5-メトキシ-2-ニトロフェニルチオノリン酸アミド類の合成と抗菌活性

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著者	香坂, 秀雄 小栗, 幸男 佐々木, 満
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Original Article

Synthesis and Antifungal Activity of 5-Methoxy-2-nitrophenylphosphoramidothioates

Hideo KOHSAKA, Yukio OGURI, Mitsuru SASAKI and Kunio MUKAI

Pesticides Research Laboratory, Takarazuka Research Center, Sumitomo Chemical Co., Ltd., Takatsukasa, Takarazuka 665, Japan

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Thirty-three 5-methoxy-2-nitrophenylphosphoramidothioates and phosphonamidothioates were synthesized and tested for their antifungal activity against downy mildew on cucumber in greenhouse pot tests. Among the compounds *O*-ethyl *O*-(5-methoxy-2-nitrophenyl)phosphoramidothioates having either an isopropylamino group, a 1-cyano-2-propylamino group, a 1-methoxy-2-butylamino group, or a *s*-butylamino group showed the highest activity. A 1-methoxy-2-propylamino group, a 3-methoxypropylamino group and a 1,1-dioxotetrahydrothiophen-3-ylamino group effectively reduced the phytotoxicity without affecting the antifungal activity. Among *N*-isopropylphosphoramidothioates and phosphonamidothioates, *O*-methyl or *O*-ethyl phosphoramidothioates showed the highest activity. Chloromethylphosphonamidothioate was also effective, but phenylphosphonamidothioate was not effective. *O*-Ethyl *O*-(5-methoxy-2-nitrophenyl) *N*-*s*-butylphosphoramidate was hardly effective.

INTRODUCTION

O-Ethyl *O*-(5-methoxy-2-nitrophenyl) *N*-*s*-butylphosphoramidothioate **8**,[1] a methoxy derivative of a herbicide Butamifos **8'**[2] (Fig. 1) has recently been found in our laboratory to possess potent antifungal activity against *Phycomycetes* pathogen. The finding initiated us into a program of work to develop the lead further by clarifying structure-activity relationships and reducing its phytotoxic activity against crops.

We describe here the synthesis of phosphoramidothioates having 5-methoxy-2-nitrophenyl group and the results of their biological evaluation using *Pseudopernospora cubensis* on cucumbers as a pathogen. In particular the study is conducted on the structural requirements for the *O*-ethyl and *N*-*s*-butyl moieties of **8**.

MATERIALS AND METHODS

Melting points are uncorrected. IR-spectra were measured on a Hitachi 270-30 spectrophotometer. ^{1}H NMR spectra were measured at 60 MH with a Hitachi R24B spectrometer using tetramethylsilane as an internal standard.

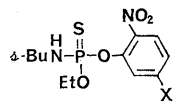
1. *Synthesis of Amines*

1-Methoxy-2-propylamine[3] was synthesized from methoxyacetone by reductive amination with sodium cyanoborohydride.[4] 1-Cyano-2-propylamine was synthesized according to the literature.[5] Other amines were commercially available. 1-Methoxy-2-butylamine[3] was provided by BASF Japan Co., Ltd.

2. *Synthesis of Phosphorus Compounds*

All phosphoramidothioates tested were synthesized either by reacting amines with chloridothioates (Method A), or by reacting 5-methoxy-2-nitrophenol[6,7] with amidochloridates (Method B) as illustrated in the following examples (Fig. 2). The results are summarized in Tables 1 and 2.

O-Ethyl O-(5-methoxy-2-nitrophenyl) N-s-butylphosphoramidate, ***25***



8: X=OMe
8′: X=Me

Fig. 1 Chemical structures of *O*-ethyl *O*-(5-methoxy-2-nitrophenyl) *N*-*s*-butylphosphoramidothioate **8** and Butamifos **8′**.

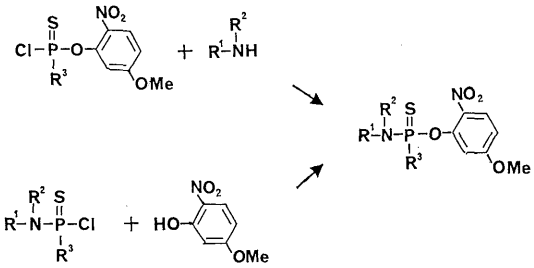


Fig. 2 Synthetic methods of 5-methoxy-2-nitrophenylphosphoramidothioates and related compounds.

To a stirred solution of *O*-ethyl phosphordichloridate (1.79 g) and 5-methoxy-2-nitrophenol (1.69 g) in toluene was added triethylamine (1.2 g) below 5°C in 20 min. Stirring was continued for 3 hr. After completion of the reaction, *s*-butylamine (720 mg) and triethylamine (1.2 g) were added as a mixture under ice-water cooling. Stirring was continued for 1 hr at room temperature. The reaction mixture was washed with water and 5% hydrochloric acid solution, and dried over magnesium sulfate. The filtered solution was evaporated and the residue was purified by silica gel column chromatography to give **25** as an oil (1.9 g, 54%). n_D^{24} 1.5240. Found: C, 46.69; H, 6.32; N, 8.37; P, 9.26, Calcd. for $C_{13}H_{21}N_2PO_6$: C, 46.99; H, 6.37; N, 8.43; P, 9.32%.

O-Ethyl O-(5-methoxy-2-nitrophenyl) N-butylmethylphosphoramidothioate, ***26***

O-Ethyl *O*-(5-methoxy-2-nitrophenyl)phosphorothiochloridate (500 mg) and methylbutylamine (140 mg) were mixed in toluene below 0°C in 30 min. Stirring was continued for further 2 hr at room temperature. Then the solution was washed with water and 5% hydrochloric acid. The dried solution was filtered, and evaporated to give **26** as an oil (375 mg, 65%). n_D^{25} 1.5271. Found: C, 46.24; H, 6.47; N, 7.63; P, 8.34, Calcd. for $C_{14}H_{23}N_2PSO$: C, 46.4; H, 6.40; N, 7.73; P, 8.55%.

O-Ethyl O-(5-methoxy-2-nitrophenyl) N-s-butylphosphoramidothioate, ***8***

O-Ethyl *N*-*s*-butylphosphoramidothiochloridate (2.15 g) was added dropwise to a stirred solution of 5-methoxy-2-nitrophenol (1.69 g) and potassium carbonate (1.50 g) in 100 ml acetonitrile in 30 min at room temperature. Stirring was continued for further 2 hr. The filtered solution was evaporated to give an oil, which was dissolved in toluene. The solution was washed with 5% sodium hydroxide solution and water. The solution was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel column chromatography to give **8** as an oil (1.72 g, 49%). n_D^{26} 1.5353. Found: C, 44.84; H, 6.16; N, 7.99; P, 9.3, Calcd. for $C_{13}H_{21}N_2PSO_5$: C, 44.82; H, 6.08; N, 8.04; P, 8.89%.

3. *Antifungal Activity against Downy Mildew of Cucumber*

Cucumber seeds (species: "Sagamihanjiro") were sowed in soil filled in plastic pots and cultivated in a greenhouse for 14 days to obtain seedlings having cotyledons. A spore suspension of *Pseudopernospora cubensis* was sprayed onto the seedlings, which were placed at 20°C under humid condition for 1 day. An aqueous dilution of the compound in the form of emulsifiable concentrate was applied onto the seedlings by foliar treatment. After the plants had been grown at 20°C under irradiation of a fluorescent lamp for 4 days, their antifungal activity was observed and their protective value was determined by the following equation.

$$\text{Protective value } (\%) = (1-(A/B)) \times 100$$

where A represents the percentage of desease on the treated plants and B represents that on untreated plants.

4. *Phytotoxicity Test against the Cucumber*

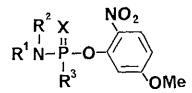
Phytotoxicity, which means growth retardant activity, was observed together with protective activity. The degree of phytotoxicity was expressed by ## (severe phytotoxicity), + (slight phytotoxicity) or — (no phytotoxicity) at 500 ppm in Table 2.

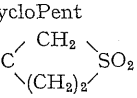
RESULTS AND DISCUSSION

Physical properties and antifungal activity of the test compounds are listed in Tables 1 and 2. The antifungal activity is based on the protective activity against downy mildew of cucumber infected by *P. cubensis*.

As shown in Table 1, a structural similarity was observed in the type of amino groups at R^1 that provided highly effective compounds. With an ethoxy group and a 5-methoxy-2-nitrophenyl group remaining constant, the

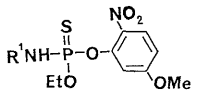
Table 1 Antifungal activity and physical properties of 5-methoxy-2-nitrophenylphosphoramidothioates and phosphonamidothioates.

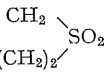


Compound					Method	Yield (%)	*n*D (°C)	Protective value (%)			
No.	R^1	R^2	R^3	X				500 ppm	200 ppm	50 ppm	12.5 ppm
1	H	H	EtO	S	A	97	1.5765 (24)	50	b)	b)	b)
2	Me	H	EtO	S	A	80	1.5675 (23.5)	100	100	81	0
3	Et	H	EtO	S	A	77	1.5539 (24.5)	100	b)	b)	b)
4	*n*-Pr	H	EtO	S	A	94	1.5429 (24)	100	100	100	50
5	*i*-Pr	H	EtO	S	B	57	1.5380 (23)	100	100	100	100
6	*n*-Bu	H	EtO	S	A	36	1.5354 (22)	100	94	0	0
7	*t*-Bu	H	EtO	S	A	34	1.5538 (23)	0			
8	*s*-Bu	H	EtO	S	B	49	1.5353 (26)	100	100	100	100
9	CH(Me)-*n*-Pr	H	EtO	S	A	12	1.5430 (26.5)	100	94	25	0
10	CH(Me)-*i*-Pr	H	EtO	S	A	14	1.5279 (22.5)	100	88	25	0
11	$CH(Et)_2$	H	EtO	S	A	15	1.5449 (22.5)	100	100	100	88
12	$(CH_2)_2OMe$	H	EtO	S	A	28	1.5570 (22)	100	100	69	38
13	$(CH_2)_3OMe$	H	EtO	S	A	28	1.5528 (22)	100	100	97	31
14	$CH(Me)CH_2OMe$	H	EtO	S	A	13	1.5445 (27.5)	100	100	97	62
15	$CH(Et)CH_2OMe$	H	EtO	S	A	37	1.5289 (20)	100	100	100	100
16	$(CH_2)_2CN$	H	EtO	S	A	72	1.5510 (24.5)	100	100	57	14
17	$CH(Me)CH_2CN$	H	EtO	S	A	15	1.5560 (24.5)	100	100	100	100
18	$(CH_2)_2Cl$	H	EtO	S	A	13	1.5670 (22.5)	100	100	100	81
19	$CH_2CH(OMe)_2$	H	EtO	S	A	35	1.5409 (21.5)	97	0	0	0
20	$CH_2C{\equiv}CH$	H	EtO	S	A	52	1.5733 (20)	100	b)	b)	b)
21	$CH_2CH{=}CH_2$	H	EtO	S	A	27	1.5530 (22.5)	100	b)	b)	b)
22	CycloPr	H	EtO	S	A	12	1.5625 (22.5)	0			
23	CycloPent	H	EtO	S	A	46	1.5600 (23)	0			
24		H	EtO	S	A	27	mp 97–98[a)]	100	97	62	31
25	*s*-Bu	H	EtO	O	A	54	1.5240 (24)	0			
26	*n*-Bu	Me	EtO	S	A	32	1.5271 (25)	0			
27	Me	Me	EtO	S	A	22	1.5512 (22.5)	0			
28	*i*-Pr	H	MeO	S	B	33	mp 60–62	100	100	100	100
29	*i*-Pr	H	*n*-PrO	S	A	17	1.5458 (23)	100	b)	b)	b)
30	*i*-Pr	H	*i*-PrO	S	B	10	1.5650 (20)	100	b)	b)	b)
31	*i*-Pr	H	*n*-BuO	S	A	9	1.5449 (23)	0			
32	*i*-Pr	H	$ClCH_2$	S	A	21	1.5820 (20)	100	b)	b)	
33	*i*-Pr	H	C_6H_5	S	A	84	mp 88–90	0			

a) Resinous material crystalized on standing.
b) Not determined.

Table 2 Phytotoxicity of selected compounds and their antifungal activity.



Compound No.	R^1	Phytotoxicity	Protective value (%) 500 ppm	200 ppm	50 ppm	12.5 ppm
13	$(CH_2)_3OMe$	−	100	100	97	31
14	$CH(Me)CH_2OMe$	+	100	100	97	62
24		+	100	97	62	31
4	*n*-Pr	##	100	100	100	50
5	*i*-Pr	##	100	100	100	100
8	*s*-Bu	##	100	100	100	100

highest activity, that is, the activity to protect completely at 12.5 ppm, was exhibited with compounds having an isopropylamino group (**5**), a *s*-butylamino group (**8**), a 1-methoxy-2-butylamino group (**15**) or a 1-cyano-2-propylamino group (**17**). These groups can be regarded as isopropyl analogs. The hydrophilic substituent such as a methoxy or a cyano group attached to an isopropyl moiety did not alter the antifungal activity against the pathogen.

The introduction of a 2-pentylamino group or a 3-methyl-2-butylamino group in place of a *s*-butylamino group decreased the activity (compounds **9** and **10**), and a *t*-butylamino group gave an ineffective compound (**7**). Cycloalkylamino compounds (**22** and **23**) showed no activity, while a compound (**24**) having a heterocyclic 1, 1-dioxotetrahydrothiophen-3-ylamino group showed high protective activity at 200 ppm. The presence of a methyl or an ethyl branch on the alkyl carbon atom adjacent to the nitrogen atom is one important molecular requirement for this series of compounds.

Among a further range of amino groups, a 2-chloroethylamino group (compound **18**), a 2, 2-dimethoxyethylamino group (compound **19**) and unsaturated alkylamino groups (compounds **20** and **21**) were also effective.

Methylation of amide nitrogen (compounds **26** and **27**) drastically decreased the activity of the parent compounds (**6** and **2**).

O-(5-Methoxy-2-nitrophenyl) *N*-isopropylphosphoramidothioates and phosphonamidothioates having a *n*-butoxy group or a phenyl group at R^3 provided no activity (compounds **31** and **33**), whereas those having a methoxy group, an ethoxy group, a *n*-propoxy group or an isopropoxy group provided complete protective activity at 500 ppm (compounds **28**, **5**, **29** and **30**).

The P=S compound (**8**) that exhibited complete protective activity at 12.5 ppm stood in sharp contrast to the corresponding P=O compound (**25**) that showed little protective activity even at 500 ppm. Such a finding is well consistent with findings on tolchlofos-methyl[8] or detalimfos.[2]

Table 2 summarizes the phytotoxicity test results of selected compounds at 500 ppm. Severe phytotoxicity of compounds **4** and **5** was significantly reduced by substitution of a methoxy group for a hydrogen atom on the methyl group of the *n*-propylamino group (compound **13**) or the isopropylamino group (compound **14**), while the antifungal activity against *P. cubensis* was not affected. The 1, 1-dioxotetrahydrothiophen-3-ylamino group also provided compound **24** with desirable properties, *i.e.*, extremely low phytotoxicity and high antifungal activity at 200 ppm.

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要　　約

5-メトキシ-2-ニトロフェニルチオノリン酸アミド類の合成と抗菌活性

香坂秀雄，小栗幸男，佐々木満，向井邦男

O-Ethyl *O*-(5-methoxy-2-nitrophenyl) *N*-*s*-butylphosphoramidothioate のキュウリベと病に対する抗菌活性を見いだし，その活性と構造との関連を各種誘導体を合成して検討した．アミノ基部分の変換から，*s*-ブチル基または *i*-プロピル基を有する化合物が供試化合物中最高の活性を示すことがわかった．さらに，1-メトキシ-2-プロピル基，あるいは 3-メトキシプロピル基，1,1-ジオキソテトラヒドロチオフェン-3-イル基を有する化合物は高い抗菌活性を示すと同時に，キュウリに対する薬害が著しく軽微なものになった．標題化合物をオキソン体へ変換することにより活性はまったく失われた．*O*-エチル基部分はメチル基，あるいは *n*-プロピル基，*i*-プロピル基を導入しても活性を維持し，さらにはクロロメチルホスホンアミドへ変換しても抗菌活性は失われなかった．