N-ホスフィノイル置換複素環化合物の合成と殺虫活性

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Original Article

Synthesis and Pesticidal Activities of *N*-Phosphinoyl Heterocycles*

Tohru KOYANAGI, Hiroshi OKADA, Osamu IMAI, Tadaaki TOKI and Takahiro HAGA

Central Research Institute, Ishihara Sangyo Kaisha, Ltd., Nishi-Shibukawa, Kusatsu 525, Japan

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Novel *N*-phosphinoyl heterocycles were synthesized by the reaction of a heterocycle against a phosphorochloridate in the presence of the strong base (*n*-BuLi or NaH). Studies on the structure-activity relationships were carried out as to acaricidal, aphicidal and nematicidal activities, respectively. With respect to the heterocyclic portion, the acidity (p*K*a) of the parent heterocycles seems to control the pesticidal activities. It is also suggested that the unsymmetrical alkoxy(alkylthio)phosphinoyl structures with the proper length of alkyl groups are crucial to the high pesticidal activities. The effect of the chiral phosphorus atom was investigated as to 3-[ethoxy(*sec*-butylthio)phosphinoyl]-1,3-thiazolidin-2-one. The levorotatory (−) isomer was shown to be more active against various pests.

INTRODUCTION

A variety of organophosphorus compounds have been reported to show unique bioactivities such as herbicidal, insecticidal, and fungicidal ones. However, there have not been enough studies on the phosphinoyl derivatives where the nitrogen atom of the heterocycle is linked to the phosphorus atom.

In the synthetic studies for the purpose of finding the candidate compounds as agrochemicals, we found that compounds **1** (Fig. 1) showed excellent insecticidal and acaricidal activities.[1] Among these derivatives, 3-chloro-5-trifluoromethylpyridine derivative **2** showed the highest activities. However, **2** possessed one drawback; LD_{50} (mouse) < 30 mg/kg. Since in compound **2**, 3-chloro-5-trifluoromethylpyridine acts as a strongly electron-withdrawing group,[2] the electron density of the nitrogen atom in the P–N bond is estimated to decrease. In the next step, in place of pyridine ring, we began to synthesize *N*-phosphinoyl heterocycles **3**, where an electron-deficient nitrogen atom in the heterocycle is directly bonded to phosphorus atom.

MATERIALS AND METHODS

1. *Apparatus*

All melting points were determined on a Mettler FP62 micro melting point apparatus and are uncorrected. All refractive indices were determined on an Atago Model 3 refractometer. NMR spectra were recorded on a JEOL JNM-GSX400 or a FX60 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS-DX303 spectrometer.

2. *Synthesis of the Compounds*

N-Phosphinoyl heterocycles were synthesized by the reaction of various heterocycles against chlorophosphates in the presence of bases. Substituted 1,3-oxazolidin-2-ones were prepared by the reactions of the corresponding 2-aminoethanol with urea according to the literature.[3] Other heterocycles were prepared by the conventional methods. Chlorophosphates were prepared according to the literature.[4]

Reaction conditions for the formation of *N*-phosphinoyl heterocycles were investigated in terms of the reaction of 1,3-thiazolidin-2-one against *S*-*sec*-butyl *O*-ethyl phosphorochloridothioate. As shown in Table 1, use of the stronger bases (*e.g.* sodium hydride, *n*-butyl lithium, sodium and 50% aqueous sodium hydroxide) is essential to promote the reaction. These results reveal that only the stronger bases can abstract the proton of the heterocycle, since the nitrogen atom of the heterocycle is a weak base. Furthermore, under these reaction conditions, phosphorylation occurred on the nitrogen atom predominantly, and the substitution on the oxygen atom of the carbonyl group was not observed. Consequently, for the synthesis of other *N*-phosphinoyl heterocycles, *n*-butyl lithium or sodium hydride in tetrahydrofuran was used.

* A part of this work was presented at the 197th American Chemical Society National Meeting, April, 1989, Dallas.

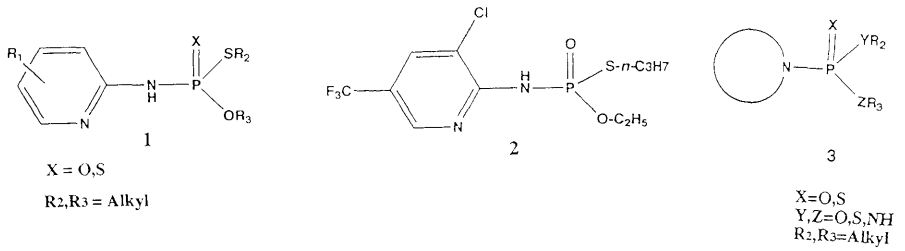
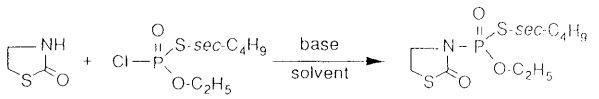


Fig. 1 Chemical structures of the compounds in the background of this study.

Table 1 Reaction conditions for the synthesis of 3-[ethoxy(*sec*-butylthio)phosphinoyl]-1, 3-thiazolidin-2-one (**8**).



Entry	Base	Solvent	Temp. (°C)	Time (hr)	Yield[a] (%)
1	*n*-BuLi	THF	0	2.5	56
2	NaH	DMF	0	2.5	51
3	Na	Toluene	15	2.5	79
4	50% NaOH	Toluene	0	2.5	46
5	Et_3N	CH_2Cl_2	Reflux	8.0	<10
6	K_2CO_3	MEK	Reflux	8.0	<10

[a] Based on 1, 3-thiazolidin-2-one.

Typical examples of synthetic procedure are as follows.

2.1 3-[Ethoxy(sec-butylthio)phosphinoyl]-1, 3-thiazolidin-2-one (8)

To a solution of 1, 3-thiazolidin-2-one (1.5 g, 0.015 mol) in THF (30 ml), *n*-butyllithium solution (1.65 M) in hexane (11 ml) was added dropwise under ice cooling. The mixture was stirred at room temperature for an additional 0.5 hr. Then the solution was cooled to 0°C again, and a THF solution (10 ml) of *S-sec*-butyl *O*-ethyl phosphorochloridothioate (5 g, 0.023 mol) was added dropwise, and at this temperature stirring was continued for 0.5 hr. And the mixture was stirred at room temperature for an additional 2 hr. Then the solution was concentrated at a reduced pressure. After dissolving the oily residue in EtOAc, it was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was purified by the silica gel column chromatography (toluene/EtOAc=3/1), to afford 2.3 g (56%) of the desired compound as a pale yellow oil : $n_D^{19.6}=1.5334$; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.81 (3H, t, $J=7.2$ Hz, $CH-CH_2-CH_3$), 1.11-1.16 (3H, m), 1.17-1.25 (3H, t, $J=6.4$ Hz, $O-CH_2-CH_3$), 1.43-1.53 (2H, m), 3.08-3.15 (2H, m), 3.21-3.34 (1H, m), 3.76-3.91 (2H, m), 3.93-4.08 (2H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm : 11.8 (CH_3), 16.0 (CH_3), 23.1 (CH_3), 28.6 (CH_2), 31.3 (CH_2), 44.8 (CH), 48.3 (CH_2), 64.1 (CH_2), 173.6 (CO) ; EI-MS *m/z* 283 (M^+).

2.2 3-[Ethoxy(sec-butylthio)phosphinoyl]-4-methyl-1, 3-oxazolidin-2-one (18)

To a solution of 4-methyl-1, 3-oxazolidin-2-one (2.0 g, 0.02 mol) in THF (40 ml), sodium hydride (60% oil dispersion) (0.87 g, 0.022 mol) was gradually added keeping the reaction temperature below 10°C. The mixture was stirred at room temperature for an additional 0.5 hr. Then a THF solution (5 ml) of *S-sec*-butyl *O*-ethyl phosphorochloridothioate (4.3 g, 0.02 mol) was added dropwise, and stirring was continued for an additional 2 hr. Then the solution was poured into ice water, extracted with EtOAc, washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The resulting crude product was purified by the silica gel column chromatography (*n*-hexane/EtOAc=1/2), to afford 1.6 g (29%) of the desired compound as a pale yellow oil : $n_D^{16.4}=1.4942$; ^{1}H NMR (60 MHz, $CDCl_3$) δ ppm : 0.76-1.17 (3H, t, $J=7.1$ Hz, $CH-CH_2-CH_3$), 1.23-2.27 (11H, m), 3.07-3.77 (1H, m), 3.8-4.7 (5H, m) ; ^{13}C NMR (15 MHz, $CDCl_3$) δ ppm : 11.3 (CH_3), 15.8 (CH_3), 21.1 (CH_3), 23.4 (CH_3), 45.1 (CH), 53.4 (CH), 64.3 (CH_2), 70.2 (CH_2), 155.4 (CO).

3. Separation of the Optical Isomers

The optical isomers of **8** were separated by preparative HPLC using Chiralcel OC (Daicel Chemical) as a chiral column (Fig. 2). The composition of the eluent was *n*-hexane/*iso*-propanol=9/1. Each fraction was concentrated *in vacuo*, to give the levorotatory isomer

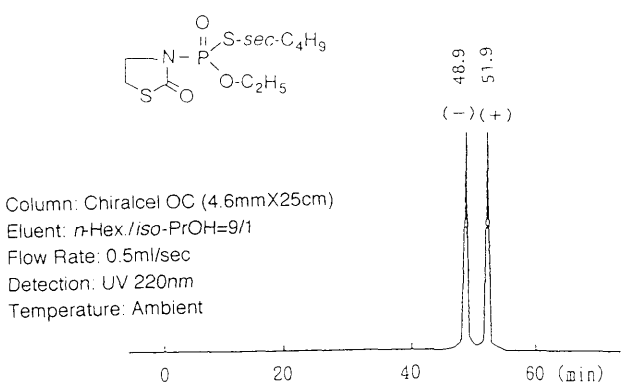


Fig. 2 HPLC chromatogram and separation conditions for the optical isomers of 3-[ethoxy(*sec*-butylthio)phosphinoyl]-1, 3-thiazolidin-2-one (**8**).

($[\alpha]_D^{27} = -42.6$, $c = 5.02$, MeOH), and dextrorotatory isomer ($[\alpha]_D^{27} = +42.6$, $c = 5.02$, MeOH), respectively.

4. Biological Tests

4.1 Acaricidal activities

The acaricidal activities were obtained against two-spotted spidermite (*Tetranychus urticae*) having the resistance to dicofol and conventional organophosphorus insecticides. A French bean leaf was dipped in the test solution, and after drying, 30 adults were released on it. The treated leaf was maintained in an incubator at 26°C, and dead mites were counted after 2 days. The acaricidal activities were graded from A to E. The range of each grade is shown in the footnote of Table 2.

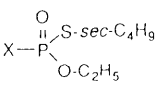
4.2 Aphicidal activities

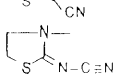
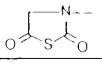
The aphicidal activities were obtained against green peach aphid (*Myzus persicae*). A cabbage leaf was dipped in a test solution, and after drying, 10 larvae were released on it. The treated leaf was maintained in an incubator at 26°C, and dead aphids were counted after 2 days. The aphicidal activities were graded from A to E in the similar way as the acaricidal one.

4.3 Nematicidal activities

The nematicidal activities were obtained against southern root-knot nematode (*Meloidogyne incognita*). Soil (500 ml) contaminated with the nematodes was put in

Table 2 Physical properties and activities of *N*-[ethoxy(*sec*-butylthio)phosphinoyl]-heterocycles.



Compd.	X	Physical property n_D (°C)	Activity		
			Mite[a]	Aphid[a]	Nematode[b]
4		1.5003 (19.6)	A	A	A
5		1.5055 (17.0)	C	C	C
6		1.5210 (28.6)	D	D	C
7		1.5132 (28.6)	D	C	C
8		1.5334 (19.6)	A	A	A
9		1.5050 (18.2)	C	B	A
10		1.5680 (18.9)	B	C	D
11		1.5742 (15.2)	D	C	D
12		1.5616 (16.4)	D	C	C
13		1.5079 (25.8)	A	A	A
14		1.4928 (17.8)	C	C	D
15		1.4932 (25.8)	D	D	D
16		1.5028 (25.8)	D	D	D
17		1.5045 (25.8)	D	D	D

[a] A : over 90% mortality below 50 ppm, B : over 90% mortality at 50–200 ppm, C : over 90% mortality at 200–800 ppm, D : not pesticidal or below 90% mortality at 800 ppm.

[b] A : 0 to 25% of roots galled below 1 kg a.i./ha, B : 0 to 25% of roots galled at 1–4 kg a.i./ha, C : 0 to 25% of roots galled at 4–8 kg a.i./ha, D : not nematicidal or more than 25% of roots galled at 8 kg a.i./ha.

each pot (1/14,000 a, 10 cm in depth). Test solution was poured into the pot, and the treated soil was uniformly mixed. Then, four tomato seedlings were transplanted in the pot. Assessment was made 3 weeks after transplanting. The nematicidal activities were graded from A to E. The range of each grade is shown in the footnote of Table 2.

RESULTS AND DISCUSSION

1. *Structure-activity Relationship*

1.1 *Heterocycles*

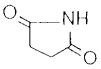
Fixing ethoxy(*sec*-butylthio)phosphinoyl group, the effect of the heterocycle was examined as to the pesticidal activities. These results are summarized in Table 2. A five-membered heterocyclic derivative (**4**) showed a superior activity to the corresponding six-membered derivative (**5**). For five-membered heterocycles, **4**, **8** and **9**, where a carbonyl group is located α to the nitrogen atom, showed higher activities than compounds **6** and **7** which have no carbonyl group. And in compound **10**, a thiocarbonyl group, which is less electron-withdrawing than a carbonyl group, caused a decrease in the activities. Furthermore, electron-withdrawing, but bulky substituents, such as dicyanomethylidene and *N*-cyanoimine are not so effective as a carbonyl group (**11**, **12**). Thus, the presence of a small and strongly electron-withdrawing group, which is located α to the nitrogen atom in the heterocycle, seems indispensable.

However, compounds **14**–**17** showed poor pesticidal activities, although α-carbonyl group is present in all these compounds. This structure-activity relationship suggests that the presence of a carbonyl group at the α-position to the nitrogen atom cannot be a sufficient condition in order to achieve a high potency. At this point, the acidity of the hydrogen (pKa) of the parent heterocycle can be taken into account as an important factor controlling the pesticidal activities. In Table 3, the relationship between the acidity constants (pKa) value of the parent heterocycles and the activities of the corresponding ethoxy(*sec*-butylthio)phosphinoyl derivatives is shown.

When the pKa value becomes higher than twenty, or lower than ten, the activities of the corresponding *N*-phosphinoyl derivatives are decreased. This relationship suggests that the heterocycle must take the appropriate pKa value in order to exhibit high activities.

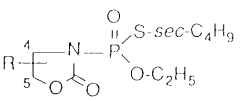
This phenomenon can be explained as follows: as the heterocycle has large pKa value, its electron-withdrawing ability is decreased, and the reactivity of the corresponding *N*-phosphinoyl derivative is simultaneously decreased, thereby lowering the pesticidal activities. As the heterocycle possesses small pKa value, its electron-withdrawing power becomes increased. However, too small pKa value results in the instability of the *N*-phosphinoyl derivative.

Table 3 Relationship between pKa of the perent heterocycles and activities of their *N*-phosphinoyl derivatives.

Heterocycle	pKa[a]	Compd.	Activity		
			Mite	Aphid	Nematode
	25.0	**6**	D	D	C
	11.8	**4**	A	A	A
	11.6	**8**	A	A	A
	10.5	**14**	C	C	D
	9.6	**16**	D	D	D

[a] pKa was experimentally obtained by the titration method.

Table 4 Physical properties and activities of 3-[ethoxy(*sec*-butylthio)phosphinoyl]-1, 3-oxazolidin-2-ones.



Compd.	R	Physical property n_D (°C)	Activity		
			Mite	Aphid	Nematode
4	H	—	A	A	A
18	4-CH_3	1.4942 (16.4)	A	A	A
19	4-C_2H_5	1.4929 (22.4)	A	A	A
20	4-*n*-C_4H_9	1.4862 (21.2)	C	D	B
21	4-OCH_3	1.4955 (14.6)	B	B	A
22	4-CO_2CH_3	1.4950 (16.1)	C	D	D
23	5-CH_3	1.4923 (20.5)	A	A	A
24	5-*tert*C_4H_9	1.4892 (16.8)	B	C	C
25	5-CH_3SO_2	1.4980 (20.2)	C	C	C
26	5-CN	1.4901 (25.4)	C	D	C
27	4, 5-$(CH_3)_2$	1.4902 (16.6)	A	B	A

Factors other than pKa can be operative in controlling the pesticidal activities. For example, poor activities of **17** may be due to an easily-hydrolyzable property of the heterocycle.

In the next step, the effect of the substituent on the heterocycle was examined for the 1, 3-oxazolidin-2-one ring. These data are summarized in Table 4. Compounds with methyl or ethyl group at 4- and/or 5-position exhibited high activities (**18**, **19**, **23**, **27**). However, as shown in the activities of **20** and **24**, substitution of a bulky *n*- or *tert*-butyl group led to inferior activities.

It is also shown that **22** (R=CO_2Me), **25** (R=$MeSO_2$) and **26** (R=CN) gave poor activities. Although a variety of the substituents are insufficient to conclude the substituent effect, the electronic and the steric effect seem to influence the activities.

1.2 *Phosphinoyl moiety*

The effects of the phosphinoyl moiety were also

examined for the 1,3-oxazolidin-2-one derivatives, and the results are summarized in Table 5. These results indicate that the unsymmetrical alkoxy(alkylthio)phosphinoyl group with the proper length of alkyl groups is crucial to high pesticidal activities, while introduction of the other types of groups leads to a dramatic decrease in activities.

As to the alkylthio group, *sec*-butylthio (**4**), *n*-propylthio (**31**) and *iso*-butylthio (**32**) derivatives gave remarkable activities, while *iso*-propylthio (**33**) and methylthio (**34**) derivatives showed poor activities. These results suggest that C_3 chain length is desirable as to the alkylthio group.

Concerning the alkoxy group, ethoxy derivative (**4**) revealed the excellent activities, while other alkoxy or haloalkoxy derivatives **35**–**37** showed inferior activities.

Since the ethoxy(*sec*-butylthio)phosphinothioyl (P=S) derivative **38** showed weaker activities than the corresponding phosphinoyl (P=O) derivative **4**, the oxidative desulfuration of P=S bond does not seem to occur predominantly in the insect bodies.

In consideration of the residual effects in the field application, compound **4** was superior to other phosphinoyl derivatives.

2. *Chiral Isomers of Alkoxy(alkylthio)phosphinoyl Derivatives*

As to compound **8**, we have succeeded in resolving the chiral isomers by using preparative HPLC, where the levorotatory (−) isomer has the shorter retention time.

In ethoxy(*sec*-butylthio)phosphinoyl moiety, there are two kinds of chiral centers : the phosphorus atom and the

Table 5 Physical properties and activities of 3-phosphinoyl-1,3-oxazolidin-2-ones.

Compd.	Y	Physical property n_D (°C) or mp (°C)	Activity		
			Mite	Aphid	Nematode
28		1.4510 (29.0)	D	D	D
29		1.5389 (17.4)	D	D	D
30		97–98	C	C	D
31		1.4964 (24.6)	A	A	B
4		—	A	A	A
32		1.4902 (28.0)	A	A	B
33		1.4948 (24.6)	C	C	C
34		1.5050 (18.2)	C	C	D
35		1.4924 (27.6)	D	C	C
36		1.4860 (20.0)	C	C	C
37		1.4929 (27.4)	C	C	D
38		1.5325 (28.3)	C	C	D

Table 6 Toxicities of the chiral isomers of 3-[ethoxy(*sec*-butylthio)phosphinoyl]-1,3-thiazolidin-2-one (**8**).

	Isomer (+)	Isomer (−)	(+)/(−)
AchE inhibition *in vitro*			
Housefly head[a]	$>10^{-3}$	$>10^{-3}$	
Toxicity to pests			
Housefly adults[b]	1.945	0.108	18.0
Two-spotted spider mite[c]	>800	35.7	>22.4
Green peach aphid[d]	53.7	13.2	4.06
Root-knot nematode[e]	2.339	0.079	29.6

[a] I_{50} (M). [b] μg/adult. [c] LC_{50}, ppm. [d] LC_{90}, ppm. [e] EC_{50}, ppm.

secondary carbon atom of *sec*-butyl group. In order to determine on which atom the resolution was carried out, 3-[ethoxy(*n*-propylthio)phosphinoyl]-1,3-thiazolidin-2-one was analyzed with the same chiral column. Since the ethoxy(*n*-propylthio)phosphinoyl derivative, which has only one chiral center at the phosphorus atom, was similarly resolved, it is suggested that compound **8** is optically resolved as to the chiral phosphorus atom, not as to the chiral secondary carbon atom.

In general, the biological activities of organophosphorus compounds are more seriously influenced by the chirality around the phosphorus atom than the chirality around the alkyl group. For example, the effect of the chirality was investigated as to *O*-*sec*-butyl *S*-2-(ethylthio)ethyl ethylphosphonothioate, which possesses the two asymmetric centers. It was shown that the chirality effect to houseflies is more than 75 at the phosphorus atom, while 1.3 at the *sec*-butyl carbon atom.[5]

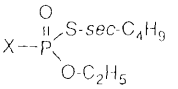
As shown in Table 6, we compared the activities of the chiral pairs. Both isomers are poor inhibitors against housefly head acetylcholinesterase.[6] On the other hand, against various pests, except for green peach aphid, the levorotatory (−) isomer is more active than the dextrotatory (+) isomer, from about twenty-fold to thirty-fold. As to green peach aphid, the activity ratio is about four. In the preliminary examination as to the toxicity to mice, a great difference was not observed between these isomers.

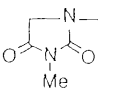
3. *Acute Toxicity to Mammals*

Judging from the data on the pesticidal activities, easiness of the preparation of the heterocycles, and the economic advantage, three compounds in Table 2 seem promising.

However, 1,3-oxazolidin-2-one (**4**) and 3-methylhydantoin (**13**) derivatives possessed high mammalian toxicities (Table 7). Decreased toxicity of the 1,3-thiazolidin-2-one derivative (**8**) may be due to the reactive thioester linkage, since the carbonyl-sulfur bond of the 1,3-thiazolidin-2-one ring may be more easily hydrolyzed in the metabolic system.[7]

Table 7 Acute toxicities of *N*-[ethoxy(*sec*-butylthio)phosphinoyl]heterocycles to mice.



Compd.	X	LD_{50}, mg/kg
4		<30
13		39
8		127

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要　　約

N-ホスフィノイル置換複素環化合物の合成と殺虫活性

小柳　徹，岡田　宏，今井　修
土岐忠昭，芳賀隆弘

複素環内の窒素原子にホスフィノイル基が直結した新しい有機リン化合物を，強塩基（*n*-BuLi, NaH）の存在下，複素環化合物とリン酸塩化物との反応により合成した．殺ダニ，殺アブラムシおよび殺線虫活性に対する構造と活性との相関を検討した．複素環部に関しては，酸性度（p*K*a）が殺虫作用を左右する要因となっていると思われる．また，適当な長さのアルキル基をもったアルコキシ（アルキルチオ）ホスフィノイル構造が強い殺虫活性を発揮するためには必須であることが明らかになった．3-[エトキシ（*sec*-ブチルチオ）ホスフィノイル]-1,3-チアゾリジン-2-オンにおける不斉リン原子の影響を調査した結果，（−）体のほうがより強い殺虫作用を示した．