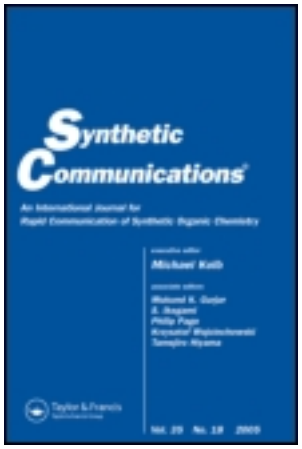

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SYNTHESIS OF NOVEL 2-IMINOTHIAZOLIDIN-4-ONES

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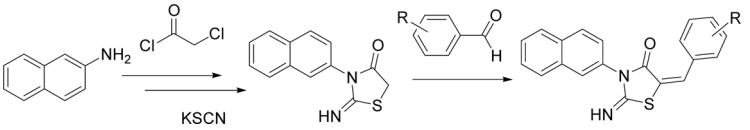
GRAPHICAL ABSTRACT



Abstract *Thiazolidin-4-ones are known to exhibit diverse biological activities such as antimicrobial, anticancer, antidiarrheal, anticonvulsant, antidiabetic, antihistaminic, and antifungal activities. In the present investigation, a series of 2-haloacetamides was prepared by reacting chloroacetyl chloride with amines in dry benzene under reflux conditions. The formed 2-haloacetamides reacted with potassium thiocyanate in refluxing dry acetone to afford new 2-iminothiazolidin-4-ones. The 5-arylidene-2-imino-3 (napthalen-2yl)-thiazolidin-4-ones were prepared by condensing 2-iminothiazolidin-4-ones with substituted benzaldehydes. All the products were characterized by infrared, mass, and ^{1}H and ^{13}C NMR techniques.*

Keywords Arylidene; 2-iminothiazolidinone; thiazolidin-4-one

INTRODUCTION

Heterocycles bearing nitrogen and sulfur constitute the core structure of a number of biologically interesting compounds. Thiazoles are one of the most intensively investigated classes of aromatic five-membered heterocycles, which display a broad spectrum of biological activities.[1–3] Thiazolidin-4-ones, a saturated form of thiazoles with a carbonyl group on the fourth carbon, have been considered a magic moiety (wonder nucleus), which possess almost all types of biological activities such as antifungal, antimycobacterial, antiviral, in vitro growth-inhibition against certain microbes, antibacterial, anti-inflammatory, analgesic, antipyretic, anticonvulsant, anticancer, antiallergen, miticidal, nematocidal or insecticidal, hypnotic, and in vitro antitoxoplasma gondii and herbicide activities.[4–11] Overviews of their synthesis, properties, reaction, and applications have been published.[12,13] 5-Arylidene derivatives of thiazolidin-4-one are also known to exhibit diverse bioactivities such as antidiarrheal,[14] anticonvulsant,[15]

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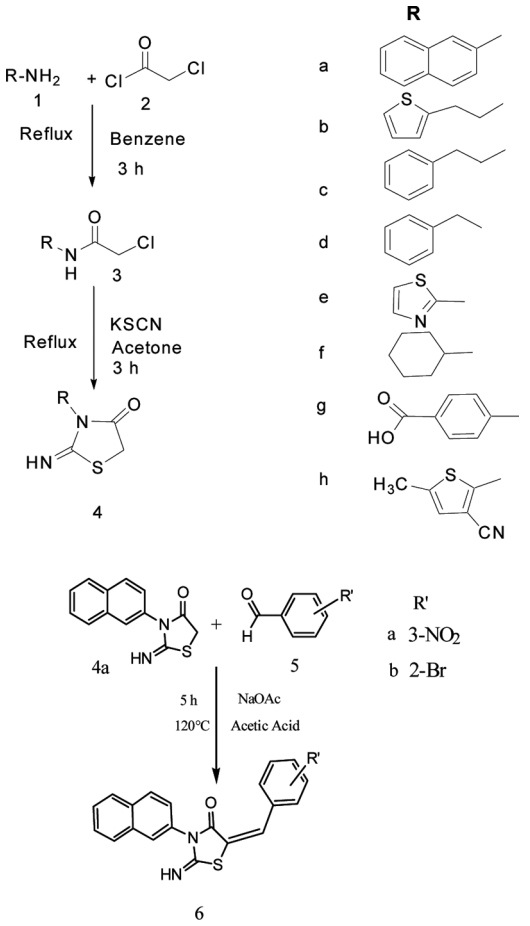
antimicrobial,[16] antihistaminic,[17] anticancer,[18] anti-HIV,[19] and antiischemic activities.[20] All these facts and our interest in the synthesis of new biologically active heterocyclic compounds[21,22] prompted us to prepare new thiazolidin-4-ones. In this article, we present the synthesis and characterization of a new series of 2-imino-thiazolidin-4-ones.

RESULTS AND DISCUSSION

We synthesized a series of new 2-iminothiazolidin-4-ones **(4a–h)** and 5-arylidene derivatives of 2-imino-3-(naphthalene-2yl)thiazolidin-4-ones **(6a, b)** as per Scheme 1. The 2-iminothiazolidin-4-ones were synthesized via the key intermediate 2-chloroacetamides. The 2-chloroacetamides were formed by the reaction of primary amines with chloroacetyl chloride. The *N*-acylation can be achieved either by simply stirring the amine with the chloroacetyl chloride in a suitable solvent or by adding base. 2-Chloroacetamide derivatives **(3a–h)** were obtained by refluxing the primary amine ($R\text{-}NH_2$) **(1a–h)** and chloroacetyl chloride in dry benzene (where, R = 2-naphthyl, 2-thiophene-2-ethyl, phenethyl, benzyl, 2-thiazolyl, cyclohexyl, 4-benzoic acid, and 5-methylthiophen-2yl-3-carbonitrile).

The compounds **3a–h** on treatment with potassium thiocyanate in refluxing acetone afforded the target compound 2-imino-3-*N*-substituted-thiazolidin-4-ones (**4a–h**). During the course of the reaction, the 2-chloroacetamide reacts with the triatomic fragment (-SCN) and leads to the cyclized product. Initially, the nucleophile added to the CN bond generates intramolecularly cyclized 2-thiocyanato acetamides and then 2-iminothiazolidin-4-ones. The interaction of 2-chloroacetamide derivatives with thiocyanate ion is quite interesting and proceeds in two steps. The first step is the nucleophilic substitution, followed by spontaneous ring closure to form thiazolidinone. These 2-iminothiazolidin-4-ones are susceptible to hydrochloric acid; the latter hydrolyze the imino group to the carbonyl group. In the present process, the product is isolated in neutral condition and the imino group is retained. The reactive methylene group present at C-5 of 2-imino-3-(naphthalene-2-yl)thiazolidin-4-one **(4a)** was condensed with 3-nitro and 2-bromobenzaldehydes to yield the related 5-arylidene-2-iminothiazolidin-4-ones (**6a, b**). The condensation was carried out in acetic acid in the presence of anhydrous sodium acetate as catalyst. The reaction gave 90% yield with 3-nitrobenzaldehyde and 60% yield with 2-bromobenzaldehyde.

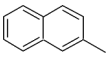
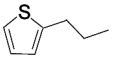
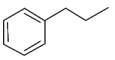
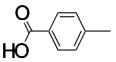
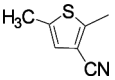
The formed 2-chloroacetamides **(3a–h)** were confirmed on the basis of infrared (IR) and mass spectral data. The IR spectrum exhibits a prominent band at $1630\,cm^{-1}$ for the amide carbonyl group. The cyclized product 2-iminothiazolidin-4-ones **(4a–h)** were characterized on the basis of IR, NMR, and mass spectral data. It is established that thiocyanate in the present reaction conditions cyclized intramoleculary and yielded only the 2-iminothiazolidinones and not 2-thiocyanatoacetamide, as evident from the absence of an IR band at $2150\,cm^{-1}$ for −CN stretching. The IR spectra of compound **4a–h** in KBr showed a band at $2915–2991\,cm^{-1}$ for −C-H stretching and at $1636–1713\,cm^{-1}$ for cyclic >C=O group. The ^1H NMR spectrum of compounds **4a–h** in



Scheme 1. Synthesis of 2-iminothiazolidin-4-one **(4a–h)** and 5-arylidene-2-imino-3-(naphthalene-2-yl) thiazolidin-4-ones **(6a, b)**.

$CDCl_3$/dimethylsulfoxide (DMSO) showed a singlet at δ 3.62−4.16 for two protons of the reactive methylene group and a broad signal at δ 6.05–12.0 for the imino group. In ^{13}C NMR the signals were observed at δ 34.8–41.1 for methylene carbons at the C-5 position and at δ 111.4–116.8 for the imino carbon at the C-2 position. The molecular ion peaks observed in the mass spectra of **4a–h** further proved the product formation. The IR spectra of compounds **6a** and **b** in KBr showed bands at 3421–3435 cm^{-1} for –NH, 2923–3057 for –CH, 1661–1720 for >C=O, and 1626 cm^{-1} for C=C stretching. The methine proton deshielded by the adjacent >C=O group was detected at δ 7.08–7.09, and a broad signal observed at δ8.02–11.95 for the imino group. Signals observed at δ 167.5–168.2 for >C=O group, δ 134.2–144.0 for =CH, and δ 116.0–116.4 for C=NH carbons in ^{13}C NMR. The mass spectra of compounds **6a** and **b** gave the corresponding molecular ion peaks, which further proved the product

Table 1. Physical constant and yield of the compounds **4a–h** and **6a, b**

Compound	Mol. formula	Subst. group	Mp (°C)	Yield (%)	Elemental analysis[a]		
					C	H	N
4a	$C_{13}H_{10}N_2OS$		219–221	60.35	63.33 (64.44)	4.08 (4.16)	10.99 (11.56)
4b	$C_9H_{10}N_2OS_2$		—	81.43	46.21 (47.76)	4.41 (4.45)	11.89 (12.38)
4c	$C_{11}H_{12}N_2OS$		59–62	75.28	59.92 (59.97)	5.32 (5.49)	12.55 (12.72)
4d	$C_{10}H_{10}N_2OS$		68–71	60.97	57.98 (58.23)	4.44 (4.89)	13.08 (13.58)
4e	$C_6H_5N_3OS_2$		189–193	74.88	36.12 (36.17)	2.52 (2.53)	21.03 (21.09)
4f	$C_9H_{14}N_2OS$		86–88	80.96	54.38 (54.52)	6.98 (7.12)	13.99 (14.13)
4g	$C_{10}H_8N_2O_3S$		292–294	60.44	48.94 (50.84)	3.32 (3.41)	11.37 (11.86)
4h	$C_9H_7N_3OS_2$		186–190	40.57	45.21 (45.55)	2.87 (2.97)	17.46 (17.71)
6a	$C_{20}H_{13}N_3O_3S$	2-NO_2	205–208	90.37	63.87 (63.99)	3.32 (3.49)	11.56 (11.19)
6b	$C_{20}H_{13}BrN_2OS$	2-Br	199–201	60.21	58.99 (58.69)	2.98 (3.20)	6.77 (6.84)

[a]Values within the parentheses are calculated.

formation. The physical constant and yield of the compounds **4a–h** and **6a** and **b** are given in Table 1.

EXPERIMENTAL

Melting points were determined in open capillaries and are not corrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-500 spectrometer operating at 400 MHz using $CDCl_3$/DMSO as solvents with Me_4Si as an internal reference. The Fourier transform (FT)–IR spectra were recorded on a Nicolet Avatar 360 FT-IR instrument using KBr pellets. Mass spectra (MS) were recorded on a Shimadzu GC-MS instrument. Elemental analysis were done on a Vario ELCHNOS analyzer. All products are purified by recrystalization. Column chromatography is performed on silica gel (60–120 mesh).

General Procedure for the Synthesis of Substituted 2-Haloacetamides (3)

A solution of appropriate (substituted heterocyclic, aryl or alkyl) primary amine (0.02 mol) in dry benzene (60 ml) was cooled to 0–5 °C. Chloroacetyl chloride (0.04 mol) 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% $NaHCO_3$ followed by a water workup. The crude product was dried and crystallized from ethanol to give corresponding 2-haloacetamides.

General Procedure for the Synthesis of 2-Imino-3(substituted)-thiazolidin-4-ones (4a–h)

A mixture of appropriate 2-haloacetamide (0.03 mol) and potassium thiocyanate (KSCN) (0.06 mol) in 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. Crude product was purified by column chromatography (silica gel) using 5% ethylacetate/chloroform mixture as eluent.

General Procedure for the Synthesis of 5-Arylidine-2-imino-3-(naphthalene-2-yl)-thiazolidin-4-ones (6a, b)

2-Imino-3-(naphthalene-2-yl)-thiazolidin-4-one (0.01 mol) and 3-nitro or 2-bromobenzaldehyde (0.02 mol) were added to a solution of anhydrous NaOAc (0.02 mol) in acetic acid (30 ml). The mixture was refluxed for 5 h at 120 °C and cooled to room temperature. The solid product was filtered from the mixture, washed with water, and dried. The crude product was purified by column chromatography (silica gel) by using 25% ethylacetate/hexane mixture as eluent.

Data

Compound 4a. ^{1}H NMR ($CDCl_3$): $\delta = 7.10$–7.85 (m, 7H, Ar-H), 3.8 (s, 2H, S-CH_2-), 7.9 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): $\delta = 116.82$ (C=NH), 122.95–148.48 (Ar-C), 34.82 (CH_2 ring), 160.34 (C=O). IR: 3421, 3287, 1720, 1626, 1508, 1400, 1370, 1020, 775 cm^{-1}; MS: base peak m/z: 168, M+ peak at m/z: 242.

Compound 4b. ^{1}H NMR ($CDCl_3$): $\delta = 6.85$–7.19 (m, 3H Ar-H), 6.78 (s, 1H, NH), 4.03 (s, 2H, S-CH_2-), 3.05 (t, 2H, CH_2), 3.54 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$): $\delta = 124.18$–140.59 (Ar-C), 169.96 (C=O), 41.10 (CH_2 ring), 42.62 (CH_2), 29.62(CH_2); IR: 3290, 2934, 1660, 1549, 1435, 1217, 847, 702 cm^{-1}; MS: base peak m/z: 110, M+ peak at m/z: 226.

Compound 4c. ^{1}H NMR ($CDCl_3$): $\delta = 7.18$–7.34 (m, 5H, Ar-H), 6.33(s, 1H, NH), 3.62 (s, 2H, S-CH_2-), 3.53 (t, 2H, CH_2), 2.83 (t, 2H, CH_2); ^{13}C NMR ($CDCl_3$): 126.73–138.26 (Ar-C), 111.61 (C=NH), 165.09 (C=O), 36.80 (CH_2), 41.44 (CH_2), 35.30 (CH_2); IR: 3272, 3102, 2870, 1644, 1573, 1410, 1315, 1150, 1025, 752, 695 cm^{-1}; MS: base peak m/z: 103, M+ peak at m/z: 220.

Compound 4d. ^{1}H NMR ($CDCl_3$): $\delta = 7.26$–7.36 (m, 5H, Ar-H), 6.78 (s, 1H, NH), 4.42 (s, 2H, CH_2), 3.64 (s, 2H, S-CH_2-); ^{13}C NMR ($CDCl)_3$: $\delta = 127.87$–136.96 (m, 5H, Ar-C), 111.47 (C=NH), 164.96 (C=O), 44.37 (CH_2), 36.75 (CH_2); IR: 3281, 3087, 1645, 1561, 1427, 1317, 1146, 1024, 742, 698 cm^{-1}; MS: base peak m/z: 43, M + peak at m/z: 206.

Compound 4e. ^{1}H NMR (DMSO): δ = 7.38–7.59 (m, 2H, Ar-H), 12.0 (s, 1H, NH), 4.00 (s, 2H, S-CH_2-); ^{13}C NMR (DMSO): δ = 139.80, 169.34, 173.98 (Ar-C), 116.43 (C=NH), 162.34 (C=O), 34.82 (CH_2-ring); IR: 3082, 2964, 1712, 1599, 1491, 1398, 1325, 1138, 800 cm^{-1}; MS: base peak m/z: 125, M+ peak at m/z: 199.

Compound 4f. ^{1}H NMR ($CDCl)_3$: δ = 1.16–1.97 (m, 10H, cyclohexyl-H), 3.73 (m, 1H,cyclohexyl-H), 6.05 (s, 1H, NH), 3.68 (s, 2H, S-CH_2-); ^{13}C NMR ($CDCl_3$): δ = 24.74–49.43 (cyclohexyl-C), 111.83 (C=NH), 164.16 (C=O), 37.08 (CH_2-thiazole ring); IR: 3269, 3098, 2934, 1636, 1571, 1447, 1342, 1085, 698, 557 cm^{-1}; MS: base peak m/z: 117, M+ peak at m/z: 199.

Compound 4g. ^{1}H NMR (DMSO): δ = 7.40–7.96 (m, 4H, Ar-H), 10.7 (s, 1H, NH), 4.16 (s, 2H, S-CH_2-); ^{13}C NMR (DMSO): δ = 118.59–142.29 (Ar-C), 112.75 (C=NH), 164.82 (C=O), 37.08 (CH_2), 166.87 (COOH); IR: 3271, 2926, 1680, 1600, 1540, 1421, 1287, 1174, 858, 771, 710, 542 cm^{-1}; MS: base peak m/z: 69, M+ peak at m/z: 236.

Compound 4h. ^{1}H NMR (DMSO): δ = 7.13 (s, 1H, Ar-H), 9.07 (s, 1H, NH), 3.88 (s, 2H S-CH_2-), 2.47 (s, 3H, CH_3); ^{13}C NMR (DMSO): δ = 113.19, 138.86, 143.72 (Ar-C), 113.33 (C=NH), 116.30 (C≡N), 164.55 (C=O), 37.632 (CH_2-ring), 90.05 (C-CN), 15.70 (CH_3); IR: 3333, 3182, 1667, 1546, 1418, 1355, 1151, 763 cm^{-1}; MS: base peak m/z: 165, M+ peak at m/z: 237.

Compound 6a. ^{1}H NMR ($CDCl_3$): δ = 7.45–7.58 (m, 4H, naphthyl-H), 7.68–7.73 (m, 3H, naphthyl-H), 7.08 (d, 1H, benzylidene-H), 8.21 (s, 1H, NH), 7.86 (d, 1H, phenyl), 7.98 (d, 1H, phenyl), 8.12 (d, 1H, phenyl); ^{13}C NMR ($CDCl_3$): δ = 151.39 (IPSO, naphthyl), 148.42 (IPSO, phenyl-C), 116.04 (C=NH), 168.22 (C=O), 144.08 (benzylidene =CH), 123.29–135.49 (Ar-C); IR: 3432, 3052, 2958, 1719, 1651, 1526, 1431, 1348, 1195, 1015, 806, 735 cm^{-1}; MS: base peak 168, M+ peak at m/z: 375.

Compound 6b. ^{1}H NMR ($CDCl_3$): δ = 7.09 (d, 1H, benzylidene-H), 7.119–7.34 (m, 3H, naphthyl-H), 7.41–7.53 (m, 3H, naphthyl-H), 7.59–7.92 (m, 4H, phenyl-H), 8.02 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 152.57 (IPSO, naphthyl-C), 143.25 (IPSO, phenyl-C), 134.28 (benzylidene =CH), 167.55 (C=O), 116.49 (C=NH), 123.16–133.76 (Ar-C). IR: 3435, 2926, 1694, 1661, 1573, 1473, 1432, 1222, 1153, 1014, 808, 781, 757 cm^{-1}; MS: base peak 168, M + peak at m/z: 410.

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