

Radziszewski-Type Oxidation of 3,5-di(α -cyanostyryl)-1,2,4-thiadiazoles [†]

Polina G. Dahno ¹, Arina G. Levchenko ¹ and Victor V. Dotsenko ^{1,2,*} 

¹ Department of Organic Chemistry and Technologies, Kuban State University, 149 Stavropolskaya Str., 350040 Krasnodar, Russia

² Department of Chemistry, North Caucasus Federal University, 1a Pushkin St., 355009 Stavropol, Russia

* Correspondence: victor_dotsenko@mail.ru

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Abstract: Due to the presence of two acrylonitrile fragments, 3,5-di(α -cyanostyryl)-1,2,4-thiadiazoles are prone to react under Radziszewski reaction conditions (oxidative hydrolysis of nitriles to amides) with the simultaneous epoxidation and formation of epoxyamides. We found that the reaction proceeds in a non-selective way and yields a mixture of products of regioisomeric oxidation. Only in one case we succeeded to isolate the product of double epoxidation. The structure of the epoxyamides products was confirmed by IR and NMR spectroscopy data.

Keywords: arylmethylene cyanothioacetamides; 1,2,4-thiadiazoles; Radziszewski oxidation; epoxyamides



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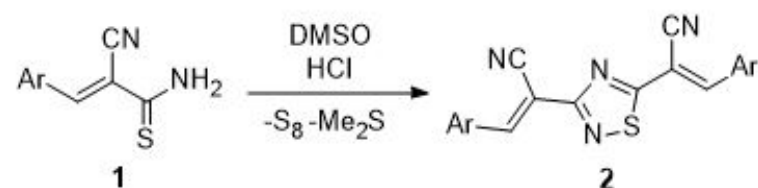
1. Introduction

In previous paper, we reported the synthesis of substituted 1,2,4-thiadiazoles by the oxidative dimerization of arylmethylene cyanothioacetamides upon treatment with DMSO-HCl system [1]. These oxidation products have highly reactive acrylonitrile moieties, so they can be further transformed to yield a plethora of new heterocyclic products.

The Radziszewski reaction is widely used in organic practice to prepare primary carboxamides from nitriles under mild oxidative conditions. It is known [2–9] that acrylonitriles react under Radziszewski conditions with a simultaneous epoxidation of C=C double bond. Therefore, due to the presence of two reactive C=C–C≡N fragments, 3,5-di(α -cyanostyryl)-1,2,4-thiadiazoles appeared to be suitable substrates for the synthesis of new epoxyamides. The aim of our study was to determine the structure of oxidation products as well as their optimal reaction conditions. The resulting amides may be of interest as reagents for heterocyclic and supramolecular synthesis.

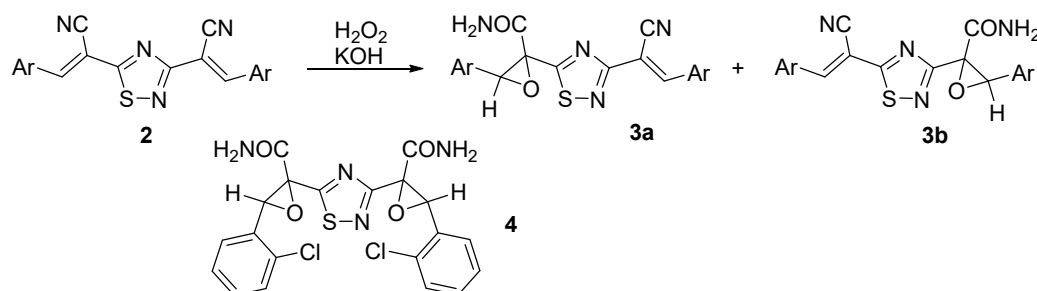
2. Results and Discussion

The starting 3,5-di(α -cyanostyryl)-1,2,4-thiadiazoles **2** were prepared by oxidative dimerization of arylmethylene cyanothioacetamides **1** in DMSO-HCl system [1] (Scheme 1).



Scheme 1. Synthesis 3,5-di(α -cyanostyryl)-1,2,4-thiadiazoles **2**.

The functionalized 1,2,4-thiadiazoles **2** were oxidized under the Radziszewski reaction conditions (H_2O_2 , KOH) with the involvement of one of the acrylonitrile fragments and the formation of epoxyamides **3a** and **3b** in moderate yields (up to 50%) (Scheme 2). We found that the oxidation is non-regioselective and yields a mixture of regioisomeric epoxides. Only in one case it was possible to isolate the product of double epoxidation **4**. The resulting amides are of interest as reagents for heterocyclic and supramolecular synthesis. The structure of the prepared compounds is confirmed by spectral data.



Scheme 2. Oxidation of 3,5-di(α -cyanostyryl)-1,2,4-thiadiazoles **2**.

Compounds **3a** and **3b** are white or yellowish powders insoluble in water or EtOH. The reaction proceeds very slowly at room temperature. The use of larger amounts of KOH favors the oxidation rate, but generally causes a decrease in yields of epoxyamides **3a** and **3b**, probably due to the partial hydrolysis of both precursors and reaction products.

The structure of the synthesized compounds was confirmed by spectral data. Thus, the IR spectra of the compounds revealed characteristic absorption bands corresponding to stretching vibrations of N–H bonds, amide C=O and the conjugated $\text{C}\equiv\text{N}$ group. It was concluded that only one acrylonitrile fragment is involved in the Radziszewski reaction. The ^1H NMR spectrum of epoxyamides is characterized by the presence of two narrow singlets of protons of the oxirane ring in the range of 4.72–4.81 ppm. The signal of the amide group and signals of the aromatic substituent are resolved as a multiplet at 7.35–7.71 ppm. The signals of the CH protons of the acrylonitrile fragment are found in the range of 8.14–8.42 ppm.

3. Experimental Section

3.1. Method for the Synthesis of Thiadiazoles **2**

Arylmethylidene cyanothioacetamide **1** (1.5 mmol) was placed in a beaker, and acetone or EtOH (3–5 mL) and DMSO (0.6 mL, 8.45 mmol) were added. For complete dissolution of thioamide, the mixture was gently heated. To a solution formed, conc. HCl (0.5 mL, 4.7 mmol) was added dropwise with constant stirring. The reaction mixture turned red for a moment, then discolored and became turbid (formation of colloidal sulfur). Within a few seconds, the product precipitated (Caution! Dimethyl sulfide has extensively evolved!). The suspension was diluted with EtOH (5 mL), maintained for 24 h at 20 °C, and the solid product was filtered off. To remove the traces of elemental sulfur, the prepared thiadiazoles were purified by recrystallization from acetone, AcOH or by re-precipitation from DMSO with aqueous EtOH.

3.2. Method for the Synthesis of Compounds **3a** and **3b**

A portion of 10% aqueous KOH solution (1.5 mmol) was added to a mixture of the corresponding thiadiazole (3 mmol), thoroughly ground to a fine powder, and 32% H_2O_2 ($d = 1.1 \text{ g/mL}$) (2.7 mL, 0.03 mol) in EtOH. The reaction mixture was heated under vigorous stirring until an exothermic reaction started. After the reaction was complete and the evolution of oxygen ceased, the crystalline solid was filtered off and washed with cold aq. EtOH to produce epoxyamides **3**.

3.3. Method for the Synthesis of Compound 4

A 50 mL beaker was charged with the starting 1,2,4-thiadiazole (1 mmol), previously thoroughly ground to a powdery state, and 10 mL of EtOH. The mixture was heated to 30 °C. A solution of 10% KOH ($d = 1.0904 \text{ g/cm}^3$) (0.07 mL, 0.1 mmol) was added drop by drop. The reaction mixture turned dark to a cherry-red color. Then, 0.95 mL (0.01 mol) of 32% H_2O_2 solution ($p = 1.112 \text{ g/cm}^3$) was added drop by drop. The mixture was heated upon vigorous stirring until a violent exothermic reaction started. The reaction was accompanied by the evolution of oxygen, the reaction mixture turned clear, and the formation of a white fine-crystalline precipitate was observed. The mixture was stirred for another 30 min until the bright-yellow color of the starting thiadiazole completely disappeared. Then, the solid was precipitated with water, filtered, and washed with alcohol and water. A white powder weighing 0.22 g (50%) was obtained. IR spectrum, ν , cm^{-1} : 3415, 3249 (NH), 1679 (C=O). NMR spectrum ^1H (400 MHz, DMSO-d_6), δ , ppm: 4.73 s (1H, $\text{CH}_{\text{oxirane}}$); 4.82 s (1H, $\text{CH}_{\text{oxirane}}$); 7.48 m (2H, H Ar); 7.50 m (2H, H Ar); 7.58 m (2H, H Ar); 7.60 m (2H, H Ar); 7.55 br s (2H, CONH_2); 7.84 br s (2H, CONH_2). $\text{C}_{20}\text{H}_{14}\text{Cl}_2\text{N}_4\text{O}_4\text{S}$ Calculated, %: C, 50.33; H, 2.96; Cl, 14.86; N, 11.74; O, 13.41; S, 6.72.

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Conflicts of Interest: The authors declare no conflict of interest.

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