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Note

Structure and Acaricidal Activity of Pyrazolecarboxamides and Thiazole-5-carboxamides

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INTRODUCTION

In our previous paper, we reported the structure-activity relationships of *N*-benzylpyrazole-5-carboxamide derivatives. Among them *N*-(4-*tert*-butylbenzyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (MK-239, tebufenpyrad, Pyranica®) was the most effective acaricide.[1-8]

In the course of our study, in order to clarify the acaricidal activity of structural isomers of *N*-(4-*tert*-butylbenzyl)pyrazolecarboxamides, their derivatives and thiazole-5-carboxamides were synthesized and their acaricial activity was examined.

MATERIALS AND METHODS

1. *Synthesis of Compounds*

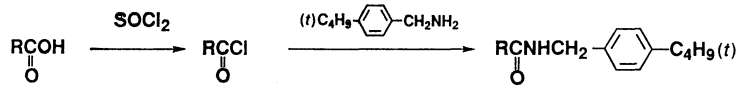
The synthetic route of pyrazole and thiazole derivatives listed in Tables 1–3 is shown in Fig. 1. Pyrazole-3- and -5-carboxylic acids,[4-8] pyrazole-4-carboxylic acids[9] and thiazole-5-carboxylic acids[10] were prepared by hydrolysis of corresponding esters which had been synthesized according to the methods described in literatures. Reaction of (**I**) with thionyl chloride gave the acid chlorides (**II**). A number of new pyrazole and thiazole derivatives (**III**) were prepared by reacting the acid chlorides (**II**) with 4-*tert*-butylbenzylamine[11-13] in the presence of triethylamine. The structures of compounds were confirmed by IR and ^{1}H NMR spectra. Melting points were measured with a Yanagimoto micro-melting point apparatus and uncorrected. Refractive indexes were measured with an Atago Abbe-refractometer IT. The following is an example of the synthetic procedures. The other compounds were synthesized in a similar manner.

N-(4-*tert*-Butylbenzyl)-3-ethyl-1-methylpyrazole-5-carboxamide (**5**): A mixture of 3-ethyl-1-methylpyrazole-5-carboxylic acid (15.4 g, 0.1 mol) and thionyl chloride (17.8 g, 0.15 mol) was heated under reflux for 1 hr. The reaction mixture was cooled, and after excess thionyl chloride was removed under reduced pressure, the residue was dissolved in toluene (200 ml). The obtained solution was added dropwise to toluene (20 ml) solution of 4-*tert*-butylbenzylamine (19.6 g, 0.12 mol) at 0–5°C in the presence of triethylamine (12.1 g, 0.12 mol). Then the mixture was stirred at 0–5°C for 2 hr, poured into ice water and extracted with toluene (100 ml). The organic layer was separated, washed twice with water (50 ml) and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel, eluted with *n*-hexane–ethyl acetate (3: 1) to give 26.9 g (90%) of **5** as colorless crystals, mp 81–83°C. ^{1}H NMR ($CDCl_3$) δ ppm: 1.23 (3H, t, J=7.5 Hz), 1.32 (9H, s), 2.63 (2H, q, J=7.5 Hz), 4.15 (3H, s), 4.55 (2H, d, J=6 Hz), 6.25 (1H, bs), 6.30 (1H, s), 7.37 (4H, d, J=7.5 Hz). IR (KBr) cm^{-1}: 3300, 2960, 1640, 1560, 1280, 1120, 815.

2. *Biological Test*

Test species of mite (*Tetranychus urticae*) and the method used were the same as previously reported.[1]

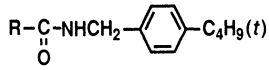
The activity rating was expressed as indexes of 0 to 3, corresponding to 0–29, 30–79, 80–99

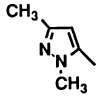
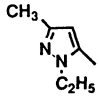
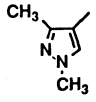
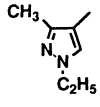


(I) (II) (III)

Fig. 1 Synthetic route of pyrazole and thiazole derivatives (**III**).

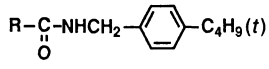
Table 1 Substituted *N*-(4-*tert*-butylbenzyl)pyrazolecarboxamides and their miticidal activity against *Tetranychus urticae*.



No.	R	mp or n_D(°C)	Activity ratings				
			500	200	50	12.5	3.1 ppm
1[a]		111–113	3	3	3	1	0
2		148–150	0	0	0	0	0
3		1.5326(25)	3	2	0	0	0
4		1.5382(25)	3	3	3	1	0

[a] Data were taken from Table 4 in our previous paper.[1]

Table 2 Four structural isomers of substituted *N*-(4-*tert*-butylbenzyl)pyrazolecarboxamides and their miticidal activity against *Tetranychus urticae*.



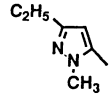
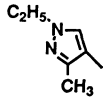
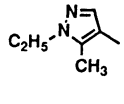
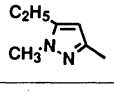
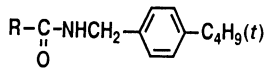
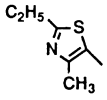
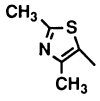
No.	R	mp or n_D(°C)	Activity ratings				
			500	200	50	12.5	3.1 ppm
5		81–83	3	3	3	3	0
4		1.5382(26.5)	3	3	3	1	0
6		132–133	0	0	0	0	0
7		235–236	0	0	0	0	0

Table 3 Substituted *N*-(4-*tert*-butylbenzyl)thiazole-5-carboxamides and their miticidal activity against *Tetranychus urticae*.



No.	R	mp(°C)	Activity ratings				
			500	200	50	12.5	3.1 ppm
8[a)]		74–76	3	3	3	1	0
9		64–67	3	3	3	0	0
10		68–69	1	0	0	0	0

[a)] Compound **8** has 4-*tert*-butyl-α-methylbenzylamino group instead of 4-*tert*-butylbenzylamino group on amino moiety.

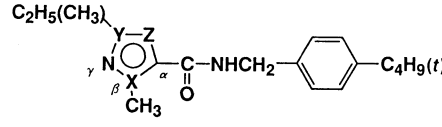
and 100% mortality respectively (Tables 1–3).

RESULTS AND DISCUSSION

N-(4-*tert*-Butylbenzyl)pyrazole-5- and -4-carboxamides[14] and their miticidal activity are summarized in Table 1. One of the pyrazole-5-carboxamides **1** was active at 50 ppm, while replacement of methyl group at 1-position on pyrazole ring by ethyl group gave **2**, which was inactive at 500 ppm.

On the other hand, one of the pyrazole-4-carboxamides **3** was active at 200 ppm, while replacement of methyl group at 1-position on pyrazole ring by ethyl group gave **4**, which increased the activity. Table 2 shows the miticidal activity of four structural isomers of pyrazolecarboxamides having both methyl and ethyl groups on pyrazole ring. Compound **5** was slightly more active than corresponding compound **1**. Substitution of alkyl groups longer than ethyl group at 3-position on pyrazole ring reduced by activity.[1,2] Isomers **4** and **5** showed high miticidal activity, but other two isomers **6** and **7** were inactive at 500 ppm. These results show that pyrazole moiety of compounds **4** and **5** plays a very important role in miticidal activity. Table 3 shows thiazole-5-carboxamides **8** and **9** having substituents similar to those of pyrazole derivatives **4** and **1**.[15] Compounds **8** and **9** were as active as the corresponding pyrazole derivatives **4** and **1**, respectively.

In this study, the presence of five membered ring involving both methyl substituted carbon or methyl substituted nitrogen atom at β-position of carbamoyl group and nonsubstituted nitrogen atom at γ-position was necessary for miticidal compounds (**1**, **3**, **4**, **5**, **8** and **9**) to be highly active. The miticidal activity of other heteroaromatic carboxamide derivatives will be reported in the future.



X, Y; C, N

Z; CH, S

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要　約

ピラゾールカルボキサミド誘導体とチアゾール-5-カルボキサミド誘導体の構造と殺ダニ活性

岡田　至，奥井周子，田中敏彦，細川明美
興村伸夫，福地俊樹，高橋洋治

われわれはさきに *N*-(4-*tert*-ブチルベンジル)-4-クロロ-3-エチル-1-メチルピラゾール-5-カルボキサミド (tebufenpyrad, Code No. MK-239, Pyranica®) が，高い殺ダニ活性を有することを報告した．4種のピラゾールカルボキサミド構造異性体のうち3-エチル-1-メチルおよび1,3-ジメチルピラゾール-5-カルボキサミド誘導体および1-エチル-3-メチルおよび1,3-ジメチルピラゾール-4-カルボキサミド誘導体に活性を認めたが，1-エチル-5-メチルピラゾール-4-カルボキサミド誘導体および5-エチル-1-メチルピラゾール-3-カルボキサミド誘導体には活性を認めなかった．一方，2-エチル-4-メチルおよび2,4-ジメチルチアゾール-5-カルボキサミド誘導体にも活性を認めた．本研究において，殺ダニ活性発現にはカルバモイル基のβ位にメチル置換炭素またはメチル置換窒素原子およびγ位に無置換窒素原子を有する5員環が必要であることがわかった．