Original Article

Synthesis and Rice-Blast Control Activity of Sulfonylamidines*

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A series of sulfonylamidines with a cleaved type of thiadiazine ring between the N-4 and C-benzene bond in 1,2,4-benzothiadiazine 1,1-dioxide were prepared, and their rice-blast control activity was examined. Some of these compounds exhibited good activity by foliar application. Substituents appeared to be important for the activity. The most effective was *N*-(*C*-Diethylamino-*n*-hexylmethylene)-*p*-toluenesulfonamide (**24**), the activity of which was stronger than that of *O,O*-diisopropyl *S*-benzyl phosphorothiolate (IBP).

INTRODUCTION

3-Alkylthio-1,2,4-benzothiadiazine 1,1-dioxides (**A** in Fig. 1) are reported to have shown some control activity against rice-blast.¹⁾ This study was aimed to obtain a new type of fungicide that is structurally related to **A** but more effective.

Judging from the structure-activity requirements of **A**, we speculated that the activity might be primarily attributable to the sulfonylamidine moiety, but substituents also must have a role in providing adequate activity. Based on the structure-activity requirements of **A**, we designed open-chain sulfonylamidine analogs (**B** in Fig. 1) derived from **A** in which the nitrogen-to-carbon bond between N-4 and C-benzene of **A** was cleaved.

This paper reports the synthesis of various kinds of sulfonylamidine derivatives and their structure-activity relationships.

MATERIALS AND METHODS

1. Chemicals

Sulfonylamidines were prepared by the [2+2]cycloaddition reaction of sulfonyliso-

cyanate with carbonyl or thiocarbonyl compounds with the synthetic scheme shown in Fig. 2. The synthetic method has been described in detail in the patent²⁾ and papers³⁻⁵⁾ on this series of compounds. 3-Ethylthio-4-methyl-4*H*-1,2,4-benzothiadiazine 1,1-dioxide was prepared according to our reported method.⁶⁾ The configuration of the sulfonylamidines reported here remains undetermined. Structures of the compounds were confirmed by ¹H NMR, IR spectra and/or elemental analysis (C, H, N). All melting points are uncorrected.

2. Disease-controlling Activity

Disease-controlling activity was assessed after preventive foliar application. Two-week-old rice seedlings (var.: AICHI-ASAHI) were transplanted into plastic cups and cultivated for 2 weeks. The test compound in a form of solution or suspension was sprayed on the foliage of the rice seedlings. The test solution or suspension was prepared by dissolving the compound in a small amount of *N,N*-dimethylformamide followed by dilution with distilled water containing a sticking agent to the desired concentration. The test plants were inoculated by spraying with a conidial suspension of *Pyricularia oryzae* previously cul-

* Cycloaddition in Synthesis of Sulfonamide Derivatives (Part 5). For Part 4, see Ref. 5).

tured on an oatmeal medium.

After being sprayed with the conidial suspension, the test plants were kept in a moist chamber (28°C, 100% R.H.) for 24 hours, followed by incubation in a greenhouse for 5 days. Six day after inoculation, the number of lesions was counted and the percent of control was calculated as follows:

$$\text{Control (\%)} = (1 - b/a) \times 100,$$

where a is the number of lesions in an un-

treated plot and b is the number of lesions in a treated plot.

RESULTS AND DISCUSSION

1. Effect of Carbon Substituents (R^3 in Fig. 2) and Amino Moiety (R^1, R^2 in Fig. 2)

The physical properties and rice-blast control activities of the tested compounds are listed in Tables 1 to 5.

At first, the effect of R^3 on the rice-blast control activity was examined with various kinds of prepared compounds in which R^1, R^2 were fixed as methyl and R^4 as 4-methyl (Tables 1 and 2). In a series of phenyl deriva-

A

B

Fig. 1 The original lead and prepared compounds.

Table 1 Rice-blast control activity of *N*-(*C*-dimethylamino-phenylmethylene)-*p*-toluenesulfonamides.

Compound No.	X	mp (°C)	Control (%) (500 ppm)
1	H	160-161	30
2	4-CH ₃	118-119	70
3	4-OCH ₃	132-133	70
4	4-N(CH ₃) ₂	155-157	0
5	4-Cl	185-188	0
6	4-NO ₂	188-190	0
7	3,4-Cl ₂	160-161	50
8	2-CO ₂ CH ₃	134-135	0

Fig. 2 General synthetic route.

Table 2 Rice-blast control activity of *N*-(*C*-dimethylamino-methylene)-*p*-toluenesulfonamides.

Compound No.	R ³	mp (°C)	Control (%) (500 ppm)
9	CH ₃	120–123	70
10	<i>n</i> -C ₃ H ₇	oil	70
11	CH=CH-CH ₃	147–149	30
12	CH ₂ CH(Br)CH ₃	103–104.5	30
13	<i>n</i> -C ₆ H ₁₃	oil	70
14	C ₆ H ₁₁ (cyc.)	121–121.5	50
15	OCH ₃	92–94	0
16	SCH ₃	59–60	30
17	N(CH ₃) ₂	140–141	30
18	COOEt	121–123	50

Table 3 Rice-blast control activity of *N*-(*C*-diethylamino-methylene)-*p*-toluenesulfonamides.

Compound No.	R ³	mp (°C)	Control (%) (500 ppm)
19	<i>i</i> -Pr	87–88	0
20	<i>i</i> -Bu	oil	0
21	<i>t</i> -Bu	77–80	0
22	<i>n</i> -Bu	oil	70
23	<i>n</i> -C ₆ H ₁₁	oil	90
24	<i>n</i> -C ₆ H ₁₃	oil	97
25	C ₆ H ₁₁ (cyc.)	102–105	30
26	<i>n</i> -C ₇ H ₁₅	oil	90
27	<i>n</i> -C ₈ H ₁₇	oil	70
28	<i>n</i> -C ₉ H ₁₉	oil	50
29	<i>n</i> -C ₁₀ H ₂₁	oil	50
30	<i>n</i> -C ₁₁ H ₂₃	oil	50
31	<i>n</i> -C ₁₃ H ₂₇	48–49	30
32	<i>n</i> -C ₁₅ H ₃₁	59–59.5	0

tives, the activity was greatly influenced by a substituent of the benzene ring. Compounds **2** and **3** which had methyl and methoxy at the 4-position of the benzene ring, respectively, were highly active, whereas 4-dimethylamino

Table 4 Rice-blast control activity of *N*-(*C*-amino-*n*-hexylmethylene)-*p*-toluenesulfonamides.

Compound No.	R ¹ R ²	mp (°C)	Control (%) (500 ppm)
33	<i>n</i> -Pr <i>n</i> -Pr	oil	50
34	<i>n</i> -Bu <i>n</i> -Bu	oil	0
35		78–80	50
36		oil	30
37		oil	30
38		91–92	30

(**4**), 4-chloro (**5**), 4-nitro (**6**) and 2-methoxycarbonyl (**8**) derivatives were inactive. Compounds **1** and **7** had lower activity (Table 1).

To define more detailed requirements of substituents (R³), various substituents were introduced and the activity was tested. As can be seen from Table 2, a series of alkyl analogs (**9**, **10**, **13**) showed high activity, whereas a cyclohexyl-substituted compound (**14**) and a methylthio-substituted compound (**16**) lowered the activity and a methoxy-substituted compound (**15**) gave an ineffective compound. Introduction of a bromine atom or a double bond into the *n*-propyl group (**11**, **12**) decreased the activity. Dimethylamino- (**17**) and carboethoxy-substituted compound (**18**) also lowered the activity. These data revealed alkyl groups are favorable for high activity.

When R³ was *n*-hexyl, compounds with ethyl as substituents in R¹ and R² (**24**) showed higher activity than those with methyl (**13**), *n*-propyl (**33**) and *n*-butyl (**34**). The effect of amino moiety on the activity was then examined. Introduction of a cyclic amino group (**35**–**38**) resulted in reduced activity (Table 4),

which indicated the importance of diethyl-amino substituents. The activity of a piperidine analog (**35**) was higher than that of pyrrolidine, 1-methylpiperidine and morpholine analogs (**36–38**). Based on these findings various kinds of alkyl substituted derivatives having ethyl at R¹ and R² were prepared and examined (Table 3).

Compounds with a branched alkyl group (**19–21**) showed no activity and a cyclohexyl-substituted compound (**25**) had only low activity. Compounds with an unbranched alkyl group (**23, 24, 26**), in contrast, had high activity. The effect of unbranched alkyl substituents on the activity depended on the length of the carbon chain, with the potency decreasing in the following order: **23, 24, 26** (C5–C7) > **22, 27** (C4) (C8) > **28–30** (C9–C11) > **31** (C13) > **32** (C15).

2. Effect of Benzene Ring Substituents (R⁴ in Fig. 2)

Since compound **24** showed high activity, we next examined the effect of ring substituents by a benzene sulfonyl group. As shown in Table 5, introduction of a chlorine atom at the 4-position of the benzene ring (**39**) decreased the activity. A 2-chloro derivative (**40**) had no activity, and an unsubstituted compound (**41**) had low activity. These results indicate that the activity is greatly dependent on the type of substituents as well as the position of substitution on the benzene ring.

3. Activity of Selected Compounds

Based on the above results, compounds **23**,

Table 5 Rice-blast control activity of *N*-(*C*-diethylamino-*n*-hexylmethylene)-*p*-toluenesulfonamides.

Compound No.	R ⁴	mp (°C)	Control (%) (500 ppm)
39	4-Cl	oil	30
40	2-Cl	oil	0
41	H	oil	30

Table 6 Selected compounds and their controlling activities on rice blast by foliar application.

Compound	Control (%)			
	500 ppm	125 ppm	31.3 ppm	7.8 ppm
23	90	90	70	30
24	97	90	90	50
26	90	90	70	30
IBP ^{a)}	70	50	30	0
3-Ethylthio-4-methyl-1,2,4-benzothiadiazine 1,1-dioxide	90	70	30	0

^{a)} *O,O*-diisopropyl *S*-benzyl phosphorothiolate.

24, 26 were chosen for the second step of evaluation. Compound **24** showed sufficient control even at 31.3 ppm, being more active than *O,O*-diisopropyl *S*-benzyl phosphorothiolate (IBP) and the original lead compound, 3-ethylthio-4-methyl-1,2,4-benzothiadiazine 1,1-dioxide (**A**, R¹=Me, R²=Et) (Table 6).

Our study has revealed that these sulfonylamidine derivatives are a new class of fungicides that are highly effective against rice-blast.

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要 約

スルホニルアミジン誘導体の合成といもち病防除活性*

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3-アルキルチオ-1,2,4-ベンゾチアジアジン 1,1-ジオキシドがいもち病防除活性を有することに着目し, この

* 環状付加反応を利用したスルホンアミド誘導体の合成研究 (第 5 報)

化合物のスルホニルアミジン部が活発発現に求められる必須構造ではないかと推論した. この推論に基づいて種々の置換基を有するスルホニルアミジン誘導体を合成し, その構造と生物活性の関係を検討した. その結果, 合成した化合物群のいくつかは, 優れた活性を示した. とくに *N*-(*C*-ジエチルアミノ-*n*-ヘキシルメチレン) パラトルエンスルホンアミドは, リード化合物および *O*, *O*-ジイソプロピル *S*-ベンジルフォスフォロチオレート (IBP) よりも, いもち病に対して高い防除活性を示した.