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NOTE

Synthesis and Characterization of Novel 1,3,4-Oxadiazole Derivatives Containing 5-(2,4-Dichlorothiazole) Substitute

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2-[(2,4-Dichlorothiazol-5-yl)methylene]hydrazinecarboxamide (**4**) was obtained from the reaction of 2,4-dichlorothiazole-5-carboxaldehyde (**2**) and semicarbazide (**3**). 2-Amino-1,3,4-oxadiazole compound (**5**) was synthesized *via* the cyclization of compound **4** in the presence of bromine. Diazotation of compound **5** in hydrochloric acid in the presence of copper powder results compound **6** in which the amino group was substituted with chlorine. All the synthesized compounds were characterized by IR, Mass, ^{1}H NMR or ^{13}C NMR spectra and elemental analysis.

Key Words: 2,4-Dichlorothiazole-5-carboxaldehyde, 1,3,4-Oxadiazole, Synthesis, Hydrazinecarboxamide.

The synthesis of compounds having 1,3,4-oxadiazole and thiazole rings has been attracting widespread attention due to their diverse pharmacological properties such as antimicrobial, antiinflammatory, antifungal, analgesic, antitumoral and antiviral activities[1-6]. It has also been reported that the 1,3,4-oxadiazole rings containing chemical active group such as OH, NH_2, SH and Cl, on their structure are the most important starting materials to prepare other important and useful compounds[7-11]. Prompted by these observations, in this paper the synthesis of new 2-amino/chloro-5-(2,4-dichlorothiazole-5-yl)-1,3,4-oxadiazole derivatives and their intermediate compounds are reported. 2,4-Dichloro(1,3-thiazole)-5-carboxaldehyde (**2**) was prepared in 2 steps. First chloroacetic acid and thiourea were refluxed for a desired time to give 1,3-thiazolidine-2,4-dione (**1**). The reaction of **1** with $POCl_3$ and DMF gave the desired aldehyde **2**[12]. In order to prepare thiazole(methylene) hydrazinecarboxamide (**4**), compound **2** was allowed to react with semcarbazide hydrochloride in aqueous solution of sodium acetate. The reaction of compound **4** with bromine in glacial acetic acid containing anhydrous sodium acetate gave compound **5**[13]. The compound **6** was prepared by reaction of the compound **5** with $NaNO_2$ in the presence of HCl and Cu powder at 0 ºC[10,11] (**Scheme-I**). The structure of all synthesized compounds were confirmed by IR, Mass, ^{1}H NMR or ^{13}C NMR spectra and elemental analysis.

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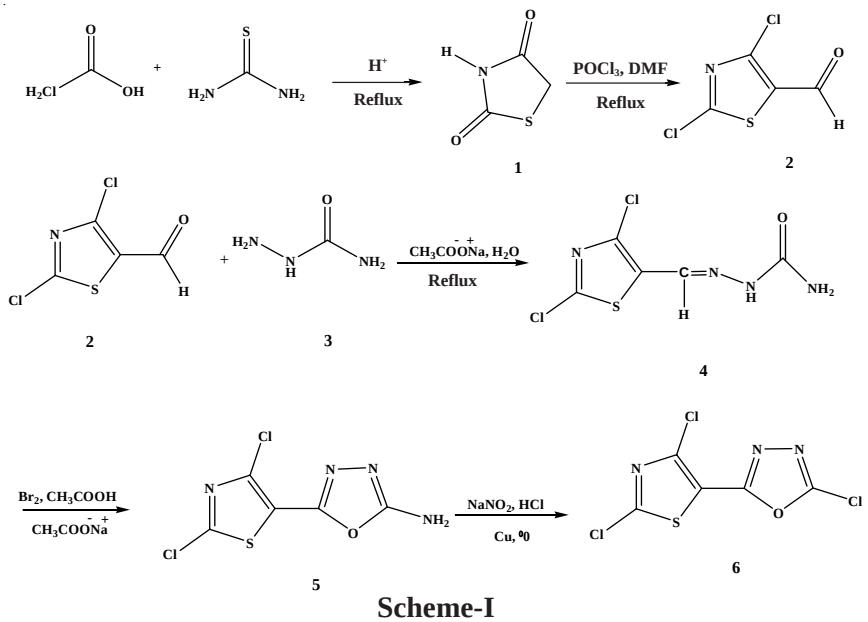

Scheme-I

Preparation of 2,4-(1,3-thiazolidine)dione (1): To stirring solution of thiourea (10.133 g, 0.133 mol) in 100 mL water was added chloroacetic acid (12.613 g, 0.133 mol) in the presence of concentrated HCl and was refluxed for 7 h. The precipitate was collected and crystallized from water to give 13 g (83 %) of **1**, m.p. 123-125 ºC; IR (KBr, cm^{-1}): 1672 ν(CO) ; ^{1}H NMR (DMSO-d^6, 80 MHz), δ: 1.59 (s, 2H, CH_2), 4.03 (s, 1H, NH); Mass: m/z (%) 117 (M^+, 85), 89 (50), 74 (65), 46 (100) Anal. calcd. for $C_3H_3O_2NS$: C, 30.76; H, 2.58; N, 11.96, Found: C, 30.70; H, 2.63; N, 12.05.

Preparation of 2,4-dichloro-5-(1,3-thiazole)carboxaldehyde (2): A mixture of compound **1** (10 g, 0.0584 mol) and $POCl_3$ (78.6 g, 0.51 mol) in 6.8 mL DMF was refluxed for 6 h and cooled to room temperature. The product was purified on the column chromatography and was crystallized in methanol to give 8.7 g (56 %) of **2**, m.p. 45-46 °C; IR (KBr, cm^{-1}): 1690 ν(CO); ^{1}H NMR ($CDCl_3$, 80 MHz), δ: 9.96 (s, 1H, CHO); Mass: m/z (%) 185 (M^+, 80), 182 (100), 154 (37), 152 (43), 91 (53), 79 (32), 57 (30); Anal. calcd. for $C_{41}H_1ONSCl_2$: C, 26.39; H, 0.55; N, 7.69; Found: C, 26.43; H, 0.54; N, 7.72.

Preparation of 2-[(2,4-dichlorothiazol-5-yl)methylene]hydrazinecarboxamide (4): A mixture of aldehyde **2** (0.1 g, 0.55 mmol), semicarbazide hydrochloride **3** (0.282 g, 2.5 mmol) and sodium acetate trihydrate (0.4 g) in 5 mL methanol was refluxed for 48 h. After cooling, the white precipitate was filtered and washed with methanol then crystallized from ethanol to give 0.121 g of **4** (93 %); m.p. 220-221 °C; IR (KBr, cm^{-1}): 3490, 3350 ν(NH_2, NH), 1673 ν(C=O); Mass: m/z (%) 238 (M^+, 29), 195 (23), 160 (100), 130 (26), 43 (91); Anal. calcd. for $C_5H_4N_4OSCl_2$: C, 25.12; H, 1.69; Cl, 29.66; N, 23.43; S, 13.41, Found: C, 25.83; H, 1.76; Cl, 29.12; N, 23.98; S, 13.05.

Preparation of the 2-amino-5-(2,4-dichlorothiazole-5-yl)-1,3,4-oxadiazole (5): To a stirring solution of **5** (7.89 g, 0.033 mol) and anhydrous sodium acetate (10.9 g, 0.133 mol,) in glacial acetic acid (120 mL) was added drop wise the solution of bromine (11.67 g, 0.073 mol) in glacial acetic acid (20 mL). The mixture was stirred for 24 h at room temperature, then poured into ice-water and was mixed for 5 min. The obtained mixture was extracted with chloform and condensed under reduced pressure to give 3.19 g of 5 (41 %), m.p. 127-128 °C; IR (KBr, cm^{-1}): 1603-1572 ν(-C=N); ^{13}C NMR (DMSO-d_6), 75 MHz, δ: 129.13 (thiazole C-5), 130.87 (thiazole C-4), 133.80 (thiazole C-2), 150.53 (oxadiazole C-5),155.70 (oxadiazole C-2); Mass: m/z (%) 236 (M^+, 71), 193 (100), 180 (26), 130 (27), 91 (32), 44 (95). Anal. calcd. for $C_5H_2N_4OSCl_2$: C, 25.33; H, 0.85; Cl, 29.91; N, 23.63; S, 13.53; Found: C, 25.81; H, 0.53; Cl, 30.17; N, 23.14; S, 13.96.

Preparation of 2-chloro-5-(2,4-dichlorothiazole-5-yl)-1,3,4-oxadiazole (6): To a stirring mixture of copper powder (0.5 g) and concentrate HCl (28 mL) in 12 mL water at 0 ºC, a mixture of compound **5** (1.96 g, 0.008 mol) and $NaNO_2$ (2.00 g, 0.029 mol) was added slowly and stirred for 1 h. The stirring continued at room temperature for 1 h. The given mixture was extracted with chloform and condensed under reduced presser to give 0.71 g of **6** (35 %), m.p. 112-113 °C; IR (KBr, cm^{-1}) : 1611-1580 ν(-C=N); ^{13}C NMR (DMSO-d_6), 75 MHz, δ: 128.24 (thiazole C-5), 131.50 (thiazole C-4), 133.02 (thiazole C-2), 150.21 (oxadiazole C-5), 161.36 (oxadiazole C-2); Mass: m/z (%) 257 (M^+, 15), 197 (21), 193 (15), 149 (42), 57 (100), 43 (95); Anal. calcd. for $C_5N_3OSCl_3$: C, 23.41; Cl, 41.47; N, 16.38; S, 12.50, Found: C, 23.65; Cl, 41.97; N, 16.61; S, 12.11.

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