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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Synthesis and Fungicidal Activity of 4-[(Alkylsulfanyl)methyl]-3,5-dimethylisoxazoles

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Abstract—Previously unknown 4-[(alkylsulfanyl)methyl]-3,4-dimethylisoxazoles were prepared by the reaction of accessible 3-[(alkylsulfanyl)methyl]pentane-2,4-diones with hydroxylamine in ethanol under microwave irradiation and without it. Performing the heterocyclization under the conditions of microwave irradiation allows the reaction time to be decreased to 15 min and the yields to be increased to 89–95%. 4-[(Butylsulfanyl)methyl]-3,5-dimethylisoxazole exhibits antifungal activity toward Rhizoctonia solani and Fusarium oxysporum phytopathogenic fungi.

Keywords: 4-[(alkylsulfanyl)methyl]-3,4-dimethylisoxazole, 3-[(alkylsulfanyl)methyl]pentane-2,4-dione, heterocyclization, hydroxylamine hydrochloride, microwave irradiation, fungicidal activity

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Functionalized isoxazoles are actively used in medicine and agriculture. Substituted isoxazoles are components of veterinary medicines, herbicides, pesticides, and fungicides such as hymexazol, pyrisoxazole, oxathiapiprolin, and drazoxolon [1, 2]. Compounds of the isoxazole class proved to be effective in fighting fungal diseases of plants [2–5]. Different approaches to preparing isoxazoles with alkyl(aryl) sulfanyl or alkyl(aryl)sulfonyl fragments have been developed recently [6–10]; these compounds show promise as antimicrobial [2] and fungicidal [9, 10] agents. Isoxazoles with diarylsulfonyl substituents [9] exhibit higher activity than related compounds with diaryl fragments, and sulfur-containing isoxazoles [10] surpass sulfur-containing pyrazoles in antimicrobial properties.

This study was aimed at preparing new (alkylsulfanyl)-containing isoxazoles by the microwave-assisted reaction of hydroxylamine with 3-[(alkylsulfanyl) methyl]pentane-2,4-diones, which, in turn, can be prepared by ternary condensation of acetylacetone with formaldehyde and thiols, and at evaluating the fungicidal activity of the compounds obtained toward *Bipolaris sorokiniana*, *Rhizoctonia solani*, and *Fusarium oxysporum* phytopathogenic fungi.

EXPERIMENTAL

Chemicals, methods, and devices. The reactions were performed in a Discover system 908010 microwave synthesis reactor (CEM Matthews NC) with the maximal radiation power of 300 W and frequency of 2455 MHz. The IR spectra were recorded with a Shimadzu JR Prestige-21 spectrometer in thin film. The ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance III 500 MHz spectrometer operating at 500 and 125 MHz, respectively, using $CDCl_3$ as a solvent and the solvent signal (7.27 ppm for residual protons, 77.1 ppm for ^{13}C) as an internal reference. The reaction completeness and the product purity were checked by gas–liquid chromatography with a Khromos 1000 chromatograph (Khromos, Russia) using a 1 m × 3 mm column; stationary phase 5% SE-30 on Chromaton N-AW-DMCS (0.16–0.20 mm), working temperature

50–300°C, flame ionization detector, carrier gas helium. The mass spectra were recorded with a Shimadzu LCMS-2010 EV liquid chromatograph–mass spectrometer with a single quadrupole in the mode of recording positive ions at a capillary potential of 4.5 kV with electrospray ionization; eluent MeCN–H_2O (95 : 5). Elemental analysis was performed with a Euro EA 3000 CHNS analyzer (HEKAtech GmbH). Chromatographic separation was performed on columns packed with MN Kieselgel 60 silica gel (0.063–0.2 μm). Ethanol (chemically pure grade, Bashspirt, Russia), hexane, ethyl acetate, and chloroform (chemically pure grade, EKOS-1) were used as solvents. The solvents were purified by standard procedures [11]. Hydroxylamine hydrochloride (analytically pure grade, Reakhim, Russia) was used without additional purification. Pentane-2,4-diones **1a–1g** were prepared by the procedure described in [12], and compounds **3–5**, by those described in [13]. The purity of reactants **3–5** was confirmed by elemental analysis and IR and NMR spectroscopy; the spectroscopic characteristics agreed with the published data [13].

Synthesis of 4-[(alkylsulfanyl)methyl]-3,5-dimethylisoxazoles 2a–2g (general procedure). (*a*) To a solution of 1.5 mmol of **1a–1g** in 10 mL of ethanol, a solution of 1.8 mmol of hydroxylamine hydrochloride in 0.5 mL of water was added with stirring. The mixture was refluxed for 5 h, after which it was diluted with water (~1 : 8), and the reaction product was extracted with chloroform (3 × 20 mL). The combined organic phase was washed with water (2 × 10 mL) and dried over $MgSO_4$. The solvent was distilled off under reduced pressure, and the residue was chromatographed on a silica gel column (eluent ethyl acetate–hexane, 1 : 5).

(b) The microwave-assisted synthesis was performed in a 10-mL reaction vessel. To a solution of 0.5 mmol of **1a–1g** in 5 mL of ethanol, 0.6 mmol of hydroxylamine hydrochloride was added, and the mixture was stirred at 78°C for 5 min. The microwave radiation power was varied from 50 W at the start of the reaction to 4–5 W on reaching the temperature of 78°C. This temperature was reached in 30 s. After the reaction completion, the mixture was worked up similarly to method *a*.

4-[(Ethylsulfanyl)methyl]-3,5-dimethylisoxazole (2a). Yield 0.23 g (88%, *a*), 0.082 g (95%, b). IR spectrum (thin film), ν, cm^{-1}: 2968, 2927, 2870, 1637 (CN), 1452, 1423, 1375, 1267, 1240, 1195, 1041, 977, 889, 738. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, $C\underline{H}_3CH_2$, ^3J = 7.4 Hz), 2.28 s (3H, CH_3C^3), 2.35 s (3H, CH_3C^5), 2.45 q (2H, $CH_3C\underline{H}_2$, ^3J = 7.4 Hz), 3.44 s (2H, CH_2S). ^{13}C NMR spectrum, δ, ppm: 10.09, 10.98 ($\underline{C}H_3C^3$, $\underline{C}H_3C^5$), 14.37 ($\underline{C}H_3CH_2$), 23.20, 25.50 (CH_2SCH_2), 110.62 (C^4), 159.59 (C^5), 165.71 (C^3). Mass spectrum, *m*/*z* (I_{rel}, %): 172 $[M + H]^+$ (47), 213 $[M + H + MeCN]^+$ (100). Found, %: C 56.09, H 7.62, N 8.10, S 18.78. $C_8H_{13}NOS$. Calculated, %: C 56.10, H 7.65, N 8.18, S 18.72.

4-[(2-Propylsulfanyl)methyl]-3,5-dimethylisoxazole (2b). Yield 0.23 g (82%, *a*), 0.084 g (91%, b). IR spectrum (thin film), ν, cm^{-1}: 2960, 2927, 2866, 1637 (CN), 1454, 1425, 1382, 1365, 1271, 1253, 1238, 1195, 1155, 1053, 889, 738. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 d [6H, $(C\underline{H}_3)_2CH$, ^3J = 6.7 Hz], 2.27 s (3H, CH_3C^3), 2.34 s (3H, CH_3C^5), 2.79 septet [2H, $(CH_3)_2C\underline{H}$, ^3J = 6.7 Hz], 3.45 s (2H, CH_2S). ^{13}C NMR spectrum, δ, ppm: 10.19, 11.07 ($\underline{C}H_3C^3$, $\underline{C}H_3C^5$), 22.33 (CH_2S), 23.17 $[(\underline{C}H_3)_2CH]$, 34.82 $[(CH_3)_2\underline{C}H]$, 112.00 (C^4), 160.98 (C^5), 166.94 (C^3). Mass spectrum, *m*/*z* (I_{rel}, %): 186 $[M + H]^+$ (68), 227 $[M + H + MeCN]^+$ (100). Found, %: C 58.29, H 8.13, N 7.51, S 17.36. $C_9H_{15}NOS$. Calculated, %: C 58.34, H 8.16, N 7.56, S 17.31.

4-[(Butylsulfanyl)methyl]-3,5-dimethylisoxazole (2c). Yield 0.25 g (83%, *a*), 0.094 g (94%, b). The IR and ^{1}H and ^{13}C NMR spectra agree with the published data [13].

4-{[(1,1-Dimethylpropyl)sulfanyl]methyl}-3,5-dimethylisoxazole (2d). Yield 0.25 g (77%, *a*), 0.095 g (89%, b). IR spectrum (thin film), ν, cm^{-1}: 2966, 2929, 2877, 1639 (CN), 1454, 1423, 1379, 1363, 1271, 1238, 1195, 1157, 1134, 1008, 887, 740. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.97 t (3H, $C\underline{H}_3CH_2$, ^3J = 7.4 Hz), 1.30 s [6H, $(CH_3)_2C$], 1.59 q (2H, $CH_3C\underline{H}_2$, ^3J = 7.4 Hz), 2.28 s (3H, CH_3C^3), 2.35 s (3H, CH_3C^5), 3.38 s (2H, CH_2S). ^{13}C NMR spectrum, δ, ppm: 9.13 ($\underline{C}H_3CH_2$), 10.09, 11.06 ($\underline{C}H_3C^3$, $\underline{C}H_3C^5$), 19.55 (CH_2S), 28.02 $[(\underline{C}H_3)_2C]$, 34.55 ($CH_3\underline{C}H_2$), 46.33 $[(CH_3)_2\underline{C}]$, 110.14 (C^4), 159.67 (C^5), 165.78 (C^3). Mass spectrum, *m*/*z* (I_{rel}, %): 214 $[M + H]^+$ (100), 255 $[M + H + MeCN]^+$ (91). Found, %: C 61.85, H 8.95, N 6.49, S 15.11. $C_{11}H_{19}NOS$. Calculated, %: C 61.93, H 8.98, N 6.57, S 15.03.

4-[(Pentylsulfanyl)methyl]-3,5-dimethylisoxazole (2e). Yield 0.25 g (77%, *a*), 0.101 g (94%, b). IR spectrum (thin film), ν, cm^{-1}: 2956, 2927, 2870, 2858, 1637 (CN), 1454, 1423, 1379, 1271, 1242, 1193, 1037, 1028, 979, 889, 742. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.86 t [3H, $C\underline{H}_3(CH_2)_4$, ^3J = 7.0 Hz], 1.24–1.35 m [4H,

$CH_3(C\underline{H}_2)_2$], 1.54 quintet [2H, $CH_3(CH_2)_2C\underline{H}_2$, ^3J = 7.4 Hz], 2.25 s (3H, CH_3C^3), 2.32 s (3H, CH_3C^5), 2.38 t [2H, $CH_3(CH_2)_3C\underline{H}_2S$, ^3J = 7.4 Hz], 3.40 s (2H, CH_2S). ^{13}C NMR spectrum, δ, ppm: 10.05, 10.93 ($\underline{C}H_3C^3$, $\underline{C}H_3C^5$), 13.86 [$\underline{C}H_3(CH_2)_4$], 22.19, 23.49 (CH_2S, $CH_3\underline{C}H_2$), 28.92, 31.03, 31.58 ($CH_3CH_2\underline{C}H_2\underline{C}H_2\underline{C}H_2S$), 110.65 ($C^4$), 159.53 ($C^5$), 165.62 ($C^3$). Mass spectrum, *m*/*z* (I_{rel}, %): 214 $[M + H]^+$ (39), 255 $[M + H + MeCN]^+$ (100). Found, %: C 61.87, H 8.96, N 6.51, S 15.08. $C_{11}H_{19}NOS$. Calculated, %: C 61.93, H 8.98, N 6.57, S 15.03.

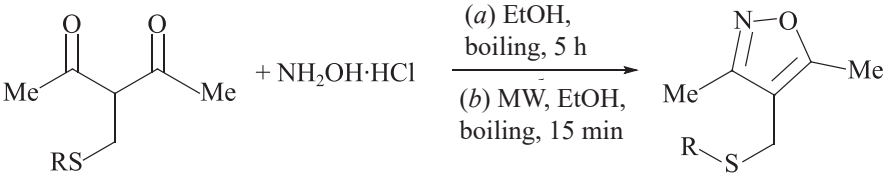
4-[(Cyclohexylsulfanyl)methyl]-3,5-dimethylisoxazole (2f). Yield 0.28 g (84%, *a*), 0.102 g (90%, b). IR spectrum (thin film), ν, cm^{-1}: 2929, 2852, 1637 (CN), 1448, 1423, 1381, 1340, 1269, 1242, 1193, 1028, 999, 887, 740. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.20–1.38 m (5H, CH_2), 1.57–1.63 m (1H, CH), 1.73–1.79 m (2H, CH_2), 1.90–1.97 m (2H, CH_2), 2.27 s (3H, CH_3C^3), 2.34 s (3H, CH_3C^5), 2.51 tt (1H, CH, ^3J = 10.4 Hz, ^3J = 3.5 Hz), 3.45 s (2H, CH_2S). ^{13}C NMR spectrum, δ, ppm: 10.15, 11.01 ($\underline{C}H_3C^3$, $\underline{C}H_3C^5$), 21.80 (CH_2S), 25.78, 26.04, 33.42 ($C^{2',6'}H_2$, $C^{3',5'}H_2$, $C^{4'}H_2$), 43.29 ($C^{1'}H$), 110.90 (C^4), 159.68 (C^5), 165.59 (C^3). Mass spectrum, *m*/*z* (I_{rel}, %): 226 $[M + H]^+$ (39), 267 $[M + H + MeCN]^+$ (100). Found, %: C 63.90, H 8.46, N 6.27, S 14.27. $C_{12}H_{19}NOS$. Calculated, %: C 63.96, H 8.50, N 6.22, S 14.23.

4-**[(Hexylsulfanyl)methyl]-3,5-dimethylisoxazole (2g).** Yield 0.24 g (70%, *a*), 0.100 g (88%, b). The IR and ^1H and ^{13}C NMR spectra agree with the published data [13].

Evaluation of the antifungal activity. As test objects we used phytopathogenic fungi from the collection of the Ufa Institute of Biology, Ufa Federal Research Center, Russian Academy of Sciences: *Bipolaris sorokiniana* (IB G-12), *Fusarium oxysporum* (VKM F-137 IB G-20), and *Rhizoctonia solani* (VKM F-895 IB G-62). The antifungal activity toward pathogens was evaluated by the method of diffusion into potato glucose agar [14]. 100-μL portions of a test culture suspension were applied onto the surface of potato glucose agar (20-mL portions poured into standard Petri dishes 90 mm in diameter). The suspension portions were thoroughly distributed over the surface with a spatula to ensure uniform continuous growth of the fungus. Four holes were made in the medium with a rubber stopper hole puncher, and 100-μL portions of **2c** and **3–5** were added into these holes. Compounds **2c** and **3–5** were tested as 0.5% solutions in dimethylformamide. Dimethylformamide did not negatively affect the test culture growth. Sterile tap water was used as a control; its 100-μL portions were added into the holes instead of the test substance. Tap water was sterilized in a VK-75-01 steam sterilizer (Mediko, Russia) under a pressure of 1 atm for 20 min. As a positive control we used fluconazole [Diflucan®, infusion solution, Pfizer; composition per milliliter: 2.0 mg of 2-(2,4-difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)-2-propanol, 9.0 mg of NaCl, water for injections to 1 mL]. 100-μL portions of the fluconazole solution were added into the holes similarly to the test substances. The results were evaluated by the diameter of the growth suppression zone of the phytopathogenic fungi after 7-day incubation at 22°C. Measurements were performed in two mutually perpendicular directions, and the suppression zone diameter was calculated as the arithmetic mean of the values obtained. Statistical processing of the results was performed using the Student's *t*-test at the critical significance level $p = 0.05$.

RESULTS AND DISCUSSION

The reaction of 3-[(alkylsulfanyl)methyl]pentane-2,4-diones **1a–1g** with 1.2 equiv of hydroxylamine hydrochloride on refluxing in ethanol for 5 h gives the corresponding 4-[(alkylsulfanyl)methyl]-3,5-dimethylisoxazoles **2a–2g** in 70–88% yields. In the microwave-assisted synthesis, the heterocyclization is complete in 15 min, and the yields of target products **2a–2g** reach 89–95%.



1a–1g **2a–2g**

where (**1**, **2**) R = Et (**a**), *i*-Pr (**b**), Bu (**c**), t-C_5H_{11} (**d**), n-C_5H_{11} (**e**), cyclo-C_6H_{11} (**f**), n-C_6H_{13} (**g**).

Table 1. Characteristics of the condensation of 3-[(pentylsulfanyl)methyl]- and 3-[(hexylsulfanyl)methyl]pentane-2,4-diones with hydroxylamine hydrochloride in refluxing ethanol

Pentane-2,4-dione	Diketone : $NH_2OH \cdot HCl$ molar ratio	Microwave radiation	Time, h	Isoxazole yield, %
3-[(Hexylsulfanyl)methyl]pentane-2,4-dione	1 : 2	No	5	72
3-[(Hexylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2	″	5	70
3-[(Hexylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2[a]	Yes	15 min	88
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 2	No	5	78
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2	″	5	77
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2	″	12	80
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2	″	1	22
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2	Yes	30 min	93
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2	″	15 min	94
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2[a]	″	15 min	94
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2	″	5 min	86
3-[(Pentylsulfanyl)methyl]pentane-2,4-dione	1 : 1.2[b]	″	15 min	–

[a] Without preliminary dissolution of hydroxylamine hydrochloride in water.

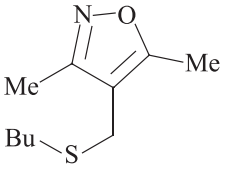
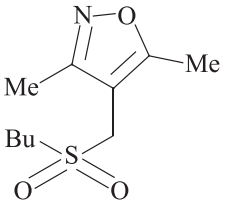
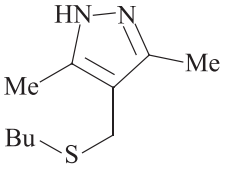
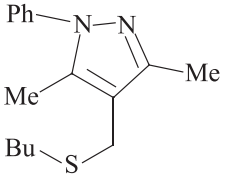
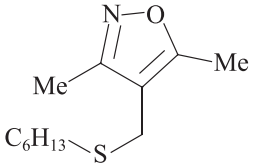
[b] Without ethanol.

Isoxazoles **2c** and **2g** and new compounds **2a**, **2b**, and **2d–2f** were prepared by the procedure described in [13] with decreased amount of hydroxylamine without a base and without purification of the starting compounds. As demonstrated by the example of pentane-2,4-diones **1e** and **1g**, with a decrease in the hydroxylamine amount the target product yields decrease or change insignificantly; microwave activation allows the reaction time to be reduced by a factor of 20 and the isoxazole yields to be increased almost to quantitative (Table 1). For example, under the conditions of refluxing in ethanol, 5 h is required to complete the reaction, whereas the microwave-assisted reaction is complete in 5–15 min. The reaction does not occur without ethanol, but hydroxylamine hydrochloride can be used without preliminary dissolution in water.

The structure of isoxazoles **2a–2g** was confirmed by the IR and ^1H, ^{13}C NMR data. In the IR spectra of all isoxazoles **2a–2g**, there is a strong absorption band of C=N stretching vibrations at 1637–1639 cm^{-1}. A characteristic feature of the ^1H NMR spectra of **2a–2g** is the presence of three singlets from CH_3C^3 and CH_3C^5 methyl protons (δ 2.25–2.28, 2.32–2.35 ppm) and $SC^{1'}H_2$ methylene protons (δ 3.38–3.45 ppm) along with the signals from protons of the alkylsulfanyl substituent. In the ^{13}C NMR spectra, the C^3 and C^5 atoms of the isoxazole ring give characteristic signals at 165.62–166.94 and 159.53–160.98 ppm, and the C^4 atoms, at 110.14–112.00 ppm. In the mass spectra of positive ions of compounds **2a–2g**, recorded in the chemical ionization mode, there are peaks of protonated molecular ions $[M + H]^+$ and ions $[(M + H) + MeCN]^+$.

For the experiments on evaluating the biological activity, we chose 4-[(hexylsulfanyl)methyl]-3,5-dimethylisoxazole **2g**, and also 4-[(butylsulfanyl) methyl]-3,5-dimethylisoxazole **2c**, the corresponding sulfone **3**, and pyrazoles **4** and **5** with the same 4-butylsulfanylmethyl substituent (Table 2). As we found, 1H-pyrazoles **4** and **5** exert no inhibiting effect on the development of *Bipolaris sorokiniana*, *Rhizoctonia solani*, and *Fusarium oxysporum* phytopathogenic fungi. In contrast to pyrazoles, isoxazole **2c** exhibits fungistatic activity toward *Fusarium oxysporum* fungi and fungicidal activity with the sterile zone formation toward *Rhizoctonia solani* fungi. Isoxazole **2c** inhibits growth of *Rhizoctonia solani* fingi to a lesser extent than fluconazole (a triazole derivative) does. However, compound **2c**, in contrast of fluconazole, exhibits fungistatic activity toward *Fusarium oxysporum* fungi, being, however, inferior to hymexazol (5-methylisoxazol-3-ol) in this respect [15]. With an increase in the size of the hydrocarbon radical in the

Table 2. Antifungal activity of some 4-[(alkylsulfanyl)methyl]-3,5-dimethylisoxazoles and -1*H*-pyrazoles

Compound	Diameter of the growth inhibition zone on the test culture lawn, mm, for indicated phytopathogenic fungi		
	Bipolaris sorokiniana	*Rhizoctonia solani*	*Fusarium oxysporum*
4-[(Butylsulfanyl)methyl]-3,5-dimethylisoxazole 	–	18.3 ± 1.2	+
4-[(Butylsulfonyl)methyl]-3,5-dimethylisoxazole 	–	–	–
4-[(Butylsulfanyl)methyl]-3,5-dimethyl-1*H*-pyrazole 	–	–	–
4-[(Butylsulfanyl)methyl]-3,5-dimethyl-1-phenyl-1*H*-pyrazole (**5**) 	–	–	–
4-[(Hexylsulfanyl)methyl]-3,5-dimethylisoxazole (**2g**) 	–	11.2 ± 1.0	–
Fluconazole (2 g L^{-1})	20.7 ± 1.2	25.8 ± 2.1	–

0.5% solutions in dimethylformamide, the solvent does not affect the test object growth; (–) no inhibition zone; (+) suppression of the development of air mycelium.

alkylsulfanyl substituent in isoxazoles 2, the fungicidal activity decreases. Oxidation of the sulfur atom in 4-[(butylsulfanyl)methyl]-3,5-dimethylisoxazole to sulfone leads to the disappearance of the fungicidal properties.

CONCLUSIONS

A procedure was developed for preparing 4-[(alkylsulfanyl)methyl]-3,5-dimethylisoxazoles by the reaction of 3-[(alkylsulfanyl)methyl]pentane-2,4-

diones with hydroxylamine under the conditions of microwave irradiation, which considerably reduces the reaction time (to 15 min) and ensures high product yield (89–95%). The synthesized 4-[(butylsulfanyl) methyl]-3,5-dimethylisoxazole exerts a fungistatic effect on *Fusarium oxysporum* and a fungicidal effect on *Rhizoctonia solani* phytopathogenic fungi. Replacement of the thioether sulfur atom by the sulfonyl group in the isoxazole studied leads to the loss of antifungal properties.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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