1-Arylsulfonyl-2-styrylsulfonylethenes – Source for a New Class of Bis Heterocycles

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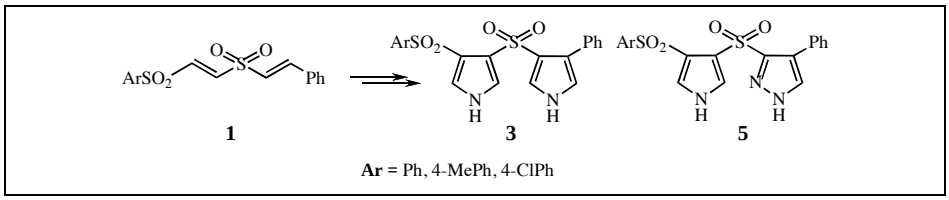

New and novel sulfone linked bis heterocycles – bis pyrroles and pyrrolyl pyrazolines are prepared from 1-arylsulfonyl-2-styrylsulfonylethenes by 1,3-dipolar cycloaddition methodology.

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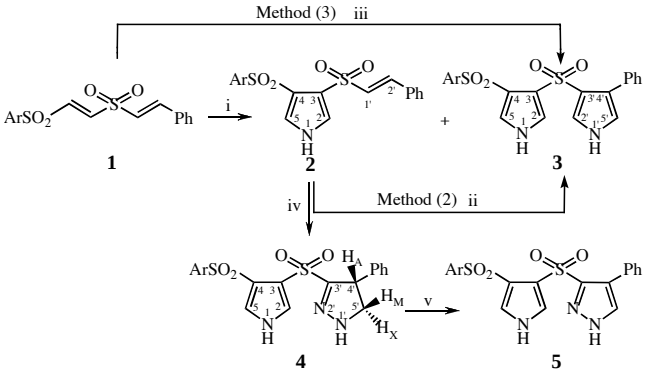
INTRODUCTION

Heterocycles have gained immense importance biologically and continue to be a major contributing nucleus in organic chemistry. Among different heterocyclic systems pyrroles and pyrazoles have gained much attention due to their varied physiological properties. Recently, pyrrole derivatives have emerged as chemotherapeutic agents potentially useful for inhibiting the activities of *M. tuberculosis* and other atypical mycobacteria, including *M. avium* complex, an opportunistic pathogen that greatly contributes to the death of AIDS patients [1]. Porretta and co-workers [2] have reported the antimicrobial activity of a pyrrole derivative. Di Santo *etal* [3] ascribed appreciable inhibiting action to pyrrolnitrin and some related nitropyrroles. In fact, a variety of pyrazole derivatives were synthesized as a new class of COX-1/COX-2 inhibitors. Although COX-2 inhibitors have anti-inflammatory properties, their greatest effect appears to be associated with pain relief and symptoms of osteoarthritis. It was found that Celecoxib, a pyrazole derivative had no effect on platelet aggregation and did not reduce increased PG levels in cerebrospinal fluids [4]. Hence, it is considered worthwhile to prepare bis(heterocycles) having both pyrrole and pyrazole units. Substantial attention has been paid to developing efficient methods for the synthesis of pyrroles which proceed mainly *via* cycloaddition or cycloisomerisation of acyclic precursors leading to 2,5-di or poly-substituted pyrroles [5]. Tosyl methyl isocyanide (TosMIC) has also been used as a reagent for the synthesis of pyrroles [6]. One of the general methods to accomplish the synthesis of pyrazolines is 1,3-dipolar cycloaddition of an ylide to an alkene [7]. The present communication deals with the synthesis hitherto unknown sulfone linked bis(heterocycles) having pyrrole with pyrazole unit by 1,3-dipolar cycloaddition of tosylmethyl isocyanide (TosMIC) and diazomethane to activated olefins.

RESULTS AND DISCUSSION

The synthetic scheme involves the reaction of 1-aryl-sulfonyl-2-styrylsulfonylethenes (**1**) with TosMIC in the presence of sodium hydride in a solvent mixture of ether and DMSO (Scheme and Mechanism 1). When the reaction is carried out with 1 mmol of **1** and 2 mmol of TosMIC, a mixture of products is obtained in a 3:1 ratio, which is separated by column chromatography (Table 1). They are identified as 4-arylsulfonyl-3-(2'-phenyl-ethene-sulfonyl)-1*H*-pyrrole (**2** major) and 3-(4'-phenyl-1'*H*-pyrrole-3'-sulfonyl)-4-phenyl-sulfonyl-1*H*-pyrrole (**3** minor) by their ^{1}H NMR spectra. The compound **2a** exhibited two singlets at δ 6.84 and 7.02 ppm, assigned to H-2 and H-5 of the pyrrole ring. Two doublets are observed at δ

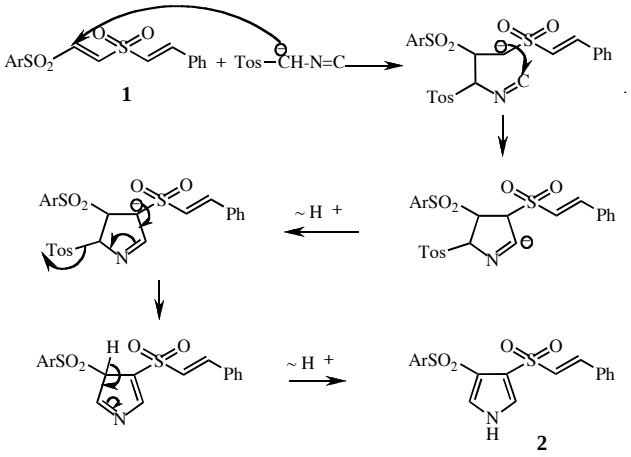
Scheme 1



i) 2TosMIC, NaH, Et_2O + DMSO; ii) TosMIC, NaH, Et_2O + DMSO ;
iii) 4TosMIC, NaH, Et_2O + DMSO; iv) CH_2N_2 / Et_2O / Et_3N; v) Chloranil, Xylene

a) Ar = Ph; b) Ar = 4-MePh; c) Ar = 4-ClPh

Mechanism 1



6.75 and 7.45 ppm corresponding to the olefinic protons, in addition to the signals of the aromatic protons. Compound **3a** presented a sharp singlet at δ 6.78 ppm corresponding to H-2,2' and two singlets at δ 7.03 and 6.98 ppm due to H-5 and H-5'. Repetition of this reaction with a twofold excess of TosMIC resulted in **3** only. In **2** and **3** there is a possibility of a mixture of diastereomeric adducts. However, we could isolate only one pure compound. A small amount of the other isomers, if any, formed could not be isolated. The IR spectra of **2** and **3** displayed absorption bands in the regions 1130-1145 and 1322-1340 (SO_2) and 3164-3182 cm^{-1} (NH). Compound **2** showed an additional band at 1628-1633 cm^{-1} (C=C) (Table 2).

The olefin group in **2** was used to develop a different heterocyclic ring, pyrazole. Treatment of **2** with diazomethane at -20 ºC to -15 ºC gave a solid, which was identified as 3'-(4-(arylsulfonyl)-1*H*-pyrrol-3-yl-sulfonyl)-4',5'-dihydro-4'-aryl-1'*H*-pyrazole (**4**) by spectral parameters (Mechanism 2). The ^1H NMR spectrum of **4a** displayed an AMX splitting pattern for pyrazoline ring protons at δ 4.49 (H_A), 3. 86 (H_M) and 3.45 ppm (H_X) respectively, in addition to the signals of the pyrrole ring protons. The observed coupling constant values J_{AM} = 11.9, J_{AX} = 5.5 and J_{MX} = 10.5 Hz indicate that H_A, H_M are *cis*, H_A, H_X are *trans* and H_M, H_X are *geminal*. Compound **4** on oxidation with chloranil in xylene [8] gave the corresponding

Mechanism 2

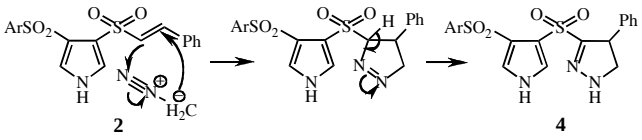


Table 1

Physical and Analytical Data of Compounds **2-5**

Compound	Mp (ºC)	Ar	Yield %	Molecular Formula	Analysis % Calcd. /Found		
					C	H	N
2a	241-243	C_6H_5	58	$C_{18}H_{15}NO_4S_2$	57.89	4.05	3.75
					58.01	4.10	3.82
2b	233-235	*p*-MeC_6H_4	56	$C_{19}H_{17}NO_4S_2$	58.90	4.42	3.61
					58.99	4.45	3.67
2c	261-263	*p*-ClC_6H_4	60	$C_{18}H_{14}ClNO_4S_2$	53.00	3.46	3.43
					52.94	3.44	3.39
3a	252-254	C_6H_5	15 68[a] 71[b]	$C_{20}H_{16}N_2O_4S_2$	58.24	3.91	6.79
					58.32	3.95	6.84
3b	238-240	*p*- MeC_6H_4	18 72[a] 74[b]	$C_{21}H_{18}N_2O_4S_2$	59.14	4.25	6.57
					59.20	4.28	6.62
3c	280-282	*p*-ClC_6H_4	20 69[a] 73[b]	$C_{20}H_{15}ClN_2O_4S_2$	53.75	3.38	6.27
					53.70	3.40	6.25
4a	249-251	C_6H_5	66	$C_{19}H_{17}N_3O_4S_2$	54.92	4.12	10.11
					54.88	4.08	10.17
4b	238-240	*p*- MeC_6H_4	70	$C_{20}H_{19}N_3O_4S_2$	55.93	4.46	9.78
					56.00	4.50	9.85
4c	273-275	*p*-ClC_6H_4	65	$C_{19}H_{16}ClN_3O_4S_2$	50.72	3.58	9.34
					50.66	3.60	9.40
5a	284-286	C_6H_5	77	$C_{19}H_{15}N_3O_4S_2$	55.19	3.66	10.16
					55.27	3.63	10.25
5b	268-270	*p*- MeC_6H_4	79	$C_{20}H_{17}N_3O_4S_2$	56.19	4.01	9.83
					56.24	4.00	9.80
5c	296-298	*p*-ClC_6H_4	80	$C_{19}H_{14}ClN_3O_4S_2$	50.95	3.15	9.38
					51.04	3.17	9.42

a yield in method - 2; b yield in method – 3.

Table 2

IR Data of Compounds **2-5**

Compound	IR (cm^{-1})				
	SO_2		C=C	C=N	NH
2a	1138	1335	1632	-	3171
2b	1145	1332	1628	-	3182
2c	1130	1340	1633	-	3164
3a	1144	1320	1630	-	3169
3b	1136	1325	1627	-	3175
3c	1142	1327	1634	-	3166
4a	1138	1334	1626	1614	3280
4b	1146	1330	1621	1609	3285
4c	1130	1335	1624	1598	3291
5a	1142	1330	1630	1613	3270
5b	1134	1328	1625	1611	3275
5c	1145	1336	1631	1609	3288

Table 3

^{1}H and ^{13}C NMR Data of Compounds **2-5**

Compound	^{1}H NMR (δ, ppm)	^{13}C NMR (δ, ppm)
2a	6.75 (d, 1H, $C_{1'}$-H, J = 18.0 Hz), 6.87 (s, 1H, C_2-H), 7.02 (s, 1H, C_5-H), 7.45 (d, 1H, $C_{2'}$-H, J = 18.0 Hz), 7.27-7.55 (m, 10H, Ar and Ar'-H), 8.79 (bs, 1H, NH)	106.6 (C-3), 110.3 (C-4), 120.2 (C-1'), 122.8 (C-2), 124.7 (C-5), 137.2 (C-2'), 129.8, 131.2, 131.7, 132.3, 132.9, 133.4, 133.9 (aromatic carbons)
2b	2.32 (s, 3H, Ar-CH_3), 6.78 (d, 1H, $C_{1'}$-H, J = 17.8 Hz), 6.86 (s, 1H, C_2-H), 7.04 (s, 1H, C_5-H), 7.48 (d, 1H, $C_{2'}$-H, J = 17.8 Hz), 7.22-7.49 (m, 9H, Ar and Ar'-H), 8.74 (bs, 1H, NH)	21.4 (Ar-*C*H_3), 107.2 (C-3), 110.9 (C-4), 119.8 (C-1'), 122.1 (C-2), 123.8 (C-5), 138.0 (C-2'), 129.2, 130.4, 131.6, 132.7, 133.8, 134.2, 135.3 (aromatic carbons)
2c	6.76 (d, 1H, $C_{1'}$-H, J = 18.1 Hz), 6.84 (s, 1H, C_2-H), 7.07 (s, 1H, C_5-H), 7.46 (d, 1H, $C_{2'}$-H, J = 18.1 Hz), 7.31-7.73 (m, 9H, Ar and Ar'-H), 8.77 (bs, 1H, NH)	107.9 (C-3), 111.4 (C-4), 120.9 (C-1'), 122.4 (C-2), 124.8 (C-5), 137.6 (C-2'), 128.3, 129.6, 130.3, 131.9, 132.6, 133.4, 135.7, 137.2 (aromatic carbons)
3a	6.78 (s, 2H, C_2-H & $C_{2'}$-H), 6.98 (s, 1H, $C_{5'}$-H), 7.03 (s, 1H, C_5-H), 7.24-7.58 (m, 10H, Ar and Ar'-H), 8.75 (bs, 2H, NH)	104.5 (C-4'), 108.6 (C-3 and 3'), 110.3 (C-4), 114.5 (C-2 and 2'), 117.7 (C-5'), 124.2 (C-5), 128.2, 129.5, 130.6, 131.3, 132.9, 133.7, 134.6, 135.2 (aromatic carbons)
3b	2.28 (s, 3H, Ar-CH_3), 6.74 (s, 2H, C_2-H & $C_{2'}$-H), 6.96 (s, 1H, $C_{5'}$-H), 7.01 (s, 1H, C_5-H), 7.20-7.51 (m, 9H, Ar and Ar'-H), 8.72 (bs, 2H, NH)	22.6 (Ar-*C*H_3), 103.9 (C-4'), 107.9 (C-3 and 3'), 109.1 (C-4), 113.7 (C-2 and 2'), 116.5 (C-5'), 124.5 (C-5), 128.6, 129.3, 130.2, 131.6, 132.2, 133.4, 133.9, 134.7 (aromatic carbons)
3c	6.76 (s, 2H, C_2-H & $C_{2'}$-H), 6.94 (s, 1H, $C_{5'}$-H), 7.05 (s, 1H, C_5-H), 7.29-7.67 (m, 9H, Ar and Ar'-H), 8.78 (bs, 2H, NH)	104.9 (C-4'), 108.4 (C-3 and 3'), 110.9 (C-4), 114.2 (C-2 and 2'), 117.1 (C-5'), 123.6 (C-5), 129.4, 130.8, 131.7, 132.6, 133.2, 135.6, 138.1 (aromatic carbons)
4a	3.45 (dd, 1H, H_X), 3.86 (dd, 1H, H_M, J_{MX} = 10.5 Hz), 4.49 (dd, 1H, H_A, J_{AM} = 11.9 Hz, J_{AX} = 5.5 Hz), 6.85 (s, 1H, C_2-H), 7.04 (s, 1H, C_5-H), 7.23-7.53 (m, 10H, Ar and Ar'-H), 8.74 (bs, 1H, NH), 10.49 (bs, 1H, NH)	46.4 (C-4'), 56.8 (C-5'), 111.7 (C-3), 113.7 (C-4), 125.2 (C-5), 126.1 (C-2), 151.2 (C-3'), 128.6, 129.2, 130.2, 131.2, 132.7, 133.4, 134.6, 136.3 (aromatic carbons)
4b	2.30 (s, 3H, Ar-CH_3), 3.47 (dd, 1H, H_X), 3.84 (dd, 1H, H_M, J_{MX} = 10.3 Hz), 4.47 (dd, 1H, H_A, J_{AM} = 11.8 Hz, J_{AX} = 5.4 Hz), 6.83 (s, 1H, C_2-H), 7.01 (s, 1H, C_5-H), 7.25-7.59 (m, 9H, Ar and Ar'-H), 8.76 (bs, 1H, NH), 10.42 (bs, 1H, NH)	22.8 (Ar-*C*H_3), 45.9 (C-4'), 57.0 (C-5'), 111.4 (C-3), 113.7 (C-4), 125.7 (C-5), 126.3 (C-2), 151.4 (C-3'), 128.7, 129.4, 130.9, 131.2, 132.7, 133.2, 134.8, 135.6 (aromatic carbons)
4c	3.44 (dd, 1H, H_X), 3.82 (dd, 1H, H_M, J_{MX} = 10.1 Hz), 4.45 (dd, 1H, H_A, J_{AM} = 11.6 Hz, J_{AX} = 5.3 Hz), 6.812 (s, 1H, C_2-H), 7.03 (s, 1H, C_5-H), 7.30-7.65 (m, 9H, Ar and Ar'-H), 8.74 (bs, 1H, NH), 10.45 (bs, 1H, NH)	47.1 (C-4'), 57.5 (C-5'), 112.6 (C-3), 114.5 (C-4), 124.2 (C-5), 127.1 (C-2), 151.2 (C-3'), 129.8, 130.6, 131.1, 131.9, 132.4, 133.8, 134.5, 137.9 (aromatic carbons)
5a	6.32 (bs, 1H, NH), 6.72 (s, 1H, C_2-H), 6.91 (s, 1H, $C_{5'}$-H), 6.96 (s, 1H, C_5-H), 7.26-7.63 (m, 10H, Ar and Ar'-H), 8.92 (bs, 1H, NH)	112.1 (C-3), 116.3 (C-4), 125.6 (C-5), 127.4 (C-2), 134.3 (C-5'), 138.6 (C-4'), 156.4 (C-3'), 128.2, 129.2, 130.6, 131.4, 132.0, 133.2, 134.5, 135.7 (aromatic carbons)
5b	2.26 (s, 3H, Ar-CH_3), 6.34 (bs, 1H, NH), 6.75 (s, 1H, C_2-H), 6.93 (s, 1H, $C_{5'}$-H), 6.98 (s, 1H, C_5-H), 7.19-7.51 (m, 9H, Ar and Ar'-H), 8.96 (bs, 1H, NH)	21.9 (Ar-*C*H_3), 111.9 (C-3), 115.9 (C-4), 124.6 (C-5), 127.1 (C-2), 134.6 (C-5'), 139.2 (C-4'), 153.8 (C-3'), 128.2, 129.2, 130.6, 131.4, 132.0, 133.2, 134.5, 135.7 (aromatic carbons)
5c	6.37 (bs, 1H, NH), 6.71 (s, 1H, C_2-H), 6.95 (s, 1H, $C_{5'}$-H), 6.95 (s, 1H, C_5-H), 7.28-7.69 (m, 9H, Ar and Ar'-H), 8.94 (bs, 1H, NH)	112.4 (C-3), 116.1 (C-4), 125.7 (C-5), 127.7 (C-2), 133.8 (C-5'), 139.5 (C-4'), 156.5 (C-3'), 129.4, 130.3, 131.4, 132.1, 132.9, 134.7, 135.2, 138.5 (aromatic carbons)

aromatized product, 3'-(4-(arylsulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-4'-aryl-1'*H*-pyrazole (**5**). The disappearance of the AMX splitting pattern and the appearance of three signals at 6.72, 6.91 and 6.96 ppm due to H-2, H-5' and H-5 in the ^{1}H NMR spectrum of **5a** confirms their formation. The structures of **2**-**5** are further confirmed by ^{13}C NMR spectra (Table 3).

CONCLUSION

New and novel sulfone linked bis (pyrroles) and pyrrolyl pyrazolines are prepared from a suitable synthetic intermediate, 1-arylsulfonyl-2-styrylsulfonylethene.

EXPERIMENTAL

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the absorptions are given in cm^{-1}. The ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian EM-360 spectrometer (300 MHz). The ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian VXR spectrometer operating at 75.5 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compound 1-arylsulfonyl-2-styrylsulfonylethene (**1**) was prepared by the literature procedure [9].

4-Arylsulfonyl-3-(2'-phenylethenesulfonyl)-1*H*-pyrrole (2) and 3-(4'-phenyl-1'*H*-pyrrole-3'-sulfonyl)-4-phenylsulfonyl-1*H*-pyrrole (3): General Procedure. A mixture of TosMIC (10 mmoles) and 1-arylsulfonyl-2-styrylsulfonylethene (**1**) (5 mmoles) in Et_2O-DMSO (2:1) was added dropwise to a stirred suspension of sodium hydride (50 mg) in Et_2O (10 mL) at room temperature and stirring was continued for about 5 hours. The reaction mixture was diluted with water and extracted with ether. The ethereal fraction was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*. The resulting mixture was separated by column chromatography (hexane-ethyl acetate; 1:4) and identified as. 3-arylsulfonyl-4-(2'-aryl-ethene-sulfonyl)-1*H*-pyrrole (**2,** major) and 3-(4-(arylsulfonyl)-1*H*-pyrrole-3-ylsulfonyl)-4'-aryl-1'*H*-pyrrole (**3,** minor).

3-(4'-Phenyl-1'*H*-pyrrole-3'-sulfonyl)-4-phenylsulfonyl-1*H*-pyrrole (3): General Procedure. Method-2. Compound **3** was also obtained by adding an equimolar (5 mmoles) mixture of 4-arylsulfonyl-3-(2'-phenylethenesulfonyl)-1*H*-pyrrole (**2**) and TosMIC in Et_2O-DMSO (2:1) was added dropwise to a stirred suspension of sodium hydride (25 mg) in Et_2O (6 mL) at room temperature and stirring was continued for about 5 hours. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate. The solvent was removed under vacuum. The resulting solid was purified by column chromatography (hexane-ethyl acetate; 1:4).

Method-3. A mixture of TosMIC (20 mmoles) and 1-arylsulfonyl-2-styrylsulfonylethene (**1**) (5 mmoles) in Et_2O-DMSO (2:1) was added dropwise to a stirred suspension of sodium hydride (100 mg) in Et_2O (20 mL) at room temperature and stirring was continued for about 5 hours. The reaction mixture was diluted with water and extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The resulting solid was purified by column chromatography (hexane-ethyl acetate; 1:4).

3'-(4-(Arylsulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-4',5'-dihydro-4'-phenyl-1'*H*-pyrazole (4): General Procedure. To a cooled solution of **2** (5 mmoles) in dichloromethane (20 mL), an ethereal solution of diazomethane (40 mL, 0.4 *M*) and triethylamine (0.12 g) were added. The reaction mixture was kept at -20 ºC to -15 ºC for 40-48 hours. The solvent was removed under reduced pressure and the resulting solid was recrystallized from 2-propanol.

3'-(4-(Arylsulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-4'-phenyl-1'*H*-pyrazole (5): General Procedure. A solution of **4** (1 mmole) and chloranil (1 mmole) in xylene (10 mL) was refluxed for 24-32 hours. The reaction mixture was treated with a 5% NaOH solution. The organic layer was separated and repeatedly washed with water, dried over anhydrous sodium sulfate and the solvent was removed on a rotary evaporator. The solid obtained was recrystallized from 2-propanol.

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