

# Synthesis of Some Sulfur-Containing Spiro-Pyrimidinetriones, Pyrazolidinediones, and Isoxazolidinediones

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## ABSTRACT

Novel sulfur-containing spiro compounds such as 7,11-diaryl-9-thia-2,4-diazaspiro [5,5] undecane-1,3,5-trione 9,9-dioxides (**2**), 6,10-diaryl-8-thia-2,3-diazaspiro[4,5]decane-1,4-dione-8,8-dioxides (**3**) and 6,10-diaryl-2-oxo-8-thia-3-azaspiro[4,5] decane-1,4-dione-8,8-dioxides (**5**) have been prepared by the condensation of 4-dimethoxycarbonyl/diethoxycarbonyl-3,5-diaryl-1-thiane 1,1-dioxides (**1**) with urea, hydrazine hydrate, and hydroxylamine hydrochloride, respectively. The *N*-substituted derivatives (**4** and **6**) of **3** and **5** have also been prepared by acylation and nitrosation. The structures of **2**, **3**, and **5** were established by IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectral studies, respectively.

## INTRODUCTION

In recent years, pyrimidinetriones, pyrazolidinediones, and isoxazolidinediones have attracted much attention from synthetic organic chemists because of the diverse nature of their chemotherapeutic properties [1]. Chlorothiazide, hydrochlorothiazide, thiomorpholine 1,1-dioxide, and dithianetetroxide which contain the sulfone functionality are also known for their pharmacological activities [2]. Therefore, it was considered that incorporation of a sulfone moiety, an effective pharmacophore into a heterocyclic system would certainly add a new dimension to the search for pharmacologi-

cally active compounds. Further, there appear to be no reports in the literature on sulfur-containing spiro-pyrimidinetriones, pyrazolidinediones, or isoxazolidinediones. These observations and our continued interest in the synthesis of new heterocycles prompted us to report on some of our findings.

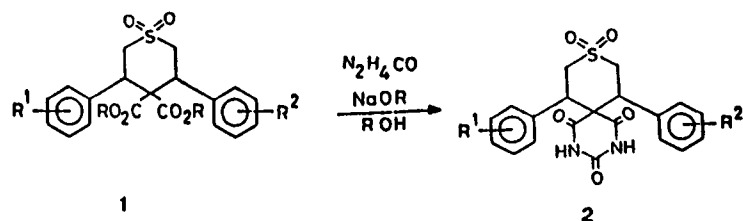
The synthons, thianedioxide dicarboxylates, have been obtained by a double Michael addition of dimethyl/diethyl malonate to *E,E*- and *Z,E*-bis(styryl)sulfones in the presence of Triton B [3]. It is of interest to observe that *E,E*- and *Z,E*-bis(styryl)sulfones give the same product, indicating that the geometry of the substrate has no influence on product formation. We have now shown that these dicarboxylates can be utilized in constructing novel sulfur-containing cycloalkano fused pyrimidinetriones, pyrazolidinediones, and isoxazolidinediones.

## RESULTS AND DISCUSSION

In this article, we wish to report the synthesis of the above-mentioned compounds by the condensation of thianedioxide dicarboxylates with urea, hydrazine hydrate, and hydroxylamine hydrochloride. Thus, a series of 7,11-diaryl-9-thia-2,4-diazaspiro[5,5]undecane-1,3,5-trione-9,9-dioxides (**2**) have been prepared by the condensation of 4,4-dimethoxycarbonyl/diethoxycarbonyl-3,5-diarylthiane 1,1-dioxides (**1**) with urea in the presence of sodium alkoxide (see Scheme 1).

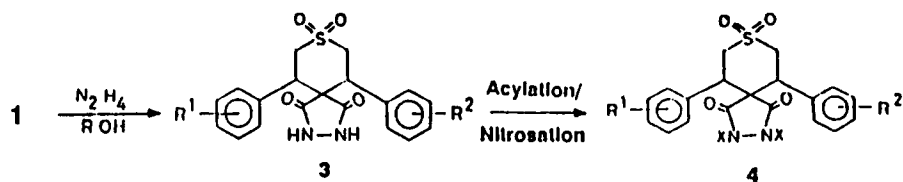
Similarly, 6,10-diaryl-8-thia-2,3-diazaspiro[4,5]decane-1,4-dione-8,8-dioxides (**3**) have been obtained by the condensation of **1** with hydrazine hydrate. The acetylation, benzylation, benzenesul-

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Product No.	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	MP (°C)	Formula	Found (%) (Required)		
						C	H	N
2a	H	H	65	296–298	C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>5</sub> S	60.42 (60.29)	4.48 4.55	7.09 7.03
2b	4-CH <sub>3</sub>	4-CH <sub>3</sub>	83	255–258	C <sub>22</sub> H <sub>22</sub> N <sub>2</sub> O <sub>5</sub> S	61.83 (61.95)	5.28 5.20	6.65 6.67
2c	4-Cl	4-Cl	68	205–207	C <sub>20</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>5</sub> S	61.62 (51.40)	3.63 3.45	6.07 6.00
2d	H	4-Cl	66	276–278	C <sub>20</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>5</sub> S	55.62 (55.49)	3.84 3.96	6.54 6.47

## SCHEME 1



Product No.	R <sup>1</sup>	R <sup>2</sup>	X	Yield (%)	MP (°C)	Formula	Found (%) (Required)		
							C	H	N
3a	H	H	—	64	275–276	C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S	61.74 (61.61)	4.97 4.90	7.62 7.56
3b	4-OCH <sub>3</sub>	4-OCH <sub>3</sub>	—	60	292–294	C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> O <sub>6</sub> S	58.72 (58.59)	5.22 5.15	6.59 6.50
3c	H	4-CH <sub>3</sub>	—	62	285–287	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S	62.62 (62.48)	5.34 5.24	7.36 7.28
3d	H	4-Cl	—	66	300–302	C <sub>19</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>4</sub> S	56.49 (56.37)	4.30 4.23	7.08 6.92
4a	H	H	COCH <sub>3</sub>	64	173–175	C <sub>23</sub> H <sub>22</sub> N <sub>2</sub> O <sub>6</sub> S	60.97 (60.78)	4.94 4.88	6.26 6.16
4b	4-OCH <sub>3</sub>	4-OCH <sub>3</sub>	COCH <sub>3</sub>	62	182–184	C <sub>25</sub> H <sub>26</sub> N <sub>2</sub> O <sub>8</sub> S	58.49 (58.36)	5.18 5.09	5.56 5.44
4c	H	4-CH <sub>3</sub>	COCH <sub>3</sub>	65	175–176	C <sub>24</sub> H <sub>24</sub> N <sub>2</sub> O <sub>6</sub> S	61.68 (61.53)	5.03 5.16	6.14 5.98
4d	H	4-Cl	COCH <sub>3</sub>	68	188–190	C <sub>23</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>6</sub> S	56.69 (56.50)	4.46 4.33	5.85 5.73
4e	H	4-Cl	COC <sub>6</sub> H <sub>5</sub>	78	157–158	C <sub>33</sub> H <sub>25</sub> ClN <sub>2</sub> O <sub>6</sub> S	64.80 (64.65)	4.18 4.11	4.68 4.57
4f	H	4-CH <sub>3</sub>	SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	75	145–146	C <sub>32</sub> H <sub>28</sub> N <sub>2</sub> O <sub>8</sub> S <sub>3</sub>	57.68 (57.82)	4.33 4.25	4.29 4.21
4g	H	H	NO	65	135–137	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> O <sub>6</sub> S	53.10 (53.27)	3.86 3.77	12.98 13.07

## SCHEME 2

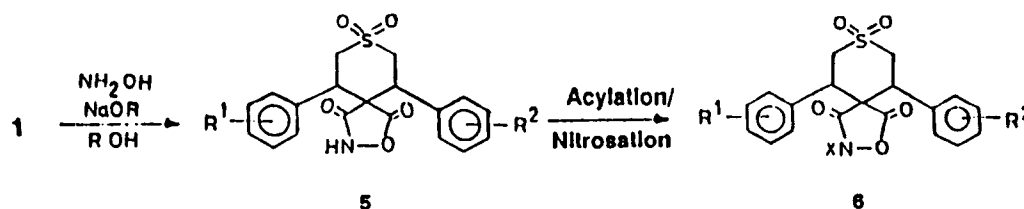
fonylation, and nitrosation of **3** gave the respective N-substituted derivatives (**4**) (see Scheme 2).

Likewise, 6,10-diaryl-8-thia-2-oxo-3-azaspiro [4,5]decane-1,4-dione-8,8-dioxides (**5**) have been synthesized by the reaction of **1** with hydroxylamine hydrochloride in the presence of sodium alkoxide. The N-substituted derivatives of **5** have been obtained by acetylation, benzylation, benzenesulfonylation, and nitrosation (**6**) (see Scheme 3). The formation of the N-substituted derivatives (**4** and **6**) clearly indicates that there is no possibility of enolisation of -NH-CO- in the pyrazolidinedione and isoxazolidinedione moieties of **3** and **5**. The condensation of methyl and ethyl esters with urea, hydrazine hydrate, and hydroxylamine hydrochloride gave the same products with similar yields. This method is a facile and convenient one for the synthesis of **2**, **3**, and **5**. In fact, **2**, **3**, and **5** are found to possess antifungal activity against *Fusarium solani* and *Curvularia lunata* and antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, and *Pseudomonas vulgaris* [4]. However, additional studies on their pharmacological activity are in progress.

The IR spectra of **2,3**, and **5** displayed medium to strong bands in the regions 3300–3475  $\text{cm}^{-1}$ , characteristic of NH stretching vibrations [5]. They also exhibited strong bands in the regions 1665–1685  $\text{cm}^{-1}$ , indicating the presence of carbonyl

groups adjacent to NH moieties [5]. However, a strong band in the region 1690–1730  $\text{cm}^{-1}$  shows the amidic carbonyl group in **5**. Two strong bands in the regions 1300–1335 and 1130–1145  $\text{cm}^{-1}$  have been observed due to asymmetric and symmetric stretching vibrations of the  $\text{SO}_2$  group [6].

The  $^1\text{H}$  NMR spectra of **2**, **3**, and **5** displayed two AMX systems for methine ( $\text{H}_A$ ) and methylene ( $\text{H}_M$  and  $\text{H}_X$ ) protons of the thianedioxide moiety. This can be explained by assuming diequatorial positions of the two aryl groups in the thianedioxide moiety which is in conformity with a *cis*-1,3-arrangement of such systems. The pyrimidinetrione, pyrazolidinedione, and isoxazolidinedione moieties, which themselves are nearly planar, should be perpendicular to the average plane of the thianedioxide unit. In fact, the Drieding model indicates the same [7]. The axial protons,  $\text{H}_M$ , fall in the deshielding zone of the sulfonyl group and hence appear at a distinctly different position than the equatorial protons,  $\text{H}_X$  [8]. The Drieding model further suggests that one of the axial protons,  $\text{H}_M$ , of **3** and **5** would be in close proximity to the paramagnetic cone of the carbonyl group at position 4 and consequently should absorb at different fields. The  $\delta'_\text{H}$  values observed for **2**, **3** and **5** are shown in Table 1. The  $\delta_\text{C}$  values for these compounds derived from their  $^{13}\text{C}$  NMR spectra have also been incorporated in Table 1.



Product No.	$R^1$	$R^2$	X	Yield (%)	MP ( $^\circ\text{C}$ )	Formula	Found (%) (Required)		
							C	H	N
<b>5a</b>	H	H	—	68	210–212	$\text{C}_{19}\text{H}_{17}\text{NO}_5\text{S}$	61.57 (61.44)	4.72 (4.61)	3.86 (3.77)
<b>5b</b>	4-OCH <sub>3</sub>	4-OCH <sub>3</sub>	—	63	242–243	$\text{C}_{21}\text{H}_{21}\text{NO}_7\text{S}$	58.32 (58.46)	4.78 (4.91)	3.32 (3.24)
<b>5c</b>	H	4-CH <sub>3</sub>	—	64	235–237	$\text{C}_{20}\text{H}_{19}\text{NO}_5\text{S}$	62.48 (62.32)	5.05 (4.97)	3.74 (3.63)
<b>5d</b>	H	4-Cl	—	69	229–231	$\text{C}_{19}\text{H}_{16}\text{ClNO}_5\text{S}$	56.23 (56.38)	3.97 (4.02)	3.45 (3.51)
<b>6a</b>	H	4-CH <sub>3</sub>	COCH <sub>3</sub>	68	126–127	$\text{C}_{22}\text{H}_{21}\text{NO}_6\text{S}$	61.68 (61.81)	4.84 (4.95)	3.36 (3.28)
<b>6b</b>	H	H	COC <sub>6</sub> H <sub>5</sub>	76	159–160	$\text{C}_{26}\text{H}_{21}\text{NO}_6\text{S}$	65.84 (65.67)	4.58 (4.45)	3.03 (2.94)
<b>6c</b>	4-OCH <sub>3</sub>	4-OCH <sub>3</sub>	SO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	62	138–140	$\text{C}_{27}\text{H}_{25}\text{NO}_9\text{S}_2$	56.85 (56.73)	4.50 (4.41)	2.54 (2.45)
<b>6d</b>	H	H	NO	63	120–121	$\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_6\text{S}$	57.14 (56.99)	4.10 (4.03)	7.09 (6.99)

SCHEME 3

**TABLE 1**  $^1\text{H}$  and  $^{13}\text{C}$  NMR Data for **2**, **3**, and **5**

Compound No.	$^1\text{H}$ NMR $\delta$ (ppm)							$^{13}\text{C}$ NMR $\delta$ (ppm)				
	NH	$H_A$	$H_M$	$H_X$	$J_{AM}$ (Hz)	$J_{AX}$ (Hz)	$J_{MX}$ (Hz)	C-1 and C-5	C-3	C-6	C-7 and C-11	C-8 and C-10
<b>2a</b>	8.75	4.32	3.95	2.94	15.70	10.48	5.20	170.07 170.34 170.01	158.40	64.15	51.68	48.15
<b>2b</b>	8.74	4.28	3.93	2.88	15.71	10.46	5.21	170.22 170.09	158.24	64.11	51.09	48.13
<b>2d</b>	8.76	4.34	3.98	2.97	15.70	10.47	5.22	170.30 C-1 and C-4	158.42 C-5	64.22 C-6 and C-10	51.17 C-7 and C-9	48.25
<b>3a</b>	9.28	4.23	3.44 3.21 3.42	3.00	15.20	10.25	5.12	168.60 168.93 168.54	64.31	51.96	48.05 47.65 48.02	
<b>3b</b>	9.26	4.20	3.18 3.47	2.98	15.18	10.25	5.11	168.86 168.62	64.27	51.93	47.61 48.07	
<b>3d</b>	9.28	4.25	3.24 3.23	3.03	15.20	10.25	5.12	168.96 169.72	64.34	51.98	47.68 48.02	
<b>4a</b>	8.50	4.02	2.99 3.21	2.83	15.32	10.21	5.10	169.93 170.04	64.03	51.90	47.41 48.34	
<b>4b</b>	8.50	4.00	2.92 3.25	2.78	15.32	10.20	5.08	170.22 169.88	64.16	51.72	47.92 48.22	
<b>4d</b>	8.52	4.03	2.96	2.87	15.31	10.21	5.09	170.00	64.14	51.95	47.54	

## EXPERIMENTAL

The melting points are uncorrected and were determined on a Mel-temp apparatus. The IR spectra were recorded on a Perkin-Elmer Grating Infrared Spectrophotometer as KBr discs. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  solution on a GE NMR Omega and on a Bruker Spectrospin nuclear magnetic resonance spectrometer operating at 500 and 125 MHz, respectively, using TMS as an internal standard. Elemental analyses were performed by Regional Sophisticated Instrumentation Centre, Central Drug Research Institute, Lucknow, India.

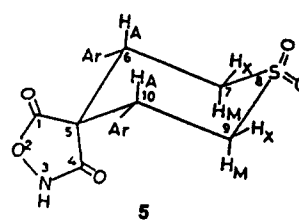
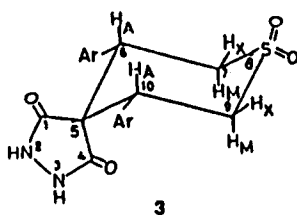
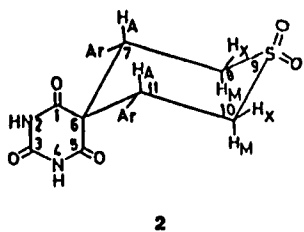
*7,11-Diaryl-2,4-diazaspiro[5,5]undecane-1,3,5-trione-9-thia-9,9-dioxides (2)*, *6,10-diaryl-8-thia-2,3-diazaspiro[4,5]decane-1,4-dione-8,8-dioxides (3)*, or *6,10-diaryl-8-thia-2-oxo-3-azaspiro[4,5]decane-1,4-dione-8,8-dioxides (5)*

A mixture of 4,4-dimethoxycarbonyl/diethoxycarbonyl-3,5-diaryl-1-thiane-1,1-dioxide [3] (10 mmol), urea (10 mmol) (in the case of **2**) or 50% hydrazine hydrate (15 mmol) (in the case of **3**) or hydroxylamine hydrochloride (10 mmol) (in the case of **5**), and 10 mL of methanol/ethanol was placed in a

100 mL round bottomed flask fitted with a reflux condenser. To this mixture 5 mL of 10% sodium methoxide/ethoxide in case of **2** and **5** was added. The contents of the flask were refluxed for 16–20 hours. The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the contents were cooled and poured onto crushed ice containing conc. hydrochloric acid. The product obtained was recrystallized from methanol or 2-propanol to yield colorless crystals. The purity of all the products was checked by TLC.

## Acylation of **3** or **5** (**4** or **6**) [9]

A solution of **3** or **5** (10 mmol) in pyridine (5 mL) was treated with benzoyl or benzenesulfonyl chloride (for acetylation, **3** or **5** (10 mmol) was taken in a mixture containing glacial acetic acid (5 mL) and acetic anhydride (2 mL). The reaction mixture was heated for 3–4 hours and cooled. The contents were poured onto crushed ice containing conc. hydrochloric acid. The product was collected, washed with water, dried, and recrystallized from methanol or ethanol. The purity was checked by TLC.



*Nitrosation of 3 or 5 (4 or 6) [9]*

A well-cooled solution of **3** or **5** (10 mmol) in 2N hydrochloric acid (8 mL) was treated with a cold saturated solution of sodium nitrite. The reaction mixture was cooled in an ice-bath for 1 hour. The solid that separated was collected, washed with water, dried, and recrystallized from 95% ethanol.

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