

Studies on Reactivity of Ketosulfones

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ABSTRACT: *The cycloaddition of diazomethane, cyclocondensation of hydrazine hydrate, and cyclopropanation of TMSOI to 1-aryl-2-styrylsulfonyl ethenes were studied and different novel products thereby obtained were characterized with spectral parameters.* © 2003 Wiley Periodicals, Inc. *Heteroatom Chem* 14:155–159, 2003; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10117

INTRODUCTION

During the last one and a half decades, we were involved in the development of novel carbocyclic and heterocyclic systems. Amongst them pyrazolines and isoxazolines constitute an important class because of their potential bioactive nature [1–4]. The synthesis of them was based on ring formation of either 2 + 3 or 3 + 2 principle of an olefin with diazomethane/ylide or hydrazine hydrate. In further developments of this strategy we have now considered the reactivity of bis-olefinic systems activated by both a carbonyl and a sulfonyl group. The present communication describes an account on these findings.

RESULTS AND DISCUSSION

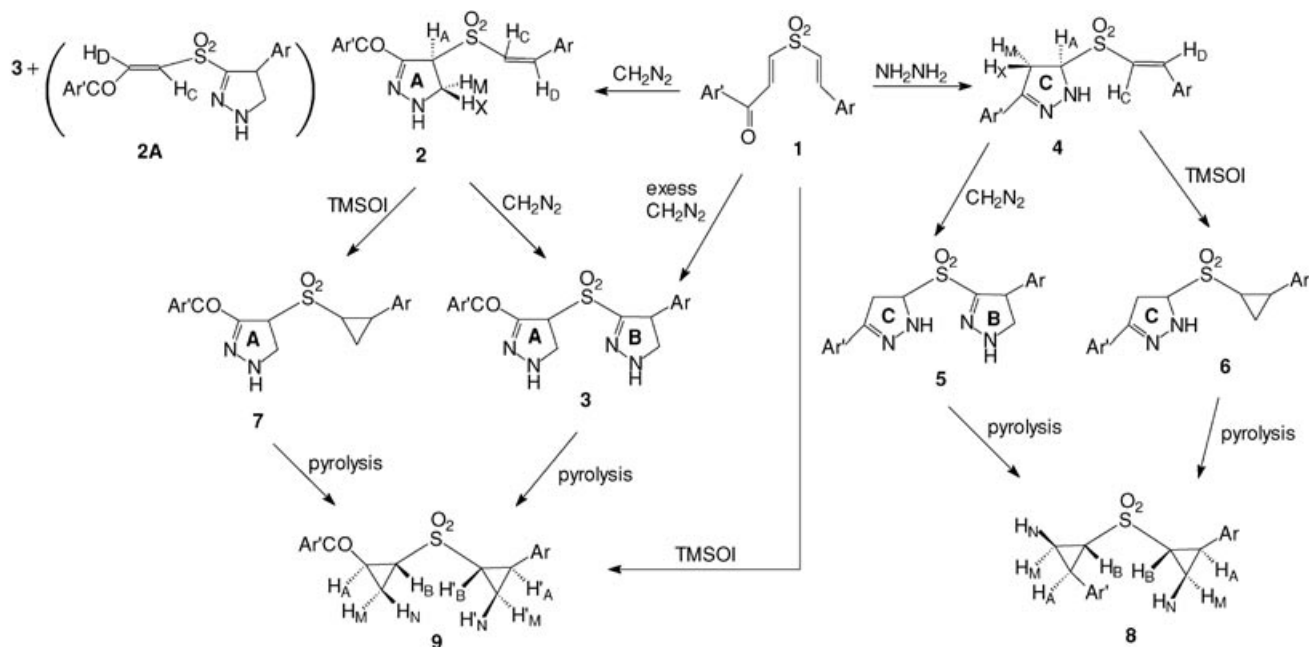
The synthetic scheme involves the reaction of 1-aryl-2-styrylsulfonyl ethenes (**1**) with 2 mol of

diazomethane in the presence of Et₃N at –20 to –15°C (Scheme 1). When progress of the reaction was monitored at frequent intervals two spots were observed in TLC, which persisted even after 48 h. The two were separated by column chromatography, which indicated the formation of 3-aryl-4-styrylsulfonyl-2-pyrazoline (**2**) as a major product and 3-aryl-2-pyrazolinyl-4'-aryl-2'-pyrazolinyl-[4,3']-sulfone (**3**) as a minor one (Table 1). The also possible 4-aryl-2-pyrazolinyl-1'-aryl-ethenyl-[3,2']-sulfone (**2A**) could not be isolated. Obviously the competition between the two ethylenic bonds favors the formation of **2** rather than **2A**. The ¹H NMR spectra of **2** indicated an AMX splitting pattern for methine and methylene protons of the pyrazoline ring [5,6] (Table 2). The coupling constants of ethylenic protons ($J_{CD} = 14.13\text{--}14.24$ Hz) indicated their trans geometry. A broad singlet around $\delta = 9.20\text{--}10.30$ was observed for NH proton which disappeared on deuteration. However, when **1** was treated with excess diazomethane in the presence of triethylamine at –20°C to –15°C it resulted in only **3**. The latter was also obtained by the cycloaddition of 1 mol of diazomethane to **2** in the presence of triethylamine. The protons of the two pyrazoline moieties A and B in **3** also exhibited AMX splitting pattern with signals at different regions which was supported by their integration. Furthermore, pyrazoline ring protons of A exhibited their resonance signals almost in the same region as in ring A of **2**.

The cyclocondensation of **1** with hydrazine hydrate in ethanol resulted in 3-aryl-5-styrylsulfonyl-2-pyrazoline (**4**) [7]. Here again the protons of pyrazoline ring C exhibited an AMX pattern. The olefinic protons displayed similar splitting pattern as in **2**. In

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SCHEME 1

addition, **4** on treatment with 1 mol of diazomethane gave 3-aryl-2-pyrazoliny-4'-aryl-2-pyrazoliny-[5,3']-sulfone (**5**), representative of a new class of heterocyclic systems with two different pyrazoline rings within the same molecule. In the ^1H NMR spectrum the pyrazoline rings B and C exhibited two different AMX splitting patterns identical to those of ring B of **3** and ring C of **4**.

The reaction of **1** with 2 mol of trimethylsulphoxonium iodide (TMSOI) under PTC conditions resulted in a biscyclopropane [8], 1-aryl-1'-aryl-bis(cyclopropyl)-sulfone (**9**). The ^1H NMR spectrum of **9** showed two different ABMN splitting patterns for cyclopropyl ring protons [9]. Likewise, the reaction of **2** and **4** with 1 mol of TMSOI furnished 3-aryl-2-pyrazoliny-2'-arylcyclopropyl-[4,2']-sulfone (**7**) and 3-aryl-2-pyrazoliny-1'-arylcyclopropyl-[5,2']-sulfone (**6**) respectively. The latter contains a pyrazoline unit together with a cyclopropane moiety in the same molecule, a novel system again. The lability of pyrazolines has been noteworthy because of their usefulness as precursors for cyclopropanes [10]. Thus **3/7** and **5/6** on pyrolysis gave **9** and 1,1'-diaryl-bis(cyclopropyl)sulfone (**8**) respectively. The ^1H NMR spectra of cyclopropane moiety in **6**, **7**, and **8** also showed ABMN splitting patterns similar to **9**. The characteristic IR frequencies observed for all these compounds also support various functionalities present in them.

Thus different small ring units, cyclopropanes, and pyrazolines were developed from an activated olefin by cycloaddition, cyclocondensation, and cyclopropanation reactions.

EXPERIMENTAL

Melting points were determined in open capillaries on Tempo Mel-Temp apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer grating Infrared spectrophotometer model 337 in KBr pellets. The ^1H NMR spectra were recorded at 200 MHz on Bruker spectropin spectrometer in CDCl_3 with TMS as an internal standard. The purity of the compounds was checked by TLC [Silica gel-G (BDH), hexane/ethyl acetate (3:1) as eluent]. Microanalyses were performed by the Regional Sophisticated Instrumentation Centre, Punjab University, Chandigarh, India.

The starting materials 1-aryl-2-styrylsulfonyl-ethenes (**1**) were prepared as per the known procedure [11].

Cycloaddition of Diazomethane to **1**

A solution of **1** (0.01 mol) in dichloromethane (20 ml) was cooled at ice-salt bath temperature. To this, an ethereal solution of diazomethane (80 ml, 0.4 mol) and a catalytic amount of triethylamine were added.

TABLE 1 Physical Data of the Compounds 2–9

	<i>mp</i> (°C)	Yield (%)	Mol. Formula (Mol. Wt)	Found (Calcd) (%)		
				C	H	N
2a	122–124	58	C ₁₈ H ₁₆ N ₂ O ₃ S (340.40)	63.59 (63.51)	4.85 (4.74)	8.29 (8.23)
2b	113–115	62	C ₁₉ H ₁₈ N ₂ O ₃ S (354.42)	64.54 (64.39)	5.00 (5.12)	8.02 (7.90)
2c	133–135	61	C ₁₈ H ₁₅ ClN ₂ O ₃ S (374.84)	57.58 (57.67)	4.13 (4.03)	7.39 (7.47)
3a	172–174	70	C ₁₉ H ₁₈ N ₄ O ₃ S (382.44)	59.85 (59.67)	4.64 (4.74)	14.81 (14.65)
3b	161–163	68	C ₂₀ H ₂₀ N ₄ O ₃ S (396.46)	60.73 (60.59)	5.13 (5.08)	14.00 (14.13)
3c	184–186	72	C ₁₉ H ₁₇ ClN ₄ O ₃ S (416.88)	54.56 (54.74)	4.02 (4.10)	13.58 (13.43)
4a	132–134	82	C ₁₇ H ₁₆ N ₂ O ₂ S (312.39)	65.22 (65.36)	5.12 (5.16)	9.04 (8.96)
4b	145–147	78	C ₁₈ H ₁₈ N ₂ O ₂ S (326.42)	66.40 (66.23)	5.48 (5.56)	8.44 (8.58)
4c	156–158	85	C ₁₇ H ₁₅ ClN ₂ O ₂ S (346.84)	58.95 (58.86)	4.41 (4.36)	8.18 (8.08)
5a	183–185	60	C ₁₈ H ₁₈ N ₄ O ₂ S (354.43)	61.15 (60.99)	5.05 (5.12)	15.98 (15.81)
5b	177–179	76	C ₁₉ H ₂₀ N ₄ O ₂ S (368.46)	61.80 (61.93)	5.59 (5.47)	15.36 (15.21)
5c	192–194	62	C ₁₈ H ₁₇ ClN ₄ O ₂ S (388.87)	55.42 (55.60)	4.32 (4.41)	14.28 (14.41)
6a	163–165	60	C ₁₈ H ₁₈ N ₂ O ₂ S (326.42)	66.11 (66.23)	5.67 (5.56)	8.49 (8.58)
6b	158–159	68	C ₁₉ H ₂₀ N ₂ O ₂ S (340.44)	67.08 (67.00)	5.86 (5.92)	8.34 (8.23)
6c	172–174	65	C ₁₈ H ₁₇ ClN ₂ O ₂ S (360.86)	60.04 (59.91)	4.84 (4.75)	7.64 (7.76)
7a	171–173	64	C ₁₉ H ₁₈ N ₂ O ₃ S (354.43)	64.50 (64.35)	5.16 (5.12)	8.04 (7.90)
7b	161–163	62	C ₂₀ H ₂₀ N ₂ O ₃ S (368.46)	65.10 (65.20)	5.42 (5.47)	7.71 (7.60)
7c	175–176	66	C ₁₉ H ₁₇ ClN ₂ O ₃ S (388.87)	58.56 (58.68)	4.53 (4.41)	7.11 (7.20)
8a	162–164	48	C ₁₈ H ₁₈ O ₂ S (298.40)	72.65 (72.45)	6.12 (6.08)	
8b	157–158	42	C ₁₉ H ₂₀ O ₂ S (312.43)	73.18 (73.01)	6.56 (6.45)	
8c	168–170	46	C ₁₈ H ₁₇ ClO ₂ S (332.85)	64.77 (64.95)	5.09 (5.15)	
9a	180–182	68	C ₁₉ H ₁₈ O ₃ S (326.41)	69.80 (69.91)	5.49 (5.55)	
9b	170–172	71	C ₂₀ H ₂₀ O ₃ S (340.44)	70.72 (70.57)	6.00 (5.92)	
9c	186–188	75	C ₁₉ H ₁₇ ClO ₃ S (360.86)	63.63 (63.24)	4.70 (4.74)	

Satisfactory elemental analyses were obtained for representative example of each series: C $\pm$ 0.24, H $\pm$ 0.12, N $\pm$ 0.19.

The reaction mixture was kept at -20°C to -15°C for 48 h. The solvent was removed under reduced pressure. The resultant product indicated a mixture of two components in TLC, which were separated by column chromatography using ethyl acetate/hexane (1:3) as eluent, and identified as **2** and **3**. However, **1** with excess diazomethane (120 ml, 0.4 mol) under

the above conditions afforded a product that was purified by recrystallization from ethanol to get **3**. Similarly **3** was also obtained when a solution of **2** (0.01 mol) was treated with an ethereal solution of diazomethane (80 ml, 0.4 mol) and triethylamine. The yield mentioned for **3** was by the reaction of **1** with excess diazomethane.

TABLE 2 ^1H NMR Spectral Data for 2–9

	$\delta^1\text{H}$ in ppm (J in Hz)
2a	4.14 (dd, 1H, H_X), 4.32 (dd, 1H, H_M , $J_{MX} = 10.54$), 4.88 (dd, 1H, H_A , $J_{AM} = 12.61$, $J_{AX} = 5.50$), 6.65 (d, 1H, H_C), 6.92–7.42 (m, 11H, Ar-H and H_D , $J_{CD} = 14.13$), 9.92 (bs, 1H, N-H).
2c	4.38 (dd, 1H, H_X), 4.45 (dd, 1H, H_M , $J_{MX} = 10.56$), 4.95 (dd, 1H, H_A , $J_{AM} = 12.58$, $J_{AX} = 5.51$), 6.68 (d, 1H, H_C), 6.98–7.52 (m, 10H, Ar-H and H_D , $J_{CD} = 14.24$), 9.94 (bs, 1H, N-H).
3a	4.15 (dd, 1H, H_X), 4.36 (dd, 1H, H_M , $J_{MX} = 10.64$), 4.92 (dd, 1H, H_A , $J_{AM} = 12.60$, $J_{AX} = 5.56$), 3.86 (dd, 1H, $\text{H}_{X'}$), 4.08 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.61$), 4.24 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.58$, $J_{A'X'} = 5.54$), 6.98–7.44 (m, 10H, Ar-H), 10.00 (bs, 2H, N-H).
3c	4.23 (dd, 1H, H_X), 4.43 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.64$), 4.94 (dd, 1H, H_A , $J_{AM} = 12.68$, $J_{AX} = 5.52$), 4.00 (dd, 1H, $\text{H}_{X'}$), 4.15 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.63$), 4.32 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.64$, $J_{A'X'} = 5.52$), 7.01–7.62 (m, 9H, Ar-H), 9.99 (bs, 2H, N-H).
4a	3.10 (dd, 1H, H_X), 3.30 (dd, 1H, H_M , $J_{MX} = 10.63$), 5.92 (dd, 1H, H_A , $J_{AM} = 12.70$, $J_{AX} = 5.53$), 6.62 (d, 1H, H_C), 7.0–7.68 (m, 11H, Ar-H and H_D , $J_{CD} = 14.15$), 10.26 (bs, 1H, N-H).
4b	2.25 (s, 3H, Ar- CH_3), 3.20 (dd, 1H, H_X), 3.36 (dd, 1H, H_M , $J_{MX} = 10.60$), 5.98 (dd, 1H, H_A , $J_{AX} = 5.52$, $J_{AM} = 12.62$), 6.68 (dd, 1H, H_C), 7.02–7.58 (m, 10H, Ar-H and H_D , $J_{CD} = 14.18$), 10.25 (bs, 1H, N-H).
5a	3.16 (dd, 1H, H_X), 3.32 (dd, 1H, H_M , $J_{MX} = 10.54$), 5.93 (dd, 1H, H_A , $J_{AM} = 12.68$, $J_{AX} = 5.51$), 3.93 (dd, 1H, $\text{H}_{X'}$), 4.09 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.62$), 4.28 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.68$, $J_{A'X'} = 5.51$), 6.92–7.58 (m, 10H, Ar-H), 9.96 (bs, 1H, N-H), 10.21 (bs, 1H, NH).
5c	3.16 (dd, 1H, H_X), 3.35 (dd, 1H, H_M , $J_{MX} = 10.60$), 5.92 (dd, 1H, H_A , $J_{AM} = 12.62$, $J_{AX} = 5.56$), 3.98 (dd, 1H, $\text{H}_{X'}$), 4.12 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.63$), 4.30 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.64$, $J_{A'X'} = 5.52$), 6.92–7.61 (m, 9H, Ar-H), 9.94 (bs, 1H, N-H), 10.22 (bs, 1H, N-H).
6a	1.32 (ddd, 1H, H_N), 1.48 (ddd, 1H, H_M), 2.78 (ddd, 1H, H_B , $J_{BM} = 5.55$, $J_{BN} = 10.12$), 2.88 (ddd, 1H, H_A , $J_{AB} = 5.72$, $J_{AN} = 6.58$, $J_{AM} = 8.55$), 3.14 (dd, 1H, $\text{H}_{X'}$), 3.33 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.71$), 5.95 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.64$, $J_{A'X'} = 5.54$), 7.05–7.62 (m, 10H, Ar-H), 10.53 (bs, 1H, N-H).
6c	1.30 (ddd, 1H, H_N), 1.45 (ddd, 1H, H_M), 2.76 (ddd, 1H, H_B , $J_{BM} = 5.57$, $J_{BN} = 10.14$), 2.94 (ddd, 1H, H_A , $J_{AB} = 5.72$, $J_{AN} = 6.59$, $J_{AM} = 8.59$), 3.17 (dd, 1H, $\text{H}_{X'}$), 3.35 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.61$), 5.97 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.64$, $J_{A'X'} = 5.54$), 7.02–7.78 (m, 9H, Ar-H), 10.21 (bs, 1H, N-H).
7a	1.28 (ddd, 1H, H_N), 1.48 (ddd, 1H, H_M), 2.74 (ddd, 1H, H_B , $J_{BM} = 5.58$, $J_{BN} = 10.14$), 2.89 (ddd, 1H, H_A , $J_{AB} = 5.74$, $J_{AN} = 6.54$, $J_{AM} = 8.54$), 4.16 (dd, 1H, $\text{H}_{X'}$), 4.32 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.63$), 4.88 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.58$, $J_{A'X'} = 5.52$), 6.95–7.52 (m, 10H, Ar-H), 9.94 (bs, 1H, N-H).
7c	1.32 (ddd, 1H, H_N), 1.52 (ddd, 1H, H_M), 2.72 (ddd, 1H, H_B , $J_{BM} = 5.52$, $J_{BN} = 10.12$), 2.92 (ddd, 1H, H_A , $J_{AB} = 5.72$, $J_{AN} = 6.59$, $J_{AM} = 8.55$), 4.28 (dd, 1H, $\text{H}_{X'}$), 4.42 (dd, 1H, $\text{H}_{M'}$, $J_{M'X'} = 10.60$), 4.92 (dd, 1H, $\text{H}_{A'}$, $J_{A'M'} = 12.62$, $J_{A'X'} = 5.55$), 6.95–7.52 (m, 9H, Ar-H), 9.98 (bs, 1H, N-H).
8a	1.25 (ddd, 2H, H_N), 1.58 (ddd, 2H, H_M), 2.74 (ddd, 2H, H_B , $J_{BM} = 5.61$, $J_{BN} = 10.08$), 2.87 (ddd, 2H, H_A , $J_{AB} = 5.74$, $J_{AN} = 6.58$, $J_{AM} = 8.54$), 6.92–7.51 (m, 10H, Ar-H).
9a	1.56 (ddd, 1H, H_N), 1.68 (ddd, 1H, H_M), 2.75 (ddd, 1H, H_B , $J_{BM} = 5.52$, $J_{BN} = 10.12$), 2.94 (ddd, 1H, H_A , $J_{AB} = 5.68$, $J_{AN} = 6.62$, $J_{AM} = 8.54$), 1.24 (ddd, 1H, $\text{H}_{N'}$), 1.42 (ddd, 1H, $\text{H}_{M'}$), 2.65 (ddd, 1H, $\text{H}_{B'}$, $J_{B'M'} = 5.05$, $J_{B'N'} = 10.10$), 2.88 (ddd, 1H, $\text{H}_{A'}$, $J_{A'B'} = 5.54$, $J_{A'N'} = 6.60$, $J_{A'M'} = 8.60$), 6.98–7.65 (m, 10H, Ar-H).

Cyclocondensation of 1 with Hydrazine Hydrate

Compound **1** (0.01 mol) in ethanol (20 ml) and hydrazine hydrate (0.02 mol) were refluxed for 2–3 h and cooled. The solid separated was recrystallized from ethanol to get pure **4**.

Cycloaddition of Diazomethane to 4

To a solution of **4** (0.01 mol) in dichloromethane (20 ml) an ethereal solution of diazomethane (100 ml, 0.4 mol) and a catalytic amount of triethylamine were added. This on work up as in **2** resulted in **5**.

Cyclopropanation of 1 (2, 4) with Trimethylsulphoxonium Iodide

A mixture of **1** (0.01 mol), trimethylsulphoxonium iodide (0.022 mol), 50% aqueous KOH solution

(50 ml), and dichloromethane (40 ml) were stirred till a clear two-phase system was obtained. To this, benzyltriethylammonium chloride (BTEAC) (100 mg) was added with continuous stirring for a period of 2–3 h. The reaction was monitored by TLC. After completion the reaction mixture was diluted with water. The organic layer was separated and washed with water and brine solution and then dried (anhydrous Na_2SO_4). Evaporation of the solvent gave a syrupy substance which solidified on treatment with 2-propanol. Recrystallization from ethanol gave **9**.

A similar procedure was adopted for **2** to get **7** and for **4** to get **6**.

Pyrolysis of 3 and 7 (5 and 6)

A solution of **3** or **7** (0.001 mol) and 1,2-ethanediol (10 ml) was heated at about 200–230°C for 30–45 min under anhydrous conditions. The contents of

the flask were diluted with water and stirred until a solid separated. The crude product obtained was recrystallized from 2-propanol to get **9**.

This procedure was adopted for **5** or **6** to obtain **8**.

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