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Chemical reactivity of 5-chloro-2-(chloroacetamido)pyridine towards some oxygen and sulfur nucleophiles

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Abstract: The reactivity of 5-chloro-2-(chloroacetamido)pyridine **(2)** towards nucleophilic substitution by various types of oxygen and sulfur nucleophiles was explored. The reaction of **2** with salicylaldehyde and/or ethyl 2-mercaptoacetate furnished the conforming substitution products **3** and **4**. Treatment of **2** with 4,6-dimethyl-2-mercaptonicotinonitrile afforded the conforming *N*-(pyridin-2-yl)-2-(pyridin-2-yl-thio)acetamide derivative **5** which underwent heating in sodium ethoxide to furnish 3-amino-*N*-(5-chloropyridine-2-yl)-thieno[2,3-*b*]pyridine-2-carboxamide **6**. Refluxing of **2** with ammonium thiocyanate gave 2-((5-chloropyridin-2-yl)imino)thiazolidine-4-one **(7)** which underwent condensation with different benzaldehyde derivative furnished the corresponding 5-arylidine-2-((5-chloropyridine-2-yl)imino)thiazolidine-4-ones **8a-e**.

keywords: 5-Chloro-2-(chloroacetamido)pyridine, Salicylaldehyde, Ammonium thiocyanate, Thiazolidine-4-one, Benzaldehyde

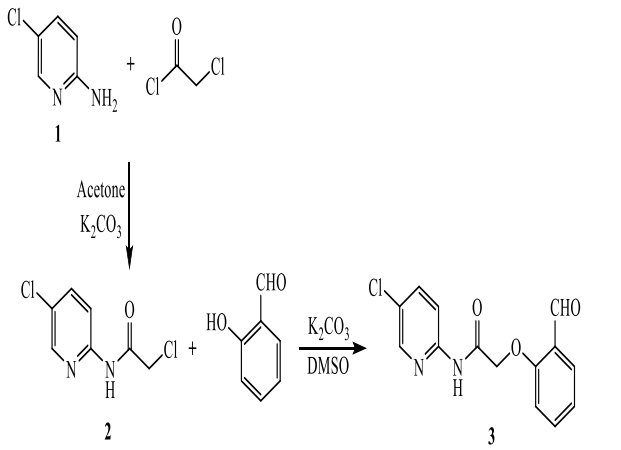
1.Introduction

Because of the ease replacement of chlorine atom and reactive N-H group, chloroacetamide and its N-substituted derivatives are highly versatile synthetic reagents for the synthesis of aziridine [1], N-lactam [2], piperazine [3], imidazolidine containing compounds [4] and macrocyclic ligands [5]. 2-Chloroacetamide reagents were applied in the field of solid-state chemistry [6], natural and pharmacologically promising compounds [7-9] and biomarkers [10]. They have been utilized as reagents for polymer modification [11], ion-exchange resins for heavy and radioactive metal sorption [12]. Chloroacetamides are well known as pesticides [13] and dyes [14]. Thus, exploring the chemistry of 2-chloroacetamides is an actual task both from theoretical and applied viewpoints. In continuation of our previous literature in the chemistry of N-substituted 2-chloroacetamides derivatives [15,16], herein we report on the reactivity of 5-chloro-2-(chloroacetamido)pyridine towards various types of oxygen and sulfur nucleophiles.

Results and Discussion

Chloroacetylation of 2-amino-5-chloropyridine **(1)** was carried out by stirring with chloroacetyl chloride in dry acetone and potassium carbonate to form the key of this study, 5-chloro-2-(chloroacetamido)pyridine **(2)** [17]. Treatment of 2-chloroacetamidopyridine scaffold **2** with salicylaldehyde (oxygen nucleophile) was achieved by stirring for 8 hours in dimethyl sulfoxide containing potassium carbonate to furnish *N*-(5-chloropyridin-2-yl)-2-(2-formylphenoxy)acetamide **(3)** (Scheme 1). The structure of phenyl ether **3** was established because of its compatible spectroscopic analyses. Thus, the IR spectrum of **3** exhibited absorptions at 3292 & 3215 and 1717 & 1682 cm^{-1} to announce the (N-H) and carbonyl (C=O) functional groups. The ^1H NMR spectrum indicated singlet for two protons at 4.73 ppm (CH_2). The aromatic protons resonated as doublet (1H) at 6.98 ppm, triplet (1H) at 7.22 ppm, multiplet (1H) at 7.60-7.63 ppm and doublet of doublet (1H) at 7.81-7.83 ppm. The three protons of pyridine were determined as doublet-doublet at 7.68-7.70 (pyridine-H_4), doublet at 8.26 ppm (pyridine-H_3), doublet at 8.37 ppm (pyridine-H_6). The proton of NH group resonated as singlet at

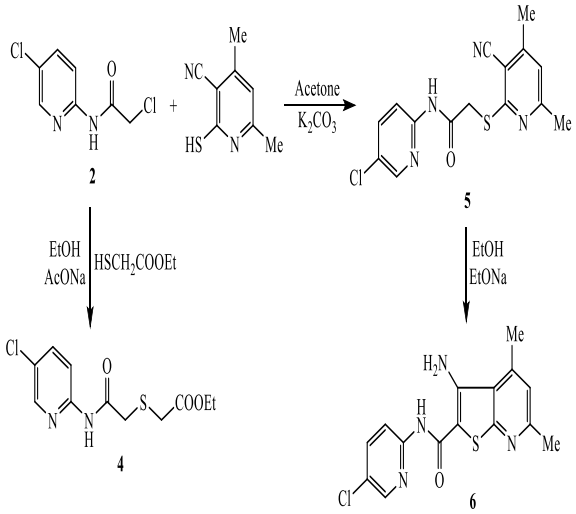
10.03 ppm. The proton of formyl group (CH=O) resonated as singlet at 10.24 ppm.



Scheme (1)

The reaction of 2-chloroacetamidopyridine scaffold **2** with ethyl 2-mercaptoacetate (sulfur nucleophile) was performed by boiling in absolute ethanol and sodium acetate to give the corresponding ethyl 3-(((5-chloropyridin-2yl)-carbamoyl)thio)propionate **(4)** (Scheme 2). The structure of **4** was secured by infrared, ^{1}H NMR and ^{13}C NMR. The presence of IR absorptions at 3274 and 1708 cm^{-1} was good announcement for the N-H and carbonyl groups, respectively. In the ^{1}H NMR spectrum, the protons of ethoxycarbonyl group ($COOCH_2CH_3$) resonated as triplet and quartet signals at 1.27 and 4.17 ppm. The protons of $–CH_2$- groups were observed as singlet signals at 3.35 and 3.51 ppm. The protons pf pyridine were observed as doublet of doublet at 7.68-7.70 ppm (pyridine-H_4), doublet at 8.22 ppm (pyridine-H_3) and doublet at 8.24 ppm (pyridine-H_6). The proton of NH group resonated as singlet at 9.45 ppm.

2-Chloroacetamidopyridine derivative **2** has been reacted with 4,6-dimethyl-2-mercaptonicotinonitrile in acetone and sodium acetate to produce the corresponding *N*-(pyridin-2-yl)-2-(pyridin-2-yl-thio)acetamide derivative **5** which affected intramolecular cyclization upon heating in sodium ethoxide to furnish 3-amino-2-(5-chloropyridin-2-yl-carboxamido)-4,6-dimethylthieno[2,3-*b*]pyridine **(6)**. The structure of compounds **5** and **6** were established by spectroscopic techniques including IR, ^{1}H NMR and ^{13}C NMR. The IR spectrum of sulfide **5** displayed the absorption of cyano group at 2221 cm^{-1} that lost from the IR absorptions of thienopyridine derivative **6**. In The ^{1}H NMR spectrum of **5**, the methylene protons resonated as singlet at 3.96 ppm, this signal was lacked from the spectrum of thieno[2,3-*b*]pyridine derivative **6**, which indicated singlet at 6.56 for the protons of amino group.

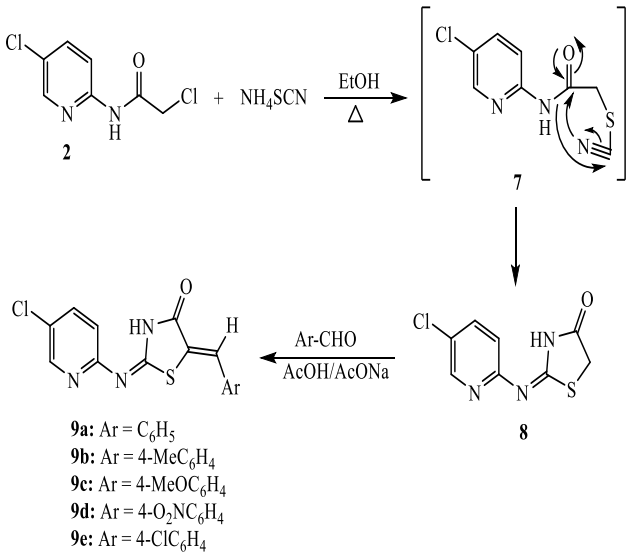


(Scheme 2)

Refluxing of equimolar amounts of 2-chloroacetamidopyridine derivative **2** with ammonium thiocyanate has been performed by boiling in ethyl alcohol to give the corresponding 2-((5-chloropyridin-2-yl)imino)thiazolidine-4-one **(7)** (Scheme 3). In the IR spectrum, the absorption of the carbonyl group (thiazolidin-4-one ring) was observed at frequency of 1721 cm^{-1}. In the ^{1}H NMR spectrum, the methylene protons resonated as singlet at 3.86 ppm, the protons of pyridine resonated as doublet of doublet at 7.06-7.10 ppm (pyridine-H_4), doublet at 7.90 ppm (pyridine-H_3), doublet at 8.43 ppm (pyridine-H_6), and the proton of NH group as singlet at 11.97 ppm.

2-((5-Chloropyridin-2-yl)imino)thiazolidine-4-one **(7)** underwent condensation with different benzaldehyde derivative in acetic acid and sodium acetate furnished the conforming 5-arylidine-2-((5-chloropyridine-2-yl)imino)thiazolidine-4-ones **8a-e** in acceptable yields. The infrared spectrum of **8c** displayed the characteristic absorptions for the N-H and carbonyl (C=O) groups at 3155 and 1706 cm^{-1}, respectively. The ^{1}H NMR announced singlet at 3.82 ppm for the methoxy protons (-OCH_3), two doublet signals at 7.20 and 7.61 ppm for the aromatic protons, singlet for one the olefinic proton at δ 7.63 ppm. The protons of pyridine were observed as doublet at 7.20 ppm

(pyridine-H_3), doublet of doublet at 7.93-7.95 ppm (pyridine-H_4), doublet at 8.55 ppm (pyridine-H_6), and the proton of NH group as singlet at 12.42 ppm.



Scheme (3)

Experimental

(1) General: Melting points were measured in degree centigrade on Gallenkamp apparatus and are uncorrected. The infrared spectra (KBr) were explored on Thermo Scientific Nicolet iS10 FTIR spectrometer. NMR spectra were measured in $CDCl_3$ or DMSO-d_6 as a solvent at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) on JEOL's NMR spectrometer. Perkin-Elmer 2400 analyzer has been used to determine the elemental analyses.

(2) Synthesis of 5-chloro-2-(chloroacetamido)pyridine (2):

The compound has been prepared in the light of the previously reported methodology as white crystals, yield 66%, m.p. = 140-142ºC, lit. m.p. = 140-142ºC [17].

(3) Synthesis of *N*-(5-chloropyridin-2-yl)-2-(2-formylphenoxy)-acetamide (3):

To a stirred suspension of 5-chloro-2-(chloroacetamido)pyridine **(2)** (0.41 g, 0.002 mol) and potassium carbonate (0.27 gm, 0.002 mol) in 15 ml DMSO, (0.24 g, 0.002 mol) of salicylaldehyde was added. The reaction components were stirred at 25-30°C for 12 h, poured into acidified ice-water with HCl. The solid that formed was collected and recrystallized from ethyl alcohol

Yellowish brown solid, yield 65%, m.p. = 135-137°C. IR (KBr): 3292, 3215 (N-H), 1717, 1682 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 4.73 (s, 2H, CH_2), 6.98 (d, J = 8.5 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.60-7.63 (m, 1H), 7.68-7.70 (dd, J = 2.5, 9.0 Hz, 1H, pyridine-H_4), 7.81-7.83 (dd, J = 2.5, 7.5 Hz, 1H), 8.26 (d, J = 9.0 Hz, 1H, pyridine-H_3), 8.37 (d, J = 3.0 Hz, 1H, pyridine-H_6), 10.03 (s, 1H, NH), 10.24 ppm (s, 1H, CH=O). Analysis of $C_{14}H_{11}ClN_2O_3$ (290): Calculated: C, 57.84; H, 3.81; N, 9.64%. Found: C, 57.75; H, 3.84; N, 9.58%.

(4) Synthesis of ethyl 2-((2-((5-chloropyridin-2-yl)amino)-2-oxoethyl)-thio)acetate (4):

To a solution of 5-chloro-2-(chloroacetamido)pyridine **(2)** (0.41 g, 0.002 mol) in 20 ml ethanol containing sodium acetate (0.16 gm, 0.002 mol), ethyl 2-mercaptoacetate (0.24 gm, 0.002 mol) was added. The reaction components were refluxed for 2 h and then cooled to 30°C. The precipitate that acquired upon addition of 20 ml ice-water was collected and purified (recrystallized) form diethyl ether.

White crystals, yield 85%, m.p. = 80-81°C. IR (KBr): 3274 (N-H), broad centered at 1708 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 1.27 (t, J = 7.25 Hz, 3H), 3.35 (s, 2H, CH_2), 3.51 (s, 2H, CH_2), 4.17 (q, J = 7.25 Hz, 2H), 7.68-7.70 (dd, J = 2.0, 9.0 Hz, 1H, pyridine-H_4), 8.22 (d, J = 9.0 Hz, 1H, pyridine-H_3), 8.24 (d, J = 2.0 Hz, 1H, pyridine-H_6), 9.45 ppm (s, 1H, NH). ^{13}C NMR ($CDCl_3$): 13.78, 33.91, 36.89, 61.69, 114.58, 126.83, 138.37, 145.52, 148.88, 166.93, 169.41 ppm. Analysis of $C_{11}H_{13}ClN_2O_3S$ (288): Calculated: C, 45.76; H, 4.54; N, 9.70%. Found: C, 45.64; H, 4.50; N, 9.62%.

(5) Synthesis of *N*-(5-chloropyridin-2-yl)-2-((3-cyano-4,6-dimethyl-pyridin-2-yl)thio)acetamide (5):

A mixture of 5-chloro-2-(chloroacetamido)pyridine **(2)** (1.0 g, 0.005 mol) and 2-mercapto-4,6-dimethylnicotinonitrile (0.82 gm, 0.005 mol) was refluxed in 25 ml acetone containing potassium carbonate (0.69 gm, 0.005 mol) for 4 h. The reaction contents were poured into ice-water, the solid product that obtained by filtration was dried and purified by recrystallization form ethanol.

White crystals, yield 61%, m.p. = 180-182ºC. IR (KBr): 3193 (N-H), 2221 (C≡N), 1690 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): 2.48

(s, 3H), 2.69 (s, 3H), 3.96 (s, 2H), 6.93 (s, 1H, pyridine-H), 7.63-7.66 (dd, *J* = 2.5, 9.0 Hz, 1H, pyridine-H_4), 8.16 (d, *J* = 9.0 Hz, 1H, pyridine-H_3), 8.18 (d, *J* = 2.5 Hz, 1H, pyridine-H_6), 10.43 ppm (s, 1H, NH). ^{13}C NMR (DMSO-d_6): 20.41, 24.63, 35.13, 105.38, 114.46, 114.85, 121.40, 126.71, 138.38, 146.03, 149.76, 153.24, 160.68, 162.13, 167.78 ppm. Analysis of $C_{15}H_{13}ClN_4OS$ (332): Calculated: C, 54.14; H, 3.94; N, 16.84%. Found: C, 54.27; H, 3.96; N, 16.76%.

(7) Preparation of 3-amino-2-(5-chloropyridin-2-yl-carboxamido)-4,6-dimethyl-thieno[2,3-*b*]pyridine (6):

A solution of *N*-(pyridin-2-yl)-2-(pyridin-2-ylthio)-acetamide derivative **5** (0.50 gm, 0.0015 mol) was heated for 45 minutes in sodium ethoxide solution (0.07 g sodium granules in 20 dry ethanol). The reaction solution was cooled and diluted with 20 ml cold water. The solid product that obtained by filtration was dried and purified by recrystallization form C_2H_5OH.

Yellowish white powder, yield 72%, m.p. m.p. = 215-217ºC. IR (KBr): 3436, 3325 (NH_2 and NH), 1654 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$): 2.65 (s, 3H), 2.80 (s, 3H), 6.56 (s, 2H, NH_2), 6.94 (s, 1H, pyridine-H), 7.67-7.69 (dd, *J* = 2.5, 9.0 Hz, 1H, pyridine-H_4), 7.92 (s, 1H, NH), 8.25 (d, *J* = 9.0 Hz, 1H, pyridine-H_3), 8.28 ppm (d, *J* = 2.5 Hz, 1H, pyridine-H_6). ^{13}C NMR ($CDCl_3$): 20.24, 24.29, 97.13, 114.64, 122.36, 123.05, 126.36, 137.77, 143.99, 146.45, 149.52, 149.83, 159.29, 159.91, 163.89 ppm. Analysis of $C_{15}H_{13}ClN_4OS$ (332): Calculated: C, 54.14; H, 3.94; N, 16.84%. Found: C, 54.31; H, 3.87; N, 16.72%.

(8) Production of 2-((5-chloropyridin-2-yl)imino)thiazolidin-4-one (8):

A mixture of 5-chloro-2-(chloroacetamido)pyridine **(2)** (1.0 g, 0.005 mol) and ammonium thiocyanate (0.53 g, 0.007 mol) in 20 ml ethyl alcohol was boiled using condenser for 4 h. The solid that acquired was filtered to give the targeted 2-(pyridin-2-ylimino)thiazolidin-4-one scaffold **8**.

Light green solid, yield 63%, m.p. = 290-292ºC. IR (KBr): 3161 (N-H), 1721, 1684 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): 3.86 (s, 2H, CH_2), 7.06-7.10 (dd, *J* = 3.0, 7.0 Hz, 1H, pyridine-H_4), 7.90 (d, *J* = 7.0 Hz, 1H, pyridine-H_3), 8.43 (d, *J* = 3.0 Hz, 1H, pyridine-H_6), 11.97 ppm (s, 1H, NH). Analysis of $C_8H_6ClN_3OS$ (227): Calculated: C, 42.21; H, 2.66; N, 18.46%. Found: C, 42.28; H, 2.64; N, 18.41%.

(9) General procedure for the synthesis of 5-arylidene-2-((5-chloro-pyridin-2-yl)imino)thiazolidin-4-ones 9a-e:

Asuspension of 2-((5-chloropyridin-2-yl)imino)thiazolidin-4-one **(8)** (0.45 gm, 0.002 mol) and the appropriate benzaldehyde derivative (0.002 mol) in 15 ml acetic acid and 0.5 g sodium acetate was refluxed for 4 h. The reaction solution was cooled and diluted with 15 ml cold water. The solid that acquired was recrystallized from acetic acid.

5-Benzylidene-2-((5-chloropyridin-2-yl)imino)thiazolidin-4-one (9a):

Buff solid, yield 41%, m.p. = 290-292ºC. IR (KBr): 3158 and 1718 cm^{-1}. Analysis of $C_{15}H_{10}ClN_3OS$ (315): Calculated: C, 57.05; H, 3.19; N, 13.31%. Found: C, 57.17; H, 3.22; N, 13.40%.

2-((5-Chloropyridin-2-yl)imino)-5-(4-methylbenzylidene)thiazolidin-4-one (9b):

Buff powder, yield 52%, m.p. = 295-297ºC. IR (KBr): 3154 and 1712 cm^{-1}. Analysis of $C_{16}H_{12}ClN_3OS$ (329): Calculated: C, 58.27; H, 3.67; N, 12.74%. Found: C, 58.11; H, 3.60; N, 12.82%.

2-((5-Chloropyridin-2-yl)imino)-5-(4-methoxybenzylidene)thiazolidin4-one (9c):

Buff powder, yield 50%, m.p. > 300ºC. IR (KBr): 3155 (N-H) and 1706 cm^{-1} (C=O). ^{1}H NMR (DMSO-d_6): 3.82 (s, 3H, OCH_3), 7.11 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H, pyridine-H_3), 7.61 (d, *J* = 9.0 Hz, 2H), 7.63 (s, 1H, olefinic CH=C), 7.93-7.95 (dd, *J* = 2.0, 9.0 Hz, 1H, pyridine-H_4), 8.55 (d, *J* = 2.0, 1H, pyridine-H_6), 12.42 ppm (s, 1H, NH). Analysis of $C_{16}H_{12}ClN_3O_2S$ (345): Calculated: C, 55.57; H, 3.50; N, 12.15%. Found: C, 55.64; H, 3.47; N, 12.08%.

2-((5-Chloropyridin-2-yl)imino)-5-(4-nitrobenzylidene)thiazolidin-4-one (9d):

Brown solid, yield 57%, m.p. > 300ºC. IR (KBr): 3168 and 1719 cm^{-1}. Analysis of $C_{15}H_9ClN_4O_3S$ (360): Calculated: C, 49.94; H, 2.51; N, 15.53%. Found: C, 49.81; H, 2.56; N, 15.64%.

5-(4-Chlorobenzylidene)-2-((5-chloropyridin-2-yl)imino)thiazolidin-4-one (9e):

Buff solid, yield 48%, m.p. > 300ºC. IR (KBr): 3161 and 1713 cm^{-1}. Analysis of $C_{15}H_9Cl_2N_3OS$ (349): Calculated: C, 51.44; H, 2.59; N, 12.00%. Found: C, 51.28; H, 2.66; N, 12.13%.

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