Synthesis and Biological Activities of *O-(E)*-(Arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] Ethanone Oxime Ethers

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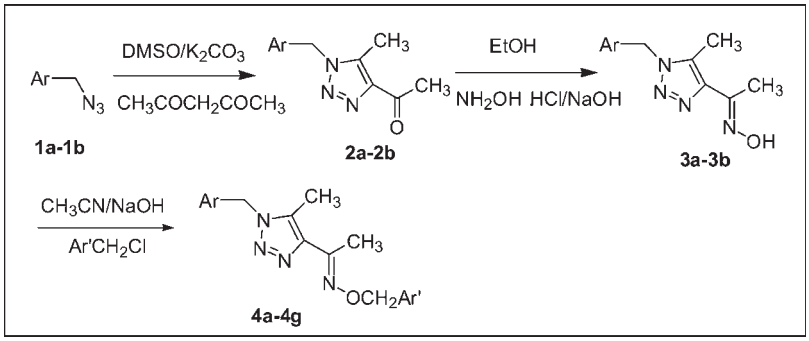

A series of novel *O*-(*E*)-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers were synthesized by the *O*-alkylation of 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oximes with various arylmethyl chlorides in the basic condition. Their structures were confirmed by IR, ^{1}H NMR, mass spectroscopy, and elemental analyses. The preliminary bioassay indicated that some of the target compounds (**4a–f**) displayed good insecticidal and moderate fungicidal activity. For example, compounds **4c** and **4g** showed 100% and 90.6% death rates against aphides at the concentration of 250 mg/L, respectively, and compounds **4f** and **4g** displayed 67% and 78.4% inhibitory rates against *Rhizoctonia solani* at the dosage of 100 mg/L, respectively.

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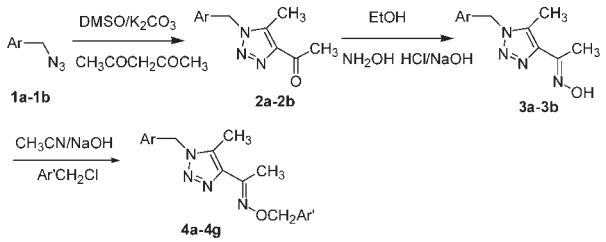
INTRODUCTION

Oxime ether derivatives are very important agrochemicals and are receiving more and more attention because of their widespread biological activities—some of them can be used as insecticides, acaricides [1,2], fungicides [3,4], and herbicides and its safener [5,6]—which are widely used in the worldwide plant protection. The 1,2,3-triazole ring has been known for more than 100 years. However, it was only in recent decades that the 1,2,3-triazole chemistry developed very fast due to the discovery of the diverse biologically active triazole derivatives. Many of them have been used as insecticides, nematocides, acaricides, and plant growth regulators [7–13]. Recently, heterocyclic compounds containing nitrogen play more and more important role in pesticide science and industry; moreover, the introduction of a pyridyl or a thiazole ring into a parent compound may improve its properties and biological activities in the looking for novel pharmaceutical and agrochemical lead compounds, and many pyridyl and thiazole containing compounds are also known to possess a wide range of biological and pharmacological activities, as well as low toxicity toward mammals, and the widely development of neonicotinic insecticides in the world are very successful examples [14–17]. As a continuation of our ongoing project aimed at investigating novel biologically nitrogen-containing heterocyclic compounds [18,19], we designed and synthesized a series of novel *O-(E)*-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers. We would like to report the synthesis and biological activities of the title compounds **4a–g** in this article (Scheme 1).

RESULTS AND DISCUSSION

2-Chloro-5-(chloromethyl)-pyridine (or thiazole) was treated with sodium azide in dry ethanol under refluxing condition to obtain 5-(azidomethyl)-2-chloro-pyridine (or thiazole) (**1**) in high yields, which was annulated with acetylacetone in DMSO in the presence of anhydrous potassium carbonate to generate compound **2**. Treatment of **2** with hydroxylamine hydrochloride

Scheme 1



4a: Ar = 6-chloropyridin-3-yl, Ar' = 6-chloropyridin-3-yl; **4b**: Ar = 6-chloropyridin-3-yl, Ar' = 2-chlorothiazol-5-yl; **4c**: Ar = 6-chloropyridin-3-yl, Ar' = phenyl; **4d**: Ar = 6-chloropyridin-3-yl, Ar' = pyridin-3-yl; **4e**: Ar = 2-chlorothiazol-5-yl, Ar' = 6-chloropyridin-3-yl; **4f**: Ar = 2-chlorothiazol-5-yl, Ar' = 2-chlorothiazol-5-yl; **4g**: Ar = 2-chlorothiazol-5-yl, Ar' = phenyl

afforded oxime **3**, which reacted with various arylmethyl chlorides in the basic condition to get the title compounds **4** in moderate yields.

To optimize the reaction condition of *O*-alkylation, we attempted to react 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl]ethanone oxime **3** with various alkyl chlorides in different base-solvent systems (e.g., Et_3N-CH_2Cl_2, Et_3N-CH_3CN, Et_3N-toluene, NaOH-CH_3CN, NaOH-DMF, and NaOH-toluene). Finally, we found that the *O*-alkylation can take place smoothly in sodium hydroxide and acetonitrile system to give the target products **4** in moderate yield (58–85%), and no other by-product was detected by TLC. In the *O*-alkylation, 2-chloro-5-(chloromethyl)-pyridine and 2-chloro-(5-chloromethyl)-thiazole are more active than 3-(chloromethyl)-pyridine and benzyl chloride. For example, when 2-chloro-5-(chloromethyl)-pyridine and 2-chloro-(5-chloromethyl)-thiazole are used as the alkylation reagents, the reaction can complete at room temperature for 4 to 5 h, however, for 3-(chloromethyl)-pyridine and benzyl chloride, the reactions underwent very slow and needed more high temperature and prolonged reation time.

Their structures of compounds **4** were confirmed by IR, ^{1}H NMR, EI-MS, and elemental analyses, which were listed in the experimental part. Because of C═N bond, it probably existed as Z and E-isomers in compounds **3** and **4a–g**. In ^{1}H NMR spectra, the CH_3 protons of the E isomer is shifted downfield relative to that of Z isomer, owing to its shorter distance between the oxygen atom in C═N─O─ moiety and stronger unshielded effect [1]. In this article, both of compounds **3** and **4** are in E configurations, which were deduced by NMR analysis and further by compared with one of its phosphorothioate analog determined by X-ray diffraction analysis [20].

Biological activity

Insecticidal activity. Compounds **4** were tested for insecticidal activities against aphides at the concentration of 250 mg/L according to a previously reported method [21]. The results of preliminary bioassays indicated that some of the target compounds displayed good insecticidal activity against aphides (Table 1). For example, compounds **4c** and **4g** exhibited 100% and 90.6% inhibitory rates against aphides at the concentration of 250 mg/L, respectively.

Fungicidal activity. The preliminary fungicidal activity of the target compounds **4** was evaluated by the classic plate method at a dosage of 100 mg/L, which was described in the experimental part. The six fungi used—*Fusarium oxysporium, Rhizoctonia solani, Botrytis cinereapers, Gibberella zeae, Dothiorella gregaria,* and *Colletotrichum gossypi*—belong to the group of field fungi and were isolated from corresponding crops. The activities data were also listed in Table 1. The results indicated that most of compounds **4** exhibit moderate to weak inhibitory activities against the above six fungi. For example, compounds **4f** and **4g** displayed 67% and 78.4% inhibitory rates against *Rhizoctonia solani* at the dosage of 100 mg/L, respectively. Further structure-activity relationships are under investigation.

In conclusion, a series of novel *O*-(*E*)-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers were synthesized by the *O*-alkylation reactions of 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oximes with various arylmethyl chlorides in the basic condition. The preliminary bioassay indicated that some of the target compounds (**4a–f**) displayed good insecticidal and moderate fungicidal activity. For example, compounds **4c** and **4g** showed 100% and 90.6% death rates against aphides at the concentration of 250 mg/L, compounds **4f** and **4g** displayed 67% and 78.4% inhibitory rates against *Rhizoctonia solani* at the dosage of 100 mg/L, respectively.

EXPERIMENTAL

Melting points were determined with a WRS-1B digital melting point apparatus and are uncorrected. ^{1}H NMR spectra was recorded with a Varian Mercury PLUS400 spectrometer with TMS as the internal reference and $CDCl_3$ as the solvent, while mass spectra were obtained with a Finnigan TRACEMS2000 spectrometer using the EI method. Infrared (IR) spectra were measured by a Nicolet NEXUS470 spectrometer. Elemental analyses were performed with an Elementar Vario ELIII CHNSO elemental analyzer. All the solvents and materials were reagent grade and purified as required. 5-(Azidomethyl)-2-chloro-pyridine (or thiazole) (**1a–b**) was prepared according to the literature procedure [22].

General procedure for the synthesis of 1-[1-(arylmethyl)-5-methyl-1H-1,2,3-triazol-4-yl] ethanone 2 [23]. 5-(Azidomethyl)-2-chloro-pyridine (or thiazole) **1** (0.05 mol) and acetylacetone (5.0 g, 0.05 mol) were added to a suspension of milled potassium carbonate (20.7 g, 0.15 mol) in DMSO (50 mL). The mixture was stirred at room temperature for 6–8 h

Table 1

The insecticidal and fungicidal activities of **4a–4g** (inhibitory rate (%).

Compd.	Insecticidal activity (250 mg/L) against aphides	Fungicidal activity (100 mg/L)					
		Fusarium oxysporium	*Rhizoctonia solani*	*Botrytis cinereapers*	*Gibberella zeae*	*Dothiorella gregaria*	*Colletotrichum gossypii*
4a	50.9	23.1	44.3	22.2	61.1	65.4	66.7
4b	45.8	30.4	52.5	33.3	54.6	52.4	45.5
4c	100	34.6	63.9	40.7	58.3	50.0	48.2
4d	23.3	26.9	52.6	25.9	55.6	53.9	55.7
4e	16.0	23.1	38.1	55.6	50.0	30.8	48.2
4f	44.8	15.4	67.0	48.2	38.9	15.4	29.6
4g	90.6	26.9	78.4	51.9	63.9	69.2	51.9

(monitored by TLC); the mixture was poured to water (500 mL). The solid was collected by filtration, washed with water and diethyl ether, and dried to give **2** as a white solid.

1-{1-[(6-Chloropyridin-3-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone (2a) [19]. White solid, yield: 81%, mp 121–122°C; ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 5.52 (s, 2H, CH_2), 7.36 (d, J = 8.4 Hz, 1H, PyH), 7.52 (d, J = 11.2 Hz, 1H, PyH), 8.36 (s, 1H, PyH).

1-{1-[(2-Chlorothiazol-5-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone (2b). White solid, yield: 78%, mp 97–98°C; ^{1}H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 7.51 (s, 1H, thiazole-H).

General procedure for the synthesis of 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime (3a–b). To the stirred mixture of hydroxylamine hydrochloride (2.2 g, 32 mmol), **2** (20.0 mmol), ethanol (40 mL), and H_2O (4 mL), sodium hydroxide (2 g, 50 mmol) was added slowly. After the addition completed, the solution was stirred at room temperature (for **3b**) or under reflux (for **3a**) for 5–6 h, the mixture was poured to water (200 mL). The solid was collected by filtration and recrystallized from toluene to get **3** as a white solid.

1-{1-[(6-Chloropyridin-3-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone oxime (3a). White solid, yield: 51%, mp 172–174°C; IR: OH 3421, CH_3 1419, 1385 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.54 (s, 1H, OH), 2.42 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 7.34 (d, J = 8.0 Hz, 1H, PyH), 7.50 (d, J = 10.8 Hz, 1H, PyH), 8.35 (s, 1H, PyH); ms: m/z 265 (M^+, 10.5), 236 (37.1), 126 (100), 90 (22.3), 77 (8.3), 73 (32.9), 63 (15.8). Anal. Calcd. for $C_{11}H_{12}ClN_5O$: C, 49.72; H, 4.55; N, 26.36. Found: C, 49.57; H, 4.75; N, 26.18.

1-{1-[(2-Chlorothiazol-5-yl) methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone oxime (3b). White solid, yield: 43%, mp 139–141°C; ^{1}H NMR ($CDCl_3$): δ 1.62 (s, 1H, OH), 2.60 (s, 3H, CH_3), 2.69 (s, 3H, CH_3), 5.62 (s, 2H, CH_2), 7.53 (s, 1H, thiazole-H). Anal. Calcd. for $C_9H_{10}ClN_5OS$: C, 39.78; H, 3.71; N, 25.77. Found: C, 39.94; H, 3.53; N, 25.89.

General procedure for the synthesis of *O-(E)*-(arylmethyl) 1-[1-(arylmethyl)-5-methyl-1*H*-1,2,3-triazol-4-yl] ethanone oxime ethers 4a–g. A solution of **3** (2 mmol) in anhydrous CH_3CN (10 mL) and NaOH powder (2 mmol) was added to a three-necked flask. After vigorously stirring for 5–10 min, a solution of arylmethyl chloride (2 mmol) in anhydrous CH_3CN (5 mL) was added dropwise. After the addition completed, the mixture was stirred at room temperature or under reflux till the reaction was complete (monitored by TLC). The solid was filtered off, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (1:1 v/v) as the eluent, giving the corresponding **4a–g** in 58–85% yields.

O-(E)-[(6-chloropyridin-3-yl)methy] 1-{1-[(6-chloropyridin-3-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl} ethanone oxime ether (4a). White crystal, yield: 85%, mp 125–127°C; IR: C=N 1589, 1566, Ar 1460, 1436, 1388, 1349, N-O-C 1019; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.13 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 7.27–8.40 (m, 6H, PyH); ms: m/z 388 (M^+, 94.1), 264 (9.2), 248(4.50), 126 (100). Anal. Calcd. for $C_{17}H_{16}Cl_2N_6O$: C, 52.19; H, 4.12; N, 21.48. Found: C, 52.33; H, 4.34; N, 21.32.

O-(E)-[(2-chlorothiazol-5-yl)methyl] 1-{1-[(6-chloropyridin-3-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4b). White crystal, yield: 82%, mp 90–91°C; IR: C=N 1590, 1566, Ar 1461, 1412, 1396, 1366, N-O-C 1017; ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 5.50 (s, 2H, CH_2), 7.26–8.35 (m, 4H, thiazole-H, PyH); ms: m/z 396 (M^+, 12.5), 131 (100), 126 (94.3), 89 (47.7), 70 (69.4). Anal. Calcd. for $C_{15}H_{14}Cl_2N_6OS$: C, 45.35; H, 3.55; N, 21.15. Found: C, 45.03; H, 3.62; N, 20.97.

O-(E)-benzyl 1-{1-[(6-chloropyridin-3-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4c). White crystal, yield: 80%, mp 75–77°C; ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.16 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 7.26–8.33 (m, 8H, PhH, PyH); Anal. Calcd. for $C_{18}H_{18}ClN_5O$: C, 60.76; H, 5.10; N, 19.68. Found: C, 60.85; H, 5.23; N, 19.84.

O-(E)-[(pyridin-3-yl)methyl] 1-{1-[(6-chloropyridin-3-yl)methyl] -5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4d). White crystal, yield: 68%, mp 80–82°C; IR: CH=N 1586, Ar-H, Py-H 1565, 1484, 1460, 1392, 1334, N-O-C 1033; ^{1}H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 5.18 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 7.26–8.62 (m, 7H, PyH); Anal. Calcd. for $C_{17}H_{17}ClN_6O$: C, 57.22; H, 4.80; N, 23.55. Found: C, 57.48; H, 4.74; N, 23.27.

O-(E)-[(6-chloropyridin-3-yl)methyl] 1-{1-[(2-chlorothiazol-5-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4e). Yellow oil, yield: 61%; IR: CH=N 1592, Ar-H, Py-H 1567, 1491, 1448, 1392, 1327, N-O-C 1039; ^{1}H NMR ($CDCl_3$): δ 2.60 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.14 (s, 2H, CH_2), 5.58 (s, 2H, CH_2), 7.27–8.40 (m, 4H, thiazole-H, PyH). Anal. Calcd. for $C_{15}H_{14}Cl_2N_6OS$: C, 45.35; H, 3.55; N, 21.15. Found: C, 45.46; H, 3.78; N, 21.36.

O-(E)-[(2-chlorothiazol-5-yl)methyl] 1-{1-[(2-chlorothiazol-5-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4f). Yellow oil, yield: 74%; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 5.22 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 7.49 (s, 1H, thiazloe-H), 7.52 (s, 1H, thiazole-H). Anal. Calcd. for $C_{13}H_{12}Cl_2N_6OS_2$: C, 38.71; H, 3.00; N, 20.84. Found: C, 38.96; H, 3.21; N, 20.93.

O-(E)-benzyl 1-{1-[(2-chlorothiazol-5-yl)methyl]-5-methyl-1H-1,2,3-triazol-4-yl}ethanone oxime ether (4g). Yellow oil, yield: 58%; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 5.57 (s, 2H, CH_2), 7.27–7.52 (m, 6H, thiazole-H, PhH); ms: *m/z* 361 (M^+, 10.9), 131 (34.8), 90 (100), 76 (60.7), 62 (25.7). Anal. Calcd. for $C_{16}H_{16}ClN_5OS$: C, 53.11; H, 4.46; N, 19.35. Found: C, 53.28; H, 4.70; N, 19.61.

Fungicidal activity testing. The fungicidal activity measurement method was adapted from the one described by Molina-Torres et al. [24]. The synthesized target compounds were dissolved in 0.5–1.0 mL of DMF to the concentration of 1000 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50°C. The mixtures were poured into petridishes. After the dished were cooled, the solidified plates were incubated with 4-mm mycelium disk, inverted, and incubated at 28°C for 48 h. Distilled water was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibitory rates were calculated with the following equation: $I = [(C-T)/C] \times 100\%$. Here, I is the growth inhibitory rate (%), T is the treatment group fungi settlement radius (mm), and C is the radius of the blank control. The results are listed in Table 1.

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