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Synthesis and isomerization of acridine substituted 1,3-thiazolidin-4-ones and 4-oxo-1,3-thiazolidin-5-ylidene acetates. An experimental and computational study

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ABSTRACT

Acridine thiosemicarbazones **3a**–**g**, obtained through a two-step reaction between aromatic isothiocyanates and hydrazine followed by the treatment with acridin-9-carbaldehyde, in reaction with bifunctional reagents; methyl bromoacetate (MBA) and diethyl acetylenedicarboxylate (DEAD) afforded acridin-thiazolidinone derivatives **4a**–**g** and **7a**–**f** and not their regioisomers **6a**–**g** and **9a**–**f**. Derivatives **4a**–**g** and **7a**–**f** exhibit $Z_{C2N6}E_{N7C8}$ configuration. Upon standing in DMSO-d_6 the thiazolidinones **4a**–**g** and **7a**–**f** spontaneously isomerized into $Z_{C2N6}Z_{N7C8}$ isomers **5a**–**g** and **8a**–**f** to give a mixture of the both stereoisomers. All compounds were fully characterized by multinuclear NMR, mass spectrometry (MS) and X-ray crystal structure of **4b** is also described. X-ray diffraction study revealed that the representative compound **4b** crystallized in the monoclinic crystal system with the *C*2/*c* space group and $Z = 4$. Intramolecular C1′–H1′···N-7 hydrogen bond between the acridine proton H-1′ and nitrogen N-7 of linker existed. This hydrogen bond is responsible for the *E* isomerism on C-8 atom which was observed in the NMR experiments. Quantum-chemical calculations and NOESY experiments confirmed $Z_{C2N6}Z_{N7C8}$ configuration of the transformed stereoisomers **5a**–**g** and **8a**–**f.**

1. Introduction

Thiazolidin-4-ones **1** (Fig. 1) are extensively investigated compounds in the last decades for a range of pharmacological activities [1]. Most studies have been devoted to substituted thiazolidin-2,4-diones and 2-thioxothiazolidin-4-ones (rhodanines), much less to 2-imino-4-thiazolidinones (**2a**) (Fig. 1). In this respect, a special attention in last years is paid to 2-hydrazono derivatives of the title compounds with $R^1R^2C{=}N{-}N{=}$substituent in the position 2 of thiazolidin-4-one.

All the positions of thiazolidinone ring have been explored to improve their biological properties such as antibacterial [2], anti-inflammatory [3], anti-HIV [4–7], COX-1 inhibiting [8]. Beyond these biological activities, special attention of medicinal chemists has been attracted to the investigation of thiazolidinones as potential lead-compounds for novel anticancer agents [9–12]. Among thiazolidinones 5-ene and 2-imino-thiazolidin-4-one derivatives are the most promising [13]. Some imino derivatives were prepared and studied for their biological properties – antimicrobial 4-[(adamantan-1-yl)1,3-(thiazol-2-ylimino)] thiazolidin-4-one and its 5-arylidene derivatives [14], antitrypanosomal 2-[1-(3,4-dichlorophenyl)ethylidene]hydrazinylidene-5-substituted-3-phenyl-1,3-thiazolidin-4-ones and 3-phenyl-2-[(thiophen-2-ylmethylidene)hydrazinylidene]-thiazolidin-4-ones [15–17], antiviral 2-[(3-fluorophenyl)imino]-3-(furan-2-ylmethyl)-5-phenyl-

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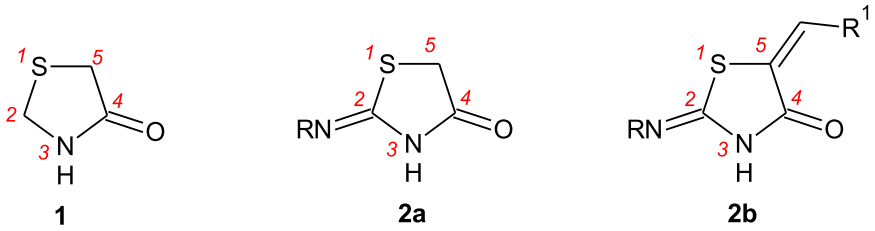

Fig. 1. The structure of thiazolidin-4-one (**1**), 2-imino-thiazolidin-4-one (**2a**) and 2-imino-5-ene-thiazolidin-4-one (**2b**).

1,3-thiazolidin-4-ones [18], anti-inflammatory 2-(2-(1-(1,2,3,4-tetrahydronaphthalen-6-yl)ethylidene)hydrazono)-3-substituted-5-methylthiazolidin-4-ones and 5-arylidene-2-phenylimino-3-substituted-thiazolidin-4-ones [19,20], and anticancer activities 5-arylidene-2-arylaminothiazol-4(5*H*)-ones and 2-aryl(benzyl) amino-1*H*-imidazol-4(5*H*)-ones, 2-arylimino-5-arylidene-thiazolidin-4-ones and their N-substituted analogues and 2-((1*H*-indol-3-ylmethylene)hydrazono)-3-(naphthalen-1-yl)thiazolidin-4-one [13,21–24].

A large variety of synthetic protocols towards functionalized 2-imino-4-thiazolidinones has been reported in the literature. The very common strategy to construct 2-imino-4-thiazolidinone derivatives is the condensation of thiourea or thiosemicarbazide with functional derivatives of α-halo acids in the presence of a base in a polar solvent. For unsymmetrical thiourea, both of the two regioisomeric products are formed. Previously, our group reported the construction of 2-imino-4-thiazolidinone rings by the reaction of unsymmetrical thioureas [25,26] and thiosemicarbazides [27] with bifunctional electrophiles in the presence of a base. We found out that regioselectivity is controlled by electronic factors and predominantly an intermediate is formed with imino nitrogen that is stabilized by conjugation. However, in some cases the reactions with bromoacetyl bromide afforded a mixture of regioisomeric iminothiazolidinones [28].

For the unsymmetrically substituted moiety $R^1R^2C{=}N{-}N{=}$ there are four theoretically possible stereoisomers about the conjugated planar C=N–N=C bond system. The four stereoisomers result from restricted rotation about each of the both coupled C=N bonds. Therefore it was surprising to us that only few of relatively many papers on 2-[2-(R)hydrazin-1-ylidene]-1,3-thiazolidin-4-ones dealt with the problem of stereochemistry of the conjugated C=N–N=C bond system in their structures. Some authors described the configuration of C=N–N=C moiety, however, without experimental or theoretical evidence. Only very few studies used nuclear Overhauser enhancement experiments for stereochemistry resolution so far. Thus, a question of stereoisomerism of C=N–N=C moiety coupled on heterocyclic system needs more attention.

In this article, we wish to report the synthesis, structure and characterization of new acridine containing 2-imino-4-thiazolidinones in continuation to our previous works on synthesis of such skeletons. The regiochemistry of the cyclized products and geometry were established by means of spectral data and verified by single crystal X-ray analysis and quantum chemical calculations.

2. Experimental

2.1. General

All reactions mentioned above were performed under an inert atmosphere of nitrogen. All reagents were used as supplied without prior purification. The progression of the reaction was monitored by analytical thin layer chromatography using TLC-sheets ALUGRAM-SIL G/UV254 (Macherey Nagel, Germany). Purification by flash chromatography was performed using silica gel (60 Å, 230–400 mesh, Merck) with the indicated eluent. Melting points were determined by a Boetius hot-stage apparatus and are uncorrected.

2.2. NMR spectroscopy

NMR spectra were recorded on a Varian VNMRS (599.87 MHz for ^{1}H, 150.84 MHz for ^{13}C, and 60.79 MHz for ^{15}N) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil at 299.15 K. Chemical shifts (δ in ppm) are given from internal solvent, DMSO-d_6 2.50 ppm for ^{1}H and 39.5 ppm for ^{13}C or $CDCl_3$ 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C. External nitromethane (0.0 ppm) was used for ^{15}N references.

2.3. HR-MS

The method used for high-resolution mass spectrometric identification of products is described in detail in literature [29]. Minor modifications are as follows: the samples were dissolved in chloroform (1 mg mL^{-1}) and diluted 1000-fold. The atmospheric solid analysis probe (ASAP) was dipped into the sample solution, placed into the ion source and analysed in full scan mode. The probe was kept at a constant temperature of 450 °C for 2 min. Mass accuracy of 1 ppm or less was achieved with the used instrumentation for all the compounds.

2.4. Single crystal X-ray diffraction studies

Diffraction data for **4b** were collected at 173 K using an Oxford Diffraction Xcalibur2 diffractometer equipped with a Sapphire2 CCD detector using a graphite monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by SHELXT [30] and refined against the F^2 data using full matrix least squares methods with the program SHELXL-2013 [31]. Anisotropic displacement parameters were refined for all non-H atoms. Hydrogen atoms of the molecule **4b** were inserted in calculated positions appropriate for the data collection temperature with isotropic displacement parameters riding on that of the parent C atom. Ethanol-H atoms were found in the difference map and then refined using a riding model. The ethanol molecule is disordered in two equivalent positions with atom C-13 (and its hydrogen atoms) being methyl and methylene groups in both orientations of the ethanol molecule.

An analysis of the hydrogen bonds was performed using SHELXL-2013, while PLATON [32] running under WinGX [33] was used to analyze the π-π interactions. DIAMOND was used for molecular graphics [34].

2.5. Computational methods

The geometries of **3c**–**6c** and their *EE*, *ZE*, *EZ* and *ZZ* isomers (if