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Synthesis and Antifungal activity of Novel unsaturated Diastereomeric (E and Z) Sulphur derivatives

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ABSTRACT

The addition of *p*-chlorobenzenethiol to benzyl *p*-bromophenylketone resulted in the formation of a mixture of diastereomers (*E*)- and (*Z*)-1-*p*-bromophenyl-2-phenyl-1-*p*-chlorophenylthioethylene (**1** and **2**). These compounds on reaction with bromine in acetic acid yielded a mixture of (*E*)- and (*Z*)-1-bromo-2-*p*-bromophenyl-1-phenyl-2-*p*-chlorophenylthioethylenes (**5a** and **5b**). Oxidation of **5a** and **5b** affords (*E*)- and (*Z*)-1-bromo-2-*p*-bromophenyl-1-phenyl-2-*p*-chlorophenylsulphonylethylenes (**6a** and **6b**), which on reaction with the *p*-chlorobenzenethiol gave (*E*)- and (*Z*)-1-*p*-bromophenyl-1-*p*-chlorophenylsulphonyl-2-phenyl-2-*p*-chlorophenylthioethylenes (**7a** and **7b**). Upon oxidation of **7a** and **7b** yielded (*E*)- and (*Z*)-1,2-bis(*p*-chlorophenylsulphonyl)-2-phenyl-1-*p*-bromophenylethylenes (**8a** and **8b**). The configurations of these compounds were established by elemental analysis, IR, ¹H NMR and mass spectra, and by their preparation from *p*-bromobenzylphenylketone and *p*-bromophenylphenylacetylene. All these new compounds exhibited pronounced *in vitro* antibacterial activity.

Keywords: (*E*)- and (*Z*)-isomers, sulphides, sulphones, sulphide-sulphones, disulphones, antibacterial activity.

INTRODUCTION

Dimethylsulphone or methylsulphonylmethane is one of the best and safe drugs¹ for the relief of arthritis,² inflammation³, lupus and other debilitating and disabling pain conditions, and is also effective in ameliorating the symptoms of gastrointestinal upset.⁴ Divinyl sulphone and hydroxydiethyl sulphone are used to give crease-resistant finishes, and other sulphones are used as fuel additives, plasticizers⁵, and anti-icing additives.⁶ Adjacent diphenylstyrene derivatives appear bridge type liquid crystal⁷ appearance. This article describes the synthesis and biological evaluation of (*E*)- and (*Z*)-1-*p*-bromophenyl-2-phenyl-1-*p*-chlorophenyl thioethylene (**1** and **2**), and (*E*)- and (*Z*)-2-*p*-bromophenyl-1-phenyl-1-*p*-chlorophenyl thioethylene (**3** and **4**) together with their corresponding bromosulphides (**5a**, **5b**, **9a** and **9b**), bromosulphones (**6a**, **6b**, **10a**, and **10b**), sulphide-sulphones (**7a**, **7b**, **11a** and **11b**), and disulphones (**8a** and **8b**). The configurations of these compounds were established following elemental analysis, IR, ¹H NMR and mass spectral studies.

MATERIALS AND METHODS

All melting points were determined in open capillary tubes on Mel-Temp apparatus, Laboratory Devices, Cambridge, MA, USA, and are uncorrected. Infrared spectra (ν_{\max} in cm^{-1}) were recorded as KBr pellets on a Perkin-Elmer 283 double beam spectrophotometer. ¹H NMR were recorded on ABX 400 MHz spectrophotometer

operating at 400 MHz for ^1H NMR, and DMSO- d_6 as solvent. The ^1H NMR chemical shifts were referenced to Tetra Methyl Silane (TMS).

General procedure for the preparation of 1 and 2 from benzyl *p*-bromophenyl ketone and 3 and 4 from *p*-bromobenzyl phenyl ketone

A solution of 27.514 g (100 mmole) benzyl *p*-bromophenyl ketone or *p*-bromobenzylphenylketone and 22.89 g (159 mmole) of *p*-chlorobenzenethiol in 100 mL of methylene chloride was taken in a 250 mL conical flask fitted with an air-condenser guarded with a calcium chloride tube. The solution was stirred at room temperature, and 4.532 g (34 mmole) anhydrous aluminium chloride was added in small portions over a period of 10 minutes. The reaction mixture turned turbid as the reaction proceeded. After the addition, the mixture was further stirred for another 60 minutes and was poured into 75 mL of water. The resulting mixture was extracted with 100 mL of methylene chloride. The extract was washed with brine solution, 2% sodiumhydroxide solution, and water. The organic layer was dried over anhydrous MgSO_4 , and the solvent was evaporated to give the solid, which was recrystallized from acetic acid (**1** or **3**). The yields varied from 65-71%.

The acetic acid solution obtained after separating **1** or **3** on evaporation of the solvent gave **2** or **4** as solid, which on recrystallization with 95% ethanol yielded needle-shaped crystals. The yields varied from 35-39%. (1a) ^1H NMR (400 MHz, CDCl_3): δ 6.25 (s, 1H), 7.25 (m, 5H), 7.5-7.65 (m, 4H), 7.75-7.9(m, 4H), IR (KBr, cm^{-1}) 1840, 1905, 1953, 2298, 2398, 3013, 3131 1586, 1638(m) (C=C), 1677, 1689, 1725, 1765 1090 Anal. Calcd for $\text{C}_{20}\text{H}_{14}\text{Cl BrS}$: C,59.79; H, 3.51; Br, 19.89; Cl,8.82; S 7.98Found: C,59.59; H, 3.3; Br, 19.11; Cl,8.80; S 7.91.

(3a) ^1H NMR (400 MHz, CDCl_3): δ 5.75 (s, 1H), 7.0-7.12(d, 2H), 7.2-7.25 (d, 2H), 7.26-7.5 (m, 5H), 7.75 (m, 2H), 7.9 (m, 2H). 876, 937, 949, 964, 1010, 1091 (s) (S-aryl) 1116, 1153, 1177, 1234, 1301, 1398, 1444, 1473, 1487, 1586, 1635(m) (C=C), 1678, 1692, 1727, 1767, 1842, 1915, 1954, 2294, 2393, 3097, 3178. Anal. Calcd for $\text{C}_{20}\text{H}_{14}\text{Br,ClS}$: C,59.79; H, 3.51; Br, 19.89; Cl,8.82; S, 7.98Found:C,59.5; H, 3.43; Br, 19.67; Cl,8.76; S 7.97.

Reaction of *p*-chlorobenzenethiol with *p*-bromophenylphenylacetylene

A solution of 25.7 g of (100 mmol) of *p*-bromophenylphenylacetylene in 150 mL of *n*-heptane was heated to its b.p., and 21.6 g (150 mmol) of *p*-chlorobenzenethiol was added. The reaction mixture was refluxed for 24 h. The solution was washed successively with 200 mL of 2% sodium hydroxide solution and water (250 mL), and dried over anhydrous calcium chloride. The residue left after the evaporation of the solvent was subjected to fractional distillation under reduced pressure to get four fractions.

The first fraction upon cooling gave a solid of 7.05 g (19.8%). It was recrystallized from 95% ethanol to give needle-shaped crystals of (*E*)-1-*p*-bromophenyl-2-phenyl-1-*p*-chlorophenylthioethylene (**1**), m.p. 124-126 $^{\circ}\text{C}$. There was no change in melting point of this compound when mixed with **1** prepared earlier from benzyl *p*-bromophenylketone.

The second fraction on cooling became a pasty mass, and solidified on treatment with petroleum spirit (16.9 g, 47.4%). It was recrystallized from 95% ethanol to give colourless crystals of (*E*)-2-*p*-bromophenyl-1-phenyl-1-*p*-chlorophenylthioethylene (**3**), m.p. 131-133 $^{\circ}\text{C}$. No change in melting point of this compound was observed on mixing with **3** synthesized earlier from *p*-bromobenzylphenylketone. The third fraction on cooling gave a solid of 4.9 g (13.7%). It was recrystallized from methanol to give (*Z*)-1-*p*-bromophenyl-2-phenyl-1-*p*-chlorophenylthioethylene (**2**) with a m.p. of 102-104 $^{\circ}\text{C}$. When mixed with **2** prepared earlier from benzyl *p*-bromophenylketone, there was no change in melting point of this compound.

The fourth fraction on cooling gave a pasty mass, and solidified on trituration with *n*-hexane yielding a solid of 3.2 g (8.9%). It was recrystallized from ethyl acetate to give (*Z*)-2-*p*-bromophenyl-1-phenyl-1-*p*-chlorophenylthioethylene (**4**), m.p. 97-99 $^{\circ}\text{C}$. The melting point of this compound also did not depress on admixture with **4** prepared earlier from benzyl *p*-bromophenylketone.

General procedure for the bromination of 1 to (*E*)- and (*Z*)-1-bromo-2-*p*-bromophenyl-1-phenyl-2-*p*-chlorophenyl thioethylenes (5a** and **5b**), and 3 to (*E*)- and (*Z*)-1-bromo-1-*p*-bromophenyl-2-phenyl-2-*p*-chlorophenyl thioethylenes (**9a** and **9b**).**

About 10.6 g (26.5 mmole) of **1** or **3** was dissolved in 100 mL of glacial acetic acid and the solution was taken in a 250 mL conical flask fitted with a magnetic stirrer. The stirrer was set in motion and a solution of 4.3 g (26.5

mmole) of bromine in 15 mL of glacial acetic acid was added dropwise. Decolourization was observed during addition, and stirring was continued for 24 hours. The solid separated was filtered and recrystallized from 95% ethanol. The yields varied from 59-63%. The filtrate from the above reaction mixture after separating the **5b** or **9b** on dilution with water gave **5a** or **9a** as solid, which was recrystallized from 95% ethanol. The yields ranged from 35-39%. (**5a**) $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.85(s,1H) δ 7.032-7.092 (d, 2H), 7.14-7.2 (d,2H), 7.3-7.4 (m, 5H) , 7.52-7.55(m,4H). 1094 (s) (S-aryl), 1157, 1187, 1269, 1298, 1347, 1394, 1444, 1483, 1514, 1579, 1654 (w) (C=C), 1694, 1758, 1799, 1877, 2279, 2568, 2862, 3050, 3721 Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{Br}_2\text{ClS}$: C, 49.98; H, 2.73; Br,33.25;Cl, 7.38; S,6.67Found: C, 49.91; H, 2.72; Br,33.23;Cl, 7.34; S,6.59

$^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.01-7.12 (m, 5H), 7.16 (d, 2H), 7.23 (d, 2H), 7.64- 7.86 (m, 4H). , 1092 (s) (S-aryl), 1185, 1262, 1294, 1397, 1441, 1473, 1568, 1641 (w) (C=C), 1759, 1890, 1954, 2620, 2786, 3003, 3421, 3779 Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{Br}_2\text{ClS}$: C, 49.98; H, 2.73; Br,33.25Cl, 7.38; S,6.67Found: C, 49.91; H, 2.70; Br,33.21Cl, 7.32; S,6.65

General procedure for the oxidation of 5a and 5b to (E)- and (Z)-1-bromo-2-p-bromophenyl-1-phenyl-2-p-chlorophenyl sulphonylethylene (6a and 6b), and 9a and 9b to (E)- and (Z)-1-bromo-1-p-bromophenyl-2-phenyl-2-p-chlorophenyl sulphonylethylene (10a and 10b).

A solution of 4.367 g (9.1 mmole) of **5a** or **5b** or **9a** or **9b** in 60 mL of glacial acetic acid was taken in a 100 mL round-bottomed flask fitted with a reflux condenser. The solution was heated to boiling and 50 mL of 30% hydrogen peroxide was added, and refluxed for two hours. The product separated on cooling was collected, filtered and recrystallized from 95% ethanol. The yields varied from 80-98%.:(**6a**) $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.71-6.78 (d, 2H),6.9-7.05 (d, 2H), 7.2-7.4 (m, 5H), 7.5-7.56(m, 2H),7.77-7.79(d, 2H). IR (KBr cm^{-1})1313 (s) (SO_2), 1388, 1444, 1483, 1573, 1627 (m) (C=C), 1814, 1911, 1959, 2104, 2836, 3089, 3127 Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{Br}_2\text{ClO}_2\text{S}$: C, 46.86; H, 2.56; Br, 31.17; Cl,6.92; S, 6.25Found : C, 46.85; H, 2.53; Br, 31.12; Cl,6.91; S, 6.22.

(**10a**) $^1\text{H NMR}$ (400 MHz, CDCl_3) : δ 6.71-6.78 (d, 2H),6.9-7.05 (d, 2H), 7.27.4 (m, 5H), 7.5-7.56(m, 2H),7.77-7.79(d, 2H).IR (KBr cm^{-1}) 1314 (s) (SO_2), 1388, 1444, 1483, 1573, 1629 (m) (C=C), 1661, 1707, 1725, 1792, 1814, 1911, 1959, 2104, 2836, 3089, 3127, 3381, 3478 Anal. Calcd for $\text{C}_{20}\text{H}_{13}\text{Br}_2\text{ClO}_2\text{S}$: C, 46.86; H, 2.56; Br, 31.17; Cl,6.92; S, 6.25Found:C, 46.81; H, 2.54; Br, 31.09; Cl,6.89; S, 6.21.

General procedure for the conversion of 6a and 6b to (E)- and (Z)-1-p-bromophenyl-2-phenyl-1-p-chlorophenylsulphonyl-2-p-chlorophenyl thioethylene (7a and 7b), and 10a and 10b to (E)- and (Z)-2-p-bromophenyl-1-phenyl-1-p-chlorophenylsulphonyl-2-p-chlorophenyl thioethylene (11a and 11b).

About 0.432 g (3 mmole) of *p*-chlorobenzenethiol was added to an ethanolic solution of sodium ethoxide prepared from 115 mg (3 mmole) of sodium dissolved in 10 mL of absolute ethanol. This solution was then added to a hot solution of 2.657 g (5.2 mmole) of **6a**, **6b**, **10a** or **10b** in 200 mL of absolute ethanol contained in a 500 mL round-bottomed flask fitted with a reflux condenser protected with calcium chloride guard tube. The mixture was refluxed for 24 hours. The colorless product separated on cooling was filtered and recrystallized thrice from 95% ethanol. They yields ranged from 38-69%. (**7a**) $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.8-6.9 (m, 2H), δ 6.97-7.19(m, 7H), 7.21-7.43 (m, 2H), 7.6-7.47 (m, 4H), 7.8-7.88 (d, 2H), IR (KBr cm^{-1}) 1326 (m) (SO_2), 1388, 1458, 1494, 1598, 1671 (w) (C=C), 1734, 1754, 1765, 1875, 1958, 2342, 2394, 2567, 2743, 2894, 3054, 3128, 3665 Anal. Calcd for $\text{C}_{26}\text{H}_{17}\text{Br Cl}_2\text{O}_2\text{S}_2$: C, 54.18; H, 2.97; Br,13.86.,Cl, 12.30; S, 11.13Found: C, 53.98; H, 2.88; Br,13.58 ,Cl, 12.17; S, 10.99.

(**11a**) $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.8-6.9 (m, 5H), 6.9—7.07 (m, 2H), 7.17-7.3 (m, 2H), 7.4-7.58 (m, 8H), IR (KBr cm^{-1}) 1155 (w) (SO_2), 1173, 1187, 1234, 1308, 1323 (m) (SO_2), 1399, 1458, 1489, 1599, 1671 (w) (C=C), 1725, 1746, 1787, 1891, 1956, 2336, 2394, 2563, 2724, 2899, 3065, 3134, 3676, Anal. Calcd for $\text{C}_{26}\text{H}_{17}\text{Br Cl}_2\text{O}_2\text{S}_2$: C, 54.18; H, 2.97; Br,13.86.,Cl, 12.30; S, 11.13Found: C, 53.98; H, 2.74; Br,13.77 ,Cl, 12.16; S, 11.04

General procedure for the oxidation of 7a and 7b or 11a and 11b to (E)- and (Z)-1,2-bis-(p-chlorophenylsulphonyl)-1-p-bromophenyl-2-phenyl ethylene (8a and 8b).

A solution of 2.3 g (4 mmole) of **7a**, **7b**, **11a** or **11b** in 50 mL of glacial acetic acid was taken in a 100 mL round-bottomed flask fitted with a reflux condenser. The solution was heated to boiling and added 10 mL of 30% hydrogen peroxide. The solution was refluxed for one hour and the colourless crystals separated on cooling were filtered and recrystallized from 95% ethanol. The yields varied from 88-95%. $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.2(d, 2H), 7.4(d, 2H), 7.5 (d, 2H), 7.65-7.67 (m, 4H), 7.7-7.8 (m, 5H), 7.9-7.98 (m, 2H), IR (KBr cm^{-1}) 1080 (s) (S-aryl), 1128, 1150

(s) (SO₂), 1284, 1298, 1327 (s) (SO₂), 1378, 1395, 1444, 1474, 1488, 1567, 1589, 1654 (w) (C=C), 1774, 1905, 2013, 2047, 2265, 2754, 2845, 3078, 3416. Anal. Calcd for C₂₆H₁₇BrCl₂O₄S₂: C, 51.33; H, 2.82; Br, 13.13Cl, 11.66; S, 10.54 Found: C, 51.22; H, 2.66; Br, 13.08Cl, 11.57; S, 10.48.

Antifungal activity

The compounds (**1** to **11b**) were screened also for their antifungal activity (Table 2) against *Candida albicans* and *Aspergillus niger* using the fungicide Clotrimazole in DMF²² as a standard. All the compounds exhibited moderate to high antifungal activity when compared with the reference compound.

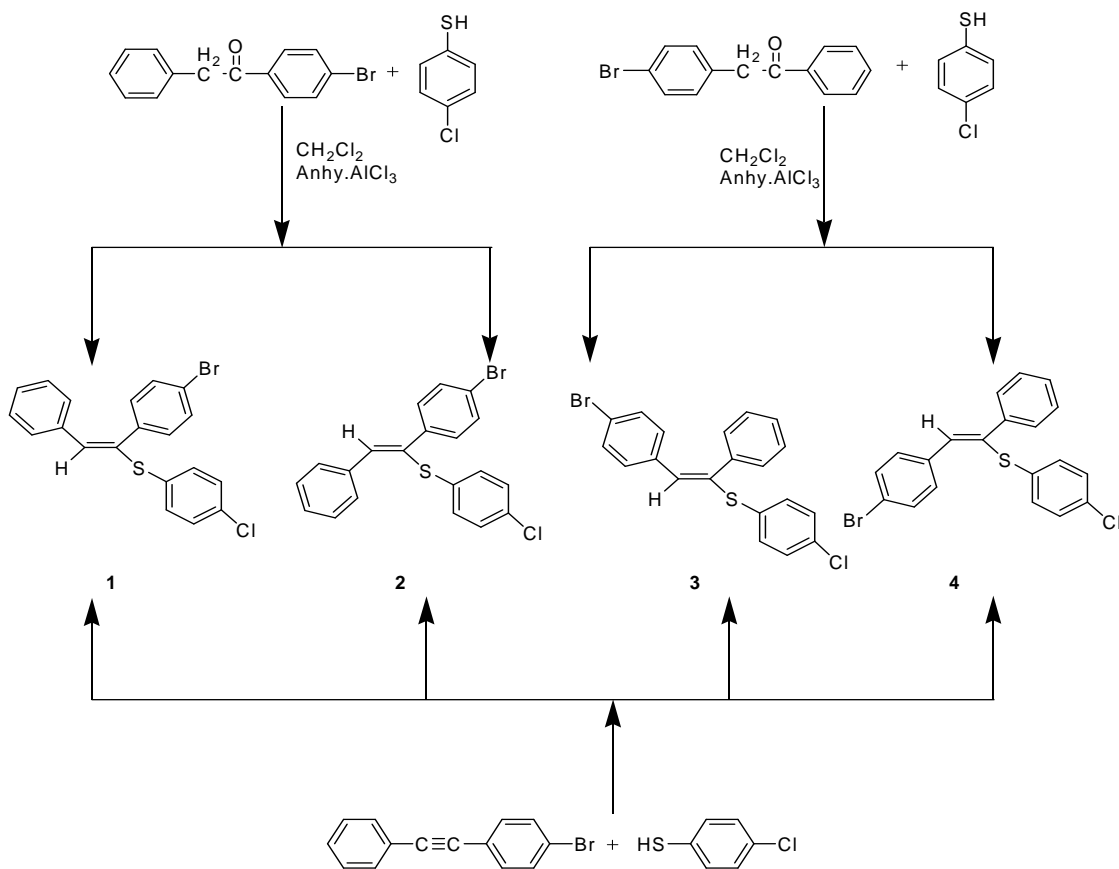
Table 1: Antifungal activity of (1 to 11b)

Compound	Zone of inhibition (in mm)	
	<i>C. albicans</i>	<i>A. niger</i>
1	13	11
2	09	13
3	15	17
4	14	17
5a	14	15
5b	12	16
6a	08	14
6b	12	16
7a	11	16
7b	09	10
8a	18	10
8b	15	14
9a	29	32
9b	27	11
10a	15	20
10b	13	28
11a	29	23
11b	12	30
Clotrimazole (10 µg/cup)	26	19

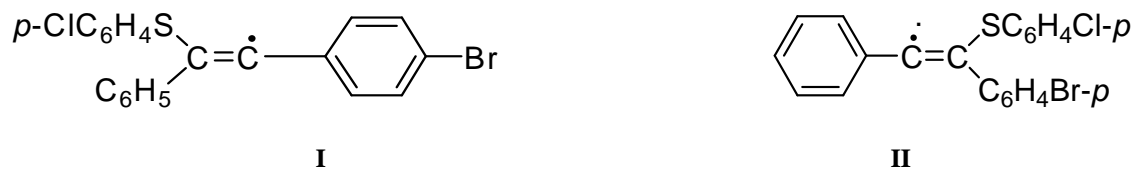
RESULTS AND DISCUSSION

Benzylphenyl ketone is known⁸ to react with benzenethiol forming a mixture of (*E*)- and (*Z*)-1-phenylthiostilbenes in which the (*E*)-isomer predominates. Similarly, the reaction of *p*-chlorobenzenethiol with benzyl *p*-bromophenylketone in the present investigation gave a mixture of (*E*)- and (*Z*)-1-*p*-bromophenyl-2-phenyl-1-*p*-chlorophenylthioethylenes (**1** and **2**) in which (*E*)-isomer was in major proportion. On the other hand, the reaction of *p*-chlorobenzenethiol with *p*-bromobenzylphenylketone gave a mixture of (*E*)- and (*Z*)-2-*p*-bromophenyl-1-phenyl-1-*p*-chloro phenylthioethylenes (**3** and **4**) in which (*E*)-isomer predominated (Scheme 1).

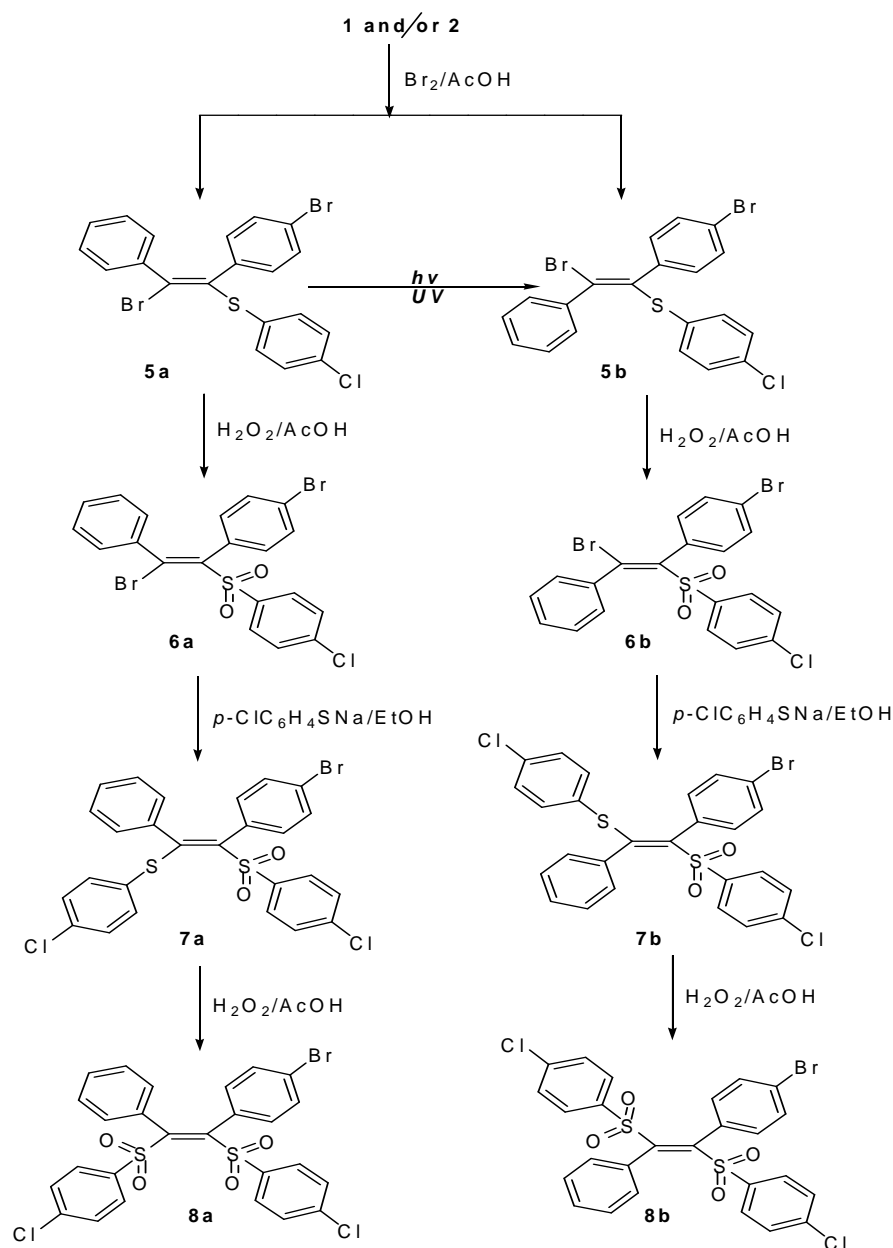
Only a pair of (*E*)- and (*Z*)-1-arylthiostilbenes are known to be formed by the addition of arene thiols to diphenylacetylene. But, the addition of *p*-chlorobenzenethiol to *p*-bromophenylphenylacetylene in the present study resulted in the formation of two pairs of diastereomeric (*E*)- and (*Z*)-1-*p*-bromophenyl-2-phenyl-1-*p*-chlorophenylthioethylenes (**1** and **2**), and (*E*)- and (*Z*)-2-*p*-bromophenyl-1-phenyl-1-*p*-chlorophenylthioethylenes (**3** and **4**) (Scheme 1). The formation of two pairs of diastereomeric (*E*)- and (*Z*)-isomers is expected because the dissimilar acetylenic carbons in *p*-bromophenylphenylacetylene can be attacked independently by the thio radical, and the addition can be both *cis* and *trans*. The *cis*-addition of thiol leads to (*E*)-isomers and the *trans*-addition leads to (*Z*)-isomers. They were separated by fractional distillation under reduced pressure. The (*E*)-isomers **1** and **3** were the major products compared to their respective (*Z*)-isomers **2** and **4**. The addition of thiols to acetylenes were reported to yield primarily the *cis*-addition products, and the *trans*-addition products were obtained in minor proportion.⁹⁻¹³ Thus, the predominant occurrence of the (*E*)-isomers **1** and **3** in the present investigation may be, in part, due to their steric preference over the corresponding (*Z*)-isomers **2** and **4**.



The synthesis of the four isomers was subsequently verified by the reaction of *p*-bromophenylphenylacetylene with *p*-chlorobenzenethiol. Of the four isomers formed in the mixture, both the diastereomers **3** and **4** were in a higher proportion when compared to the diastereomers **1** and **2**. This may be attributed to the stabilities of the intermediate radicals involved (Scheme 2). Thus, the formation of compounds **3** and **4** involves the intermediate radical **I**, and those of **1** and **2** involve the intermediate radical **II**. The radical **I** is expected to be more stable than **II** due to the contribution of more number of resonance structures. The (*E*)-isomers **1** and **3** obtained from ketone have the same m.p. and there is no depression in the mixed melting point. Also, the (*Z*)-isomers **2** and **4** have the same m.p. with no change of mixed melting point. The IR spectra of all the isomers formed following two methods were identical.

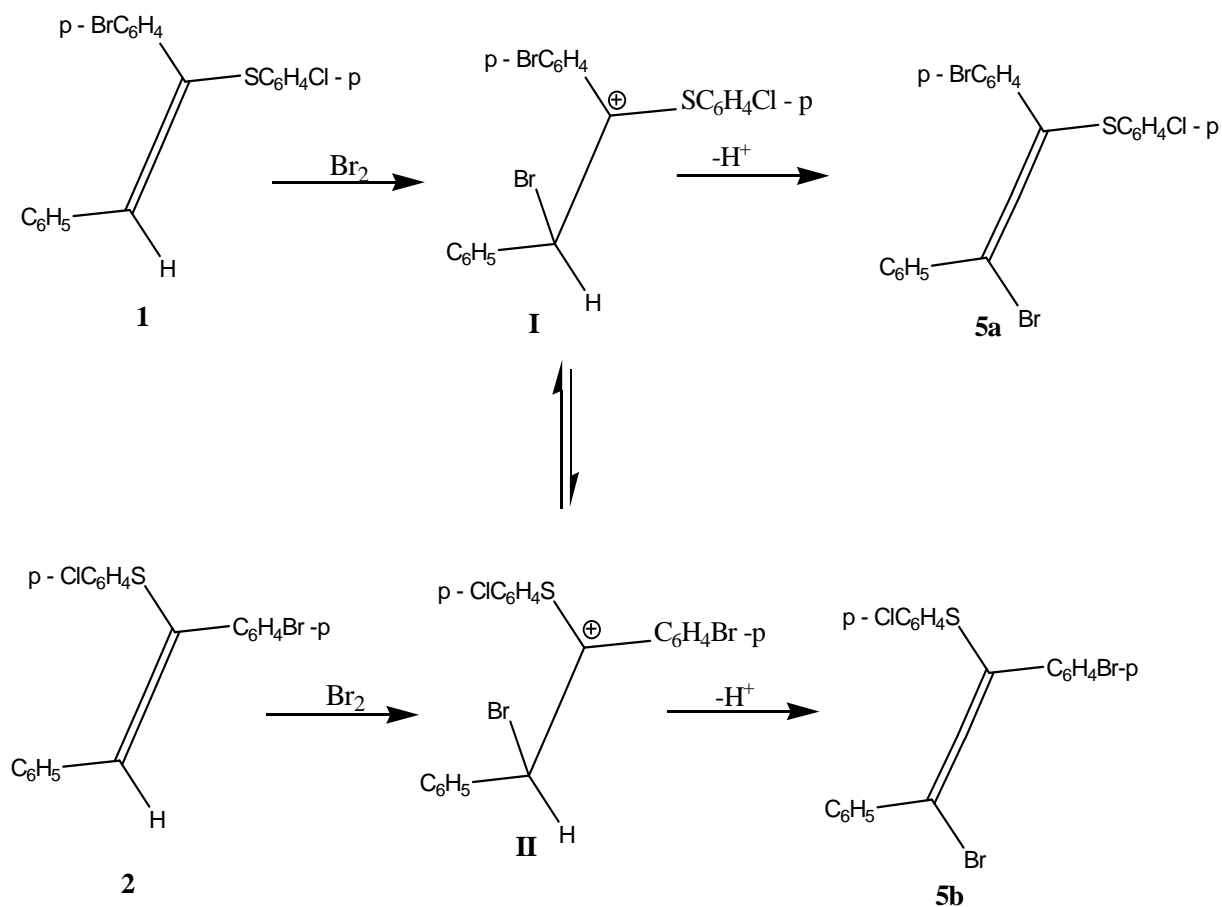


Reaction of **1** and/or **2** with Br_2 in AcOH at room temperature gave a mixture of **5a** and **5b** (Scheme 3). They were separated by fractional crystallization from methanol. Compound **5a** was in a major proportion (64%), while **5b** was a minor product (32%). This is expected because of the formation of carbocation (Scheme 4).



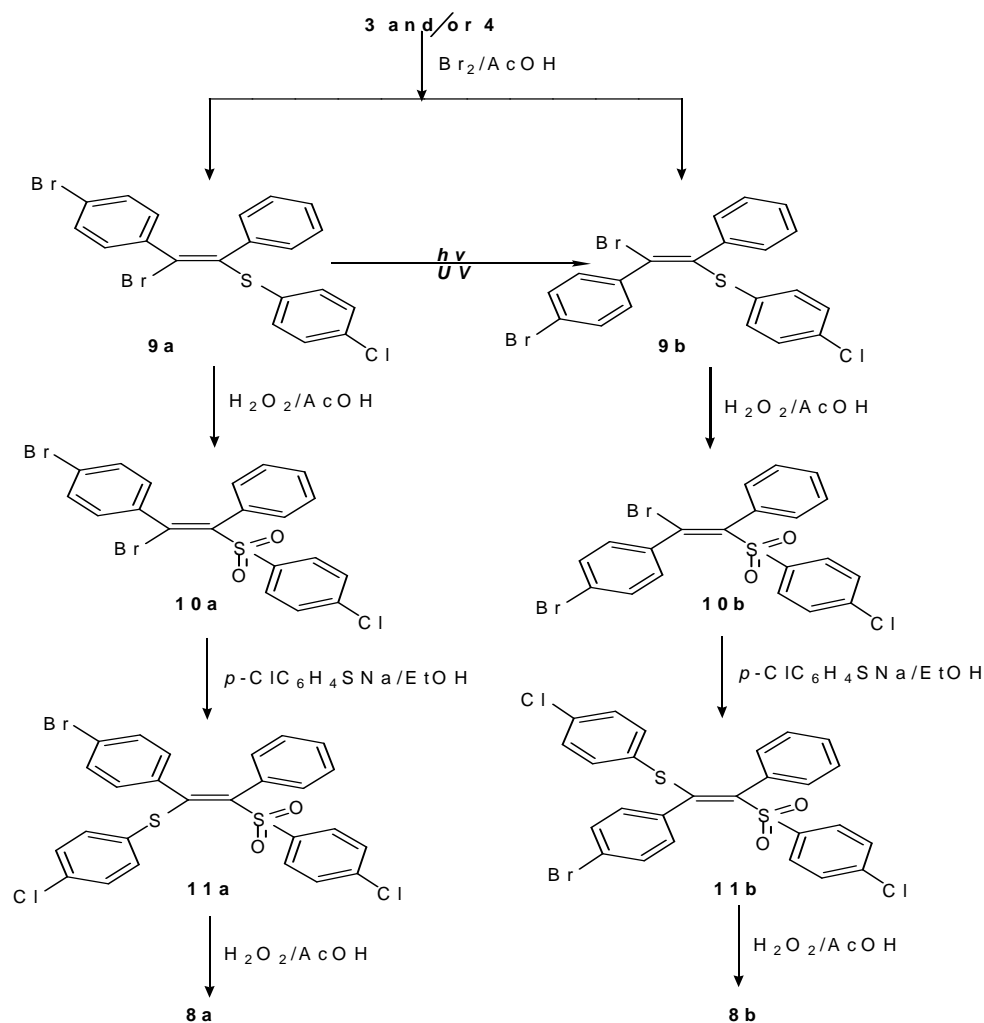
SCHEME 3

The carbocations **I** and **II** are interconvertible by rotation of central carbon-carbon single bond. The expulsion of a proton from carbocation **I** results in the formation of (Z)-isomer (**5a**), and the expulsion of a proton from carbocation **II** gives (E)-isomer (**5b**). In carbocation **I**, the $p\text{-ClC}_6\text{H}_4\text{S}$ group is gauche to H on the adjacent carbon, whereas in carbocation **II** the $p\text{-ClC}_6\text{H}_4\text{S}$ group is gauche to C_6H_5 . Since the formation of (Z)-isomer involves a more stable carbocation (**I**) than (E)-isomer, the (Z)-isomer forms in a major proportion. The identity of compound (**5a**) has been confirmed as (Z)-isomer.



SCHEME 4

Compound **5a** on irradiation with UV light⁶ gave **5b**. Oxidation of **5a** and **5b** afforded (*E*)- and (*Z*)-1-bromo-2-*p*-bromophenyl-1-phenyl-2-*p*-bromophenylsulphonylethylenes (**6a** and **6b**), respectively. Compounds **6a** and **6b** when heated with sodium salt of *p*-chlorobenzenethiol yielded (*E*)- and (*Z*)-1-*p*-bromophenyl-1-*p*-chlorophenylsulphonyl-2-phenyl-2-*p*-chlorophenylthioethylenes (**7a** and **7b**) with retention of configuration.^{14,15} Oxidation of **7a** and **7b** afforded **8a** and **8b**, respectively (Scheme 3). The stereoisomers **3** and **4** also yielded the final compounds **8a** and **8b** (Scheme 5)



In the IR region, $\nu_{c=c}$ mode was not observed for all sulphide-sulphones and bis-sulphones. This may be attributed to the tetrasubstituted nature of the compounds.^{16,17} The strong bands at 1150 and 1375 cm^{-1} in bis-sulphones were assigned to $\nu_{as} \text{SO}_2$ and $\nu_s \text{SO}_2$ modes, and the bands observed in sulphide-sulphones and bis-sulphones at 1086 cm^{-1} were assigned to ν_{c-c} (aryl) mode.¹⁸ Because the compounds **1** through **4** are trisubstituted ethylenes, the ^1H NMR spectra chemical shifts^{19,20} are used, rather than coupling constants, to differentiate between (*E*)- and (*Z*)-isomers. The chemical shifts of vinyl protons of *cis*-(*E*)-thioethylenes **1** and **3** occur at a lower field strength (δ 7.29 and 7.39) than their corresponding *trans*-(*Z*)-thioethylenes **2** and **4** (δ 6.9 and 7.0). A similar observation was made with monosulphides by Hussain *et al*²¹ wherein all aromatic hydrogens resonated as multiplets at δ 6.99-7.9.

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