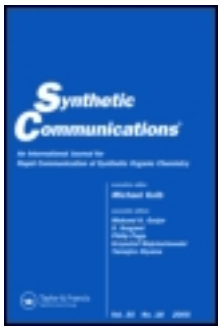

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The Cyclocondensation of Thioamides and Haloacetic Acid Derivatives Provides Only 4-Thiazolidinones; Isomeric 5-Thiazolidinones were Not Observed

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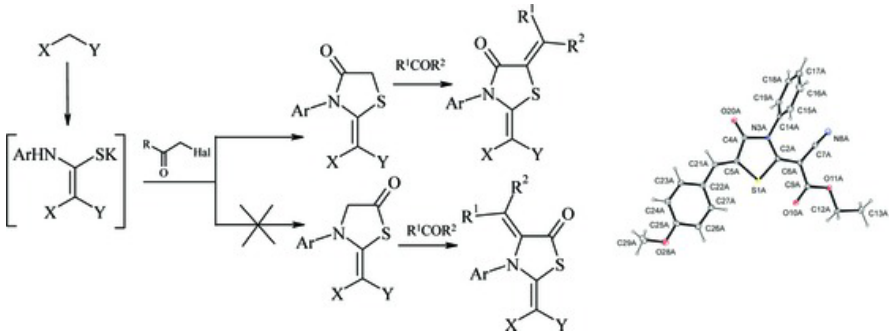
Abstract

Cycloaddition of intermediates formed from the nucleophilic addition of aryl isothiocyanate to acidic cyanomethylenes and α-halocarbonyl compounds gave only 4-thiazolidinones. 5-Thiazolidinones were not observed. Cyano-(4-oxo-3-phenylthiazolidin-2-ylidene)-acetic acid ethyl ester(**1**) and cyano-[5-(4-methoxybenzylidene)-4-oxo-3-phenylthiazolidin-2-ylidene]-acetic acid ethyl ester (**2a**)also were shown to exhibit moderate antiviral activity.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: 4-thiazolidinones, 5-thiazolidinones, cyclocondensation, X-ray.

INTRODUCTION

Among small-molecule heterocyclic compounds thiazolidinones are recognized in drug design as privileged scaffolds. The various avenues of chemical transformations in the generation of a diverse variety of pendants on the thiazolidinone scaffold led to exploration of the multiple biological effects. The prominent success in thiazolidinone field is related especially to 4-thiazolidinone derivatives.[1,2] Antimicrobial, anti-inflammatory, antidiabetic, and anticancer activities are a few among many other biological responses had been shown for this scaffold.[3-6] However, the reports about 5-thiazolidinones as isomers of the above mentioned 4-thiazolidinones concerning both the information about the synthetic protocols and biological activity data[7,8]are rather scarce. The methylene carbon atom at the 4-position of 5-thiazolidinone possesses nucleophilic activity and can attack an electrophilic center affording the 4-ylidene derivatives.[9] The latter are of special interest due to crucial role of the presence and/or nature of the C-5 substituent of the 4-thiazolidinone core plays in their biological activity.[5,6,10]

One of the most prominent and referenced protocol for 2-ylidene thiazolidinones synthesis is the cyclocondensation reaction of reactants bearing the N=C=S fragment with α-halocarbonyl compounds.[9] However, there are conflicting data regarding the cyclization reaction product of chloroacetyl chloride with *in situ* intermediate formed from nucleophilic addition of aryl isothiocyanate to acidic cyanomethylenes (scheme 1).

The target compounds have been previously reported as 2-ylidene-4-thiazolidinones[11–13] or often as 2-ylidene-5-thiazolidinones.[14–17] In both cases the structures of compounds were confirmed by IR, NMR spectroscopy and mass-spectrometry. Moreover, the spectral data didn't contradict with the presented structures. However, the datas didn't provide answersregardingthe positionof the carbonyl group, i.e. the formation of 4- or 5-thiazolidinone moieties. Hence, the aim of the communication is to describe the synthesis and the structures determination of the ylidene thiazolidinones.

RESULTS AND DISSCUSION

Based on the above mentioned approach, the thiazolidinone **1** was synthesized and transformed into ylidene derivatives **2a-c** (scheme 2) under Knoevenagel reaction conditions (acetic acid medium in the presence of sodium acetate).

The cyclocondensation reaction was performed at room temperature in the DMF medium. Single crystal X-ray diffraction study corroborated the structures of compounds as presented on Scheme 2. The molecular structures of compounds **1** and **2a** with labeling schemes are shown in Figs. 1 and 2, respectively. Target compounds were the 4-thiazolidinone derivatives instead of 5-oxo isomers as it was described previously. Moreover the structure of compound **1** was presented [18] and obtained from the reaction of 2,4-bis(carboethoxycyanomethylene)-1,3-dithietane with amine and phenyl isocyanate.

As follows from the X-ray analysis, the asymmetric unit of **1** and **2a** contains two symmetry-independent molecules (Figs. 1 and 2), which differ slightly in their conformation. In both compounds the dissimilarities concern the angular arrangement of the (N)-phenyl ring as well as the positioning of the ethoxy group (O11, C12, C13 atoms). The latter group in molecule B of **1** exhibits orientational disorder. The atoms O11, C12 and C13 occupy two alternative positions B and C. The atoms assigned to B position have the site occupancy factor of 82% while that assigned to C position have the factor of 18%. In **1** and **2a**, the cyano group reveals an *E* configuration with respect to the sulfur atom of the 1,3-thiazol-4-one system.

Chloroacetyl chloride and ethyl chloroacetate were used to study thiazolidinone ring formation reaction under the same conditions. The reaction product was cyano-(4-oxo-3-phenylthiazolidin-2-ylidene)-acetic acid ethyl ester (**1**) in both cases. Moreover, the different non-thiazolidinone product was formed upon the reaction mixture heating.[13]

The primary antiviral assay of the compounds (**1** and **2a**) was performed according toNIAID's Antimicrobial Acquisition and Coordinating Facility program at the biodefense viruses panel (Dengue Virus Type 2, Respiratory Syncytial Virus, Rift Valley Fever Virus, Venezuelan Equine Encephalitis Virus, Tacaribe Virus) and the respiratory viruses panel (Flu A (H3N2, H1N1, H5N1), Flu B, SARS) in accordance with standard protocols.[19] The results for each tested compound were reported as virus-inhibitory concentration 50% endpoint – EC_{50}, and cell-inhibitory concentration 50% endpoint – CC_{50}. The general selectivity index (SI) was calculated as a ratio of $(EC_{50})/(CC_{50})$. The

tested compounds showed low to moderate activity against Flu panel viruses with the highest action on the Influenza Virus Type A H_5N_1(EC_{50} = 18 μM, CC_{50} = > 100 μM, SI = >5.6 for compound **1**) (data available in the Supporting information).

EXPERIMENTAL

Synthesis Of Cyano-(4-Oxo-3-Phenylthiazolidin-2-Ylidene)-Acetic Acid Ethyl Ester (1)

The ethyl cyanoacetate (36 mmol) followed by phenyl isothiocyanate (36 mmol) were added to a cold suspension of KOH (36 mmol) in dry DMF. The mixture was stirred at room temperature for 12 h, then cooled to 0°C, treated with the chloroacetyl chloride (36 mmol) (*method a*) or ethyl chloroacetate (36 mmol) (*method b*) and left to stand for 24 h at room temperature. The mixture was poured into ice-cold water, and the resulting precipitate was filtered off, dried and crystallized from DMF-EtOH or acetic acid. Yield 86% (*method a*) and 84% (*method b*); mp 208-210°C (AcOH), lit. 210°C;[20] ^{1}H NMR (400 MHz, DMSO-d_6): 1.18 (t, J = 7.0 Hz, 3H, CH_3), 4.07 (s, 2H, CH_2S), 4.19 (q, J = 7.0 Hz, 2H, CH_2), 7.38-7.42 (m, 2H, arom.), 7.47-7.55 (m, 3H, arom.). ^{13}C NMR (100 MHz, DMSO-d_6): 174.0, 172.9, 165.5, 135.3, 131.0, 129.8, 129.8, 112.6, 76.6, 61.6, 32.6, 14.7. Anal. calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.20; N, 9.72; Found: C, 58.55; H, 4.38; N, 9.96. LC-MS: m/z (%) = 289.6 (98%, M^++1).

General Procedure For Synthesis Of Cyano-(5-Ylidene-4-Oxo-3-Phenylthiazolidin-2-Ylidene)-Acetic Acid Ethyl Esters (2a–C)

A mixture of compound **1** (3 mmol), appropriate oxocompound (3 mmol) and anhydrous sodium acetate (3 mmol) was refluxed for 3 h in glacial acetic acid (10 mL). The resulting precipitate was filtered off, washed with water and EtOH and then recrystallized with DMF : EtOH (1:2) mixture or AcOH.

Cyano-[5-(4-Methoxybenzylidene)-4-Oxo-3-Phenylthiazolidin-2-Ylidene]-Acetic Acid Ethyl Ester (2a)

Yield 82%; mp 252-254°C (DMF : EtOH); ^{1}H NMR (400 MHz, DMSO-d_6): 1.23 (t, J = 6.5 Hz, 3H, CH_3), 3.88 (s, 3H, OCH_3), 4.24 (q, J = 7.0 Hz, 2H, CH_2), 7.20 (d, J = 8.7 Hz, 2H, arom.), 7.50-7.58 (m, 5H, arom.), 7.74 (d, J = 8.7 Hz, 2H, arom.), 7.87 (s, 1H, CH-arom).Anal. calcd. for $C_{22}H_{18}N_2O_4S$: C, 65.01; H, 4.46; N, 6.89. Found: C, 64.92; H, 4.35; N, 6.78. LC-MS: m/z (%) = 407.5 (95%, M^++1).

SUPPORTING INFORMATION

Structural characterization, NMR, LC-MS spectral data for synthesized compounds, crystal data and refinement details for **1** and **2a** as well as data of primary antiviral assay are available. Crystallographic data (CCDC-900752 for compound **1**, CCDC-900753 for compound **2a**) have been deposited at the Cambridge Crystallographic Database Centre (www.ccde.cam.ac.uk).

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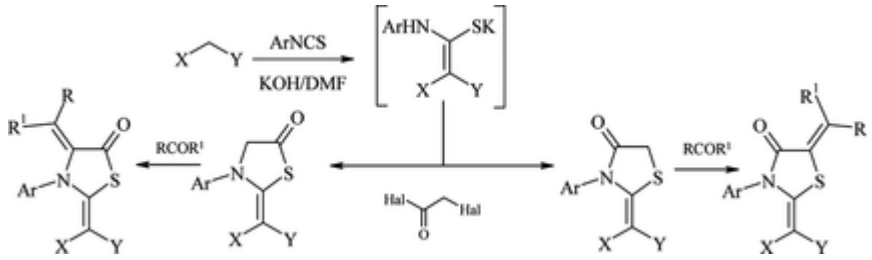
Scheme 1. Synthetic protocol to the 4(5)-ylidene-5(4)-thiazolidinone formation.



Scheme 2. Synthesis of 2,5-diylidene-4-thiazolidinones.

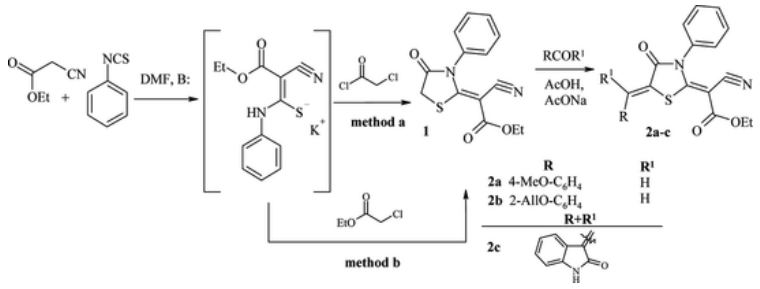


Figure 1. Two symmetry-independent molecules (ORTEP plot) of **1** showing the atomic labelling scheme. Non-H atoms are drawn as 30% probability displacement ellipsoids and H atoms are drawn as spheres of an arbitrary size.

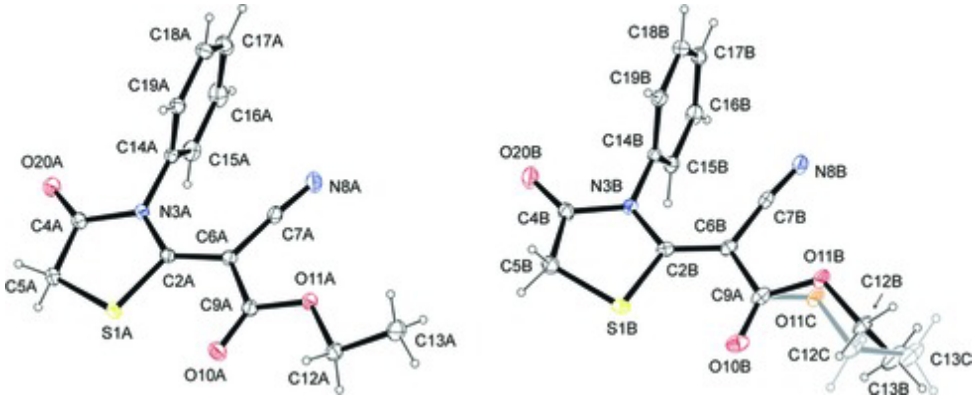


Figure 2. Two symmetry-independent molecules (ORTEP plot) of **2a** showing the atomic labelling scheme. Non-H atoms are drawn as 30% probability displacement ellipsoids and H atoms are drawn as spheres of an arbitrary size.