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**Note**

# Synthesis and Acaricidal Activity of *N*-(3-Pyridylmethyl)pyrazolecarboxamide Derivatives

Itaru OKADA, Shigeru SUZUKI, Shuko OKUI, Toshiki FUKUCHI and Yoji TAKAHASHI

*Yokohama Research Center, Mitsubishi Chemical Corporation, Aoba-ku, Yokohama 227, Japan*

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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.[1,2]

In the course of our study, in order to obtain more effective compounds, a series of *N*-(3-pyridylmethyl)pyrazolecarboxamide derivatives were synthesized and their acaricidal activity was examined.[3]

This paper describes the strucrture-activity relationships of acaricidal *N*-(3-pyridylmethyl)pyrazolecarboxamides.

## MATERIALS AND METHODS

*1. Synthesis of Compounds*

The synthetic route of pyrazolecarboxamide derivatives listed in Tables 1 and 2 is shown in Fig. 1.

4-Chloro-3-ethyl-1-methylpyrazole-5-carboxylic acid (**I**) was prepared according to literature.[4] Reaction of compound **I** with thionyl chloride gave the acid chlorides (**II**). A number of new pyrazolecarboxamide derivatives (**IV**) were prepared by reacting the acid chlorides (**II**) with 3-pyridylmethylamines (**III**) in the presence of triethylamine. The synthetic routes of 3-pyridylmethylamines (**IIIa**, **IIIb**) are shown in Fig. 2. 6-Alkyl-3-pyridylmethylamines (**IIIa**)[5] were prepared by the reduction of corresponding 6-alkyl-2-chloronicotinonitriles[6] which had been synthesized according to the methods described in literature. 6-Alkoxy-3-pyridylmethylamines (**IIIb**) were prepared by the reduction of corresponding 6-alkoxynicotinonitriles which had been synthesized by reacting 6-chloronicotinonitrile[7] with corresponding alcohols.

The structures of compounds were confirmed by IR and $^1$H NMR spectra. Melting points were measured with a Yanagimoto micromelting point apparatus and uncorrected. Refractive indexes were measured with an Atago Abbe-refractometer IT.

The following are examples of the synthetic procedures. The other compounds were synthesized in a similar manner.

*1.1 6-Butyl-3-pyridylmethylamine*

To a solution of 6-butyl-2-chloronicotinonitrile (bp 114–116°C/0.3 mmHg; 19.5 g, 0.1 mol) which had been prepared by the methods of Youngdale & Oglia[6] in ethyl alcohol (200 ml) was added 10% Pd-C catalyst (1.5 g). After the catalytic hydrogenation at 60°C, the catalyst was removed by filtration. The solvent was removed under reduced pressure, the residue was poured into water (100 ml) and extracted with toluene (50 ml). The water layar separated was alkalized by sodium hydroxide and extracted with toluene (100 ml). The organic layer was washed with water (30 ml) and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was destilled under reduced pressure to give 13.9 g (85%) of 6-butyl-3-pyridylmethylamine as colorless oil, bp 108°C/3 mmHg.

$^1$H NMR ($CDCl_3$) $\delta$ ppm: 0.94 (3H, t), 1.40 (2H, m), 1.45 (2H, s), 1.70 (2H, m), 2.78 (2H, t), 3.85 (2H, s), 7.11 (1H, d), 7.56 (1H, d), 8.46 (1H, s). IR (KBr) $cm^{-1}$: 2960, 2940, 2850, 1600, 1490.

*1.2 6-Isopropoxy-3-pyridylmethylamine*

To a solution of isopropyl alcohol (1.80 g, 0.03 mol) in *N*, *N*-dimethylformamide (20 ml) was added 60% sodium hydride (0.90 g), and then 6-chloronicotinonitrile[7] (2.77 g, 0.02 mol). After 1 hr of stirring at room temperature, the reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (100 ml). The organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, eluted with hexane–ethyl acetate (4 : 1) to give 2.75 g (85%) of 6-isopropoxynicotinonitrile as colorless crystals, mp 62–63°C.

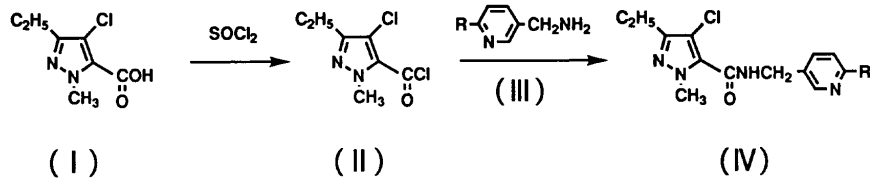
$^1$H NMR ($CDCl_3$) $\delta$ ppm: 1.36 (6H, d), 5.37 (1H, m), 6.73 (1H, d), 7.74 (1H, d), 8.46 (1H, s). IR (KBr) $cm^{-1}$: 2980, 2930, 2240, 1600, 1480, 1380, 1290, 1100.

6-Isopropoxynicotinonitrile (3.24 g, 0.02 mol) in methyl alcohol (30 ml) was reduced with hydrogen in a similar way described above. The residue was purified by column chromatography on silica gel, eluted with chloroform–methyl alcohol (100 : 5) to give 2.32 g (70%) of 6-isopropoxy-3-pyridylmethylamine as colorless oil, $n_D^{25}$ 1.5100.

$^1$H NMR ($CDCl_3$) $\delta$ ppm: 1.34 (6H, d), 1.51 (2H, s), 3.79 (2H, s), 5.27 (1H, m), 6.59 (1H, d), 7.54 (1H, dd), 8.05 (1H, d). IR (KBr) $cm^{-1}$: 2980, 1605, 1480, 1280, 1110, 950.

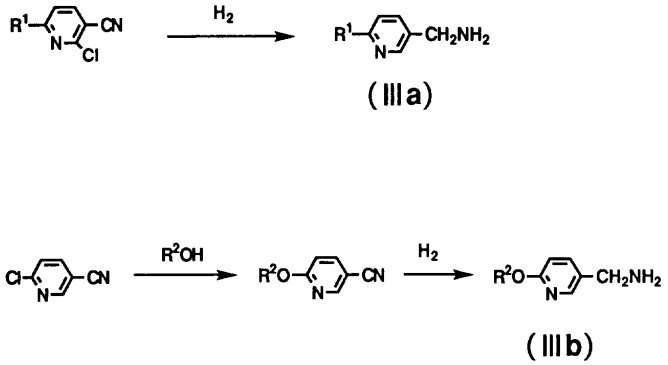
*1.3 N-(6-Butyl-3-pyridylmethyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (4)*

A mixture of 4-chloro-3-ethyl-1-methylpyrazole-5-carboxylic acid (2.07 g, 0.01 mol) and thionyl chloride (1.78 g, 0.015 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 (5 ml). The obtained solution was added dropwise



(I) (II) (III) (IV)

Fig. 1 Synthetic route of pyrazolecarboxamide derivatives (**IV**).



(IIIa) (IIIb)

Fig. 2 Synthetic routes of 3-pyridylmethylamines (**IIIa**, **IIIb**).

to toluene (20 ml) solution of 6-butyl-3-pyridylmethylamine (1.97 g, 0.012 mol) at 0–5°C in the presence of triethylamine (1.21 g, 0.012 mol). Then the mixture was stirred at 0–5°C for 2 hr, poured into ice water and extracted with toluene (10 ml). The organic layer was separated, washed twice with water (10 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 hexane–ethyl acetate (1 : 1) to give 3.10 g (90%) of **4** as colorless crystals, mp 87–88°C.

$^1$H NMR ($CDCl_3$) $\delta$ ppm : 0.94 (3H, t), 1.15–1.90 (4H, m), 1.25 (3H, t), 2.63 (2H, q), 2.81 (2H, t), 4.15 (3H, s), 4.63 (2H, d), 7.08 (1H, b),7.17 (1H, d), 7.63 (1H, dd), 8.56 (1H, d). IR (KBr) cm$^{-1}$ : 3270, 2955, 1640, 1555, 1485, 1460, 1400, 1290, 1090, 1035.

*1.4 N-(6-Isopropoxy-3-pyridylmethyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamide (11)*

This compound was prepared in a similar manner described above. Compound **11** was obtained as colorless crystals, yield 2.96 g (88%), mp 94–95°C.

$^1$H NMR ($CCl_4$) $\delta$ ppm : 1.20 (3H, t), 0.35 (6H, d), 2.55 (2H, q), 4.10 (3H, s), 4.50 (2H, d), 5.30 (1H, m), 6.60 (1H, d), 6.85 (1H, b), 7.55 (1H, dd), 8.05 (1H, d). IR (KBr) cm$^{-1}$ : 3300, 2975, 1645.

*2. Biological Test*

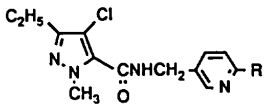
Test species of mite (*Tetranychus urticae*) and the method used were the same as previously reported.[1]

The activity rating was expressed as indexes, 0 to 3, corresponding to 0–29, 30–79, 80–99 and 100% mortality respectively.

## RESULTS AND DISCUSSION

*N*-(6-Alkyl-3-pyridylmethyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamides and their miticidal activity are summarized in Table 1. Non substituted derivative (**1**) at the 6-position of pyridine ring was inactive at 200 ppm. Among alkyl derivatives, *tert*-butyl derivative (**6**) was the most active, but less active than tebufenpyrad (**7**) having 4-*tert*-butylbenzyl group instead of 6-*tert*-butyl-3-pyridylmethyl group on the amide nitrogen atom. The relative order of activity : *tert*-butyl (**6**) > *neo*-amyl (**9**) > amyl (**8**) > isopropyl

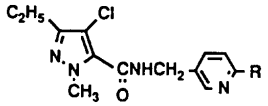
Table 1 *N*-(6-Alkyl-3-pyridylmethyl)-4-chloro-3-ethyl-1-methylpyrazolecarboxamides and their miticidal activity against *Tetranychus urticae*.



| No. | R | mp or $n_D$ (°C) | Activity rating (ppm) | | | | |
|---|---|---|---|---|---|---|---|
| | | | 500 | 200 | 50 | 12.5 | 3.1 |
| **1** | H | 72–74 | 1 | 0 | 0 | 0 | 0 |
| **2** | *n*-$C_3H_7$ | 77–79 | 3 | 2 | 1 | 0 | 0 |
| **3** | *i*-$C_3H_7$ | 72–74 | 3 | 3 | 3 | 1 | 0 |
| **4** | *n*-$C_4H_9$ | 87–88 | 3 | 3 | 3 | 1 | 0 |
| **5** | *i*-$C_4H_9$ | 94–95 | 3 | 3 | 3 | 1 | 0 |
| **6** | *t*-$C_4H_9$ | 1.5458 (25) | 3 | 3 | 3 | 3 | 2 |
| **7**[a] | *t*-$C_4H_9$ | 61–62 | 3 | 3 | 3 | 3 | 3 |
| **8** | *n*-$C_5H_{11}$ | 65–66 | 3 | 3 | 3 | 3 | 0 |
| **9** | *neo*-$C_5H_{11}$ | 1.5340 (25) | 3 | 3 | 3 | 3 | 1 |

[a] Tebufenpyrad, which has 4-*tert*-butylbenzyl group instead of 6-*tert*-butyl-3-pyridylmethyl group on the amide nitrogen atom. Data were taken from Table 5 in our privious paper.[1]

Table 2 *N*-(6-Alkoxy-3-pyridylmethyl)-4-chloro-3-ethyl-1-methylpyrazolecarboxamides and their miticidal activity against *Tetranychus urticae*.



| No. | R | mp (°C) | Activity rating (ppm) | | | | |
|---|---|---|---|---|---|---|---|
| | | | 500 | 200 | 50 | 12.5 | 3.1 |
| **10** | $n$-$C_3H_7O$ | 99–100 | 2 | 1 | 1 | 0 | 0 |
| **11** | $i$-$C_3H_7O$ | 94–95 | 3 | 3 | 2 | 1 | 0 |
| **12** | $CF_3CH(CH_3)O$ | 76–78 | 3 | 3 | 3 | 3 | 1 |
| **13** | $CF_2HCF_2CH_2O$ | 87–89 | 3 | 3 | 3 | 2 | 1 |
| **14** | $CF_3CF_2CH_2O$ | 84–85 | 3 | 3 | 3 | 2 | 1 |
| **15** | $n$-$C_4H_9O$ | 79–80 | 3 | 3 | 2 | 1 | 1 |
| **16** | $CF_3CH_2CH_2CH_2O$ | 92–94 | 3 | 3 | 3 | 2 | 1 |
| **17** | $CF_3CF_2CF_2CH_2O$ | 63–65 | 3 | 3 | 3 | 3 | 2 |

(**3**), butyl (**4**), isobutyl (**5**)＞propyl (**2**)＞hydrogen (**1**).

*N*-(6-Alkoxy-3-pyridylmethyl)-4-chloro-3-ethyl-1-methylpyrazole-5-carboxamides and their miticidal activity are summarized in Table 2. Perfluoro alkoxy derivatives showed more active than the corresponding alkoxy derivatives (**13**, **14** and **10**; **12** and **11**; **16**, **17** and **15**). The relative order of activity: 2, 2, 3, 3, 4, 4, 4-heptafluorobutoxy (**17**)＞1-(trifluoromethyl)ethoxy (**12**)＞2, 2, 3, 3-tetrafluoropropoxy (**13**), 2, 2, 3, 3, 3-pentafluoropropoxy (**14**), 4, 4, 4-trifluorobutoxy (**16**)＞butoxy (**15**)＞isopropoxy (**11**)＞propoxy (**10**).

In this study, *tert*-butyl derivative (**6**) was as active as 2, 2, 3, 3, 4, 4, 4-heptafluorobutoxy derivative (**17**), and they showed the most active against *Tetranychus urticae*, while they were less active than tebufenpyrad (**7**).

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## 要　　約


### *N*-(3-ピリジルメチル)ピラゾールカルボキサミド誘導体の合成と殺ダニ活性

岡田　至，鈴木　茂，奥井周子，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, Pyranica®) が，高い殺ダニ活性を有することを報告した．本研究では，さらに高い殺ダニ活性化合物を得ることを目標に16種の *N*-(3-ピリジルメチル)ピラゾールカルボキサミド誘導体を合成し，殺ダニ活性を試験した．ピリジン環上に *tert*-ブチル基や2, 2, 3, 3, 4, 4, 4-ヘプタフルオロブトキシ基を有するピラゾールカルボキサミド誘導体は，殺ダニ剤 tebufenpyrad よりは劣るものの，なかでももっとも高い殺ダニ活性を示した．