

Short Note

(Z)-3-Amino-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one

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Abstract: 3-Aminorhodanine reacts with aldehydes to form either 5-[(aryl)alkylidene]-substituted products or Schiff bases or derivatives substituted at both the 3-amino group and the 5-methylene group, depending on the reaction conditions. In this note, synthesis and characterization of 3-amino-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one is reported.

Keywords: 3-aminorhodanine; aldehydes; condensation products

1. Introduction

Rhodanine is one of the privileged scaffolds in drug discovery. Biological effects of various rhodanine derivatives have been reviewed by Tomasic and Masic [1,2]. Our research group has studied derivatives of rhodanine as potential antifungal and antimycobacterial agents [3–6]. Their influence on some photosynthetic processes was studied as well [7]. Some derivatives of 3-aminorhodanine were also prepared within these studies.

Initially, 3-aminorhodanine **1** was prepared for the first time by Andreasch [8]. With aldehydes it can form either 5-[(aryl)alkylidene]-substituted products **2** or Schiff bases **3** or derivatives substituted at both the 3-amino group and C(5) **4** (Figure 1), depending on the reaction conditions [9,10].

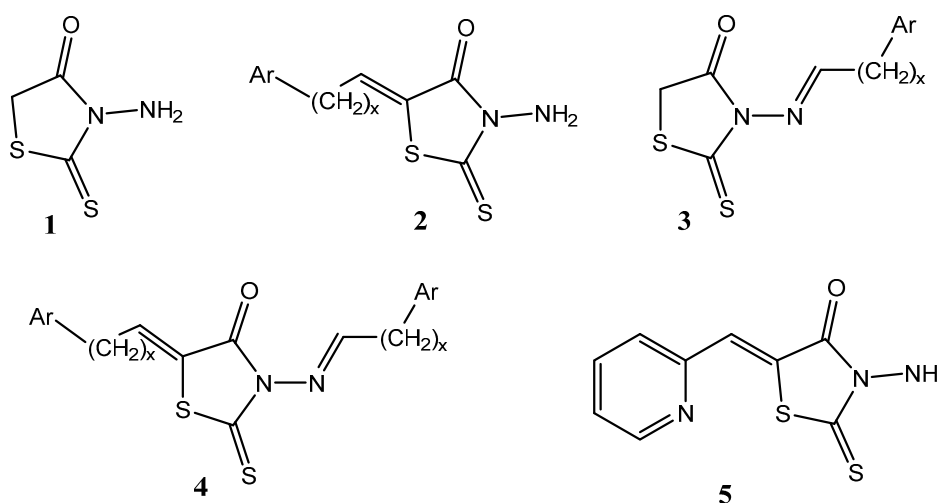
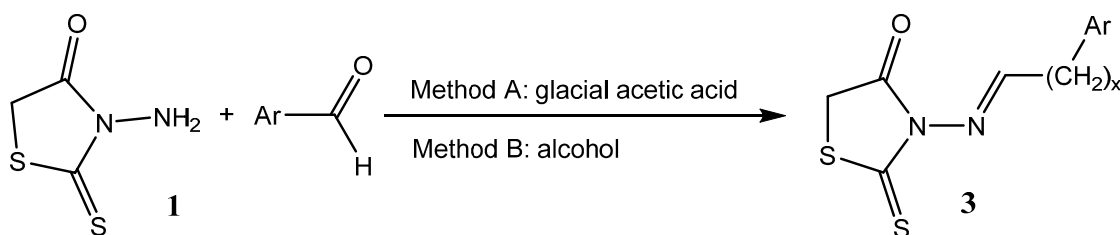


Figure 1. Graphic representation of 3-aminorhodanine and its condensation products with aldehydes.

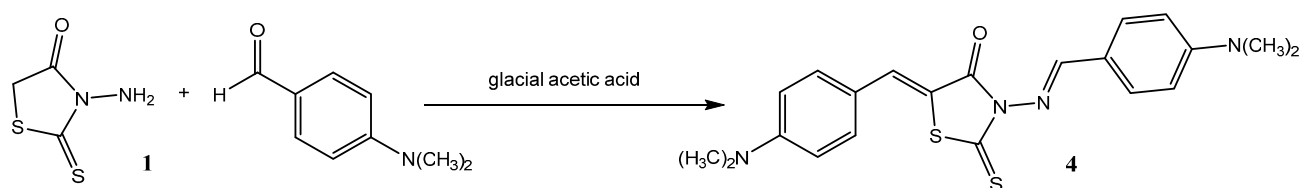
Stainier and Lapiere [9,10] used three different methods. When they performed condensation of equivalent amounts of 3-aminorhodanine **1** and an aldehyde in the presence of glacial acetic acid (method A) or in alcohol (method B), the derivative of the general formula **3** was obtained (Scheme 1).



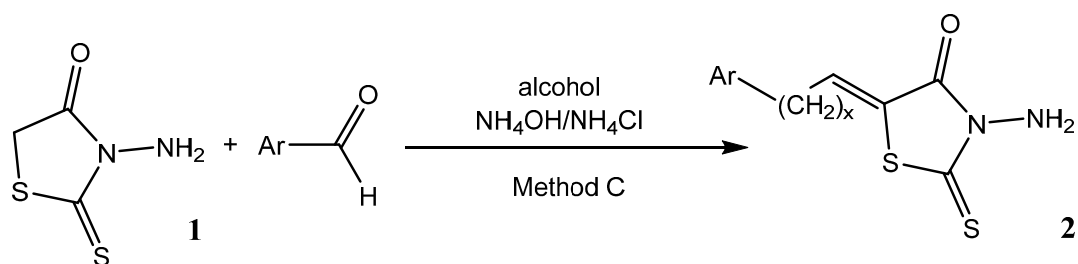
Scheme 1. Condensation of 3-aminorhodanine with an aldehyde in glacial acetic acid (method A) or alcohol (method B).

However, condensation of 3-aminorhodanine with 4-dimethylaminobenzaldehyde in glacial acetic acid (method A) gave disubstituted product **4** (Scheme 2).

Condensation in alcoholic solution in the presence of $\text{NH}_4\text{OH}/\text{NH}_4\text{Cl}$ (method C, so-called Girard's method) always resulted in 5-[(aryl)alkylidene]-3-aminorhodanine **2** (Scheme 3).



Scheme 2. Condensation of 3-aminorhodanine with 4-dimethylaminobenzaldehyde in glacial acetic acid (method A).



Scheme 3. Condensation of 3-aminorhodanine with an aldehyde in alcoholic solution in the presence of $\text{NH}_4\text{OH}/\text{NH}_4\text{Cl}$ (method C).

Similar results were also reported by Petlichnaya and co-workers [11–16]. These authors found that 3-aminorhodanine exists in two tautomeric forms (Figure 2).

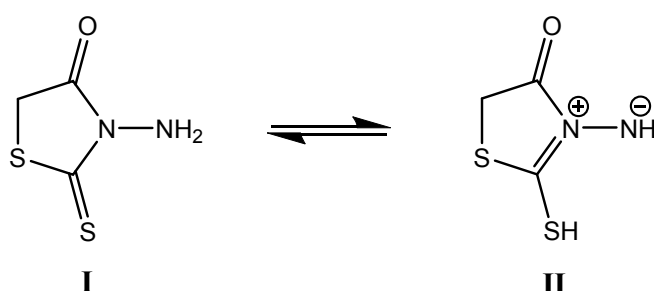


Figure 2. Tautomeric forms of 3-aminorhodanine.

In an alcohol, 3-aminorhodanine **1** reacts in the “hydrazine” form **I** to give Schiff bases **3**. In ammonia solution, 5-substituted derivatives **2** arise. Disubstituted derivatives **4** can be obtained by reacting **1** with an excess of aldehyde in glacial acetic acid. Nonetheless, in some cases, a two-step reaction must be used. It is possible to condense an aldehyde with a Schiff base **3** in ammonia solution or with a 5-substituted derivative **2** in an alcohol. Unsymmetrically substituted products can be prepared by these two-step reactions.

Several modified methods [17–26] for the condensation of 3-aminorhodanine with aldehydes have been reported. They clearly show that in basic medium the components react to yield 3-amino-5-[(aryl)alkylidene]-2-thioxo-1,3-thiazolidin-4-ones **2**. Heating in alcohols gives 3-[(aryl)alkylidene] amino-2-thioxo-1,3-thiazolidin-4-one **3**, while acidic catalysis results in **3** and/or disubstituted products **4**.

In this note we wish to report on the synthesis (method C) and characterization of 3-amino-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one **5** (Figure 1).

2. Results and Discussion

Originally, 3-amino-5-(pyridin-3-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one (CAS Registry Number 101714-49-2) and 3-amino-5-(pyridin-4-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one (CAS Registry Number 101714-18-5) were reported by Lapiere in 1959 [10]. The compound 3-amino-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one (**5**) has been registered with CAS Number 1082891-88-0. However, there are no references and no experimental data. Therefore, we tried to prepare and characterize the compound within our studies. Its structure (Figure S1) was corroborated by ¹H-NMR spectrum (Figure S2), ¹³C-NMR spectrum (Figure S3) and HRMS (Figure S4), and the purity confirmed by elemental analysis.

Arylmethylidenerhodanines can form two isomers. According to references [27–31], syntheses of these compounds result in (*Z*)-isomers. The same has recently been proved for 3-aminorhodanine derivatives [25]. Configuration on the exocyclic double-bond can be determined on the basis of NMR spectra where ¹H-NMR signals of the methine-group hydrogen for (*Z*)-isomers are more downfield compared to those expected for (*E*)-isomers. In our previous papers [5,7], the experimental signals of the –CH= group of various rhodanine derivatives were compared with the values reported previously in literature and the values predicted *in silico*. The (*Z*)-Isomers of arylmethylidenerhodanines exhibited experimental methine group shifts between 7.39–7.94 ppm, while (*E*)-isomers had methine group shifts in the range 6.78–7.01 ppm [5].

In the ¹H-NMR spectrum of the 3-amino-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one (**5**) reported in this note, only one set of signals was observed and the shift of –CH= is 7.85 ppm. The shifts predicted *in silico* (ChemDraw Professional 15.0, PerkinElmer Informatics, Waltham, MA, USA) were 7.63 ppm for (*Z*)-isomer and 7.01 ppm for (*E*)-isomer. Hence, it can be concluded that the prepared compound is (*Z*)-isomer.

3. Experimental Section

3.1. General Information

First, 3-aminorhodanine, 99% (Sigma-Aldrich, Steinheim, Germany) and pyridin-2-carbaldehyde, 99% (Sigma-Aldrich, Steinheim, Germany) were used as starting compounds. TLC was performed on TLC aluminium sheets, silica gel 60 F₂₅₄ (Merck, Darmstadt, Germany). Mixtures light petroleum + ethyl acetate (4:6) and toluene + acetone (1:1) were used as mobile phases. Analytical sample was dried over anhydrous phosphorus pentoxide under reduced pressure at room temperature. Melting point was determined on a Boëtius apparatus PHMK 05 (VEB Kombinat Nagema, Radebeul, Germany) and is uncorrected. Elemental analysis was performed on an EA 1110 CHNS instrument (CE Instruments, Milano, Italy). ¹H- and ¹³C-NMR spectra were recorded at ambient temperature on a Varian Mercury-Vx BB 300 spectrometer (Varian Corp., Palo Alto, CA, USA) operating at 300 MHz for ¹H and 75 MHz for ¹³C. Chemical shifts were recorded as δ values in ppm, and were indirectly referenced to tetramethylsilane (TMS) via the solvent signal (2.49 for ¹H, 39.7 for ¹³C in DMSO-*d*₆). UHPLC system Acquity UPLC I-class (Waters, Millford, CT, USA) coupled to high resolution mass spectrometer (HRMS,) Synapt G2Si (Waters, Manchester, UK) based on Q-TOF were used for HRMS spectra measurement. Chromatography was performed using Acquity UPLC BEH C18 (2.1 mm \times 50 mm, 1.7 μ m) column

using gradient elution with acetonitrile and 0.1% formic acid at flow rate 0.4 mL/min. Electrospray ionization was operated in positive mode. The ESI spectra were recorded in the range 50–1200 m/z using leucine-enkephalin as a lock mass reference and sodium formate for calibration.

3.2. Experimental Procedure for the Preparation of 3-Amino-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one (5)

Mixture of pyridin-2-carbaldehyde (1.0 g, 0.009 mol), 3-aminorhodanine (1.7 g, 0.009 mol) and concentrated ammonia (0.7 mL) in 15 mL of ethanol was heated to boiling. Ammonium chloride (0.7 g) dissolved in 2 mL of water heated to 80 °C was added to a clear solution, and the mixture refluxed for 2 h. After cooling, separated crystals were filtered off, washed with 50 mL of water and then 50 mL of ethanol diluted with water (1:1, v/v). The product was crystallized from acetone.

3-Amino-5-(pyridin-2-ylmethylidene)-2-thioxo-1,3-thiazolidin-4-one (5). Yellow solid; yield 73%; m.p. 228–231 °C (decomp.) $^1\text{H-NMR}$ (DMSO- d_6 , 300 MHz, δ ppm) 8.79–8.77 (m, 1H, Ar), 7.93–7.90 (m, 2H, Ar), 7.85 (s, 1H, CH), 7.45–7.42 (m, 1H, Ar), 5.89 (bs, 2H, NH $_2$); $^{13}\text{C-NMR}$ (DMSO- d_6 , 75 MHz, δ ppm) 194.4, 164.0, 151.5, 149.7, 137.9, 129.0, 128.5, 125.0, 124.4; EA for C $_9$ H $_7$ N $_3$ OS $_2$ (237.30) calculated 45.55%C, 2.97%H, 17.71%N, 27.02%S, found 45.35%C, 3.23%H, 17.67%N, 27.44%S; HRMS (ESI): Calculated for C $_9$ H $_8$ N $_3$ OS $_2$ [M + H] $^+$ m/z 238.0109, found m/z 238.0109.

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Author Contributions

Petra Hirsova prepared the compound within her diploma work under supervision of Jan Dolezel. Marta Kucerova-Chlupacova checked the physicochemical data and wrote the experimental part; Jiri Kunes recorded and interpreted NMR data; Veronika Pilarova performed UHPLC, recorded and interpreted HRMS under supervision of Lucie Novakova. Veronika Opletalova proposed the subject, designed the study, and wrote the introduction and discussion. All the authors read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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