Synthesis and Evaluation of 2-Imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones and Their 5-Arylidene Derivatives as Potential Fungicides†

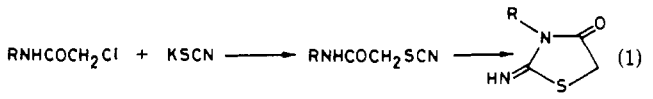
Ram Lakhan* and Ram Lakhan Singh

Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi 221005, India

A series of new 2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones and their 5-arylidene derivatives have been synthesized from 2-amino-4-arylthiazoles as starting materials. The reaction mechanism has also been critically examined. Of all the synthetic compounds tested against *Trichoderma harzianum* and *Curvularia lunata*, two of them, namely 2-imino-3-(4-*p*-chlorophenylthiazol-2-yl)-4-thiazolidinone and 5-benzylidine-2-imino-3-(4-*p*-tolylthiazol-2-yl)-4-thiazolidinone, exhibited the most potent fungicidal effect.

INTRODUCTION

Over the years, 4-thiazolidinones have enjoyed a prominent place in heterocyclic chemistry largely due to the wide-ranging biological activity demonstrated by this class of compounds (Bhargava and Chaurasia, 1969; Mousseron, 1972; Lakhan et al., 1982, 1984a, 1987; Troutman and Long, 1948). An overview of the chemistry of this ring system has been given in depth recently (Newkome and Nayak, 1979). A convenient method of synthesis involves the 2,3 bond formation. Thus, 2-haloacetamides react with potassium thiocyanate to give the intermediate 2-(thiocyanato)acetamides, which cyclize in anhydrous acetone to the corresponding 2-imino-4-thiazolidinones (eq 1) (Schröpl and Pohloudek-Fabini, 1968; Ebetino and Gever, 1962).



(1)

Moreover, it is well-known that the thiazole moiety has significant biological activity in its own right (Lakhan and Singh, 1984b; Bhargava et al., 1981, 1982). We have therefore aimed at synthesizing a series of thiazol-2-yl-substituted 4-thiazolidinones (**3**) and their 5-arylidene derivatives (4) and evaluating them as potential agricultural fungicides.

The target compounds (**3** and **4**) were obtained from 2-amino-4-arylthiazoles as the key intermediate (Scheme I). The interaction of substituted acetophenones, thiourea, and iodine by literature methods (Dodson and King, 1945; King and Hlavacek, 1950; Bhargava et al., 1982; Lakhan and Singh, 1984b) gave 2-amino-4-arylthiazoles, which were reacted with chloroacetyl chloride to afford the corresponding 2-chloroacetamido-4-arylthiazoles (**1**). The latter on treatment with potassium thiocyanate in refluxing acetone gave the related 4-thiazolidinones (**3**). Condensation of **3** with different aromatic aldehydes occurred at the reactive methylene group present at position 5 of the thiazolidinone ring and resulted in the formation of 5-arylidene-2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (**4**).

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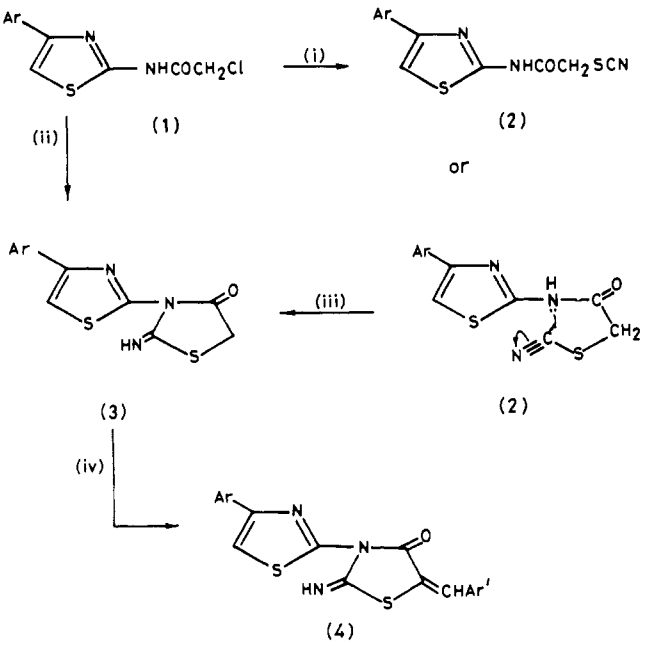
Scheme I[a]



[a] Reagents: (i) and (ii) KSCN, Me_2CO, boil, 3 h; (iii) DMF, 150–160 °C, 4 h; (iv) Ar'CHO, xylene, pyridine, 150–160 °C, 3 h.

The fungicidal activity of **3** and **4** was seen on *Trichoderma harzianum* and *Curvularia lunata* by food poison technique. *T. harzianum* is an established mycoparasite that is being used in biological control of some plant pathogens (Baker and Cook, 1979); *C. lunata* infects some important crop plants in India (Butler and Bisby, revised by Vasudeva, 1960). The activity of the compounds has been compared with that of a commercially used fungicide, Cuman (80% Ziram).

EXPERIMENTAL PROCEDURES

General Methods. All melting points were taken in open capillaries with a Gallenkamp apparatus and are uncorrected. The purity of compounds was routinely checked by TLC using silica gel G (Merck). Elemental analyses (C, H, and N) were carried out with a Coleman analyzer. The IR spectra were recorded on Perkin-Elmer 257 and 783 grating spectrophotometers and ^1H NMR spectra on JEOL FX 90Q Fourier-transform spectrometer as $CDCl_3$ or DMSO-d_6 solutions with Me_4Si as an internal reference.

2-Amino-4-(2,4-dimethoxyphenyl)thiazole. A mixture of 2,4-dimethoxyacetophenone (18.0 g, 0.1 mol), thiourea (15.2 g,

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Table I. 2-Imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (3)

no.	substituent Ar	% yield	mp, °C	formula[a]	% carbon found	% carbon calcd	% nitrogen found	% nitrogen calcd	characteristic IR peaks, cm^{-1}
3a	C_6H_5	62	240–241	$C_{12}H_9N_3OS_2$	52.5	52.4	15.2	15.3	3350, 1710, 1560, 1150
3b	p-$CH_3C_6H_4$	70	200–201	$C_{13}H_{11}N_3OS_2$	54.0	54.0	14.3	14.5	3350, 1710, 1630, 1560
3c	p-ClC_6H_4	65	290–291	$C_{12}H_8ClN_3OS_2$	46.8	46.5	13.6	13.6	3400, 1700, 1590, 1530
3d	p-BrC_6H_4	55	300–301	$C_{12}H_8BrN_3OS_2$	40.9	40.7	11.6	11.9	3350, 1710, 1620, 1560
3e	m-$CH_3OC_6H_4$	58	235–236	$C_{13}H_{11}N_3O_2S_2$	51.2	51.1	13.8	13.8	3400, 1660, 1550, 1500
3f	p-$CH_3OC_6H_4$	65	262–263	$C_{13}H_{11}N_3O_2S_2$	51.0	51.1	13.9	13.8	3120, 1735, 1610, 1575
3g	m-$O_2NC_6H_4$	60	244–246	$C_{12}H_8N_4O_3S_2$	45.2	45.0	17.3	17.5	3300, 1690, 1580, 1530
3h	p-$O_2NC_6H_4$	75	188–190	$C_{12}H_8N_4O_3S_2$	44.9	45.0	17.6	17.5	3310, 1700, 1580, 1560
3i	2,4-$(CH_3O)_2C_6H_3$	60	183–184	$C_{14}H_{13}N_3O_3S_2$	49.8	50.1	12.3	12.5	3400, 1720, 1600, 1560

[a] Satisfactory analyses for hydrogen and sulfur were also obtained.

Table II. 5-Arylidene-2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (4)

no.	substituents Ar	substituents Ar′	% yield	mp, °C	formula[a]	% carbon found	% carbon calcd	% nitrogen found	% nitrogen calcd	characteristic IR peaks, cm^{-1}
4a	C_6H_5	C_6H_5	72	289–291	$C_{19}H_{13}N_3OS_2$	62.7	62.6	11.5	11.6	3300, 1700, 1580, 1150
4a′	C_6H_5	p-$CH_3OC_6H_4$	65	257–258	$C_{20}H_{15}N_3O_2S_2$	61.7	61.6	10.6	10.7	3300, 1690, 1570, 1140
4b	p-$CH_3C_6H_4$	C_6H_5	58	283–284	$C_{20}H_{15}N_3OS_2$	63.4	63.7	11.4	11.1	3250, 1715, 1560, 1170
4c	p-ClC_6H_4	p-$CH_3OC_6H_4$	52	303–304	$C_{20}H_{14}ClN_3O_2S_2$	56.3	56.1	10.0	9.8	3300, 1710, 1580, 1160
4d	p-BrC_6H_4	p-$CH_3OC_6H_4$	78	263–265	$C_{20}H_{14}BrN_3O_2S_2$	50.6	50.8	9.0	8.9	3350, 1700, 1570, 1150
4e	m-$CH_3OC_6H_4$	C_6H_5	75	231–232	$C_{20}H_{15}N_3O_2S_2$	61.0	61.1	10.9	10.7	3350, 1720, 1580, 1150
4f	p-$CH_3OC_6H_4$	C_6H_5	60	222–223	$C_{20}H_{15}N_3O_2S_2$	61.4	61.1	10.6	10.7	3350, 1730, 1590, 1190
4g	m-$O_2NC_6H_4$	p-$CH_3OC_6H_4$	73	322	$C_{20}H_{14}N_4O_4S_2$	54.9	54.8	12.7	12.8	3350, 1700, 1590, 1150
4h	p-$O_2NC_6H_4$	C_6H_5	55	271	$C_{19}H_{12}N_4O_3S_2$	55.7	55.9	13.9	13.7	3200, 1720, 1590, 1160
4h′	p-$O_2NC_6H_4$	p-$CH_3OC_6H_4$	75	264–265	$C_{20}H_{14}N_4O_4S_2$	55.0	54.8	12.6	12.8	3350, 1710, 1590, 1160

[a] Satisfactory analyses for hydrogen and sulfur were also obtained.

0.2 mol), and iodine (25.0 g, 0.2 mol) was heated in a water bath with occasional shaking for 8 h. The solid obtained was triturated with ether to remove unreacted 2,4-dimethoxyacetophenone. It was further washed with aqueous sodium thiosulfate to remove the excess iodine and then with water. The crude product was dissolved in hot water and 2-amino-4-(2,4-dimethoxyphenyl)-thiazole was precipitated by the addition of ammonia. Recrystallization from ethanol–benzene (3:1) gave 70% yield as brown crystals: mp 102 °C [lit. (Societe de Recherches Industrielles, 1968) mp 102 °C]; IR ν_{max}^{Nujol} 3450, 3260, 1620, 1590, 1520 cm^{-1}; ^1H NMR $\delta_{Me_4Si}^{CDCl_3}$ 3.62 and 3.70 (two singlets, 3 H each, two OCH_3 groups), 5.52 (broad, 2 H, NH_2), 6.92–7.84 (m, 4 H, aromatics). Anal. Calcd for $C_{11}H_{12}N_2O_2S$: N, 11.9. Found: N, 12.0.

Other 2-amino-4-arylthiazoles were prepared by known methods (loc. cit.).

2-Chloroacetamido-4-(2,4-dimethoxyphenyl)thiazole (1i). To a chilled solution of 2-amino-4-(2,4-dimethoxyphenyl)thiazole (9.4 g, 0.04 mol) in dry benzene (50 mL) was added chloroacetyl chloride (5.2 g, 0.046 mol) dissolved in dry benzene (20 mL) dropwise with vigorous stirring. When the addition was complete, the reaction mixture was refluxed on a water bath at 80 °C for 3 h. Benzene and excess chloroacetyl chloride were removed by distillation. The residue was washed with 5% sodium hydrogen carbonate followed by water. The crude product was dried and recrystallized from ethanol to give colorless crystals: mp 126–127 °C (65% yield); IR ν_{max}^{Nujol} 3400, 1650, 1550, 1500, 1100 cm^{-1}. Anal. Calcd for $C_{13}H_{13}ClN_2O_3S$: N, 9.0; S, 10.2. Found: N, 9.1; S, 10.0.

Other 2-chloroacetamido-4-arylthiazoles (**1a–h**) were prepared according to literature methods (Sharma, 1966; Bhargava et al., 1982; Lakhan and Singh, 1984b).

2-Imino-3-[4-(*p*-methoxyphenyl)thiazol-2-yl]-4-thiazolidinone (3f). A mixture of 2-chloroacetamido-4-(*p*-methoxyphenyl)thiazole (**1f**; 4.0 g, 0.014 mol), potassium thiocyanate (2.0 g, 0.02 mol), and dry acetone (50 mL) was refluxed on a water bath for 3 h. Excess acetone was distilled off, and the residue was agitated with water (40 mL). The solid product was filtered under suction, washed with water, and dried. It was crystallized from ethanol to afford colorless needles: mp 262–263 °C (65% yield); IR ν_{max}^{Nujol} 3120, 1735, 1700, 1610, 1575, 1250, 745 cm^{-1}; ^1H NMR $\delta_{Me_4Si}^{Me_2SO\text{-}d_6}$ 3.75 (s, 3 H, OCH_3), 4.00 (s, 2 H, $>CH_2$), 6.75–7.90 (m, 5 H, aromatics), 9.62 (broad, 1 H, >N*H*). Anal. Calcd for $C_{13}H_{11}N_3O_2S_2$: C, 51.1; H, 3.6; N, 13.8; S, 21.0. Found: C, 51.0; H, 3.8; N, 13.9; S, 21.2.

Table III. Fungicidal Activity Results of 2-Imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (3)[a]

no.	substituent Ar	% inhibition of *T. harzianum* 1000 ppm	% inhibition of *T. harzianum* 200 ppm	% inhibition of *C. lunata* 1000 ppm	% inhibition of *C. lunata* 200 ppm
3a	C_6H_5	62	48	64	43
3b	p-$CH_3C_6H_4$	56	34	100	45
3c	p-ClC_6H_4	100	100	100	100
3d	p-BrC_6H_4	83	45	100	57
3e	m-$CH_3OC_6H_4$	60	58	80	71
3f	p-$CH_3OC_6H_4$	68	66	67	60
3g	m-$O_2NC_6H_4$	64	46	100	93
3h	p-$O_2NC_6H_4$	65	33	100	100
3i	2,4-$(CH_3O)_2C_6H_3$	100	51	100	79
cuman[b] (80% Ziram)		32 (40)	14 (17.5)	60 (75)	52 (65)

[a] Medium: Czapek's agar. Time: 5 days. Temperature: 25 ± 1 °C. [b] Values in parentheses denote the extrapolated percentage inhibition of this commercial fungicide for 100% Ziram content.

Similarly, other 2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (**3a–h**) were also prepared. Their characterization data are recorded in Table I.

Reaction of 2-Chloroacetamido-4-(2,4-dimethoxyphenyl)-thiazole with Potassium Thiocyanate: Formation of 2-(Thiocyanato)acetamido-4-(2,4-dimethoxyphenyl)thiazole (2i). A mixture of 2-chloroacetamido-4-(2,4-dimethoxyphenyl)thiazole (**1i**; 4.0 g, 0.013 mol), potassium thiocyanate (1.94 g, 0.02 mol), and dry acetone (50 mL) was heated under reflux on a water bath for 6 h. The product was worked up as described above, and the crude material was crystallized from ethanol to give 3.0 g of colorless crystals: mp 149–150 °C (70% yield); IR ν_{max}^{Nujol} 3230, 2050, 1720, 1630, 1590 cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_3S_2$: C, 50.1; H, 3.9; N, 12.5; S, 19.1. Found: C, 50.2; H, 4.0; N, 12.3; S, 19.0.

Thermal Cyclization of 2-(Thiocyanato)acetamido-4-(2,4-dimethoxyphenyl)thiazole: Formation of 2-Imino-3-[4-(2,4-dimethoxyphenyl)thiazol-2-yl]-4-thiazolidinone (3i). Finely powdered 2-(thiocyanato)acetamido-4-(2,4-dimethoxyphenyl)-thiazole (**2i**) (2.5 g) suspended in 25 mL of dimethylformamide was refluxed in an oil bath at 150–160 °C for 4 h. The solvent was removed by distillation under vacuum and the crude product crystallized from ethanol to give colorless crystals of the expected

Table IV. Fungicidal Activity Results of 5-Arylidene-2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (4)[a]

no.	substituent Ar	substituent Ar′	% inhibition of fungi at given dilutions: *T. harzianum* 1000 ppm	*T. harzianum* 200 ppm	*C. lunata* 1000 ppm	*C. lunata* 200 ppm
4a	C_6H_5	C_6H_5	76	54	73	54
4a′	C_6H_5	p-$CH_3OC_6H_4$	34	18	58	36
4b	p-$CH_3C_6H_4$	C_6H_5	100	100	100	100
4c	p-ClC_6H_4	p-$CH_3OC_6H_4$	23	17	67	51
4d	p-BrC_6H_4	p-$CH_3OC_6H_4$	21	12	56	33
4e	m-$CH_3OC_6H_4$	C_6H_5	80	61	78	64
4f	p-$CH_3OC_6H_4$	C_6H_5	66	42	78	56
4g	m-$O_2NC_6H_4$	p-$CH_3OC_6H_4$	57	34	56	38
4h	p-$O_2NC_6H_4$	C_6H_5	67	46	64	40
4h′	p-$O_2NC_6H_4$	p-$CH_3OC_6H_4$	66	24	44	31
cuman[b]			32	14	60	52
(80% Ziram)			(40)	(17.5)	(75)	(65)

[a] Medium: Czapek's agar. Time: 5 days. Temperature: 25 ± 1 °C. [b] Values in parentheses denote the extrapolated percentage inhibitions of this commercial fungicide for 100% Ziram content.

thiazolidinone: mp 183–184 °C (60% yield); IR ν_{max}^{Nujol} 3400, 1720, 1600, 1560, 1170 cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3O_3S_2$: C, 50.1; H, 3.9; N, 12.5; S, 19.1. Found: C, 49.8; H, 3.9; N, 12.3; S, 19.5.

An attempted thermal cyclization of 2-(thiocyanato)acetamido-4-(2,4-dimethoxyphenyl)thiazole (**2i**) in boiling 3-pentanone (bp 102 °C) as solvent failed to give the desired 4-thiazolidinone. However, the starting material was isolated quantitatively.

5-Benzylidene-2-imino-3-[4-(*p*-methoxyphenyl)thiazol-2-yl]-4-thiazolidinone (4f). A mixture of 2-imino-3-[4-(*p*-methoxyphenyl)thiazol-2-yl]-4-thiazolidinone (**3f**; 0.9 g, 0.027 mol), benzaldehyde (0.6 g, 0.056 mol), xylene (10 mL), and pyridine (4 drops) was heated under reflux in a paraffin bath at 150–160 °C for 3 h. The solvent was removed by distillation, and the residue was washed with hot water. It was crystallized from ethanol to form brown crystals: mp 222–223 °C (60% yield); IR ν_{max}^{Nujol} 3350, 1730, 1590, 1520, 1190, 840 cm^{-1}. Anal. Calcd for $C_{20}H_{15}N_3O_2S_2$: C, 61.1; H, 3.8; N, 10.7; S, 16.3. Found: C, 61.4; H, 3.9; N, 10.6; S, 16.4.

Similarly, other 2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (**3**) were condensed with benzaldehyde and/or *p*-anisaldehyde. The characterization data of the products (**4**) are recorded in Table II.

RESULTS AND DISCUSSION

The interaction of 2-chloroacetamido-4-arylthiazoles (**1**) with potassium thiocyanate for 3 h in boiling acetone results in the nucleophilic displacement of chloride by the thiocyanate ion forming 2-(thiocyanato)acetamido-4-arylthiazoles (**2**) as the intermediates. The latter with a nucleophilic amino nitrogen favorably situated with respect to the electrophilic cyano group undergo intramolecular cyclization in situ almost invariably. Thus, the 2-imino-3-(4-arylthiazol-2-yl)-4-thiazolidinones (**3**) are isolated as the end products in all cases with one exception (i.e., with Ar = 2,4-dimethoxyphenyl).

Under identical conditions the reaction of 2-chloroacetamido-4-(2,4-dimethoxyphenyl)thiazole (**1i**) with KSCN gives 2-(thiocyanato)acetamido-4-(2,4-dimethoxyphenyl)-thiazole (**2i**) in about 70% yield. The same product was isolated when the heating period was prolonged from 3 to 6 h or the reaction temperature was raised by replacing boiling acetone (bp 56 °C) with 3-pentanone (bp 102 °C). The 2-(thiocyanato)acetamide derivative cyclizes into the corresponding 4-thiazolidinone (**3i**) by heating in a highly polar aprotic solvent, DMF, at 150–160 °C for 4 h. The isolation of 2-(thiocyanato)acetamido-4-(2,4-dimethoxyphenyl)thiazole (**2i**) and its conversion into related 4-thiazolidinone (**3i**) by intramolecular cyclization confirm the actual intermediacy of the 2-(thiocyanato)acetamide derivatives in the formation of the 4-thiazolidinones (**3**).

The reactive methylene group of **3** has been successfully condensed with aromatic aldehydes in the presence of pyridine, yielding the related 5-arylidene derivatives (**4**).

The structure of the intermediates and products has been established on the basis of microanalyses and spectral data. The IR spectrum of 2-(thiocyanato)acetamido-4-(2,4-dimethoxyphenyl)thiazole (**2i**) in Nujol shows absorption bands at 3230 for N–H stretching, a strong band at 2050 cm^{-1} for SCN stretching, at 1720 cm^{-1} for carbonyl stretch, and at 1630 and 1590 cm^{-1} for the aromatic rings.

Similarly, the IR spectrum of 2-imino-3-[4-(*p*-tolylthiazol)-2-yl]-4-thiazolidinone (**3b**) in Nujol shows absorption bands at 3350 cm^{-1} for N—H stretch, at 1710 cm^{-1} (C=O stretch), and at 1630 and 1560 cm^{-1} for the aromatic rings. Its ^1H NMR spectrum in DMSO-d_6 displays a singlet of 3 H intensity at δ 2.40 for the methyl protons. Another singlet is observed at δ 3.92 (2 H) for the methylene protons attached to C-5 of the thiazolidinone ring, and a multiplet is observed between 6.98 and 7.92 for the five aromatic protons. A broad signal is displayed for one proton at δ 9.52 for the imino group.

Fungicidal Activity. The synthesized compounds **3** and **4** were screened for their potential fungicidal activity against the agricultural fungi *T. harzianum* and *C. lunata* by the agar growth food poison technique at two dilutions (1000 and 200 ppm). The percentage inhibition of growth by an inhibitor at a particular dilution is determined by comparison with growth in controls, i.e., untreated Petri dishes. The experiments were performed in triplicate for each dilution of the test compounds and replicates of the controls, and the results are shown in Tables III and IV.

From the screening results it is evident that overall the compounds are remarkably more fungicidal than the standard chosen. In particular **3c** (Table III) and **4b** (Table IV) are 100% active fungicides at both dilutions against the experimental fungi. The introduction of benzylidene and *p*-methoxybenzylidene groups at position 5 of the 4-thiazolidinone ring shows mixed effects with regard to activity. Generally the fungicidal activity decreases, having some marginal cases where the activity remains more or less similar to that of the parent 4-thiazolidinones themselves (e.g., **4e** and **4f**). On the other hand, in two instances (**4a** and **4b**) the fungicidal activities are considerably enhanced for the 5-benzylidene-4-thiazolidinones. It is also noteworthy that the compounds are more fungicidal against *C. lunata* than *T. harzianum*, a trend also observed with the standard fungicide Cuman.

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