Indian Journal of Chemistry
Vol. 47B, November 2008, pp.1707-1712

Synthesis of novel bis heterocycles: Bis pyrroles, pyrrolyl pyrazolines and pyrrolyl isoxazolines

V Padmavathi*, T Radhalakshmi, K Mahesh & A V Nagendra Mohan

Department of Chemistry, Sri Venkateswara University, Tirupati 517 502, India

E-mail: vkpuram2001@yahoo.com

Received 27 February 2008; accepted (revised) 20 August 2008

The Michael acceptors, 1-arylsulfonyl-2-styrylsulfonylethenes have been used as synthons to develop bis pyrroles, pyrrolyl pyrazolines and pyrrolyl isoxazolines by 1,3-dipolar cycloaddition of tosylmethyl isocyanide, nitrile imines and nitrile oxides.

Keywords: Unsaturated sulfone, tosylmethyl isocyanide, nitrile imines, nitrile oxides, 1,3-dipolar cyclo-addition, chloramines-T

The heterocyclic compounds particularly nitrogen containing heterocycles are synthetically challenging models for a number of physiologically active natural products. One such class of compounds include pyrroles, pyrazoles and isoxazoles. Pyrroles are molecular frame works of numerous natural products such as haeme, chlorophyll, vitamin B_{12} or enzymes like various cytochromes[1]. In addition, polysubstituted pyrroles are the important constituents of many biologically active compounds and have emerged as chemotherapeutic agents[2]. Further, pyrazolines and isoxazolines have gained importance due to their varied chemotherapeutic properties. Celecoxib, a pyrazole derivative and veledecoxib an isoxzole derivative are now widely used in the market as anti-inflammatory drugs[3]. Hence, it is considered worthwhile to prepare bis(heterocycles) having pyrrole with pyrazole or isoxazole rings. In the literature, multistep synthetic routes to 3,4-disubstituted pyrroles have been reported either by coupling imines and nitroalkanes or by using Friedel-Crafts acylation in the presence of an electron-withdrawing group on the pyrrole nitrogen or on 3,4-silylated precursors[4]. However, these synthetic routes are often complicated and limited to only some substituents.

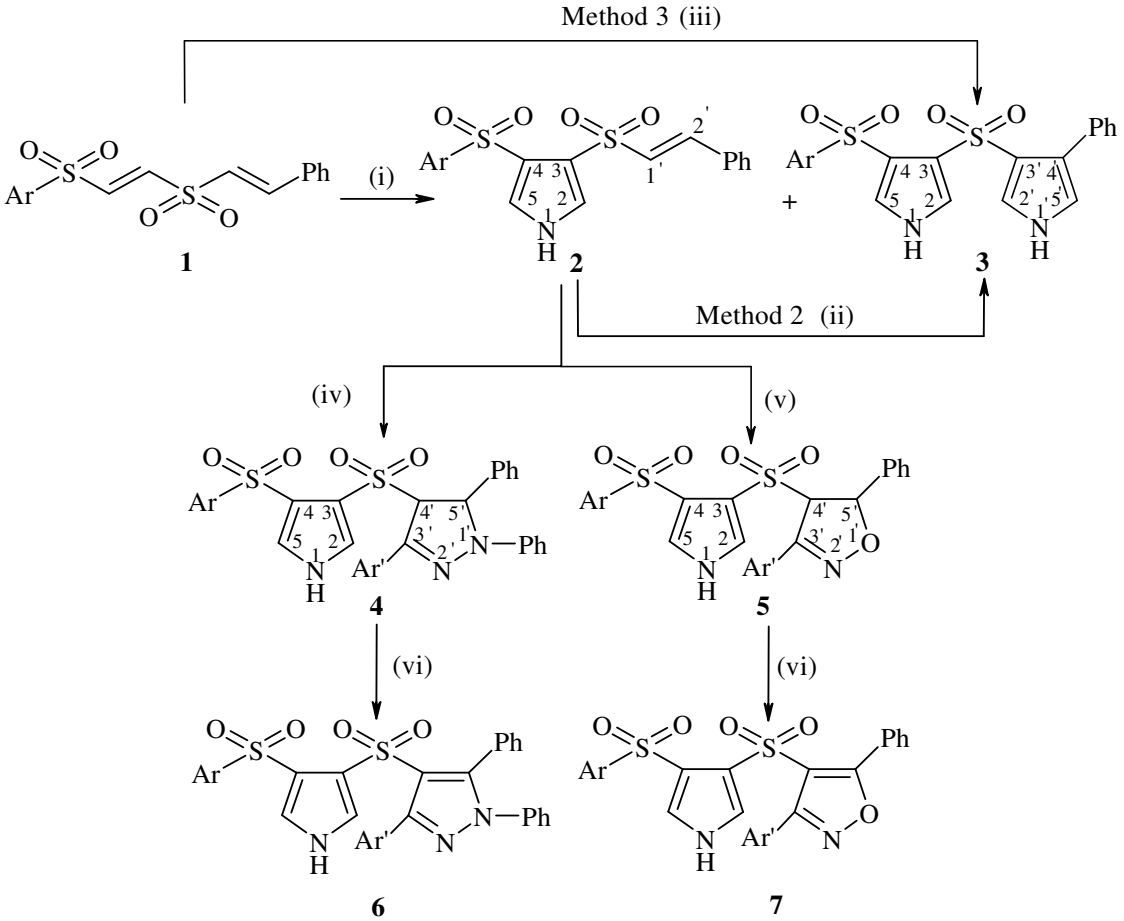
Previously, 3,4-disubstituted pyrroles have also been synthesized from Michael acceptors and tosylmethyl isocyanide (TosMIC)[5]. Following this synthetic methodology, a new regioselective one-step procedure was recently reported using TosMIC, leading to a series of 3,4-disubstituted pyrroles in good yield[6]. Similarly, pyrazolines and isoxazolines have been synthesized by 1,3-dipolar cycloaddition of an ylide to an alkene involving 3+2 principle[7]. Among the ylides, diazomethane, nitrile imines and nitrile oxides have been used as reactive intermediates. These nitrile imines and nitrile oxides can be generated by the dehydrogenation of araldehyde phenylhydrazones and araldoximes with lead tetracetate[8], mercury acetate[9], 1-chlorobenzotriazole[10], chloramine-T[11], *etc*. Use of the latter for *in situ* generation of dipolar reagents has enthused many organic chemists. In fact, the 1,3-dipolar cycloaddition reaction of chloramine-T catalyzed dipolar reagents is already reported with a variety of activated mono and bis(olefins)[12]. The present communication deals with the synthesis of sulfone linked bis(heterocycles), pyrrole together with pyrazole or isoxazole units.

Results and Discussion

The synthetic method involves the articulation of pyrrole in combination with pyrazole and isoxazole rings from an intermediate 1-arylsulfonyl-2-styrylsulfonylethene **1**. The reaction of **1** with TosMIC in the presence of sodium hydide in a solvent mixture of ether and DMSO gave mixture of compounds in 3:1 ratio. They were identified as 4-arylsulfonyl-3-(2'-phenylethenesulfonyl)-1*H*-pyrrole **2**

(major) and 3-(4'-phenyl-1'*H*-pyrrole-3'-ylsulfonyl)-4-arylsulfonyl-1*H*-pyrrole **3** (minor) by ^{1}H NMR spectra. (**Scheme I**, **Table I**). The ^{1}H NMR spectra of **2a** exhibited two singlets at δ_H 6.87 and 7.02 assigned to H-2 and H-5 of pyrrole ring protons. Two doublets are observed at δ_H 6.75 and 7.45 corresponding to olefinic protons, in addition to the signals of aromatic protons. Compound **3a** presented a sharp singlet at δ_H 6.78 corresponding to H-2, 2' and two singlets at δ_H 7.03 and 6.98 due to H-5 and H-5'. The 70 eV mass spectra of **2a** and **3a** displayed low intensity molecular ion peaks at *m/z* 373 and 412 in accordance with their chemical composition (**Table II**). Repetition of this reaction with twofold excess of TosMIC resulted in **3** only. In **2** and **3** there is a possibility of a mixture of diastereomeric adducts. However, it was possible to 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 1320-1345 (SO_2) and 3160-3185 cm^{-1} (NH). Compound **2** showed an additional band at 1625-1640 cm^{-1} (C=C).

The olefin group in **2** was used to develop a different heterocyclic ring, pyrazole or isoxazole. The 1,3-dipolar cycloaddition of nitrile imines generated from araldehyde phenyl hydrazones in the presence of chloramine-T to **2** resulted in 4'-(4-(arylsulfonyl)-1*H*-



i) 2 TosMIC/ NaH/ Et_2O + DMSO
ii) TosMIC/ NaH/ Et_2O + DMSO
iii) 4 TosMIC/ NaH/ Et_2O + DMSO
iv) Ar'-CH=NNHPh / Chloramine-T.3H_2O /MeOH
v) Ar'-CH=NOH / Chloramine-T.3H_2O/ MeOH
vi) Chloranil/ xylene

Ar	Ar'
a) Ph	Ph
b) 4-Me Ph	4-OMe Ph
c) 4-Cl Ph	4-ClPh

Scheme I

Table I — Physical characterization data of compounds **2**-**7**

Compd	m.p. °C	Yield (%)	Mol. formula (Mol. wt.)	Found % (Calcd.) C	H	N
2a	241-43	58	$C_{18}H_{15}NO_4S_2$ (373.45)	58.01 (57.89	4.10 4.05	3.82 3.75)
2b	233-35	56	$C_{19}H_{17}NO_4S_2$ (387.47)	58.99 (58.90	4.45 4.42	3.67 3.61)
2c	261-63	60	$C_{18}H_{14}ClNO_4S_2$ (407.89)	52.94 (53.00	3.44 3.46	3.39 3.43)
3a	252-54	15 68[a] 71[b]	$C_{20}H_{16}N_2O_4S_2$ (412.48)	58.32 (58.24	3.95 3.91	6.84 6.79)
3b	238-40	18 72[a] 74[b]	$C_{21}H_{18}N_2O_4S_2$ (426.51)	59.20 (59.14	4.28 4.25	6.62 6.57)
3c	280-82	20 69[a] 73[b]	$C_{20}H_{15}ClN_2O_4S_2$ 446.93	53.70 (53.75	3.40 3.38	6.25 6.27)
4a	168-70	68	$C_{31}H_{25}N_3O_4S_2$ (567.68)	65.51 (65.59	4.40 4.44	7.43 7.40)
4b	165-67	74	$C_{33}H_{29}N_3O_5S_2$ (611.73)	64.84 (64.79	4.79 4.78	6.82 6.87)
4c	176-78	76	$C_{31}H_{23}Cl_2N_3O_4S_2$ (636.57)	58.57 (58.49	3.70 3.64	6.63 6.60)
5a	153-55	72	$C_{25}H_{20}N_2O_5S_2$ (492.57)	61.02 (60.96	4.03 4.09	5.62 5.69)
5b	159-61	69	$C_{27}H_{24}N_2O_6S_2$ (536.62)	60.45 (60.43	4.55 4.51	5.20 5.22)
5c	174-76	74	$C_{25}H_{18}Cl_2N_2O_5S_2$ (561.46)	53.52 (53.48	3.25 3.23	5.04 4.99)
6a	175-77	65	$C_{31}H_{23}N_3O_4S_2$ (565.66)	65.76 (65.82	4.14 4.10	7.40 7.43)
6b	184-86	67	$C_{33}H_{27}N_3O_5S_2$ (609.71)	65.08 (65.01	4.43 4.46	6.93 6.89)
6c	198-200	66	$C_{31}H_{21}Cl_2N_3O_4S_2$ (634.55)	58.73 (58.68	3.38 3.34	6.58 6.62)
7a	181-83	69	$C_{25}H_{18}N_2O_5S_2$ (490.55)	61.24 (61.21	3.72 3.70	5.75 5.71)
7b	172-74	64	$C_{27}H_{22}N_2O_6S_2$ (534.6)	60.59 (60.66	4.19 4.15	5.20 5.24)
7c	195-97	71	$C_{25}H_{16}Cl_2N_2O_5S_2$ (559.44)	53.69 (53.67	2.89 2.88	4.97 5.01)

a: yield in Method 2; b: yield in Method 3

pyrrol-3-ylsulfonyl)-4',5'-dihydro-1',5'-diphenyl-3'-aryl-1'*H*-pyrazole **4**. Similarly, the cycloaddition of nitrile oxide generated from araldoximes in the presence of chloramine -T to **2** produced 4'-(4-(arylsulfonyl)- 1*H*-pyrrol-3-ylsulfonyl)-4',5'-dihydro-3'-aryl-5'-phenylisoxazole **5** (**Scheme I**). The ^{1}H NMR spectra of **4a** and **5a** displayed two doublets at δ_H 5.21, 5.16 and 5.61, 5.65 respectively, which are assigned to H-4' and H-5', the two methine protons of pyrazoline and isoxazoline rings. The *J* values indicated that they are in *trans* geometry. Apart from this, two singlets are observed at δ_H 6.74, 6.76 and 7.04, 7.01 due to H-2 and H-5 of pyrrole ring in **4a** and **5a,** respectively. Low intensity molecular ion peaks are observed at *m/z* 567 and 492 in the 70 eV mass spectra of **4a** and **5a** respectively. Compounds **4** and **5** on oxidation with chloranil in xylene gave 4'-(4-(arylsulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-1',5'-diphenyl-3'-aryl-1'*H*-pyrazole **6** and 4'-(4-(arylsulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-3'-aryl-5'-phenylisoxazole **7** (**Table II**). The absence of two doublets corresponding to pyrazoline/isoxzoline ring protons in the

Table II — Spectral characterization data for **2-7**

Compd	^{1}H NMR (δ, ppm) (*J* in Hz)	^{13}C NMR (δ, ppm)	MS (*m/z*)
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)	$M^{+\cdot}$ 373
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-CH_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 and 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)	$M^{+\cdot}$ 412
3b	2.28 (s, 3H, Ar-CH_3), 6.74 (s, 2H, C_2-H and 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-CH_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 and 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	5.21 (d, 1H, C_4-H, *J* = 7.6 Hz), 5.61 (d, 1H, C_5-H, *J* = 7.6 Hz), 6.74 (s, 1H, C_2-H) 7.04 (s, 1H, C_5-H), 7.22-7.53 (m, 20H, Ar-H), 8.75 (bs, 1H, NH)	63.8 (C-4'), 87.0 (C-5'), 111.5 (C-3), 114.2 (C-4), 126.1 (C-2), 124.2 (C-5), 154.7 (C-3'), 128.4, 129.5, 130.2, 131.3, 132.8, 133.7, 134.2, 135.4, 135.9 (aromatic carbons)	$M^{+\cdot}$ 567
4b	2.25 (s, 3H, Ar-CH_3), 3.81 (s, 3H, Ar-OCH_3), 5.25 (d, 1H, C_4'-H, *J* = 7.8 Hz), 5.64 (d, 1H, C_5-H, *J* = 7.8 Hz), 6.77 (s, 1H, C_2-H) 7.02 (s, 1H, C_5-H), 7.12-7.62 (m, 18H, Ar-H), 8.77 (bs, 1H, NH)	22.7 (Ar-CH_3), 55.4 (Ar-OCH_3), 63.2 (C-4'), 87.4 (C-5'), 107.8 (C-3), 109.4 (C-4), 114.1 (C-2), 123.9 (C-5), 154.2 (C-3'), 128.1, 129.0, 129.8, 130.5, 131.1, 132.4, 133.1, 134.9, 135.7 (aromatic carbons)	-
4c	5.27 (d, 1H, C_4'-H, *J* = 7.2 Hz), 5.62 (d, 1H, C_5-H, *J* = 7.2 Hz), 6.79 (s, 1H, C_2-H) 7.04 (s, 1H, C_5-H), 7.18-7.67 (m, 18H, Ar-H), 8.81 (bs, 1H, NH)	63.8 (C-4'), 87.9 (C-5'), 108.7 (C-3), 110.6 (C-4), 114.8 (C-2), 121.6 (C-5), 154.9 (C-3'), 128.9, 129.6, 130.9, 131.6, 132.8, 133.5, 134.2, 135.5, 137.5 (aromatic carbons)	-
5a	5.16 (d, 1H, C_4'-H, *J* = 5.8 Hz), 5.65 (d, 1H, C_5-H, *J* = 5.8 Hz), 6.76 (s, 1H, C_2-H) 7.01 (s, 1H, C_5-H), 7.10-7.64 (m, 15H, Ar-H), 8.86 (bs, 1H, NH)	64.2 (C-4'), 84.3 (C-5'), 107.5 (C-3), 110.1 (C-4), 114.2 (C-2), 124.3 (C-5), 154.6 (C-3'), 128.1, 129.5, 130.4, 131.8, 132.3, 133.7, 134.0, 134.9, 135.7 (aromatic carbons)	$M^{+\cdot}$ 492
5b	2.28 (s, 3H, Ar-CH_3), 3.84 (s, 3H, -OCH_3), 5.19 (d, 1H, C_4'-H, *J* = 5.9 Hz), 5.67 (d, 1H, C_5-H, *J* = 5.9 Hz), 6.74 (s, 1H, C_2-H) 7.03 (s, 1H, C_5-H), 7.14-7.68 (m, 13H, Ar-H), 8.89 (bs, 1H, NH)	22.4 (Ar-CH_3), 55.8 (Ar-OCH_3), 64.5 (C-4'), 84.5 (C-5'), 108.6 (C-3), 109.3 (C-4), 114.8 (C-2), 124.1 (C-5), 154.9 (C-3'), 128.4 129.0, 130.7, 131.2, 132.0, 133.4, 134.6, 135.1, 136.2 (aromatic carbons)	-
5c	5.22 (d, 1H, C_4'-H, *J* = 5.7 Hz), 5.69 (d, 1H, C_5-H, *J* = 5.8 Hz), 6.71 (s, 1H, C_2-H) 7.08 (s, 1H, C_5-H), 7.09-7.72 (m, 13H, Ar-H), 8.91 (bs, 1H, NH)	64.1 (C-4'), 84.7 (C-5'), 107.7 (C-3), 110.5 (C-4), 114.1 (C-2), 123.7 (C-5), 154.3 (C-3'), 129.5, 130.9, 131.6, 132.3, 133.0, 134.9, 135.7, 136.1, 137.3 (aromatic carbons)	-
6a	6.74 (s, 1H, C_2-H) 7.04 (s, 1H, C_5-H), 7.18-7.79 (m, 20H, Ar-H), 8.94 (bs, 1H, NH)	108.4 (C-3), 110.2 (C-4), 122.4 (C-2), 123.7 (C-5), 134.8 (C-5'), 147.2 (C-4'), 156.1 (C-3'), 129.1, 130.5, 131.4, 132.0, 132.7, 133.0, 134.2 (aromatic carbons)	$M^{+\cdot}$ 565

—Contd

Table II — Spectral characterization data for **2-7**—*Contd*

Compd	^{1}H NMR (δ, ppm) (*J* in Hz)	^{13}C NMR (δ ppm)	MS (*m/z*)
6b	2.24 (s, 3H, Ar-CH_3), 3.82 (s, 3H, -OCH_3), 6.71 (s, 1H, C_2-H) 7.02 (s, 1H, C_5-H), 7.14-7.75 (m, 18H, Ar-H), 8.98 (bs, 1H, NH)	22.3 (Ar-CH_3), 55.6 (Ar-OCH_3), 108.0 (C-3), 110.5 (C-4), 121.8 (C-2), 123.1 (C-5), 134.2 (C-5'), 147.7 (C-4'), 156.5 (C-3'), 129.4, 130.8, 131.5, 132.7, 133.4, 133.9, 135.2, 136.8 (aromatic carbons)	-
6c	6.74 (s, 1H, C_2-H) 7.06 (s, 1H, C_5-H), 7.08-7.82 (m, 18H, Ar-H), 8.85 (bs, 1H, NH)	108.5 (C-3), 110.1 (C-4), 122.2 (C-2), 124.9 (C-5), 134.6 (C-5'), 147.2 (C-4'), 156.1 (C-3'), 128.6, 129.7, 130.3, 131.8, 132.3, 133.9, 135.6, 136.1 (aromatic carbons)	-
7a	6.77 (s, 1H, C_2-H) 7.02 (s, 1H, C_5-H), 7.14-7.75 (m, 15H, Ar-H), 8.82 (bs, 1H, NH)	107.9 (C-3), 110.6 (C-4), 121.6 (C-2), 124.7 (C-5), 134.1 (C-5'), 147.5 (C-4'), 156.7 (C-3'), 128.4, 129.0, 130.6, 131.3, 132.8, 133.0, 133.8, 134.3 (aromatic carbons)	$M^{+\cdot}$ 490
7b	2.27 (s, 3H, Ar-CH_3), 3.79 (s, 3H, -OCH_3), 6.72 (s, 1H, C_2-H) 6.98 (s, 1H, C_5-H), 7.18 - 7.82 (m, 13H, Ar-H), 8.88 (bs, 1H, NH)	22.6 (Ar-CH_3), 55.6 (Ar-O*C*H_3), 107.9 (C-3), 110.1 (C-4), 122.2 (C-2), 124.3 (C-5), 134.6 (C-5'), 147.2 (C-4'), 156.1 (C-3'), 128.0, 128.9, 129.5, 130.2, 131.6, 132.1, 133.2, 133.5, 134.1 (aromatic carbons)	-
7c	6.76 (s, 1H, C_2-H) 7.01 (s, 1H, C_5-H), 7.09 - 7.88 (m, 13H, Ar-H), 8.86 (bs, 1H, NH)	107.4 (C-3), 110.6 (C-4), 121.7 (C-2), 124.9 (C-5), 134.3 (C-5'), 147.6 (C-4'), 156.6 (C-3'), 128.2, 129.3, 130.4, 131.2, 132.6, 133.9, 134.6, 137.3 (aromatic carbons)	-

^{1}H NMR spectra confirms their formation. The 70 eV mass spectra **6a** and **7a** displayed molecular ion peaks at *m/z* 565 and 490 in accordance with their chemical composition. The structures of the compounds **2**-**7** are further confirmed by ^{13}C NMR spectra (**Table II**).

Experimental Section

Melting points were determined in open glass capillaries on a Mel-Temp apparatus and are uncorrected. The homogeneity 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 wave numbers were 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 were reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat B at 70 eV with an emission current of 100 μA. The starting material 1-arylsulfonyl-2-styrylsulfonylethene **1** was prepared by the literature procedure[13].

General procedure for the preparation of 4-arylsulfonyl-3-(2'-phenylethenesulfonyl)-1*H*-pyrrole, 2/3-(4'-phenyl-1'*H*-pyrrole-3'-ylsulfonyl)-4-arylsulfonyl-1*H*-pyrrole, 3

A mixture of TosMIC (0.001 mole) and 1-arylsulfonyl-2-styrylsulfonylethene **1** (0.005 mole) in Et_2O-DMSO (2:1) was added dropwise under stirring to a suspension of NaH (50 mg) in Et_2O (10 mL) at RT and stirring was continued for 5-6 hr. Then, water was added and the reaction mass extracted with Et_2O. The ethereal fraction was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The resulting mixture was separated by column chromatography (hexane-ethyl acetate; 4:1) and identified as 4-arylsulfonyl-3-(2'-phenylethenesulfonyl)-1*H*-pyrrole **2** (major) and 3-(4'-phenyl-1'*H*-pyrrole-3'-ylsulfonyl)-4-arylsulfonyl-1*H*-pyrrole **3** (minor).

General procedure for the preparation of 3-(4'-phenyl-1'*H*-pyrrole-3'-ylsulfonyl)-4-arylsulfonyl-1*H*-pyrrole 3, Method-2

The compound **3** was also obtained by adding an equimolar (0.005 mole) mixture of 4-arylsulfonyl-3-(2'-phenylethenesulfonyl)-1*H*-pyrrole **2** and TosMIC in Et_2O-DMSO (2:1) dropwise under stirring to a suspension of NaH (25 mg) in Et_2O (6 mL) at RT.

Stirring was continued for 4-5 hr. Then, the contents were diluted with water and extracted with Et_2O. The ethereal layer was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The resultant solid was purified by column chromatography (ethyl acetate/ hexane, 1:4).

Method 3

A mixture of TosMIC (0.02 mole) and 1-aryl-sulfonyl-2-styrylsulfonylethene **1** (0.005 mole) in Et_2O-DMSO (2:1) was added dropwise under stirring to a suspension of NaH (100 mg) in Et_2O (20 mL) at RT and stirring was continued for about 3-4 hr. Then, water was added and the reaction mass extracted with Et_2O. The ethereal layer was dried (anhyd. Na_2SO_4) and the solvent was removed *in vacuo*. The solid obtained was purified by column chromatography (ethyl acetate/ hexane, 1:4).

General procedure for the preparation of 4'-(4-(aryl-sulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-4',5'-dihydro-1', 5'-diphenyl-3'-aryl- 1'*H*-pyrazole, 4

A mixture of **2** (0.001 mole), araldehyde phenyl hydrazone (0.002 mole) and chloramine –T (0.002 mole) in methanol (15 mL) was refluxed for 16-18 hr on a water bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Recrystallization of crude product from ethanol resulted in pure **4**.

General procedure for the preparation of 4'-(4-(arylsulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-4',5'-dihydro-3'-aryl-5'-phenylisoxazole, 5

A mixture of **2** (0.001 mole), araldoxime (0.002 mole) and chloramine –T (0.002 mole) in methanol (15 mL) was refluxed for 14-16 hr on a water-bath. The precipitated inorganic salts were filtered off. The filtrate was concentrated and the residue was extracted with dichloromethane. The organic layer was washed with water, saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The solid obtained was purified by recrystallization from ethanol.

General procedure for the preparation of 4'-(4-(aryl-sulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-1',5'-diphenyl-3'-aryl-1'*H*-pyrazole, 6 / 4'-(4-(arylsulfonyl)-1*H*-pyrrol-3-ylsulfonyl)-3'-aryl-5'-phenylisoxazole, 7

A solution of **4** or **5** (0.001 mole) and chloranil (0.0014 mole) in xylene (10 mL) was refluxed for 24-32 hr. Then, the reaction mixture was treated with a 5% NaOH solution. The organic layer was separated and repeatedly washed with water. It was then dried over anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The resultant solid was purified by recrystallization from 2-propanol.

References

1 (a) Yates F S, Boulton A J & McKillop A, *Comprehensive Heterocyclic Chemistry*, 2, **1984**, 511; (b) Jones R A, *Pyrroles: The Synthesis, Reactivity and Physical Properties of Substituted Pyrroles*, Part II (John Wiley and Sons, New York), **1992**.

2 (a) Di Santo R, Costi R, Artico M, Massa S, Lampis G, Deidda D & Pompei R, *Bioorg Med Chem Lett*, 6, **1998**, 2931; (b) Rango R, Marshall G R, Di Santo R, Costi R, Massa S, Rompei R & Artico M, *Bioorg Med Chem Lett*, 8, **2000**, 1423.

3 Dannahardt G, Kiefer W, Kramer G, Maehrlein S, Nowe U & Fiebich B, *Eur J Med Chem*, 35, **2000**, 499.

4 (a) Shiraishi H, Nishitani T, Nishihara T, Sakaguchi S & Ishii Y, *Tetrahedron*, 55, **1999**, 13957; (b) Zelikin A, Shastri V R & Langer R, *J Org Chem*, 64, **1999**, 3379; (c) Liu J H, Chan H W & Wong H N C, *J Org Chem*, 65, **2000**, 3274.

5 (a) Van Leusen A M, Siderius H, Hoogenboom B E & Van Leusen D, *Terahedron Lett*, **1972**, 5337; (b) Pavri N P & Trudell M L, *J Org Chem*, 62, **1997**, 2649.

6 Padmavathi V, Reddy B J M, Sarma M R G & Thriveni P, *J Chem Res (S)*, **2004**, 79.

7 (a) Lee A G, *Synthesis*, **1982**, 508; (b) Bao-Xiang Z, Yang Yu & Shoji E, *Tetrahedron*, 52, **1996**, 12049.

8 Just G & Dhal K, *Tetrahedron*, 24, **1968**, 5251.

9 Lokanath Rai K M, Linganna N, Hassner A & Murthy C A, *Org Prep Proc Intl*, 24, **1992**, 91.

10 Kim J N & Ryu E K, *Synth Commun*, 20, **1990**, 1373.

11 (a) Lokanath Rai K M & Hassner A, *Indian J Chem*, 36B, **1997**, 242; (b) Lokanath Rai K M & Hassner A, *Synth Commun*, 27, **1997**, 467; (c) Hassner A & Lokanath Rai K M, *Synthesis*, **1989**, 57; (d) Lokanath Rai K M & Hassner A, *Synth Commun*, 19, **1989**, 2799.

12 (a) Padmavathi V, Bhaskar Reddy A V, Sumathi R P & Bhaskar Reddy D, *Indian J Chem*, 37B, **1998**, 1286; (b) Padmavathi V, Sumathi R P, Chandrasekhar Babu N & Bhaskar Reddy D, *J Chem Res (S)*, 2, **1999**, 610; (c) Padmavathi V, Sumathi R P, Reddy K V, Reddy A S & Bhaskar Reddy D, *Synth Commun*, 30, **2000**, 4007; (d) Padmavathi V, Reddy K V, Padmaja A & Bhaskar Reddy D, *Synth Commun*, 32, **2002**, 1227; (e) Padmavathi V, Reddy K V, Balaiah A, Ramana Reddy T V & Bhaskar Reddy D, *Heteroatom Chem*, 13, **2002**, 677.

13 Bhaskar Reddy D, Chandrasekhar Babu N, Reddy K V & Padmavathi V, *Indian J Chem*, 40B, **2001**, 416.