Regioselective Synthesis of New 2-(E)-Cyano(thiazolidin-2-ylidene)thiazoles

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Abstract: Cyclocondensation of 2-[bis(methylthio)methylene]malononitrile (1) and cysteamine (2) afforded 2-(thiazolidin-2-ylidene)malononitrile (3). This compound on treatment with NaSH gave the corresponding thioamide derivative 4a in a regioselective manner on the basis of its single crystal X-ray diffraction analysis. Reaction of this compound with several α-bromocarbonyl compounds gave new 2-(E)-cyano(thiazolidin-2-ylidene)thiazoles 5a-g.

Keywords: thiazole; thiazolidine; Hantzsch’s synthesis; heterocyclization; regioselective synthesis; X-ray crystallography

Introduction

Thiazole is an important scaffold in heterocyclic chemistry and 1,3-thiazole ring is present in many pharmacologically active substances [1]. For example thiazole-5-ylacetic acid derivatives possess strong anti-inflammatory activity [2]. Other compounds containing the thiazole ring have been reported as being histamine H3 antagonists [3], with herbicidal [4], antitumoral [5] and selective cardiodepressant activities [6].
Several methods for the synthesis of thiazole derivatives have been developed [7-11], the most widely used method being the Hantzsch’s synthesis utilizing thioamides and α-halocarbonyl compounds as the starting materials [12]. The preparation of thioamides has been reviewed elsewhere [13]. One procedure involves nitriles which can be converted to thioamides through treatment with elemental sulfur, S₈ [14,15], gaseous hydrogen sulfide in the presence of anion exchange resin (Dowex 1X8, SH- form) at room temperature [16], sodium hydrosulfide hydrate and magnesium chloride hexahydrate in DMF or methanol [17], ammonium sulfide in methanol [18] and phosphorus pentasulfide [19].

Our interest in the synthesis of heterocyclic compounds of biologically importance has encouraged us to study the synthesis of some new functionalized thiazoles. In this context we wish to report on the reactions and single crystal X-ray diffraction analysis of a newly synthesized thioamide which on treatment with various α-bromocarbonyl compounds afforded some new 2-(E)-cyano(thiazolidin-2-ylidene)thiazoles.

**Results and Discussion**

2-(E)-Cyano(thiazolidin-2-ylidene)thiazoles 5a-g were prepared in a three-step procedure starting from the dinitrile 3 (Scheme 1). Cyclocondensation of 2-[bis(methylthio)methylene]malononitrile (1) and cysteamine (2) in ethanol afforded thiazolidine 3, which was filtered off and thionated by sodium hydrosulfide hydrate in water to give 2-cyano-2-(thiazolidin-2-ylidene)ethanethioamide (4) that can form either E and/or Z geometric isomers 4a,b.

**Scheme 1.** Synthesis of 2-(E)-cyano(thiazolidin-2-ylidene)thiazoles 5a-g. For substituents R¹ and R² see Table 1.
Table 1. Results of reaction 4a and α-bromocarbonyl compounds in DMF at room temperature.

| Entry | R¹ | R² | Substrate | α-Bromocarbonyl          | Time, h | Yield, % |
|-------|----|----|-----------|--------------------------|--------|---------|
| 1     | H  | CO₂Et | 5a        | Ethyl bromopyruvate      | 2      | 71      |
| 2     | H  | CH₃   | 5b        | Bromoacetone             | 2      | 73      |
| 3     | H  | C₆H₅  | 5c        | Phenacyl bromide         | 2      | 79      |
| 4     | H  | p-NO₂C₆H₄ | 5d | p-Nitrobrmocaceto phenone | 2      | 82      |
| 5     | COCH₃ | CH₃ | 5e        | 3-Bromo acetyl acetone   | 2      | 77      |
| 6     | CO₂Et | CH₃ | 5f        | Ethyl 2-bromoacetoacetate| 2      | 77      |
| 7     | -   | -    | 5g        | Ethyl bromoacetate       | 8      | 75      |

For exact determination of these geometric isomers 4a,b, single crystal X-ray analysis would seem to be preferable to other available techniques but all our efforts to prepare a suitable single crystal from compound 4 were unsuccessful, but instead we obtained a single crystal from the derivative ethyl 2-(E)-cyano(thiazolidin-2-ylidene)methyl)thiazole-4-carboxylate (5a). X-ray quality crystals were grown from ethanol with slow evaporation. A crystal structure was determined for product 5a and is shown in Figure 1. The molecule exists in the E geometric form with respect to C1-C4 bond. This observation clearly indicates that compound 4 must have the E isomeric structure 4a. The packing diagram of 5a shows that there is intermolecular hydrogen bonding between the hydrogen atom on the N1 and the N2 atom. Another intramolecular interaction is Van der Waals interaction between molecules. The high contact interaction between S1…S1 (3.777 Å) and O1…H9A (2.709 Å) gives rise to crystal growth expansion along b axis (see Figure 2).

Figure 1. Molecular plot of 5a with the thermal ellipsoids representing 50% probability.
The bond lengths of five-membered ring C5S2C7C6N2 are shorter than that ring C1S1C3C2N1, confirming the aromacity of the former ring. In this compound the C4C11N3 bond and the aromatic ring are in the same plane.

The thioamide 4a was treated with α-bromocarbonyl compounds in DMF to afford the new 2-(E)-cyano(thiazolidin-2-ylidene)thiazoles 5a-g (Table 1). The structures of compounds 3, 4a and 5a-g were deduced from their elemental analyses and 1H-NMR spectral data. The 1H-NMR spectra of compounds 3, 4a and 5a-g showed triplet signals at 3.47-3.63 ppm and 3.99-4.32 ppm (J ~ 7.6 Hz) due to the two methylene groups of the thiazolidine rings, and broad signals due to the NH group at 6.84-12.17 ppm. The 13C-NMR spectrum of 4a showed signals due to nitrile and thiocarbonyl groups at 119.42 ppm and 189.56 ppm. IR spectroscopy also confirmed the structure of products.

**Experimental**

**General**

All of the melting points are uncorrected and were recorded on an Electrothermal type 9100 melting point apparatus. The mass spectra observed on a Varian Mat CH-7 at 70 ev. The infrared spectra were determined on 4300 Shimadzu spectrometer and only noteworthy absorptions are listed. The 1H-NMR spectra were recorded on a Bruker Avance DRX-500 Fourier transform spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard. All solvents and chemicals were of research grade and were used as obtain from Merck. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer. Compound 1 was prepared according to the procedure reported in the literature [20].

**Synthesis of 2-(thiazolidin-2-ylidene)malononitrile (3)**

A suspension of 2-[bis(methylthio)methylene]malononitrile 1 (3.4 g, 0.02 mol) and cysteamine 2 (1.54 g, 0.02 mol) in ethanol (96%) (40 mL) was stirred at room temperature for 4 h. The white
powder of 3 that precipitated was collected by suction filtration, washed with ethanol (2 × 10 mL), and
dried in air to give 2.2 g (73%) of 3, mp 209-212 °C; IR (KBr): 3,195, 2,207, 1,571 cm⁻¹; ¹H-NMR
d(CDCl₃) δ 3.48 (t, J = 6.9 Hz, 2H, SCH₂), 3.99 (t, J = 6.9 Hz, 2H, NCH₂), 6.84 (s, 1H, NH); MS (70
eV) m/z: 151 (M⁺); Anal. Calcd. for C₆H₅N₃S: C, 47.66; H, 3.34; N, 27.79; S, 21.21. Found: C, 47.56;
H, 3.43; N, 27.71; S, 21.30.

**Synthesis of (E)-2-cyano-2-(thiazolidin-2-ylidene)ethanethioamide (4a)**

A solution of thiazolidine 3 (1.5 g, 0.01 mol) and sodium hydrosulfide hydrate (68%) (1.65 g,
0.02 mol) in water (10 mL) was heated at 50 °C for 22 h. The reaction mixture was cooled to room
temperature and the product was precipitated by addition of acetic acid. The precipitate was collected
by suction filtration, washed with ethanol (2 × 5 mL), dried in air, and recrystallized from CH₃CN, to
give 1.21g (65%) of 4a as white needles, mp 217-219 °C; IR (KBr): 3,435, 3,320, 2,182, 1,613, 1,570
cm⁻¹; ¹H-NMR (acetone-d₆) δ: 3.61 (t, J = 7.1 Hz, 2H, SCH₂), 4.32 (t, J = 7.1 Hz, 2H, NCH₂), 7.50 (s,
2H, NH₂), 12.17 (1H, s, NH); ¹³C-NMR (DMSO-d₆) δ: 30.28, 52.86, 75.45, 119.42, 175.53, 189.56;
MS (70 eV) m/z: 185 (M⁺); Anal. Calcd. for C₆H₇N₃S₂: C, 38.90; H, 3.81; N, 22.68; S, 34.61. Found:
C, 38.95; H, 3.74; N, 22.76; S, 34.55.

**General procedure for the synthesis of 2- (E)-cyano(thiazolidin-2-ylidene)thiazoles 5a-g**

A suspension of thioamide 4a (1.85 g, 1 mmol), the appropriate α-bromocarbonyl (1 mmol) and
sodium bicarbonate (0.84 g, 1 mmol) in DMF (1 mL) was stirred at room temperature for 2-8 h. After
dilution with water (5 mL), the solid obtained was filtered off, washed with water (1 × 5 mL) and
ethanol (1 × 5 mL), dried in air, and recrystallized from CH₃CN, to give 5a-g in 71–82% yield.

**Ethyl 2-[(E)-cyano(thiazolidin-2-ylidene)methyl]thiazole-4-carboxylate (5a):** mp 264-267 °C; IR
(KBr): 3,430, 2,186, 1,597, 1,561 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 1.34 (t, J = 6.6 Hz, 3H, CH₃), 3.52 (t,
J = 7.2 Hz, 2H, SCH₂), 4.12 (t, J = 7.2 Hz, 2H, NCH₂), 4.31 (q, J = 6.6 Hz, 2H, OCH₂), 8.24 (s, 1H,
C=C-H), 9.93 (s, 1H, NH); MS (70 eV) m/z: 281 (M⁺); Anal. Calcd. for C₁₁H₁₁N₃O₂S₂: C, 46.96; H,
3.94; N, 14.94; S, 22.79. Found: C, 47.07; H, 4.02; N, 14.90; S, 22.63.

**Ethyl 2-[(E)-cyano(thiazolidin-2-ylidene)methyl]thiazole-4-carboxylate (5b):** mp 264-267 °C; IR
(KBr): 3,430, 2,186, 1,597, 1,561 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 1.34 (t, J = 6.6 Hz, 3H, CH₃), 3.52 (t,
J = 7.2 Hz, 2H, SCH₂), 4.12 (t, J = 7.2 Hz, 2H, NCH₂), 4.31 (q, J = 6.6 Hz, 2H, OCH₂), 8.24 (s, 1H,
C=C-H), 9.93 (s, 1H, NH); MS (70 eV) m/z: 281 (M⁺); Anal. Calcd. for C₁₁H₁₁N₃O₂S₂: C, 46.96; H,
3.94; N, 14.94; S, 22.79. Found: C, 47.07; H, 4.02; N, 14.90; S, 22.63.

**(E)-2-(4-Methylthiazol-2-yl)-2-(thiazolidin-2-ylidene)acetonitrile (5b):** mp 166-168 °C; IR
(KBr): 3,438, 2,180, 1,563 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 2.32 (s, 3H, CH₃), 3.47 (t, J = 7.7 Hz, 2H,
SCH₂), 4.01 (t, J = 7.7 Hz, 2H, SCH₂), 6.91 (s, 1H, C=C-H), 9.94 (s, 1H, NH); MS (70 eV) m/z: 223 (M⁺);
Anal. Calcd. for C₉H₉N₃S₂: C, 48.41; H, 4.06; N, 18.82; S, 28.71. Found: C, 48.40; H, 4.10; N, 18.74;
S, 28.76.

**(E)-2-(4-Phenylthiazol-2-yl)-2-(thiazolidin-2-ylidene)acetonitrile (5c):** mp 181-184 °C; IR
(KBr): 3,438, 2,187, 1,563 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 3.53 (t, J = 7.9 Hz, 2H, SCH₂), 4.12 (t, J = 7.9 Hz,
2H, NCH₂), 7.41, 8.05 (5H, Ph), 7.85 (s, 1H, C=C-H), 9.81 (s, 1H, NH); MS (70 eV) m/z: 285 (M⁺);
Anal. Calcd. for C₁₄H₁₁N₃S₂: C, 58.92; H, 3.88; N, 14.73; S, 22.47. Found: C, 58.94; H, 3.77; N,
14.41; S, 22.78.
(E)-2-(4-(4-Nitrophenyl)thiazol-2-yl)-2-(thiazolidin-2-ylidene)acetonitrile (5d): mp 264-267 °C; IR (KBr): 3,433, 2,193, 1,569 cm⁻¹; ¹H NMR (DMSO-d₆) δ: 3.62 (t, J = 7.8 Hz, 2H, SCH₂), 4.13 (t, J = 7.8 Hz, 2H, SCH₂), 8.15 (s, 1H, C=C-H), 8.31 (s, 4H, Ph), 9.65 (s, 1H, NH); MS (70 eV) m/z: 330 (M⁺); Anal. Calcd. for C₁₄H₁₀N₄O₂S₂: C, 50.90; H, 3.05; N, 16.96; S, 19.41. Found: C, 51.12; H, 2.97; N, 17.02; S, 19.56.

(E)-2-(5-Acetyl-4-methylthiazol-2-yl)-2-(thiazolidin-2-ylidene)acetonitrile (5e): mp 255-257 °C; IR (KBr): 3,421, 2,191, 1,648, 1,557 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 2.52 (s, 3H, COCH₃), 2.65 (s, 3H, CH₃), 3.52 (t, J = 7.7 Hz, 2H, SCH₂), 4.12 (t, J = 7.7 Hz, 2H, NCH₂), 10.13 (s, 1H, NH); MS (70 eV) m/z: 265 (M⁺); Anal. Calcd. for C₁₁H₁₁N₃O₂S₂: C, 49.79; H, 4.18; N, 15.84; S, 24.16. Found: C, 49.68; H, 4.02; N, 15.60; S, 24.42.

Ethyl 2-((E)-cyano(thiazolidin-2-ylidene)methyl)-4-methylthiazole-5 carboxylate (5f): mp 253-255 °C; IR (KBr): 3,443, 2,190, 1,706, 1,562 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 1.26 (t, J = 7.1 Hz, 3H, CH₂CH₃), 2.60 (s, 3H, CH₃), 3.57 (t, J = 7.6 Hz, 2H, SCH₂), 4.06 (t, J = 7.6 Hz, 2H, NCH₂), 4.16 (t, J = 7.1 Hz, 2H, OCH₂), 10.13 (s, 1H, NH); MS (70 eV) m/z: 295 (M⁺); Anal. Calcd. for C₁₂H₁₃N₃O₂S₂: C, 48.80; H, 4.44; N, 14.23; S, 21.71. Found: C, 48.76; H, 4.27; N, 14.05; S, 21.77.

(2E)-2-(4,5-Dihydro-4-oxothiazol-2-yl)-2-(thiazolidin-2-ylidene)acetonitrile (5g): mp 248-252 °C; IR (KBr): 3,422, 2,193, 1,688, 1,573 cm⁻¹; ¹H-NMR (DMSO-d₆) δ: 3.63 (t, J = 7.8 Hz, 2H, SCH₂), 4.01 (s, 2H, COCH₂), 4.12 (t, J = 7.8 Hz, 2H, NCH₂), 10.53 (s, 1H, NH); MS (70 eV) m/z: 225 (M⁺); Anal. Calcd. for C₈H₇N₃O₄S₂: C, 42.65; H, 3.13; N, 18.65; S, 28.46. Found: C, 42.74; H, 3.00; N, 18.46; S, 28.68.

Crystal data for 5a

Crystallographic data and details of 5a are presented in Tables 2 and 3. The X-ray diffraction data for crystals of 5a were collected on Bruker AXS Smart Apex II CCD diffractometer at 100 K. The raw intensity data frames were integrated with the SAINT program, which also applied corrections [21]. Data were corrected for absorption effects by the SADABAS procedure [22]. The software package SHELXTL v6.12 was used for the space group determination, structure solution and refinement. The structures were solved by direct methods (SHELXS-97) [23], completed with difference Fourier syntheses and refined with full-matrix least-squares using SHELXL-97 minimizing w =1/[σ²(Fo)²+(0.0440P)²+0.8400P] where P=(Fo²+2Fc²)/3. CCDC 711896 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/conts/retrieving.html.

| Table 2. Crystallographic data for compound 5a. |
|-----------------------------------------------|
| **Empirical formula**  | C₁₁H₁₁N₃O₂S₂ |
| **Formula weight**     | 281.35       |
| **Temperature**        | 100(2) K     |
| **Crystal system**      | Monoclinic   |
| **Crystal size**        | 0.30 × 0.08 × 0.04 mm³ |
Table 2. Cont.

| Property                          | Value                       |
|----------------------------------|-----------------------------|
| Space group                      | $P2_1/n$                    |
| $a$                              | 14.9127(16) Å               |
| $b$                              | 4.6129(5) Å                 |
| $c$                              | 18.658(2) Å                 |
| $\beta$                          | 106.175(2)°                |
| $V$                              | 1232.7(2) Å$^3$             |
| $Z$                              | 4                          |
| $D_{calc}$                       | 1.516 Mgm$^{-3}$            |
| $\mu$                            | 0.429 mm$^{-1}$             |
| $F(000)$                         | 584                         |
| $\theta$ range                   | 1.55 to 30.66°              |
| Index ranges                     | -21 <= h <= 21, -6 <= k <= 6, -26 <= l <= 26 |
| Reflections collected            | 15302                       |
| Data/restraints/parameters       | 3802/0/164                  |
| Goodness-of-fit on $F^2$          | 1.006                       |
| Radiation                        | Mo K$\alpha$ 0.71073 (\AA) |
| Independent reflections          | 3802 [R(int) = 0.0473]      |
| Completeness to theta = 30.66°   | 99.2%                       |
| Absorption correction            | Semi-empirical from equivalents |
| Refinement method                | Full-matrix least-squares on $F^2$ |
| Final R indices [for 4865 rfln. with $I>2\sigma(I)$] | R1 = 0.0419, wR2 = 0.0947 |
| R indices (all data)             | R1 = 0.0588, wR2 = 0.1022  |
| Largest diff. peak and hole      | 0.368 and -0.257 e.Å$^{-3}$ |

Table 3. Selected bond lengths [Å] and angles [°] for compound 5a.

| Bond                  | Length [Å] | Angle [°]       |
|-----------------------|------------|-----------------|
| S(1)-C(1)             | 1.7507(17) |                 |
| S(1)-C(3)             | 1.8222(19) |                 |
| S(2)-C(7)             | 1.7141(18) |                 |
| S(2)-C(5)             | 1.7459(17) |                 |
| O(1)-C(8)             | 1.207(2)   |                 |
| O(2)-C(8)             | 1.342(2)   |                 |
| O(2)-C(9)             | 1.462(2)   |                 |
| N(1)-C(1)             | 1.333(2)   |                 |
| N(1)-C(2)             | 1.463(2)   |                 |
| N(2)-C(5)             | 1.315(2)   |                 |
| N(2)-C(6)             | 1.382(2)   |                 |
| N(3)-C(11)            | 1.153(2)   |                 |
| C(1)-C(4)             | 1.385(2)   |                 |
| C(2)-C(3)             | 1.522(3)   |                 |
| C(4)-C(11)            | 1.418(2)   |                 |
| C(4)-C(5)             | 1.443(2)   |                 |
| C(6)-C(7)             | 1.358(2)   |                 |
| C(6)-C(8)             | 1.484(2)   |                 |
| C(9)-C(10)            | 1.506(3)   |                 |
| S(1)-C(1)-C(3)        | 90.58(8)   |                 |
| C(7)-S(2)-C(5)        | 89.28(8)   |                 |
| C(8)-O(2)-C(9)        | 115.60(14) |                 |
| N(1)-C(1)-C(4)        | 125.56(15) |                 |
| N(2)-C(5)-S(2)        | 120.53(13) |                 |
| C(7)-C(6)-N(2)        | 116.01(16) |                 |
| C(7)-C(6)-C(8)        | 125.49(16) |                 |
| C(9)-C(10)-N(3)       | 179.5(2)   |                 |
Conclusions

We have reported synthesis of novel 2-(E)-cyano(thiazolidin-2-ylidine)thiazoles from dinitrile 3 as a starting material. Application of these compounds to the synthesis of other heterocyclic ring systems is currently under investigation and the results will be published in due course.

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