1,2,4-triazole derivatives containing 1,3,4-oxadiazole nucleus in the present paper.

Scheme I

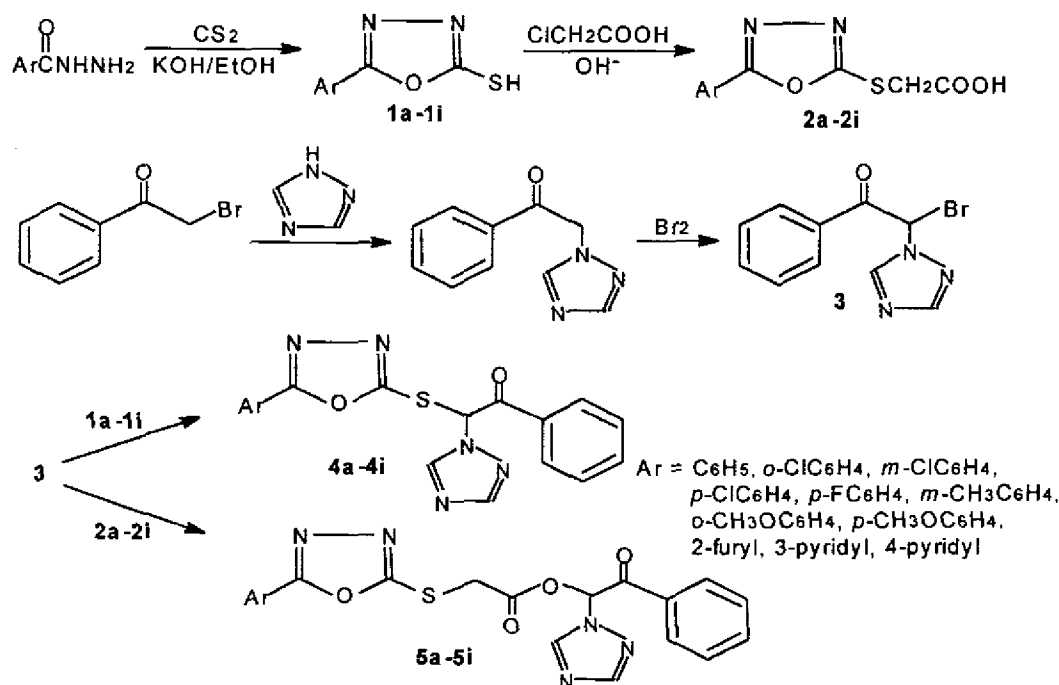


Table 1. Yields, Melting Points, Formulae and Elemental Analyses of Compounds 4 and 5

Compd.	Aryl	Yield (%)	M.p. (°C)	Formula	Found (required) (%)		
					C	H	N
4a	C ₆ H ₅	90	162-163	C ₁₈ H ₁₃ N ₅ O ₂ S	59.32 (59.49)	3.17 (3.61)	19.45 (19.27)
4b	<i>o</i> -ClC ₆ H ₄	85	154-155	C ₁₈ H ₁₂ ClN ₅ O ₂ S	53.97 (54.34)	2.92 (3.04)	17.20 (17.60)
4c	<i>p</i> -ClC ₆ H ₄	88	166-167	C ₁₈ H ₁₂ ClN ₅ O ₂ S	53.85 (54.34)	2.87 (3.04)	17.26 (17.60)
4d	<i>m</i> -ClC ₆ H ₄	87	151-152	C ₁₈ H ₁₂ ClN ₅ O ₂ S	53.89 (54.34)	2.88 (3.04)	17.16 (17.60)
4e	<i>m</i> -CH ₃ C ₆ H ₄	86	165-166	C ₁₉ H ₁₅ N ₅ O ₂ S	60.09 (60.47)	3.76 (4.01)	18.28 (18.56)
4f	<i>p</i> -CH ₃ OC ₆ H ₄	84	166-167	C ₁₉ H ₁₅ N ₅ O ₃ S	57.81 (58.01)	3.45 (3.84)	17.31 (17.80)
4g	4-pyridyl	80	167-168	C ₁₇ H ₁₂ N ₆ O ₂ S	55.82 (56.04)	3.52 (3.32)	22.70 (23.06)
4h	2-furyl	86	163-164	C ₁₆ H ₁₁ N ₅ O ₃ S	53.98 (54.39)	3.11 (3.13)	19.95 (19.82)
4i	3-pyridyl	82	193-194	C ₁₇ H ₁₂ N ₆ O ₂ S	55.87 (56.04)	3.61 (3.32)	22.79 (23.06)
5a	<i>m</i> -CH ₃ C ₆ H ₄	87	132-133	C ₂₁ H ₁₇ N ₅ O ₄ S	58.20 (57.92)	3.95 (3.93)	16.41 (16.08)
5b	<i>p</i> -CH ₃ OC ₆ H ₄	74	159-160	C ₂₁ H ₁₇ N ₅ O ₅ S	55.71 (55.87)	4.10 (3.93)	15.61 (16.08)
5c	<i>o</i> -ClC ₆ H ₄	83	130-131	C ₂₀ H ₁₄ ClN ₅ O ₄ S	52.26 (52.69)	3.01 (3.09)	15.10 (15.36)
5d	<i>o</i> -CH ₃ OC ₆ H ₄	72	139-140	C ₂₁ H ₁₇ N ₅ O ₅ S	55.79 (55.87)	3.84 (3.93)	15.71 (16.08)
5e	2-furyl	78	147-149	C ₁₈ H ₁₃ N ₅ O ₅ S	52.42 (52.68)	3.21 (2.94)	16.76 (17.06)
5f	<i>m</i> -ClC ₆ H ₄	81	129-130	C ₂₀ H ₁₄ ClN ₅ O ₄ S	52.89 (52.69)	3.35 (3.09)	15.08 (15.36)
5g	<i>p</i> -ClC ₆ H ₄	84	165-166	C ₂₀ H ₁₄ ClN ₅ O ₄ S	52.80 (52.69)	3.01 (3.09)	14.91 (15.36)
5h	<i>p</i> -FC ₆ H ₄	80	151-152	C ₂₀ H ₁₄ FN ₅ O ₄ S	54.44 (54.67)	3.48 (3.21)	15.69 (15.94)
5i	C ₆ H ₅	89	154-155	C ₂₀ H ₁₅ N ₅ O ₄ S	56.90 (57.00)	3.67 (3.58)	16.86 (16.60)

RESULTS AND DISCUSSION

When 5-aryl-1,3,4-oxadiazol-2-thiols (**1a-1i**) were allowed to treat with ω -bromo- ω -(1*H*-1,2,4-triazol-1-yl)acetophenone (**3**) in anhydrous ethanol at room temperature, the reaction proceeded with good yields and afforded ω -(5-aryl-1,3,4-oxadiazol-2-thio)- ω -(1*H*-1,2,4-triazol-1-yl)acetophenones (**4a-4i**) (Scheme I). The IR spectra showed two characteristic peaks in the range of 1677-1685 cm⁻¹ and 1594-1617 cm⁻¹ due to -PhCO- and C=N functions, respectively. The absorption band in the range of 1123-1129 cm⁻¹ was assigned to the C-O-C stretching vibration. The ¹H NMR spectra displayed two singlets for the 1*H*-1,2,4-triazole protons at δ 8.49-9.22 ppm and δ 7.96-8.64 ppm, respectively. The signal at δ 6.59-8.12 ppm was attributable to -CHTr- and aromatic protons.

As would be anticipated, the attempted reaction between 5-aryl-1,3,4-oxadiazol-2-thioacetic acids (**2a-2i**) and ω -bromo- ω -(1*H*-1,2,4-triazol-1-yl)acetophenone (**3**) in the presence of triethylamine furnished smoothly the corre-

sponding ω -(5-aryl-1,3,4-oxadiazol-2-thiolacetoxyl)- ω -(1*H*-1,2,4-triazol-1-yl)acetophenones (**5a-5i**). Compounds **2a-2i** were prepared by refluxing **1a-1i** with chloroacetic acid under basic conditions (Scheme I). In comparison with **4a-4i**, the IR spectra of **5a-5i** exhibited a strong absorption peak around 1755 cm⁻¹ corresponding to -CO₂- stretching vibration, and in their ¹H NMR spectra a characteristic singlet appeared for SCH₂ protons at δ 4.19-4.22 ppm.

By analyzing the mass spectra of **4** and **5**, it was found that the molecular ion peaks were very weak probably due to their chain structures. The base peak at *m/z* 105 corresponded to PhCO⁺. The ion peak formed by the direct loss of a 1*H*-1,2,4-triazole molecule from the molecular ion could be observed in compound **4**. The fragmentation of **5** involved the expulsion of 1*H*-1,2,4-triazolopropiolactone moiety from the molecular ion (Scheme II).

The representative compounds **4c**, **4g**, **4h**, **5c**, **5g** and **5h** were screened for their fungicidal activity employing the agar diffusion technique. The preliminary results indicated that they exhibited mild inhibitory activity against plant

Scheme II

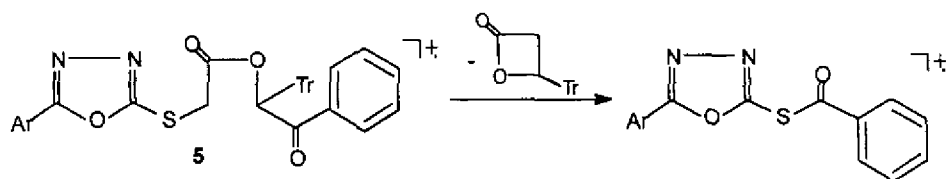


Table 2. IR, ^1H NMR and Mass Spectral Data of Compounds 4 and 5

Compd.	IR (KBr, cm^{-1})	^1H NMR (CDCl_3 , ppm)
4a	1680 (C=O), 1607 (C=N), 1124 (C-O-C)	8.59 (s, 1H, Tr-H), 8.14 (s, 1H, Tr-H), 8.06-7.30 (m, 11H, ArH and CH)
4b	1684 (C=O), 1594 (C=N), 1126 (C-O-C)	8.82 (s, 1H, Tr-H), 8.08 (s, 1H, Tr-H), 8.02-7.36 (m, 10H, ArH and CH)
4c	1680 (C=O), 1603 (C=N), 1126 (C-O-C)	8.64 (s, 1H, Tr-H), 8.11 (s, 1H, Tr-H), 7.96-7.29 (m, 10H, ArH and CH)
4d	1683 (C=O), 1594 (C=N), 1125 (C-O-C)	8.63 (s, 1H, Tr-H), 8.39 (s, 1H, Tr-H), 8.09-7.37 (m, 10H, ArH and CH)
4e	1685 (C=O), 1594 (C=N), 1127 (C-O-C)	8.80 (s, 1H, Tr-H), 8.02 (s, 1H, Tr-H), 7.96-7.28 (m, 10H, ArH and CH), 2.40 (s, 3H, CH_3)
4f	1679 (C=O), 1617 (C=N), 1129 (C-O-C)	8.80 (s, 1H, Tr-H), 7.96 (s, 1H, Tr-H), 7.92-6.92 (m, 10H, ArH and CH), 3.86 (s, 3H, OCH_3)
4g	1677 (C=O), 1606 (C=N), 1123 (C-O-C)	8.83 (s, 1H, Tr-H), 8.14 (s, 1H, Tr-H), 7.96-7.48 (m, 10H, PyH, ArH and CH)
4h	1679 (C=O), 1594 (C=N), 1126 (C-O-C)	8.49 (s, 1H, Tr-H), 8.27 (s, 1H, Tr-H), 8.12-6.59 (m, 9H, ArH, Fur-H and CH)
4i	1681 (C=O), 1604 (C=N), 1123 (C-O-C)	9.22 (s, 1H, Tr-H), 8.64 (s, 1H, Tr-H), 8.04-7.36 (m, 10H, PyH, ArH and CH)
5a	1760 ($-\text{CO}_2-$), 1707 (C=O), 1594 (C=N), 1132 (C-O-C)	8.43 (s, 1H, Tr-H), 7.96 (s, 1H, Tr-H), 7.92-7.24 (m, 10H, ArH and CH), 4.20 (s, 2H, CH_2), 2.42 (s, 3H, CH_3)
5b	1756 ($-\text{CO}_2-$), 1698 (C=O), 1613 (C=N), 1147 (C-O-C)	8.41 (s, 1H, Tr-H), 7.97 (s, 1H, Tr-H), 7.85-6.94 (m, 10H, ArH and CH), 4.19 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3)
5c	1763 ($-\text{CO}_2-$), 1704 (C=O), 1593 (C=N), 1154 (C-O-C)	8.42 (s, 1H, Tr-H), 7.96 (s, 1H, Tr-H), 7.92-7.24 (m, 10H, ArH and CH), 4.20 (s, 2H, CH_2)
5d	1756 ($-\text{CO}_2-$), 1710 (C=O), 1602 (C=N), 1160 (C-O-C)	8.46 (s, 1H, Tr-H), 7.96 (s, 1H, Tr-H), 7.88-6.97 (m, 10H, ArH and CH), 4.20 (s, 2H, CH_2), 3.92 (s, 3H, OCH_3)
5e	1746 ($-\text{CO}_2-$), 1708 (C=O), 1596 (C=N), 1157 (C-O-C)	8.44 (s, 1H, Tr-H), 7.98 (s, 1H, Tr-H), 7.92-6.54 (m, 9H, ArH, Fur-H and CH), 4.20 (s, 2H, CH_2)
5f	1758 ($-\text{CO}_2-$), 1692 (C=O), 1588 (C=N), 1147 (C-O-C)	8.43 (s, 1H, Tr-H), 7.96 (s, 1H, Tr-H), 7.90-7.22 (m, 10H, ArH and CH), 4.20 (s, 2H, CH_2)
5g	1754 ($-\text{CO}_2-$), 1694 (C=O), 1600 (C=N), 1147 (C-O-C)	8.43 (s, 1H, Tr-H), 7.98 (s, 1H, Tr-H), 7.88-7.42 (m, 10H, ArH and CH), 4.22 (s, 2H, CH_2)
5h	1754 ($-\text{CO}_2-$), 1702 (C=O), 1606 (C=N), 1148 (C-O-C)	8.42 (s, 1H, Tr-H), 8.09 (s, 1H, Tr-H), 7.99-7.08 (m, 10H, ArH and CH), 4.20 (s, 2H, CH_2)
5i	1759 ($-\text{CO}_2-$), 1702 (C=O), 1592 (C=N), 1144 (C-O-C)	8.42 (s, 1H, Tr-H), 7.94 (s, 1H, Tr-H), 7.88-7.24 (m, 11H, ArH and CH), 4.19 (s, 2H, CH_2)

pathogenetic fungi such as *gray mold of cucumber*, *early blight of tomato*, *sclerotium blight of rape* and *leaf spot of beet*. The degree of inhibition ranged from 7.6% to 44.4%. Moreover, compounds **4b** and **4e** displayed mild plant growth regulative effects. Further investigation on the biological activity of **4** and **5** is in progress.

EXPERIMENTAL SECTION

The melting points were determined on a kofler melting point apparatus and are uncorrected. Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer. IR spectra were obtained in KBr discs on a Nicolet FT-IR 170SX spectrophotometer. Mass were performed on

an HP-5988A spectrometer (EI at 70 eV). ^1H NMR spectra (CDCl_3) were recorded on a JEOL FX-90X instrument with TMS as an internal standard.

ω -Bromo- ω -(1-*H*-1,2,4-triazol-1-yl)acetophenone (**3**) and 5-aryl-1,3,4-oxadiazol-2-thiols (**1a-1i**) were prepared following methods in the literature, respectively.¹¹⁻¹²

General Procedure for the Preparation of 5-Aryl-1,3,4-oxadiazol-2-thioacetic Acids (**2a-2i**)

1a-1i (0.01 mol), dissolved in potassium hydroxide (1.2 g KOH in 15 mL water) and methanol (35 mL), was treated with chloroacetic acid (0.01 mol) and the mixture was refluxed for 3-5 h. After methanol was evaporated, the mixture was diluted with ice water (50 mL), filtered and acidified with diluted hydrochloric acid. The resultant pre-

Table 3. Mass Spectral Data of Compounds 4 and 5

Compd.	MS (<i>m/z</i> , %)
4a	363 (M ⁺ , 3), 294 (5), 258 (11), 187 (2), 178 (5), 105 (100), 103 (4), 77 (20)
4b	397 (M ⁺ , 2), 328 (3), 292 (5), 212 (9), 187 (5), 139 (17), 137 (11), 105 (100)
4c	377 (M ⁺ , 3), 308 (6), 272 (14), 193 (3), 187 (4), 135 (20), 119 (17), 105 (100)
4f	393 (M ⁺ , 6), 324 (10), 288 (40), 135 (32), 107 (7), 105 (100), 91 (4), 77 (18)
4g	364 (M ⁺ , 2), 295 (3), 259 (2), 187 (4), 179 (7), 106 (12), 105 (100), 77 (17)
5a	435 (M ⁺ , 3), 296 (2), 233 (6), 173 (17), 159 (12), 119 (52), 105 (100), 91 (49)
5d	451 (M ⁺ , 6), 312 (8), 278 (19), 249 (39), 175 (40), 135 (53), 105 (100), 77 (15)
5e	411 (M ⁺ , 8), 272 (19), 209 (28), 202 (42), 149 (32), 105 (100), 95 (20), 77 (14)
5f	455 (M ⁺ , 1), 316 (9), 253 (35), 219 (60), 159 (29), 145 (29), 105 (100), 77 (19)
5i	421 (M ⁺ , 8), 282 (32), 219 (60), 202 (40), 159 (29), 145 (29), 105 (100), 77 (19)

cipitate was collected by filtration, washed well with water and recrystallized from 50% ethanol to give **2a-2i**.

General Procedure for the Preparation of ω -(5-Aryl-1,3,4-oxadiazol-2-thio)- ω -(1-*H*-1,2,4-triazol-1-yl)acetophenones (4a-4i)

A solution of **1a-1i** (2 mmol) in 20 mL of anhydrous ethanol was added dropwise to a solution of **3** (2 mmol) in 20 mL of anhydrous ethanol. The mixture was stirred at room temperature for 3-5 h and the solvent was evaporated. The resultant precipitate was filtered, dried and then recrystallized from 95% ethanol to afford **4a-4i**.

General Procedure for the Preparation of ω -(5-Aryl-1,3,4-oxadiazol-2-thioacetoxyl)- ω -(1-*H*-1,2,4-triazol-1-yl)acetophenones (5a-5i)

A mixture of **2a-2i** (2 mmol) and triethylamine (2 mmol) in 20 mL of anhydrous acetone was added dropwise with stirring to a solution of **3** in 20 mL of anhydrous acetone at 0 °C. After an hour, the mixture was stirred at room temperature over night, the formed salt was filtered and the solvent was evaporated. The precipitate was filtered and then recrystallized from 95% ethanol to afford **5a-5i**.

ACKNOWLEDGMENT

Financial support from the State Key Laboratory of Elemento-Organic Chemistry of Nankai University is gratefully acknowledged.

Received November 3, 1998.

Key Words

1*H*-1,2,4-Triazole; 1,3,4-Oxadiazole; Biological activity.

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