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Microwave Synthesis and Biological Activity of Hydrazone Derivatives Containing 1,2,3-Thiadiazole

XING-HAI LIU*, JIAN-QUAN WENG and CHENG-XIA TAN

College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou 310014, Zhejiang, P.R. China

*Corresponding author: E-mail: xhliu@zjut.edu.cn

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A new group of hydrazone derivatives containing 1,2,3-thiadiazole moiety were synthesized under microwave irradiation. The structures of the present hydrazone derivatives were characterized by ^{1}H NMR, MS and elemental analysis. The biological activities of the presents compunds were investigated. The bioassay results indicated that some of these compounds exhibit moderate fungicidal activities, one compound showed 100 % inhibitory activity on cotyledon root of cucumber and all the compounds displayed no insecticidal activity.

Key Words: Hydrazone, 1,2,3-Thiadiazole, Biological activity, Microwave irradiation synthesis.

INTRODUCTION

Sulfur and nitrogen linked heterocyclic compounds have received considerable attentions in recent years because of their pharmacological and pesticidal importance[1-3]. 1,2,3-Thiadiazole moiety has been claimed to have beneficial medicinal and agricultural applications[4,5]. Because of its good bioactivity and usefulness as intermediates in organic synthesis, the 1,2,3-thiadiazole chemistry has been widely studied. For instance, after the plant inducers such as thiadinal[6], BTH[7], was discovered (Fig. 1). 1,2,3-Thiadiazoles pesticide has become one of the focuses of developing agrochemicals in academia and industries.

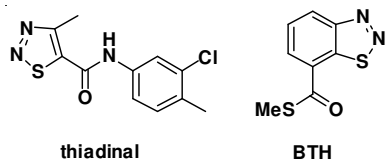

Fig. 1. Commercial pesticides containing 1,2,3-thiadiazole group

Furthermore, it is reported that hydrazones possess a diverse range of bioactivities in medicinal and agrochemical field, such as anticancer[8], antiinflammatory[9], antimicrobial[10], herbicidal[11], fungicidal[12] and insecticidal[13] activity. In addition, hydrazones are very useful starting materials in many reactions for the synthesis of various bioactive molecules[14].

Microwave-assisted synthesis has shown to be valuable method in organic synthesis[15,16], since it can often reduce the reaction times dramatically, typically from days or hours to minutes or even seconds.

In view of these facts and also as a part of our work on the development of bioactive heterocyclic compounds, herein we report the synthesis, characterization and biological study of a series of hydrazone derivatives containing 1,2,3-thiadiazole rings. The synthesis of these compounds was greatly facilitated by the microwave irradiation.

EXPERIMENTAL

Melting points were determined using an X-4 apparatus without calibration. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using tetramethylsilane as an internal standard and deuterochloroform as solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were performed on a Vario EL elemental analyzer. LWMC-250 domestic microwave oven was used to do microwave reaction.

All starting materials were used as purchased or of analytic grade purity. $SOCl_2$ was distillated before use. Analytical TLC was performed on silica gel GF_{254}.

Synthesis of compounds: The title compounds were synthesized according to the route as shown in Fig. 2.

General procedure for the synthesis of 5a-l: Ethyl 4-methyl-1,2,3-thiadiazole-5-carboxylate was prepared by reacting ethyl 3-oxobutanoate with ethyl hydrazinecarboxylate, according to the so-called Hurd-Mori reaction[17,18]. Next, 80 % hydrazine hydrate was added into the solution of ethyl 4-methyl-1,2,3-thiadiazole-5-carboxylate in EtOH and the mixture

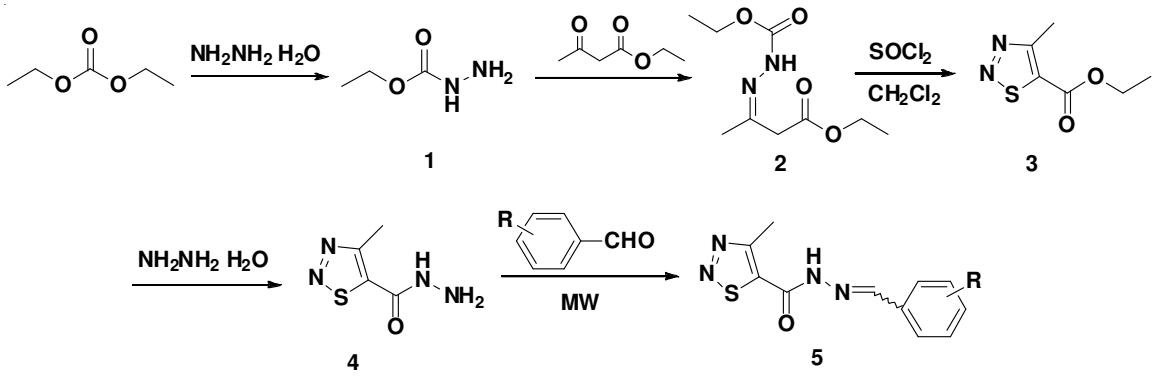

Fig. 2. Synthesis route for compounds **5a-5l**

was refluxed for a further 6 h. After evaporation under reduced pressure, the residue was washed with 40 mL of petroleum ether and then filtered to give a light yellow solid with a yield of 75 %. Subsequently, the substituted aldehydes were added to a solution of 4-methyl-1,2,3-thiadiazole-5-carbohydrazide in ethanol. The reaction was kept under microwave irradiation at 300 W for 4 min and stopped immediately afterwards. Then the reaction mixture was filtered and the solid was washed with ethanol, dried and recrystallized from EtOH to afford the title compounds **5a-l**.

N'-(4-(Dimethylamino)benzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5a): The compound was obtained in 90.1 % yield as a red crystal; m.p. 234-235 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.98 (s, CH, 1H), 7.81 (s, NH, 1H), 6.74-7.66 (m, ArH, 4H), 3.11 (s, N-CH_3, 3H), 3.08 (s, N-CH_3, 3H), 1.55 (s, Het-CH_3, 3H). MS (ESI), m/z: 288 [M-1]$^-$. Anal. calcd. for $C_{13}H_{15}N_5OS$: C, 53.96; H, 5.23; N, 24.20; found: C, 53.80; H, 5.41; N, 24.51.

N'-(3-Methoxybenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5b): The compound was obtained in 93.5% yield as a yellow crystal; m.p. 209-210 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.88 (s, CH, 1H), 7.95 (s, NH, 1H), 6.89-7.34 (m, ArH, 4H), 3.88 (s, CH_3, 3H), 1.45 (s, Het-CH_3, 3H). MS (ESI), m/z: 275 [M-1]$^-$. Anal. calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28; found: C, 52.49; H, 4.25; N, 20.06.

N'-(2-Bromobenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5c): The compound was obtained in 92.5 % yield as a yellow crystal; m.p. 141-142 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.74(s, CH, 1H), 8.42 (s, NH, 1H), 7.35-8.13 (m, ArH, 4H), 1.58 (s, Het-CH_3, 3H). MS (ESI), m/z: 324 [M-1]$^-$. Anal. calcd. for $C_{11}H_9N_4OSBr$: C, 40.63; H, 2.79; N, 17.23; found: C, 40.53; H, 2.77; N, 17.58.

N'-(4-Chlorobenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5d): The compound was obtained in 94.6 % yield as a yellow crystal; m.p. 200-201 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.14 (s, CH, 1H), 8.12 (s, NH, 1H), 6.88-7.68 (m, ArH, 4H), 1.51 (s, Het-CH_3, 3H). MS (ESI), m/z: 279 [M-1]$^-$. Anal. calcd. for $C_{11}H_9N_4OSCl$: C, 47. 06; H, 3.23; N, 19.96; found: C, 46.95; H, 3.05; N, 20.32.

N'-(4-Fluorobenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5e): The compound was obtained in 90.0 % yield as a yellow crystal; m.p. 179-180 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.26 (s, CH, 1H), 8.23 (s, NH, 1H), 7.14-8.08 (m, ArH, 4H), 1.57(s, Het-CH3, 3H). MS (ESI), m/z: 263[M-1]$^-$. Anal. calcd. for $C_{11}H_9N_4OSF$: C, 49.99; H, 3.43; N, 21.20; found: C, 49.88; H, 3.77; N, 21.49.

N'-(4-Methoxybenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5f): The compound was obtained in 95.3 % yield as a yellow crystal; m.p. 224-225 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.42 (s, CH, 1H), 8.34 (s, NH, 1H), 7.34-7.99 (m, ArH, 4H), 3.79 (s, OCH_3, 3H), 1.52 (s, Het-CH_3, 3H). MS (ESI), m/z: 334 [M-1]$^-$. Anal. calcd. for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28; found: C, 52.11; H, 4.55; N, 20.44.

N'-(4-Methybenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5g): The compound was obtained in 93.3 % yield as a yellow crystal; m.p. 235-236 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.33 (s, CH, 1H), 8.54 (s, NH, 1H), 7.04-8.08 (m, ArH, 4H), 2.45(s, CH3, 3H), 1.57(s, Het-CH3, 3H). MS (ESI), m/z: 259 [M-1]$^-$. Anal. calcd. for $C_{12}H_{12}N_4OS$: C, 55.37; H, 4.65; N, 21.52; found: C, 55.62; H, 4.35; N, 21.88.

N'-(4-Bromobenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5h): The compound was obtained in 92.5 % yield as a yellow crystal; m.p. 272-273 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.55 (s, CH, 1H), 8.63 (s, NH, 1H), 6.98-7.89 (m, ArH, 4H), 1.50 (s, Het-CH_3, 3H). MS (ESI), m/z: 324 [M-1]$^-$. Anal. calcd. for $C_{11}H_9N_4OSBr$: C, 40.63; H, 2.79; N, 17.23; found: C, 40.53; H, 2.77; N, 17.58.

N'-(3-Hydroxy-4-methoxybenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5i): The compound was obtained in 94.5 % yield as a yellow crystal; m.p. 225-226 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 8.81 (s, CH, 1H), 7.83 (s, NH, 1H), 6.99-7.45 (m, ArH, 3H), 3.11 (s, CH_3, 3H) 1.56 (s, Het-CH_3, 3H). MS (ESI), m/z: 291 [M-1]$^-$. Anal. calcd. for $C_{12}H_{12}N_4O_3S$: C, 49.31; H, 4.14; N, 19.17; found: C, 49.62; H, 4.39; N, 19.54.

N'-(2-Fluorobenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5j): The compound was obtained in 91.2 % yield as a yellow crystal; m.p. 233-234 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.47 (s, CH, 1H), 8.26 (s, NH, 1H), 7.14-7.52 (m, ArH, 4H), 1.59 (s, Het-CH_3, 3H). MS (ESI), m/z: 263 [M-1]$^-$. Anal. calcd. for $C_{11}H_9N_4OSF$: C, 49.99; H, 3.43; N, 21.20; found: C, 50.12; H, 3.44; N, 21.30.

N'-(4-Hydroxybenzylidene)-4-methyl-1,2,3-thiadiazole-5-carbohydrazide (5k): The compound was obtained in 90.7 % yield as a yellow crystal; m.p. > 300 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.27 (s, CH, 1H), 8.43 (s, NH, 1H), 7.28-7.98 (m, ArH, 4H), 1.54 (s, Het-CH_3, 3H). MS (ESI), m/z: 261 [M-1]$^-$.

Anal. calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.37; H, 3.84; N, 21.36; found: C, 50.34; H, 3.53; N, 20.98.

N'-(4-Nitrobenzylidene)-4-methyl--1,2,3-thiadiazole-5-carbohydrazide (5l): The compound was obtained in 93.2 % yield as a yellow crystal; m.p. 257-258 ºC; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.34 (s, CH, 1H), 8.56 (s, NH, 1H), 6.97-7.53 (m, ArH, 4H), 1.56 (s, Het-CH_3, 3H). MS (ESI), m/z: 290 $[M-1]^-$. Anal. calcd. for $C_{11}H_9N_5O_3S$: C, 45.36; H, 3.11; N, 24.04; found: C, 45.09; H, 3.42; N, 24.33.

Biological activity: The biological activities were determined according to previous methods[15,16].

RESULTS AND DISCUSSION

By treating 4-methyl-1,2,3-thiadiazole-5-carbohydrazide with different substituted aldehydes under microwave irradiation (Fig. 2), a group of 12 hydrazones was produced. The microwave irradiation was carried out with LWMC-250 domestic microwave oven. Several procedures are available for the one-step synthesis of hydrazone derivatives. In this paper, the optimal reaction conditions were established by several reaction times. As demonstrated in Table-1, for the compound **5b**, the microwave irradiation is extremely efficient, which promotes the reaction to completion in only 4 min and also in excellent yield (93.5 %, 300 W). However, if using the conventional reaction conditions, the yield is even lower (< 90 %) at refluxing or 25 ºC condition and longer reaction time (50 min or 4 h). The reaction time is preferably to be no longer than 4 min, because the yield will be lowered. The yield of this method is comparable with that of references[10].

TABLE-1
EFFECT OF DIFFERENT REACTION CONDITIONS AT 300 W

Compd. No.	Method	Time (min)	Yield (%)
5b	Reflux	50	88.5
5b	Room temperature	240	84.8
5b	MW	2	84.6
5b	MW	3	89.4
5b	MW	4	93.5
5b	MW	5	92.1
5b	MW	6	92.4

In the ^{1}H NMR spectra of compound **5**, the -NH proton signals of the title compounds appear at δ 7.81-8.63 ppm. The singlet at δ 8.88-9.74 ppm is assigned to the CH proton, which indicated the transformation of -CH=N- group.

Biological activities: Fungicidal activity, plant growth regulator activity and insecticidal activity of present compounds **5a-5l** against *Gibberella zeae* (Schwein.)Petch. (GZ), *Alternaria solani* (Ellis et Martin) Jones et Grout. (AS), *Cercospora arachidicola* (CA), *Botryosphaeria berengeriana* f.sp. *piricola* (Nose) koganezawa et Sakuma (BB), *Fusarium oxysporum* f.sp. *cucumerinum* (FO), cotyledon root of cucumber (CC), *Mythimna separata* Walker (MS) were determined. The results are listed in Table-2. At the dose of 50 μg/mL, all compounds display weak fungicidal activity, except that the compound **5g** and **5l** have moderate fungicidal activity against *Botryosphaeria berengeriana* f. sp. *piricola* (Nose) koganezawa et Sakuma (43.1 %) and *Cercospora arachidicola* (40.9 %), respectively. All these compounds had no insecticidal activity against *Mythimna separata* Walker at the dose of 200 μg/mL. Surprisingly, compound **5g** showed 100 % inhibitory activity on cotyledon root of cucumber at the dose of 10 μg/mL.

TABLE-2
BIOLOGICAL ACTIVITY OF TITLE COMPOUNDS

Compd. No.	GZ	AS	CA	BB	FO	CC	MS
5a	0	23.5	13.6	33.8	0	32.0	0
5b	0	29.4	31.8	38.5	0	3.7	0
5c	13.0	0	13.6	33.8	8.6	13.2	0
5d	30.4	17.6	31.8	33.8	8.6	13.2	0
5e	0	0	13.6	21.5	13.0	27.3	0
5f	2.7	11.7	18.2	38.5	8.6	22.6	0
5g	17.4	17.6	13.6	43.1	17.4	-100	0
5h	30.4	0	36.4	18.5	8.6	-33.9	0
5i	13.0	11.7	22.7	23.1	8.6	-15.0	0
5j	26.1	11.7	0	21.5	13.0	22.6	0
5k	0	23.5	18.2	21.5	26.1	36.7	0
5l	34.8	11.7	40.9	33.8	13.0	-0.9	0

Note: The test concentration of fungicidal activity is at 50 μg/mL, the cotyledon root of cucumber is at 10 mg/mL and the insecticidal activity is at 200 mg/mL.

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