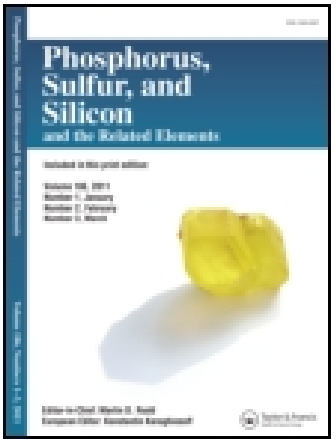

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Microwave-Induced Synthesis and Bioactivity of [3-Phenoxy-methyl-4-phenyl-1,2,4-triazole-5-yl-thio]acetyl Hydrazone Derivatives

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MICROWAVE-INDUCED SYNTHESIS AND BIOACTIVITY OF [3-PHENOXY-METHYL-4-PHENYL-1,2,4-TRIAZOLE-5-YL-THIO]ACETYL HYDRAZONE DERIVATIVES

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A convenient method for the preparation of hydrazone derivatives from condensation reaction of [3-phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio]acetyl hydrazine with various substituted benzaldehydes under conditions of microwave irradiation has been developed. This method has many merits including high yields, short reaction times, ease of work-up, and simple operation. All of the compounds have been characterized by ^{1}H NMR, ^{13}C NMR, IR spectra and elemental analysis. In addition, the preliminary biological activity tests showed that some of the title compounds remarkably enhanced the root elongation of rape seedings; moreover, some compounds possessed antibacterial activity against **Bacillus subtilis.**

Supplemental materials are available for this article. Go to the publisher's online edition of **Phosphorus, Sulfur, and Silicon and the Related Elements** ***to view the free supplemental file.***

Keywords Antibacterial activity; biological activity; hydrazone; triazole

INTRODUCTION

In recent years, a number of hydrazone derivatives have been claimed to possess a wide range of biological activities, such as antituberculosis,[1] antibacterial,[2,3] analgesic/anti-inflammatory,[4] and antimicrobial activities.[5] In addition, high-speed synthesis with microwaves has attracted a considerable amount of attention. The main benefits of performing reactions under microwave irradiation conditions are the significant rate enhancements and higher product yields. In view of this, and as a part of our previous work, a series of novel [3-phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio]acetyl hydrazone derivatives has been synthesized by the condensation reaction of [3-phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio]acetyl hydrazine with various substituted benzaldehydes under conditions of microwave irradiation.

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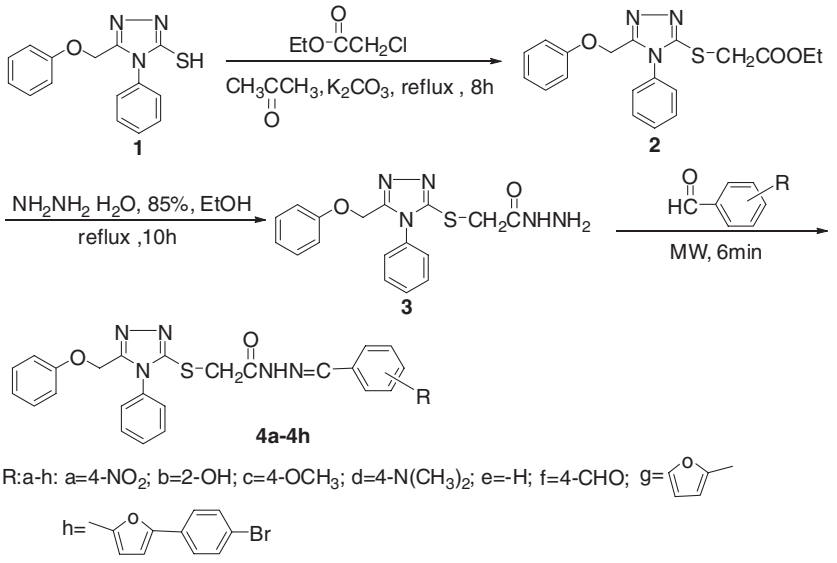

Scheme 1

In this article, we have developed a facile and convenient method for the synthesis of compounds **4a–4h** under conditions of microwave irradiation (Scheme 1). The reaction here has the following advantages: mild conditions, simple operation, short reaction times, and high yield. In addition, the preliminary biological activity tests showed that the compounds remarkably enhanced the root elongation of rape seedings.

RESULTS AND DISCUSSION

IR and NMR Investigation

The IR (KBr) spectra of all compounds exhibit intense sharp bands at 3185–3244 cm^{-1}, which are attributed to the stretching mode of the N—H group. The absorption bands that appeared at 1576–1602 cm^{-1} are assigned to the stretching vibration of the C=N group. Also it is worth mentioning that the spectra of all compounds exhibit a strong band at 1703–1663 cm^{-1}, which can be assigned to the stretching mode for the C=O group. In the ^1H NMR spectra, an example of the compound **4a** revealed signals at δ 4.54 and 4.13 ppm, which were attributed to the protons of $SCH_2C{=}O$, compared with the foregoing spectral data, which only appeared between δ 1.5 ppm and δ 2.5 ppm, owing to the CH_2 group that was connected with S atom and the electron-attracting C=O group, which resulted in its appearance at a lower frequency field. In addition, because the triazole ring system acted as a better electron-withdrawing group than the C=O group, δ 4.54 was assigned as linking to the triazole ring, and δ 4.13 as connecting with the C=O group. The signals at δ 12.07, 11.96 ppm and δ 8.31, 8.28 ppm were attributed to the protons of N—H and N=CH groups, respectively. From the ^{13}C NMR spectra, it could be found that in the CONH group exist cis-trans conformers, and the N=CH group could give rise to the formation of *Z/E* isomers, which shows that the number of carbon absorption peaks were obviously increased. As in the title compounds **4a–4h**, the peaks resonated at about δ 33.71–34.74 ppm and δ 59.63–59.88 ppm belonging to —S—C and —O—C groups, respectively; furthermore,

the signals at around δ 140–150 ppm and δ 160–170 ppm correspond to N=C- and C=O groups, respectively.

Solvent Effects on the ^{1}H NMR Spectra

The effects of varying the solvent for ^{1}H NMR spectra of compounds **4a–4h** were studied in organic solvents of various polarities: $CDCl_3$, CD_3CN, and DMSO. It was observed that the ^{1}H NMR spectra of a series of hydrazones derivatives were considerably influenced by changing the solvent. Moreover, *Z/E* geometrical isomers and *cis/trans* amide conformers have been found for hydrazone derivatives by ^{1}H NMR investigation. For example, in the ^{1}H NMR spectra of the title compounds, all the SCH_2C=O, CONH, and N=CH groups of proton peaks appeared as doublet in polar DMSO-d_6 or CD_3CN. However, they appeared as singlet in less polar $CDCl_3$. According to the literature,[6] in the highly polar DMSO-d_6 or CD_3CN, the N=CH protons mainly exist in the *E* form, and proton peaks were assigned for *cis* conformer in the high field, and for *trans* at low field, but CONH and SCH_2C=O of proton peaks were assigned to *trans* conformer at the high field, and for *cis* in the low field, respectively. The percentage of conformers in DMSO-d_6, CD_3CN, and $CDCl_3$ are summarized in Table I according to the peak area.

Biological Activity

All the synthesized compounds were investigated for plant growth regulation activity. Method of plate culture was adopted, and the compound solutions were prepared in concentrations of 100, 10, 1, 0.1, 0.01 and 0.001 ppm, whereafter, rape seeds were cultured in a 10 cm Petri dish with 10 mL of different solution and a circular fiter paper. (See the Supplemental Materials and Table S1, available online.)

EXPERIMENTAL

Melting points were recorded using a digital model X-4 apparatus and are uncorrected. The reactions were carried out with a domestic microwave oven under atmospheric pressure. IR spectra were recorded on a digital FTS-3000 infrared spectrometer (KBr pellet). ^{1}H NMR and ^{13}C NMR spectra were determined as $CDCl_3$ or DMSO-d_6 solutions using a Varian Mercury Plus-400 MHz spectrometer. Elemental analyses were determined using PE-2400 C H N elemental analyzer. All commercially available products were used without further purification. [3-Phenoxymethyl-4- phenyl-1H-1,2,4-triazole-5(4*H*)]-thione **1** was prepared according to the procedures in the literature.[7–9]

Table I Conformer percentage[a] of compounds **4a–4h**

Isomer	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
Z	31	50	35	46	50	30	50	50
E	69	50	65	54	50	70	50	50
cis	58	50	66	57	50	69	51	50
trans	42	50	34	43	50	31	49	50

[a]CH=N group is used as *cis/trans* referenced datum; CONH group and SCH_2C=O are used as *cis*/*trans* referenced datum.

General Procedure for the Synthesis of Compounds 4a–4h

The general synthesis routes of these compounds was as follows (Scheme 1).

[3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio]ethyl Acetate 2

A mixture of the [3-phenoxymethyl-4-phenyl-1H-1,2,4-triazole-5(4*H*)]-thione (20 mmol) **1**, ethyl chloroacetate (22 mmol), and anhydrous potassium carbonate (25 mmol) in acetone (50 mL) was heated under reflux on an oil bath for 8 h. Then the mixture was filtered off, and the filtrate was evaporated and recrystallized from EtOH-H_2O. Yield 79%, white solid, mp 90–91°C. IR (KBr): ν = 689 (C—S—C), 1237 (C—O—C), 1752 (C=O) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H = 1.23–1.28 (m, 3H, CH_3), 4.06 (s, 2H, SCH_2), 4.08–4.22 (m, 2H, CH_2), 5.04 (s, 2H, OCH_2);^{13}C NMR ($CDCl_3$): δ_C = 14.11, 36.12, 59.76, 62.42, 114.73, 125.46, 128.27, 129.05, 129.30, 129.54, 147.38, 155.93, 160.79, 168.69. Anal. Calcd. for $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.79; H, 5.16; N, 11.38.

[3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio]acetyl Hydrazine 3

[3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio]ethyl acetate (20 mmol) **2** was added to a solution of ethanol (30 mL) in 85% hydrazine hydrate (20 mmol). The solution was heated under reflux on an oil bath for 10 h. The mixture was filtered off and recrystallized from EtOH-DMF-H_2O. Yield 88%, white flaky crystal, mp 123–124°C. IR (KBr): ν = 693 (C—S—C), 1232 (C—O—C), 1665 (C=O), 3054 (Ar-H), 3262, 3333 ($NHNH_2$) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 3.90 (s, 2H, NH_2), 4.30 (s, 2H, SCH_2), 5.08 (s, 2H, OCH_2), 6.85–7.57 (m, 10H, Ar-H), 9.36 (s, 1H, NH);^{13}C NMR (DMSO-d_6): δ_C = 34.05, 59.63, 114.72, 121.39, 126.93, 129.40, 129.71, 130.05, 132.53, 151.62, 157.26, 165.91. Anal. Calcd. for $C_{17}H_{17}N_5O_2S$: C, 57.45; H, 4.82; N, 19.70. Found: C, 57.43; H, 4.81; N, 19.73.

[3-Phenoxymethyl-4-phenyl-1,2,4-triazol-5-yl-thio]acetyl Hydrazone Derivatives 4a–4h

[3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio]acetyl hydrazine (2 mmol) **3**, the substituted benzaldehydes (2 mmol) or dialdehydes (1 mmol), and DMF (6 mL) were placed in a dried round-bottomed flask, and the reaction mixture was subjected to microwave irradiation (230 W) for 1 min periods up to a total of 5 min irradiation (400 W) again. The mixture was cooled to room temperature and then recrystallized from EtOH-DMF. The structures of these compounds have been elucidated by spectral (IR, ^1H NMR, ^{13}C NMR) and elemental analysis data.

2-[(3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-4-nitro-benzylidenehy-drazine (4a). Yield 97%, light yellow solid, mp 200–202°C. IR (KBr): ν = 1573 (C=N), 1524 (C=N-N), 3058 (Ar-H), 1688 (C=O), 1174 (C-O-C), 691 (C—S—C), 1344 (NO_2), 3185 (N—H) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 12.07 (s, 1H, NH), 11.96 (s, 1H, NH), 8.28 (s, 1H, N=CH), 8.31 (s, 1H, N=CH), 4.13 (s, 2H, SCH_2C=O), 4.54 (s, 2H, SCH_2C=O), 5.08 (s, 2H, OCH_2), 6.85–8.12 (m, 14H, Ar-H);^{13}C NMR (DMSO-d_6): δ_C = 34.65, 59.72, 114.79, 121.45, 124.06, 127.01, 127.83, 128.07, 129.45, 130.10, 132.54, 140.21, 140.41, 141.51, 144.60, 147.78, 147.90, 151.38, 151.57, 151.69, 157.33, 163.79, 168.81. Anal. Calcd. for $C_{24}H_{20}N_6O_4S$: C, 59.01; H, 4.13; N, 17.20. Found:C, 59.03; H, 4.11; N, 17.18.

2-[(3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-2-hydroxybenzylidene-hydrazine (4b). Yield 89%, white solid, mp 224–226°C. IR (KBr): ν = 1619 (C=N), 1580 (C=N-N), 3059 (Ar-H), 1682 (C=O), 1231 (C−O−C), 691 (C−S−C), 3177 (N−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H=11.74 (s, 1H, NH), 11.04 (s, 1H, OH), 8.28 (s, 1H, N=CH), 3.92 (s, 2H, SCH_2C=O), 5.07 (s, 2H, OCH_2), 6.84–7.63 (m, 13H, Ar-H); ^{13}C NMR ($CDCl_3$): δ_C = 33.96, 59.65, 114.75, 117.12, 117.35, 119.19, 122.01, 126.69, 129.60, 130.09, 130.77, 130.93, 131.78, 131.88, 150.71, 152.39, 154.25, 157.26, 158.59, 164.17. Anal. Calcd. for $C_{24}H_{21}N_5O_3S$: C, 62.73; H, 4.61; N, 15.24. Found: C, 62.70; H, 4.64; N 15.27.

2-[(3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-4-methoxybenzyliden-ehydrazine (4c). Yield 92%, white solid, mp 210–212°C. IR (KBr): ν = 1600 (C=N), 1502 (C=N-N), 3072 (Ar-H), 1672 (C=O), 1190 (C−O−C), 689 (C−S−C), 3188 (N-H) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 11.63 (s, 1H, NH), 11.56 (s, 1H, NH), 8.13 (s, 1H, N=CH), 7.95 (s, 1H, N=CH), 4.07 (s, 2H, SCH_2C=O), 4.48 (s, 2H, SCH_2C=O), 5.07 (s, 2H, OCH_2), 6.85–7.66 (m, 14H, Ar-H); 3.80 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6): δ_C = 33.71, 53.43, 59.63, 112.79, 115.45, 121.64, 121.75, 125.01, 127.23, 128.63, 129.46, 129.68, 130.47, 130.62, 132.44, 132.61, 133.73, 138.81, 141.93, 147.73, 148.14, 157.33, 162.72, 168.01. Anal. Calcd. for $C_{25}H_{23}N_5O_3S$: C, 63.41; H, 4.90; N, 14.79. Found: C, 63.43; H, 4.88; N, 14.77.

2-[(3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-4-N,N-dimethylbenzyl-idenehydrazine (4d). Yield 92%, gray solid, mp 188–190°C. IR (KBr): ν = 1602 (C=N), 1524 (C=N−N), 3020 (Ar-H), 1669 (C=O), 1184 (C−O−C), 691 (C−S−C), 3184 (N−H) cm^{-1} ^1H NMR (CD_3CN): δ_H = 10.84 (s, 1H, NH), 9.89 (s, 1H, NH), 8.32 (s, 1H, N=CH), 8.52 (s, 1H, N=CH), 4.46 (s, 2H, SCH_2C=O), 4.95 (s, 2H, SCH_2C=O), 5.57 (s, 2H, OCH_2), 7.29–8.11 (m, 14H, Ar-H), 2.51 (s, 3H, CH_3), 2.49 (s, 3H, CH_3). Anal. Calcd. for $C_{26}H_{26}N_6O_2S$: C, 64.18; H, 5.39; N, 17.27. Found: C, 64.20; H, 5.41; N, 17.24.

2-[(3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-benzyl-idenehydrazine (4e). Yield 93%, white solid, mp 182–183°C. IR (KBr): ν = 1594 (C=N), 1492 (C=N−N), 3055 (Ar-H), 1687 (C=O), 1215 (C−O−C), 689 (C−S−C), 3244 (N−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H = 11.55 (s, 1H, NH), 8.14 (s, 1H, N=CH), 3.93 (s, 2H, SCH_2C=O), 5.07 (s, 2H, OCH_2), 6.86∼7.82 (m, 14H, Ar-H); ^{13}C NMR ($CDCl_3$): δ_C = 34.29, 59.88, 115.05, 121.93, 122.25, 126.98, 127.27, 127.66, 128.08, 128.82, 129.75, 129.85, 130.33, 130.43, 130.73, 132.22, 133.74, 148.98, 152.62, 154.56, 157.57, 165.15. Anal. Calcd. for $C_{24}H_{21}N_5O_2S$: C, 64.99; H, 4.77; N, 15.79. Found: C, 64.95; H, 4.80; N, 15.82.

4-Bis{2-[(3-phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-benzylidenehydrazine} (4f). Yield: 96%, yellow power solid, mp 253–255°C, IR (KBr): ν = 1594 (C=N), 1494 (C=N−N), 3059 (Ar-H), 1663 (C=O), 1213 (C−O−C), 689 (C−S−C), 3179 (N−H) cm^{-1}. ^1H NMR (DMSO-d_6): δ_H = 11.85 (s, 1H, NH), 11.76 (s, 1H, NH), 8.21 (s, 1H, N=CH), 8.03 (s, 1H, N=CH), 4.11 (s, 2H, SCH_2C=O), 4.52 (s, 2H, SCH_2C=O), 5.08 (s, 2H, OCH_2), 6.85–7.77 (m, 14H, Ar-H). ^{13}C NMR (DMSO-d_6): δ_C = 34.74, 59.72, 114.79, 121.44, 126.99, 127.02, 127.27, 127.54, 129.45, 129.77, 130.10, 132.57, 132.67, 135.24, 135.39, 143.14, 146.34, 151.76, 157.33, 163.36, 168.48. Anal. Calcd. for $C_{42}H_{36}N_{10}O_4S_2$: C, 62.36; H, 4.49; N, 17.32. Found: C, 62.39; H, 4.46; N, 17.29.

2-[(3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-2-furan-methylenehyd-razine (4g). Yield: 94%, coffee solid, mp 169–170°C. IR (KBr): ν = 1593 (C=N), 1496 (C=N−N), 3062 (Ar-H), 1699 (C=O), 1210 (C−O−C), 691 (C−S−C), 3219 (N−H) cm^{-1}. ^1H NMR (CD_3CN): δ_H = 11.15 (s, 1H, NH), 10.24 (s, 1H, NH), 8.34 (s, 1H, N=CH), 8.56 (s, 1H, N=CH), 4.49 (s, 2H, SCH_2C=O), 4.93 (s, 2H, SCH_2C=O), 5.57 (s, 2H, OCH_2), 7.09–8.11 (m, 10H, Ar-H and 2H, furan). Anal. Calcd. for $C_{22}H_{19}N_5O_3S$: C, 60.96; H, 4.42; N, 16.16. Found C, 60.93; H, 4.45; N, 16.18.

2-[(3-Phenoxymethyl-4-phenyl-1,2,4-triazole-5-yl-thio)-acetyl]-5-(4-bro-mophenyl)-2-furanmethylenehydrazine (4h). Yield: 95%, yellow solid, mp 190–191°C. IR (KBr): ν = 1593 (C=N), 1495 (C=N−N), 3057 (Ar-H), 1679 (C=O), 1187 (C−O−C), 692 (C−S−C), 3200 (N−H) cm^{-1}. ^1H NMR ($CDCl_3$): δ_H = 11.66 (s, 1H, NH), 8.11 (s, 1H, N=CH), 3.93 (s, 2H, SCH_2C=O), 5.07 (s, 2H, OCH_2), 6.69–7.78 (m, 14H, Ar-H and d, 2H, furan); ^{13}C NMR ($CDCl_3$): δ_C = 34.08, 59.73, 107.83, 114.75, 115.39, 121.67, 122.12, 125.66, 126.70, 127.01, 128.64, 129.58, 129.75, 130.04, 130.69, 131.83, 131.92, 134.84, 138.19, 148.75, 152.04, 154.62, 157.42, 164.74, 169.17. Anal. Calcd. for $C_{28}H_{22}N_5O_3SBr$: C, 57.15; H, 3.77; N, 11.90. Found C, 57.13; H, 3.79; N, 11.92.

REFERENCES

1. B. K. Kaymakcıoglu and S. Rollas, *Farmaco.*, **57,** 595 (2002).
2. Q. Chen, D. Q. Long, J. Cheng, J. Li, Z. M. Liu, and G. F. Yang, *Chem. J. Chin. Univ.*, **27,** 454 (2006) (in Chinese).
3. T. B. Wei, M. L. Li, Q. Lin, H. Liu, and Y. M. Zhang, *Chin. J. Org. Chem.*, **26,** 477 (2006) (in Chinese).
4. S. G. Umut, G. K. Nesrin, G. Ozgur, K. Yavuz, K. Ekrem, I. Samil, A. Goknur, and O. Meral, *Bioorg. Med. Chem.*, **15,** 5738 (2007).
5. K. A. Metwally, L. M. Abdel-Aziz, El-S. M. Lashine, M. I. Husseiny, and R. H. Badawy, *Bioorg. Med. Chem.*, **14,** 8675 (2006).
6. P. P. Domianop, *Tetrahedron*, **42**(13), 3649 (1986).
7. T. B. Wei, J. Tang, Q. Lin, H. Liu, and Y. M. Zhang, *Chem. J. Chin. Univ.*, **28**(6), 1080 (2007) (in Chinese).
8. T. B. Wei, R. Xu, J. Tang, and Y. M. Zhang, *Chin. J. Org. Chem.*, **28**(11), 1959 (2008) (in Chinese).
9. T. B. Wei, M. L. Li, Q. Li, H. Liu, and Y. M. Zhang, *Phosphorus, Sulfur, and Silicon*, **181,** 1583 (2006).