



Regioselective synthesis of new 2-(*E*)-cyano(oxazolidin-2-ylidene)thiazoles

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ABSTRACT

Reaction of 2-(oxazolidin-2-ylidene)malononitrile (**1**) with phosphorus pentasulfide gave the corresponding thioamide derivative (**2a**) in a regioselective manner. Reaction of this compound with several α -bromocarbonyl compounds gave new 2-(*E*)-cyano(oxazolidin-2-ylidene)thiazoles (**3a-g**). The chemical structures of novel compounds were confirmed by ¹H NMR, elemental analysis, FT-IR spectrometry and mass spectrophotometric analyses.

1. 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], antimicrobial [5], antitumoral [6] and selective cardio-depressant activities [7].

Several methods for the synthesis of thiazole derivatives have been developed [8-12], the most widely used method being the Hantzsch's synthesis utilizing thioamides and α -halocarbonyl compounds as the starting materials [13]. Also the factors which affect on the orientation of cyclization reactions of functionalized 1,2,4-triazine derivatives with α -halocarbonyl compounds were reviewed [14].

In connection with our interest in the synthesis of new polyfunctionalized thiazoles as potential precursors for the synthesis of biologically important fused thiazoles, we previously described the regioselective synthesis of new 2-(*E*)-cyano(thiazolidin-2-ylidene)thiazoles from reaction of (*E*)-2-cyano-2-(thiazolidin-2-ylidene)ethanethioamide with various α -bromocarbonyl compounds. Corresponding thioamide was prepared as pure geometric isomer from the reaction of 2-(thiazolidin-2-ylidene)malononitrile with sodium hydrosulfide hydrate (Scheme 1) [15].

To extend the scope of this reaction, we have studied the reaction of (*E*)-2-cyano-2-(oxazolidin-2-ylidene)ethanethioamide (**2a**) with several α -bromocarbonyl compounds in order to synthesize the new 2-(*E*)-cyano(oxazolidin-2-ylidene)thiazoles (**3a-g**).

2. Experimental

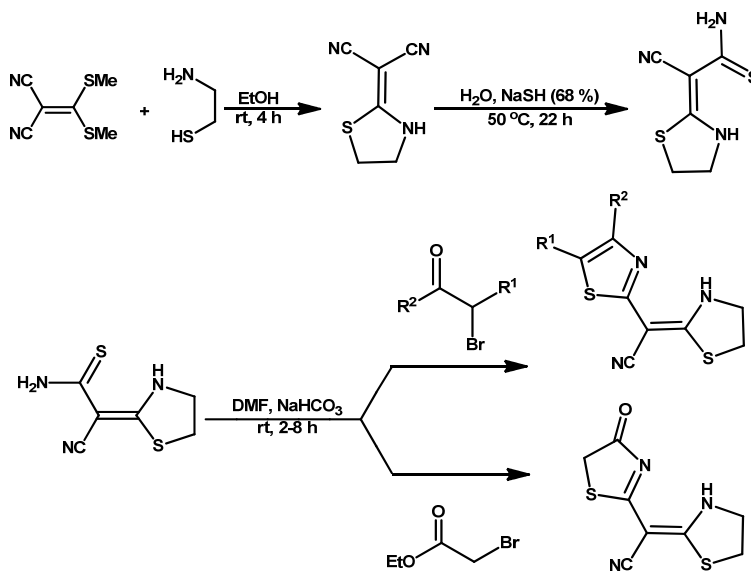
2.1. Instrumentation

Compound **1** was obtained according to the published method [16]. All reagents and chemicals were purchased from commercial sources and used without further purification. Melting points were taken on an Electrothermal type 9100 melting point apparatus and are uncorrected. The ¹H NMR spectra were recorded on a Bruker AC 100 spectrometer with Me₄Si as an internal standard. Chemical shifts are reported in parts per million (ppm) from the tetramethylsilane resonance in the indicated solvent. Coupling constants are reported in Hertz (Hz), spectral splitting partners are designed as follow: singlet (s); doublet (d); triplet (t); quartet (q); multiplet (m). The mass spectra were obtained with a Varian Mat. CH-7 at 70 eV. The FT-IR spectra were recorded with a 4300 Shimadzu spectrometer in KBr discs and only noteworthy absorptions are listed. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer.

2.2. Synthesis

2.2.1. Preparation of (*E*)-2-cyano-2-(oxazolidin-2-ylidene)ethanethioamide (**2a**)

The title compound was synthesized according to a literature procedure [17] with slight modification as follows: to a stirred solution of P₄S₁₀ (4.44 g, 0.02 mol) in methanol (20 mL), dinitrile **1** (2.70 g, 0.02 mol) was added and the resulting mixture was stirred for another 2 h. The precipitated solid was filtered, washed with methanol, air dried, and crystallized from acetonitrile to give **2a** (Scheme 2). White needles. Yield: 86 %. M.p.: 290-291 °C. FT-IR (KBr, cm⁻¹): 3455, 3170 ν(NH, NH₂), 2197 ν(C≡N), 1622 ν(C=C). ¹H NMR (Aceton-*d*₆): 4.05 (t, *J* = 8.4 Hz, 2H, NCH₂), 4.77 (t, *J* = 8.4 Hz, 2H, OCH₂), 7.48 (br., 2H, NH₂, D₂O exchangeable), 11.38 (br., 1H, NH, D₂O exchangeable).



Scheme 1

MS (EI, m/z (%)): 169 (M^+ , 5 %). Anal. calcd. for $C_6H_7N_3OS$: C, 42.59; H, 4.17; N, 24.83; S, 18.95. Found: C, 42.66; H, 4.25; N, 24.80; S, 18.88%.

2.2.2. Preparation of 2-(E)-Cyano(oxazolidin-2-ylidene)thiazoles (3a-g)

General Procedure: A suspension of thioamide **2a** (0.34 g, 2 mmol), the appropriate α -bromocarbonyl (2 mmol) and sodium bicarbonate (0.17 g, 2 mmol) in DMF (1 mL) was stirred at room temperature for 2-8 h. After dilution with water, the solid obtained was filtered off, washed with water and ethanol, air dried, and crystallized from acetonitrile to give **3a-g**.

Ethyl 2-((E)-cyano(oxazolidin-2-ylidene)methyl)thiazole-4-carboxylate (3a): White needles. Yield: 68 %. M.p.: 203-204 °C. FT-IR (KBr, cm^{-1}): 3413 ν (NH), 2196 ν (C \equiv N), 1733 ν (C=O), 1620 ν (C=C). 1H NMR (DMSO- d_6): 1.27 (t, J = 6.7 Hz, 3H, CH_3), 3.80 (t, J = 8.4 Hz, 2H, NCH_2), 4.26 (q, J = 6.7 Hz, 2H, OCH_2CH_3), 4.69 (t, J = 8.4 Hz, 2H, OCH_2), 8.10 (s, 1H, C=C-H), 9.30 (br., 1H, NH, D_2O exchangeable). MS (EI, m/z (%)): 265 (M^+ , 7). Anal. Calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84; S, 12.09. Found: C, 49.78; H, 4.21; N, 15.84; S, 12.14%.

(E)-2-(4-Methylthiazol-2-yl)-2-(oxazolidin-2-ylidene)acetonitrile (3b): White needles. Yield: 72 %. M.p.: 164-165 °C. FT-IR (KBr, cm^{-1}): 3426 ν (NH), 2202 ν (C \equiv N), 1613 ν (C=C). 1H NMR (DMSO- d_6): 2.30 (s, 3H, CH_3), 3.83 (t, J = 8.5 Hz, 2H, NCH_2), 4.66 (t, J = 8.5 Hz, 2H, OCH_2), 6.83 (s, 1H, C=C-H), 9.48 (br., 1H, NH, D_2O exchangeable). MS (EI, m/z (%)): 207 (M^+ , 4 %). Anal. Calcd. for $C_9H_9N_3OS$: C, 52.16; H, 4.38; N, 20.27; S, 15.47. Found: C, 52.23; H, 4.45; N, 20.24; S, 15.41%.

((E)-2-(4-(4-Chlorophenyl)thiazol-2-yl)-2-(oxazolidin-2-ylidene)acetonitrile (3c): Yellow needles. Yield: 76 %. M.p.: 240-241 °C. FT-IR (KBr, cm^{-1}): 3423 ν (NH), 2203 ν (C \equiv N), 1617 ν (C=C). 1H NMR (DMSO- d_6): 3.90 (t, J = 8.4 Hz, 2H, NCH_2), 4.68 (t, J = 8.4 Hz, 2H, OCH_2), 7.44 (d, J = 8.3 Hz, 2H, Ar-H), 7.76 (s, 1H, C=C-H), 8.08 (d, J = 8.3 Hz, 2H, Ar-H), 9.26 (br., 1H, NH, D_2O exchangeable). MS (EI, m/z (%)): 304 (M^+ , 24 %). Anal. Calcd. for $C_{14}H_{10}ClN_3OS$: C, 55.35; H, 3.32; N, 13.83; S, 10.56. Found: C, 55.29; H, 3.40; N, 13.88; S, 10.51%.

((E)-2-(4-(4-Bromophenyl)thiazol-2-yl)-2-(oxazolidin-2-ylidene)acetonitrile (3d): Yellow needles. Yield: 77 %. M.p.: 245-

246 °C. FT-IR (KBr, cm^{-1}): 3433 ν (NH), 2203 ν (C \equiv N), 1610 ν (C=C). 1H NMR (DMSO- d_6): 3.89 (t, J = 8.3 Hz, 2H, NCH_2), 4.68 (t, J = 8.3 Hz, 2H, OCH_2), 7.56 (d, J = 8.3 Hz, 2H, Ar-H), 7.76 (s, 1H, C=C-H), 8.00 (d, J = 8.3 Hz, 2H, Ar-H), 9.25 (br., 1H, NH, D_2O exchangeable). MS (EI, m/z (%)): 348 (M^+ , 18 %). Anal. Calcd. for $C_{14}H_{10}BrN_3OS$: C, 48.29; H, 2.89; N, 12.07; S, 9.21. Found: C, 48.26; H, 2.93; N, 12.02; S, 9.27%.

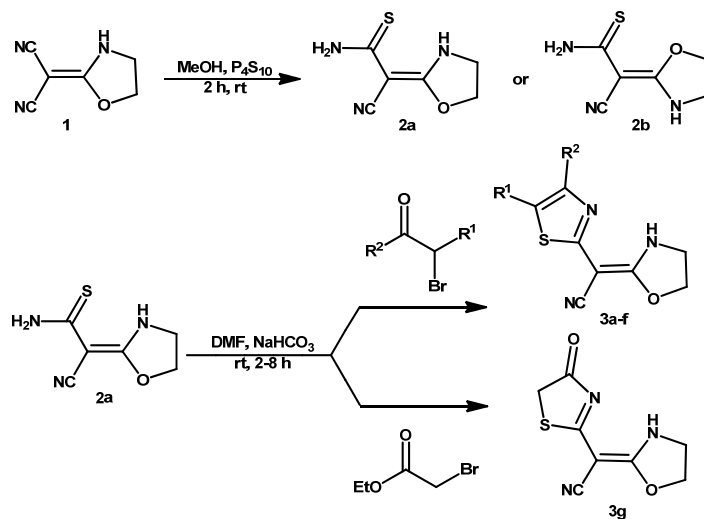
(E)-2-(5-Acetyl-4-methylthiazol-2-yl)-2-(oxazolidin-2-ylidene)acetonitrile (3e): Yellow needles. Yield: 79 %. M.p.: 296-297 °C. FT-IR (KBr, cm^{-1}): 3441 ν (NH), 2200 ν (C \equiv N), 1648 ν (C=O), 1606 ν (C=C). 1H NMR (DMSO- d_6): 2.44 (s, 3H, $COCH_3$), 2.61 (s, 3H, CH_3), 3.88 (t, J = 8.5 Hz, 2H, NCH_2), 4.71 (t, J = 8.5 Hz, 2H, OCH_2), 9.75 (br., 1H, NH, D_2O exchangeable). MS (EI, m/z (%)): 249 (M^+ , 9 %). Anal. Calcd. for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 53.08; H, 4.49; N, 16.80; S, 12.82%.

Ethyl 2-((E)-cyano(oxazolidin-2-ylidene)methyl)thiazole-5-carboxylate (3f): White needles. Yield: 75 %. M.p.: 247-248 °C. FT-IR (cm^{-1}): 3447 ν (NH), 2204 ν (C \equiv N), 1696 ν (C=O), 1612 ν (C=C). 1H NMR (DMSO- d_6): 1.23 (t, J = 7.0 Hz, 3H, CH_2CH_3), 2.55 (s, 3H, CH_3), 3.57 (t, J = 8.5 Hz, 2H, NCH_2), 4.18 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 4.68 (t, J = 8.5 Hz, 2H, OCH_2), 9.67 (br., 1H, NH, D_2O exchangeable). MS (EI, m/z (%)): 279 (M^+ , 10 %). Anal. Calcd. for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04; S, 11.48. Found: C, 51.59; H, 4.75; N, 14.97; S, 11.53%.

(2E)-2-(4,5-Dihydro-4-oxothiazol-2-yl)-2-(oxazolidin-2-ylidene)acetonitrile (3g): Red needles. Yield: 70 %. M.p.: 222-223 °C. FT-IR (KBr, cm^{-1}): 3442 ν (NH), 2205 ν (C \equiv N), 1684 ν (C=O), 1618 ν (C=C). 1H NMR (DMSO- d_6): 3.87 (t, J = 8.6 Hz, 2H, NCH_2), 3.98 (s, 2H, $COCH_2$), 4.76 (t, J = 8.6 Hz, 2H, OCH_2), 10.00 (br., 1H, NH, D_2O exchangeable). MS (EI, m/z (%)): 209 (M^+ , 11 %). Anal. Calcd. for $C_8H_7N_3O_2S$: C, 45.92; H, 3.37; N, 20.08; S, 15.33. Found: C, 45.84; H, 3.40; N, 20.13; S, 15.39%.

3. Results and discussion

2-(E)-Cyano(oxazolidin-2-ylidene)thiazoles (**3a-g**) were prepared in a two-step procedure starting from the dinitrile (**1**) (Scheme 2). Reaction of 2-(oxazolidin-2-ylidene)malononitrile (**1**) with phosphorus pentasulfide in methanol afforded 2-cyano-2-(oxazolidin-2-ylidene)ethanethioamide (**2**) as either E or Z isomers (**2a,b**).



Scheme 2

Table 1. Results of reaction 2a and α -bromocarbonyl compounds.

Compound	R ¹	R ²	α -Bromocarbonyls	Time, h
3a	H	CO ₂ Et	Ethyl bromopyruvate	2
3b	H	CH ₃	Bromoacetone	2
3c	H	<i>p</i> -ClC ₆ H ₄	<i>p</i> -Chlorophenacylbromide	2
3d	H	<i>p</i> -BrC ₆ H ₄	<i>p</i> -Bromophenacylbromide	2
3e	COCH ₃	CH ₃	3-Bromoacetylacetone	2
3f	CO ₂ Et	CH ₃	Ethyl 2-bromoacetoacetate	2
3g	-	-	Ethyl bromoacetate	8

An unequivocal decision between these two geometric isomers was possible on the basis of our previously reported work on 2-(*E*)-cyano(thiazolidin-2-ylidene)thiazoles [15]. In this context, the *E* isomer is preferred over its *Z* counterpart.

Subsequent reaction of this isomer with various α -bromocarbonyl compounds led to the formation of the new thiazole derivatives (**3a-g**) (Table 1).

The structural assignments of compounds **2a**, **3a-g** were based on their analytical and spectral data. For example, the ¹H NMR spectrum of compounds **2a** and **3a-g** showed triplet signals due to two methylene groups of oxazolidine ring within $\delta = 3.57$ -4.05 and 4.68-4.77 ppm regions ($J \cong 8.5$ Hz), and broad signals due to NH group within $\delta = 9.25$ -11.38 ppm region. The FT-IR spectra of **2a**, **3a-g** in KBr disk showed the absorption bands within $\nu = 3413$ -3455 cm⁻¹ corresponding to NH groups, within $\nu = 2196$ -2205 cm⁻¹ belonging to nitrile groups and within $\nu = 1606$ -1622 cm⁻¹ attributed to the C=C exocyclic bonds. All this evidence plus the mass spectral and microanalytical data strongly support the formation of all products.

4. Conclusion

In summary, several new functionalized thiazoles have been synthesized regioselectively from the reaction of a single thioamide with several various α -bromocarbonyl compounds. The thioamide itself was synthesized in a regioselective manner from functionalized oxazolidine with phosphorus pentasulfide. The geometry of the regioisomers was determined on the basis of our previously reported work. Synthesis of alternative thiazoles is currently in progress in our laboratory.

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