有機ケイ素ピレスロイドの合成と殺虫活性

誌名	日本農薬学会誌
ISSN	03851559
著者	山田, 好美 矢野, 俊彦 板谷, 信重
巻/号	12巻4号
掲載ページ	p. 683-688
発行年月	1987年11月

J. Pesticide Sci. **12**, 683–688 (1987)

Original Article

Syntheses and Insecticidal Activity of Organosila-Pyrethroids

Yoshimi YAMADA, Toshihiko YANO and Nobushige ITAYA

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

(Received March 31, 1987)

A new class of organosila-pyrethroids were synthesized and their insecticidal activity was examined against the tobacco cutworm (*Spodoptera litura*). Among them, 4-ethoxyphenylsilane derivatives, *e.g.* 4-ethoxyphenyl(3-phenoxy-4-fluorobenzyloxymethyl)dimethylsilane, were the most active.

INTRODUCTION

There are many reports on the pharmaceutical activities of sila-substitutes (sila-drugs),[1,2] but very little is known about the sila-substituted agrochemicals.[2] Synthetic pyrethroids are a group of insecticides which originate from natural pyrethrins. Their insecticidal activity has been best in relation to their ability to adopt a conformation: in the conformation, all the structural features essential for the potency are appropriately oriented with respect to each other and to a complementary receptor.[3-6] Ethofenprox and a series of its analogs (**1a** and **1b**) are a new class of pyrethroids recently reported.[7] The structural characteristics of **1a** and **1b** are, (a) they have a quarternary carbon atom which bears a gem-dimethyl group, and (b) their 2-methyl-2-(4-ethoxyphenyl)propyl group is linked *via* an oxygen (**1a**, Y=O) or methylene (**1b**, Y=CH_2) bridge to a 3-phenoxybenzyl group.

Thus the quarternary center seems to play an important role in determining the biologically active conformation of the molecules. Our interest lies in the sila-substitution effects on their insecticidal activities, since a silicon atom has a larger van der Waals radius and lower electronegativity than a carbon atom.

Herein we report on the syntheses and insecticidal activity of the sila-analogs of the new pyrethroids.

MATERIALS AND METHODS

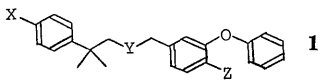
1. Synthesis

All boiling points were uncorrected. Yields were not optimized.

*1.1 Syntheses of compounds **2a–g** (Fig. 2)*

The following procedure for the synthesis of **2b** represents a typical example. The other compounds (**2a**, **c–g**) were prepared in a similar manner. The synthetic pathways and the results were summarized in Scheme 1 and Table 1, respectively.

A solution of chloro(chloromethyl)dimethylsilane (4.29 g, 30.0 mmol) in 5 ml of ether was added dropwise into an ice-cooled THF solution of 4-fluorophenylmagnesium bromide which had been prepared from 4-fluorobromobenzene (5.51 g, 31.5 mmol), magnesium (turnings, 0.802 g, 33.0 mmol) and 20 ml of THF. After stirring at room temperature for 12 hr, the mixture was poured into ice water, extracted with ether (50 ml), and the ether layer was washed successively with 0.5 N HCl aq. (20 ml), sat. $NaHCO_3$ aq. (20 ml) and water (20 ml). The ethereal solution was dried over $MgSO_4$, evaporated, and the residue was subjected to distillation (Kugelrohr, bp 129–131°C at 38 mmHg) to give 4-fluorophenyl(chloromethyl)dimethylsilane (**3b**, X=F, 4.55 g, 74.9%) as an oil.



	X	Y	Z	
1a	EtO	O	H	Ethofenprox (MTI-500)
1b	EtO	CH_2	F	MTI-800

Fig. 1 Ethofenprox and its alkane-type analog.

Then **3b** (4.55 g, 22.5 mmol), potassium acetate (2.65 g, 27.0 mmol) and *N*,*N*-dimethylformamide (14 ml) were heated under nitrogen at 70°C for 3 hr. The mixture was poured into ice water, extracted with ether (40 ml), and the ether solution was washed twice with sat. $NaHCO_3$ aq. (30 ml). Column chromatography (silica gel, hexane-EtOAc gradient) of the evaporated residue gave an oily product, 4-fluorophenyl(acetoxymethyl)dimethylsilane **4b** (4.29 g, 84.3%). Conventional hydrolysis of acetate (4.29 g, 19.0 mmol) in methanolic KOH (85% KOH 1.25 g, 19.0 mmol and MeOH 20 ml) gave 4-fluorophenyl(hydroxymethyl)dimethylsilane **5b** (3.04 g, 87.0%) after usual work-up and column chromatography (silica gel, hexane-EtOAc gradient).

Finally, NaH (60% dispersion in mineral oil, 0.727 g, 18.2 mmol) was added dropwise into an ice-cooled mixture of **5b** (3.04 g, 16.5 mmol), 3-phenoxybenzyl bromide (4.34 g, 16.5 mmol) and *N*,*N*-dimethylformamide (17 ml). After stirring at room temperature for 12 hr, the mixture was poured into water and extracted with ether (40 ml). The ethereal solution was washed twice with water (30 ml), dried over $MgSO_4$ and evaporated to dryness. The residue was subjected to column chromatography (silica gel, hexane-EtOAc gradient) to give 4-fluorophenyl(3-phenoxybenzyloxymethyl)dimethylsilane **2b** (4.59 g, 76.0%) as an oil.

*1.2 Synthesis of compound **2h***

Synthetic pathways are given in Scheme 2.

A solution of ethylene oxide (2.47 ml, 50.0 mmol) in 6 ml of ether was added dropwise into an ice-cooled solution of (4-ethoxyphenyldimethylsilyl)methylmagnesium chloride which had been prepared from **3e** (5.71 g, 25.0 mmol), magnesium (turnings, 0.608 g, 25.0 mmol) and 24 ml of ether. After stirring at room temperature for 3 days, the mixture was poured into ice water, extracted with ether (50 ml), and the ether solution was successively washed with 0.5 N HCl aq. (20 ml), sat. $NaHCO_3$ aq. (20 ml) and water (20 ml). The ethereal extract was dried over $MgSO_4$, evaporated, and the residue was subjected to column chromatography on silica gel (hexane-EtOAc gradient) to give 3-(4-ethoxyphenyldimethylsilyl)propan-1-ol **6** (2.83 g, 47.6%) as an oil.

Then silylpropyl alcohol **6** (726 mg, 3.05 mmol) was treated with *p*-toluenesulfonyl chloride (641 mg, 3.36 mmol) and pyridine (965 mg, 12.2 mmol). After standing at room temperature for 12 hr, the mixture was poured into ice-colled 0.5 N HCl aq. (10 ml) and extracted with ether (20 ml). The ethereal extract was washed with sat. $NaHCO_3$ aq. (10 ml), dried over $MgSO_4$ and evaporated. The residue was dried *in vacuo* to give tosylate **7** (1.03 g, 86.3%). This tosylate **7** (1.03 g, 2.63 mmol) was diluted with 4 ml of THF and the solution was added dropwise into a cooled ethereal solution (dry ice acetone, −78°C) of 3-phenoxyphenylmagnesium bromide which had been prepared from 3-phenoxyphenyl bromide (912 mg, 3.66 mmol), magnesium (turnings, 93.4 mg, 3.84 mmol) and 4 ml of ether. At the same temperature 0.36 ml of Li_2CuCl_4 solution (0.1 M in THF) was added and the mixture was gradually warmed to room temperature. After stirring at room temperature for 12 hr, the mixture was diluted with ether (20 ml) and successively washed with 0.5 N HCl aq. (10 ml), sat. $NaHCO_3$ aq. (10 ml) and water (10 ml). The ethereal extract was dried over $MgSO_4$, evaporated, and the residue was subjected to column chromatography (silica gel, hexane-EtOAc gradient) to give 4-ethoxyphenyl(dimethyl)[3-(3-phenoxyphenyl)propyl]silane **2h** (440 mg, 42.9%) as an oil.

*1.3 Synthesis of compound **2i***

Scheme 3 shows the synthetic route of compound **2i**.

First, 3-(3-phenoxy-4-fluorophenyl)propan-1-ol **8** (2.33 g, 42.1%) was prepared from 3-phenoxy-4-fluorobenzyl bromide (6.33 g, 22.5 mmol), magnesium (turnings, 0.547 g, 22.5 mmol) and ethylene oxide (1.67 ml, 34.0 mmol)

according to the same procedure as described in the synthesis of **6** from **3e** (previous section, 1.2). Then, **8** (2.33 g, 9.47 mmol) was dissolved in 14 ml of CH_2Cl_2 together with tetrabromomethane (4.08 g, 12.3 mmol), and the ice-cooled mixture was treated with triphenylphosphine (2.86 g, 10.9 mmol). After stirring at room temperature for 12 hr, the mixture was subjected to column chromatography on silica gel (hexane-EtOAc gradient) to give 3-(3-phenoxy-4-fluorophenyl)propyl bromide **9** (2.15 g, 73.3%) as an oil. Bp 185°C at 3 mmHg (Kugelrohr distillation).

Into an ethereal Grignard solution from **9** (927 mg, 3.00 mmol), magnesium (turnings, 73.0 mg, 3.00 mmol) and ether (3 ml) was added a solution of chlorodimethylsilane (284 mg, 3.00 mmol) and THF (1 ml) at 0°C. After stirring at room temperature for 12 hr, the mixture was heated at reflux for 30 min, diluted with ether (20 ml) and successively washed with 0.5 N HCl aq. (10 ml), sat. $NaHCO_3$ aq. (10 ml) and water (10 ml). The ethereal extract was dried over $MgSO_4$, evaporated, and the residue was subjected to distillation (bp 150°C at 3 mmHg, Kugelrohr) to give 3-(3-phenoxy-4-fluorophenyl)propyl(dimethyl)silane **10** (546 mg, 63.2%) as an oil.

Finally, a solution of hydrosilane **10** (259 mg, 0.899 mmol) in 2 ml of ether was added dropwise at −78°C into a THF solution of 4-ethoxyphenyllithium that had been prepared at −78°C from 4-ethoxybromobenzene (235 mg, 1.17 mmol), 2 ml of THF and 0.690 ml of *n*-BuLi (1.56 M in *n*-hexane, 1.08 mmol). The mixture was gradually warmed to room temperature, refluxed for 2 hr, diluted with ether (20 ml) and successively washed with 0.5 N HCl aq. (10 ml), sat. $NaHCO_3$ aq. (10 ml) and water (10 ml). After dried over $MgSO_4$, the extract was evaporated and subjected to distillation (110°C at 0.1 mmHg for 1 hr, Kugelrohr) in order to eliminate low-boiling substances. The residue was chromatographed on silica gel (hexane-EtOAc gradient) to give 4-ethoxyphenyl(dimethyl)[3-(3-phenoxy-4-fluorophenyl)propyl]silane **2i** (298 mg, 68.0%) as an oil.

2. Insecticidal Activity against the Tobacco Cutworm (Spodoptera litura)

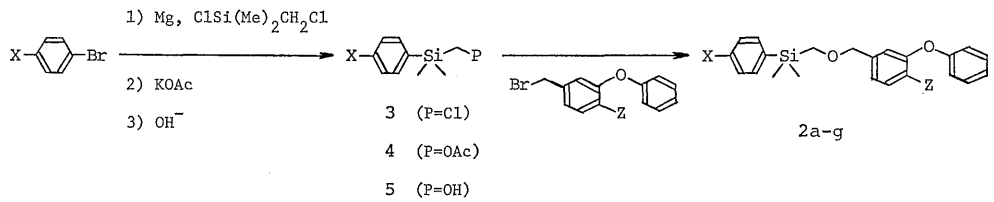
Artificial diet method: Two ml of an aqueous dilute solution of the predetermined concentrations prepared from the emulsifiable concentrates of test chemicals, were dropped on an artificial diet (13 g) for tobacco cutworms in a polyethylene cup, and 10 fourth-instar larvae were released on the diet. The mortality was observed 6 days after application.

The LC_{50} values were obtained by using the probit method.

RESULTS AND DISCUSSION

The quarternary center of compounds **2a–h** was conveniently constructed by the reaction of arylmagnesium halides with chloro(chloromethyl)dimethylsilane which is commercially available. As the chlorine atom of **3** was hardly substituted by sodium 3-phenoxybenzylalkoxide, it was converted to a hydroxy group *via* acetate **4** (Scheme 1). Then silylmethanol **5** was reacted with 3-phenoxybenzyl bromides to give desired ether **2**. All of ether-type compounds **2a–g** were prepared using this scheme in fairly good yields. The results are summarized in Table 1.

Alkane-type compound **2h** was synthesized by successively elongating the carbon skeleton originated from chloromethylsilane **3e**, as shown in Scheme 2. The Grignard reagent from **3e** was allowed to react with ethylene oxide to give silylpropan-1-ol **6**, and then converted to

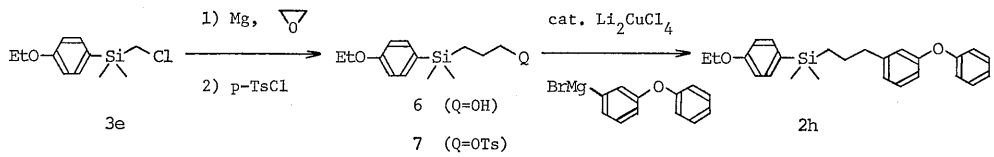


Scheme 1 Syntheses of sila-pyrethroids (**2a–g**).

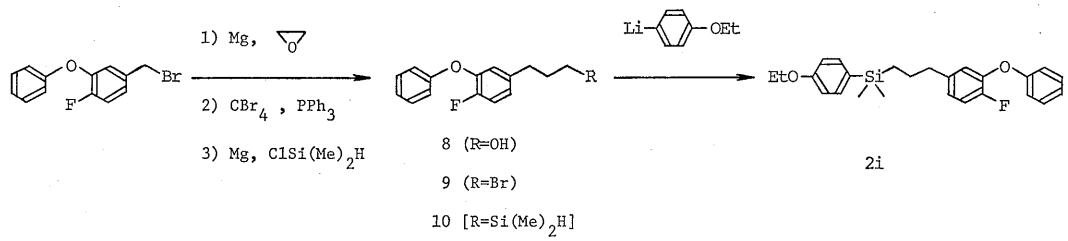
Table 1 Syntheses of sila-pyrethroids **2a–g**.[a)]

Compounds	Substituent		Yield of **3** (%)	Yield of **4** (%)	Yield of **2** (%)
	X	Z			
a	Cl	H	56.8	87.7	41.4
b	F	H	74.9	73.3	76.0
c	Et	H	88.1	84.2	39.7
d	MeO	H	69.7	56.3	95.0
e	EtO	H	91.3	81.6	71.0
f	EtO	F	91.3	81.6	39.5
g	*i*-PrO	H	88.0	65.2	60.0

a) Refer to Scheme 1 and Fig. 2.



Scheme 2 Synthesis of sila-pyrethroid (**2h**).



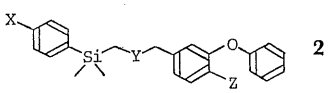
Scheme 3 Synthesis of sila-pyrethroid (**2i**).

tosylate **7**. In a final step, a copper-catalyzed coupling reaction of Grignard reagent with alkyl tosylate was exploited.[8,9)]

In the synthesis of another alkane-type compound **2i**, the hydride-substitution reaction of trialkylhydrosilane **10** with 4-ethoxyphenyllithium[10)] was utilized, as shown in Scheme 3.

Table 2 summarizes the physical properties of all compounds (**2a–i**) prepared.

All of sila-pyrethroids (**2a–i**) exhibited high insecticidal activity against tobacco cutworms (*Spodoptera litura*). Table 3 summarizes the LC_{50} values of compounds **2a–i** and carbon compounds **1a** and **1b**. Table 3 reveals the following structure-activity relationships: (a) the ethoxy group was the most efficient substituent on phenylsilyl group (**2**, X=EtO) and the insecticidal activity decreased in the



2

	X	Y	Z
2a	Cl	O	H
2b	F	O	H
2c	Et	O	H
2d	MeO	O	H
2e	EtO	O	H
2f	EtO	O	F
2g	*i*-PrO	O	H
2h	EtO	CH_2	H
2i	EtO	CH_2	F

Fig. 2 Organosila-pyrethroids.

Table 2 Physical properties of sila-pyrethroids **2a–i**.[a)]

Compd. No.	Refractive index	Formula	C (%)		H (%)	
			Calcd.	Found	Calcd.	Found
2a	$n_D^{27.0}$1.5651	$C_{22}H_{23}ClO_2Si$	69.00	69.21	6.05	6.09
2b	$n_D^{22.0}$1.5502	$C_{22}H_{23}FO_2Si$	72.10	72.25	6.33	6.41
2c	$n_D^{23.0}$1.5604	$C_{24}H_{28}O_2Si$	76.55	76.58	7.49	7.32
2d	$n_D^{25.5}$1.5738	$C_{23}H_{26}O_3Si$	72.98	73.04	6.92	6.80
2e	$n_D^{24.5}$1.5668	$C_{24}H_{28}O_3Si$	73.62	73.87	7.21	7.05
2f	$n_D^{22.0}$1.5685	$C_{24}H_{27}FO_3Si$	70.39	70.53	6.65	6.78
2g	$n_D^{22.0}$1.5567	$C_{25}H_{30}O_3Si$	76.87	76.95	7.74	7.54
2h	$n_D^{20.5}$1.5598	$C_{25}H_{30}O_2Si$	76.87	77.05	7.74	7.48
2i	$n_D^{21.5}$1.5615	$C_{25}H_{29}FO_2Si$	73.49	73.72	7.15	7.18

a) Refer to Scheme 1–3 and Fig. 2.

Table 3 Insecticidal activity of sila-pyrethroids against the tobacco cutworm (*Spodoptera litura*).

Compd. No.	X	Y	Z	LC_{50} (ppm)
2a	Cl	O	H	37
2b	F	O	H	32
2c	Et	O	H	27
2d	MeO	O	H	21
2e	EtO	O	H	18
2f	EtO	O	F	8.6
2g	*i*-PrO	O	H	39
2h	EtO	CH_2	H	8.6
2i	EtO	CH_2	F	8.6
1a	EtO	O	H	5.0
1b	EtO	CH_2	F	2.7

following order X: EtO>MeO>Et>F>Cl, *i*-PrO [for **2** (Y=O, Z=H)], (b) the 4-fluoro substitution on 3-phenoxybenzyl group (**2**, Z=F) enhanced the activity of ether-type compounds (**2**, Y=O), but not of alkane-type compounds (**2**, Y=CH_2), (c) the insecticidal potency was slightly improved by the skeletal conversion of an ether-type (**2**, Y=O) compound to an alkane-type one (**2**, Y=CH_2), and (d) the insecticidal activity was depressed by the sila-substitution of a quarternary carbon atom in **1**. The potency fell to about one-third compared with the corresponding carbon compounds (**2e** *vs.* **1a** and **2i** *vs.* **1b**, respectively).

Thus the overall features of our sila-pyrethroids seem to resemble those of carbon compounds,[4)] but **2e** and **2i** did not exceed **1a** and **1b** in insecticidal potency, respectively.[7)] It may be due to their slightly inadequate fitting to receptor sites compared with the corresponding carbon compounds.

The present study provides evidence that a silicon atom works well as a unique isoster of a quarternary carbon atom. It may be possible to enhance biological activity through "proper" sila-substitution of certain carbon compounds. We are now engaged in active exploration along this course.

REFERENCES

1) R. Tacke: "Organosilicon and Bioorganosilicon Chemistry," ed. by H. Sakurai, John Wiley & Sons, New York, p. 251, 1985
2) R. Tacke & U. Wannagat: "Topics in Current Chemistry," ed. by F. L. Boschke, No. 84, Springer Verlag, Berlin, Heidelberg and New York, p. 1, 1979
3) M. Elliot: "Synthetic Pyrethroids," ACS Symposium Series 42, American Chemical Society, Washington D. C., p. 1, 1977
4) H. Yoshioka: *Rev. Plant Prot. Res.* **11**, 39 (1978)
5) M. Miyakado, N. Ohno, Y. Okuno, M. Hirano, K. Fujimoto & H. Yoshioka: *Agric. Biol. Chem.* **39**, 267 (1975)
6) T. Matsuo, T. Nishioka, M. Hirano, Y. Suzuki, K. Tsushima, N. Itaya & H. Yoshioka: *Pestic. Sci.* **11**, 202 (1980)
7) T. Udagawa: Abstr. Symp. Dev. Biol. Act. Compd. Jpn. Manage. Assoc., Tokyo, p. 3-4-1, 1986

8) G. Fouquet & M. Schlosser: *Angew. Chem. Int. Ed.* **13**, 82 (1974)
9) K. Mori, T. Suguro & M. Uchida: *Tetrahedron* **34**, 3119 (1978)
10) R. N. Meals: *J. Am. Chem. Soc.* **68**, 1880 (1946)

要　　約

有機ケイ素ピレスロイドの合成と殺虫活性

山田好美，矢野俊彦，板谷信重

非エステル型の新規ピレスロイド (*e.g.* ethofenprox) について，その4級炭素をケイ素に変換した化合物の合成を行ない，ケイ素置換が殺虫活性に及ぼす影響を検討した．合成した9点の化合物はいずれも，ハスモンヨトウ (*Spodoptera litura*) に対して LC_{50}(ppm) 8.6～39 と高い活性を示した．とくに 4-ethoxyphenyl(3-phenoxy-4-fluorobenzyloxymethyl)dimethylsilane 等，4位にエトキシ基を有する化合物に高活性が見いだされた．これらの結果，ケイ素原子が4級炭素原子の等価体 (isoster) として有用であることが明らかとなった．