Synthesis and reactions of 2-cyano-2-(5-oxo-3-phenyl-thiazolidin-2-ylidene)-acetamides

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The base promoted nucleophilic addition of cyanoacetamide derivatives **2a**,**b** to equimolar amount of phenyl isothiocyanate in DMF containing potassium hydroxide afforded the corresponding potassium sulfide salts **3a**,**b** which were not isolated but which underwent heterocyclisation upon treatment with chloroacetyl chloride to give the corresponding 2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide derivatives **4a**,**b**. The reactions of **4a**,**b** with aryl diazonium salts, bromine and aromatic aldehydes were studied in order to obtain compounds **5–11**.

Keywords: isothiocyanates, thiazolidin-5-ones, 2-aminothiazoles

Thiazolidinones have been shown to possess diverse biological activities[1-8] which may be attributed to the presence of the N–C–S fragment. The 2-aminothiazole derivatives are of widespread use in chemistry,[9] medicine[10,11] and pharmacology.[12] In view of these reports and in continuation of our research on the synthesis of some new thiazolidinone derivatives of pharmaceutical interest,[13,14] we have synthesised 2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamides 4 and studied their reactions with aryl diazonium salts, bromine and aromatic aldehydes.

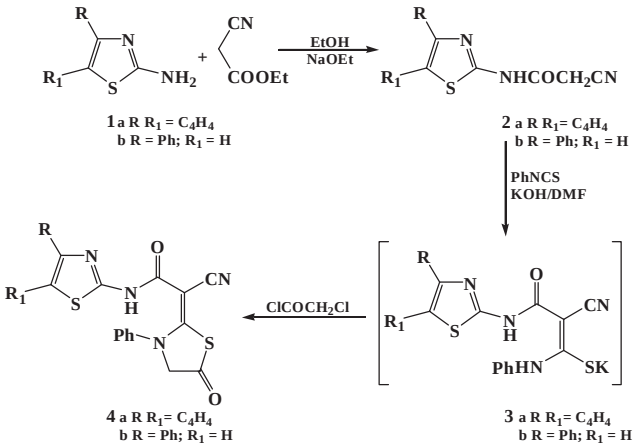
The reaction of 2-thiazolylamines **1a,b** with ethyl cyanoacetate in sodium ethoxide in ethanol solution afforded the corresponding cyanoacetamide derivatives **2a** [15] and **2b,**[16] respectively (Scheme 1).

The base promoted nucleophilic addition of cyanoacetamide derivatives **2a,b** to equimolar amount of phenyl isothiocyanate in DMF containing potassium hydroxide afforded the corresponding potassium sulfide salts **3a,b** which were not isolated. Heterocyclisation of the intermediate **3a,b** with chloroacetyl chloride gave the corresponding 2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide derivatives **4a,b**. The structures of **4a,b** were confirmed on the basis of elemental analyses and spectral data. The IR spectrum of **4b** (as an example) showed peaks at 3394 cm^{-1} (NH), 2201 cm^{-1} (CN), 1732 cm^{-1} (ring CO) and 1662 cm^{-1} (amide CO). The ^1H NMR spectrum of the same compound confirmed the presence of methylene protons signal at δ 4.10 in addition to the signals corresponding to the thiazole C-5 proton, the aromatic protons at δ 7.30–7.90 and broad singlet at δ 11.50 due to NH.

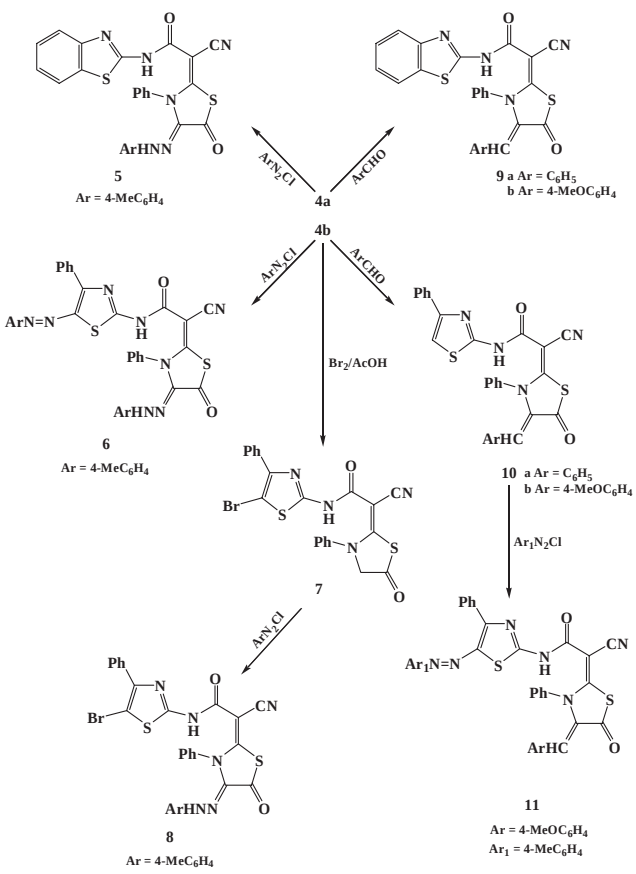
The reactivity of the active methylene group (C(4) – CH_2) present in the thiazolidin-2-ylidene moiety of **4a,b** was studied.

The coupling of *N*-benzothiazol-2-yl-2-cyano-2-(5-oxo-3-phenyl-thiazolidin-2-ylidene)-acetamide **4a** with equimolar amount of *p*-tolyl diazonium chloride at 0–5 °C in pyridine afforded the corresponding monoazo derivative **5**. The molecular structure of the monoazo derivative **5** was established by analytical and spectral data. The ^1H NMR spectrum of **5** showed a singlet at δ 2.27 assignable to the methyl protons, multiplet at δ 7.21–7.87 due to the aromatic protons, singlet at δ 11.23 for the hydrazino proton NNH and singlet at δ 13.41 for the NH.

Compound **4b** possesses two active sites (active methylene and thiazole C-5) for electrophilic substitution by aromatic diazonium salts. The methylene group in compound **4b** proved to be reactive toward coupling reaction with diazonium salts by the same extent as the thiazole C-5. Thus, compound **4b** reacted with one mole or two moles of aryl diazonium chloride at 0–5 °C to yield the corresponding bis-azo coupling product **6** by reaction at the two reactive sites (Scheme 2).



Scheme 1



Scheme 2

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Treatment of 2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-N-(4-phenyl-thiazol-2-yl)-acetamide **4b** with bromine in acetic acid afforded a product with the molecular formula $C_{21}H_{13}BrN_4O_2S_2$. Its IR spectrum revealed a band at 3391 cm^{-1} that was attributed to the presence of NH group in addition to bands at 2186 cm^{-1}, 1738 cm^{-1} and 1651 cm^{-1}corresponding to CN, exo cyclic CO and amide CO groups. Its ^{1}H NMR spectrum showed only signals at δ 4.20, 7.20–7.80 and 12.10 which were assigned to the methylene protons, aromatic protons and NH proton. The mass spectrum exhibited the molecular ion peak at *m/z* = 496 [M^+] and 498 [M^+ + 2] in addition to other peaks at 418, 244, 215, 169, 132 and 77. Based on these facts, the product was assigned as: *N*-(5-bromo-4-phenylthiazol-2-yl)-2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide **7**.

The azo coupling of **7** with aryl diazonium salt afforded the corresponding monoazo derivative **8**. The structure of product **8** was assigned on the basis of its elemental analysis and spectroscopic data. The ^{1}H NMR spectrum of **8** revealed a singlet signal at δ 2.35 corresponding to one CH_3 protons in addition to a multiplet in the region δ 7.25–7.85 for aromatic protons.

N-Benzothiazol-2-yl-2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide **4a** was condensed with aromatic aldehydes by refluxing in glacial acetic acid with fused sodium acetate to give the corresponding 4-arylidene derivatives **9a,b**. The structures of these products were confirmed on the basis of their elemental analyses and spectroscopic data. The ^{1}H NMR spectrum of **9b** displayed signals at δ 3.88 (singlet for OCH_3 protons), δ 7.21–7.87 (multiplet for the aromatic protons and olefinic CH) and δ 13.40 (singlet for NH proton).

Similarly, 2-cyano-2-(5-oxo-3-phenyl-thiazolidin-2-ylidene)-N-(4-phenyl-thiazol-2-yl)-acetamide **4b** underwent an Aldol type condensation with aromatic aldehydes, to give the corresponding 4-arylidene derivatives **10a,b**. The structures of the latter were confirmed on the basis of their elemental analyses and spectral data. The ^{1}H NMR spectrum of **10b** displayed signals at δ 3.90 (singlet for OCH_3 protons), δ 7.10–7.75 (multiplet for the aromatic protons) and δ 8.05 (singlet for the olefinic CH).

The azo coupling of **10b** afforded the product **11**. The structure of the product **11** was assigned on the basis of its elemental analysis and spectral data. The ^{1}H NMR spectrum of **11** revealed a singlet signal at δ 2.40 corresponding to one CH_3 protons, singlet at δ 3.90 for OCH_3 protons in addition to a multiplet in the region δ 7.50–8.00 for aromatic protons and singlet for olefinic proton at δ 8.15.

Experimental

All melting points were uncorrected. Elemental analyses were carried out in the microanalytical unit, Faculty of Science, University of Cairo. IR spectra were recorded on a Mattson 5000 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker WP 300 in $CDCl_3$, DMSO or CF_3COOD as solvent, using TMS as an internal standard. Mass spectra were recorded on a Finnigan MAT 212 instrument.

The purity of the synthesised compounds were tested by TLC and no by products were observed.

N-(Benzothiazol-2-yl) cyanoacetamide **(2a)** and *N*-(4-Phenyl-thiazol-2-yl) cyanoacetamide **(2b)** were prepared according to the reported method[15,16].

Synthesis of 2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide derivatives **4**: To a cold suspension of finally divided KOH (0.56 g, 0.01 mol) in DMF (20 ml) were added the cyanoacetamide derivatives **2a,b** (0.01 mol) followed by phenyl isothiocyanate (1.20 ml, 0.01 mol). The mixture was stirred at room temperature overnight, and treated with chloroacetyl chloride (0.8 ml, 0.01 mol) and left to stand at room temperature for 24 h. The mixture was poured into cold water. The solid products that separated were filtered off, washed with water and recrystallized from EtOH-DMF (1:1).

N-Benzothiazol-2-yl-2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide **(4a)**: Compound **4a** was obtained as red crystals; m.p. 245–246 °C; yield 77 %; IR (KBr): 3292 (NH), 2211 (CN), 1728 (C=O) and 1669 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$/ CF_3COOD): δ 4.10 (s, 2H, CH_2) and 7.30–7.90 ppm (m, 9H, Ar–H); MS(M+H; CI iso-butane): *m/z* (%): 393(100), 147(40), 47(70). Found: C, 58.24; H, 3.16; N, 14.22 %. $C_{19}H_{12}N_4O_2S_2$ (392.45) requires C, 58.15; H, 3.08; N, 14.28%.

2-Cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-N-(4-phenylthiazol-2-yl)-acetamide **(4b)**: Compound **4b** was obtained as yellow crystals; m.p. 270–271°C; yield 68 %; IR (KBr): 3394 (NH), 2201 (CN), 1732 (C=O) and 1662 cm^{-1} (C=O).^{1}H NMR (DMSO-d_6): δ 4.10 (s, 2H, CH_2), 7.30–7.90 (m, 11H, Ar-H and thiazole H-5) and 11.50 ppm (br.s, 1H, NH). Found: C, 60.33; H, 3.26; N, 13.47%. $C_{21}H_{14}N_4O_2S_2$ (418.49) requires C, 60.27; H, 3.37; N, 13.39%.

Synthesis of N-Benzothiazol-2-yl-2-cyano-2-(5-oxo-3-phenyl-4-tolylhydrazono-thiazolidin-2-ylidene)-acetamide **(5)**: Preparation of the diazonium salt: A solution of sodium nitrite (0.7 g, in 10 ml water) was gradually added to a well cooled solution of *p*-toluidine (1.07 g, 0.01 mol) in conc. HCl (3.0 ml). The diazonium salt solution was added with constant stirring to a cold solution of **4a** in pyridine (20 ml). The reaction mixture was stirred at 0–5 °C for 2 h. The arylazo derivative **5** thus obtained, was filtered off, dried and recrystallised from EtOH-DMF mixture (2:1).

Compound **5** was obtained as red crystals; m.p. 217–218 °C; yield 78 %; IR (KBr): 3402 (NH), 2202 (CN), 1715 (C=O) and 1650 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 2.27 (s, 3H, CH_3), 7.21–7.87 (m, 13H, Ar–H), 11.23 (br.s , 1H, NH) and 13.41 ppm (br.s , 1H, NH). Found: C, 61.02; H, 3.44; N, 16.64%. $C_{26}H_{18}N_6O_2S_2$(510.59) requires C, 61.16; H, 3.55; N, 16.46%.

Synthesis of 2-Cyano-2-(5-oxo-3-phenyl-4-tolylhydrazono-thiazolidin-2-ylidene)-N-(4-phenyl-5-tolylazo-thiazol-2-yl)-acetamide **(6)**: *Preparation of the diazonium salt*: A solution of sodium nitrite (0.7 g, 0.01 mol in 10 ml water) was gradually added to a well cooled solution of p-toluidine (1.07 g, 0.01 mol) in conc. HCl (3 ml). The diazonium salt solution was added with continuous stirring to a cold solution of **4b** (0.005 mol) in pyridine (30 ml). The reaction mixture was allowed to stand in cold for 2 h, diluted with water and then filtered. The arylazo derivative **6** thus obtained was filtered off, dried and recrystallised from EtOH–DMF mixture (1:1).

Compound **6** was obtained as orange crystals; m.p. > 300 °C; yield 63 %. IR (KBr): 3395(NH), 2202 (CN), 1729 (C=O) and 1653 cm^{-1} (C=O). ^{1}H NMR ($CDCl_3$/CF_3COOD): δ 2.35 (s, 3H, CH_3), 2.40 (s, 3H, CH_3) and 7.20–7.75 ppm (m, 18H, Ar–H). MS: *m/z* (%): 654 (M^+, 20), 536 (63), 361 (30), 334 (61), 202 (100), 134 (54), 169 (49), 106 (76). Found:C, 64.32; H, 3.86; N, 17.01%. $C_{35}H_{26}N_8O_2S_2$ (654.76) requires C, 64.20; H, 4.00; N, 17.11%.

Synthesis of N-(5-bromo-4-phenylthiazol-2-yl)-2-cyano-2-(5-oxo-3-phenylthiazolidin-2-ylidene)-acetamide **(7)**: A solution of bromine (0.01 mol in 10 ml glacial acetic acid) was added dropwise to a cold solution of **4b** (0.01 mol) in glacial acetic acid (30 ml) with continuous stirring for 2 h. The reaction mixture was poured into cold water. The solid product that separated was filtered off, dried well and recrystallised from ethanol.

Compound **7** was obtained as red crystals; m.p. 284–285 °C; yield 72 %; IR (KBr): 3391 (NH), 2186 (CN), 1738 (C=O) and 1651 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 4.20 (s, 2H, CH_2), 7.20–7.80 (m, 10H, Ar–H) and 12.10 ppm (br.s, 1H, NH). MS : *m/z* (%) = 496 (M^+ , 19), 498 (M^+ + 2, 18), 418 (20), 244 (34), 215 (100), 169 (47), 132 (52), 77 (90). Found: C, 50.62; H, 2.78; N, 11.34%. $C_{21}H_{13}BrN_4O_2S_2$ (497.39) requires C, 50.71; H, 2.63; N, 11.26%.

Synthesis of N-(5-bromo-4-phenylthiazol-2-yl)-2-cyano-2-(5-oxo-3-phenyl-4-tolylhydrazonothiazolidin-2-ylidene)-acetamide **(8)**: To a cold solution (0–5 °C) of **7** (2.48 g, 0.005 mol) in pyridine (30 ml), a cold solution of 4-tolyl diazonium chloride (0.005 mol) (prepared by adding cold sodium nitrite solution [0.35 g, 0.005 mol] to a cold suspension of *p*-toluidine [0.53 g, 0.005 mol] in conc. HCl [1.5 ml] with stirring) was added with continuous stirring. The reaction mixture was allowed to stand for 2 h, diluted with water and then filtered. The arylazo derivative **8** thus obtained, was dried and recrystallised from DMF.

Compound **8** was obtained as brown crystals; m.p. 130–132 °C; yield 65 %; IR (KBr): 3390 (NH), 2198 (CN), 1728 (C=O) and 1661 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$/CF_3COOD): δ 2.35 (s, 3H, CH_3) and 7.25–7.85 ppm (m, 14H, Ar-H). Found: C, 54.71; H, 3.25; N, 13.66%. $C_{28}H_{19}BrN_6O_2S_2$ (615.52) requires C, 54.64; H, 3.11; N, 13.65%.

Synthesis of 4-arylidene derivatives **9** *and* **10**: *General procedure*: A solution of **4a** or **4b** (0.01 mol), anhydrous sodium acetate (0.5 g), the appropriate aromatic aldehyde (0.01 mol) in acetic acid (20 ml)

was heated under reflux for 3 h. After cooling, water (20 ml) was added to the reaction mixture. The resulted arylidene derivatives were filtered off, washed with water, dried and recrystallised from EtOH–DMF mixture (1:1).

N-Benzothiazol-2-yl-2-(4-benzylidene-5-oxo-3-phenylthiazolidin-2-ylidene)-2-cyano-acetamide **(9a)**: Compound **9a** was obtained as yellow crystals; m.p. > 300 °C; yield 86 %; IR (KBr): 3390 (NH), 2194 (CN), 1712 (C=O) and 1660 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 7.30–7.90 (m, 15H, Ar-H and olefinic CH) and 12.80 ppm (br.s, 1H, NH). Found: C, 64.86; H, 3.28; N, 11.58%. $C_{26}H_{16}N_4O_2S_2$ (480.56) requires C, 64.98; H, 3.36; N, 11.66%.

N-Benzothiazol-2-yl-2-[4-(4-methoxybenzylidene)-5-oxo-3-phenylthiazolidin-2-ylidene]-2-cyanoacetamide **(9b)**: Compound **9b** was obtained as yellow crystals; m.p. > 300 °C; yield 89 %. IR (KBr): 3390 (NH), 1709 (C=O) and 1651 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): δ 3.88 (s, 3H, OCH_3), 7.21–7.87 (m, 14H, Ar–H and olefinic CH) and 13.40 ppm (br.s, 1H, NH). Found: C, 63.44; H, 3.48; N, 10.80%. $C_{27}H_{18}N_4O_3S_2$ (510.59) requires C, 63.51; H, 3.55; N, 10.97%.

2-(4-Benzylidene-5-oxo-3-phenylthiazolidin-2-ylidene)-2-cyano-N-(4-phenyl-thiazol-2-yl)-acetamide **(10a)**: Compound **10a** was obtained as yellow crystals; m.p. > 300 °C; yield 82 %; IR (KBr): 3390 (NH), 2190 (CN), 1720 (C=O) and 1653 cm^{-1} (C=O).^{1}H NMR ($CDCl_3$/CF_3COOD): δ 7.20–7.80 (m, 16H, Ar–H and thiazole H-5) and 8.00 ppm (s, 1H, olefinic CH). Found: C, 66.27; H, 3.46; N, 10.92%. $C_{28}H_{18}N_4O_2S_2$ (506.60) requires C, 66.38; H, 3.58; N, 11.06%.

2-Cyano-2-[4-(4-methoxybenzylidene)-5-oxo-3-phenylthiazolidin-2-ylidene]-N-(4-phenylthiazol-2-yl)-acetamide **(10b)**: Compound **10b** was obtained as yellow crystals; m.p. > 300 °C; yield 92 %; IR (KBr): 3394 (NH), 2198 (CN), 1712 (C=O) and 1650 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$/CF_3COOD): δ 3.90 (s, 3H, OCH_3), 7.10–7.75 (m, 15H, Ar–H and thiazole H-5) and 8.05 ppm (s, 1H, olefinic CH); MS (M+H; CI iso-butane): *m/z* (%): 537(80), 335(45), 217(35), 203(100), 177(42). Found: C, 64.83; H, 3.55; N, 10.36%. $C_{29}H_{20}N_4O_3S_2$ (536.62) requires C, 64.91; H, 3.76; N, 10.44%.

Synthesis of 2-cyano-2-[4-(4-methoxybenzylidene)-5-oxo-3-phenylthiazolidin-2-ylidene]-N-(4-phenyl-5-p-tolylazo-thiazol-2-yl)-acetamide **(11)**: Preparation of the diazonium salt: A solution of sodium nitrite (0.35 g, 0.005 mol in 5.00 ml water) was gradually added to a well cooled solution of p-toluidine (0.53 g, 0.005 mol) in conc. HCl (1.5 ml). The diazonium salt solution was added with continuous stirring to a cold solution of 10b (0.005 mol) in pyridine (30 ml). The reaction mixture was stirred at 0 °C for 3 h and the formed solid product was collected by filtration. The arylazo derivative 11 was dried and recrystallised from DMF.

Compound **11** was obtained as red crystals; m.p. > 300 °C; yield 81 %; IR (KBr): 3397 (NH), 2190 (CN), 1716 (C=O) and 1666 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$/ CF_3COOD): δ 2.45 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.50–8.00 (m, 18H, Ar–H) and 8.15 ppm (s, 1H, olefinic CH); MS (M+H; CI iso-butane): *m/z* (%): 655 (10), 335 (70), 203 (100),177 (25). Found: C, 66.16; H, 4.18; N, 12.93%. $C_{36}H_{26}N_6O_3S_2$ (654.76) requires C, 66.04; H, 4.00; N, 12.84%.

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