Abbas Shafiee*[1], Mohammad Z. Kassaee[2], Ahamad R. Bekhradnia[3]

[1]Department of Chemistry and Pharmaceutical Science Research Center,
Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Chemistry, University of Tarbiat Modarres, Pole-Gisha, Tehran, Iran
[3]Department of Chemistry and Pharmaceutical Science Research Center,
Mazandaran University of Medical Sciences, Sari, Iran

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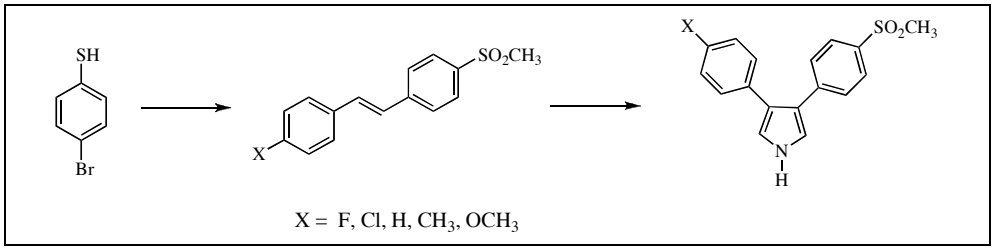

The synthesis of a series of novel 3,4-diaryl-1*H*-pyrroles and related arylalkenes from *p*-bromo thiophenol, tosylmethyl isocyanide and commercially available materials is reported. Arylalkenes having electron-withdrawing substituents gave higher yield of 3,4-diaryl-1*H*-pyrroles.

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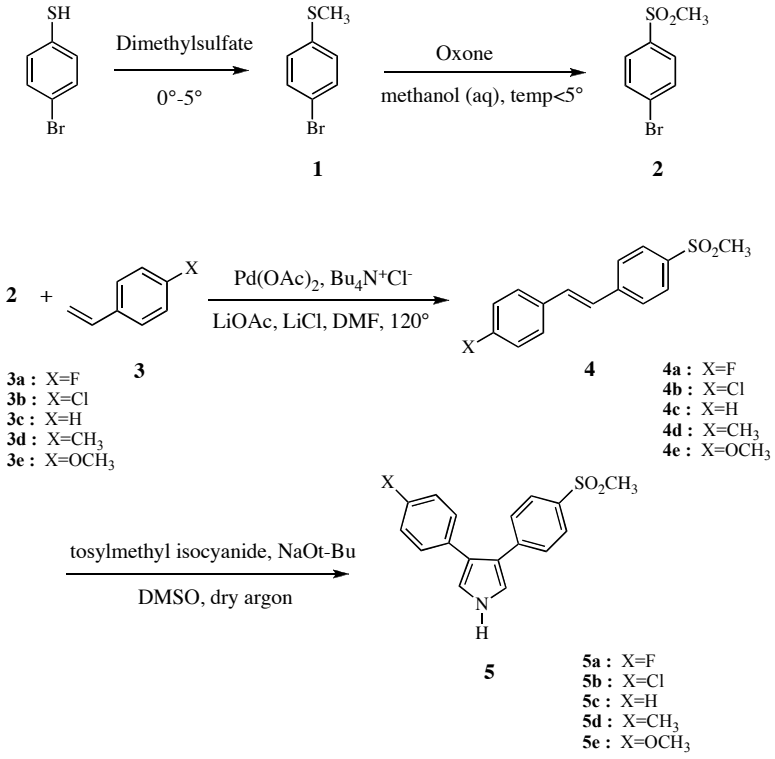
INTRODUCTION

The pyrrole ring is an important heterocycle in biological system being incorporated into the porphyrin ring systems of chlorophyll, heme, Vitamin B12, bile pigments, and the anti-inflammatory drugs [1]. Hence, the syntheses of pyrroles are by all means an attractive area in heterocyclic chemistry, due primarily to the fact that many pyrroles are subunits of natural products [2]. A number of these compounds have been shown to possess antibacterial and fungicidal properties [3].

Previously, 4,5-diarylpyrroles having phenyl sulfone substituent have been known as anti-inflammatory drugs and COX-2 inhibitors [4]. In continuation of our research program dealing with the syntheses of 1,2-diaryl five membered heterocycles [5-8], we were interested in the synthesis of 3,4-diaryl-1*H*-pyrroles as a possible effective

Scheme 1



anti- inflammatory drug. However, it is noteworthy to mention that 3,4-disubstituted pyrrole system is probably the most difficult to be prepared [9], but several approaches have been recorded [10,11]. As such, a lot of effort has been spent developing practical methods for the synthesis of pyrrole units that incorporate appropriate functionality [12]. However, there are no reports of the synthesis of 3,4-diaryl-(1*H*)-pyrroles from sulfonyl stilbenes [13].

RESULTS AND DISCUSSION

The synthesis of new 3,4-disubstituted-1*H*-pyrroles having phenyl sulfone substituent is shown in Scheme 1. In the first step, the related stilbenes as new Michael acceptors were synthesized. Thus, *p*-bromothiophenol was methylated with dimethyl sulfate to produce *p*-bromothioanisole **1** at 0-5°C and then oxidized to corresponding sulfone **2** using potassium hydrogen persulfate.

Compound **2** was reacted with suitable styrenes (**3a-e**) at various temperatures to give related stilbenes (**4a-e**) (Table 1) [14].

Thus, *p*-flourostyrene **3a**, *p*-chlorostyrene **3b**, styrene **3c**, *p*-methylstyrene **3d**, and *p*-methoxystyrene **3e** gave corresponding *trans*-stilbenes (**4a-e**) after 8-12 h in 81%-94% yields (Table 1). Reaction of compound **4** with tosylmethyl isocyanide *via* cannula in the presence of NaO*t*-Bu in DMSO gave the desired 3,4-diaryl-1*H*-pyrroles (**5a-e**) after purification using silica gel column chromatography.

In general, higher yields of the desired 3,4-diaryl-1*H*-pyrroles were obtained at lower temperature and with shorter reaction times when the aryl group of the related stilbenes was more electron–withdrawing (Table 1).

In summary, we have demonstrated a convenient method for the preparation of 3,4-diaryl-1*H*-pyrroles and related arylalkenes in high yield starting from *p*-bromo thiophenol using tosylmethyl isocyanide.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker DRX500 AVANCE spectrometer at 500.13 MHz (^{1}H), 125.75 MHz (^{13}C). Chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The IR spectra were obtained using a Nicolet FT-IR Magna 550 spectrograph. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometer at 70 eV. Melting points were measured in open capillary tubes with an Electrothermal-9200 melting point apparatus and are uncorrected.

Preparation of trans-Diarylstilbenes 4. General Procedure. To a solution of suitable styrene (6 mmoles) in DMF (40 mL) at rt was added methyl-4- bromophenyl sulfone (7 mmoles), LiCl (0.4 g), LiOAc- $2H_2O$ (1.5 g), $Bu_4N^+Cl^-$ (3.5 g) and $Pd(OAc)_2$ (50 mg). The mixture was heated in appropriate temperature for the optimized reaction time (Table 1) and then cooled to room temperature. The mixture was quenched with an NH_4OAc solution and extracted with ethyl acetate. The organic phase was washed with water, saturated $NaHCO_3$ solution, brine and dried ($MgSO_4$). The solvent was evaporated and the residue was crystallized from ethanol/water to give the title compounds **4** (Table 1, Table 2).

Preparation of 3,4-Diaryl-1H-pyrroles 5. General procedure. All experiments were carried out under an atmosphere of dry argon. A solution of related stilbene **4** (2 mmoles) and tosylmethyl isocyanide (2.6 mmol) in DMSO (20 mL) was added to a suspension of NaO*t*-Bu (4 mmoles) in dry DMSO (20 mL) at room temperature *via* cannula. The mixture was stirred at the desired temperatures for 6-9 h (Table 1) then cooled to room temperature and diluted with ethyl acetate (70 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent, the crude product was purified by silica gel column chromatography with ethyl acetate/hexane (6:4), to give corresponding 3,4-diaryl-(1*H*)-Pyrroles in good yields (Table 1, Table 2).

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Table 1

Physical and Analytical Data of Compounds **4** and **5**.

Compounds	X	t°C/time	Yield (%)	m.p.°C	Formula	Calcd. (%)			Found (%)		
						C	H	N	C	H	N
4a	F	115/12h	81	171-173	$C_{15}H_{13}FO_2S$	65.20	4.74	-	65.35	4.96	-
4b	Cl	110/10h	85	179-181	$C_{15}H_{13}ClO_2S$	61.53	4.48	-	61.35	4.29	-
4c	H	110/9h	88	178-179	$C_{15}H_{14}O_2S$	69.74	5.46	-	69.96	5.68	-
4d	CH_3	105/8h	91	179-181	$C_{16}H_{16}O_2S$	70.56	5.92	-	70.39	5.98	-
4e	OCH_3	105/8h	94	181-183	$C_{16}H_{16}O_3S$	66.64	5.59	-	66.46	5.78	-
5a	F	65/6h	91	164-165	$C_{17}H_{14}FNO_2S$	64.75	4.47	4.44	64.93	4.65	4.64
5b	Cl	75/7h	86	185-186	$C_{17}H_{14}ClNO_2S$	61.53	4.25	4.22	61.35	4.06	4.43
5c	H	85/8h	80	174-175	$C_{17}H_{15}NO_2S$	68.66	5.08	4.71	68.85	5.23	4.90
5d	CH_3	85/9h	75	175-177	$C_{18}H_{17}NO_2S$	69.43	5.50	4.50	69.61	5.73	4.32
5e	OCH_3	95/9h	71	179-180	$C_{18}H_{17}NO_3S$	66.03	5.23	4.28	66.21	5.41	4.49

Table 2
Spectroscopic Data of compounds **4** and **5**

Compounds	^{1}HNMR (δ, ppm)	^{13}CNMR(δ, ppm)
4a	3.12 (s, 3H, CH_3); 7.32 (d, 1H, J= 16.4Hz), 7.47 (d, 1H, J= 16.4Hz) (Olefinic hydrogens); 7.18 (dd, 2H, JHH= 8.5Hz, JHF= 8.6Hz), 7.71 (dd, 2H, JHH= 8.5Hz, JHF= 7.2Hz), 7.83 (d, 2H, J=8.1Hz), 7.93 (d, 2H, J=8.1Hz) (Aromatic hydrogens)	44.8 (CH_3); 128.0, 128.4 (Olefinic carbons); 118.1, 131.1, 131.8, 132.2, 134.2, 140.3, 142.1, 162 (Aromatic carbons)
4b	3.07 (s, 3H, CH_3); 7.09 (d, 1H, J=16.3Hz), 7.20 (d, 1H, J=16.3Hz) (Olefinic hydrogens); 7.36 (d, 2H, J=7.9Hz), 7.47 (d, 2H, J=7.9Hz), 7.67 (d, 2H, J=7.9 Hz), 7.92 (d, 2H, J=7.9Hz) (Aromatic hydrogens)	44.6 (CH_3); 127.8, 128..3 (Olefinic carbons); 130.8, 131.1, 131.6, 134.0, 134.2, 135.1, 140.2, 141.8 (Aromatic carbons)
4c	3.06 (s, 3H, CH_3); 7.01 (d, 1H, J=16.1Hz), 7.12 (d, 1H, J=16.1Hz) (Olefinic hydrogens); 7.23-7.40 (m, 5H), 7.66 (d, 2H, J=7.3Hz), 7.90 (d, 2H, J=7.3Hz) (Aromatic hydrogens)	44.5 (CH_3); 126.5, 128.9 (Olefinic carbons); 127.1, 127.9, 129.2, 131.5, 133.8, 136.3, 140.0, 142.1 (Aromatic carbons)
4d	3.08 (s, 3H, CH_3), 2.41 (s, 3H, Ar-CH_3); 7.14 (d, 1H, J=16.2Hz), 7.38 (d, 1H, J=16.2Hz) (Olefinic hydrogens); 7.20 (d, 2H, J=7.2Hz), 7.48 (d, 2H, J=7.2Hz), 7.60 (d, 2H, J=7.7Hz), 7.97 (d, 2H, J=7.7Hz) (Aromatic hydrogens)	44.6 (SO_2-CH_3), 21.3 (Ar-CH_3); 125.5, 126.8 (Olefinic carbons); 129.0, 130.1, 131.7, 134.1, 134.2, 137.8, 140.4, 142.5 (Aromatic carbons)
4e	3.07 (s, 3H, CH_3), 3.70 (s, 3H, Ar-OCH_3); 7.13 (d, 1H, J=16.4Hz), 7.19 (d, 1H, J=16.4Hz) (Olefinic hydrogens); 7.24 (d, 2H, J=7.1Hz), 7.60 (d, 2H, J=7.1Hz), 7.65 (d, 2H, J=7.9Hz), 7.96 (d, 2H, J=7.9Hz) (Aromatic hydrogens)	44.9 (SO_2-CH_3), 55.2 (Ar-OCH_3); 126.3, 127.5 (Olefinic carbons); 116.8, 129.9, 130.2, 131.8, 134.2, 159.8, 140.4, 142.6 (Aromatic carbon)
5a	3.30 (s, 3H, CH_3); 7.04 (s, 1H), 7.53 (s, 1H) (Heterocyclic hydrogens); 7.10 (dd, 2H, JHH= 8.4Hz, JHF= 8.4Hz), 7.22 (d, 2H, J= 7.7Hz), 7.37 (dd, 2H, JHH= 8.4, JHF= 9.11Hz), 7.42 (d, 2H, J= 7.7Hz) (Aromatic hydrogenes); 11.2 (bs, 1H, N-H)	44.9 (CH_3); 87.7, 114.8, 117.0 (Heterocyclic carbons); 111.1, 126.9, 128.2, 131.1, 135.1, 137.8, 137.9, 161.5 (Aromatic carbons)
5b	3.29 (s, 3H, CH_3); 7.02 (s, 1H), 7.51 (s, 1H) (Heterocyclic hydrogens); 7.12 (d, 2H, J=8.2Hz), 7.23 (d, 2H, J=7.4Hz), 7.40 (d, 2H, J=8.2Hz), 7.55 (d, 2H, J=7.4Hz) (Aromatic hydrogenes); 11.4 (bs, 1H, N-H)	44.9 (CH_3); 84.8, 115.1, 117.1 (Heterocyclic carbons); 126.8, 127.1, 131.0, 131.3, 132.1, 133.2, 137.8, 137.9 (Aromatic carbons)
5c	3.29 (s, 3H, CH_3); 6.92 (s, 1H), 7.42 (s, 1H) (Heterocyclic hydrogens); 6.40- 6.71 (m, 5H), 7.27 (d, 2H, J=7.3Hz), 7.44 (d, 2H, J=7.3Hz) (Aromatic hydrogenes); 10.6 (bs, 1H, N-H)	44.9 (CH_3); 83.3, 117.0, 118.0 (Heterocyclic carbons); 124.8, 126.3, 125.9, 128.5, 130.2, 133.9, 136.7, 138.1 (Aromatic carbons)
5d	3.29 (s, 3H, SO_2-CH_3); 2.54 (s, 3H, Ar-CH_3); 6.94 (s, 1H), 7.48 (s, 1H) (Heterocyclic hydrogens); 6.85 (d, 2H, J=7.8Hz), 7.29 (d, 2H, J=7.5Hz), 7.44 (d, 2H, J=7.8Hz), 7.50 (d, 2H, J=7.5Hz) (Aromatic hydrogenes); 10.9 (bs, 1H, N-H)	44.9 (SO_2-CH_3); 22.1 (Ar-CH_3); 84.2, 117.0, 117.2 (Heterocyclic carbons); 126.7, 128.4, 130.9, 131.3, 131.5, 137.6, 138.6, 140.1 (Aromatic carbons)
5e	3.30 (s, 3H, SO_2-CH_3); 3.77 (s, 3H, Ar-OCH_3); 6.99 (s, 1H), 7.50 (s, 1H) (Heterocyclic hydrogens); 6.05 (d, 2H, J=8.3Hz), 6.90 (d, 2H, J= 8.3Hz), 7.24 (d, 2H, J=7.6Hz), 7.43 (d, 2H, J=7.6Hz) (Aromatic hydrogenes); 11.1 (bs, 1H, N-H)	44.9 (SO_2-CH_3); 56.2 (Ar-OCH_3); 84.3, 117.2, 119.3 (Heterocyclic carbons); 114.2, 126.7, 126.8, 130.2, 131.1, 137.7, 138.9, 157.1 (Aromatic carbons)

REFERENCES

[1] Unverferth, K.; Engel, J.; Hofgen, N.; Rostock, A.; Gunther, R.; Lankau, H. J.; Menzer, M.; Rolfs, A,; Liebscher, J.; Muller. B.; Hofmann, H. J. *J. Med. Chem.*, **1998**, *41*, 63.

[2] Franck, B.; Nonn, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1795.

[3a] Umio. S.; Kariyone, K. Japane Patent 68,14,699, 1968; *Chem. Abstr.* **1969**, *70*, 87560z; [b] Nippon Soda Co. Ltd., Jpn. Kokai Tokkyo Koho Patent 81,79,672, 1981; *Chem. Abstr.* **1981**, *95*, 187069f.

[4] Wilkerson, W. W.; Copeland, R. A.; Covington, M.; Trzaskos, J. M. *J. Med. Chem.* **1995**, *38*, 3895.

[5] Salimi, M.; Amini, M.; Shafiee, A. Phosphorus, Sulfur and Silicon, **2005**, *180*, 1587.

[6] Karimi, L.; Navidpour, L.; Amini, M.; Shafiee, A. *Phosphorus, Sulfur and Silicon*, **2005**, *180*, 1593.

[7] Johari Daha, F.; Matloubi, H.; Tabatabai, S. A.; Shafii, B.; Shafiee, A. *J. Heterocyclic Chem.*, **2005**, *42*, 33.

[8] Navidpour, L.; Shafaroodi, H.; Abdi, K.; Amini, M.; Ghahremani, M. H.; Dehpour, A. R.; Shafiee, A. *Bioorg. Med. Chem.*, **2006**, *14*, 2507.

[9] Anderson, H. J.; Loader, C. E.; Xu, R. X.; Le, N.; Gogan, N. J.; McDonald, R.; Edwards, L. G. *Can. J. Chem.*, **1985**, *63*, 896.

[10] Liu, J. H.; Chan, H. W.; Wong, H. N. C. *J. Org. Chem.*, **2000**, *65*, 3274.

[11a] Senio, H.; Ishii, Y.; Hidai, M. *J. Am. Chem. Soc.*, **1994**, *116*, 7433; [b] Cooper, J. M.; Morris, D. G.; Ryder, K. S. *J. Chem. Soc., Chem. Commun.*, **1995**, 697; [c] Shiraishi, H.; Nishitani, T.; Nishihara, T.; Sakaguchi, S.; Ishii, Y. *Tetrahedron*, **1999**, *55*, 13957; [d] Brown, D. G.; Siddens, J. K.; Diehl, R. E.; Wright, J.; Donald, P. United States Patent 5,010,098, 1991; *Chem. Absrt.* **1989**, *111*, 194576w; [e] Kuhn, D. G.; Furch, J. A.; Kamhi, V. M. United States Patent 5,180,734, 1993; *Chem. Absrt.* **1992**, *117*, 131058g; [f] Reid, B. L.; Farlow, R. A. United States Patent 6,077,863, 2000; *Chem. Absrt.* **2000**, *133*, 27665e.

[12] Sundberg, R. G. *Comprehensive Heterocyclic Chemistry*,

Pergamon Press, Oxford, **1984**, Vol. IV, P 313.

[13a] Ten Have, R.; Leusink, F. R.; Van Leusen, A. M. *Synthesis*, **1996**, 871; [b] Dijkstra, H. P.; Ten Have, R.; Van Leusen, A. M. *J. Org. Chem.*, **1998**, *63*, 5332.

[14] Gyorkos, A. C.; Stille, J. K.; Hegedus, L. S. *J. Am. Chem. Soc.*, **1990**, *112*, 8465.