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Arylation of the readily available 3-alkylthio-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.

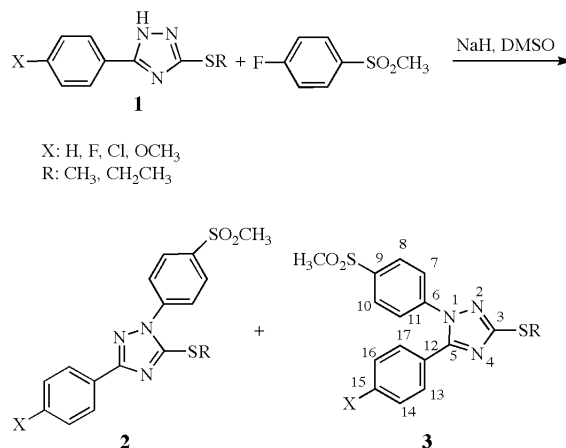
Moreover, many infections due to *Candida* spp are actually refractory to antifungal therapy. While these new classes of compounds are now frequently used in treatment of fungal infections, resistance of these drugs is rising, which clearly indicates an urgent need for new antifungal agents [6]. To overcome 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 diaryl triazole 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).

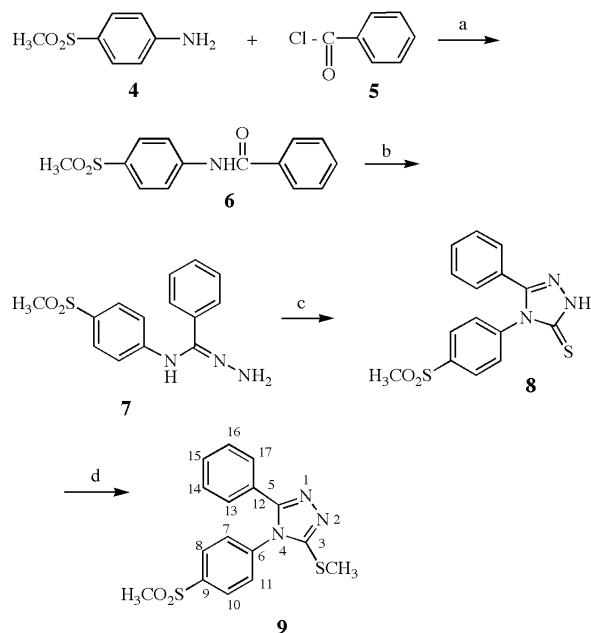
The differentiation between the structure **3a**, **2a** and **9** was possible on the basis of a D-NOE experiment. Irradiation of the methylthio group of **3a** (Figure 1) did not result in an enhancement of any of the aromatic hydrogen signals, therefore the 4-methylsulfonylphenyl moiety is in position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

Scheme 1



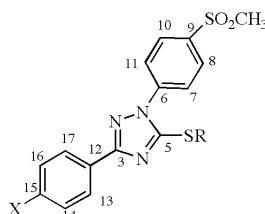
Arylation of 3-thioalkyl-5-aryl-1,2,4-triazole.

Scheme 2



Preparation of 4,5-diaryl-3-thiomethyl-1,2,4-triazole. a) Et₃N, 18 h, r.t., b) PCl₅, 3 h, reflux then dry NH₂NH₂, 1 h, r.t., c) 1,1'-thiocarbonyldiimidazole, 18 h, r.t., d) CH₃I, NaOH, 12 h, r.t.

Table 1
Analytical Data of Compounds **2a-j**



Comp. No.	X	R	M.p.(°C)	Yield (%)	Molecular Formula	Analysis %		
						C	H	N
2a	H	CH ₃	163-164	21	C ₁₆ H ₁₅ N ₃ O ₂ S ₂	55.63/55.42	4.37/4.60	12.16/11.89
2b	H	C ₂ H ₅	132-133	24	C ₁₇ H ₁₇ N ₃ O ₂ S 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 ₃ O ₂ S ₂	52.88/52.60	3.88/4.05	11.56/11.47
2d	F	C ₂ H ₅	140-142	33	C ₁₇ H ₁₆ FN ₃ O ₂ S 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 ₃ O ₂ S ₂	50.58/50.69	3.71/3.49	11.06/11.29
2f	Cl	C ₂ H ₅	123-124	25	C ₁₇ H ₁₆ ClN ₃ O ₂ S 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 ₃ O ₂ S ₂	56.80/56.99	4.77/4.69	11.69/11.91
2h	CH ₃	C ₂ H ₅	135-137	21	C ₁₈ H ₁₉ N ₃ O ₂ S 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 ₃ O ₃ S ₂	54.38/54.40	4.56/4.69	11.19/10.98
2j	OCH ₃	C ₂ H ₅	137-139	33	C ₁₈ H ₁₉ N ₃ O ₃ S 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 %		
				C	H	N
6	178-180	95	C ₁₄ H ₁₃ NO ₃ S	61.07/61.22	4.76/4.60	5.09/5.29
7	205-207	90	C ₁₄ H ₁₅ N ₃ O ₂ S	58.11/58.29	5.22/5.46	14.52/14.58
8	240-242	52	C ₁₅ H ₁₃ N ₃ O ₂ S ₂	54.36/54.45	3.95/3.77	12.68/12.21
9	208-210	90	C ₁₆ H ₁₅ N ₃ O ₂ S ₂	55.63/55.97	4.37/4.39	12.16/12.47
3a	184-186	3	C ₁₆ H ₁₅ N ₃ O ₂ S 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 ¹³C-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 deshielded 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].

In compound **3a** (Figure 1), C₃ is situated between two pyridine-like nitrogen atoms, therefore its chemical shift is higher than C₅, 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 C₅ and C₃ 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.

N₁-Aryl and N₁-alkyl regioisomers for 5-amino-3-thiomethyl 1,2,4-triazole were reported as main product

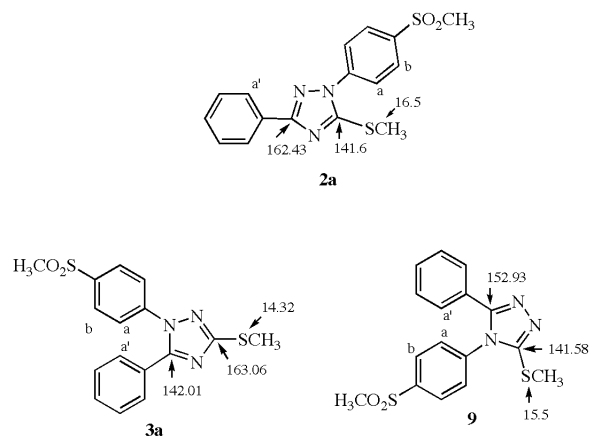


Table 3
¹H and ¹³C-NMR of Compounds **2a-2j**

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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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 ₂ CH 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, SO ₂ CH 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 (OCH ₃), 44.62 (SO ₂ CH ₃), 28.26 (SCH ₂), 16.10 (CH ₃).

via direct arylation and alkylation [9,10]. Amino group at C₅ as expected oriented the alkylation or arylation to N₁. Our result showed that the presence of an aryl group instead of an amino group in C₅ changed the orientation of arylation from N₁ to N₂ (Scheme 1). Apparently, the aryl group at C₅ because of its hindrance oriented the next aryl group to the N₂ 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. ¹H and ¹³C-NMR spectra were recorded on a Varian Utility plus 400 spectrometer (400 MHz for ¹H-NMR and 100 MHz for ¹³C-NMR) using chloroform-d₁ and DMSO-d₆ 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)-1H-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, ¹H NMR (400 MHz, CDCl₃): δ = 2.68 (s, 3H, SCH₃), 3.09 (s, 3H, SO₂CH₃), 7.46 (m, 5H, phenyl), 7.57 (d, 2H, H_{7,11}), 7.97 (d, 2H, H_{8,10}) ppm; ¹³C NMR (100 MHz, CDCl₃): δ = 163.06 (C₃-triazole), 155.36 (C₆), 142.01 (C₅-triazole), 140.02 (C₉), 130.80 (C₁₅), 130.20 (C₁₂), 128.98 (C_{8,10}), 128.43 (C_{13,17}), 128.75 (C_{14,16}), 125.53 (C_{7,11}), 44.46 (SO₂CH₃), 14.33 (SCH₃) 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 N₂ 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 Et₃N•HCl, concentrated and recrystallized from methanol to give 450 mg (95%) of **6**, mp: 178-180 °C; ¹H NMR (400 MHz, CDCl₃): δ = 7.96-6.7 (m, 9H, aromatic), 3.05 (s, 3H, SO₂CH₃) 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 N₂, and phosphorus pentachloride (416 mg, 2 mmol) was added. The solution was heated at reflux for 3 h. It was concentrated to remove POCl₃, the residue was taken up in THF (15 ml) and added dropwise into a stirred THF (9 ml) solution of anhydrous hydrazine (0.6 ml) at 0 °C under N₂. 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 (Na₂SO₄) to give 470 mg (90%) of **7** mp: 205-207 °C; ¹H 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, SO₂CH₃) ppm; IR (KBr): ν = 3432 (NH), 3360 & 3278 (NH₂), 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 N₂, 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 (Na₂SO₄). The solvent was evaporated and the residue was recrystallized from acetonitrile to give 320 mg (52%) of **8**; mp 240-242 °C; ¹H 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, SO₂CH₃) 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; ¹H NMR (400 MHz, CDCl₃+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, SO₂CH₃), 2.75 (s, 3H, SCH₃) ppm; ¹³C NMR (100 MHz, CDCl₃+DMSO-*d*₆): δ = 154.63 (C₆), 152.93 (C₅-triazole), 141.58 (C₃-triazole), 138.44 (C₉), 129.87 (C₁₅), 128.96 (C_{8,10}), 128.56 (C_{13,17}), 128.07 (C_{14,16}), 128.06 (C_{7,11}), 125.86 (C₁₂), 44.12 (SO₂CH₃), 14.85 (SCH₃) ppm.

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