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Synthesis of Sulfur-Containing Heterocycles: Spiropyrimidinetriones, Thioxopyrimidinediones, Pyrazolidinediones, and Isoxazolidinediones—Part II*

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ABSTRACT: *1-Aroyl-2-styrylsulfonylethene is the precursor for 4,4-dimethoxycarbonyl-2′,5-diaryl-3-(1′,3′-dioxolano)-1-thia-1,1-dioxide (***4***), which is the key intermediate for the synthesis of 7-aroyl-11-aryl-2,4-diazaspiro[5,5]undecane-1,3,5-trione-9-thia-9,9-dioxide(***10***)/3-thioxo-1,5-dione-9-thia-9,9-dioxide (***11***), 6-aroyl-10-aryl-2,3-diazaspiro[4,5]decane-1,4-dione-8-thia-8,8-dioxide (***12***)/2-oxo-3-azaspiro [4,5]decane-1,4-dione-8-thia-8,8-dioxide (***13***). The new compounds were characterized by IR and ^{1}H NMR spectral data.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:131–135, 2001

INTRODUCTION

Recent developments in our laboratory permitted the elaboration of general methods for the synthesis of asymmetric spiroheterocycles. A review of this work, as well as our successful synthesis of sulfur-containing spiro-heterocycles, prompted us to report the present communication. Our synthetic studies in this area have focused on exploiting the relationship between Michael acceptors and Michael donors, which has led to the development of sulfur containing spiropyrimidinetriones, thioxopyrimidinediones, pyrazolidinediones, and isoxazolidinediones [1].

RESULTS AND DISCUSSION

The key intermediates, 4,4-dimethoxycarbonyl-2′,5-diaryl-3-(1′,3′-dioxolano)-1-thia-1,1-dioxides (**4**), for the synthesis of the target molecules have been prepared by the double Michael addition of dimethyl malonate to 1-(2′-aryl-1′,3′-dioxolano)-2-styrylsulfonylethenes (**3**). When the same reaction was carried out with 1-aroyl-2-styrylsulfonylethenes (**1**), an open-chain product, 1-aroyl-5-aryl-6,6-dimethoxycarbonyl-3-thian-1-hexene-3,3-dioxide (**2**), was obtained the structure of which was confirmed by IR (ν, cm^{-1}) and ^{1}H NMR (δ, ppm) spectra. Absorption bands for olefinic (1604), carbonyl (1640 *CO*Ar, 1720 *CO*OCH$_3$), and sulfonyl groups (1340, 1120) were observed. The ^{1}H NMR spectrum indicates two doublets and a quartet for methylene and methine protons apart from two doublets for two olefinic protons at 2.24 (C$_6$-H), 2.92 (C$_5$-H), 3.95 (C$_4$-H), 7.20 (C$_1$-H), and 7.94 (C$_2$-H), and a sharp singlet for OCH$_3$ at 3.90.

The cyclized product **4** was not obtained because of the inertness of the olefinic bond toward Michael addition, as it was flanked by two electron withdrawing groups CO and SO$_2$. However, the protection of the carbonyl group in **1** by refluxing it with ethylene glycol in benzene in the presence of *p*-tolunesulfonic acid (*p*-TSA), followed by the reaction with dimethyl malonate in the presence of Triton-B in benzene, fur-

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Part I. Ref. [1].

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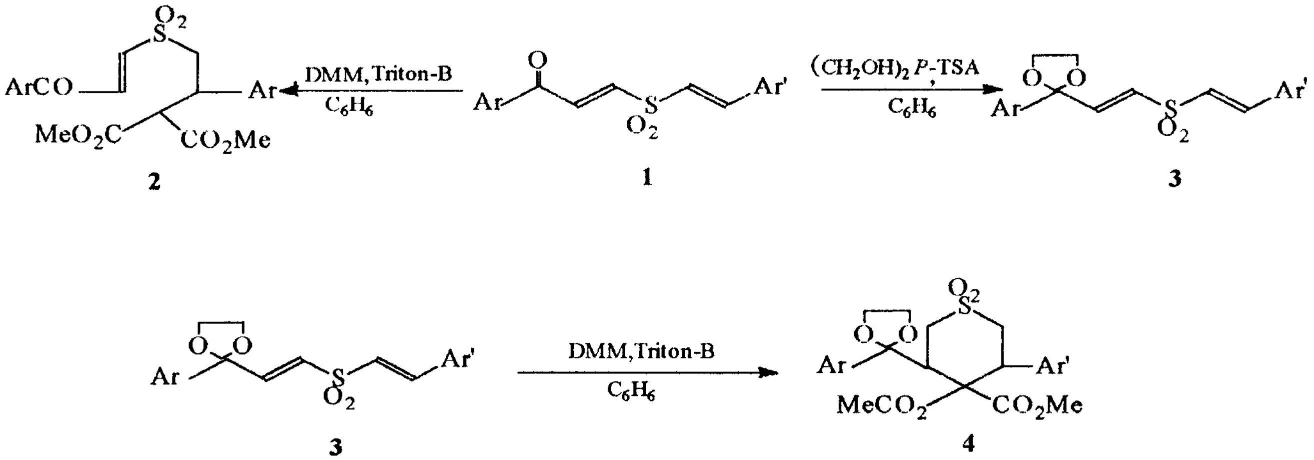


	Ar	Ar'
a	Ph	Ph
b	4-MePh	Ph
c	4-ClPh	Ph

SCHEME 1

nished 4 in fairly good yield. The absence of the free carbonyl absorption peak at 1682 and the presence of carbonyl absorption peaks of carbomethoxy groups in the region 1760 were observed in the IR spectra. The ^{1}H NMR spectrum showed two triplets for methine protons at C_3–H and at C_5–H in the region 4.38 and 3.87, respectively. The methylene protons at C_2 and C_6 are magnetically nonequivalent. The C_2–H_{ax} and C_6–H_{ax} showed signals at relatively much downfield and as such merged with the signals due to OCH_3 of the carbomethoxy group and appeared as a multiplet in the region 3.28–3.83. However, the C_2–H_{eq} and C_6–H_{eq} displayed double doublets at two distinctly different regions, 2.68–2.74 and 2.91–2.98, respectively. The downfield absorption of C_6–H_{eq} may be due to an anisotropic effect of the aryl moiety. The methylene protons of the dioxolane ring displayed a multiplet at 3.62–3.69. The two carbomethoxy groups showed two sharp singlets at 3.58 and at 3.49. The splitting pattern thus suggests that the two substituents in the thiandioxide ring in its preferred rigid chair conformation adopt a *cis*-1,3-diequatorial position [2]. (See Figure 1).

Compound 4 was made to react with urea, thiourea, hydrazine hydrate, and hydroxylamine hydrochloride to give 7-[2′aryl-(1′-3′-dioxolano)]-11-aryl-2,4-diazaspiro[5,5]-undacane-1,3,5-trione-9,9-dioxides (6)/3-thioxo-1,5-dione-9-thia-9,9-dioxides 7 and 6-[2′aryl(1′,3′-dioxolano)]10-aryl-2,3-diazaspiro[4,5] decane-1,4-dione-8-thia-8,8-dioxides 8/2-oxo-3-azaspiro[4,5]decane-1,4-di-one-8-thia-8,8-dioxides 9.

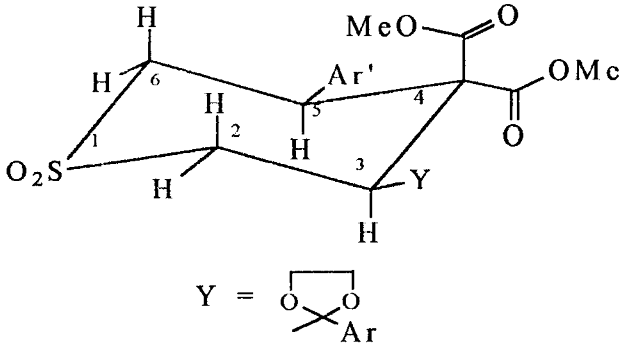
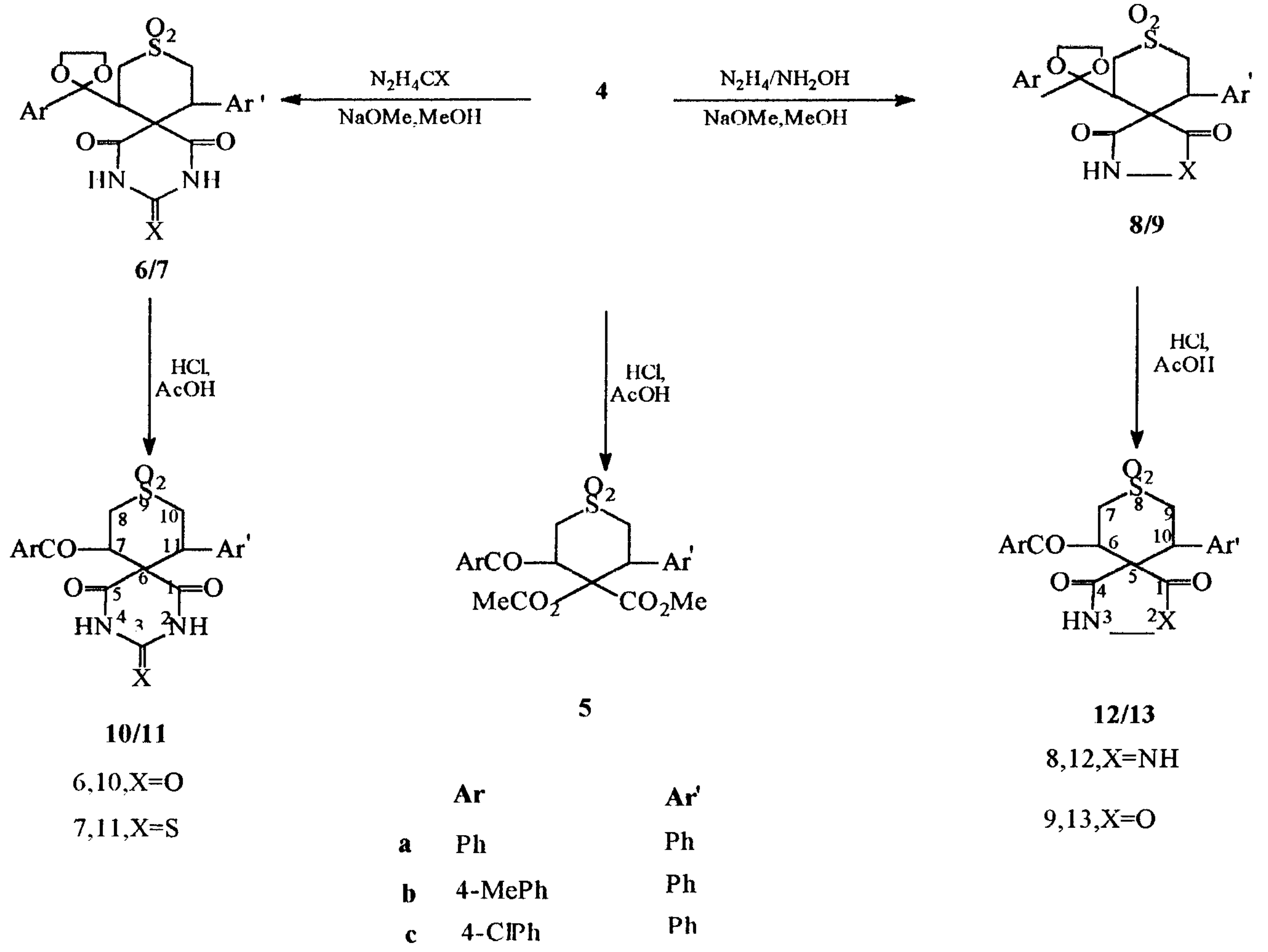


FIGURE 1

The absence of the carbonyl absorption band of the carbomethoxy group around 1760 and the presence of NH stretching vibrations (3300–3475), carbonyl groups adjacent to the NH moiety (1665–1685) in the IR confirmed their formation. A strong band for the amidic carbonyl group (1690–1730) was observed in 9. The ^{1}H NMR spectra of these compounds showed a different type of splitting pattern when compared to 4. The C_7–H, C_{11}–H, and C_8–H, C_{10}–H in 6 and 7 and C_6–H, C_{10}–H, and C_7–H, C_9-H in 8 and 9 showed multiplets in the regions 4.65–4.84 and 3.45–3.54, respectively. The signal due to the NH proton was observed around 8.65–10.80, which disappeared on deuteration. The splitting pattern and Drieding



6/7

8/9

10/11

5

12/13

6,10,X=O
7,11,X=S

8,12,X=NH
9,13,X=O

	Ar	Ar'
a	Ph	Ph
b	4-MePh	Ph
c	4-ClPh	Ph

SCHEME 2

model indicates that these compounds may adopt a flexible conformation in order to minimize trans annular interactions of the substituents with the thiandioxide moiety (See Figure 2).

Deprotection of the carbonyl group in **4** and **6**–**9** was carried out by refluxing the compounds with HCl in acetic acid in a 1:3 ratio, which selectively hydrolyzed the 1,3-dioxolane ring to give 3-aroyl-5-aryl-4,4-dimethoxycarbonyl-1-thian-1,1-dioxides (**5**) and 7-aroyl-11-aryl-2,4-diazaspiro[5,5] undecane-1,3,5-trione-9-thia-9,9-dioxides (**10**)/3-thioxo-1,5-dione-9-thia-9,9-dioxide (**11**) and 6-aroyl-10-aryl-2,3-diazaspiro[4,5]-decane-1,4-dione-8-thia-8,8-dioxides (**12**)/2-oxo-3-azaspiro[4,5]decane-1,4-dione-8-thia-8,8-dioxides (**13**). In all these compounds, an absorption band due to a carbonyl group was observed around 1680–1684, which indicates the presence of an aroyl substituent. The ^1H NMR spectrum of **5** is the replica of **4**, except for the signals due to the methylene group of the 1,3-dioxolane moiety. However, in **10**–**13**, the methine proton adjacent to the aroyl moiety exhibited a double doublet at 5.26, whereas the other methine proton adjacent to the aryl group displayed a triplet at 4.32, which may be due to the anisotropic effect of the carbonyl group. A multiplet was observed for the methylene protons in the region 3.50–3.58 in all the cases. However, the preferred conformation of all these compounds, as suggested by the spectra and Drieding model, is found to be similar to those of **6**–**9**.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. IR spectra (KBr-disc) were recorded on a Beckman IR-18 spectrophotometer, ^1H NMR spectra were recorded in ($CDCl_3$/DMSO-d_6) with 300 MHz on a varian EM-360 spec-

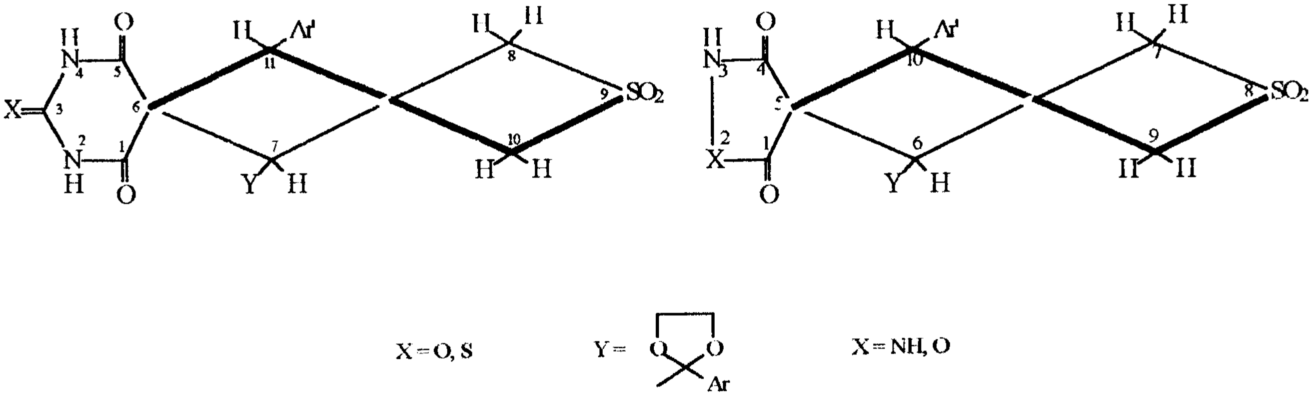


FIGURE 2

trophotometer using tetramethylsilane (TMS) as a standard. Elemental analyses were obtained from the University of Pune, Pune, India.

1-Aroyl-2-styrylsulfonylethenes (1)

A solution of 1-aroyl-2-chloroethene [3] (5 mmol) in methanol (20 mL) was added dropwise to sodium styrylsulfinate [4] (5.5 mmol) in water (20 mL) with stirring at 0–10°C for 3 hours. The crystallized solid was filtered off, washed with water, dried, and recrystallized from methanol.

1-(2'Aryl-1'3'dioxolano)-2-styrylsulfonylethenes (3)

A mixture of 1-aroyl-2-styrylsulfonylethene [5] (1 mmol), ethylene glycol (2 mmol), and *p*-toluenesulfonic acid (1 mmol) in benzene (40 mL) was refluxed for 15 hours using a Dean-Stark apparatus. The reaction mixture was poured into crushed ice and extracted with benzene, dried, and the solvent removed by use of a rotary evaporator. The solid obtained was recrystallized from methanol to give pure **3**. The physical data of these compounds are given in Table 1.

4,4-Dimethoxycarbonyl-2',3-diaryl-5-(1'3'-dioxolano)-1-thia-1,1-dioxides (4)

A mixture of **3** (1.0 mmol) and dimethyl malonate (1.5 mmol) was dissolved in benzene (10 mL) to which a catalytic amount of Triton-B had been added, and the mixture was refluxed for 3–4 hours. The solvent was distilled off and the syrupy substance obtained was treated with methanol to provide a solid that was recrystallized from methanol. The physical data of these compounds are presented in Table 1.

TABLE 1 Physical Data of Compounds **3–13**

Compound	*m.p. (°C)*	*Yield (%)*	*Compound*	*m.p. (°C)*	*Yield (%)*
3a	150–152	80	**9a**	180–182	70
3b	159–160	83	**9b**	187–189	73
3c	149–151	88	**9c**	183–185	72
4a	198–200	68	**10a**	280–282	85
4b	205–207	77	**10b**	289–291	88
4c	189–191	74	**10c**	290–292	86
5a	208–210	80	**11a**	279–281	81
5b	211–213	79	**11b**	286–288	83
5c	207–209	83	**11c**	273–275	88
6a	210–212	70	**12a**	292–294	80
6b	210–212	74	**12b**	291–293	80
6c	207–209	75	**12c**	299–301	87
7a	208–209	69	**13a**	220–222	79
7b	214–215	76	**13b**	227–229	83
7c	217–219	72	**13c**	220–224	85
8a	221–223	66			
8b	231–233	69			
8c	228–230	68			

Note: Satisfactory elemental analyses were obtained for **5**, **10–13**: C ± 0.33; H ± 0.14; N ± 0.22.

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

A mixture of **4** (10 mmol), urea (10 mmol)/thiourea (10 mmol)/50% hydrazine hydrate (15 mmol)/hydroxylamine hydrochloride (10 mmol), and 10 mL of methanol was prepared. To this, 5 mL of 10% sodium methoxide was added, and the mixture was refluxed for 8–12 hours. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, the contents were cooled and poured on to crushed ice containing concentrated hydrochloric acid. The product obtained was recrystallized from methanol to give **6–9**, respectively. The physical data of these compounds are given in Table 1.

Hydrolysis of **4** *and* **6–9**

The hydrolysis was carried out by refluxing **4** and **6–9** with HCl in AcOH (1:3 ratio) for 3–4 hours. The reaction mixture was cooled and poured into crushed ice. The solid obtained was filtered off and recrystallized from methanol to give **5** and **10–13**. The physical data of these compounds are given in Table 1.

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