Synthesis and Antifungal Evaluation of Novel Dicyanoderivatives of Rhodanine

Braulio Insuasty,[a]* Alberto Insuasty,[a] Alexis Tigreros,[a] Jairo Quiroga,[a] Rodrigo Abonia,[a] Manuel Nogueras,[b]* Justo Cobo,[b] Marcos Derita,[c] and Susana Zacchino[c]

[a]Grupo de Investigación de Compuestos Heterocíclicos, Departamento de Química, Universidad del Valle, A.A. 25360 Cali, Colombia
[b]Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain
[c]Farmacognosia, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, (2000), Rosario, Argentina
*E-mail: brainsu@univalle.edu.co or mmontiel@ujaen.es

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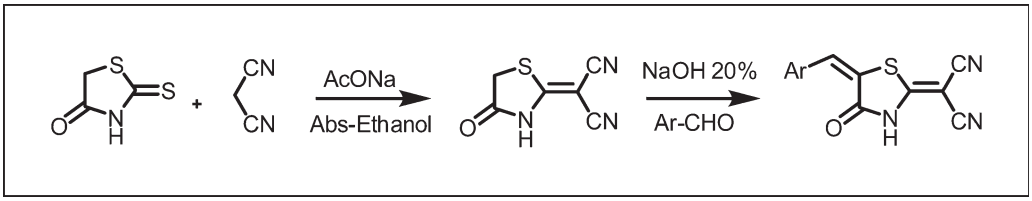

This work describes the synthesis and antifungal evaluation of 5-arylidene-(*Z*)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-ones **5** obtained from the reaction of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one **3** and benzaldehydes **4**. The starting material **3** was synthesized by a condensation reaction of rhodanine **1** and malononitrile **2**. The structures of the obtained products were established by IR, NMR, mass spectrometry, and elemental analysis.

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INTRODUCTION

Rhodanine (2-thioxo-1,3-thiazolidin-4-one, **1**) has given place to a very important group of heterocyclic compounds for drug discovery programs. Arylidene derivatives of rhodanine have attracted great interest for the synthetic organic chemists because of the broad biological activities shown by these compounds, with demonstrated antiviral [1], antimicrobial [2], cardiac [3], anti-inflammatory [4], and antifungal activities [5]. Additionally, rhodanine derivatives can potentially be used in the treatment of diabetes, obesity, Alzheimer's disease, cystic fibrosis, thrombocytopenia, cancer, sleep, mood, and central nervous system disorders as well as chronic inflammation [6]. We have previously prepared some of these compounds to determine their antifungal activity [5(a)], and most recently [5(b)], arylidene derivatives containing the α,β-unsaturated carbonyl moiety have been used as bielectrophiles in cyclocondensation reactions with heterocyclic amines [7].

As an ongoing work, here we provide a simple and efficient method for the synthesis of new arylidene derivatives of rhodanine **5a–i**, by converting rhodanine into its dicyanoderivative **3** and its subsequent condensation reaction with aromatic aldehydes **4a–i** (Scheme 1).

RESULTS AND DISCUSSION

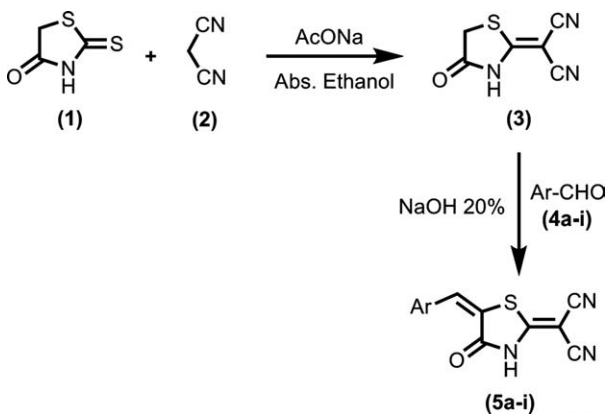
To prepare the 5-arylidene-(*Z*)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-ones **5a–i**, a mixture of equimolar amounts of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one **3** and benzaldehydes **4a–i** and aqueous 20% sodium hydroxide (0.3 mL) and ethanol (10 mL) was stirred at room temperature during 12–20 h (Scheme 1, Table 1). The starting material **3** was prepared previously by the reaction of rhodanine **1**, malononitrile **2**, and sodium acetate in absolute ethanol.

The formation of compounds **5** as the unique reaction products was confirmed from the thin layer chromatography (TLC) monitoring and by their spectroscopic data (IR, 1D- and 2D NMR, high-resolution mass spectrometry, and elemental analysis).

Previously it has been reported that although arylalkylidenerhodanines may exist in both *Z* and *E* isomeric forms, the thermodynamically more stable *Z* isomer is the preferred [8–11]. In such reports, configuration on the exocyclic double bond was determined on the basis of NMR spectra. The ^{1}H-NMR signals of the methine-group hydrogens appeared in the range of 7.30–7.70 ppm for *Z* isomers and 6.60–7.10 ppm for *E* isomers. Our experimental NMR data showed the methine protons in the range 7.44–7.60 ppm, confirming that our compounds **5** were obtained in the single *Z* isomeric form.

The main vibration bands in the IR spectra for compounds **5a–i** correspond to: NH at 3401–3459 cm^{-1}, C≡N (only one band) at 2211–2220 cm^{-1}, and C=O at 1639–1671 cm^{-1}.

Scheme 1. Synthesis of dicyanoarylidenerhodanine derivatives **5**.



The ^{1}H- and ^{13}C-NMR spectra of products show that the number of protons and carbon atoms agrees with the proposed structures **5**. The NH signal is not observed in the ^{1}H-NMR spectra of all compounds **5**. For example, in the ^{1}H-NMR spectrum of compound **5c** (Fig. 1), it is observed a singlet at 7.50 ppm (1H) assigned to H-5′, and it is also observed two doblets at 7.61 and 7.57 ppm (2H) assigned to H*m* and H*o*, respectively, whereas the most relevant signals in the ^{13}C-NMR spectra correspond to the two CN groups at 116.8 and 118.2 ppm, the C-5′ carbon atom at 126.8 ppm, and the C=O function at 180.8 ppm. Moreover, the unambiguous assignment of the above signals was performed through HSQC and HMBC experiments.

On the other hand, compounds **5a–i** were tested for antifungal properties with the microdilution technique following the guidelines of Clinical and Laboratory Standards Institute against a panel of yeasts (*Candida albicans*, *Saccharomyces cerevisiae*, and *Cryptococcus neoformans*), *Aspergillus* spp. (*A. niger*, *A. fumigatus*, and *A. flavus*) and dermatophytes in a similar way as previously reported for some other rhodanine derivatives [5(a)].

Results showed that any of compounds **5** assayed displayed antifungal activity below of 250 μg/mL. These findings constitute an important data for our current purposes of structure–activity relationship (SAR) study on the antifungal properties of arylidenerhodanines. In fact, as we have reported previously, [5(a)] compounds **6a–d** (Fig. 2, Table 2) showed moderate to strong antifungal activity against yeasts, *Aspergillus* spp. as well as dermatophytes, being the clinically relevant *C. albicans* and *C. neoformans* particularly sensitive toward compounds **6b** and **6c** [5(a)]. Contrary to the observed above, any of the analog compounds **5a–d** displayed antifungal activity below of 250 μg/mL. This finding clearly indicates that the dicyano substituent in C-2 led to a loss of the antifungal activity of arylidenerhodanines.

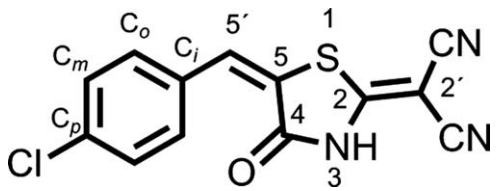


Figure 1. Numbering of structure **5c**.

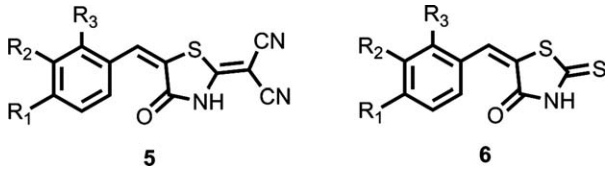


Figure 2. Structures of dicyanorhodanines **5** and rhodanines **6**.

CONCLUSIONS

In conclusion, we have developed a novel procedure to synthesize new dicyanoarylidenerhodanine derivatives, which were evaluated for antifungal properties against a panel of human opportunistic and pathogenic fungi with standardized procedures. Results demonstrated the versatility and high regioselectivity of the process and added interesting data for the SAR study on the arylidenerhodanine derivatives.

EXPERIMENTAL

General procedures. Melting points were taken in open capillaries on a Thomas Hoover melting point apparatus (Thomas Hoover Capillary Apparatus, Philadelphia, PA) and are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were run on a Bruker DPX 400 spectrometer operating at 400 and 100 MHz, respectively, using dimethyl sulfoxide-d_6 as solvent and TMS as internal standard (Bruker BioSpin GmbH, Rheinstetten, Germany). High-resolution mass spectra (HRMS) were recorded in a Waters Micromass Auto-Spec NT spectrometer (Waters, Manchester, UK) (STIUJA, Servicios Técnicos de Investigación de la Universidad de Jaén).

Experimental procedures. ***Synthesis of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (3) [12].*** A mixture of rhodanine **1** (1 mmol), malononitrile **2** (1.2 mmol), sodium acetate (1.2 mmol), and absolute ethanol (15 mL) was refluxed for 12 h. The precipitate formed was filtered off and washed with water and ice-cooled ethanol. The solid was purified by recrystallization from ethanol, 74% yield; m.p. 225–227°C; IR (KBr) cm^{-1}, 3445 (N—H), 2212 and 2196 (2C≡N), 1647 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 3.79 (s, 2H, CH_2); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 39.2 (C-5), 46.4 (C-2′), 117.7 (C≡N), 119.0 (C≡N), 188.7 (C-2), 188.9 (C=O); HRMS (EI): $C_6H_3N_3OS$ requires: 164.9997. Found: 164.9998. Anal. Calcd. for $C_6H_3N_3OS$: C, 43.63; H, 1.83; N, 25.44. Found: C, 43.71; H, 1.87; N, 25.35.

General procedure for the synthesis of 5-arylidene-(Z)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-ones 5a–i. A mixture of 2-(1,1-dicyanomethylene)-1,3-thiazol-4-one **3** (1 mmol), aldehyde **4** (1 mmol), ethanol (15 mL), and aqueous 20% sodium

Table 1

Synthesis of dicyanoarylidenerhodanine analogs **5**.

Entry	Compound	Ar	m.p. (°C)	Yield (%)	r.t. (h)[a]
1	**3**	–	225–227	74	12
2	**5a**	C_6H_5	334–336	45	13
3	**5b**	4-F—C_6H_4	323–325	85	15
4	**5c**	4-Cl—C_6H_4	341–343	60	20
5	**5d**	4-Br—C_6H_4	>350	85	18
6	**5e**	4-NO_2—C_6H_4	>350	80	14
7	**5f**	4-CH_3—C_6H_4	342–343	59	13
8	**5g**	4-OCH_3—C_6H_4	>350	63	13
9	**5h**	3,4,5-$(CH_3O)_3$—C_6H_2	343–345	74	16
10	**5i**	3,4-(OCH_2O)—C_6H_3	>350	81	18

[a] r.t.(h) refers to the reaction times in hours for the conversion of **3–5**.

hydroxide (0.3 mL) was stirred at room temperature for 12–20 h. The precipitate formed was filtered off, washed with water and ice-cooled ethanol. The solids were purified by recrystallization from ethanol.

*(Z)-5-Benzylidene-2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (**5a**)*. This compound was obtained according to general procedure as a yellow powder, 45% yield; m.p. 334–336°C; IR (KBr) cm^{-1}, 3459 (N—H), 2214 (2C≡N), 1651 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.52 (s, 1H, =CH), 7.59 (d, 2H, J = 7.63 Hz, H*o*), 7.52 (dd, 2H, J = 7.63, and 7.36 Hz, H*m*), 7.41 (t, 1H, J = 7.36 Hz, H*p*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 48.2 (C-2′), 116.9 (C≡N), 118.3 (C≡N), 128.2 (C-5′), 134.9 (C-5), 129.8 (C*o*), 130.0 (C*i*), 129.5 (C*m*), 129.6 (C*p*), 180.0 (C-2), 181.0 (C=O); HRMS (EI): $C_{13}H_7N_3OS$ requires: 253.0310. Found: 253.0320. Anal. Calcd. for $C_{13}H_7N_3OS$: C, 61.65; H, 2.79; N, 16.59. Found: C, 61.78; H, 2.84; N, 16.67.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-fluorobenzylidene)-1,3-thiazol-4-one (**5b**)*. This compound was obtained according to general procedure as a yellow powder, 85% yield; m.p. 323–325°C; IR (KBr) cm^{-1}, 3456 (N—H), 2214 (2C≡N), 1656 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.51 (s, 1H, =CH), 7.65 (dd, 2H, J = 8.75, and 5.50 Hz, H*o*), 7.35 (dd, 2H, J = 8.75 Hz, and 7.35 Hz, H*m*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 48.2 (C-2′), 116.9 (C≡N), 118.3 (C≡N), 127.1 (C-5′), 131.5 (C-5), 132.2 (d, C*o*, $^3J_{C-F}$ = 8.7 Hz), 129.7 (C*i*), 116.7 (d, C*m*, $^2J_{C-F}$ = 21.9 Hz), 162.6 (d, C*p*, $^1J_{C-F}$ = 248.5 Hz), 179.9 (C-2), 181.0 (C=O); HRMS (EI): $C_{13}H_6FN_3OS$ requires: 271.0216. Found: 271.0208. Anal. Calcd. for $C_{13}H_6FN_3OS$: C, 57.56; H, 2.23; N, 15.49. Found: C, 57.65; H, 2.30; N, 15.40.

*(Z)-5-(4-Chlorobenzylidene)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (**5c**)*. This compound was obtained according to general procedure as a yellow powder, 60% yield; m.p. 341–343°C; IR (KBr) cm^{-1}, 3448 (N—H), 2215 (2C≡N), 1648 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.50 (s, 1H, =CH), 7.61 (d, 2H, J = 7.96 Hz, H*m*), 7.57 (d, 2H, J = 7.96 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 49.4 (C-2′), 116.8 (C≡N), 118.2 (C≡N), 126.8 (C-5′), 134.1 (C-5), 129.7 (C*o*), 130.7 (C*i*), 131.6 (C*m*), 133.8 (C*p*), 179.7 (C-2), 180.8 (C=O); HRMS (EI): $C_{13}H_6ClN_3OS$ requires: 286.9920. Found: 286.9923. Anal. Calcd. for $C_{13}H_6ClN_3OS$: C, 54.27; H, 2.10; N, 14.60. Found: C, 54.20; H, 2.02; N, 14.52.

*(Z)-5-(4-Bromobenzylidene)-2-(1,1-dicyanomethylene)-1,3-thiazol-4-one (**5d**)*. This compound was obtained according to general procedure as a yellow powder, 85% yield; m.p. >350°C; IR (KBr) cm^{-1}, 3446 (N—H), 2218 (2C≡N), 1671 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.47 (s, 1H, =CH), 7.70 (d, 2H, J = 8.54 Hz, H*m*), 7.47 (d, 2H, J = 8.54 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 48.4 (C-2′), 116.8 (C≡N), 118.2 (C≡N), 126.8 (C-5′), 130.9 (C-5), 131.7 (C*o*), 122.8 (C*i*), 132.6 (C*m*), 134.2 (C*p*), 179.7 (C-2), 180.9 (C=O); HRMS (EI): $C_{13}H_6BrN_3OS$ requires: 330.9415. Found: 330.9458. Anal. Calcd. for $C_{13}H_6BrN_3OS$: C, 47.01; H, 1.82; N, 12.65. Found: C, 47.10; H, 1.89; N, 12.58.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-nitrobenzylidene)-1,3-thiazol-4-one (**5e**)*. This compound was obtained according to general procedure as a brown powder, 80% yield; m.p.

Table 2

Comparative antifungal activity (MICs in μg/mL) of compounds **6a–d** from Ref. 5(a) with their current dicyanoarylidenerhodanine analogs **5a–d**.

					MICs[a] (μg/mL) for compounds **6** [5a]			MICs (μg/mL) for compounds **5**
Entry	Compound	R_1	R_2	R_3	Yeasts	*Aspergillus* spp.	Dermatophytes	All fungi assayed
1	**6a/5a**	H	H	H	62.5–125	62.5–125	3.9–7.8	>250
2	**6b/5b**	F	H	H	7.8	250	7.8–32	>250
3	**6c/5c**	Cl	H	H	15.6–250	125–250	62.5	>250
4	**6d/5d**	Br	H	H	62.5–(>250)	>250	>250	>250

[a] Minimum inhibitory concentration.

>350°C; IR (KBr) cm^{-1}, 3406 (N—H), 2214 (2C≡N), 1661 (C=O), 1498, 1286 (NO_2); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 7.60 (s, 1H, =CH), 8.33 (d, 2H, J = 8.88 Hz, H*m*), 7.84 (d, 2H, J = 8.54 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 49.2 (C-2′), 116.5 (C≡N), 117.9 (C≡N), 125.6 (C-5′), 134.4 (C-5), 130.8 (C*o*), 141.5 (C*i*), 124.7 (C*m*), 147.2 (C*p*), 179.4 (C-2), 180.5 (C=O); HRMS (EI): $C_{13}H_6N_4O_3S$ requires: 298.0161. Found: 298.0159. Anal. Calcd. for $C_{13}H_6N_4O_3S$: C, 52.35; H, 2.03; N, 18.78. Found: C, 52.26; H, 1.98; N, 18.86.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-methylbenzylidene)-1,3-thiazol-4-one (**5f**).* This compound was obtained according to general procedure as a yellow powder, 59% yield; m.p. 342–343°C; IR (KBr) cm^{-1}, 3441 (N—H), 2213 (2C≡N), 1650 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 2.34 (s, 3H, CH_3), 7.47 (s, 1H, =CH), 7.48 (d, 2H, J = 8.04 Hz, H*m*), 7.32 (d, 2H, J = 8.04 Hz, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 21.5 (CH_3), 47.9 (C-2′), 117.0 (C≡N), 118.5 (C≡N), 128.3 (C-5′), 128.7 (C-5), 130.2 (C*o*), 139.7 (C*i*), 130.0 (C*m*), 132.1 (C*p*), 180.0 (C-2), 181.2 (C=O); HRMS (EI): $C_{14}H_9N_3OS$ requires: 267.0466. Found: 267.0461. Anal. Calcd. for $C_{14}H_9N_3OS$: C, 62.91; H, 3.39; N, 15.72. Found: C, 62.84; H, 3.31; N, 15.65.

*(Z)-2-(1,1-Dicyanomethylene)-5-(4-methoxybenzylidene)-1,3-thiazol-4-one (**5g**).* This compound was obtained according to general procedure as a yellow powder, 63% yield; m.p. > 350°C; IR (KBr) cm^{-1}, 3401 (N—H), 2212 (2C≡N), 1645 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 3.81(s, 3H, OCH_3), 7.47 (s, 1H, =CH), 7.54 (d, 2H, J = 8.76 Hz, H*o*), 7.08 (d, 2H, J = 8.76 Hz, H*m*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 55.8 (CH_3O), 47.6 (C-2′), 117.1 (C≡N), 118.6 (C≡N), 128.2 (C-5′), 127.2 (C-5), 131.7 (C*o*), 127.4 (C*i*), 115.2 (C*m*), 160.5 (C*p*), 179.9 (C-2), 181.3 (C=O); HRMS (EI): $C_{14}H_9N_3O_2S$ requires: 283.0415. Found: 283.0414. Anal. Calcd. for $C_{14}H_9N_3O_2S$: C, 59.35; H, 3.20; N, 14.83. Found: C, 59.28; H, 3.29; N, 14.76.

*(Z)-2-(1,1-Dicyanomethylene)-5-(3,4,5-trimethoxybenzylidene)-1,3-thiazol-4-one (**5h**).* This compound was obtained according to general procedure as a yellow powder, 74% yield; m.p. 343–345°C; IR (KBr) cm^{-1}, 3451 (N—H), 2220 (2C≡N), 1663 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 3.73 (s, 3H, OCH_3), 3.84 (s, 6H, OCH_3), 7.48 (s, 1H, =CH), 6.90 (s, 2H, H*o*); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 56.5 (2OCH_3-*m*), 60.7 (OCH_3-*p*), 48.0 (C-2′), 117.0 (C≡N), 118.3 (C≡N), 128.6 (C-5′), 129.1 (C-5), 107.6 (C*o*), 130.6 (C*i*), 153.6 (C*m*), 139.2 (C*p*), 179.7 (C-2), 181.0 (C=O); HRMS (EI): $C_{16}H_{13}N_3O_4S$ requires: 343.0627. Found: 343.0615. Anal. Calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 56.06; H, 3.90; N, 12.16.

*(Z)-2-(1,1-Dicyanomethylene)-5-(3,4-methylendioxybenzylidene)-1,3-thiazol-4-one (**5i**).* This compound was obtained according to general procedure as a yellow powder, 81% yield; m.p. > 350°C; IR (KBr) cm^{-1}, 3421 (N—H), 2211 (2C≡N), 1639 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6, δ) ppm, 6.10 (s, 2H, —OCH_2O—), 7.44 (s, 1H, =CH), 7.12 (d, 1H, J = 1.64 Hz, H*o*), 7.14 (dd, 1H, J = 8.10 and 1.64 Hz, H*o*′), 7.05 (d, 1H, J = 8.10 Hz, H*m*′); ^{13}C-NMR (100 MHz, DMSO-d_6, δ) ppm, 47.7 (C-2′), 102.2 (OCH_2O), 117.0 (C≡N), 118.5 (C≡N), 128.3 (C-5′), 127.9 (C-5), 109.3 (C*o*), 125.0 (C*o*′), 129.2 (C*i*), 148.7 (C*m*), 109.4 (C*m*′), 148.5 (C*p*), 179.8 (C-2), 181.1 (C=O); HRMS (EI): $C_{14}H_7N_3O_3S$ requires: 297.0208. Found: 297.0204. Anal. Calcd. for $C_{14}H_7N_3O_3S$: C, 56.56; H, 2.37; N, 14.13. Found: C, 56.49; H, 2.30; N, 14.21.

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