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Note

Synthesis and Acaricidal Activity of *N*-(1,3,4-Thiadiazol-2-yl)pyrazole-5-carboxamides and *N*-(1,3,4-Thiadiazol-2-yl)-thiazole-5-carboxamides

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Key words: acaricidal acitivity, *Tetranychus urticae*, *N*-(1,3,4-thiadiazol-2-yl)pyrazole-5-carboxamides, *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides.

INTRODUCTION

In our previous paper, we reported the structure-activity relationships of acaricidal *N*-(1,3,4-thiadiazol-2-yl)carboxamides[1] and *N*-(1,3,4-thiadiazol-2-yl)cyclopropanecarboxamides.[2] In the course of our study, a series of *N*-(1,3,4-thiadiazol-2-yl)pyrazole-5-carboxamides and *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides were synthesized and their acaricidal activity was examined.[3,4] This paper describes the structure-activity relationships of acaricidal *N*-(1,3,4-thiadiazol-2-yl)pyrazole-5-carboxamides and *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides.

MATERIALS AND METHODS

1. Synthesis of Compounds

Synthetic route of *N*-(1,3,4-thiadiazol-2-yl)pyrazole-5-carboxamides and *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides is shown in Fig. 1. Pyrazole-5-carboxylic acids were synthesized by the standard method.[5,6] 2-Amino-5-substituted-1,3,4-thiadiazoles were purchased from commercial sources or synthesized according to the reported procedure.[7,8] Reaction of pyrazole-5-carboxylic acids with thionyl chloride gave acid chlorides. *N*-(1,3,4-Thiadiazol-2-yl)pyrazole-5-carboxamides were prepared by reacting acid chlorides with 2-amino-5-substituted-1,3,4-thiadiazoles in the presence of potassium carbonate. Reaction of thiazole-5-carboxylic acids[9] with 1,1′-carbonyldiimidazole (CDI) gave 1-(thiazole-5-carbonyl)imidazoles, which were then treated with 2-amino-5-substituted-1,3,4-thiadiazoles to give *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides.

*1.1. 3-tert-Butyl-4-chloro-N-(5-heptafluoropropyl-1,3,4-thiadiazol-2-yl)-2-methylpyrazole-5-carboxamide (**16**)*

A mixture of 3-*tert*-butyl-4-chloro-1-methylpyrazole-5-carboxylic acid (1.06 g, 5.0 mmol) and thionyl chloride (5 ml) was refluxed for 1 hr. The reaction mixture was cooled and excess thionyl chloride was removed under reduced pressure. To the residue, toluene (10 ml), 2-amino-5-heptafluoropropyl-1,3,4-thiadiazole (mp : 229–230°C, 1.35 g, 5.0 mmol) and potassium carbonate (0.83 g, 6.0 mmol) were added and the resulting mixture was refluxed for 1 hr. The reaction mixture was cooled and poured into ice water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by chromatography on silica gel with hexane-ethyl acetate (5 : 1) to give **16** (1.82 g, 78%). mp : 111–113°C ; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.42 (9H, s), 4.19 (3H, s), 11.60 (1H, br).

*1.2. 2-tert-Butyl-N-(5-heptafluoropropyl-1,3,4-thidiazol-2-yl)-4-methylthiazole-5-carboxamide (**23**)*

A mixture of 2-*tert*-butyl-4-methylthiazole-5-carboxylic acid (0.40 g, 2.0 mmol) and 1,1′-carbonyldiimidazole (0.36 g, 2.2 mmol) in tetrahydrofuran (THF, 3 ml) was stirred for 30 min and

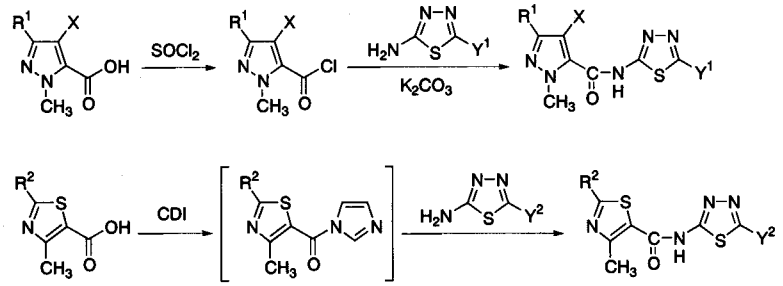

Fig. 1. Synthetic route of *N*-(1,3,4-thiadiazol-2-yl)pyrazole-5-carboxamides and *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides.

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concentrated under reduced pressure. To this, toluene (5 ml) and 2-amino-5-heptafluoropropyl-1,3,4-thidiazole (0.54 g, 2.0 mmol) were added and the resulting mixture was refluxed for 2 hr. The mixture was cooled to room temperature and purified by chromatography on silica gel with hexane-ethyl acetate (5 : 1) to give **23** (0.65 g, 72%). mp : 131-132°C ; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.47 (9H, s), 2.80 (3H, s), 11.64 (1H, br).

2. Biological Tests

Test species of mites (*Tetranychus urticae*) and the method used were the same as previously reported.[10]

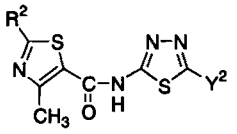
The activity rating was expressed as indices of A, B, C and D, corresponding to over 80% mortality at 50, 200, 500 ppm and less than 80% mortality at 500 ppm, respectively.

RESULTS AND DISCUSSION

Table 1 shows the structure-activity relationships of *N*-(1,3,4-thiadiazol-2-yl)pyrazole-5-carboxamides. To examine the substitution effect at the 3-position on the pyrazole ring, some alkyl groups were introduced (**1**-**9**). Among these, the *tert*-butyl analog (**9**) was the most active. The effect of a halogen atom at 4-positon on the pyrazole ring was then examined (**10**-**12**). Replacement of the chlorine atom with a bromine resulted in reduced activity (**11**). The unsubstituted (**10**) and the iodo (**12**) analogs were inactive at 500 ppm. Finally, the substitution effect at the 5-position on the thiadiazole ring was examined (**13**-**19**). Among perfluoroalkyl analogs, the C1-C5 analogs (**9**, **14** and **16**-**18**) were active at 50 ppm, but the longer perfluorohexyl analog (**19**) was inactive. Replacement of the fluorine atom with a hydrogen atom (**13** and **15**) resulted in reduced activity.

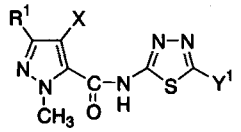
Table 2 shows the structure-activity relationship of *N*-(1,3,4-thiadiazol-2-yl)thiazole-5-carboxamides. First, the effect of alkyl groups at the 2-position on the thiazole ring was examined

Table 2. *N*-(1,3,4-Thiadiazol-2-yl)thiazole-5-carboxamides and their acaricidal activity against *Tetranychus urticae*



No.	R^2	Y^2	mp (°C)	Activity rating
20	methyl	$(CF_2)_2CF_3$	164-165	C
21	ethyl	$(CF_2)_2CF_3$	152-153	D
22	isopropyl	$(CF_2)_2CF_3$	165-166	D
23	*tert*-butyl	$(CF_2)_2CF_3$	131-132	A
24	*tert*-butyl	CF_3	92-94	D
25	*tert*-butyl	CF_2CF_3	82-84	A
26	*tert*-butyl	$(CF_2)_3CF_3$	98-100	A

Table 1. *N*-(1,3,4-Thiadiazol-2-yl)pyrazole-5-carboxamides and their acaricidal activity against *Tetranychus urticae*



No.	R^1	X	Y^1	mp (°C)	Activity rating
1	methyl	Cl	CF_3	129-131	B
2	ethyl	Cl	CF_3	128-130	B
3	propyl	Cl	CF_3	100-101	B
4	isopropyl	Cl	CF_3	121-122	B
5	cyclopropyl	Cl	CF_3	147-148	C
6	butyl	Cl	CF_3	86-87	C
7	isobutyl	Cl	CF_3	92-94	B
8	*sec*-butyl	Cl	CF_3	109-110	B
9	*tert*-butyl	Cl	CF_3	128-129	A
10	*tert*-butyl	H	CF_3	172-173	D
11	*tert*-butyl	Br	CF_3	122-124	B
12	*tert*-butyl	I	CF_3	155-157	D
13	*tert*-butyl	Cl	CHF_2	142-143	D
14	*tert*-butyl	Cl	CF_2CF_3	112-113	A
15	*tert*-butyl	Cl	CF_2CHF_2	134-135	D
16	*tert*-butyl	Cl	$(CF_2)_2CF_3$	111-113	A
17	*tert*-butyl	Cl	$(CF_2)_3CF_3$	60-61	A
18	*tert*-butyl	Cl	$(CF_2)_4CF_3$	91-92	A
19	*tert*-butyl	Cl	$(CF_2)_5CF_3$	121-122	D

(**20**–**23**). Among these, only the *tert*-butyl analog (**23**) showed high activity. Some perfluoroalkyl groups were then introduced into the 5-position on the thiadiazole ring (**24**–**26**). The pentafluoroethyl (**25**), heptafluoropropyl (**23**) and nonafluorobutyl (**26**) analogs were active, but the trifluoromethyl analog (**24**) was inactive at 500 ppm. This suggests that appropriate steric size or hydrophobicity is important in activity.

In this study, thiazole derivatives having substituents similar to those of pyrazole derivatives (*tert*-butyl and methyl groups) were almost as active as pyrazole derivatives. These results are in good agreement with those reported for *N*-(4-*tert*-butylbenzyl)carboxamides.[11]

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