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·Research Note·

Synthesis and Fungicidal Activities of N-Carboalkoxy(aryloxy)-2-thiazolidinones

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Abstract: In order to find new fungicidal lead compounds, eleven N-carboalkoxy(aryloxy)-2-thiazolidinones, ten of which are novel compounds, were prepared from a condensation reaction of 2-thiazolidinone and chloroformate, and their structures were confirmed by ^{1}H NMR, MS, IR and elemental analysis. The results of fungicidal tests, at the concentration of 2 000 mg/L, indicated that some of them exhibited good activities toward various plant disease fungi. Compounds **5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j** showed excellent inhibitory activities (100%) against Sclerotinia sclerotiorum. Compound **5i** showed excellent inhibitory activities (100%) against Botrytis cinerea, Penicillium italicum and S. sclerotiorum, and also showed inhibitory activities against Xanthomonas oryzae, Pseudomonas solanacearum.

Key words: N-Carboalkoxy(aryloxy)-2-thiazolidinones; synthesis; fungicidal activity
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N-烃氧羰基-2-噻唑烷酮衍生物的合成及其杀菌活性

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摘 要:为了寻求新的杀菌先导化合物,通过2-噻唑烷酮与氯甲酸酯的缩合反应得到11个N-烃氧羰基-2-噻唑烷酮衍生物(**5a**～**5k**),其中10个为新化合物,其结构均经^{1}H NMR、MS、IR和元素分析表征。初步离体杀菌实验结果表明,大多数化合物较之母体2-噻唑烷酮具有更高的杀菌活性。在浓度为2 000 mg/L下,化合物**5c**、**5d**、**5e**、**5f**、**5g**、**5h**、**5i**、**5j**对油菜菌核病菌Sclerotinia sclerotiorum的抑制率为100%,**5i**对番茄灰霉病菌Botrytis cinerea、柑桔青霉病菌Penicillium italicum和油菜菌核病菌的抑制率均为100%。

关键词: N-烃氧羰基-2-噻唑烷酮衍生物;合成;杀菌活性
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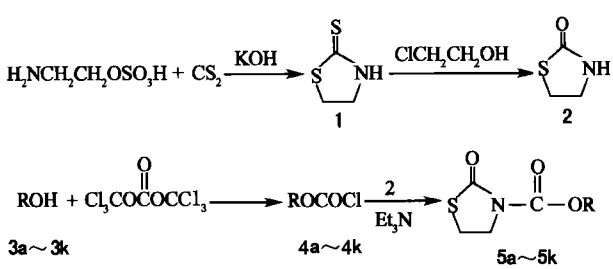
1 Introduction

2-Thiazolidinone is not only a useful intermediate, but also has good fungicidal activities toward various plant disease fungi[1]. Furthermore, much research has shown that some N-substituted-2-thiazolidinones are endowed with important biological activities, and these derivatives have been widely used in pharmaceuticals and pesticides. For instance, N-(substituted-benzyl)-2-thiazolidinones show a gastric acid secretion-inhibiting effect and therefore, they are useful for the treatment of gastric and duodenal ulcers[2]; Some 3-benzyl-2-thiazolidinone derivatives exert excellent antiinflammatory activity, thus can be active ingredients of pharmaceutical compositions[3]; Some N-phosphorylated-2-thiazolidinones show excellent activities as active ingredients for insecticides, miticides and nematocides[4,5]. Therefore, we tried to synthesize a series of N-carboalkoxy(aryloxy)-2-thiazolidinones by a condensation reaction of 2-thiazolidinone and chloroformate, and tested their fungicidal activities toward various plant disease fungi in order to find new fungicidal lead compounds.

We describe here the synthesis of eleven N-carboalkoxy(aryloxy)-2-thiazolidinones (**Scheme 1**), ten of which are novel compounds, and the biological activities of the known compound **5k** have not been reported before. Their structures were confirmed by ^{1}H NMR, MS, IR and elemental analysis. The results of preliminary fungicidal tests indicated that some of them exhibited good activities toward various plant disease fungi.

Scheme 1



2 Experimental

2.1 Apparatus

Melting points were measured on an X-4 melting-point apparatus and uncorrected. Elemental analysis was carried out on a Carlo-Erba 1110 instrument. Mass spectra were recorded on a HP 5989B MS spectrometer. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer. ^{1}H NMR spectra were determined on a Bruker AC-400 instrument with $CDCl_3$ used as solvent, tetramethylsilane as internal standard.

2.2 Thiazolidine-2-thione (1)

Compound **1** was prepared by the method of literature[4].

2.3 2-Thiazolidinone (2)

Compound **2** was prepared by the method of literature[6].

2.4 General procedure for the preparation of chloroformate 4a～4k

Bis(trichloromethyl) carbonate (19.8 g, 0.067 mol) and alcohol (or phenol) **3a～3k** (0.2 mol) were dissolved in chloroform (100 mL) with stirring. Triethylamine (28.2 mL, 0.2 mol) was added dropwise to the mixture in an ice bath. The mixture was stirred at 0℃ for 1 h and then at room temperature for 2 h. The mixture was washed with iced water three times, dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The residue was distilled under reduced pressure to obtain chloroformate **4a～4k**.

2.5 General procedure for the preparation of N-carboalkoxy(aryloxy)-2-thiazolidinones (5a～5k)

2-Thiazolidinone (0.52 g, 5 mmol) and triethylamine (0.72 g, 7 mmol) were dissolved in dichloromethane (10 mL) with stirring. Chloroformate **4a～4k** (6 mmol) was added dropwise to the mixture in an ice bath. The mixture was stirred at 0℃ for 10 h and washed with water three times, dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The residue was purified by chromatography on a column of silica gel with petroleum ether-ethyl acetate (1∶1, V/V) as eluent, or recrystallization from absolute ethanol to yield products **5a～5k**.

3 Results and discussions

Physical constants and elemental analysis data of compounds **2** and products **5a～5k** were shown in Table 1, and their MS, IR and ^{1}H NMR data were shown in Table 2.

Table 1 Physical constants and elemental analysis data of compounds **2** and **5a～5k**

Compd.	R	Yield (%)	M. p. / ℃	Formula	Elemental analysis (%, Calcd.)		
					C	H	N
2		84	49～50	C_3H_5NOS	35.07 (34.93)	5.13 (4.89)	13.21 (13.58)
5a	Me	87	32～34	$C_5H_7NO_3S$	37.29 (37.26)	4.71 (4.38)	8.43 (8.69)
5b	Et	83	oil	$C_6H_9NO_3S$	40.97 (41.13)	5.28 (5.18)	7.69 (8.00)
5c	$ClCH_2CH_2$	68	oil	$C_6H_8ClNO_3S$	34.40 (34.37)	4.02 (3.84)	6.40 (6.68)
5d	n-Pr	88	oil	$C_7H_{11}NO_3S$	44.27 (44.43)	6.14 (5.86)	7.41 (7.40)
5e	i-Pr	78	oil	$C_7H_{11}NO_3S$	44.15 (44.43)	5.72 (5.86)	7.13 (7.40)
5f	n-Bu	76	oil	$C_8H_{13}NO_3S$	47.43 (47.27)	6.69 (6.44)	6.85 (6.89)
5g	i-Bu	74	oil	$C_8H_{13}NO_3S$	47.20 (47.27)	6.60 (6.44)	6.80 (6.89)
5h	$n\text{-}C_5H_{11}$	81	oil	$C_9H_{15}NO_3S$	49.93 (49.75)	7.22 (6.96)	6.15 (6.45)
5i	$i\text{-}C_5H_{11}$	81	oil	$C_9H_{15}NO_3S$	49.73 (49.75)	7.11 (6.96)	6.33 (6.45)
5j	Ph	90	125～126	$C_{10}H_9NO_3S$	53.85 (53.80)	4.22 (4.06)	6.47 (6.28)
**5k*	CH_2Ph	32	oil(lit [7], oil)	$C_{11}H_{11}NO_3S$	55.74 (55.68)	4.83 (4.67)	5.62 (5.90)

Table 2 MS, IR and ^{1}H NMR data of compounds **2** and **5a～5k**

Compd.	$M^+ + 1$ (%)	IR, $\nu_{C=O}$ / cm^{-1}	^{1}H NMR, δ
2	104 (6.67)	1 670	3.37 (t, 2H, J = 3.6 Hz, -SCH_2-), 3.59 (t, 2H, J = 3.6 Hz, -NCH_2-), 6.99 (s, 1H, -NH)
5a	162 (100)	1 724, 1 778	3.34 (t, 2H, J = 4.5 Hz, -SCH_2-), 3.85 (s, 3H, -OCH_3), 4.15 (t, 2H, J = 4.5 Hz, -NCH_2-)
5b	176 (100)	1 721, 1 773	1.35 (t, 3H, J = 4.5 Hz, -$CH_2\underline{CH_3}$), 3.31 (t, 2H, J = 4.6 Hz, -SCH_2-), 4.14 (t, 2H, J = 4.6 Hz, -NCH_2-), 4.30 (q, 2H, -$\underline{CH_2}CH_3$)
5c	211 (9.91)	1 722, 1 775	3.33 (t, 2H, J = 4.5 Hz, -SCH_2-), 3.78 (t, 2H, J = 3.4 Hz, -$CH_2\underline{CH_2}Cl$), 4.16 (t, 2H, J = 4.5 Hz, -NCH_2-), 4.48 (t, 2H, J = 3.5 Hz, -$\underline{CH_2}CH_2Cl$)
5d	190 (100)	1 723, 1 772	0.81 (t, 3H, J = 4.6 Hz, -$CH_2CH_2\underline{CH_3}$), 1.51～1.60 (m, 2H, -$CH_2\underline{CH_2}CH_3$), 3.15 (t, 2H, J = 4.5 Hz, -SCH_2-), 3.97 (t, 2H, J = 4.5 Hz, -$\underline{CH_2}CH_2CH_3$), 4.02 (t, 2H, J = 4.2 Hz, -NCH_2-)
5e	190 (2.44)	1 726, 1 771	1.33 (d, 6H, J = 4.0 Hz, $2CH_3$), 3.28 (t, 2H, J = 4.5 Hz, -SCH_2-), 4.11 (t, 2H, J = 4.5 Hz, -NCH_2-), 5.04～5.08 (m, 1H, -OCH)
5f	204 (100)	1 724, 1 775	0.95 (t, 3H, J = 4.6 Hz, -$CH_2CH_2CH_2\underline{CH_3}$), 1.39～1.45 (m, 2H, -$CH_2CH_2\underline{CH_2}CH_3$), 1.66～1.73 (m, 2H, -$CH_2\underline{CH_2}CH_2CH_3$), 3.29 (t, 2H, J = 4.5 Hz, -SCH_2-), 4.13 (t, 2H, J = 4.5 Hz, -NCH_2-), 4.25 (t, 2H, J = 4.2 Hz, -$\underline{CH_2}CH_2CH_2CH_3$)
5g	204 (2.86)	1 723, 1 777	0.86 (d, 6H, J = 4.3 Hz, $2CH_3$), 1.88～1.94 (m, 1H, -CH), 3.21 (t, 2H, J = 4.5 Hz, -SCH_2-), 3.91 (d, 2H, J = 4.0 Hz, -OCH_2-), 4.04 (t, 2H, J = 4.5 Hz, -NCH_2-)
5h	218 (100)	1 724, 1 775	0.91 (t, 3H, J = 4.1 Hz, -$CH_2CH_2CH_2CH_2\underline{CH_3}$), 1.35～1.73 (m, 6H, -$CH_2(\underline{CH_2})_3CH_3$), 3.29 (t, 2H, J = 4.5 Hz, -SCH_2-), 4.13 (t, 2H, J = 4.5 Hz, -NCH_2-), 4.24 (t, 2H, J = 4.2Hz, -OCH_2)
5i	218 (100)	1 724, 1 775	0.93 (d, 6H, J = 4.1 Hz, $2CH_3$), 1.58～1.63 (m, 2H, -$\underline{CH_2}CH$), 1.71～1.75 (m, 1H, -CH), 3.29 (t, 2H, J = 4.5 Hz, -SCH_2-), 4.12 (t, 2H, J = 4.3 Hz, -NCH_2-), 4.27 (t, 2H, J = 3.2Hz, -OCH_2)
5j	224 (1.51)	1 677, 1 777	3.34 (t, 2H, J = 4.5 Hz, -SCH_2-), 4.25 (t, 2H, J = 4.5 Hz, -NCH_2-), 7.17～7.41 (m, 5H, -Ph)
5k	238 (0.59)	1 717, 1 775	3.20 (t, 2H, J = 4.5 Hz, -SCH_2-), 4.07 (t, 2H, J = 4.5 Hz, -NCH_2-), 5.25 (s, 2H, -OCH_2), 7.25～7.41 (m, 5H, -Ph)

The in vitro fungicidal activities of the title compounds **5a～5k** (5% EC: 5% compounds **5**, 8% emulsifier, dimethylbenzene to 100%.) have been evaluated by poisoned food technique[8]. Their fungicidal activities to different fungi at a concentrate of 2 000 mg/L, contrasting with 2-thiazolidinone, were shown in Table 3. Most of them have higher activities than 2-thiazolidinone. Compounds **5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j** showed excellent inhibitory activities against S. sclerotiorum. Compound **5i** showed excellent inhibitory activities against B. cinerea, P. italicum and S. sclerotiorum, and also showed inhibitory activities against X. oryzae, P. solanacearum.

Table 3 Fungicidal activities of N-carboalkoxy(aryloxy)-2-thiazolidinones **5a～5k**

Compd.	Botrytis cinerea	Penicillium italicum	Sclerotinia sclerotiorum	Xanthomonas oryzae	Pseudomonas solanacearum
2	1	4	3	5	5
5a	3	2	2	4	5
5b	3	5	4	3	4
5c	2	4	0	3	5
5d	3	3	0	3	5
5e	2	5	0	5	5
5f	1	4	0	5	4
5g	1	3	0	5	4
5h	2	5	0	5	5
5i	0	0	0	3	4
5j	3	4	0	5	5
5k	3	5	2	3	4
Blank	5	5	5	5	5

Note: "0": 100% (inhibition rate), "1": 90%～99%, "2": 70%～89%, "3": 50%～69%, "4": 30%～49%, "5": 0%～29%.

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