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Heterocyclization of 2-(4-Oxo-4,5-Dihydro-Thiazol-2-yl) Acetamide with α-β unsaturated Nitrile Compounds

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Abstract: 2-(4-Oxo-4,5-dihydro-thiazol-2-yl)acetamide (1) was condensed with aromatic aldehydes either (1:1 molar ratio) or (1:2 molar ratio) and furnished the newly 4,5-dihydro-4-oxo-thiazole derivatives (2a-d) and (3a-c), respectively. Thiazo-lopyridine (4a-d) were produced by reaction of 4-thiaozlinone (1) with malononitrile and aromatic aldehydes (1:2 molar ratios) in refluxing ethanol. Cyclization of compound (2a) with α- substituted cinnamonitriles (6a-d) and (10a-c) yielded the newly thiazolo[3,2-a]pyridine derivatives (9a-d) and (13a-c), respectively.

Key words: 2-(4-Oxo-4,5-dihydro-thiazol-2-yl)acetamide · 4-Oxo-thiazoles · Thiazolo[3, 2-a]pyridines

INTRODUCTION

Thiazole and their derivatives are important class in heterocyclic compounds, found in many potent biological active molecules such as sulfathiazole (antimicrobial drug), Ritonavir (antiretroviral), Abafungin (antifungal drug) and Bleomycine (antineoplastic drug) [1,2]. Recently the applications of thiazoles were found in drug development for the treatment of allergies[3], hypertension[4], inflammation [5], schizophrenia [6], bacterial [7], HIV infections [8], hypnotics [9] and more recently for the treatment of pain[10], as fibrinogen receptor antagonists with antithrombotic activity [11] and as new inhibitors of bacterial DNA gyrase B[12] In view of these benefits and in continuation of our program, the authors were interested to synthesize thiazoles and thiazolo[3,2-a]pyridines [13-21]. Therefore some newly 4,5-dihydro- 4-oxo-thiazoles and thiazolo [3,2-a] pyridines were reported

MATERIAL AND METHODS

Melting points are uncorrected. IR spectra were recorded on a Shimadzu 440 infrared spectrophotometer (υ; cm^{-1}) using the KBr technique (Shimadzu, Japan). ^1H NMR spectra were recorded on a Varian Gemini spectrometer (δ; ppm) 200 MHz using TMS as internal standard. Mass spectra were recorded on a Jeol-JMS-600 mass spectrometer. Micro analytical data were obtained from the Micro analytical Research Centre, Faculty of Science, Cairo University. Compound (1), was prepared accord -ing to the reported method [22].

(5-Arylmethylidine-4-oxothiazolidin-2-ylidene) acetamides (2a-d): To a solution of 1 (0.01 mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml), aromatic aldehydes (0.01 mol) were added. The reaction mixture was heated under reflux (time of reflux). The solid products formed were collected by filtration to give 2a-d.

2a: Yellow crystals, yield 67 %, m.p 244-246 °C(Solvent of crystallization). IR (ν,cm^{-1}): 3417, 3309 (NH_2), 2923 (CH-aliph.) and 1721, 1674 (C=O thiazolidinone and amide). ^1H NMR (DMSO-d_6, δ, ppm): 2.41 (s, 3H, CH_3), 5.12(s, 2H, NH_2, exchangeable with D_2O), 5.63 (s, 1H, methylidene-H), 6.70-7.30 (m, 5H, Ar-H + methylidene-H), 11.22 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{13}H_{12}N_2O_2S$ (260): C, 60.00, H; 4.61; N; 10.76. Found: C, 60.10, H; 4.70, N; 10.60.

2b: Yellow crystals, yield 72 %, m.p 234-236 °C(Solvent of crystallization).IR (ν,cm^{-1}): 3380, 3148 (NH_2), 2938(CH-aliph.) and 1720, 1664 (C=O thiazolidinone and amide). ^1H NMR (DMSO-d_6): δ / ppm: 4.01 (s, 3H, OCH_3), 5.10(s, 2H, NH_2, exchangeable with D_2O), 5.51 (s, 1H, methylidene-H), 6.50-7.41 (m, 5H, Ar-H + methylidene-H), 11.10 (s, 1H, NH,

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exchangeable with D_2O). Anal. Calcd for $C_{13}H_{12}N_2O_3S$ (276): C, 56.52, H; 4.34; N; 10.14. Found: C, 56.70, H; 4.20, N; 10.10.

2c: Yellow crystals, yield 69 %, m.p 236-238°C (Solvent of crystallization) IR (ν,cm^{-1}): 3379, 3147 (NH_2), 2940(CH.aliph.) and 1720, 1666 (C=O thiazolidinone and amide). ^1H NMR (DMSO-d_6):δ / ppm: 4.01 (s, 3H, OCH_3), 5.11(s, 2H, NH_2, exchangeable with D_2O), 5.51 (s , 1H, methylidene-H), 6.41 (s, 1H, NH, exchangeable with D_2O), 6.81-7.30 (m, 4H, Ar-H + methylidene-H), 11.42 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{13}H_{12}N_2O_4S$ (292): C, 53.42, H; 4.10; N; 9.58. Found: C, 53.50, H; 4.20, N; 9.70.

2d: Yellow crystals, yield 69 %, m.p 238-240 °C(Solvent of crystallization). IR (ν,cm^{-1}): 3379, 3147 (NH_2), 2931 (CH.aliph.) and 1720, 1658 (C=O thiazolidinone and amide). ^1H NMR (DMSO-d_6): δ / ppm: 5.02(s, 2H, NH_2, exchangeable with D_2O), 5.30 (s, 1H, methylidene-H), 6.70-7.80 (m, 8H, Ar-H + methylidene-H), 11.21 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{16}H_{12}N_2O_2S$ (296): C, 64.86, H; 4.05; N; 9.45. Found: C, 65.10, H; 4.20, N; 9.20.

5-Arylmethylidine-4-oxo-4,5-dihydro-thiazol-2-yl)-3-aryl*acr ylamides (3a-c):* To a solution of 1 (0.01 mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml), aromatic aldehydes (0.02 mol) were added. The reaction mixture was heated under reflux(time of reflux). The solid products formed were collected by filtration to give 3a-c.

3a: Yellow crystals, yield 74 %, m.p 225-227 °C (Solvent of crystallization).IR (ν,cm^{-1}): 3410, 3200 (NH_2), 3040(CH-arom.) and 1712, 1648 (C=O thiazolidinone and amide). ^1H NMR (DMSO-d_6): δ / ppm: 5.98 (s, 1H, methylidene-H), 6.90 -7.68 (m, 9H, Ar-H+, methylidene-H), 8.91 (hump, 2H, NH_2, exchangeable with D_2O), Anal. Calcd for $C_{19}H_{12}Cl_2N_2O_2S$ (403): C, 56.57, H; 2.97; N; 6.94. Found: C, 56.50, H; 2.90, N; 7.10.

3b: Yellow crystals, yield 64 %, m.p 235-237 °C (from ethanol). IR (ν,cm^{-1}): 3432, 3300 (NH_2), 3050 (CH-arom.), 1692, 1664 (C =O thiazolidinone, amide). ^1H NMR (DMSO-d_6):δ / ppm: 5.78 (s, 1H, methylidene-H), 6.87 -7.50 (2d, 8H, Ar-H), 7.36 (S, 1H, methylidene-H), 10.14 (hump, 2H, NH_2, exchangeable with D_2O), 11.76 (hump, 2H, 2 OH, exchangeable with D_2O). Anal. Calcd for $C_{19}H_{14}N_2O_4S$ (366): C, 62.29, H; 3.82; N; 7.65. Found: C, 62.00, H; 3.70, N; 7.40.

3c: Yellow crystals, yield 65 %, m.p. 180-182 °C(Solvent of crystallization) IR (ν,cm^{-1}): 3380, 3216 (NH_2), 3052 (CH-arom.), 1704, 1648 (C=O thiazolinone, amide). ^1H NMR (DMSO-d_6): δ / ppm: 5.80 (s, 1H, methylidene-H), 7.58- 8.05 (m, 15H, Ar-H + methylidene-H), 9.00 (hump, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{27}H_{18}N_2O_2S$ (434): C, 74.65, H; 4.14; N; 6.45. Found: C, 74.80, H; 4.10, N; 6.60.

2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-amino-6-cyano-7-aryl-8-carboxamido-1,3-thiazolo[3,2-a]pyridines (4a-d): To a solution of 1 (0.01 mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml), aromatic aldehydes (0.02 mol) and malononitrile (0.02 mol) were added. The reaction mixture was heated under reflux(time of reflux). The solid products formed were collected by filtration to give 4a-d.

4a: Yellow crystals, yield 56 %, m.p 250-252 °C(Solvent of crystallization). IR (ν,cm^{-1}): 3480, 3296 (NH_2), 2190 (C=N), 1702 (C=O thiazolidinone, amide).^1H NMR (DMSO-d_6): δ / ppm: 4.72 (s, 1H, pyridine-H), 7.06-7.56 (m, 13H, Ar-H + methylidene-H+ 2 NH_2; exchangeable with D ₂O). Anal. Calcd for $C_{22}H_{14}Cl_2N_4O_2S$ (469): C, 56.28, H; 3.01 ; N; 11.94. Found: C, 56.60, H; 2.90, N; 12.10.

4b: Yellow crystals, yield 61 %, m.p 262-264 °C(Solvent of crystallization). IR (ν,cm^{-1}): 3471, 3379 (NH_2), 2191 (C=N), 1674 (C=O thiazolidinone, amide).^1H NMR (DMSO-d_6): δ / ppm: 2.27, 2.35 (2s, 6H, 2 CH_3), 4.71 (s, 1H, pyridine-H), 5.59 (s, 1H, NH, exchangeable with D_2O), 6.87 (hump, 2H, NH_2; exchangeable with D_2O), 6.91-7.61 (m, 9H, Ar-H + methylidene-H), 12.11 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{24}H_{20}N_4O_2S$ (428): C, 67.28, H; 4.67; N; 13.08. Found: C, 67.30, H; 4.50, N; 13.20.

4c: Yellow crystals, yield 70 %, m.p 258-60 °C(Solvent of crystallization) IR (ν,cm^{-1}): 3480, 3380 (NH_2), 2190 (C=N), 1708 (C=O thiazolidinone, amide). ^1H NMR (DMSO-d_6): δ / ppm: 3.74, 3.80 (2s, 6H, 2 OCH_3), 5.91 (s, 1H, pyridine-H), 5.84 (s, 1H, NH, exchangeable- with D_2O), 6.98 (hump, 2H, NH_2; exchangeable with D_2O), 7.34-7.81 (m, 9H, Ar-H + methylidene-H), 12.00 (s, 1H, OH, exchang eable with D_2O). Anal. Calcd for $C_{24}H_{20}N_4O_4S$ (460): C, 62.60, H; 4.34; N; 12.17. Found: C, 62.10, H; 4.10, N; 12.10.

4d: Yellow crystals, yield 52 %, m.p 260-262 °C(Solvent of crystallization). IR (ν,cm^{-1}): 3476, 3358 (NH_2), 2191 (C=N), 1686 (C=O thiazolidinone, amide). ^1H NMR (DMSO-d_6): δ / ppm: 3.83, 3.85 (2s, 6H, 2 OCH_3), 4.60 (s, 1H, pyridine-H), 5.76(s, 2H, NH_2, exchangeable with D_2O), 6.83-7.43 (m, 9H,

Ar-H + methylidene-H + NH_2 exchangeable with D_2O), 11.80 (2s, 2H, OH, exchangeable with D_2O). Anal. Calcd for $C_{24}H_{20}N_4O_6S$ (492): C, 58.53, H; 4.06; N; 11.38. Found: C, 58.30, H; 4.10, N; 11.70.

2,3,6-Trihydro-2-arylmethylidine-3,5-dioxo-7-aryl-8-carbox- amido- 1,3-thiazolo- [3,2-a]pyridines (9a-d): To a solution of 2a (0.01 mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml), α-carboxamidocinnamonitrile (0.01 mol), was added. The reaction mixture was heated under reflux (time of reflux). The solid products formed were collected by filtration to give 9a-d.

9a: Yellow crystals, yield 63 %, m.p 275-277 °C(Solvent of crystallization) IR (ν,cm^{-1}): 3338, 3190 (NH_2), 3050 (CH-arom.), 2910(CH-aliph.), 1686, 1654 (C = O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ / ppm: 2.37 (s, 3H, CH_3), 5.82 (s, 1H, pyridine-H), 7.51-8.14 (m, 9H, Ar-H + methylidene-H), 8.38 (s, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{22}H_{15}ClN_2O_3S$ (422.5): C, 62.48, H; 3.55; N; 62.60. Found: C, 58.30, H; 3.70, N; 6.80.

9b: Yellow crystals, yield 57 %, m.p 292-294 °C(Solvent of crystallization). IR (ν,cm^{-1}): 3386, 3170 (NH_2), 3026 (CH-arom.). ^{1}H NMR (DMSO-d_6): δ / ppm: 2922 (CH-aliph.), 1696, 1640 (C =O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ 2.29, 2.38 (2s, 6H, $2CH_3$), 5.78 (s, 1H, pyridine-H), 7.20-7.60 (m, 9H, Ar-H + methylidene-H), 8.01 (s, 1H, NH, exchangeable with D_2O), 10.31 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{23}H_{18}ClN_2O_3S$ (402): C, 68.65, H; 4.47; N; 6.96. Found: C, 68.50, H; 4.70, N; 6.80.

9c: Yellow crystals, yield 63 %, m.p. 290-292 °C(Solvent of crystallization). IR (KBr, ν,cm^{-1}): 3312, 3184 (NH_2), 3030 (CH-arom.), 2928 (CH-aliph.), 1684, 1654 (C =O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ / ppm: 2.37 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3) 5.78 (s, 1H, pyridine-H), 6.94-7.51 (m, 8H, Ar-H + methyllidene-H), 8.59 (s, 2H, NH_2, exchangeable with D_2O), 10.31 (s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{23}H_{18}N_2O_5S$ (434): C, 63.59, H; 4.14; N; 6.45. Found: C, 63.60, H; 3.99, N; 6.80.

9d: Yellow crystals, yield 61 %, m.p. >300°C(Solvent of crystallization). IR (ν,cm^{-1}): 3450, 3174 (NH_2), 3048 (CH-arom.), 2930 (CH-aliph.) 1686, 1654 (C = O thiazolidinone, amide). ^{1}H NMR (DMSO-d_6): δ / ppm: 2.35 (s, 3H, CH_3), 5.94 (s, 1H, pyridine-H), 7.35-8.31 (m, 12H, Ar-H + methylidene-H), 10.40 (s, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{26}H_{18}N_2O_3S$ (438): C, 71.23, H; 4.10; N; 6.39. Found: C, 71.00, H; 4.20, N; 6.50.

2,3,7-Trihydro-2-arylmethylidine-3-oxo-5-amino-6-ethoxycarbonyl-7-aryl-8-carboximido-1,3-thiazolo[3,2-a]pyridines(13a-c): To a solution of 2a (0.01 mol) in absolute ethanol (20 ml) containing catalytic amount of piperidine (0.5 ml), α-ethoxycarbontlcinnamonitrile (0.01 mol), was added. The reaction mixture was heated under reflux (time of reflux). The solid products formed were collected by filtration to give 13a-c.

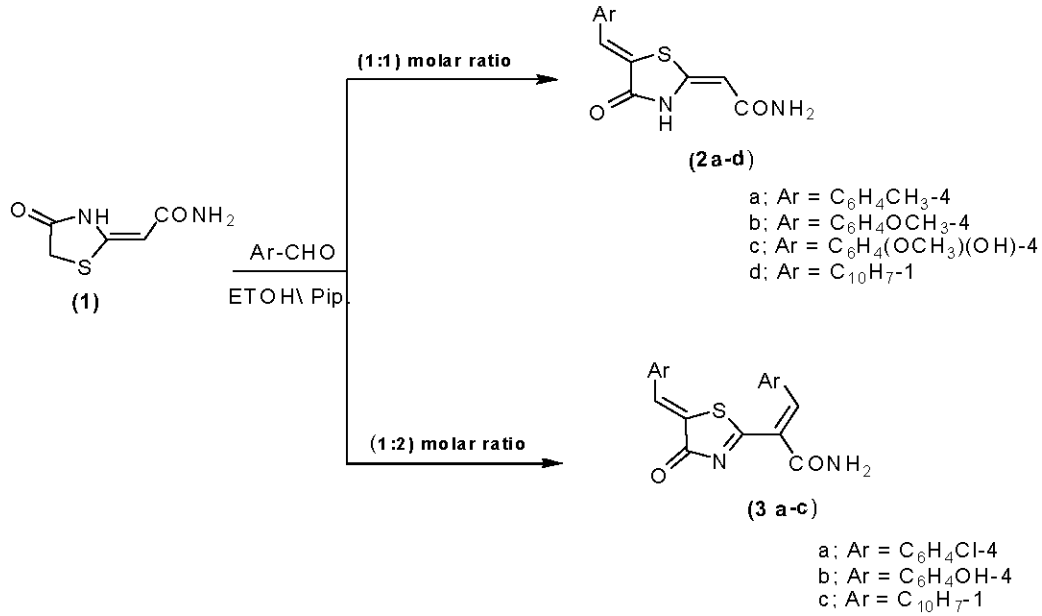
13a: Yellow crystals, yield 54 %, m.p 258-260 °C (Solvent of crystallization). IR (ν,cm^{-1}): 3330, 3196 (NH_2), 2980 (CH-aliph.), 1710, 1654 (C =O thiazolidinone, amide, ester). ^{1}H NMR (DMSO-d_6): δ / ppm: 1.31 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.90 (s, 2H, NH_2, exchangeable with D_2O), 4.31 (q, 2H, CH_2), 4.94 (s, 1H, pyridine-H), 7.20-8.09 (m, 9 H, Ar-H + methylidene-H), 8.41 (s, 2H, NH_2, exchange- able with D_2O). Anal. Calcd for $C_{25}H_{22}ClN_3O_4S$ (495.5): C, 60.54, H; 4.43; N; 8.47. Found: C, 60.70, H; 4.60, N; 8.30.

13b: Yellow crystals, yield 72 %, m.p180-182 °C(Solvent of crystallization). IR (ν,cm^{-1}): 3330, 3196 (NH_2), 2980 (CH-aliph.), 1710, 1654 (C =O thiazolidinone, amide, ester). ^{1}H NMR (DMSO-d_6): δ / ppm: 1.33 (t, 3H, CH_3), 2.29, 2.38 (2s, 6H, CH_3), 2.89 (s, 2H, NH_2, exchangeable with D_2O), 4.31 (q, 2H, CH_2), 4.94 (s, 1H, pyridine-H), 7.16-7.98 (m, 9 H, Ar-H + methylidene-H), 8.34 (s, 2H, NH_2, exchangeable with D_2O). Anal. Calcd for $C_{26}H_{25}N_3O_4S$ (475): C, 65.68, H; 5.26; N; 8.84. Found: C, 65.90, H; 5.10, N; 8.80.

13c: Yellow crystals, yield 79 %, m.p195-97 °C (from ethanol). IR (KBr, ν, cm^{-1}): 3370, 3184 (NH_2), 2930 (CH-aliph.), 1702, 1656 (C =O thiazolidinone, amide, ester). ^{1}H NMR (DMSO-d_6): δ / ppm: 1.34 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.89 (s, 2H, NH_2, exchangeable with D_2O), 3.87 (s, 3H, OCH_3), 4.26 (q, 2H, CH_2), 4.87 (s, 1H, pyridine-H), 7.12-8.10 (m, 9 H, Ar-H + methylidene-H), 8.34 (s, 2H, NH_2, exchange- able with D_2O).Anal. Calcd for $C_{26}H_{25}N_3O_5S$ (491): C, 63.54, H; 5.09; N; 8.55. Found: C, 63.40, H; 5.20, N; 8.40.

RESULTS AND DISCUSSION

4,5-Dihydro-4-oxo-thiazole nucleus has been well known in the preparation of some novel thiazolo[3,2-a]pyridine [20] and pyrano[2,3-d]thiazole derivatives [21] Thus, the work described here started by formation of thiazolidinone anion through removal a proton from active methylene moiety of 2-(4-oxo-4,5-dihydro-thiazol-2-yl) acetamide (1), which added to the deficient centers of α-substituted cinnam-onitriles. Thus, on

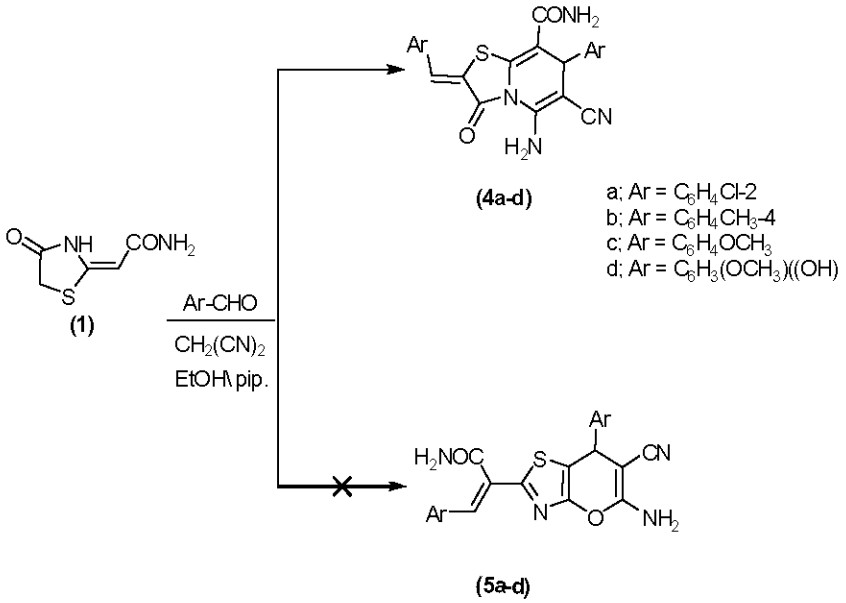


Scheme 1

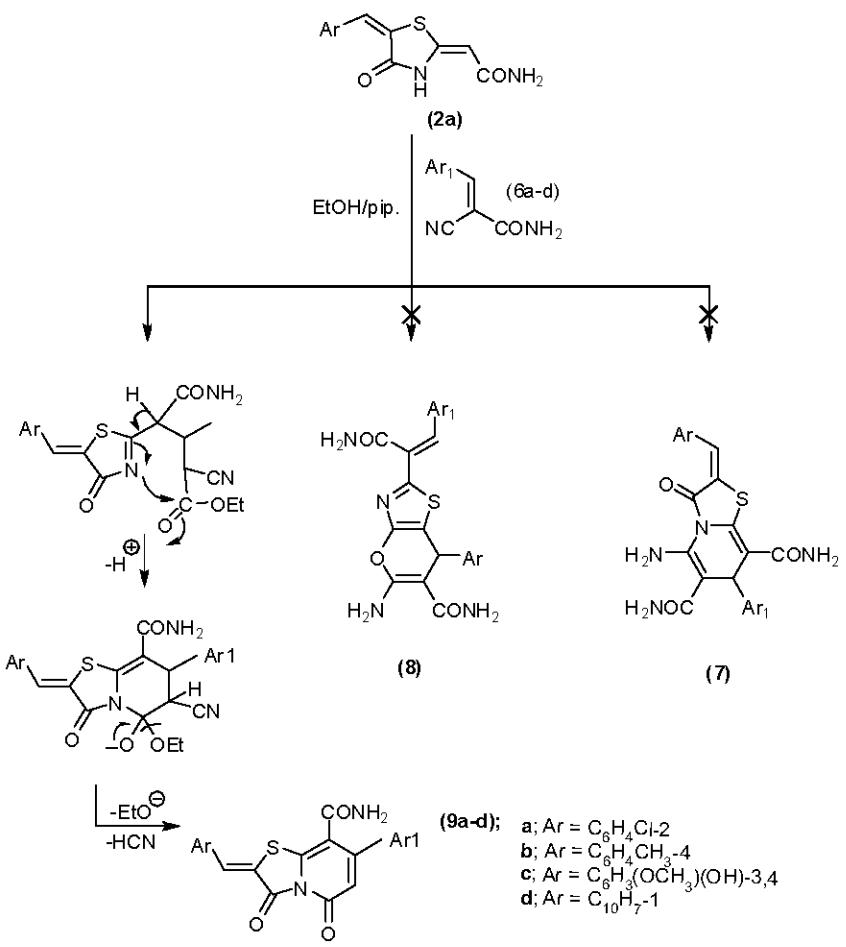
refluxing, compound (1), with aromatic aldehydes (1:1 molar ratio), give 4,5-dihydro-4-oxo-thiazoles(2a-d) on the basis of elemental analysis and spectral data. IR spectra of compounds (2a-d), exhibited absorption bands at, 3417, 3309,3380, 3184, 3379, 3147,3379, 3147 due to amino groups and at 1721, 1647, 1720, 1664, 1720, 1666, 1720 and 1658 cm^{-1} due to presence carbonyl functional groups of the precursor. Their ^1H NMR in DMSO-d_6 spectra revealed a lack of significant signal at δ 3.80 ppm, for methylene protons. The author was interested to synthesize thiazoles containing two arylmethylidine moieties (3a-c) in 2,5- positions, as intermediates between thiazoles having one arylmethylidine moiety and thiazolo[3,2-a] pyridines. Thus, 2-(4-oxo-4,5-dihydro-thiazol-2-yl) acetamide (1), react with aromatic aldehydes (1: 2 molar ratio) in ethanol solution having few drops of piperidine to give 2,5-diarylmethylidine-4,5-dihydro-4-oxo-thiazoles(3a-c). The structure of compounds (3a-c), was confirmed by the correct elemental analysis and spectral data. ^1H NMR spectra of thiazolidinone derivatives (3a-c) in DMSO-d_6 showed a lack of signal at δ 3.80 ppm, which attributed to methylene protons, (Scheme 1).

(4-Oxo- 4,5-dihydro-thiazol-2-yl) acetamide (1), was added to a mixture of malononitrile and aromatic aldehydes (1:1:2 molar ratio) in refluxing ethanolic piperidine lead to the formation of an adduct which has two possible structures (4a-d) and (5a-d), However, elemental analyses and spectral data were in complete accordance with the thiazolopyridines structure (4a-d) and ruled out the other possible structure (5a-d), (Scheme 2). The IR spectrum of compound (4a) was devoid of the absorption bands at, 3480, 3226, 2190 and 1702 cm^{-1} due to an amino, cyano and carbonyl functional groups, respectively. The ^1H NMR spectra of (4a), in DMSO-d_6 showed presence of the characteristic signals for aromatic, methine and NH_2 protons at δ 7.06-7.56, 4-H pyridine proton at δ 4.72, two methyl protons at δ 2.28, 2.39 ppm, (Scheme2).

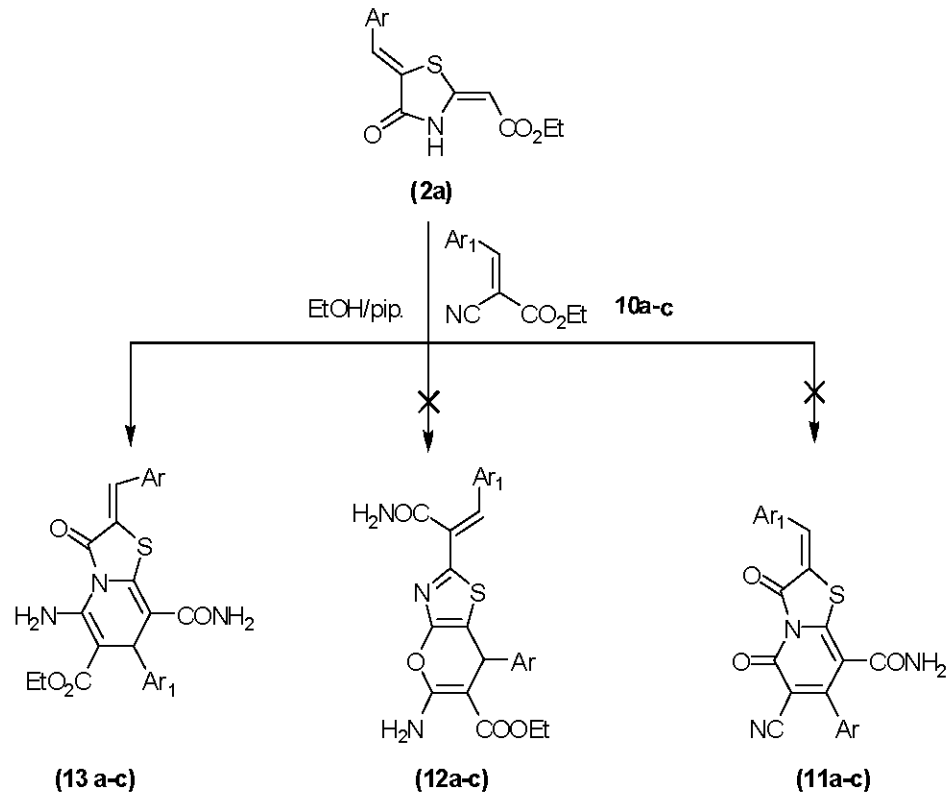
Thiazolinone derivative (2a), on heating with α-carboxamidocinnamonitriles (6a-d), in ethanolic solution catalyzed with piperidine yield the novel 2,3,6-trihydro-2-arylmethylidine -3-oxo-7-aryl-8-carboxamidothiazolo[3,2-a]pyridine-3,5-diones (9a –d), (Scheme 3). Analytical and spectral data were in agreement with thiazolo[3,2-a] pyridine-3,5-dione structure (9a-d) and the other expected structures thiazolo[3,2-a] pyridines (7a-d) and pyrano[2,3-d]thiazoles (8a-d), were excluded. IR spectrum of the reaction product (9a), showed absorption bands at 3338, 3190, 1686 and, 1654 cm_{-1} due to amino and two carbonyl functional groups, respectively. The ^1H NMR spectrum of compound (9b), revealed signals at δ 2.37, 5.82 and 8.38 due to methyl, 4 H-pyridine and amido-NH_2 protons, in addition to a multiplet signal for aromatic and methine protons in the region δ 7.51-8.14 ppm. The reaction mechanism for the formation of the novel thiazolo[3,2-a]pyridine-3,5-dione (9a-d), is assumed to proceed via the initial Micheal addition of the 4-thiazolidinone anion to the deficient β-carbon of α-carboxamidocinnamonitriles (6a-d), to form an intermediate which underwent an interamolecular cyclization followed by elimination of hydrocyanic acid, as in the following, (Scheme 3).



Scheme 2



Scheme 3



a; Ar = C_6H_4Cl-2 , Ar_1= $C_6H_4CH_3$-4
b; Ar = $C_6H_4CH_3$-4, Ar_1= $C_6H_4CH_3$-4
c; Ar = $C_6H_4OCH_3$-4, Ar_1= $C_6H_4CH_3$-4

Scheme 4

Moreover, a convenient one-step cyclization reaction lead to the synthesis of compounds (13a-c), from 4,5-dihydro-4-oxo-thiazole (2a) and α-thoxycarbnyl-cinnamonitrile (10a-c),The structure of compounds (13a-c), were formulated as thiazolo[3,2-a]pyridines on the basis of elemental and spectral data the and other possible structures (11a-c) and (12a-c) were excluded, respectively. IR spectra of compounds (13a-c), showed the presence of absorption bands corresponding to NH_2, (C=O amide, ester and thiazolidinone) functional groups. Also, their ^1H NMR data displayed significant signals corresponding to 4H-pyridine. ^{1}HNMR data for (13c), in DMSO-d_6 exhibited a strong significant signals, three proton singlet and triplet for two methyl groups at δ1.34, 2.36, methoxy protons at δ 3.87, one proton singlet for 4 -pyridine-H at δ 4.87, two protons singlet at δ 2.89, 8.21,s for two amino protons, two protons quartet at δ 4.26, for methylene group, in addition to aromatic and methine protons at 7.21-8.10 ppm, (Scheme 4).

REFERENCES

1. Quiroga, J.P., B.H. Insuasty, R. Abonia, J. Cobo, A. Sanchez and Nogueras J. Low, 2002. Control of the reaction between 2-aminobenzothiazoles and mannich bases: Synthesis of pyrido[2,1-*b*][1,3] benzothiazoles versus [1,3]benzothiazolo[2,3-b]quinazolines. J. Chem. Soc. Perkin. Trans., 1(4): 555.
2. Hutchinson, I., S. Jennings, B. Vishnuvajjala, A. Westwell and M. Stevens, 2002. Antitumor Benzothiazoles. 16 Synthesis and pharmaceutical Properties of antitumor 2-(4- aminophenyl) benzothiazole amino Acid Prodrugs. J. Med. Chem., 45: 744.
3. Hargrave, K., F. Hess and J. Oliver, 1983. N-(4-Substituted-thiazolyl) oxamic acid derivatives, new series of potent, orally active antiallergy agents. J. Med. Chem., 26: 1158.

4. Patt, W., H. Hamilton, M. Taylor, M. Ryan, J. Taylor, D.C. Connolly, A. Doherty, S. Klutchko, I. Sircar, B. Steinbaugh, B. Batley, C. Painchaud, S. Rapundalo, B. Michni-ewicz and S. Olson, 1992. Structure-activity relationships of a series of 2-amino-4-thiazole containing renin inhibitors. J. Med. Chem., 35: 2562.
5. Sharma, R., F.P. Xavier, K. Vasu, S. Chaturvedi and S. Pancholi, 2009. Synthesis of 4-benzyl-1,3-thiazole derivatives as potential anti-inflammatory agents: An analo-gue-based drug design approach. J. Enz. Inhib. Med. Chem., 24: 890.
6. Jaen, J., L. Wise, B. Caprathe, H. Tecle, S. Bergmeier, C. Humblet, T. Heffner, L. Meltzner and T. Pugsley, 1990. 4-(1,2,5,6-Tetrahydro-1-alkyl-3-pyridinyl)-2-thiazola mines. A Novel class of compounds with central dopamine agonist properties. J. Med. Chem., 33: 311.
7. Tsuji, K. and V. Ishikawa, 1994. Synthesis and anti-pseudomonal activity of new 2-isocephems with a dihydroxypyridone moiety at C-7. Bioorg. Med. Chem. Lett., 4: 1601.
8. Bell, F., A. Cantrell, M. Hogberg, S. Jaskunas, N. Johansson, C., M. Jordon, P. Kinnick, J. Lind, J.M. Morin, R. Noreen, B. Oberg, J. Palkowitz, C. Parrish, P. Pranc, C. Sahlberg, R. Ternansky, R. Vasileff, L. Vrang, S. West, H. Zhang and X. Zhou, 1995. Phene-thylthiazole thiourea (PETT) compounds, a new class of HIV-1 reverse transcriptase inhibitors, 1995. Synthesis and basic structure-ctivity relationship studies of PETT analogs. J. Med. Chem., 38: 4929.
9. Ergenc, N., G. Capan, N. Gunay, S. Ozkirimli, M. Gungor, S. Ozbey and E. Kendi, 1999. Synthesis and hypnotic activity of new 4-thiazolidinone and 2-thioxo- 4,5-imidazolidinedione derivatives. Arch. Pharm. Med. Chem., 332: 343.
10. Carter, J., S. Kramer, J. Talley, T. Penning, P. Collins, M. Graneto, K. Seibert, C. Koboldt, J. Masferrer and B. Zweifel, 1999. Synthesis and activity of sulfonamide-substituted 4,5-diaryl thiazoles as selective cyclooxygenase-2 inhibitors. Bioorg. Med. Chem. Lett., 9: 1171.
11. Badorc, A., M. Bordes, D. Cointet, P. Savi, A. Bernat, A. Lale, M. Petitou, J. Maffrand and J. Herbert, 1997. New orally active non-peptide fibrinogen receptor (GpIIb-IIIa) antagonists: Identification of ethyl 3-[N-[4-[4-amino [(ethoxycarbonyl) imin-o]methyl]phenyl]-1,3-thiazol-2-yl]-N-[1-(ethoxycarbonyl)methyl]piperid-4-yl] amino] propionate (SR 121787) as a potent and long-acting antithrombotic Agent. J. Med. Chem., 40: 3393.
12. Rudolph, J., H. Theis, R. Hanke, R. Endermann, L. Johannsen and F. Geschke, 2001. New concise synthesis, inhibitory activity toward bacterial and human DNA topoisomerases, and antibacterial properties. J. Med. Chem., 44: 619.
13. Lamphon, R.Q., M.S.A. El-Gaby, M.M. Khafagy, G.A.M. El-Hag Ali, A.A. El- Maghraby, H.A. Eyada and M.H. Helal, 2004. Studies on thiazolo pyridines. Part. 5. Synthesis of of hitherto unknown thiazolidinone and thiazolo[3,2-a] pyridine derivatives having in their structures the morpholine-4-yl-moiety. Phosphorus, sulfur and silicon, 179: 1279.
14. El-Gaby. M.S.A., M.M. Khafagy, G.A.M. El-Hag Ali, A.A. El-Maghraby and M.H.M. Helal, 2003. Studies on thiazolo pyridines. Part. 4.Synthesis of hitherto unknown 1,4- bis (thiazolopyridines) benzene derivatives, Phosphorus, sulfur and silicon, 178: 1681.
15. El-Hag Ali, G.A.M., A. Khalil, A.H.A. Ahmed and M.S.A. El-Gaby, 2002. Part. 2. Synthesis and antimicrobial activity of some novel thiazolo[3,2-a]pyridine and thiazolo[3,2-a][1,8] naphthyridine derivatives having two different aryl moieties. Acta Chim. Slov., 49: 365.
16. El-Gaby, M.S.A., G.A.M. El-HagAli, A.A. Al-Maghraby, M.T. Abd El-Rahman and M.H. Helal, 2009. Synthesis, characterization and *in vitro* antimicrobial activity of novel 2-thioxo-4-thiazolidinones and 4,4`-bis (2-thioxo-4-thiazolidinone-3-yl) diphenylsulfones. European J. Med. Chem., 44(10): 4148.
17. El-Hag Ali, G.A.M., 2003 Studies on thiazolopyridines, Part. 3. Reactivity of thiazolo[3,2-a]-3-aza-[1,8] naphthyridine towards.some. nucleophiles Phosphorus Su-lfur and Silicon, 178(4): 711.
18. El-Hag Ali, G.A.M., A. Khalil, A.H.A. Ahmed and M.S.A. El-Gaby, 2002. Studies on thiazolopyridines. Part. 2. Synthesis and antimicrobial activity of some novel thiazolo[3,2-a]pyridine and thiazolo[3,2-a][1,8] naphthyridine derivatives having two different aryl moieties. Acta. Chim. Slo., 49 : 365.
19. Azab, M.E., G.A.M. El-Hag Ali and Ashraf H.F. Abd El-Wahab, 2003. A novel synthesis of bisthiazolopyridines as promising antimicrobial agents. Acta Pharm., 53: 213.
20. El-Maghraby, A.A., G.A.M. El-Hag Ali, A.H.A. Ahmed and M.S.A. El-Gaby, 2002. Studies on thiazolopyridines,Part. 1. Antimicrobial activity of some novel fluor-inated thiazolo[3,2-a] and thiazolo[2`,3`-1,6] pyrido [2,3-d] pyrimidines. Phosphorus, Sulfur and Silicon, 177(2): 293.

21. El-Hagali, G.A.M., M.T. Abdelrhman, M.H. Helal and M.S. ElGaby, 2008. Novel synthesis of pyrano[2,3-d]thiazole, thiazolo[3,2-a]pyridine and pyrazolo [3_,4: 4, 5], thiazolo[3,2-a]pyridine derivatives, Phosphorus, Sulfur and Silicon, 183: 3023.

22. Sadek, K.U., E.A. Hafez, A.E. Mourad and M.H. Elnagdy, 1984. Activated nitrile in heterocyclic synthesis, The reaction of substituted cinnamonitriles with 2-functionaly substituted methyl -2-thiazolin -4-one derivatives, *Z. Naturforsch*, 39b: 824.