Design, synthesis and biological activities of novel 1,2,3-thiadiazole derivatives containing oxime ether

Wei-li Dong, Hong-wei Yao, Zheng-ming Li and Wei-guang Zhao*

State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071 China

A series of novel 2-methoxyimino-1,2,3-thiadiazole-5-acetamide derivatives were synthesised. Their structures were identified by means of elemental analysis, IR, ^{1}H NMR and MS spectra. The preliminary biological activity tests showed that some of the compounds showed some fungicidal activity.

Keywords: 1,2,3-thiadiazole, oxime ether, biological activity

In the investigation of new agrochemicals, we found 1,2,3-thiadiazole derivatives, which had good biological and pharmaceutical activities,[1-3] had received only limited attention, but commercial pesticides containing 1,2,3-thiadiazole often possess simple structure and unique active mechanism. For example, thidiazuron (TDZ),[4] a cotton defoliant, has been found to exhibit more significant plant growth regulative activity than 6-benzyladenine (6-BA) and zeatin. Benzothiadiazole (BTH)[5] was the first commercial plant activator. Tiadinil was an excellent plant activator[6] (Fig. 1). Furthermore, 1,2,3-thiadiazolecarboxamides also displayed good fungicidal activities.[7,8] We herein became interested in making 1,2,3-thiadiazoleacetamides, analogues of three commercial pesticides.

In the previous paper, we had reported some 1,2,3-thiadiazoleacetamides exhibited better anti-tobacco mosaic virus (anti-TMV) activity, plant growth-regulating activity and showed some anti-hepatitis B virus (anti-HBV) activity.[9-12] Considering the oxime ethers are very important active compounds, many of them are used as insecticide, fungicide, herbicide and so on, and oxime ether group is often used in new pesticide discovery because of their high biological activites and their good environmental profiles.[13] In order to search for novel 1,2,3-thiadiazole derivatives which have high activities, we report here our synthesise a series of novel 2-methoxyimino-1,2,3-thiadiazole-5-acetamides **6.** Their structures were confirmed by elemental analysis, IR, ^{1}H NMR and MS spectra. And we also synthesised commercial Tiadinil. Fungicidal activities of these 1,2,3-thiadiazole compounds synthesised were evaluated through disc paper method. The results showed that these compounds exhibited weak fungicidal activities.

Experimental

Instruments

Melting points were conducted on a Yanaco MP-500 micro melting-point apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ as solvent on Bruker AC-300 instrument using TMS as an internal standard. Elemental analysis was performed on a Yanaco CHN Corder MF-3 automatic elemental analyser. Mass spectra were recorded with VG ZAB-HS, 8kV, 1 mA using the Fast Atom Bombardment (FAB) method. Microwave activation was carried out with LWMC-201.

Synthesis of diethyl 2-(1,2,3-thiadiazol-5-yl)malonate (**2**): The starting material, 5-chloro-1,2,3-thiadiazole **1** was obtained by synthesis.[14] To 100 ml of absolute ethanol in a 250 ml three-necked round-bottomed flask equipped with a reflux condenser bearing a calcium chloride tube is added 1.38 g (60 mmol) of sodium cut in pieces of suitable size. When all the sodium has reacted, diethyl malonate (9.60 g, 60 mmol) was added dropwise at room temperature and the mixture was stirred for 20 min, then 5-chloro-

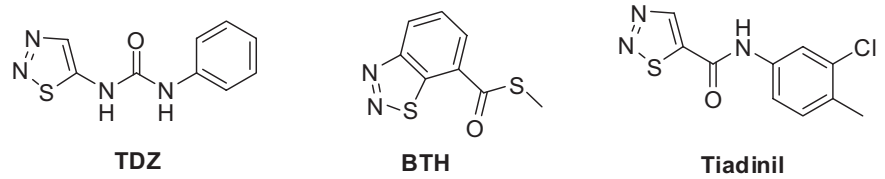
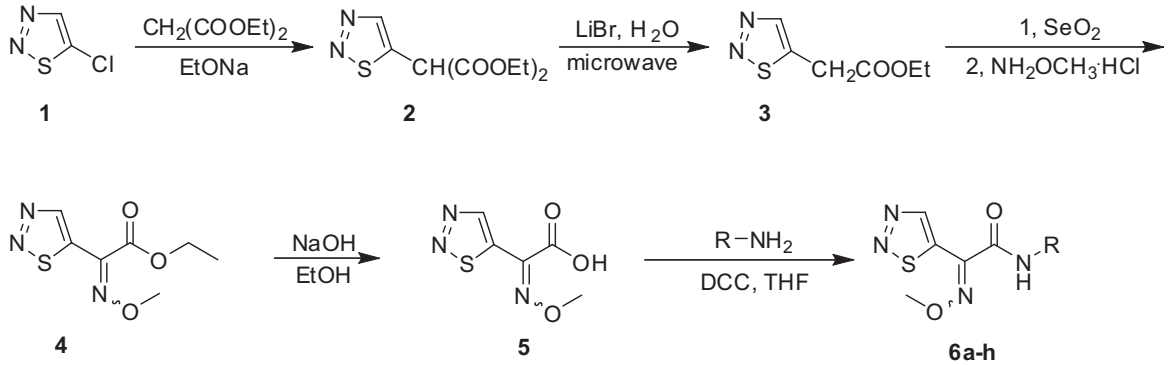


Fig. 1 Structures of TDZ, BTH, Tiadinil.



Scheme 1 Synthesis routes of the derivatives of 1,2,3-thiadiazole (**6a–6h**). **6a** R = 4-methylphenyl; **6b** R = 3-chloro-4-methylphenyl; **6c** R = 3,4-dichlorophenyl; **6d** R = 3-nitrophenyl; **6e** R = 4-methylpyrimidin-2-yl; **6f** R = 2,5-dichlorophenyl; **6g** R = naphthalen-2-yl; **6h** R = 3,4-dimethoxyphenethyl

* Correspondent. E-mail: zwg@nankai.edu.cn

1,2,3-thiadiazole **1** (6.63 g, 55 mmol) was slowly added, the mixture was stirred at room temperature for 24 h. After removal of solvent, the residue was treated with 200 ml water, acidified to *ca* pH = 4 with 6 mol/l HCl. The solution was extracted with ethyl acetate (2 × 100 ml). The combined ethyl acetate extracts were washed with water (2 × 50 ml), dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio1:10) to obtain **2** (8.06 g, 60.0%) as a yellow liquid; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.26–1.31 (m, 6H, CH_3), 4.25–4.31 (m, 4H, CH_2), 4.15 (s, 1H, CH), 8.73 (s, 1H, thiadiazole-H); Elemental anal. (%), calculated for $C_9H_{12}N_2O_4S$: C, 44.25; H, 4.95; N, 11.47; found: C, 43.99; H, 4.90; N, 11.29.

*Synthesis of ethyl 2-(1,2,3-thiadiazol-5-yl)acetate (**3**): A mixture of the malonate ester* **2** (2.44 g, 10 mmol), lithium bromide (1.73 g, 20 mmol), tetrabutylammonium bromide (0.32 g, 1 mmol) and 5 ml water. The reaction mixture was heated for 30 min under MW heating conditions with an irradiation power of 120 W. After being cooled to room temperature, water (10 ml) was added, the mixture was extracted with ethyl acetate (2 × 20 ml), dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio 1:10) to obtain **3** (1.50 g, 87.1%) as a white solid; m.p. 32–34°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.31 (t, J = 7.2 Hz, 3H, CH_3), 4.11 (s, 1H, CH), 4.25 (q, J = 7.2 Hz, 4H, CH_2), 8.64 (s, 1H, thiadiazole-H); Elemental anal. (%), calculated for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27; found: C, 41.56; H, 4.94; N, 16.35.

Synthesis of ethyl 2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl)acetate (**4**): A mixture of selenium dioxide (0.23 g, 11 mmol) dissolved in 30 ml 1,4-dioxane and 0.5 ml H_2O was heated under reflux, then the solution of monoesters **3**(1.9 g, 11 mmol) in 20 ml 1,4-dioxane was added dropwise. After the mixture was refluxed for 8 h, cooled, evaporated *in vacuo* to give the residue. Subsequently, a solution of the residue, NaOH (0.47 g, 11.8 mol), and hydroxylamine hydrochloride (0.99 g, 11.8 mol) in absolute ethanol (30 ml) was heated under reflux for 3 h. After the mixture was cooled, evaporated in vacuo to give the residue, the solid residue was purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio 1:3) to give compound **4** (1.32 g, 56.0%) as a yellow solid; m.p. 44–46°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 1.44 (t, J = 6.9 Hz, 3H, CH_3), 4.41 (s, 1H, CH), 4.42 (q, J = 6.9 Hz, 4H, CH_2), 9.69 (s, 1H, thiadiazole—H); Elemental anal. (%), calculated for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.52; found: C, 38.86; H, 4.19; N, 19.49.

Synthesis of 2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl)acetic acid (**5**): Aqueous NaOH (15%, 80 ml) was added to a solution of ester **4** (3.31 g, 15.4 mmol) in MeOH-tetrahydrofuran (40 ml, volume ratio 1:1). After the mixture had been stirred for 1 h at room temperature the organic solvents were evaporated off, water was added, and the solution was and acidified using dilute HCl to pH 1.5. The aqueous solution was extracted with ethyl acetate (2 × 100 ml), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give product **5** (2.7 g, 93%, yellow solid) as a yellow solid; m.p. 126–132°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.463 (s, 1H, CH), 9.882 (s, 1H, thiadiazole-H); Elemental anal. (%), calculated for $C_5H_5N_3O_3S$: C, 32.08; H, 2.69; N, 22.45; found: C, 31.79; H, 2.69; N, 22.00.

General procedure for 2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl)acetamide (**6a–g**): 2-(Methoxyimino)2-(-1,2,3-thiadiazol-5-yl)acetic acid **5** (1.5 mmol), the amine (1.5 mmol), DCC (1.55 mmol), and a catalytic amount of DMAP (0.15 mmol) were suspended in anhydrous THF (20 ml). After the mixture was heated under reflux for 12 h, the solvent was removed *in vacuo*, and the solid residue was purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio 1/3) to give the amides **6a–g**.

2-(Methoxyimino)-2-(1,2,3-thiadiazol-5-yl)-N-(p-tolyl)acetamide (**6a**): The compound was obtained in 54.3% yield as a white solid; m.p. 125–127°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.86 (t, J = 7.2 Hz, 2H, CH_2), 3.63–3.70 (q, J = 6.6 Hz, 2H, CH_2), 3.88 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.28 (s, 3H, CH_3), 6.76–6.85 (m, 3H, Ph), 7.06 (br, 1H,NH), 9.82 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3458, 3236, 3037, 3002, 1735, 1602, 1583, 1450, 1364. Elemental anal. (%), calculated for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 21.27; found: C, 51.90; H, 4.50; N, 20.98.

N-(3-Chloro-4-methylphenyl)-2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl)acetamide (**6b**): The compound was obtained in 69.8% yield as a white solid; m.p. 155–156°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.36 (s, 3H, CH_3), 4.41(s, 3H, CH_3), 7.23–7.73 (m, 3H, Ph), 8.70 (br, 1H,NH), 9.89 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3454, 3148, 3025, 2979, 1741, 1605, 1583, 1447, 1312. MS (ESI), *m/z*: 310 (M -1). Elemental anal. (%), calculated for $C_{12}H_{11}ClN_4O_2S$: C, 46.38; H, 3.57; N, 18.03; found: C, 46.15; H, 3.46; N, 18.29.

N-(3,4-Dichlorophenyl)-2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl)acetamide (**6c**): The compound was obtained in 55.6% yield as a white solid; m.p. 163–166°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.44 (s, 3H, CH_3), 7.31–8.46 (m, 3H, Ph), 9.43 (br, 1H,NH), 9.91 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3429, 3329, 3132, 3104, 2951, 1690, 1604, 1589,1451, 1420, 1230. Elemental anal. (%), calculated for $C_{11}H_8Cl_2N_4O_2S$: C, 39.89; H, 2.43; N, 16.92; found: C, 39.78; H, 2.75; N, 16.51.

N-(3-Nitrophenyl)-2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl) acetamide (**6d**): The compound was obtained in 56.0% yield as a white solid; m.p. 208–214°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.46 (s, 3H, CH_3), 7.57–8.514 (m, 4H, Ph), 9.99 (br, 1H, NH), 9.92 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3430, 3227, 3106, 2987, 1732, 1609, 1584, 1550, 1453, 1349. Elemental anal. (%), calculated for $C_{11}H_9N_5O_4S$: C, 43.00; H, 2.95; N, 22.79; found: C, 43.42; H, 3.21; N, 22.58.

N-(4-Methylpyrimidin-2-yl)-2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl)acetamide (**6e**): The compound was obtained in 54.0% yield as a white solid; m.p. 129–133°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.56 (s, 3H, CH_3), 4.44 (s, 3H, OCH_3), 6.99–8.60 (m, 2H, pyrimidin-H), 9.48 (br, 1H, NH), 9.95 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3409, 3231, 3194, 3020, 1714, 1605, 1558, 1524, 1400. Elemental anal. (%), calculated for $C_{10}H_{10}N_6O_2S$: C, 43.16; H, 3.62; N, 30.20; found: C, 43.45; H, 3.82; N, 29.93.

N-(2,5-Dichlorophenyl)-2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl) acetamide (**6f**): The compound was obtained in 58.6% yield as a white solid; m.p. 182–185°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.38 (s, 3H, CH_3), 7.03–8.51 (m, 3H, Ph), 9.43 (br, 1H,NH), 9.85 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3423, 3337, 3117, 3004, 2949, 1686, 1580, 1518, 1445, 1407. Elemental anal. (%), calculated for $C_{11}H_8Cl_2N_4O_2S$: C, 39.89; H, 2.43; N, 16.92; found: C, 39.65; H, 2.70; N, 17.22.

N-(Naphthalen-2-yl)-2-(methoxyimino)-2-(1,2,3-thiadiazol-5-yl) acetamide (**6g**): The compound was obtained in 50.0% yield as a white solid; m.p. 173–175°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 4.38 (s, 3H, CH_3), 7.38–8.28 (m, 7H, naphthalene-H), 8.87 (br, 1H, NH), 9.87 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3442, 3386, 3304, 3044, 2933, 1670, 1582, 1534, 1437, 1363. Elemental anal. (%), calculated for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94; found: C, 57.36; H, 4.13; N, 18.18.

Synthesis of N-[2-(3,4-dimethoxyphenyl)ethyl]-2-(methoxyimino)-1,2,3-thiadiazole-5-acetamide (**6h**): A mixture of ethyl 2-(methoxyimino)-2-(1,2,3-thiadiazol-5-ly)acetic acid, ethyl ester **4** (0.215 g 1 mmol) and 2-(3,4-dimethoxyphenyl)ethanamine (0.36 g, 2 mmol) was stirred at 120~140°C for 2 h, cooled, the solid residue was purified by silica-gel column eluted with ethyl acetate/petroleum ether (volume ratio 1:3) to give the amides **6h** (0.21 g, 60%) as a yellow solid; m.p. 126–132°C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 2.86 (t, J = 7.2 Hz, 2H, CH_2), 3.65 (q, J = 6.6 Hz, 2H, CH_2), 3.88 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.28 (s, 3H, CH_3), 6.76–6.85 (m, 3H, Ph), 7.06 (br, 1H, NH), 9.82 (s, 1H, thiadiazole-H); IR (KBr), ν/cm^{-1}: 3423, 3277, 3002, 2941, 2866, 2836, 1665, 1589, 1519, 1452, 1270, 1230. Elemental anal. (%), calculated for $C_{15}H_{18}N_4O_4S$: C, 51.42; H, 5.18; N, 15.99; found: C, 51.18; H, 5.27; N, 16.25.

Synthesis of N-(3-chloro-4-methylphenyl)-2-(1,2,3-thiadiazol-5-yl) carboxamide (Tiadinil)

Tiadinil obtained according to the literature.[15]

Results and discussion

Synthesis

In the step of removing a balkoxy carbonyl group from the malonic ester **2**, Krapcho's method [16,17] was unsuitable, because the malonic ester contains an 1,2,3-thiadiazole which is liable to decompound in DMSO (>160°C), in order to avoid he use of DMSO at high temperatures, we exploited the method of coupling microwave irradiation and solvent-free PTC(NBu_4Br),[18] but considering instability of 1,2,3-thiadiazole, in the reaction procedure, the water as solvent added excessively to control reaction temperature, the malonate ester **2** can easily be converted into the monoesters **3** by dealkoxycarbonylation, the method has the advantage of comparative and produces higher overall yields than the classical procedure which involves saponification, decarboxylation and esterification.

Biological activities of compounds

The preliminary biological tests showed that both the title compound and Tiadinil shows have little bactericidal activity against *Gibberella zeae*, *Alternaria solani*, *Cercosporsa arachidicola*, *Physalospora piricola Nose*, *Phomaasparagi* (Table 1), it may be that tiadinil is a

Table 1 Fungicidal activity of some compounds (50 μg/ml)

NO.	Inhibition rate/%				
	Gibberella zeae	*Alternaria solani*	*Cercosporsa arachidicola*	*Physalospora piricola Nose*	*Phomaasparagi*
6b	27.3	33.3	23.5	23.9	32.0
6e	28.7	27.6	34.2	36.6	21.5
6f	27.3	28.6	29.4	34.8	20.0
6h	15.4	23.5	29.4	35.5	12.0
Tiadinil	30.8	23.5	17.7	38.7	24.0

plant activator by inducing the plant defense mechanism against a pathogen, but without direct antimicrobial activity. A further study of their plant activator is underway.

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