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Microwave-assisted, one-pot syntheses and fungicidal activity of polyfluorinated 2-benzylthiobenzothiazoles

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Abstract—Polyfluorinated 2-benzylthiobenzothiazoles **3a–l** are prepared via a microwave-assisted, one-pot procedure. The advantages, such as good to excellent yields, shorter reaction time (14–21 min), readily available starting material, and simple purification procedure, distinguish the present protocol from other existing methods used for the synthesis of 2-benzylthiobenzothiazoles. Bioassay indicated that most of the compounds showed significant fungicidal activity against *Rhizoctonia solani*, *Botrytis cinereapers*, and *Dothiorella gregaria* at a dosage of 50 μg/mL. Interestingly, compared to the control of commercial fungicide, triadimefon, compound **3c** exhibited much higher activities against *R. solani*, *B. cinereapers*, and *D. gregaria*, which showed that the polyfluorinated 2-benzylthiobenzothiazoles can be used as lead compound for developing novel fungicides.

1. Introduction

2-Substituted benzothiazoles constitute an important class of compounds for medicinal, agricultural, and organic chemists. The benzothiazole-moiety can be found as a common substructure in a large number of compounds with a wide range of biological activities.[1] These compounds possess antitumor, antiviral, antimicrobial, and antiglutamate properties. Some of these compounds have been widely used in agriculture. For example, Bentaluron, Chlobenthiazone, and TCMTB, which have been used for many years, are commercial fungicides belonging to benzothiazole derivatives (Scheme 1). 2-Benzothiazole thioether derivatives possess anticandious, antimicrobacterial, photosynthesis-inhibiting, fungicidal, insecticidal, and herbicidal properties.[2]

Although numerous synthetic methods are available for the construction of benzothiazole ring, facile and scalable routes to highly versatile benzothiazole building blocks, such as 2-(substituted)benzylthiobenzothiazole derivatives, are still lacking.[3] Microwave-assisted organic synthesis (MAOS) continues to affect synthetic chemistry significantly by enabling rapid, reproducible, and scalable chemistry development.[4] Numerous microwave-assisted reactions have been developed in the field of medicinal chemistry and total syntheses of natural products.[5] The methods applied for the synthesis of benzothiazoles under microwave irradiation conditions have also been reported.[6] However, no report is so far available on the one-pot synthesis of 2-benzylthiobenzothiazoles under microwave irradiation.

It is well known that incorporation of fluorine atom in heterocycles not only affected the reaction course, but also influenced the biological activity of the target compounds. Many examples had demonstrated that introducing a fluorine atom or a CF_3 group to the molecular structure of heterocyclic compounds always resulted in the improvement of pharmacological properties of the compounds as compared to their non-fluorine analogs.[7]

As a part of our extensive research program to rapidly synthesize novel bioactive heterocycles, we developed herein a microwave accelerated approach for a highly efficient assembly of polyfluorinated 2-benzylthiobenzothiazoles by one-pot reaction from readily available materials. The preliminary in vitro bioassay against four kinds of fungi indicated that these polyfluorinated deriv-

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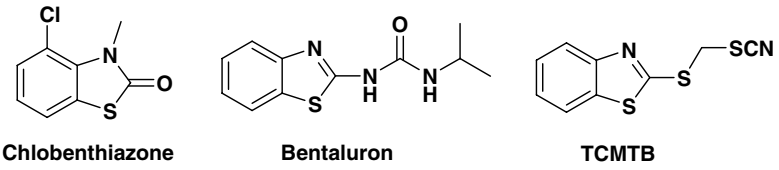


Scheme 1. Structures of Bentaluron, Chlobenthiazone, and TCMTB.

atives displayed excellent fungicidal activity, some of which exhibited higher activity against *R. solani*, *B. cinereapers*, and *D. gregaria* than commercial Triadimefon.

2. Results and discussion

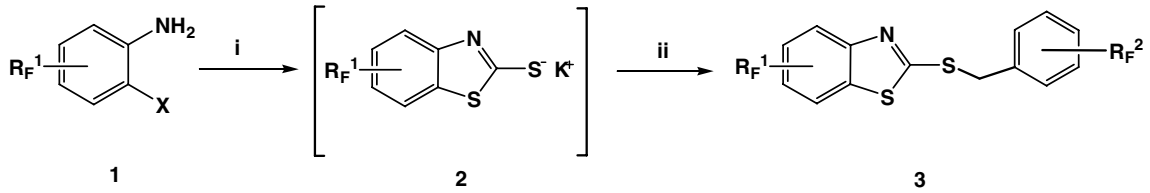
Conventional synthesis of 2-(substituted)benzylthiobenzothiazoles involves two steps: (i) The synthesis of 2-mercaptobenzothiazole by nucleophilic aromatic substitution reaction of *ortho*-haloanilines with potassium/sodium *O*-ethyl dithiocarbonate. (ii) The nucleophilic substitution of 2-mercaptobenzothiazole by various substituted benzyl halide.[2] It should be noted that the second step usually gave the desirable products in good yields, however, the first step always suffered from drawbacks, such as longer reaction time (3–20 h) and the difficulty to isolate and purify the products.[3]

It should be kept in mind that the last procedure to afford 2-mercaptobenzothiazole in the first step reaction is acidification of the intermediate, potassium benzothiazole-2-thiolate. Meanwhile, the following nucleophilic substitution of 2-mercaptobenzothiazole should be carried out under the basic condition. Therefore, it is possible to develop a one-pot procedure for the synthesis of 2-(substituted)benzylthiobenzothiazoles without the isolation of the intermediate (Scheme 2). By optimizing the temperature, the reaction time and molar ratios of reagents, the best results were obtained and are summarized in Table 1, which correspond to the results under conventional condition.

As shown in Table 1, by using microwave irradiation, various 2-haloanilines reacted with 2.2 equiv. of potassium *O*-ethyl dithiocarbonate at 120 °C for 8–15 min. The resulting mixture reacted with various fluorinated benzyl bromide at 90 °C for 6 min to successfully afford the desirable 2-(substituted)benzylthiobenzothiazoles in good to excellent isolated yields (84–93%). Compared to the reaction time of 7–21 h under the conventional heating, it only took 14–21 min to finish the reaction under microwave irradiation. Under conventional condition, as expected, the reaction with *ortho*-chloroanilines was observed to be slower than with *ortho*-fluoroanilines. In addition, the one-pot reactions with 2-chloroanilines under traditional conditions always gave low yields (58–65%) within 21 h, while 2-fluoroanilines afforded higher yields (74–82%) within the same reaction time. However, the same level of yields under microwave irradiation was obtained for 2-chloroanilines and 2-fluoroanilines.

The structures of all products were confirmed by ^{1}HNMR, elemental analysis, and mass spectroscopy. The single-crystal structure of **3h** was determined by X-ray crystallography[8] as shown in Scheme 3. The crystal packing revealed various non-covalent intra- and intermolecular interactions, such as π–π stacking and H-bonding, which played a fundamental role in three-dimensional organization of the molecules in solid state. An intermolecular hydrogen bond between the F atom and aromatic hydrogen was observed. The distance of C—H···F is 2.50 Å, and the angle of C—H···F is 145.3°. In addition, the π–π stacking interactions between the phenyl and the benzothiazolyl were obviously observed.

The fungicidal activities of compound **3a**–**l** were screened against four kinds of fungi, *R. solani*, *Botrytis cinereapers*, *D. gregaria*, and *Colletotrichum gossypii*,



R_F^1	X
4-F	Cl
5-F	F
6,7-F_2	F
4-Cl,6-CF_3	Cl

3	R_F^1	R_F^2
a	4-F	2-F
b	4-F	2,6-F_2
c	4-F	3,4-F_2
d	5-F	2-F
e	5-F	2,6-F_2
f	5-F	3,4-F_2

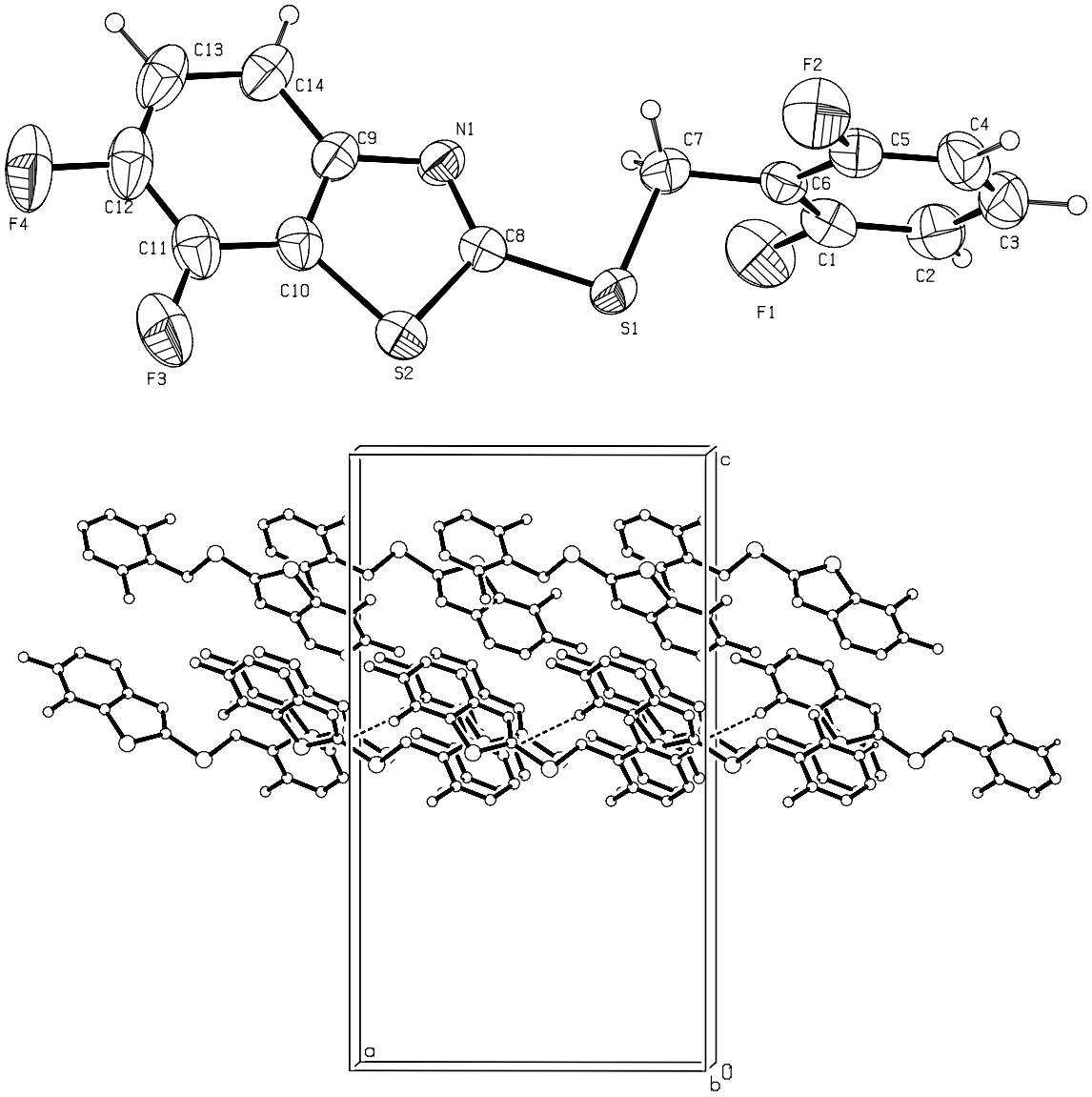
3	R_F^1	R_F^2
g	6,7-F_2	2-F
h	6,7-F_2	2,6-F_2
i	6,7-F_2	3,4-F_2
j	4-Cl,6-CF_3	2-F
k	4-Cl,6-CF_3	2,6-F_2
l	4-Cl,6-CF_3	3,4-F_2

Scheme 2. Synthesis of polyfluorinated 2-benzylthiobenzothiazole derivatives. Reagents and conditions: (i) potassium *O*-ethyl dithiocarbonate, DMF, MW, 120 °C; (ii) benzyl bromide, MW, 90 °C.

Table 1. Results of synthesis of fluorinated benzothiazole thioethers

Compound	R_F^1	R_F^2	Traditional heating		Microwave irradiation	
			Time (h)[a]	Isolated yield (%)	Time (min)[a]	Isolated yield (%)
3a	4-F	2-F	18[b] + 3[c]	65	15[b] + 6[c]	90
3b	4-F	2,6-F_2	18 + 3	62	15 + 6	86
3c	4-F	3,4-F_2	18 + 3	65	15 + 6	86
3d	5-F	2-F	4 + 3	82	8 + 6	92
3e	5-F	2,6-F_2	4 + 3	76	8 + 6	90
3f	5-F	3,4-F_2	4 + 3	74	8 + 6	89
3g	6,7-F_2	2-F	4 + 3	80	8 + 6	92
3h	6,7-F_2	2,6-F_2	4 + 3	78	8 + 6	90
3i	6,7-F_2	3,4-F_2	4 + 3	80	8 + 6	93
3j	4-Cl, 6-CF_3	2-F	18 + 3	61	15 + 6	88
3k	4-Cl, 6-CF_3	2,6-F_2	18 + 3	58	15 + 6	84
3l	4-Cl, 6-CF_3	3,4-F_2	18 + 3	60	15 + 6	85

[a] Time to finish the reaction monitored by TLC.
[b] Reaction time of the first step.
[c] Reaction time of the second step.



Scheme 3. X-ray crystal structure and stacking spectrum of 2-BenzylthioBenzothiazole (**3h**).

Table 2. Fungicidal activities of compounds **3a**–**3l**

Compound	Inhibition rate (%, 50 μg/mL)			
	Rhizoctonia solani	*Botrytis cinereapers*	*Dothiorella gregaria*	*Colletotrichum gossypii*
3a	82 ± 1	81 ± 2	78 ± 2	67 ± 1
3b	74 ± 1	78 ± 1	63 ± 3	52 ± 2
3c	92 ± 2	97 ± 2	89 ± 3	78 ± 1
3d	82 ± 2	83 ± 1	81 ± 3	67 ± 2
3e	80 ± 2	78 ± 2	74 ± 2	56 ± 1
3f	86 ± 1	69 ± 2	78 ± 3	74 ± 2
3g	84 ± 4	86 ± 1	81 ± 4	74 ± 2
3h	82 ± 1	69 ± 2	81 ± 3	63 ± 3
3i	85 ± 1	72 ± 2	85 ± 3	80 ± 1
3j	83 ± 1	83 ± 2	70 ± 3	70 ± 1
3k	69 ± 2	67 ± 4	62 ± 4	44 ± 3
3l	40 ± 5	67 ± 3	35 ± 4	37 ± 4
Triadimefon	90 ± 1	84 ± 2	61 ± 3	95 ± 2

at a concentration of 50 μg/ml according to the reported method.[9,10] Triadimefon, a commercial fungicide, was used as a control. As indicated in Table 2, most of the compounds showed significant fungicidal activity against *R. solani*, *B. cinereapers*, and *D. gregaria* at a dosage of 50 μg/mL. Generally, fluorine-substituted compounds showed higher activity than trifluoromethyl substituted compounds, and the derivatives containing 2-fluorobenzyl had greater activity than other fluorinated benzyl derivatives. Compounds **3c**, **3d**, **3g**, and **3i** exhibited broad spectrum activity and over 80% inhibition rate against the growth of at least three kinds of fungi. Interestingly, compound **3c** exhibited much higher activities against *R. solani*, *B. cinereapers*, and *D. gregaria* than triadimefon. In addition, all compounds except **3l** showed higher activity against *D. gregaria* than triadimefon. It should be noted that triadimefon is one of the most important fungicides used for the control of *R. solani*, *B. cinereapers*, *D. gregaria*, and *C. gossypii* in China. The results shown in Table 2 indicate that polyfluorinated 2-benzylthiobenzothiaozloe derivatives might be used as a new lead compound for fungicidal development.

3. Conclusion

In conclusion, we described the first report on the microwave-assisted, one-pot synthesis of polyfluorinated 2-benzylthiobenzothiaozloe derivatives. This protocol presented many advantages, such as good to excellent yields, shorter reaction time (14–21 min), readily available starting material, and simple purification procedure, which distinguished the present protocol from other existing methods used for the synthesis of 2-benzylthiobenzothiazoles. Bioassay of the compounds indicated that the polyfluorinated 2-benzylthiobenzothiazoles can be used as lead structure for developing novel fungicides. Further bioassay, optimization and structure–activity relationships of the title compounds are underway.

4. Experimental

4.1. Materials

All materials were commercially available and were used directly without further purification. *R. solani*, *Botrytis cinereapers*, *D. gregaria*, and *C. gossypii* were provided through the courtesy of the Center for Bioassay, Central China Normal University.

4.2. Analysis and instruments

^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ solution on a Varian VNMR 400 MHz spectrometer. MS spectra were determined using a TraceMS 2000 organic mass spectrometry, and the signals were given in *m*/*z*. Melting points were taken on a Buchi B-545 melting point apparatus. Element analysis (EA) was carried out on a Vario EL III CHNSO elemental analyzer. Conventional heating was carried out on Corning stirrer/hotplates in oil baths. Microwave syntheses were carried out on a Smith synthesizer™.

4.3. General procedure for the microwave-assisted synthesis of the title compounds 3

In a microwave tube, potassium *O*-ethyl dithiocarbonate (2.2 mmol) was added into a solution of fluorinated aniline (1 mmol) in 2 mL of DMF. Then, the sealed microwave tube was placed in a Smith synthesizer™ and irradiated at 120 °C for 8–15 min, followed by cooling of the reaction mixture. Next, fluorinated benzyl bromide (1 mmol) was added. The sealed microwave tube was irradiated at 90 °C for another 6 min. Completion of the reaction was checked by TLC. The resulting mixture was cooled, diluted with 10 mL of ice water. The obtained solid product was filtered and recrystallized from acetone/petroleum ether (30–60 °C) to afford fluorinated benzothiazole thioether **3**.

4.4. General procedure for the conventional synthesis of the title compounds 3

Potassium *O*-ethyl dithiocarbonate (2.2 mmol) was added into a solution of fluorinated aniline (1 mmol) in 2 mL of DMF. The resulting solution was heated by oil bath at 120 °C for 4 ~ 18 hour, and the mixture was then cooled. Next, the fluorinated benzyl bromide (1 mmol) was added. The mixture was then heated at 90 °C in an oil bath. Completion of the reaction was confirmed by TLC. The purification procedure of the products as described above was achieved at the end of 3 h.

4.4.1. 4-Fluoro-2-(2-fluoro-benzylsulfanyl)-benzothiazole (3a). mp 55–57 °C. ^{1}H NMR ($CDCl_3$): δ 7.59 (t, J = 8.0, 1H), 7.50 (d, J = 8.0, 1H), 7.24–7.29 (m, 2H), 7.04–7.15 (m, 3H), 4.67 (s, 2H). EIMS (probe) 70 eV, *m*/*z* (rel. int.): 293 $[M]^+$ (7.83), 260 (2.60), 0126 (5.72), 109 (100), 83 (15.58); Anal. Calcd for $C_{14}H_9F_2NS_2$: C, 57.32; H, 3.09; N, 4.77. Found: C, 57.12; H, 3.19; N, 4.66.

4.4.2. 2-(2,6-Difluoro-benzylsulfanyl)-4-fluoro-benzothiazole (3b). mp 93–94 °C. ^{1}H NMR ($CDCl_3$) δ 7.53 (d, J = 8.0, 1H), 7.24–7.29 (m, 2H), 7.14 (t, J = 8.0, 1H), 6.92 (t, J = 8.0, 2H), 4.74 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 311 $[M]^+$ (17.49), 278 (3.51), 175 (98.3), 109 (70.87), 93 (100); Anal. Calcd for $C_{14}H_8F_3NS_2$: C, 54.01; H, 2.59; N, 4.50. Found: C, 53.94; H, 2.74; N, 4.41.

4.4.3. 2-(3,4-Difluoro-benzylsulfanyl)-4-fluoro-benzothiazole (3c). Mp 56–58 °C. ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 8.0, 1H), 7.07–7.35 (m, 5H), 4.57 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 311 $[M]^+$ (6.68), 278 (2.89), 184 (2.42), 140(14.91), 127 (100), 101 (16.16); Anal. Calcd for $C_{14}H_8F_3NS_2$: C, 54.01; H, 2.59; N, 4.50. Found: C, 53.91; H, 2.65; N, 4.42.

4.4.4. 5-Fluoro-2-(2-fluoro-benzylsulfanyl)-benzothiazole (3d). Mp 54–55 °C. ^{1}H NMR ($CDCl_3$) δ 7.57 (dt, J = 8.0, J = 2.5, 1H), 7.51 (d, J = 8.0, 1H), 7.22–7.29 (m, 2H), 7.04–7.14 (m, 3H), 4.68 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 293 $[M]^+$ (3.04), 260 (1.41), 185 (3.15), 126(4.92), 109 (100), 83 (20.61); Anal. Calcd for $C_{14}H_9F_2NS_2$: C, 57.32; H, 3.09; N, 4.77. Found: C, 57.20; H, 3.22; N, 4.68.

4.4.5. 2-(2,6-Difluoro-benzylsulfanyl)-5-fluoro-benzothiazole (3e). Mp 92–93 °C. ^{1}H NMR ($CDCl_3$) δ 7.67 (dd, J = 8.8, J = 5.2, 1H), 7.60 (dd, J = 9.6, J = 2.4, 1H), 7.23–7.30 (m, 1H), 7.08 (dt, J = 8.8, J = 2.4, 1H), 6.91 (t, J = 8.0, 1H), 4.70 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 311 $[M]^+$ (3.96), 184 (5.98), 140(9.35), 127 (100), 101 (15.86); Anal. Calcd for $C_{14}H_8F_3NS_2$: C, 54.01; H, 2.59; N, 4.50. Found: C, 53.89; H, 2.74; N, 4.30.

4.4.6. 2-(3,4-Difluoro-benzylsulfanyl)-5-fluoro-benzothiazole (3f). Mp 62–63 °C. ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, J = 8.8, J = 5.2, 1H), 7.57 (dd, J = 9.6, J = 2.4, 1H), 7.26–7.32 (m, 1H), 7.05–7.16 (m, 3H), 4.53 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 311 $[M]^+$ (5.08), 184 (9.51), 140(14.91), 127 (100), 101 (15.20); Anal. Calcd for $C_{14}H_8F_3NS_2$: C, 54.01; H, 2.59; N, 4.50. Found: C, 53.92; H, 2.75; N, 4.53.

4.4.7. 6,7-Difluoro-2-(2-fluoro-benzylsulfanyl)-benzothiazole (3g). Mp 61–62 °C. ^{1}H NMR ($CDCl_3$) δ 7.61 (d, J = 8.8, 1H), 7.50 (t, J = 7.6, 1H), 7.25–7.30 (m, 2H), 7.05–7.11 (m, 2H), 4.64 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 311 $[M]^+$ (11.69), 278 (3.26), 201 (4.42), 144 (8.54), 108 (100), 83 (20.1); Anal. Calcd for $C_{14}H_8F_3NS_2$: C, 54.01; H, 2.59; N, 4.50. Found: C, 53.88; H, 2.69; N, 4.40.

4.4.8. 2-(2,6-Difluoro-benzylsulfanyl)-6,7-difluoro-benzothiazole (3h). Mp 78–79 °C. ^{1}H NMR ($CDCl_3$): δ 7.63 (dd, J = 8.8, J = 3.6, 1H), 7.24–7.31 (m, 2H), 6.92 (t, J = 8.0, 2H), 4.77 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 329 $[M]^+$ (7.04), 158 (4.81), 127 (100), 101 (10.89); Anal. Calcd for $C_{14}H_7F_4NS_2$: C, 51.06; H, 2.14; N, 4.25. Found: C, 50.89; H, 2.31; N, 4.19.

4.4.9. 2-(3,4-Difluoro-benzylsulfanyl)-6,7-difluoro- benzothiazole (3i). Mp 71–72 °C. ^{1}H NMR ($CDCl_3$): δ 7.61 (d, J = 8.0, 1H), 7.24–7.32 (m, 2H), 7.08–7.17 (m, 2H), 4.54 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 329 $[M]^+$ (6.52), 296 (2.99), 202 (3.59), 158 (7.51), 127 (100), 101 (6.89); Anal. Calcd for $C_{14}H_7F_4NS_2$: C, 51.06; H, 2.14; N, 4.25. Found: C, 50.86; H, 2.33; N, 4.17.

4.4.10. 4-Chloro-2-(2-fluoro-benzylsulfanyl)-6-trifluoromethyl- benzothiazole (3j). Mp 59–60 °C. ^{1}H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.66–7.70 (m, 2H), 7.25–7.30 (m, 1H), 7.05–7.11 (m, 2H), 4.69 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 377 [M]+ (10.7), 109 (100), 83 (31.6); Anal. Calcd for $C_{15}H_8ClF_4NS_2$: C, 47.69; H, 2.13; N, 3.71. Found: C, 47.48; H, 2.32; N, 3.58.

4.4.11. 4-Chloro-2-(2,6-difluoro-benzylsulfanyl)-6-trifluoromethyl-benzothiazole (3k). Mp 107–108 °C. ^{1}H NMR ($CDCl_3$): δ 7.93 (s, 1H), 7.70 (s, 1H), 7.25–7.32 (m, 1H), 6.93 (t,J = 8.0 Hz, 1H), 4.69 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 395 $[M]^+$ (5.32), 157 (5.60), 127 (100), 101 (4.71); Anal. Calcd for $C_{15}H_7ClF_5NS_2$: C, 45.52; H, 1.78; N, 3.54. Found: C, 45.34; H, 1.92; N, 3.41.

4.4.12. 4-Chloro-2-(3,4-difluoro-benzylsulfanyl)-6-trifluoromethyl-benzothiazole (3l). Mp 60–61 °C. ^{1}H NMR ($CDCl_3$): δ 7.92 (s, 1H), 7.70 (s, 1H), 7.40 (dt, J = 8.0, J = 2.4, 1H), 7.25–7.28 (m, 1H), 7.07–7.14 (m, 1H), 4.69 (s, 2H). EIMS (probe) 70 eV, *m/z* (rel. int.): 395 $[M]^+$ (7.69), 157 (8.23), 127 (100), 101 (6.45); Anal. Calcd for $C_{15}H_7ClF_5NS_2$: C, 45.52; H, 1.78; N, 3.54. Found: C, 45.37; H, 1.94; N, 3.39.

4.5. Bioassays of fungicidal activities

The fungicidal activities were tested according to our previous methods.[10] The tested samples were dissolved in 0.5 mL of acetone at a concentration of 500 mg/L. The solutions (1 mL) were mixed rapidly with thawed potato glucose agar culture medium (9 mL) under 50 °C. The mixtures were poured into Petri dishes. After the dishes were cooled, the solidified plates were incubated with 4 mm mycelium disk, inverted, and incubated at 28 °C for 48 h. The mixed medium without sample was used as the blank control. Three replicates of each test were carried out. The mycelial elongation radius (mm) of fungi settlements was measured after 48 h of culture. The growth inhibition rates were calculated with the following equation: $I = [(C - T)/C] \times 100\%$. Here, I is the growth inhibition rate (%), C is the control settlement radius (mm), and T is the treatment group fungi settlement radius (mm).

Acknowledgments

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References and notes

1. (a) Chua, M.; Shi, D.; Wrigley, S.; Bradshaw, T. D.; Hutchinson, I.; Shaw, P. N.; Barrett, D. A.; Stanley, L. A.; Stevens, M. F. G. *J. Med. Chem.* **1999**, *42*, 381; (b) Hutchinson, I.; Chua, M.; Browne, H. L.; Trapani, V.; Bradshaw, T. D.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2001**, *44*, 1446; (c) Hutchinson, I.; Jennings, S. A.; Vishnuvajjala, B. R.; Westwell, A. D.; Stevens, M. F. G. *J. Med. Chem.* **2002**, *45*, 744; (d) Mortimer, C. G.; Wells, G.; Crochard, J.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2006**, *49*, 179.
2. (a) Koci, J.; Klimesova, V.; Waisser, K.; Kaustova, J.; Dahse, H. M.; Mollmann, H. M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3275; (b) Sidoova, E.; Loos, D.; Bujdakova, H. *Molecules* **1997**, *2*, 36; (c) Sidoova, E.; kralovam, K.; Loos, D. *Molecules* **1998**, *3*, 135; (d) Sidoova, E.; kralovam, K.; Loos, D. *Molecules* **1999**, *4*, 73.
3. (a) Zhu, L.; Zhang, M. B.; Dai, M. *J. Heterocycl. Chem.* **2005**, *42*, 727; (b) Zhu, L.; Zhang, M. B. *J. Org. Chem.* **2004**, *69*, 7371; (c) Chaudhuri, N. C. *Synth. Commun.* **1996**, *26*, 3783; (d) Singh, B.; Pennock, P. O.; Lesher, G. Y.; Bacon, E. R.; Page, D. F. *Heterocycles* **1993**, *36*, 133.
4. (a) Kappe, C. O.; Dallinger, D. *Nat. Rev. Drug Discov.* **2006**, *5*, 55; (b) Shipe, W. D.; Wolkenberg, S. E.; Lindsley, C. W. *Drug Discov. Today Technol.* **2005**, *2*, 155; (c) Leadbeater, N. E. *Chem. Commun.* **2005**, 2881; (d) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; (e) Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225; (f) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199, and references cited therein.
5. (a) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194; (b) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481; (c) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706; (d) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674; (e) Geske, G. D.; Wezeman, R. J.; Siegel, A. P.; Blackwell, H. E. *J. Am. Chem. Soc.* **2005**, *127*, 12762; (f) Liu, J.-F.; Ye, P.; Zhang, B.-L.; Bi, G.; Sargent, K.; Yu, L.; Yohannes, D.; Baldino, C. M. *J. Org. Chem.* **2005**, *70*, 6339; (g) Zhou, Z. Z.; Zhao, P. L.; Huang, W.; Yang, G. F. *Adv. Synth. Catal.* **2006**, *348*, 63–67.
6. (a) Villemin, D.; Hammadi, M.; Martin, B. *Synth. Commun.* **1996**, *26*, 2895; (b) Bougrin, K.; Loupy, A.; Soufiaoui, M. *Tetrahedron* **1998**, *54*, 8055; (c) Poul, S.; Gupta, M.; Gupta, R. *Synth. Commun.* **2002**, *32*, 3541; (d) Rann, B. C.; Jana, R.; Dey, S. S. *Chem. Lett.* **2004**, *33*, 274.
7. (a) Elliott, A.J.; Hudlicky, M. In *Chemistry of Organic Fluorine Compounds. II. A Critical Review*, Avlath, A.E., Eds.; American Chemical Society: Washington, DC, 1995, pp 1119–1125; (b) Smart, B. E. *J. Fluorine Chem.* **2001**, *121*, 3.
8. Crystal data of **3h**. $C_{14}H_7F_4NS_2$, $M = 329.33$, Orthorhombic, $a = 13.138(1)$, $b = 9.305(1)$, $c = 22.684(1)$ Å, $\beta = 90°$, $V = 2773(1)$ Å^3, $T = 292(2)$ K, space group $Pca2(1)$, $Z = 8$, $D_c = 1.358$ g/cm^3, μ(Mo-Kα) = 0.269 mm^{-1}, $F(000) = 1328$. 15073 reflections measured, 5995 unique ($R_{int} = 0.0556$), which were used in all calculation. Fine $R_1 = 0.0619$, wR (F^2) = 0.1100 (all data). Full crystallographic details of **3h** have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 611756.
9. Hostettmann, K.; Harborne, J.B. In *Methods in Plant Biochemistry*, Dey, P.M., Eds.; Academic Press: London, 1991; vol. 6, pp 33–46.
10. Liu, Z. M.; Yang, G. F.; Qing, X. H. *J. Chem. Technol. Biotechnol.* **2001**, *76*, 1154.