

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

Hui-Ling Liu<sup>1,2</sup>, Zongcheng Li<sup>1</sup> and Thorleif Anthonsen<sup>2,\*</sup>

<sup>1</sup>Pesticide Lab 3, Shenyang Research Institute of Chemical Industry, 110021 Shenyang, P.R. China

<sup>2</sup>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

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**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-thiazolidinone and 2-imino-3-(2,4-dichlorophenylthiazol-2-yl)-4-thiazolidinone, 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.

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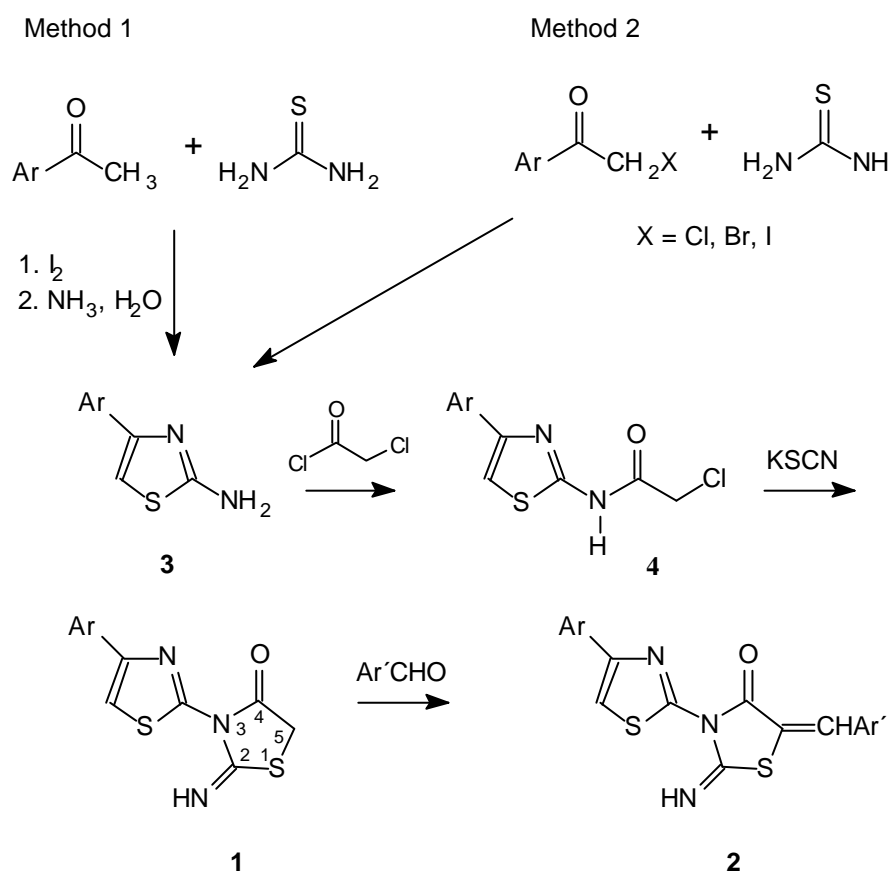
### Introduction

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, %
<b>1a</b>	C <sub>6</sub> H <sub>5</sub>		240-242	61
<b>1b</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>		290-291	81
<b>1c</b>	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>		187-190	75
<b>1d</b>	2,4-(Cl) <sub>2</sub> -5-FC <sub>6</sub> H <sub>2</sub>		173-175	70
<b>1e</b>	2,4-(Cl) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>		232-234	60
<b>2a</b>	C <sub>6</sub> H <sub>5</sub>	<i>o</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	256-260	52
<b>2b</b>	C <sub>6</sub> H <sub>5</sub>	<i>m</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	288-290	74
<b>2c</b>	C <sub>6</sub> H <sub>5</sub>	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	278-280	21
<b>2d</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>o</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	238-240	58
<b>2e</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>m</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	286-287	75
<b>2f</b>	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	282-286	25
<b>2g</b>	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<i>o</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	>300	61
<b>2h</b>	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<i>m</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	>300	75
<b>2i</b>	<i>p</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	>300	17
<b>2j</b>	2,4-(Cl) <sub>2</sub> -5-FC <sub>6</sub> H <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	258-260	27
<b>2k</b>	2,4-(Cl) <sub>2</sub> -5-FC <sub>6</sub> H <sub>2</sub>	<i>o</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	289-292	53
<b>2l</b>	2,4-(Cl) <sub>2</sub> -5-FC <sub>6</sub> H <sub>2</sub>	<i>m</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	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  $\alpha$ -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  $\alpha$ -halo-acetophenones, obtained by substitution of  $\alpha$ -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 graminearum* (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-thiazolidinones was low.

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

% Inhibition of <b>1a-1e</b> and <b>2a-2l</b> at 50 ppm against F1-F7							
	F1	F2	F3	F4	F5	F6	F7
<b>1a</b>	82.6	54.3	8.8	60.0	21.1	58.8	3.5
<b>1b</b>	72.4	52.3	3.8	51.3	29.7	58.8	0
<b>1c</b>	12.4	56.2	8.8	26.7	2.2	38.1	0
<b>1d</b>	95.0	58.8	12.5	91.3	38.8	76.3	38.2
<b>1e</b>	97.2	62.8	0	86.7	48.6	79.4	0
<b>2a</b>	84.1	54.3	3.8	0	61.9	20.2	64.7
<b>2b</b>	5.9	49.7	25.0	0	20.6	3.2	0
<b>2c</b>	0	23.6	17.2	0	37.4	0	27.5
<b>2d</b>	84.8	60.8	12.5	0	58.8	14.8	66.7
<b>2e</b>	84.1	58.8	16.3	0	61.9	26.5	71.3
<b>2f</b>	0	40.8	46.2	0	31.8	0	0
<b>2g</b>	7.2	62.8	16.3	0	24.7	3.2	33.3
<b>2h</b>	29.8	52.3	0	0	51.6	0	4.7
<b>2i</b>	0	42.7	28.0	37.1	28.0	2.1	60.8
<b>2j</b>	11.5	47.7	0	0	38.1	4.1	28.7
<b>2k</b>	15.2	49.7	0	0	48.5	50.4	2.0
<b>2l</b>	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.  $^1\text{H}$  NMR spectra were recorded in  $\text{CDCl}_3$  solutions, with  $\text{Me}_4\text{Si}$  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  $\text{C}_{12}\text{H}_6\text{Cl}_2\text{FN}_3\text{OS}_2$ : C 39.81, H 1.71, N 11.54 and **1e** %C 46.68, %H 2.28, %N 13.61, calcd. for  $\text{C}_{12}\text{H}_7\text{ClN}_3\text{OS}_2$ : 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 graminearum*, *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<sub>2</sub> (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<sub>2</sub>O 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<sub>3</sub> × H<sub>2</sub>O. 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<sup>-1</sup>, <sup>1</sup>H 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<sup>-1</sup>, <sup>1</sup>H 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<sub>3</sub>, 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<sup>-1</sup>, <sup>1</sup>H NMR δ 7.87 (2H, m, aromatic), 7.39 (2H, m, aromatic), 6.93 (1H, s, thiazole), 4.09 (2H, m, -CH<sub>2</sub>-). 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  $\text{cm}^{-1}$ ,  $^1\text{H NMR}$   $\delta$  7.97 (1H, s, aromatic), 7.81 (1H, s, aromatic), 7.26 (1H, s, thiazole), 4.20 (2H, s,  $-\text{CH}_2-$ ). 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  $\text{cm}^{-1}$ ,  $^1\text{H NMR}$   $\delta$  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).

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*Samples Availability:* Not available.