Molecules **2000**, *5*, 1055-1061

molecules

ISSN 1420-3049

http://www.mdpi.org

Synthesis and Fungicidal Activity of 2-Imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and Their 5-Arylidene Derivatives

Hui-Ling Liu[1,2], Zongcheng Li[1] and Thorleif Anthonsen[2,*]

[1]Pesticide Lab 3, Shenyang Research Institute of Chemical Industry, 110021 Shenyang, P.R. China
[2]Department of Chemistry, Norwegian University of Science and Technology, N-7491 Trondheim, Norway
Tel.: +47 73596206, Fax: +47 73596255, E-mail: Thorleif.Anthonsen@chembio.ntnu.no

Received: 15 August 2000 / Accepted: 29 August 2000 / Published: 5 September 2000

Abstract: Five derivatives of 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and a series of their 5-arylidene derivatives have been synthesized and tested for antifungal activity against seven agricultural fungi. 2-Imino-3-(2,4-dichloro-5-fluorophenylthiazol-2-yl)-4-thiazolidi-none and 2-imino-3-(2,4-dichlorophenylthiazol-2-yl)-4-thiazolidione, both of them new compounds, exhibited higher fungicidal effects than the other compounds prepared.

Keywords: 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones, 5-arylidene derivatives, antifungal activity.

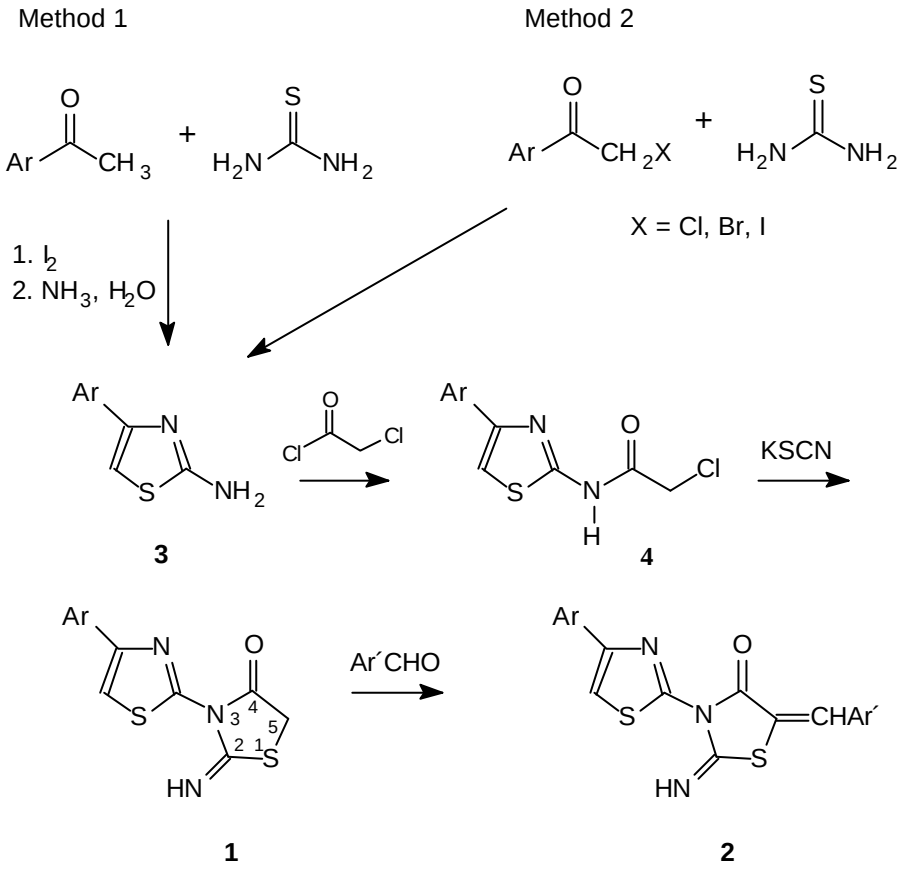
Introduction

Thiazolidin-4-ones are important compounds due to their broad range of biological activities [1-7]. Overviews of their synthesis, properties, reactions and applications have been published[8,9]. 2-Imino-thiazolidin-4-ones have been found to have antifungal activity[10-12], and a convenient method for synthesis involves the reaction of 2-haloacetamides with potassium thiocyanate to produce 2-imino-thiazolidin-4-ones. The R-*N*-group at the 3-position of thiazolidin-4-ones may be varied to be alkyl, aryl, heterocyclic groups etc. It is also well known that the thiazole moiety can be important for significant biological activity [13-16].

Results and Discussion

Syntheses

We have synthesized five thiazol-2-yl substituted 2-imino-thiazolidin-4-ones (**1a-e**) and a series of their 5-arylidene derivatives (**2a-l**) via the key intermediates **3** (Scheme 1 and Table 1). The 2-amino-4-arylthiazoles (**3**) were reacted with chloroacetyl chloride to produce the corresponding 2-chloro-acetamido-4-arylthiazoles (**4**). The latter was treated with potassium thiocyanate in refluxing acetone to afford the related 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones (**1**). No 2-(thiocyanato)-acetamido-4-arylthiazole intermediates were detected. Condensation of **1** with different aromatic aldehydes gave the 5-arylidene-2-imino-3- (4-arylthiazol-2-yl)-thiazolidin-4-ones (**2**).



Scheme 1. Synthesis of thiazol-2-yl substituted 2-imino-thiazolidin-4-ones (**1a-e**) and a series of their 5-arylidene derivatives (**2a-l**). For substituents Ar and Ar´see Table 1.

The different 2-imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones (**1a-e**) were condensed with aromatic aldehydes to yield the related 5-arylidene derivatives (**2a-l**) (See Table 1 for structures). The reaction gave good yields (50-75%) only when the aromatic part of the aldehyde was substituted with a nitro group. The yield of the reaction of chloro-substituted aromatic aldehyde with **1** was low, and benzaldehyde reacted only with **1d** (27%). The condensation was carried out in acetic acid with anhydrous sodium acetate as catalyst. When pyridine was used as catalyst, the yield of the reaction was low (< 20%).

Table 1. Structure of compounds **1a-1e** and **2a-2l**, their melting points and yields of synthesis.

	Substituent Ar	Substituent Ar´	Mp,°C	Yield,%
1a	C_6H_5		240-242	61
1b	*p*-ClC_6H_4		290-291	81
1c	*p*-$O_2NC_6H_4$		187-190	75
1d	2,4-$(Cl)_2$-5-FC_6H_2		173-175	70
1e	2,4-$(Cl)_2C_6H_3$		232-234	60
2a	C_6H_5	*o*-$O_2NC_6H_4$	256-260	52
2b	C_6H_5	*m*-$O_2NC_6H_4$	288-290	74
2c	C_6H_5	*o*-ClC_6H_4	278-280	21
2d	*p*-ClC_6H_4	*o*-$O_2NC_6H_4$	238-240	58
2e	*p*-ClC_6H_4	*m*-$O_2NC_6H_4$	286-287	75
2f	*p*-ClC_6H_4	*o*-ClC_6H_4	282-286	25
2g	*p*-$O_2NC_6H_4$	*o*-$O_2NC_6H_4$	>300	61
2h	*p*-$O_2NC_6H_4$	*m*-$O_2NC_6H_4$	>300	75
2i	*p*-$O_2NC_6H_4$	*o*-ClC_6H_4	>300	17
2j	2,4-$(Cl)_2$-5-FC_6H_2	C_6H_5	258-260	27
2k	2,4-$(Cl)_2$-5-FC_6H_2	*o*-$O_2NC_6H_4$	289-292	53
2l	2,4-$(Cl)_2$-5-FC_6H_2	*m*-$O_2NC_6H_4$	270-274	70

The starting materials, the 2-amino-4-arylthiazoles (**3**), were synthesized by two different methods, either starting with an arylketone (Method 1, Scheme 1)[17,18] or an α-halo arylketone (Method 2)[19]. Method 1, which involves the reaction of substituted acetophenone, thiourea and iodine, was a solid phase reaction. The yield was low due to phase transfer limitations. Furthermore, iodine had to be recycled because of its high price and the pollution problems. In order to overcome these drawbacks, the second method was employed. When substituted α-halo-acetophenones, obtained by substitution of α-H of acetophenones by halogen, were reacted with thiourea in 1-propanol (Method 2), the yield could be raised to about 90% and the reaction time was decreased.

Fungicidal Activity

Compounds (**1a-e** and **2a-i**) were tested for fungicidal activity against 7 agricultural fungi, Pleurotus ostreatus (F1), Aspergillus niger (F2), Pythium aphanidermatum (F3), Gaeumannomyces graminis (F4), Fusarium graminearium (F5), Pyricularia oryzae (F6) and Botrytis cinerea (F7). The results (Table 2) show that the two new compounds (**1d** and **1e**) have higher fungicidal activity than the others, the percentage inhibition of **1d** and **1e** against Pythium aphanidermatum (F1) and of **1d** against Gaeumannomyces graminis (F4) were higher than 90. It may also be noticed that several of the compounds did not inhibit the growth of this fungus. Compounds **1a**, **1b**, **1d** and **1e** were more fungicidal against Pythium aphanidermatum than against the other 6 fungi. Introduction of benzylidene group at C-5 decreased the fungicidal activity. The inhibition of all of the 5-arylidene-4-thazolidinones was low.

Table 2. Percentage inhibition of compounds **1a-1e** and **2a-2l** against the fungi F1-F7*.

% Inhibition of **1a-1e** and **2a-2l** at 50 ppm against F1-F7							
	F1	F2	F3	F4	F5	F6	F7
1a	82.6	54.3	8.8	60.0	21.1	58.8	3.5
1b	72.4	52.3	3.8	51.3	29.7	58.8	0
1c	12.4	56.2	8.8	26.7	2.2	38.1	0
1d	95.0	58.8	12.5	91.3	38.8	76.3	38.2
1e	97.2	62.8	0	86.7	48.6	79.4	0
2a	84.1	54.3	3.8	0	61.9	20.2	64.7
2b	5.9	49.7	25.0	0	20.6	3.2	0
2c	0	23.6	17.2	0	37.4	0	27.5
2d	84.8	60.8	12.5	0	58.8	14.8	66.7
2e	84.1	58.8	16.3	0	61.9	26.5	71.3
2f	0	40.8	46.2	0	31.8	0	0
2g	7.2	62.8	16.3	0	24.7	3.2	33.3
2h	29.8	52.3	0	0	51.6	0	4.7
2i	0	42.7	28.0	37.1	28.0	2.1	60.8
2j	11.5	47.7	0	0	38.1	4.1	28.7
2k	15.2	49.7	0	0	48.5	50.4	2.0
2l	32.6	69.3	33.8	0	45.4	11.7	24.7

Experimental

General

Melting points were recorded in open capillaries and are not corrected. IR spectra (KBr disks) were recorded using a Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ solutions, with Me_4Si as an internal reference. Chemical shifts are in ppm and coupling constants in Hz. Elemental analyses (C, H and N) were carried out with a Coleman analyzer. The new compounds gave the following analytical results: **1d** %C 39.79, %H 1.67, %N 11.60, calcd. for $C_{12}H_6Cl_2FN_3OS_2$: C 39.81, H 1.71, N 11.54 and **1e** %C 46.68, %H 2.28, %N 13.61, calcd. for $C_{12}H_7ClN_3OS_2$: C 46.67, H 2.31, N 13.58. Compounds **1a-1c**, **2j** and **2l** all gave values in accordance with the calculated values based on the elemental compositions.

Test for Fungicidal Activity

Compounds (**1a**-**e** and **2a**-**i**) were tested for fungicidal activity against 7 agricultural fungi, Pleurotus ostreatus, Aspergillus niger, Pythium aphanidermatum, Gaeumannomyces graminis, Fusarium graminearium, Pyricularia oryzae and Botrytis cinerea, by the agar growth medium poison technique [12]. The concentration of the test compounds was 50 ppm. After 48 h treatment, the growth diameter of the fungus on the agar was measured and the percentage inhibition of growth by an inhibitor was calculated by comparison with the growth in controls, i.e. untreated petri-dishes. The experiments were performed in triplicate. The results are shown in Table 2.

*2-Amino-4-phenylthiazole (***3a***). Method 1*

Thiourea (30.4 g, 0.4 mole) and I_2 (50.8 g, 0.2 mole) were triturated and mixed with acetophenone (24.0 g, 0.2 mole). The mixture was heated on a water bath with occasional stirring for 8 h. The obtained solid was triturated with Et_2O to remove unreacted acetophenone, washed with aqueous sodium thiosulfate to remove excess iodine and then with water. The crude product was dissolved in hot water, filtered to remove the sulphone, and 2-amino-4-phenylthiazole (**3a**) was precipitated by addition of $NH_3 \times H_2O$. Crystallization from EtOH gave white crystals, yield 22.2 g (0.13 mole, 65%) m.p. 146-148°C, IR 3420, 3240, 1600, 1520, 770, 710 cm^{-1}, ^1H NMR δ 7.87 (2H, m, aromatic), 7.54 (3H, m, aromatic), 7.47 (1H, s, thiazole-H5).

*2-Amino-4-(2,4-dichlorophenyl)thiazole (***3e***). Method 2*

A solution of 2-chloro-1-(2,4-dichlorophenyl) ethanone (12.2 g, 0.05 mole) and thiourea (4.2 g, 0.05 mole) in 1-propanol (40 mL) was refluxed for 2 h. After addition of pyridine (5 mL) and continued reflux for 5 h, the solvent was removed *in vacuo*. The crude product was dried and crystallized from EtOH to give yellow crystals, yield 11.0 g (0.045 mole, 90.4%), mp 138-140°C, IR 3450, 3260, 1610, 1570, 1500 cm^{-1}, ^1H NMR δ 9.85, 8.10 (3H, m, aromatic), 7.85 (1H, s, thiazole).

*2-Chloroacetamido-4-(4-chlorophenyl)thiazole (***4b***)*

A solution of 2-amino-4-(4-chlorophenyl)thiazole (3.7 g, 0.02 mole) in dry benzene (60 mL) was cooled to 0-5°C. Chloroacetyl chloride (5 mL, 0.04 mole) dissolved in dry benzene (20 mL) was slowly added to the solution with vigorous stirring. When the addition was complete, the reaction mixture was refluxed for 3 h. Benzene was removed *in vacuo*. The residue was washed with 5% $NaHCO_3$, and subsequently with water. The crude product was dried and crystallized from EtOH to give colorless crystals, yield 3.70 g (0.013 mole, 64.4%), m.p 160-164°C, IR 3360, 3100, 1690, 1540, 840, 510 cm^{-1}, ^1H NMR δ 7.87 (2H, m, aromatic), 7.39 (2H, m, aromatic), 6.93 (1H, s, thiazole), 4.09 (2H, m, $-CH_2-$). Other 2-chloroacetamido-4-arylthiazoles were prepared by the same method.

*2-Imino-3-[4-(2,4-dichloro-5-fluorophenyl)thiazol-2-yl]-thiazolidin-4-one (***1d***)*

A mixture of 2-chloroacetamido-4-(2,4-dichloro-5-fluorophenyl)thiazole (10.0 g, 0.03 mole), KSCN (6.0 g, 0.06 mole) and dry acetone (100 mL) was refluxed for 3 h. Excess acetone was removed *in vacuo* and the residue was stirred with water (50 mL). The solid product was filtered, washed with water, and dried. The thiazolidinone **1d** was obtained by crystallization from EtOH: yield 7.61g, (0.021 mole, 70%), m.p. 173-175°

C, IR 3180, 3080, 1710, 1650, 1570, 1350, 730 cm^{-1}, ^1H NMR δ 7.97 (1H, s, aromatic), 7.81 (1H, s, aromatic), 7.26 (1H, s, thiazole), 4.20 (2H, s, $-CH_2-$). Similarly, other 2-imino-3-arylthiazol-2-yl-thiazolidin-4-ones (**1a**-**c**, **1e**) were also synthesized. No intermediates, 2-(thiocyanato)acetoamido-4-arylthiazoles, were isolated in the procedure.

*5-(3-Nitrobenzylidene)-2-imino-3-(4-phenylthiazol-2-yl)-thiazolidin-4-one (***2b***)*

2-Imino-3-(4-phenylthiazol-2-yl)-thiazolidin-4-one (2.0 g, 0.01 mole) and 3-nitrobenzaldehyde (3.0 g, 0.02 mole) were added to a solution of anhydrous NaOAc (2.0 g, 0.02 mole) in AcOH (30 mL). The mixture was refluxed for 5 h at 120°C and cooled to room temp. The solid product was filtered from the mixture, washed with water, dried and crystallized from EtOH to form yellow crystals, yield 3.0 g (7.34 mmole, 73.4%), m.p. 290-294°C, IR 3400, 1710, 1590, 1520, 1340, 1170, 770, 710 cm^{-1}, ^1H NMR δ 7.34 (3H, m, Ar), 7.93 (2H, m, Ar), 7.61 (1H, s, thiazole-5), 7.95 (1H, s, =CH), 7.96 (1H, s, Ar'-5), 8.38 (1H, s, Ar'-6), 8.60 (1H, s, Ar'-4), 8.75 (1H, s, Ar'-2).

Acknowledgments: We are grateful to Pesticide Lab 5 of Research Institute of Chemical Industry, Shenyang, P.R. China for antifungal screening; and the Physical Chemistry Lab, for spectroscopy and elemental analyses.

References and Notes

1. Doran, W. J.; Shonle, H. A. Dialkyl thiazolidinones. *J. Org. Chem.* **1938**, *3*, 193-197.
2. Troutman, H. D.; Long, L. M. The synthesis of 2,3-disubstituted-4-thiazolidones. *J. Am. Chem. Soc.* **1948**, *70*, 3436-3439.
3. Rout, M. K.; Mahapatra, G. N. 2-β-Naphtyliminino-4-thiazolidone and its derivatives. *J. Am. Chem. Soc.* **1955**, *77*, 2427-2428.
4. Gaikwad, N. J.; Tirpude, R. N. Substituted 4-thiazolidones as anticonvulsants. *Indian Drugs* **1994**, *31*, 593-594.
5. El-Gendy, Z.; Abdel-Rahman, R. M.; Fawzy, M. M.; Mahmoud, M. B. Biologically active thiazolidinone. Part II. Synthesis and fungitoxicities of isolated and fused thiazolidinones derived from thiosemicarbazones. *J. Ind. Chem. Soc.* **1990**, *67*, 927-929.
6. Diurno, M. V.; Mazzoni, O.; Piscopo, E.; Calignano, A.; Giordano, F.; Bolognese, A. Synthesis and antihistaminic activity of some thiazolidin-4-ones. *J. Med. Chem.* **1992**, *35*, 2910-2912.
7. Shah, V.; Pant, C. K.; Joshi, P. C. Synthesis and antifungal activity of some bis (2-arylimino-3-yl-thiazolidinones) and bis (1-aryl-3-yl-thiohydantoins). *Asian J. Chem.* **1993**, *5*, 83-88.
8. Brown, F. C. thiazolidin-4-ones. *Chem. Revs.* **1961**, *61*, 463-521.
9. Newcome, G. R.; Nayak, A. thiazolidin-4-ones. *Adv. Heterocycl. Chem.* **1979**, *25*, 83-112.
10. Lakhan, R.; Singh, O. P. Potential fungicides. Part III. Synthesis and evaluation of 5-methyl-thiazolidin-4-ones and 5-methyl-2,thiazolidin-4-ones. *J. Ind. Chem. Soc.* **1984**, *61*, 784-787.
11. Bhargava, P. N.; Prakash, S.; Lakhan, R. Synthesis of 2-(4′,5′-disubstituted thiazol-2′-ylimino)-3-(*m*-methylphenyl)-5-methyl (or H)-thiazolidin-4-ones and their fungicidal activity. *Ind. J. Chem.* **1981**, *20B*, 927-929.
12. Lakhan, R. Potential fungicides: Studies of 2-arylimino-3-aryl-thiazolidin-4-ones, their 1,1-dioxides and

5-phenylazo derivatives. *Agric. Biol. Chem.* **1982**, *46*, 557-560.
13. Alaimo, R. J. *N*-(6-Ethyl-4-thiocyanato-2-benzothiazolyl)-5-nitrofuramide. *U.S. Patent 4012409* **1977**.
14. Bhagarva, P. N.; Lakhan, R.; Tripathi, R. Local anestics. Part II. Synthesis of 2-(*N,N*-disubstituted aminoacetamido)-4-*p*-fluorophenyl and -*m*-methoxyphenyl thiazoles. *J. Ind. Chem. Soc.* **1982**, *59*, 773-775.
15. Moulard, T.; Lagorce, J. F.; Thomas, J. C.; Raby, C. Biological evaluation of compounds with -NCS-group or derived from thiazole and imidazole-Activity on prostaglandin synthetase complex. *J. Pharm. Pharmacol.* **1993**, *45*, 731-735.
16. Tsuruoka, A.; Kaku, Y. Y.; Kakinuma, H.; Tsukada, I.; Yanagishawa, M.; Naito, T. Synthesis and antifungal activity of novel thiazole-containing triazole antifugals. *Chem. Pharm. Bull.* **1997**, *45*, 1169-1176.
17. Dodson, R. M.; Carroll King, L. The reaction of ketones with halogens and thiourea. *J. Am. Chem. Soc.* **1945**, *67*, 2242-2243.
18. Carroll King, L.; Hlavek, R. J. The reaction of ketones with iodine and thiourea. *J. Am. Chem. Soc.* **1950**, *72*, 3722-3725.
19. Naoto, I.; Masumi, N.; Hiroshi, A. Production of 2-amino-4-substituted thiazole. *J.P. 60056970A* **1985**.

Samples Availability: Not available.