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Arylation of the readily available 3-alkythio-5-aryl-1,2,4-triazoles gave 5-alkylthio-1,3-diaryl-1,2,4-triazoles in moderate yield. The structures of the latter were confirmed by NOE and ^{13}C-NMR.

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Triazoles and in particular the 1,2,4-triazole nucleus have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants, sedatives, antianxiety and antimicrobial agents [2,3].

Their antifungal activity is also documented [4,5]. Newer classes of antifungals including azole derivatives such as Fluconazole, an orally active triazole agent, and Itrazonazole are systemic antifungal agents actually employed in patients with impaired immunity such as those who have AIDS or are neutropenic as a result of cancer therapy.

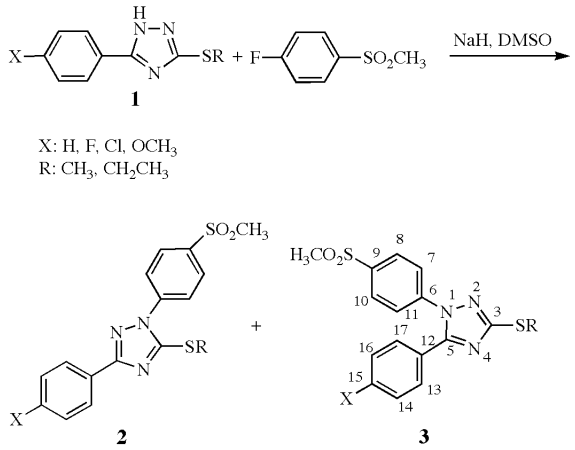
Moreover, many infections due to *Candida* spp are actually refractory to antifungal therapy. While these new classes of compounds are now frequently used in treatment of fungal infections, resistance of these drugs is rising, which clearly indicates an urgent need for new antifungal agents [6]. To overcome rapid development of drug resistance, new agents should preferably have chemical characteristics that clearly differ from those of existing agents.

In the present paper we report on the arylation of 3-alkylthio-5-(4-substituted phenyl)-1*H*-1,2,4-triazole (**1**) with fluorobenzene activated by a methylsulfonyl group to prepare diaryltriazole derivatives. Alkylation and arylation of 5- amino-3-methylthio-1,2,4-triazole derivative with activated alkyl or aryl halide have been studied [7,8] and the N_1-arylated and alkylated regioisomers were obtained as the main product.

The main product of direct arylation of 5-aryl-3-thioalkyl-1*H*1,2,4-triazole (**1**, Scheme 1) was in all cases the corresponding 2-arylated derivative **2**. However, N_1-arylated derivative **3** was also formed in low yield. Only **3a** was isolated and characterized. The amount of N_4-arylation was insignificant. In order to elucidate the definite structure of **2a** and **3a**, N_4-arylated derivative **9** was prepared *via* an alternative procedure with conclusive structure [9] (Scheme 2).

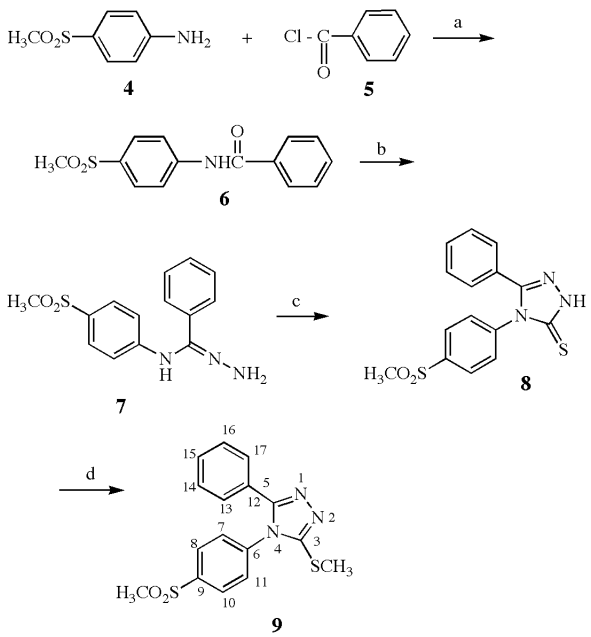
The differentiation between the structure **3a**, **2a** and **9** was possible on the basis of a D-NOE experiment. Irradiation of the methylthio group of **3a** (Figure1) did not result in an enhancement of any of the aromatic hydrogen signals, therefore the 4-methylsulfonylphenyl moiety is in position 1 of triazole ring. Furthermore, the observation of NOE enhancement on the phenyl hydrogen atoms signals

Scheme 1



Arylation of 3-thioalkyl-5-aryl-1,2,4-triazole.

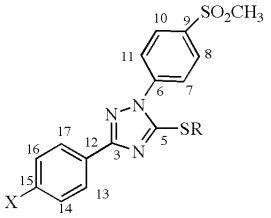
Scheme 2



Preparation of 4,5-diaryl-3-thiomethyl-1,2,4-triazole. a) Et_3N, 18 h, r.t., b) PCl_5, 3 h, refluxed then dry NH_2NH_2, 1h, r.t., c) 1.1'-thiocarbonyldiimidazole, 18 h, r.t., d) CH_3I, NaOH, 12 h, r.t.

Table 1

Analytical Data of Compounds **2a-j**



Comp. No.	X	R	M.p.(°C)	Yield (%)	Molecular Formula	Analysis % Calcd./Found C	H	N
2a	H	CH_3	163-164	21	$C_{16}H_{15}N_3O_2S_2$	55.63/55.42	4.37/4.60	12.16/11.89
2b	H	C_2H_5	132-133	24	$C_{17}H_{17}N_3O_2S_2$	56.80/57.05	4.77/4.58	11.69/11.65
2c	F	CH_3	173-175	28	$C_{16}H_{14}FN_3O_2S_2$	52.88/52.60	3.88/4.05	11.56/11.47
2d	F	C_2H_5	140-142	33	$C_{17}H_{16}FN_3O_2S_2$	54.09/53.87	4.27/4.39	11.13/11.33
2e	Cl	CH_3	134-145	36	$C_{16}H_{14}ClN_3O_2S_2$	50.58/50.69	3.71/3.49	11.06/11.29
2f	Cl	C_2H_5	123-124	25	$C_{17}H_{16}ClN_3O_2S_2$	51.83/51.56	4.09/4.36	10.67/10.51
2g	CH_3	CH_3	133-135	20	$C_{17}H_{17}N_3O_2S_2$	56.80/56.99	4.77/4.69	11.69/11.91
2h	CH_3	C_2H_5	135-137	21	$C_{18}H_{19}N_3O_2S_2$	57.88/57.49	5.13/4.91	11.25/11.49
2i	OCH_3	CH_3	149-150	32	$C_{17}H_{17}N_3O_3S_2$	54.38/54.40	4.56/4.69	11.19/10.98
2j	OCH_3	C_2H_5	137-139	33	$C_{18}H_{19}N_3O_3S_2$	55.50/55.88	4.92/4.81	10.79/10.55

Table 2

Analytical Data of Compounds **6**-**9** and **3a**

Comp. No.	M.p. (°C)	Yield (%)	Molecular Formula	Analysis % Calcd./Found C	H	N
6	178-180	95	$C_{14}H_{13}NO_3S$	61.07/61.22	4.76/4.60	5.09/5.29
7	205-207	90	$C_{14}H_{15}N_3O_2S$	58.11/58.29	5.22/5.46	14.52/14.58
8	240-242	52	$C_{15}H_{13}N_3O_2S_2$	54.36/54.45	3.95/3.77	12.68/12.21
9	208-210	90	$C_{16}H_{15}N_3O_2S_2$	55.63/55.97	4.37/4.39	12.16/12.47
3a	184-186	3	$C_{16}H_{15}N_3O_2S_2$	55.63/55.65	4.37/4.56	12.16/12.22

a' in **3a** by irradiation of hydrogen-a and also enhancement of the signal for hydrogen-a when the a'-hydrogen was irradiated clearly showed that the two aryl groups are in neighboring positions 1 and 5. For compound **2a** (Figure 1) following irradiation of the methylthio group, a NOE enhancement was observed on the aromatic hydrogen atoms a and b signals. This indicates that the presence of 4-methylsulfonylphenyl group is in positions 2 or 4 of triazole ring. For compound **9**, a cross NOE effect between the two-aryl groups and also between the thiomethyl group and aromatic hydrogens of the 4-methylsulfonylphenyl groups were observed. The structure of compounds **3a**, **2a** and **9** could also be confirmed by ^{13}C-NMR. It is known [10-12] that where heteroaromatic carbon atoms have otherwise identical chemical environment, the carbon attached to a pyridine-like nitrogen atom is more deshilded than that bound to pyrrole-like nitrogen. The difference between the two types of chemical shifts values in isomers where the structure is fixed by alkyl groups, and also in the case of different tautomeric forms measured at low temperatures, is about 8-12 ppm. Multi-regression analysis of different azoles also led to the same results [9].

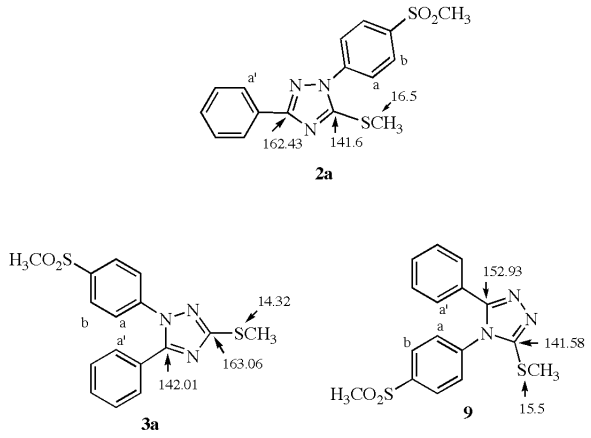


Figure 1 Structures of **2a**, **3a** and **9**.

In compound **3a** (Figure 1), C_3 is situated between two pyridine-like nitrogen atoms, therefore its chemical shift is higher than C_5, which is situated between pyrrole-like and pyridine-like nitrogen atoms. These rules are also valid for **2a** and similar discussion could be given. For compound **9** both C_5 and C_3 are situated between pyridine-like and pyrrole-like nitrogen atoms. The difference of the chemical shift is the result of the effect of phenyl and thiomethyl group on carbon chemical shift.

On the basis of the above discussion, the chemical shift of compounds **2a-2j** were assigned and summarized in Table 3.

N_1-Aryl and N_1-alkyl regioisomers for 5-amino-3-thiomethyl 1,2,4-triazole were reported as main product

Table 3

^{1}H and ^{13}C-NMR of Compounds **2a-2j**

Comp. No.	^{1}H-NMR	^{13}C-NMR
2a	8.17 (m, 2H, $H_{13,17}$), 8.10 (d, J=8.8 Hz, 2H, $H_{8,10}$), 7.96 (d, J=8.8 Hz, 2H, $H_{7,11}$), 7.4-7.5 (m, 3H, $H_{14,15,16}$), 3.10 (s, 3H, SO_2CH_3), 2.81 (s, 3H, SCH_3).	162.45 (C_3-triazole), 154.83 (C_6), 141.64 (C_5-triazole), 139.47 (C_9), 130.10 (C_{12}), 129.76 (C_{15}), 128.83 ($C_{8,10}$), 128.63 ($C_{13,17}$), 126.55 ($C_{14,16}$), 123.32 ($C_{7,11}$), 44.05 (SO_2CH_3), 16.2 (SCH_3).
2b	8.18 (m, 2H, $H_{13,17}$), 8.08 (d, J=8.8 Hz, 2H, $H_{8,10}$), 7.94 (d, J=8.8 Hz, 2H, $H_{7,11}$), 7.4-7.5 (m, 3H, $H_{14,15,16}$), 3.43 (q, J=7 Hz, 2H, CH_2), 3.10 (s, 3H, SO_2CH_3), 1.50 (t, J=7 Hz, 3H, CH_3).	162.43 (C_3-triazole), 154.12 (C_6), 141.55 (C_5-triazole), 139.25 (C_9), 130.12 (C_{12}), 129.61 (C_{15}), 128.65 ($C_{8,10}$), 128.42 ($C_{13,17}$), 126.41 ($C_{14,16}$), 123.33 ($C_{7,11}$), 44.22 (SO_2CH_3), 28.3 (CH_2), 16.2(CH_3).
2c	8.15 (dd, J=8.8 Hz, J=5.6 Hz, 2H, $H_{13,17}$), 8.10 (d, J= 9.2 Hz, 2H, $H_{8,10}$),7.96 (d, J=9.2 Hz, 2H, $H_{7,11}$),7.15 (t, J=8.8 Hz, 2H, $H_{14,16}$), 3.12 (s, 3H, SO_2CH_3), 2.85 (s, 3H, SCH_3).	164.92 (C_3-triazole), 162.15 (d, J=85 Hz, C_{15}), 154.32 (C_6), 141.64 (C_5-triazole), 139.57 (C_9), 128.88 ($C_{8,10}$), 128.64 (d, J=8.3 Hz, $C_{13,17}$), 126.30(d, J=3.4 Hz, C_{12}), 123.61 ($C_{7,11}$), 115.70 (d, J=22 Hz, $C_{14,16}$), 44.32 (SO_2CH_3), 14.50 (CH_3).
2d	8.15 (dd, J=8.8 Hz, J=5.6 Hz, 2H, $H_{13,17}$), 8.09 (d, J= 9.2 Hz, 2H, $H_{8,10}$), 7.95 (d, J=9.2 Hz, 2H, $H_{7,11}$), 7.14 (t, J=8.8 Hz, 2H, $H_{14,16}$), 3.42 (q, J=7 Hz, 2H, CH_2), 3.11 (s, 3H, SO_2CH_3), 1.49 (t, J=7 Hz, 3H, CH_3).	164.98 (C_3-triazole), 162.07 (d, J=85 Hz, C_{15}), 154.19 (C_6), 141.53 (C_5-triazole), 139.38 (C_9), 128.75 ($C_{8,10}$), 128.44 (d, J=8.3 Hz, $C_{13,17}$), 126.34 (d, J=3.4 Hz, C_{12}), 123.43 ($C_{7,11}$), 115.59 (d, J=22 Hz, $C_{14,16}$), 44.52 (SO_2CH_3), 28.25 (SCH_2), 14.58 (CH_3).
2e	8.06 (m, 6H, $H_{13,17,7,8,10,11}$), 7.43 (d, J=8 Hz, 2H, $H_{14,16}$), 3.12 (s, 3H, SO_2CH_3), 2.85 (s, 3H, SCH_3).	161.50 (C_3-triazole), 155.02 (C_6), 141.50 (C_5-triazole), 139.4 (C_9), 135.80 (C_{15}), 128.85 ($C_{8,10,13,17}$), 128.61 (C_{12}), 127.82 ($C_{14,16}$), 123.31 ($C_{7,11}$), 44.50 (SO_2CH_3), 16.03 (SCH_3).
2f	8.02 (m, 6H, $H_{13,17,7,8,10,11}$), 7.42 (d, J=8 Hz, 2H, $H_{14,16}$), 3.41 (q, J=7 Hz, 2H, SCH_2), 3.10 (s, 3H, SO_2CH_3), 1.48 (t, J=7 Hz, 3H, CH_3).	161.59 (C_3-triazole), 154.34 (C_6), 141.52 (C_5-triazole), 139.49 (C_9), 135.67 (C_{15}), 128.84 ($C_{8,10}$), 128.79($C_{13,17}$), 128.64 (C_{12}), 127.81 ($C_{14,16}$), 123.51 ($C_{7,11}$), 44.57 (SO_2CH_3), 28.29 (SCH_2), 14.62(CH_3).
2g	8.02 (m, 6H, $H_{13,17,7,8,10,11}$), 7.25 (d, J=8 Hz, 2H, $H_{14,16}$), 3.09 (s, 3H, SO_2CH_3), 2.83 (s, 3H, SCH_3), 2.40 (s, 3H, CH_3).	162.50 (C_3-triazole), 154.59 (C_6), 141.64 (C_5-triazole), 139.82 (C_9), 139.29 (C_{12}), 129.28 ($C_{8,10}$), 128.76 ($C_{13,17}$), 127.26 (C_{15}), 126.42 ($C_{14,16}$), 123.24 ($C_{7,11}$), 44.51 (SO_2CH_3), 21.43 (C_{15}-CH_3), 16.02 (SCH_3).
2h	7.98 (m, 6H, $H_{13,17,7,8,10,11}$), 7.25 (d, J=8 Hz, 2H, $H_{14,16}$), 3.42 (q, J=7 Hz, 2H, SCH_2), 3.09 (s, 3H, SO_2CH_3), 2.40 (s, 3H, CH_3), 1.44 (t, J=7 Hz, 3H, CH_3).	162.45 (C_3-triazole), 154.43 (C_6), 141.65 (C_5-triazole), 139.83 (C_9), 139.28 (C_{12}), 129.22 ($C_{8,10}$), 128.75 ($C_{13,17}$), 127.28 (C_{15}), 126.40 ($C_{14,16}$), 123.46 ($C_{7,11}$), 44.54 (SO_2CH_3), 28.26 (SCH_2), 21.43 (C_{15}-CH_3), 14.60 (CH_3).
2i	8.15 (d, J=8.8 Hz, 2H, $H_{13,17}$), 8.12 (d, J=8.4 Hz, 2H, $H_{8,10}$), 7.95 (d, J=8.4 Hz, 2H, $H_{7,11}$), 6.96 (d, J=8.8 Hz, 2H, $H_{14,16}$), 3.86 (s, 3H, OCH_3), 3.09 (s, 3H, SO_2CH_3), 2.83 (s, 3H, SCH_3).	162.25 (C_3-triazole), 160.93(C_{15}), 154.82 (C_6), 141.71 (C_5-triazole), 139.22 (C_9), 128.80 ($C_{13,17}$), 128.02 ($C_{8,10}$), 123.23 ($C_{7,11}$), 122.77 (C_{12}), 113.99 ($C_{14,16}$), 55.32(OCH_3), 44.57 (SO_2CH_3), 16.06(SCH_3).
2j	8.12(d, J=8.8 Hz, 2H, $H_{13,17}$), 8.09(d, J=8.4 Hz, 2H, $H_{8,10}$), 7.95(d, J=8.4 Hz, 2H, $H_{7,11}$), 6.99(d, J=8.8 Hz, 2H, $H_{14,16}$), 3.89(s, 3H, OCH_3), 3.45(q, J= 7 Hz, 2H, SCH_2), 3.10 (s, 3H, $SO2CH_3$), 1.48(t, J=7 Hz, 3H, CH_3).	162.19 (C_3-triazole), 160.82(C_{15}), 154.89 (C_6), 141.69 (C_5-triazole), 139.27 (C_9), 128.86 ($C_{13,17}$), 128.12 ($C_{8,10}$), 123.28 ($C_{7,11}$), 122.70 (C_{12}), 113.95 ($C_{14,16}$), 55.37(OCH3), 44.62 (SO_2CH_3), 28.26 (SCH_2), 16.10 (CH_3).

via direct arylation and alkylation [9,10]. Amino group at C_5 as expected oriented the alkylation or arylation to N_1. Our result showed that the presence of an aryl group instead of an amino group in C_5 changed the orientation of arylation from N_1 to N_2 (Scheme 1). Apparently, the aryl group at C_5 because of its hindrance oriented the next aryl group to the N_2 position. Therefore, Scheme 1 could be used for the preparation of 1,3-diaryl-1,2,4-triazoles.

EXPERIMENTAL

Melting points were determined on a Reichert hot stage apparatus and are uncorrected. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Utility plus 400 spectrometer (400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR) using chloroform-d_1 and DMSO-d_6 as solvent. Chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Infrared spectra were recorded on a Nicolet Magna FT-IR 550 spectrometer. Elemental analyses were carried out with a Perkin-Elmer Model 240-C apparatus (Perkin Elmer, Norwalk, CT, USA). The results of the elemental analyses (C, H, N) were within ± 0.4% of the calculated amounts. The analytical data of compounds **6-9** and **3a** are summarized in Table 2.

General Procedure for Arylation of 3-Alkylthio-5-(4-substituted-phenyl)-1*H*-1,2,4-triazoles.

To a solution of 3-alkylthio-5-(4-substituted phenyl)-1,2,4-triazole [13,14] (6.9 mmol) in DMSO (10 ml) was added sodium hydride (168 mg, 6.9 mmol). After 20 min of stirring at room temperature, 4-fluorophenyl methyl sulfone (1.2 g, 6.9 mmol) was added. The reaction mixture was heated at 120-130 °C for 20 h, cooled to room temperature, and poured onto ice. The residue was filtered and the crude yellowish solid was chromatographed (silica gel, chloroform-methanol 20:1 v/v). The fast moving fraction gave compound **3** (only **3a** was separated and crystallized from ethanol, yield 3 %). The slow moving fraction was crystallized from ethanol to give compounds **2a-j** (see Tables 1 and 3).

1-[4-(Methylsulfonyl)phenyl]-3-(methylthio)-5-phenyl-1*H*-1,2,4-triazole (**3a**).

This compound has mp 184-186 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68 (s, 3H, SCH_3), 3.09 (s, 3H, SO_2CH_3), 7.46 (m, 5H, phenyl), 7.57 (d, 2H, $H_{7,11}$), 7.97 (d, 2H, $H_{8,10}$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.06 (C_3-triazole), 155.36 (C_6), 142.01 (C_5-triazole), 140.02 (C_9), 130.80 (C_{15}), 130.20 (C_{12}), 128.98 ($C_{8,10}$), 128.43 ($C_{13,17}$), 128.75 ($C_{14,16}$), 125.53 ($C_{7,11}$), 44.46 (SO_2CH_3), 14.33 (SCH_3) ppm.

N-(4-Methylsulfonylphenyl)benzamide (**6**).

To a solution of 4-methylsulfonylaniline (300 mg, 1.75 mmol) in THF (20 ml) was added dropwise benzoyl chloride (250 mg, 1.78 mmol) dissolved in THF (5 ml) under N_2 at 0 °C followed by addition of triethylamine (0.25 ml, 1.8 mmol). The reaction mixture was stirred for 18 h at 24 °C, filtered to remove Et_3N•HCl, concentrated and recrystallized from methanol to give 450 mg (95%) of **6**, mp: 178-180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-6.7 (m, 9H, aromatic), 3.05 (s, 3H, SO_2CH_3) ppm; IR (KBr): ν = 3319 (NH), 1665 (CO) cm^{-1}. The spectral data were similar with those reported [15].

N-(4-Methylsulfonylphenyl)benzene Carbohydrazonamide (**7**).

Compound **6** (500 mg, 1.8 mmol) was dissolved in benzene (10 ml) under N_2, and phosphorus pentachloride (416 mg, 2 mmol) was added. The solution was heated at reflux for 3 h. It was concentrated to remove $POCl_3$, the residue was taken up in THF (15 ml) and added dropwis into a stirred THF (9 ml) solution of anhydrous hydrazine (0.6 ml) at 0 °C under N_2. The reaction mixture was stirred for 1 h at room temperature and poured into water (20 ml) and extracted with ethyl acetate. The organic phase was washed with brine and dried (Na_2SO_4) to give 470 mg (90%) of **7** mp: 205-207 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.61 (m, 4H, aromatic), 7.31 (m, 3H, aromatic), 6.72 (d, J=7.5 Hz, 2H, aromatic), 2.98 (s, 3H, SO_2CH_3) ppm; IR (KBr): ν = 3432 (NH), 3360 & 3278 (NH_2), 1558 (C=N) cm^{-1}.

4-(4-Methylsulfonylphenyl)-3-phenyl-1,4-dihydro-5*H*1,2,4-triazol-5-thione (**8**).

Compound **7** (500 mg, 1.73 mmol) was dissolved in THF (100 ml) under N_2, and 1,1'-thiocarbonyldiimidazole (340 mg, 2 mmol) was added. The solution was stirred for 18 h at room temperature. The solvent was removed under reduced pressure. The residue was taken up in ethyl acetate and washed with 0.1 *N* HCl solution, water and brine prior to drying (Na_2SO_4). The solvent was evaporated and the residue was recrystallized from acetonitrile to give 320 mg (52%) of **8**; mp 240-242 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.05 (d, J=7.8 Hz, 2H, $H_{8,10}$), 7.56 (d, J=7.8 Hz, 2H, $H_{7,11}$), 7.30 (m, 5H, phenyl), 3.14 (s, 3H, SO_2CH_3) ppm; IR (KBr): ν = 3104 (NH) cm^{-1}.

4-(4-Methylsulfonylphenyl)-3-methylthio-5-phenyl-4*H*-1,2,4-triazole (**9**).

To a solution of compound **8** (330 mg, 1 mmol) and ethanol (5 ml) methyl iodide (0.2 ml) and 10 % sodium hydroxide solution (1 ml) were added. The mixture was stirred overnight. It was diluted with water (10 ml). The precipitate was filtered and crystallized from n-butanol to give 310 mg (90 %) of **9** mp, 208-210 °C; ^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6/1:1): δ = 8.08 (d, J=7.8 Hz, 2H, $H_{8,10}$), 7.51 (d, J= 7.8 Hz, 2H, $H_{7,11}$), 7.27 (m, 5H, phenyl), 3.09 (s, 3H, SO_2CH_3), 2.75 (s, 3H, SCH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$+DMSO-d_6): δ = 154.63 (C_6), 152.93 (C_5-triazole), 141.58 (C_3-triazole), 138.44 (C_9), 129.87 (C_{15}), 128.96 ($C_{8,10}$), 128.56 ($C_{13,17}$), 128.07 ($C_{14,16}$), 128.06 ($C_{7,11}$), 125.86 (C_{12}), 44.12 (SO_2CH_3), 14.85 (SCH_3) ppm.

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REFERENCES AND NOTES

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[1] Partially presented in Colloquium Spectroscopicum International XXXIII, Granada, Spain, 7-12 September, P. 27 (2003)

[2] N. D. Heindel and J. R. Reid, *J. Heterocyclic Chem.*, **17**, 19087 (1980).

[3] B. S. Holla, B. Kalluraya, K. R. Srinhar, E. Drake, L. M. Thomas, K. K. Bhandary and M. J. Levine, *Eur. J. Med. Chem.*, **29**, 301 (1994).

[4] M. A. Ghannoum, N. F. Eweiss, A. Bahajaj and M. A. Qureshi, *Microbios*, **37**, 151 (1983).

[5] S. Demirayak, K. Benkli and K. Guven, *Eur. J. Med. Chem.*, **35**, 1037 (2000).

[6] B. D. Alexander, *Perfect Drugs*, **54**, 657 (1997).

[7] P. Trinka and J. Reiter, *J. Heterocyclic Chem.*, **32**, 3302 (1995).

[8] J. Reiter, T. Sormorai, P. Dvortsak and G. Bujtas, *J. Heterocyclic Chem.*, **22**, 385 (1985).

[9] J. L. Romine, S. W. Martin, V. K. Gribkoff, C. G. Boissard, S. L. Dworetzky, J. Natale, Y. Li, N. A. Meanwell and J. E. Starrett, *J. Med. Chem.*, **45**, 2942 (2002).

[10] J. Elguero, C. Marzin and D. Roberts, *J. Org. Chem.*, **39**, 357 (1974).

[11] S. Gelin, R. Gelin and D. Hartmann, *J. Org. Chem.*, **43**, 2665 (1978).

[12] A. N. Nesmeyanov, E. B. Zavelovich, V. N. Babin, N. S. Kochetkova and E. I. Fedin, *Tetrahedron*, **31**, 1463 (1975).

[13] M. H. Shah, Y. Mhasalkar, V. M. Palki, C. V. Deliwala and U. K. Shett, *J. Pharm. Sci.*, **58**, 1398 (1969).

[14] A. Shafiee, E. Naimi, P. Mansobi, A. R. Foroumadi and M. Shekari, *J. Heterocyclic Chem.*, **32**, 1235 (1995).

[15] A. Heesing, W. K. Homann and W. Mullers, *Chem. Ber.*, **113**, 152 (1980).