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Synthesis and Insecticidal Activity of Novel Dihydropyrrole Derivatives with *N*-Sulfanyl, Sulfinyl, and Sulfonyl Moieties

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Abstract—This paper reports the synthesis and insecticidal activity of a new type of dihydropyrrole derivatives with sulfur moieties such as sulfanyl, sulfinyl, and sulfonyl groups at the 1-position. These derivatives exhibited high insecticidal potency against *Nilaparvata lugens* and *Nephotettix cincticeps*. Investigation of the structure–activity relationships revealed that the alkoxycarbonyloxy groups at the 4-position tended to increase the systemic insecticidal activity.

Introduction

Hemiptera insects such as the brown rice planthopper (*Nilaparvata lugens*) and green rice leafhopper (*Nephotettix cincticeps*) are the sucking pests that cause serious damage to rice plant in a paddy field.[1,2] Once they pierce a plant and suck its sap, often the plant is blighted, or at the very least its market value is reduced. Although several effective insecticides have been used to control them,[3,4] a new compound with a novel mode of action is always hankered because those pests multiple so rapidly that the chemical-resistant strains frequently emerge.[5,6]

In our previous study, we reported the synthesis and insecticidal activity of a new series of *N*-oxydihydropyrrole derivatives (**1**)[7,8] that were designed based on the insecticidal and acaricidal agents reported by Bayer's groups (Fig. 1).[9–12] Our interest focused on how the modification of the 1-position (–OR group in structure **1**) would influence the insecticidal activity. The derived compounds demonstrated significantly high insecticidal activity against the sucking pests such as the brown planthopper and green peach aphid (*Myzus persicae*). In an investigation of the early structure–activity study, it was revealed that small alkoxy and alkoxyalkoxyl groups are more favorable than others. The affected insects died before or during ecdysis without completing molting. This symptom is unique for hemiptera pests, and the mode of action appears to be entirely new. In addition, the compounds had systemic property, being absorbed from a plant's roots and effectively transferred to other parts of the plant such as young leaves. This property is especially advantageous when combating the above sucking pests, for a systemic insecticide can spread all through a plant and kill any targeted insects that feed on it.[6]

The above results prompted further exploration of the related structures. It has often been observed that the introduction of a sulfur atom to a biologically active agent leads to interesting biological as well as physicochemical features.[13] Thus, we decided to replace the oxygen atom

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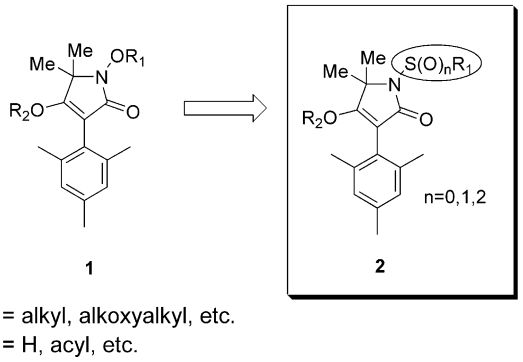


Figure 1. Structures of the lead compound (**1**) and derivatives studied in the present work (**2**).

in the structure (**1**) with a sulfur atom and designed a structure (**2**). This dihydropyrrole skeleton (**2**) bearing both a sulfur moiety and an enolated 1,3-dione system is unique to our knowledge and has the potential to provide a novel mode of action as an insecticide.

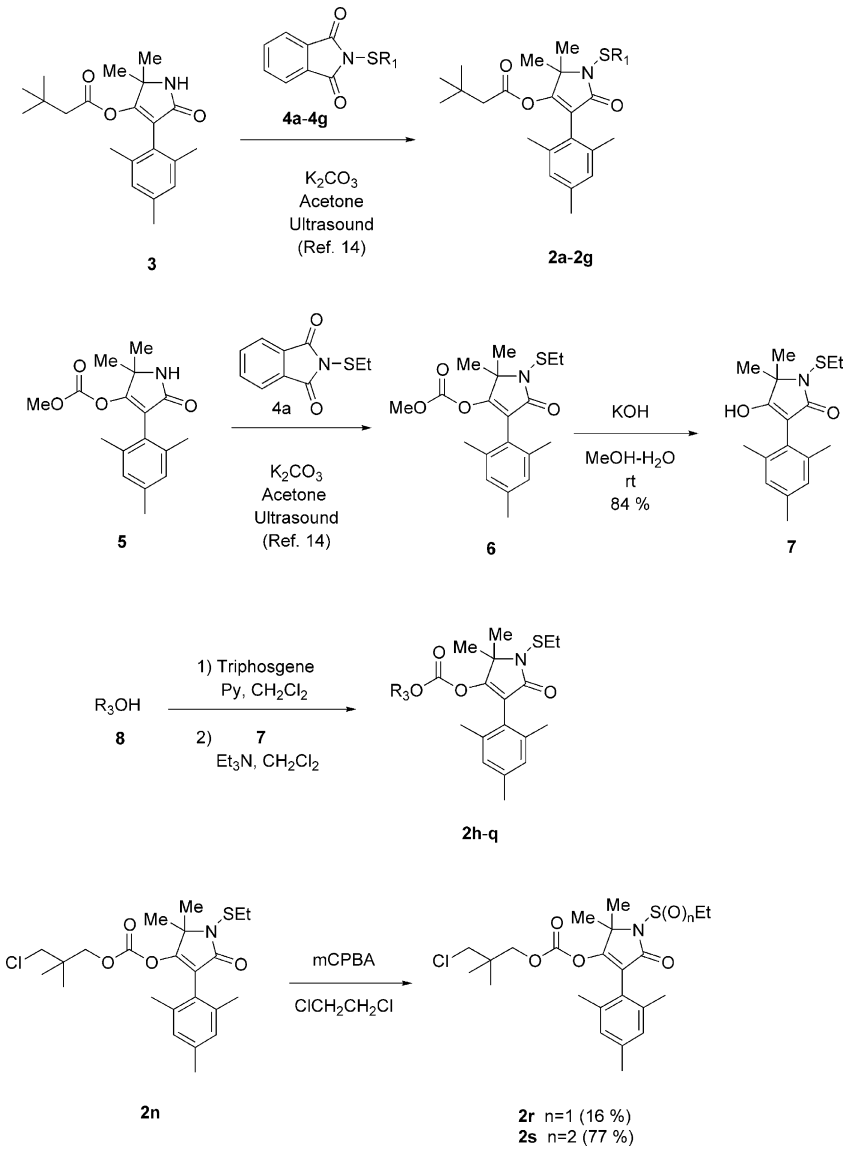
On the other hand, the lead compounds (**1**) showed some phytotoxicity against crops such as rice and cucumber. Although the modification of the 1-position could somewhat alleviate this damage as demonstrated in the previous work,[7] sufficient crop safety was still not obtained. Therefore, it is another important objective to seek the possibility of alleviating the phytotoxicity by the modifications in the present work.

In this article we report the preparation of a new series of dihydropyrrole derivatives (**2**) and their insecticidal activity against *N. lugens* and *N. cincticeps*. We also make a few brief remarks on their phytotoxicity against rice plant.

Results and Discussion

Chemistry

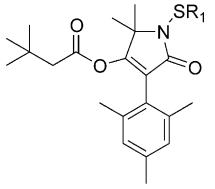
Scheme 1 illustrates the synthetic routes used to prepare the derivatives.



Scheme 1. Synthetic routes to novel dihydropyrrole derivatives with *N*-sulfanyl, sulfinyl, and sulfonyl moieties.

We developed a new facile method for the introduction of sulfur moiety to the 1-position of the dihydropyrrole ring.[14] Ultrasound treatment of dihydropyrrole derivative and *N*-sulfanyl phthalimides in the presence of base successfully provided the desired *N*-sulfanylated products.

Table 1. Insecticidal activity and phytotoxicity of the *N*-sulfanyldihydropyrrole derivatives[a]—effects of the 1-position



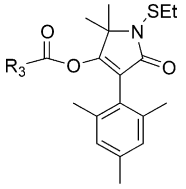
Compd	R_1	*N. lugens*		*N. cincticeps*		*OS*[b]
		Systemic test 1 ppm	Contact test 1 ppm	Systemic test 1 ppm	Contact test 1 ppm	Spray test 100 ppm
2a	Et	2	4	1	1	2
2b	Pr	2	2	4	4	2
2c	*i*-Pr	0	4	2	4	1
2d	Bu	0	4	0	3	0
2e	*i*-Bu	0	4	0	4	0
2f	Ph	0	3	0	4	0
2g	Bn	2	3	3	4	0

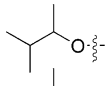
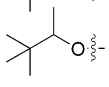
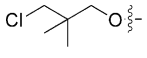
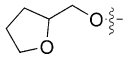
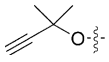
[a]Insecticidal activity and phytotoxicity were each graded into 5 classes from 0 to 4. See text.
[b]*OS*, *Oryza sativa* (rice).

Alkylsulfanyl and phenylsulfnanyl moieties were readily introduced to the 1-position, yielding corresponding *N*-sulfanylated dihydropyrrole derivatives (**2a**–**2g**).

In order to modify the 4-position of the dihydropyrrole ring, we initially tried to remove the 3,3-dimethylbutyroyl group of **2a** by treating the compound with several bases or acids. This approach proved fruitless, as we found that the conditions strong enough to hydrolyze the acyl moiety also removed the ethylsulfanyl group. Surmising that the methylcarbonate groups could be selectively hydrolyzed in milder condition without affecting the alkylsulfanyl group, we applied the above ultrasound method to the substrate **5** and successfully obtained *N*-ethylsulfanylated intermediate (**6**).[14] The methylcarbonate group of **6** could be easily removed by the treatment with potassium hydroxide in a methanol-water solution at ambient temperature, thereby producing 1-ethylsulfanyl-4-hydroxy dihydropyrrole derivative (**7**). The transformation of the hydroxyl group in **7** was mainly a strategy for improving the systemic insecticidal activity while maintaining the contact potency. We chose carbonate groups for this purpose because they seemed to have an appropriate balance of lipophilicity and hydrophilicity, properties requisite for contact and systemic activities, respectively. Then the hydroxyl group of **7** was converted to a variety of alkyl carbonate groups (**2h**–**2q**) by standard methods.

Table 2. Insecticidal activity and phytotoxicity of the *N*-sulfanyldihydropyrrole derivatives[a]—effects of the 4-position



Compd	R_3	*N. lugens*				*N. cincticeps*				*OS*[b]
		Systemic test		Contact test		Systemic test		Contact test		Spray
		1 ppm	0.1 ppm	1 ppm	0.1 pm	1 ppm	0.1 ppm	1 ppm	0.1 ppm	100 ppm
2a	*t*-$BuCH_2$—	2	0	4	2	2	0	4	1	2
2h	i-PrO—	4	2	4	3	4	1	4	4	4
2i	*t*-$BuCH_2O$—	2	0	4	0	0	0	4	0	4
2j		1	0	4	1	1	0	4	0	4
2k		0	—[c]	4	0	1	0	4	1	0
2l	$(i\text{-Pr})_2CHO$—	0	—	0	0	1	1	1	0	0
2m	*c*-Hex-O—	4	1	2	2	4	0	4	3	4
2n		3	0	4	0	0	—	4	0	4
2o	*i*-PrO-CH_2CH_2O—	4	1	4	2	4	1	4	1	4
2p		4	2	4	1	4	0	4	0	4
2q		4	0	4	2	4	0	4	1	4

[a]Insecticidal activity and phytotoxicity were each graded into five classes from 0 to 4. See text.
[b]*OS*, *Oryza sativa* (rice).
[c]Not determined.

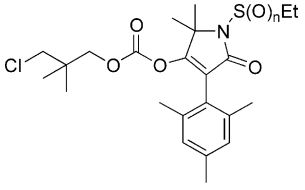
It was also interesting to note that the sulfur atom in the structure (**2n**) could be further oxidized to corresponding sulfoxide (**2r**) and sulfone (**2s**), respectively, by treatment with 3-chloroperbenzoic acid (mCPBA).

Biological evaluation

Table 1 shows the insecticidal activity of the *N*-sulfanyldihydropyrrole derivatives with various alkylsulfanyl and phenylsulfanyl groups at the 1-position in both systemic and contact tests against *N. lugens* and *N. cincticeps*, along with the results of an evaluation of their phytotoxicity against rice. In these tests, the affected insects died before or during ecdysis without completion of molting. This symptom is unique for hemiptera pests, and these compounds might possess a novel mode of action. Although these derivatives tended to demonstrate high contact activity against both pests, almost all of them showed relatively poor control in systemic tests. The only exception was **2b** (R = Pr), which exerted complete control of *N. cincticeps* at 1 ppm. In assessments of the phytotoxicity, several compounds caused moderate damage to rice at 100 ppm.

Table 2 shows the results of biological assays of the derivatives in which the substituents at the 4-position were variously transformed to alkoxycarbonyloxy groups in an effort to improve the systemic insecticidal activity. In comparison with the acyl compound (**2a**), several of the modified compounds (**2h**, **2o**, **2p**, and **2q**) exhibited clearly improved systemic activity against both *N. lugens* and *N. cincticeps* with no change in their contact activity. Compound (**2m**) exhibited improved systemic and contact activities against *N. cincticeps* while its contact efficacy against *N. lugens* was decreased. The other compounds tended to exhibit decreases in both systemic and contact activity.

Table 3. Insecticidal activity and phytotoxicity of the *N*-sulfinyl- and *N*-sulfonyldihydropyrrole derivatives[a]



Compd	*n*	*N. lugens*				*N. cincticeps*				*OS*[b]
		Systemic test		Contact test		Systemic test		Contact test		Spray
		1 ppm	0.1 ppm	1 ppm	0.1 pm	1 ppm	0.1 ppm	1 ppm	0.1 ppm	100 ppm
2n	0	3	0	4	0	0	—	4	0	4
2r	1	0	—[c]	0	—	0	—	0	—	3
2s	2	4	0	4	0	1	0	3	0	1

[a]Insecticidal activity and phytotoxicity were each graded into five classes from 0 to 4. See text.
[b]*OS*, *Oryza sativa* (rice).
[c]Not determined.

Unfortunately, derivatives with improved insecticidal activity were also more phytotoxic.

Interestingly, when the sulfur atom was oxidized to the corresponding sulfoxide (**2r**), a drastic loss of activity was observed (Table 3). On the other hand, the sulfone derivative (**2s**) seemed to maintain the activity of the original sulfanyl compound while exerting weaker phytotoxic effects against rice.

Conclusion

In this developmental study on a potential new class of insecticides, we designed and prepared a new series of dihydropyrrole derivatives with sulfur moieties such as sulfanyl, sulfinyl, and sulfonyl groups at the 1-position. In our biological evaluation, all of the derivatives but the sulfinyl type exhibited high insecticidal activity against *N. lugens* and *N. cincticeps*, and the alkoxycarbonyloxy groups at the 4-position of the dihydropyrrole ring tended to improve the systemic insecticidal activity.

Experimental

All melting points (mp) are uncorrected. IR spectra were measured on a Perkin–Elmer 1600 spectrometer. ^{1}H NMR spectra were recorded at 200 MHz on a Varian Gemini 200 spectrometer, or at 270 MHz on a JEOL GX 270 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 mass spectrometer and a VG Auto Spec M mass spectrometer.

Synthetic preparation

Details on the preparation of compounds **2a**–**2g**, and **6** are described in ref 14.

1-Ethylsulfanyl-4-hydroxy-3-mesityl-5,5-dimethyl-1,5-dihidropyrrol-2-one (7). A 1.65 mL volume of 1 N NaOH aq (1.65 mmol) was added to a stirred solution of **6** (0.59 g, 1.61 mmol) in ethanol (4 mL) at 0 °C, and then the reaction mixture was stirred at 0 °C for 10 min and at ambient temperature for 30 min. After adding 1 N HCl aq to the reaction mixture to neutralize the solution and extracting the water layer with EtOAc, the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to a solid. Treatment of this solid by silica gel column chromatography (EtOAc/hexane, 1/4) yielded the title compound (**7**, 412.1 mg, 84%) as a colorless solid. Mp 142–145 °C; ^{1}H NMR ($CDCl_3$) δ: 6.90 (2H, s), 6.80 (1H, br s), 2.83 (2H, q, J = 7.4 Hz), 2.27 (3H, s), 2.11 (6H, s), 1.47 (6H, s), 1.25 (3H, t, J = 7.4 Hz); IR (KBr) cm^{-1}: 2974, 1649, 1603, 1484, 1437, 1365, 1320, 1213, 1155, 1072, 1032; HRMS(EI) calcd for $C_{17}H_{23}NO_2S$ 305.1450, found 305.1449.

2-Chloro-1,1-dimethylethyl 1-(ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl carbonate (2n). Triphosgene (130.0 mg, 0.44 mmol) and pyridine

(0.12 mL, 1.48 mmol) were added to a stirred solution of 2-chloro-1,1-dimethylethyl alcohol (164.9 mg, 1.34 mmol) in dichloromethane (CH_2Cl_2) at 0 °C, and then the reaction mixture was stirred at 0 °C for 45 min. Next, the mixture was added to a stirred solution of **7** (197.8 mg, 0.65 mmol) and triethylamine (Et_3N; 0.185 mL, 1.3 mmol) in CH_2Cl_2 (2 mL) at 0 °C, then stirred at 0 °C for another 1 h. After pouring the mixture into water and extracting the mixture with EtOAc, the combined organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to a solid. Treatment of this solid by silica gel column chromatography (EtOAc/hexane, 1/4) yielded the title compound (**2n**, 249.4 mg, 85%) as a colorless solid. Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.84 (2H, s), 3.85 (2H, s), 3.21 (2H, s), 2.89 (5H, q, J = 7.3 Hz), 2.24 (3H, s), 2.15 (6H, s), 1.56 (6H, s), 1.28 (6H, t, J = 7.3 Hz), 0.84 (9H, s); IR (KBr) cm^{-1}: 2975, 1775, 1711, 1684, 1614, 1464, 1312, 1257, 1210, 1186, 1146; HRMS(EI) calcd for $C_{23}H_{32}ClNO_4S$ 454.1741, found 454.1742.

Compounds **2h**–**2m** and **2o**–**2q** were synthesized by the same procedure.

1-(Ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl isopropyl carbonate (2h). Yield: 89.3%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.84 (2H, s), 3.74 (2H, d, J = 6.6 Hz), 2.89 (2H, q, J = 7.3 Hz), 2.25 (3H, s), 2.15 (6H, s), 1.76 (1H, sep, J = 6.6 Hz), 1.50 (6H, s), 1.29 (3H, t, J = 7.3 Hz), 0.77 (6H, d, J = 6.6 Hz); IR (KBr) cm^{-1}: 2972, 1778, 1715, 1683, 1613, 1464, 1377, 1309, 1215, 1187, 1155, 1025; HRMS(EI) calcd for $C_{22}H_{31}NO_4S$ 405.1974, found 405.1975.

1-(Ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl neopentyl carbonate (2i). Yield: 69.2%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.83 (2H, s), 3.67 (2H, s), 2.89 (2H, q, J = 7.3 Hz), 2.24 (3H, s), 2.15 (6H, s), 1.50 (6H, s), 1.28 (3H, t, J = 7.3 Hz), 0.77 (9H, s); IR (KBr) cm^{-1}: 2973, 1776, 1710, 1683, 1613, 1455, 1310, 1217, 1184; HRMS(EI) calcd for $C_{23}H_{33}NO_4S$ 419.2130, found 419.2131.

1,2-Dimethylpropyl 1-(ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl carbonate (2j). Yield: 71.6%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.83 (2H, s), 4.23 (1H, m), 2.89 (2H, q, J = 7.3 Hz), 2.23 (3H, s), 2.15 (6H, s), 1.65–1.55 (1H, m), 1.50 (6H, s), 1.28 (3H, t, J = 7.3 Hz), 0.97 (3H, d, J = 6.6 Hz), 0.74 (6H, dd, J = 7.0, 1.8 Hz); IR (KBr) cm^{-1}: 2976, 1777, 1715, 1682, 1613, 1463, 1309, 1219, 1188, 1154, 1123, 1104; HRMS(EI) calcd for $C_{23}H_{33}NO_4S$ 419.2130, found 419.2129.

1-(Ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 1,2,2-trimethylpropyl carbonate (2k). Yield: 71.9%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.82 (2H, s), 4.28 (1H, q, J = 6.6 Hz), 2.89 (2H, q, J = 7.3 Hz), 2.22 (3H, s), 2.15 (6H, s), 1.50 (6H, s), 1.28 (3H, t, J = 7.3 Hz), 0.94 (3H, d, J = 6.6 Hz), 0.75 (9H, s); IR (KBr) cm^{-1}: 2979, 1771, 1709, 1678, 1612, 1459, 1367, 1310, 1214, 1190, 1156, 1077; HRMS(EI) calcd for $C_{24}H_{35}NO_4S$ 433.2287, found 433.2286.

1-(Ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-methylene-2,5-dihydro-1*H*-pyrrol-3-yl 1-isopropyl-2-methylpropyl carbonate (2l). Yield: 57.8%; mp 89–90 °C; ^{1}H NMR ($CDCl_3$) δ: 6.80 (2H,s), 4.14 (1H, t, J = 6.2 Hz), 2.89 (2H, q, J = 7.3 Hz), 2.21 (3H, s), 2.15 (6H, s), 1.89–1.72 (2H, m), 1.58 (6H, s), 1.28 (3H, t, J = 7.3 Hz), 0.67 (12H, dd, J = 6.6, 3.7 Hz); IR (KBr) cm^{-1}: 2972, 1774, 1708, 1687, 1612, 1463, 1309, 1296, 1218, 1130, 1094; HRMS(EI) calcd for $C_{25}H_{37}NO_4S$ 447.2443, found 447.2443.

Cyclohexyl 1-(ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl carbonate (2m). Yield: 77.2%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.85 (2H, s), 4.84–4.80 (1H, m), 2.88 (2H, q, J = 7.3 Hz), 2.25 (3H, s), 2.15 (6H, s), 1.69–1.36 (8H, m), 1.28 (3H, t, J = 7.3 Hz); IR (KBr) cm^{-1}: 2975, 1777, 1714, 1682, 1613, 1456, 1360, 1311, 1216, 1152, 1034; HRMS(EI) calcd for $C_{23}H_{31}NO_4S$ 417.1974, found 417.1974.

1-(Ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl 2-isopropoxyethyl carbonate (2o). Yield: 59.2%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.85 (2H, s), 4.11–4.06 (2H, m), 3.54–3.39 (3H, m), 2.88 (2H, q, J = 7.3 Hz), 2.25 (3H, s), 2.15 (6H, s), 1.50 (6H, s), 1.28 (3H, t, J = 7.3 Hz), 1.11 (6H, d, J = 6.2 Hz); IR (KBr) cm^{-1}; HRMS(EI) calcd for $C_{23}H_{33}NO_5S$ 435.2079, found 435.2080.

1-(Ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl tetrahydrofuran-2-ylmethyl carbonate (2p). Yield: 70.4%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.85 (2H, s), 4.02–3.88 (3H, m), 3.80–3.70 (2H, m), 2.88 (2H, q, J = 7.3 Hz), 2.25 (3H, s), 2.15 (6H, s), 1.89–1.60 (4H, m), 1.49 (6H, s), 1.27 (3H, t, J = 7.3 Hz); IR (KBr) cm^{-1}: 2978, 1783, 1708, 1686, 1614, 1446, 1378, 1286, 1204, 1185, 1158, 1204; HRMS(EI) calcd for $C_{23}H_{31}NO_5S$ 433.1923, found 433.1924.

1,1-Dimethyl-2-propynyl 1-(ethylsulfanyl)-4-mesityl-2,2-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-3-yl carbonate (2q). Yield: 10.6%; colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.83 (2H, s), 2.88 (2H, q, J = 7.3 Hz), 2.43 (1H, s), 2.23 (3H, s), 2.15 (6H, s), 1.50 (6H, s), 1.42 (6H, s), 1.27 (3H, t, J = 7.3 Hz); IR (KBr) cm^{-1}: 2925, 1775, 1710, 1470, 1451, 1373, 1300, 1226, 1199, 1183, 1104; HRMS(EI) calcd for $C_{23}H_{29}NO_4S$ 415.1817, found 415.1819.

3-Chloro-2,2-dimethylpropyl 1-(ethylsulfinyl)-4-mesityl-2,2-dimethyl-5-oxo- 2,5-dihydro-1*H*-pyrrol-3-yl carbonate (2r) and 3-chloro-2,2-dimethylpropyl 1-(ethylsulfonyl)-4-mesityl-2,2-dimethyl-5-oxo- 2,5-dihydro-1*H*-pyrrol-3-yl carbonate (2s). mCPBA (98.7 mg, ca. 0.57 mmol) was added to a solution of **2n** (110.0 mg, 0.24 mmol) in 1,2-dichloroethane (5 mL) at ambient temperature, and then the mixture was stirred at the same temperature for 4 h. After pouring the reaction mixture into saturated sodium bicarbonate aqueous solution and extracting with EtOAc, the combined organic layer was washed with brine, dried (Mg_2SO_4), and evaporated under reduced pressure to an oil. Treatment of this oil by preparative thin layer chromatography (EtOAc/hexane = 1/3) gave the title compounds, **2r** (18.2 mg, 16%) and **2s** (90.0 mg, 77%), separately.

2r. Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.85 (2H, s), 4.18–4.00 (1H, m), 3.84 (2H, s), 3.60–3.42 (1H, m), 3.21 (2H, s), 2.24 (3H, s), 2.18 (3H, s), 2.15 (3H, s), 1.80 (3H, s), 1.53 (3H, s), 1.29 (3H, t, $J=7.7$ Hz), 0.84 (9H, s); IR (neat) cm^{-1}: 2923, 1786, 1724, 1686, 1612, 1458, 1350, 1292, 1207, 1180, 1155, 1026; HRMS(EI) calcd for $C_{23}H_{32}NO_5S$ 469.1703, found 469.1706.

2s. Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 6.86 (2H, s), 3.84 (2H, s), 3.61 (2H, q, $J=7.3$ Hz), 3.21 (2H, s), 2.25 (3H, s), 2.15 (6H, s), 1.80 (6H, s), 1.40 (3H, t, $J=7.3$ Hz), 0.84 (6H, s); IR (neat) cm^{-1}: 2934, 1782, 1692, 1458, 1375, 1211, 1040; HRMS(EI) calcd for $C_{23}H_{32}NO_6S$ 485.1639, found 485.1640.

Biological tests

Insecticidal tests. Both systemic and contact tests were conducted against *N. lugens* and *N. cincticeps*. Each compound was formulated as an emulsifiable concentrate (EC) and then diluted with water containing a surfactant (Gramin-S; 0.01% v/v) to give the active ingredient (AI) concentration required to assess activity levels. The activity ratings were expressed by a five-point index (0, 1, 2, 3, and 4) corresponding to 0–29, 30–59, 60–89, 90–99, and 100% mortality.

Tests against *N. lugens* and *N. cincticeps*. Systemic test. A 30 mL volume of the test solution was poured into a conical test unit (4 cm diam. × 15 cm high). Four rice seedlings were positioned in the unit by a notched sponge disk that sustained the stems and shielded the solution from contact with insects. The rice seedlings were allowed to absorb the compound from the solution for 3 h in a growth chamber held at 25 °C and 60% relative humidity. Ten third-instar nymphs of *N. lugens* or *N. cincticeps* were transferred into a test tube. The test units were then held in the growth chamber under long-day (16L/8D) conditions at 25 °C and 60% relative humidity. Duplicate experiments were performed. Counts were taken of the numbers of live and dead insects after 5 days of treatment. Immobile insects were counted as dead.

Contact test. Four rice stems were immersed in the test solution for 20 s. After drying, the stems were transferred into a glass tube (2 cm diam. × 10 cm high) containing a small amount of water. Ten third-instar nymphs or adults of *N. lugens* or *N. cincticeps* were released into the tube and kept there at 25 °C and 60% relative humidity under long-day (16L/8D) conditions. Duplicate experiments were performed. Counts were taken of the numbers of live and dead insects 5 days after insect release. Immobile insects were counted as dead.

Phytotoxicity evaluation. Compounds were formulated as EC and sprayed in a post-emergence glasshouse test for rice (*Oryza sativa*) seedlings at doses of 100 ppm. Seven days after treatment, damage to the plants was visually assessed by comparison with untreated plants using a scale of 0 to 4: 0, <10% growth inhibition; 1, 11–30% growth inhibition; 2, 31–60% growth inhibition; 3, 61–90% growth inhibition; 4, >91% growth inhibition.

References and Notes

1. Dent, D. *Insect Pest Management*; CABI Publishing: London, 2000.
2. Conway, G.; In *The Doubly Green Revolution—Food for All in the 21st Century*; Penguin: London, 1997; p 205.
3. Holan, G.; Winkler, D. A. In *Rational Approaches to Structure, Activity, and Ecotoxicology of Agrochemicals*; Draber, W., Fujita, T., Eds.; CRC: FL, 1992; p 123.
4. Baker, D.R.; Fenyes, J. G.; Lahm, G. P.; Selby, T. P.; Stevenson, T. M. In *Synthesis and Chemistry of Agrochemicals VI (ACS Symposium Series 800)*; Baker, D. R., Fenyes, J. G., Lahm, G. P., Selby, T. P., Stevenson, T. M., Eds.; American Chemical Society (Oxford University Press): Washington, DC, 2002; p 219.
5. Ishaaya, I.; Horowitz, A. R. In *Insecticides with Novel Modes of Action*; Ishaaya, I., Degheele, D., Eds., Springer: Berlin, 1998; p 1.
6. Cremlyn, R. J. In *Agrochemicals*; John Wiley & Sons: Chichester, 1991; p 1.
7. Ito, M.; Okui, H.; Nakagawa, H.; Mio, S.; Kinoshita, A.; Obayashi, T.; Miura, T.; Nagai, J.; Yokoi, S.; Ichinose, R.; Tanaka, K.; Kodama, K.; Iwasaki, T.; Miyake, T.; Takashio, M.; Iwabuchi, J. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 2406.
8. Ito, M.; Okui, H.; Nakagawa, H.; Mio, S.; Iwasaki, T.; Iwabuchi, J. *Heterocycles* **2002**, *57*, 881.
9. Fisher, R.; Bretshneider, T.; Krueger, W.; Bachmann, J.; Erdeln, C.; Wachendorff-Neumann, U.; Stantel, H. J.; Luerssen, K.; Schmidt, R. R.; DE Patent 4216814, 1993; *Chem. Abstr.* **1993**, *119*, 117088b.
10. Fischer, R.;, Dumas, J.; Bretschneider, T.; Erdelen, C.; Wachendorff-Neumann, U.; DE Patent 4410420, 1995; *Chem. Abstr.* **1996**, *124*, 29593k.
11. Fischer, R.; Dumas, J.; Bretschneider, T.; Erdelen, C.; Wachendorff-Neumann, U.; Santel, H.-J.; Dollinger, M.; Mencke, N.; Turberg, A.; DE Patent 19518962, 1996; *Chem. Abstr.* **1996**, *124*, 231916g.
12. Krauskopf, B.; Luerssen, K.; Stantel, H.-J.; Schmidt, R. R.; Wachendorff-Neumann, U.; Fisher, R.; Erdelen, C.; EP Patent 456063, 1991; *Chem. Abstr.* **1992**, *116*, 106083 h.
13. Kudo, N.; Yoneda, T.; Sato, K.; Honma, T.; Sugai, S. *Chem. Pharm. Bull.* **2000**, *48*, 509.
14. Ito, M.; Okui, H.; Nakagawa, H.; Mio, S.; Iwasaki, T.; Iwabuchi, J. *Heterocycles* **2002**, *57*, 909.