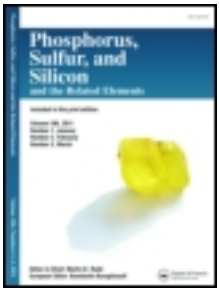

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Synthesis of Some Novel 5-(Arylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one Derivatives

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*Treatment of 2-aminopyridine (**1**) with chloroacetyl chloride in dry benzene gave 2-chloro-N-(pyridin-2-yl)acetamide (**3**), which on further reaction with potassium thiocyanate gave 2-imino-3-(pyridin-2-yl)thiazolidin-4-one (**4**) as an intermediate compound for the synthesis of pyridin-2-yl substituted 2-imino-thiazolidine-4-one derivatives. Cyclocondensation reaction of (**4**) with a series of aromatic aldehydes gave 5-arylidene derivatives of pyridin-2-yl substituted 2-imino-thiazolidine-4-ones **5a–j**. ^{1}H and ^{13}C NMR spectroscopy, as well as elemental analyses, were used for the identification of these new compounds.*

Keywords Benzylidene; pyridine; thiazolidin-4-one

INTRODUCTION

The thiazolidin-4-one nucleus has been reported to possess broad and diverse pharmacological activities.[1–9] In view of the many biological activities of thiazolidin-4-ones, their synthesis has attracted considerable attention in recent years. Several modified preparative methods have been reported for the preparation of simple thiazoles.[6–10] However, to date there have been no reports on the synthesis of derivatives with the thiazolidin-4-one nucleus attached to a pyridine ring, which may show interesting biological activities. Due to incessant interest in the chemistry of substituted thiazolidin-4-ones, substantial attention should be paid to the synthesis of novel pyridin derivatives, particularly of pyridin-2-yl substituted 2-imino-thiazolidin-4-one derivatives. In view of these reports, we present in this article the synthesis of some novel 5-arylidene derivatives of pyridin-2-yl substituted 2-iminothiazolidin-4-ones.

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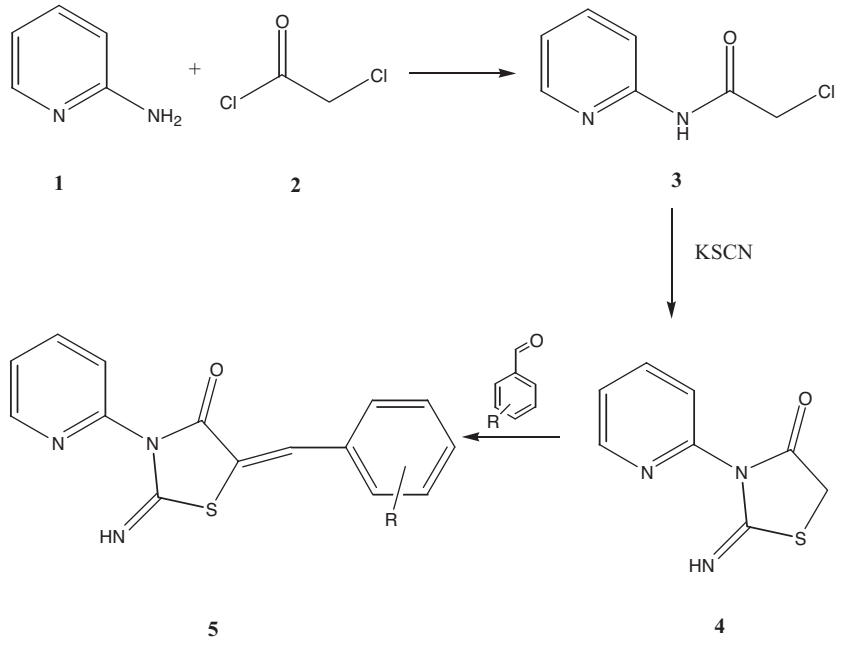
RESULTS AND DISCUSSION

2-Aminopyridine was reacted with chloroacetyl chloride to give 2-chloro-*N*-(pyridin-2-yl)acetamide **3**. Reaction of **3** with potassium thiocyanate under reflux conditions afforded 2-imino-3-(pyridin-2-yl) thiazolidin-4-one **4** as an intermediate for the synthesis of 5-(arylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one derivatives **5** as shown in Scheme 1.



1 **2** **3** **4** **5**

5	R	5	R
a	H	**f**	4-Br
b	2-NO_2	**g**	2-Cl
c	4-NO_2	**h**	4-Cl
d	4-OCH_3	**i**	5-Br-2-OH
e	4-CH_3	**j**	4-OH

SCHEME 1

The yields of the products after recrystallization from ethanol were in the order of 54%–80%. The ^{1}H and ^{13}C NMR spectra as well as the elemental analyses data of all synthesized compounds are consistent with the expected structures. The ^{1}H NMR spectra of the 5-(arylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one derivatives **5** consist of a multiplet and a singlet resulting from the aromatic protons and the NH

group, respectively. The signal of the =CH– moiety appears in the same range as those of the aromatic protons.

EXPERIMENTAL

Melting points were determined with an electrothermal digital melting point apparatus Mettler Toledo Type FP62 and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance (300 MHz) spectrometer in DMSO-d_6 solutions using TMS as internal standard. Microanalyses were performed with an Elemental Analyzer (Elemental, Vario EL III) at the Arak University. Reactions were monitored by thin layer chromatography using silica gel F_{254} aluminum sheets (Merck). All chemicals used were reagent grade and were used without further purification.

Preparation of 2-Chloro-*N*-(pyridin-2-yl)acetamide (3)

Chloroacetyl chloride (0.02 mol, 1.6 mL) was slowly added to a solution of 2-aminopyridine (0.01 mol, 0.94 g) in dry benzene, which was kept at 0–5°C. The reaction mixture was refluxed for 5 h, and the excess of solvent was removed under vacuum. The residue was washed with 5% aqueous solution of $NaHCO_3$ (20 mL) and then with water (20 mL). The crude product was recrystallized from ethanol (15–20 mL) to give pink crystals. Yield: 88% (1.5 g), mp 124–126°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 4.35$ (s, 2H, CH_2), 7.12–8.34 (m, 4H, arom-H), 10.79 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 43.9$, 114.0, 120.3, 138.8, 148.4, 151.8, 165.9.

Preparation of 2-Imino-3-(pyridine-2-yl)thiazolidin-4-one (4)

A mixture of 2-chloro-*N*-(pyridin-2-yl)acetamide **3** (0.01 mol, 1.71 g), potassium thiocyanate (0.02 mol, 1.94 g), and acetone (30 mL) was refluxed for 8 h. The excess of solvent was then removed under vacuum. The solid product was filtered and washed with water (30–40 mL). Recrystallization from ethanol (15–20 mL) gave pure orange crystals. Yield: 76% (1.48 g), mp 245–247°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 3.84$ (s, 2H, CH_2), 7.12–8.39 (m, 4H, arom-H), 11.96 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 35.8$, 118.1, 120.1, 139.1, 147.1, 156.3, 167.6, 179.0.

Synthesis of 5-(Arylidene)-2-imino-3-(pyridin-2-yl) thiazolidin-4-ones (5): General Procedure

A solution of sodium acetate (0.002 mol, 0.16 g) in acetic acid (5 mL) was added slowly to a solution of 2-imino-3-(pyridin-2-yl)thiazolidin-4-one **4** (0.001 mol, 0.20 g) in acetic acid (5–10 mL). The resulting mixture was stirred for 5 min, and then the respective aromatic aldehyde (0.002 mol) was added. The mixture was refluxed for 5–24 h depending on the aldehyde used. The precipitate was filtered, washed with water (20 mL), and then recrystallized from ethanol (10–15 mL).

5-Benzylidene-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5a)

Orange crystals. Yield: 61% (0.17 g), mp 278–280°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.20$–8.52 (m, 10H, arom-H, =CH–), 12.47 (s, 1H, NH). ^{13}C-NMR (DMSO-d_6, 75 MHz): $\delta = 119.6$, 120.7, 126.9, 129.7, 130.5, 131.4, 134.2, 139.4, 147.5, 156.3, 157.5, 157.9, 170.0. Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94%. Found: C, 64.33; H, 4.22; N, 14.81%.

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

Light yellow crystals. Yield: 64% (0.21 g), mp 289–290°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.20$–8.42 (m, 9H, arom-H, =CH–), 12.57 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 119.7$, 120.8, 125.8, 127.6, 130.0, 130.2, 131.0, 131.6, 134.8, 139.4, 147.4, 148.3, 156.0, 157.0, 169.1. Anal. Calcd. for $C_{15}H_{10}N_4O_3S$: C, 55.21; H, 3.09; N, 17.17%. Found: C, 55.50; H, 3.15; N, 17.28%.

5-(4-Nirobenzylidene)-2-imino-3-(pyridin-2-yl) thiazolidin-4-one (5c)

Light yellow crystals. Yield: 76% (0.25 g), mp 345–346°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.23$–8.51 (m, 9H, arom-H, =CH–), 12.59 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{10}N_4O_3S$: C, 55.21; H, 3.09; N, 17.17%. Found: C, 55.02; H, 3.27; N, 17.44%.

5-(4-Methoxybenzylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5d)

Light yellow crystals. Yield: 67% (0.21 g), mp 268–270°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 3.84$ (s, 3H, CH_3), 7.12–8.51 (m, 9H, arom-H, =CH–), 12.37 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 55.9$, 114.7, 115.3, 119.6, 120.5, 123.7, 126.7, 131.5, 132.5, 139.3, 147.5,

156.4. 161.0. 169.0. Anal. Calcd. for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50%. Found: C, 61.51; H, 4.43; N, 13.73%.

5-(4-Methylbenzylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5e)

Yellow crystals. Yield: 58% (0.17 g), mp 269–271°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 3.34$ (s, 3H, CH_3), 7.20–8.52 (m, 9H, arom-H, =CH–), 12.42 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.06; H, 4.44; N, 14.23%. Found: C, 65.23; H, 4.50; N, 14.11%.

5-(4-Bromobenzylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5f)

Cream crystals. Yield: 75% (0.27 g), mp 320–321°C.^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.21$–8.51 (m, 9H, arom-H,=CH–), 12.50 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{10}BrN_3OS$: C, 50.01; H, 2.80; N, 11.66%. Found: C, 50.21; H, 2.72; N, 11.81%.

5-(2-Chlorobenzylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5g)

Yellow crystals. Yield: 54% (0.17 g), mp 298–300°C.^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.20$–8.49 (m, 9H, arom-H, =CH–), 12.57 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{10}ClN_3OS$: C, 57.05; H, 3.19; N, 13.31%. Found: C, 56.86; H, 3.47; N, 13.20%.

5-(4-Chlorobenzylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5h)

Cream crystals. Yield: 61% (0.19 g), mp 303–305°C.^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 7.21$–8.52 (m, 9H, arom-H, =CH–), 12.49 (s, 1H, NH). Anal. Calcd. for $C_{15}H_{10}ClN_3OS$: C, 57.05; H, 3.19; N, 13.31%. Found: C, 57.16; H, 3.23; N, 13.48%.

5-(5-Bromo-2-hydroxybenzylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5i)

Orange crystals. Yield: 73% (0.27 g), mp 263–264°C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta = 6.92$–8.48 (m, 8H, arom-H, =CH–), 10.79 (s, 1H, OH), 12.44 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta = 110.9$, 118.6, 119.7, 120.7, 123.6, 125.0, 126.9, 130.9, 134.2, 135.3, 139.3, 147.4, 156.3, 156.7. 169.7. Anal. Calcd. for $C_{15}H_{10}BrN_3O_2S$: C, 47.89; H, 2.68; N, 11.17%. Found: C, 47.91; H, 2.50; N, 11.36%.

5-(4-Hydroxybenzylidene)-2-imino-3-(pyridin-2-yl)thiazolidin-4-one (5j)

Yellow crystals. Yield: 81% (0.24 g), mp 308–309°C.^{1}H NMR (DMSO-d_6, 300 MHz): $\delta =$ 6.93–8.52 (m, 9H, arom-H, =CH−), 10.26 (s, 1H, OH), 12.32 (s, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta =$ 116.7, 119.5, 120.4, 122.5, 125.2, 132.0, 132.8, 139.2, 147.5, 156.5, 157.9, 159.9, 170.1. Anal. Calcd. for $C_{15}H_{11}N_3O_2S$: C, 60.59; H, 3.73; N, 14.13%. Found: C, 60.50; H, 3.85; N, 13.90%.

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