Synthesis of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles

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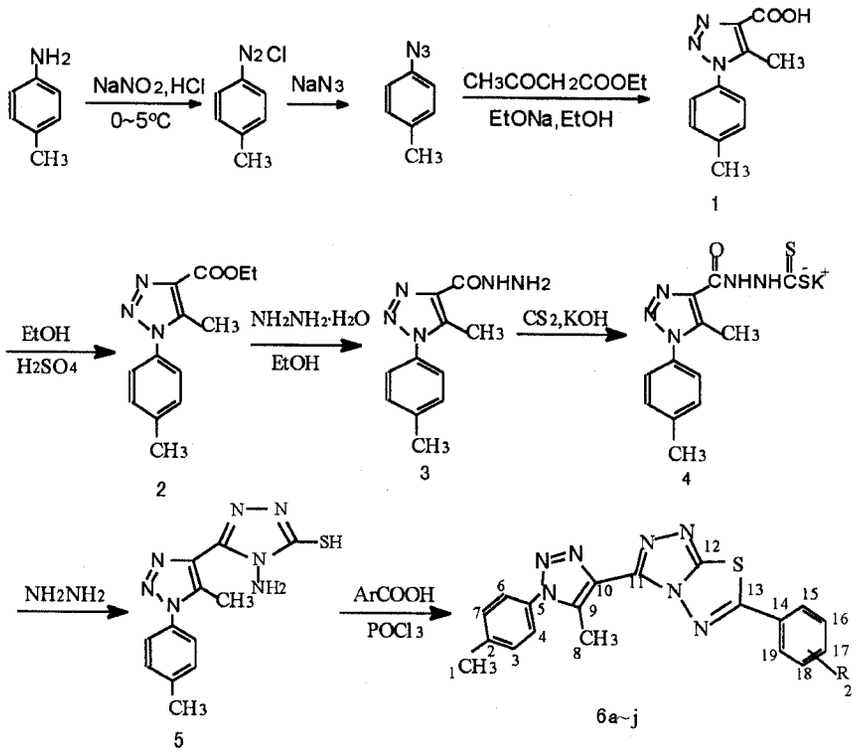
Several 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-1,3,4-triazolo[3,4-b]-1,3,4-thiadiazoles have been synthesized and the structures of these compounds were established by elemental analysis, MS, IR and ^{1}H NMR spectral data.

INTRODUCTION

In various publications it was found that the 1,3,4-triazole nucleus possesses fungicidal,[1] insecticidal,[2] antimicrobial,[3] bactericidal[4] properties, and the 1,2,3-triazole nucleus possesses antibacterial,[5] antifungal,[6] antiviral,[7] anti-inflammatory and analgesic[8] properties. Recently some new 1,3,4-triazole derivatives have been reported as possible anticonvulsants,[9] antidepressants, and plant growth regulators[10] and 1,2,3-triazole derivatives have been reported as inhibiting tumor proliferation, invasion, and metastasis.[11] Likewise, the 1,3,4-thiadiazole nucleus which incorporates an N-C-S linkage exhibits a large number of biological activities.[12] The fused 1,3,4-triazolo[3,4-b]-1,3,4-thiadiazoles derivatives show various biological effects, such as antifungal,[13] antibacterial, hypotensive and CNS depressant activities.[14] A triazolo-thiadiazole system may be viewed as a cyclic analogue of two very important components: thiosemicarbazide and biguanide, which often display diverse biological activities. We also demonstrated that 6-aryl-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles can study their properties.



The title compounds were prepared according to the following method.

RESULTS AND DISCUSSION

The novel 6-aryl-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles (**6a-j**) have been synthesized by the condensation of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-4-amino-5-mercapto-*s*-triazole (**5**) with various aromatic carboxylic acids in the presence of phosphorus oxychloride. The structures of these compounds were characterized with MS, IR, ^{1}H and ^{13}C NMR spectroscopy and the results are given in Tables 2, 3 and 4. The IR spectra data of compound (**5**) characteristic bands at 3167, 3270 and 2578 cm^{-1} could be found. These bands could be assigned to NH_2 and SH. After cyclization, the characteristic band of SH disappeared in compounds **6a-j** and the characteristic band of $\nu_{c\text{-}s\text{-}c}$ was exhibitive at 690 cm^{-1}. It demonstrated that the *s*-triazolo[3,4-b]-1,3,4-thiadiazole nucleus was a stronger electron acceptor. The vibration bands of N-N=C and N-N=N were in the region of 1250-1290 cm^{-1} and C=N was in the region of 1590-1680 cm^{-1}. These data were very similar to previous reports.[15]

Table 1. Structures, Yields and Melting Points of the Compounds **6a-j**

Compound	Ar	Yield(%)	M.p.(°C)
3		91	177-178
5		71	189-190
6a	C_6H_5	63	207-208
6b	p-BrC_6H_4	66	251-252
6c	p-FC_6H_4	69	242-243
6d	m-FC_6H_4	68	179-180
6e	o-FC_6H_4	51	200-201
6f	o-$MeOC_6H_4$	60	258-259
6g	o-BrC_6H_4	60	219-220
6h	m-BrC_6H_4	80	214-215
6i	o-MeC_6H_4	75	193-194
6j	o-ClC_6H_4	54	198-199

Satisfactory microanalyses were obtained for all the compounds.

Comparing the ^{1}H NMR spectra of **5** with **6**, we found that after cyclization the evident change is that the signals of amino protons are at δ5.6 ppm and the mercapto proton is at δ13.92 ppm. The chemical shifts of the triazole methyl group show in the range of δ2.30-2.51 ppm, while the aromatic protons resonate are at δ7.15-7.85 ppm. The ^{13}C NMR spectra exhibit characteristic signals for C-9 and C-10 of the triazole

Table 2. IR and ^{1}H NMR Spectral Data for Compounds **6a-j**

Compound[a]	IR(cm^{-1}) (KBr disc)	^{1}H NMR($CDCl_3$-*d*) δ (ppm)
3	3380,3100-3200,1680, 1620	7.34 (s, 4H, Ar1), 4.80 (broad peak, 3H, N-H), 2.599 (s, 3H, $ArCH_3$), 2.46 (s, 3H, CH_3)
5	3290,2920,1625,1565,1485	7.40 (s, 4H, Ar1), 3.6-4.4 (broad, 2H, N-H), 13.46 (s, 1H, SH), 2.57 (s, 3H, $ArCH_3$), 2.50 (s, 3H, CH_3)
6a	2919-3029,1608,1253,711	7.44 (s, 4H, Ar_1), 7.56-8.08 (m, 5H, Ph), 2.51 (s, 3H, CH_3), 2.76 (s, 3H, $ArCH_3$)
6b	2916-3055,1606,1259,710	7.44 (s, 4H, Ar_1), 7.28-8.21 (m, 4H, Ar_2), 2.51 (s, 3H, CH_3), 2.75 (s, 3H, $ArCH_3$)
6c	2921-3045,1610,1268,713	7.43 (s, 4H, Ar_1), 7.15-8.14 (m, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.75 (s, 3H, $ArCH_3$)
6d	2925-3035,1608,1269,712	7.44 (s, 4H, Ar_1), 7.28-7.85 (m, 4H, Ar_2), 2.51 (s, 3H, CH_3), 2.75 (s, 3H, $ArCH_3$)
6e	2923-3023,1611,1249,712	7.43 (s, 4H, Ar_1), 7.17-8.50 (m, 4H, Ar_2), 2.49(s, 3H, CH_3), 2.76 (s, 3H, $ArCH_3$)
6f	2925-3040,1599,1257,711	7.43 (s, 4H, Ar_1), 7.06-8.52 (m, 4H, Ar_2), 4.09 (s, 3H, OCH_3), 2.50 (s, 3H, CH_3), 2.74 (s, 3H, $ArCH_3$)
6g	2917-3063,1615,1270,711	7.43 (s, 4H, Ar_1), 7.28-8.21 (m, 4H, Ar_2), 2.51(s, 3H, CH_3), 2.76 (s, 3H, $ArCH_3$)
6h	2911-3067,1613,1272,710	7.44 (s, 4H, Ar_1), 7.28-8.21 (m, 4H, Ar_2), 2.51(s, 3H, CH_3), 2.76 (s, 3H, $ArCH_3$)
6i	2916-3023,1612,1268,711	7.42 (s, 4H, Ar_1), 7.28-7.70 (m, 4H, Ar_2), 2.49(s, 3H, CH_3), 2.71 (s, 3H, Ar_2CH_3), 2.76 (s, 3H, $ArCH_3$)
6j	2921-3047,1614,1273,713	7.43 (s, 4H, Ar_1), 7.48-8.30 (m, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.76 (s, 3H, $ArCH_3$)

Table 3. ^{13}C NMR Spectral Data for Compounds

No:[a]	C-1/C-11	C-2/C-12	C-3/C-13	C-4/C-14	C-5/C-15	C-6/C-16	C-7/C-17	C-8/C-18	C-9/C-19	C-10/C-20
3	21.19	140.25	130.15	124.98	132.96	124.98	130.15	9.59	137.10	136.78
	162.09									
5	20.72	139.82	130.13	125.01	131.83	125.01	130.13	9.43	135.32	132.88
	165.55	143.14								
6a	21.22	140.18	130.18	124.98	132.74	124.98	130.18	10.13	134.49	133.25
	166.99	141.11	154.09	132.74	127.49	129.30	130.18	129.30	127.49	
6b	21.24	140.25	130.21	124.98	132.65	124.98	130.21	10.12	134.60	133.21
	165.86	141.18	153.91	134.60	128.78	132.65	127.56	132.65	127.78	
6c	21.21	140.20	130.18	124.97	132.75	124.97	130.18	10.11	134.51	133.20
	165.66	141.11	154.00	125.59	129.73	116.68	165.29	116.68	129.73	
					($^3J_{F-C}$=8.8Hz)	(^{2}J=22.6Hz)	(^{1}J=255.4Hz)	(^{2}J=22.6Hz)	($^3J_{F-C}$=8.8Hz)	
6d	21.19	140.19	130.17	124.94	132.65	124.94	130.17	10.10	134.54	133.18
	165.47	141.19	153.65	131.09	114.38	163.18	119.76	131.09	123.29	
				(^{3}J=8.1Hz)	(^{2}J=24.1Hz)	(^{1}J=249.5Hz)	(^{2}J=21.1Hz)	(^{3}J=8.1Hz)		
6e	21.12	140.07	130.08	124.85	132.75	124.85	130.08	10.04	134.24	133.11
	161.57	140.75	155.04	117.78	159.07	111.61	133.64	121.37	129.05	
				(^{2}J=9.9Hz)	(^{1}J=258.3Hz)	(^{2}J=21.8Hz)	(^{3}J=8.9Hz)			
6f	21.18	140.20	130.13	124.92	133.11	124.92	130.13	10.10	134.24	133.66
	162.71	140.06	157.14	117.77	153.29	111.61	133.64	121.37	129.05	55.89
6g	21.26	140.25	130.02	125.04	132.34	125.04	130.02	10.20	134.23	133.26
	169.44	140.98	155.17	134.22	122.25	134.23	133.10	132.34	127.98	
6h	21.22	140.22	130.19	124.95	132.68	124.95	130.19	10.13	134.58	133.18
	165.27	141.20	153.68	134.17	117.28	116.53	134.08	129.26	125.01	
6i	21.22	140.15	130.17	124.96	132.91	124.96	130.17	10.15	134.38	133.26
	166.72	141.04	154.34	138.06	128.54	131.73	131.88	130.11	126.48	21.48

[a] All spectra were recorded at 297K.

ring are at δ134.23-134.60 and 133.15-133.26 ppm and C-11, C-12 and C-13 of the fused ring are at δ161.57-166.99, 140.06-141.20 and 153.65-157.14 ppm, respectively.

There is no systematic study on the fragmentation rules of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-1,3,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives in the literature. We investigated the MS spectra of the compounds **6a-j**. The results are shown in Table 4. Compounds **6a-j** had weak molecular ion peaks (their relative intensities were about 3-6%), but their base peaks were 91(except for 4-methylphenyl). But when analyzing the fragments of the subsequent cleavage of the molecular ions, we found that the MS spectra of **6a-j** exhibited some important ion peaks at *m/z* 242 (8-24%), 213 (45-70%), and 170 (36-44%). Compound **6a** had *m/z* 77 (46%); **6b**, **6g**, **6h** had *m/z* 155 (18-19%); **6c-e** had *m/z* 95 (17-24%); **6f** had *m/z* 107 (22%); **6i** had *m/z* 91; and **6j** had *m/z* 111 (22%).

EXPERIMENTAL SECTION

All melting points were uncorrected and determined on an XT_4-100x microscopic melting point apparatus. IR spectra were obtained in KBr discs on a Shimadzu IR-435 spectrome-

Table 4. MS Spectral Data for Compounds **6a-j**

No	M^+	*m/z*(%)
6a	373(6)	342(52) 242(10) 213(59) 170(39) 169(69) 121(66) 103(28) 91(100) 77(46) 76(24) 65(85) 51(38)
6b	451(5)	423(63) 242(10) 213(57) 199(34) 181(18) 170(36) 169(68) 155(18) 91(100) 77(16) 65(87)
6c	391(3)	363(36) 242(11) 213(62) 170(44) 169(81) 139(63) 121(41) 95(24) 91(100) 65(99)
6d	391(11)	363(100) 242(15) 213(91) 170(48) 169(88) 139(61) 121(23) 95(21) 91(82) 65(58)
6e	391(13)	363(100) 242(14) 213(78) 170(43) 169(81) 139(66) 121(23) 95(17) 91(79) 65(58)
6f	403(12)	375(98) 242(12) 213(59) 170(43) 169(71) 151(36) 133(9) 107(22)103(10) 92(13) 91(100) 65(60)
6g	451(4)	423(36) 242(19) 213(91) 199(51) 181(19) 170(47) 169(87) 155(18) 91(100) 77(12) 65(65)
6h	451(4)	423(44) 242(18) 213(100) 199(48) 181(21) 170(50) 169(94) 155(19) 91(98) 77(10) 65(67)
6I	387(9)	359(63) 242(12) 213(61) 199(20) 181(9) 170(42) 169(65) 155(11) 91(100) 77(11) 65(62)
6j	407(6)	379(54) 242(24) 213(55) 199(21) 181(9) 170(36) 169(62) 155(45) 111(22) 91(92) 77(17) 65(84) 43(100)

ter. MS analyses were performed on a HP-5988A spectrometer (EI at 70eV). ^{1}H NMR spectra ($CDCl_3$) were recorded on a JEOL FX-90Q instrument with TMS as an internal standard. Elemental analyses were carried out on a Yanaco CHN Corder MT-3 analyzer.

Phosphorus oxychloride was redistilled (b.p. 105 °C). 5-Methyl-1-(4-methylphenyl)-1,2,3-triazol-4-carboxylic acid (**1**) was prepared by the following the methods in the literature.[16]

The esterification of 5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-carboxylic acid was achieved with absolute ethanol. In a 150 mL round bottomed flask was placed a mixture of (**1**) (21.7g, 0.10 mole), absolute ethanol 46g, 59 mL, 1.0 mole and concentrated sulfuric acid 6 ml and the mixture was refluxed gently for 10 hours, cooled to room temperature, and then refrigerated for 10-12 hours. A white solid was obtained and filtered; the solid was washed with absolute ethanol and recrystallized from absolute ethanol. The 81% yield of (**2**) was produced as a white crystalline solid (m.p. 130-132 °C).

5-Methyl-1-(4-methylphenyl)-1,2,3-triazol-4-carbonylhydrazine (**3**) was prepared using procedures in the literature.[17]

1-Amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-1,3,4-triazole (**5**) was prepared using methods in the literature.[18]

General procedure of preparation of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-aryl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole derivatives 6a-j

A mixture of 1-Amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-1,3,4-triazole (1 mmole), aryl carboxylic acid (1 mmole) and $POCl_3$ (5 mL) was refluxed for 6 hours. After removal of excess $POCl_3$, the mixture was cooled and residue was poured into ice water, basicified by adding potassium hydroxide and the resulting solid was filtered. The crude solid was recrystallized from ethanol to give the title compound.

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Key Words

s-Triazolo[3,4-b]-1,3,4-thiadiazoles; 1,2,3-Triazole; Synthesis.

REFERENCES

1. Hausach, C.; Sachse, B.; Buerstell, H. *Ger Offen*, 2,826,760 (*Chem Abstr*: **1980**, *92*, 181200h).
2. Tanka, G. *Japan Kokai*, 7,495,973 (*Chem Abstr*: **1975**, *82*, 156320h).
3. Griffin, A. D.; Sally, K. *EP* 119474 (*Chem Abstr*: **1986**, *106*, 98120).
4. Van Reet, G.; Heeres, J. *US Pat*, 4,160,838 (*Chem Abstr*: **1979**, *91*, 753612).
5. Zhang, Z. Y.; Liu, Y.; Yang, S. Y. *Pharmaceutica Sinica* **1991**, *26(11)*, 809.
6. Abdou, N. A.; Soliman, I. N.; Sier Abou, A. H. *Bull Facpharm* (Cairo Univ.) **1991**, *28(6)*, 29.
7. Srivatava, A. J.; Swarup, S.; Saxena, V. K. *J. Indian Chem. Soc.* **1991**, *68*, 103.
8. Cooper, K.; Steele, J. *EP* 329357 (*Chem Abstr*: **1990**, *112*, 76957).
9. Husain, M I.; Amir Mol, *J. Indian Chem. Soc.* **1986**, *63*, 317.
10. Raymond, E.; Raymond, S.; Alan, G. S. *GB* 2,175,301 (*Chem Abstr*: **1987**, *107*, 134310).
11. Kohn, E. C.; Liotta, L. A. *US* 637145 (*Chem Abstr*: **1991**, *115*, 248099).
12. Omar A Mohsen, M. E.; Aboul, W.; Omainma, M. *J. Heterocycl. Chem.*, **1986**, *23*, 1339.
13. Bano, Q.; Tiwari, N.; Giyi, S.; Nizamudolin, *Indian J. Chem.* **1992**, *31B*, 714.
14. Zhang, Z. Y.; Chen, X. *Chin. J. Chem.* **1992**, *10*, 59.
15. Mody, M. K.; Prasad, A. R.; Ramalingam, T.; Sattur, P. B. *J. Indian Chem. Soc.* **1982**, *59*, 769.
16. Khaclem, H. E. L.; Mansour, H. A. R.; Meshreki, M. H. *J. Chem. Soc(c)*. **1968**, 1329.
17. Yale, H. I., Losee, K.; Martin, J.; Hervy, H.; Pervy, F. M.; Bernstain, J. *J. Amer. Chem. Soc.* **1953**, *75*, 1933.
18. El-Barbary, A. A.; Fahmy, M.; El-Badawi, M.; El-Bremaly; El-Brollosi, N. R. *Revue Roumaine de Chimie* **1991**, *36(4-7)*, 619.