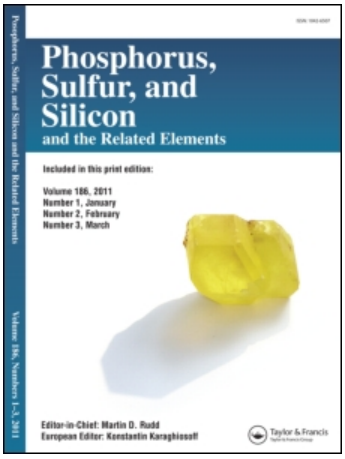

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A NEW ROUTE FOR THE SYNTHESIS OF STYRYLBENZYLSULFONES, PRECURSORS OF 1-BENZYLSULFONYL-2-ARYLCYCLOPROPANES

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A novel method for the synthesis of *E*-styrylbenzylsulfones from *E*-sodium styrysulfinates and benzyl chlorides has been described. The cyclopropanation of these compounds with dimethylsulfonium methylide gave *E*-1-benzylsulfonyl-2-arylcyclopropanes in good yields. The corresponding *Z*-isomers have been obtained by the cycloaddition of benzylthiocarbenes to styrenes under phase transfer catalysis. Their geometry has been assigned based on IR and ^{1}H NMR spectral data.

Key words: Benzylthiocarbene, configuration, cyclopropanation, dimethylsulfonium methylide, phase transfer catalysis, sodium styrylsulfinate.

INTRODUCTION

The chemistry of cyclopropanes has emerged in recent times as a versatile tool in organic synthesis.[1,2] The cyclopropyl group is found as a basic structural element in a wide range of naturally occurring compounds in plants and in microorganisms, both fungal and bacterial. This is also generated transiently in primary and secondary metabolisms. Therefore, the cyclopropyl group is present in compounds of biological importance.[3] A number of cyclopropanoid compounds were known to be pharmacologically important. Amongst them, Chrysanthemic acid is a natural insecticide, Sirenin is a potent sperm attractant, Illudin-S is an effective antibacterial agent apart from a number of such other compounds being biologically important. Some sulfones ($RSO_2CH{=}CHSR$) are also known to possess inhibitory activity on some algae and fungi.[4] A series of 1-aryl-3-arylsulfonyl-2-propenones are found to be active against Alternaria mali, Piricularia oryzae.[5] Recently, it was also reported that [2,2-bis(arylsulfonyl)cyclopropyl]arylmethanones exhibit significant fungicidal activity.[6] Thus, in recent times there is a greater stimulation in the development of research on the synthetic strategies for newer cyclopropanoids of bioactive nature. Therefore, it was considered that the synthesis of a number of new cyclopropyl sulfones by a viable route would be of considerable biological importance.

The Knoevenagal condensation of sulfonylacetic acid with araldehydes in the presence of a base as a catalyst[7] was acclaimed as an elegant and simpler method for the synthesis of unsaturated sulfones. In fact, in our earlier communication[8] we have followed the same method for the synthesis of E,E- and Z,Z-1,3-bis(styrylsulfonyl)benzene. A number of mono[9]- and bis[7] unsaturated sulfones have been reported earlier from our laboratories adopting the above mentioned procedure.

In this communication we report yet another facile method for the synthesis of E-styrylbenzylsulfones which were used as precursors for cyclopropane derivatives. Thus, a series of *cis*- and *trans*-1-benzylsulfonyl-2-arylcyclopropanes have been prepared and their biological studies are under progress.

RESULTS AND DISCUSSION

The E-styrylbenzylsulfones (**4**) have been prepared by the alkylation of E-sodium styrylsulfinates (**3**). The latter were obtained from E-styrylsulfonyl chlorides (**2**) which were the products of addition of sulfuryl chloride to styrene and 4-methyl styrene. The alkylation of p-toluenesulfinate with dimethyl sulfate[10] or sodium p-toluenesulfinate with methyl iodide[11,12] or with methyl potassiumsulfate[13] were reported earlier. Thus, it is evident that the alkylation of styrylsulfinates is a

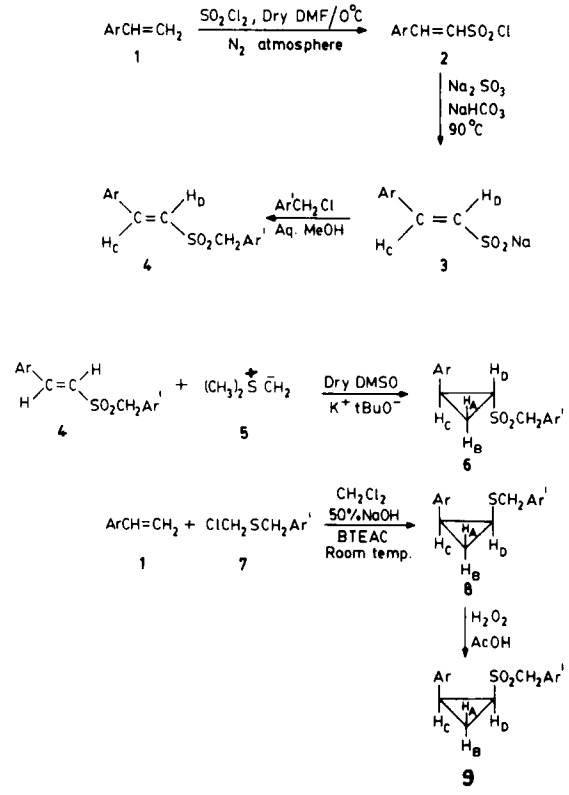

TABLE I

E-Styrylbenzylsulfones; ArCH=CH—SO_2CH_2Ar'

No.	Ar	Ar'	Yield (%)	m.p. (°C)	IR C=C	IR SO_2	^{1}H NMR CH=CH (ppm)	^{1}H NMR J_{CD} (Hz)
1	C_6H_5	C_6H_5	89	145–146 (145–146)				
2	C_6H_5	4-$CH_3C_6H_4$	87	124–125 (2-propanol)	1622	1315 1128	6.92 7.64	16.2
3	C_6H_5	2-ClC_6H_4	84	103–105 (105–106)				
4	C_6H_5	4-ClC_6H_4	92	169–170 (165–166)				
5	C_6H_5	1-$C_{10}H_7$	83	82–84 (2-propanol)	1628	1330 1115	6.88 7.74	16.0
6	4-$CH_3C_6H_4$	C_6H_5	92	126–128 (128–130)				
7	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	88	118–1120 (2-propanol)	1630	1320 1130	6.97 7.68	16.2
8	4-$CH_3C_6H_4$	2-ClC_6H_4	86	115–117 (2-propanol)	1618	1334 1128	6.94 7.84	15.8
9	4-$CH_3C_6H_4$	4-ClC_6H_4	87	176–178 (183–184)				
10	4-$CH_3C_6H_4$	1-$C_{10}H_7$	84	133–134 (2-propanol)	1625	1340 1125	6.96 7.78	16.2

successful method. However, to our knowledge the alkylation of styrylsulfinates is not known although the preparation of aromatic vinyl sulfonyl chlorides were reported in 1968.[14] Therefore, it was considered that, it would be a convenient synthetic route to convert the styrylsulfonyl chlorides to stytylbenzylsulfones. The IR spectra of **4** showed bands in the regions 1630–1615 (ν C=C)[15], 1340–1320 and 1140–1115 (ν SO_2)[16] (see Table I). These compounds also displayed bands in the region 1000–980 (δ CH out-of-plane) characteristic of *E*-configuration.[17]

The ^{1}H NMR spectra of **4** exhibited δ_H values for vinylic protons in the region 6.88–6.97 (d, H_C) and 7.60–7.84 (d, H_D) (see Table II). The coupling constants

TABLE II

Melting points and analytical data of **6** and **9**

No.	Ar	Ar'	Yield (%)	m.p. (°C)	Calcd. % C	Calcd. % H	Found % C (ppm)	Found % H (Hz)
6a	C_6H_5	C_6H_5	69	98–100	70.54	5.92	70.82	6.14
6b	C_6H_5	4-$CH_3C_6H_4$	72	104–105	71.28	5.99	71.02	6.19
6c	C_6H_5	2-ClC_6H_4	68	92–93	62.62	4.93	64.46	4.98
6d	C_6H_5	4-ClC_6H_4	74	152–153	62.62	4.93	62.78	5.08
6e	4-$CH_3C_6H_4$	C_6H_4	64	102–103	71.28	5.99	72.54	5.86
6f	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	78	130–132	72.00	6.71	71.74	6.88
6g	4-$CH_3C_6H_4$	2-ClC_6H_4	62	85–86	63.67	5.34	63.48	5.58
6h	4-$CH_3C_6H_4$	4-ClC_6H_4	66	155–156	63.67	5.34	63.54	5.26
9a	C_6H_5	C_6H_5	54	125–126	70.54	5.92	70.30	6.12
9b	4-$CH_3C_6H_4$	C_6H_5	42	119–121	71.28	5.99	71.32	5.84

of vinylic protons (J_{CD}) were found to be around 15.8–16.2 Hz, characteristic of *E*-configuration.[18] These compounds also showed a singlet around 4.50–4.60 ppm for the methylene protons of the benzyl group.[9]

The *trans*-1-benzylsulfonyl-2-arylcyclopropanes (**6**) have been prepared by the cyclopropanation of *E*-styrylbenzylsulfones (**4**) with trimethylsulfonium iodide (**5**) in dry dimethylsulfoxide under anhydrous conditions. However, the *cis*-1-benzylsulfonyl-2-arylcyclopropanes (**9**) were obtained by the addition of benzylthiocarbenes to styrene and 4-methylstyrene (**1**) under phase transfer conditions[19] and oxidizing the resultant product **8**.

The IR spectra of *cis* and *trans*-1-benzylsulfonyl-2-arylcyclopropanes (**9** and **6**) showed characteristic bands for methylene group, cyclopropane ring system and sulfonyl group in the regions 3060–3010, 1060–1030, 1330–1310 and 1150–1140 cm^{-1} respectively.[20] Apart from these bands **6** also exhibited bands of varying intensities at 110–1090 and 945–928 cm^{-1} which were considered to be characteristic of *trans*-configuration,[20] while **9** showed strong to medium bands in the region of 850–830 cm^{-1}, characteristic of *cis*-configuration.[21]

The strongest evidence for the configurational assignment of *cis* and *trans*-isomers of cyclopropane derivatives comes from their proton magnetic resonance spectra.[20–22] Analysis of the spectra of these isomers (**9** and **6**) showed four sextets in the region 1.25–2.65 ppm for methylene (H_A and H_B) and methine (H_C and H_D) as a result of deshielding effect (see Table III). The H_C proton which was geminaly connected to the aromatic ring experiences more deshielding effect and consequently appears at a lower field than H_D.

A study of the chemical shifts of ring protons and other substituents in cyclopropanes has indicated, in general, that all the substituents tend to cause protons *cis*, to them to appear at higher fields than those *trans* to them.[23]

The H_A and H_B protons of **6** appear at 1.28–1.44 and 1.53–1.73 ppm while that of **9** at 1.52–1.64 and 2.13–2.24 ppm respectively. Thus, it is clear that the methylene protons (H_A and H_B) of **9** are quite distinguishable in comparison to those of **6**. In case of **6** both H_A and H_B protons have substituents *cis* to them and therefore appreciable change could not be observed in their chemical shift values. However, in case of **9** H_A has substituents *cis* to it while H_B has no such

TABLE III

PMR Spectra of *cis* and *trans*-arylcyclopropanes

No.	Cyclopropyl				J_{Cd} (Hz)	$ArCH_2$	Ar—H
	H_A	H_B	H_D	H_C			
6a	1.29–1.37	1.63–1.72	2.38–2.48	2.50–2.62	4.99	4.28	6.90–7.48
6b	1.26–1.33	1.62–1.70	2.40–2.48	2.50–2.64	4.87	4.28	6.88–7.44
6c	1.28–1.34	1.60–1.70	2.38–2.48	2.52–2.64	4.93	4.26	6.84–7.34
6d	1.30–1.36	1.58–1.68	2.36–2.45	2.50–2.65	5.04	4.30	4.94–7.38
6e	1.28–1.34	1.58–1.73	2.38–2.48	2.50–2.62	4.93	4.28	6.98–7.51
6f	1.25–1.32	1.63–1.72	2.39–2.48	2.50–2.62	5.06	4.45	6.82–7.55
6g	1.29–1.36	1.55–1.62	2.36–2.47	2.50–2.60	4.98	4.32	6.89–7.39
6h	1.32–1.40	1.62–1.70	2.40–2.48	2.52–2.62	4.96	4.34	6.80–7.38
9a	1.52–1.62	2.13–2.22	2.52–2.65	2.74–2.85	8.69	4.30	7.05–7.35
9b	1.54–1.64	2.13–2.24	2.50–2.64	2.72–2.84	8.63	4.32	7.10–7.58

substituents. As a consequence of this, a considerable difference in chemical shift values between H_A and H_B could be observed and this has been used as a criteria to distinguish between *cis* and *trans*-1-benzylsulfonyl-2-arylcyclopropanes.[20,21] The *cis* protons on a cyclopropyl ring have also larger coupling constants than *trans* protons.[22,24] In fact, H_C and H_D of **9** have coupling constants around 8.6 Hz while those of **6** have 4.9 Hz which confirm their geometry.

EXPERIMENTAL

All the melting points are uncorrected and are measured on Mel Temp II apparatus. The infrared spectra are recorded on a Perkin-Elmer 781 model spectrometer. The ^{1}H NMR spectra are obtained on Bruker 250 MHz and 500 MHz spectrometers with tetramethylsilane as an internal standard. Micro analyses are performed by Central Drug Research Institute, Lucknow, India.

E-Sodium styrylsulfinate (**3**). Sulfuryl chloride (55 g, 0.5 mol) was added dropwise to a stirred dry dimethyl formamide (37 ml) cooled to 0°C under nitrogen. After the addition was completed, the mixture was warmed to room temperature and stirred further for 30 min. Styrene, (25 g, 0.24 mol) was added in three portions and the reaction mixture was gradually heated on a water bath at 90°C for 4 hr. It was then poured on to the crushed ice and the separated oily layer was extracted with ether and dried. Evaporation of the solvent gave 39.5 g (82%) of **2** as colourless crystals, m.p. 85–86°C. Recrystallization from chloroform light petroleum mixture yielded pure **2**, m.p. 89–90°C;[24] IR(KBr) 1365, 1160, 990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.98 (d, 1H, J = 16.3 Hz), 7.18–7.62 (m, Ar—H), 7.78 (d, 1H, J = 16.3 Hz).

E-4-Methylstyrylsulfonyl chloride (**2**) was also prepared in a similar manner from 4-methyl styrene (11.4 g, 56%) m.p. 114–115°C;[24] IR(KBr) 1358, 1145, 995 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H), 6.92 (d, 1H, 16.2 Hz), 7.08–7.57 (m, Ar—H), 7.68 (d, 1H, J = 16.2 Hz).

A solution of sodium sulfite (37.58 g, 0.3 mol) and sodium hydrogen carbonate (26.00 g, 0.31 mol) in 200 ml of water was stirred on water bath maintained at 80–90°C. The appropriate styrylsufonyl chloride (**2**) (0.16 mol) was added to this solution in portions over a period of 45 min with stirring. After completion of the addition, the mixture was stirred at 80–90°C for a further period of 3 hr and then allowed to cool to room temperature. The sodium styrylsulfinate thus separated as long colourless crystals was collected on a Buchner filter and dried.

E-Styrylbenzylsulfone (**4**). General procedure: A solution of **3** (10 mmol) in acqueous methanol was combined with benzyl chloride (10 mmol) and refluxed for 2 hr. The reaction mixture was cooled and poured on to the crushed ice. The colourless solid separated was filtered, dried and recrystallized from 2-propanol to give **4**.

trans-1-Benzylsulfonyl-2-arylcyclopropane (**6**). General procedure: A mixture of **4** (10 mmol), **5**[25] (10 mmol) and dry dimethylsulfoxide (20 ml) was stirred until a clear solution was obtained. To this, a solution of 1.12 g (10 mmol) of potassium t-butoxide in 15 ml of dry dimethyl sulfoxide was added dropwise, with stirring, at room temperature. After the addition, the reaction mixture was stirred for 1 hr more at room temperature. Then the contents were diluted with 250 ml of water and stirred until the crude cyclopropyl sulfone was separated as a solid. The product was collected, dried and recrystallised from methanol.

cis-1-Benzylsulfonyl-2-arylcyclopropane (**9**). General procedure: In a 250 ml conical flask **1** (10 mmol) and **7**[26] (10 mmol) were dissolved in methylene chloride (20 ml) and was treated with 50% sodium hydroxide solution (15 ml) in the presence of benzyltriethylammonium chloride (0.5 g). The organic layer separated was washed with water, brine and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to get the *cis*-1-benezylthio-2-phenylcyclopropane (**8**); b.p. 130–132°C (6 mm) and 1-benzylthio-2-(4-methylphenyl)-cyclopropane (**8**); b.p. 124–126°C (3 mm).

An ice cold solution of **8** (10 mmol) in 20 ml of glacial acetic acid was treated with 8 ml of 30% hydrogen peroxide. The mixture was refluxed for 24 hr, cooled and then poured on to crushed ice. The solid separated was filtered, dried and recrystallized from 2-propanol to give **9**.

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