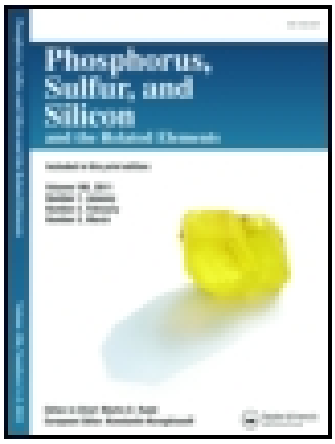

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Synthesis and bioactivities of novel 1,3,4-oxadiazole derivatives containing 1,2,3-thiadiazole moiety

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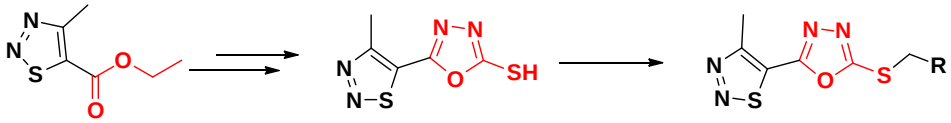
Abstract: *Some novel 1,3,4-oxadiazole derivatives containing 1,2,3-thiadiazole were synthesized under microwave assistant condition by multi-step reactions. The structures were characterized by ^{1}H NMR, MS and elemental analyses. The target compounds were evaluated for their herbicidal activities against Brassica campestris and Echinochloa crusgalli, and the results indicated that some of the title compounds displayed good herbicidal activities.*



Keywords: 1,3,4-oxadiazole, 1,2,3-thiadiazole, Herbicidal activity, Microwave synthesis

INTRODUCTION

In recent years, nitrogen-containing heterocyclic compounds had received considerable attention due to their pharmacological and pesticidal importance [1-4], especially 1,3,4-oxadiazole and 1,2,3-thiadiazole. 1,3,4-Oxadiazole, and its derivatives, represent one of the most biologically active classes of compounds with exhibited diversity in medicinal and agrochemical fields, including anti-inflammatory activities [5], antibacterial activities[6], herbicidal activities[7], insecticidal activities [8], antifungal activities [9]. Some compounds have been developed as commercial fungicides or herbicides, such as Triadimefon, Triadimenol, Flusilazole and Flupoxam. On the other hand, the 1,2,3-thiadiazole moiety has been claimed to have many applications, because its derivatives exhibited wide spectrum biological properties, such as antiviral [10], herbicidal [11, 12], antifungal activities [13]. There are many reports about each of the two heterocycles, but the combination of 1,2,3-thiadiazole ring with 1,2,4-triazole ring in one molecule is seldom reported both in chemistry and their biological activity studies.

In view of these facts mentioned above, and also as a part of our work [14] on the synthesis of bioactive lead compounds, the title compounds were designed by introducing 1,2,3-thiadiazole pharmacophore into 1,3,4-oxadiazole scaffold. Some novel 1,3,4-oxadiaiazole derivatives were synthesized and characterized by ^{1}H NMR, MS and elemental analysis. The herbicidal activities of these compounds were tested *in vivo*.

RESULTS AND DISCUSSION

The synthesis procedures for title compounds were shown in Scheme **1**. The key intermediate ethyl 4-methyl-1,2,3-thiadiazole-5-carboxylate was synthesized using the Hurd-Mori method[16]. Then the intermediate 3 was reacted with 85% hydrazine hydrate to give intermediate **4**. The intermediate **4** was easily cyclized with CS_2 to give intermediate **5** under alkaline conditions, such as KOH. Furthermore intermediate **5** was reacted with substituted benzyl chlorides to afford compounds **6** under microwave irradiation. The microwave irradiation assisted synthesis and conventional methods were also employed in this experiment. In the microwave irradiation reaction system, NaOH/DMF/H_2O was added to the reaction mixture. From the Table **1**, the best microwave irradiation reaction condition is at 90 ^oC for 15 min. The yield of title compound is higher than that of the conventional method; also the microwave reaction time is shorter.

All the proposed structures were fully confirmed by ^1H NMR, MS, elemental analysis and ESI-MS or HRMS. The signal peak of CH_2 protons of the thioether adjacent to the oxadiazole ring was observed at δ 4.51 ~ 4.65 ppm respectively. The chemical shifts around 3.0 ppm are the CH_3 of 4-methyl-1,2,3-thiadiazole group. The ESI-MS spectra showed that the m/z of molecular ion, was in accorded with its molecular formula. The elemental analyses also confirmed this.

The herbicidal activity against *Echinochloa crusgalli* and *Brassica campestris* of the title compounds was evaluated and the data were shown in Table S 1 (Supplemental materials). As

can be seen from the data, all the compounds exhibited a good inhibition against *Brassica campestris* at 100 $\mu g \cdot ml^{-1}$. Especially, compounds 6c and 6e displayed good herbicidal activity at 100 mg/mL with 75.3% and 71.9% inhibitory, respectively. Even at 10$\mu g \cdot ml^{-1}$, compound **6c** still exhibited moderate herbicidal activity (50.6%). All the other compounds showed moderate herbicidal activity against *Brassica campestris.* But all these compounds showed weak herbicidal activity against *Echinochloa crusgalli,* except compound 6i which exhibited moderate activity.

EXPERIMENTAL

Materials and Methods

All the reagents were of analytical grade. Melting points were determined using an X-4 apparatus and uncorrected. ^{1}H NMR spectra were measured on a Bruker AC-P500 (300Hz) instrument using TMS as an internal standard and $CDCl_3$ as solvent. Elemental analyses were performed on a Vario EL elemental analyzer.

Microwave assistant synthesis was carried out in a CEM Discover Focused Synthesizer.

Representative 1H NMR for products 6a, 6c and 6i are presented in the Supplemental Materials (Figures S 1 – S 3)

Synthesis

Intermediate 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide **4** was synthesized according to the literature [16].

Carbonic acid diethyl ester (11.8 g, 0.1 mol) and hydrazine hydrate (5.6 mL, 0.095 mol, 85%) were added into a 250 mL round-bottom flask equipped with a condenser. The reaction mixture was heated to 50 ^{o}C and stirred for 20 min, and then cooled down to room temperature and further stirred for 30 h. Water, ethanol, and excess carbonic acid diethyl ester were distilled off under reduced pressure. After drying, a white crystal (**2**) (9.88 g) was obtained with a yield of 95%.

To a stirred solution of compound 2 (6.36 g, 0.06 mol) in ethanol (16.7 mL), a solution of ethyl acetoacetate (7.8 g, 0.06 mol) in ethanol (3.7 mL) was added at room temperature. After stirring for 6 h, then, the solvent was removed in vacuo and the crude product 3-ethoxy carbonyl hydrazonoacetic acid ethyl ester was directly used in the next step without further purification. 3-Ethoxy carbonyl hydrazonoacetic acid ethyl ester (12.8 g, 0.06 mol) was dissolved in dry dichloromethane (25 mL), and thionyl chloride (20 mL) was further added into the stirred reaction mixture dropwisely at 0 ^{o}C for 1 h. Next, the reaction mixture was permitted to stand for 20 h at room temperature. The excess thionyl chloride and dichloromethane were distilled off, and the remaining residue was subjected to fractional distillation under reduced pressure. A slightly yellowish oil 3 (7.95 g) was obtained in yield of 77%.

A mixture of 4-methyl-1,2,3-thiadiazole-5-carboxylic acid ethyl ester (1.72 g, 10 mmol) and hydrazine hydrate (12 mmol) in 10 mL of methanol was stirred vigorously for 0.5 h at room

temperature, the resulted mixture was then filtered, and the solid was washed with cold methanol. After drying, the solid was recrystallized from methanol to give intermediate (**4**).

Preparation of 5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole-2-thiol (5)

A solution of 4-methyl-1,2,3-thiadiazole-5-carbohydrazide **4** (1.58 g, 10 mmol), potassium hydroxide (0.56 g, 10 mmol) and ethanol (15 mL) was heated under reflux for 6 h. Methanol was distilled off under reduced pressure and the yellow product was acidified with dilute hydrochloric acid. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol to afford a white solid 1.4 g; yield 70%; mp147-148 ˚C. ^{1}H NMR(400 MHz, $CDCl_3$) δ: 11.20(s, 1H, SH), 3.28 (s, 3H, CH_3).

General procedure for thioether **(6)**

A CEM designed 10 mL pressure-rated vial was charged with DMF (15 mL), **5** (1.5 g, 5.1 mmol) and K_2CO_3 (0.2 g, 5.6 mmol) and 2,4-dichlorobenzyl chloride (5.1 mmol). The mixture was irradiated in a CEM Discover Focused Synthesizer (150 W, 90°C, 200 psi, 15 min). The mixture was cooled to room temperature by passing compressed air through the microwave cavity for 2 min. It was poured into cold ice (40 mL) and the precipitate that formed with filtered. The crude solid was recrystallized from EtOH to give the title compounds **6a**. All the other compounds were synthesized according the same procedure.

2-(2,4-dichlorobenzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6a: Yield 86%, yield as white crystals; m.p. 85-86 ◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:3.06(s, 3H, Het-Me),

4.60(s, 2H, SCH_2), 7.22(d, *J*=8.49Hz, 1H, ArH), 7.44(s, 1H, ArH), 7.61(d, *J* = 8.27 Hz, 1H, ArH). MS (ESI), m/z: 360 (M+1). Elemental anal. (%), calculated: C, 40.12; H, 2.24; N, 15.60; found: C, 39.88; H, 2.55; N,15.79.

2-(3-chlorobenzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6b: Yield 73.5%, white crystal; m.p. 88-89◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:3.06(s, 3H, Het-Me), 4.51(s, 2H, SCH_2), 7.30(s, 2H, ArH), 7.34-7.39(m, 1H, ArH), 7.47(s, 1H, ArH). MS (ESI), m/z: 326 (M+1). Elemental anal. (%), calculated: C, 44.37; H, 2.79; N, 17.25; found: C, 44.67; H, 2.85; N,17.43.

2-(3-fluorobenzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6c: Yield 88%, white crystal; m.p. 63-64◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:3.06(s, 3H, Het-Me), 4.53(s, 2H, SCH_2), 7.04(t, *J*=7.46Hz, 1H, ArH), 7.19(d, *J*=9.27Hz, 1H, ArH), 7.29-7.35(m, 2H, ArH). MS (ESI), m/z: 309 (M+1). Elemental anal. (%), calculated: C, 46.74; H, 2.94; N, 18.17; found: C, 46.45; H, 3.12; N, 18.44.

2-(2-chlorobenzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6d: Yield 83%, white crystal; m.p. 98-99◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:3.06(s, 3H, Het-Me), 4.65(s, 2H, SCH_2), 7.26-7.30(m, 2H, ArH), 7.41(d, *J*=7.45Hz, 1H, ArH), 7.63(d, *J*=7.14Hz, 1H, ArH). MS (ESI), m/z: 326 (M+1). Elemental anal. (%), calculated: C, 44.37; H, 2.79; N, 17.25; found: C, 44.64; H, 2.99; N, 17.01.

2-(2-fluorobenzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6e: Yield 84%, white crystal; m.p. 78-79◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:3.06(s, 3H, Het-Me), 4.58(s, 2H, SCH_2),

7.07-7.14(m, 2H, ArH), 7.29-7.33(m, 1H, ArH), 7.55(t, *J*=8.20Hz, 1H, ArH). MS (ESI), m/z: 309 (M+1). Elemental anal. (%), calculated: C, 46.74; H, 2.94; N, 18.17; found: C, 46.88; H, 3.12; N, 18.43.

2-(4-methyl-1,2,3-thiadiazol-5-yl)-5-(2-methylbenzylthio)-1,3,4-oxadiazole 6f: Yield 90%, white crystal; m.p. 79-80◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:2.45(s, 3H, Ar-Me), 3.06(s, 3H, Het-Me), 4.59(s, 2H, SCH_2), 7.8-7.23(m, 2H, ArH), 7.29-7.34(m, 1H, ArH), 7.42(d, *J*=6.11Hz, 1H, ArH). MS (ESI), m/z: 305 (M+1). Elemental anal. (%), calculated: C, 51.30; H, 3.97; N, 18.41; found: C, 51.55; H, 3.87; N, 18.49.

2-(4-fluorobenzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6g: Yield 87%, white crystal; m.p. 84-85◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:2.45(s, 3H, Ar-Me), 3.06(s, 3H, Het-Me), 4.52(s, 2H, SCH_2), 7.06(t, *J*=8.55Hz, 2H, ArH), 7.46(d, *J*=5.76Hz, 2H, ArH). MS (ESI), m/z: 305 (M+1). Elemental anal. (%), calculated: C, 46.74; H, 2.94; N, 18.17; found: C, 46.88; H, 3.06; N, 17.99.

2-(benzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6h: Yield 90%, white crystal; m.p. 72-73◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:3.05(s, 3H, Het-Me), 4.55(s, 2H, SCH_2), 7.30-7.37(m, 3H, ArH), 7.46(d, *J*=7.21Hz, 2H, ArH). MS (ESI), m/z: 291 (M+1). Elemental anal. (%), calculated: C, 49.64; H, 3.47; N, 19.30; found: C, 50.01; H, 3.78; N, 19.12.

2-(4-methoxybenzylthio)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-oxadiazole 6i: Yield 91%, white crystal; m.p. 56-57◦C; ^{1}H NMR ($CDCl_3$, 400 MHz), δ:3.05(s, 3H, Het-Me), 3.80(s, 3H,

OMe), 4.52(s, 2H, SCH_2), 6.87(d, *J*=8.41Hz, 2H, ArH), 7.41(d, *J*=8.46Hz, 2H, ArH). MS (ESI), m/z: 321 (M+1). Elemental anal. (%), calculated: C, 48.73; H, 3.78; N, 17.49; found: C, 48.78; H, 3.99; N, 17.54.

Herbicidal Activity Assay

The herbicidal activities were determined according the reference method[17]. Each sample was repeated three times.

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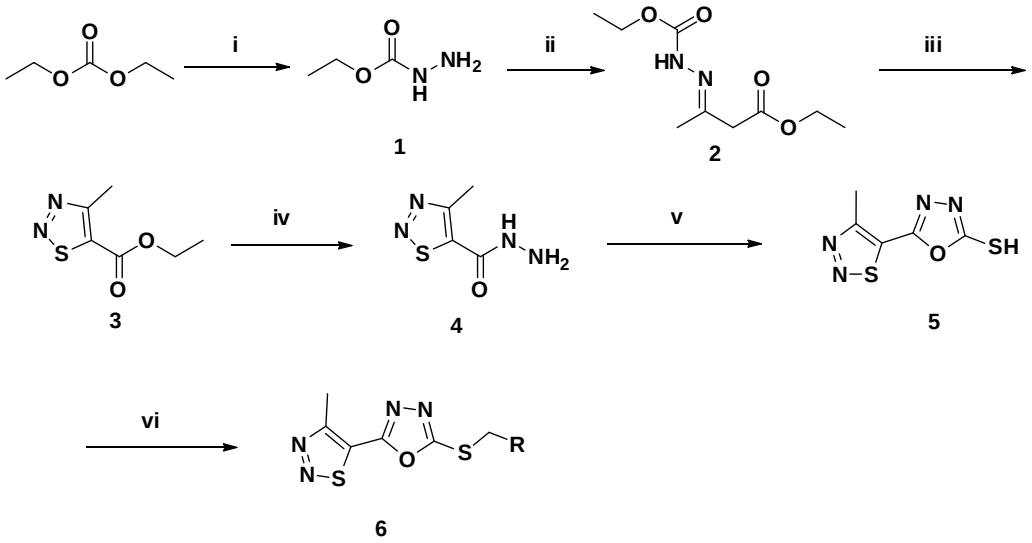

Scheme 1. Reagents and conditions: (i) $NH_2NH_2\,H_2O$, EtOH, reflux; (ii) ethyl 3-oxobutanoate, EtOH, room temperature; (iii) $SOCl_2$, room temperature (iv) $NH_2NH_2\,H_2O$, EtOH, reflux; (v) CS_2, KOH, MeOH, reflux,HCl; (vi) R_2CH_2Cl,NaOH, DMF, MW

Table 1 Comparison of yields of 6a through methods with orwithout microwave irradiation

No.	Method	Time	Temperature/℃	Yield/%
6a	No-MW	24h	r.t.	78
6a	No-MW	4h	90	84
6a	MW	10min	90	74
6a	MW	15min	90	86
6a	MW	20min	90	85