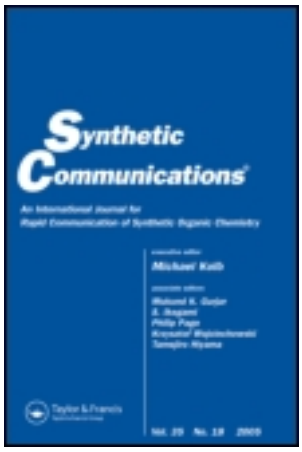

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SYNTHESIS OF 3-[5-METHYL-1-(4-METHYLPHENYL)-1,2,3-TRIAZOL-4-YL]-6-ARYL/HETEROARYL-SUBSTITUTED-S-TRIAZOLO- [3,4-b]-1,3,4-THIADIAZOLES

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SYNTHESIS OF 3-[5-METHYL-1-(4-METHYLPHENYL)-1,2,3-TRIAZOL-4-YL]-6-ARYL/HETEROARYL-SUBSTITUTED-*S*-TRIAZOLO-[3,4-b]-1,3,4-THIADIAZOLES

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ABSTRACT

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.

In recent years, fused heterocycles have been found to possess many unique properties in synthesis and pharmacology. Especially, *s*-triazolo[3,4-b]-1,3,4-thiadiazole derivatives have been attracting the attention of chemists and pharmacologists. Certain compounds having 1,3,4-triazole nucleus have been reported as fungicidal (1), insecticidal (2), antimicrobial (3), and bactericidal (4). Compounds

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with 1,2,3-triazole nucleus have been reported as antibacterial (5), antifungal (6), antiviral (7), anti-inflammatory, and analgesic (8). Recently, some new 1,3,4-triazole derivatives have been synthesized as possible anticonvulsants (9) and plant growth regulators (10), and 1,2,3-triazole derivatives have been synthesized to inhibit 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). 1,3,4-Triazolo[3,4-b]-1,3,4-thiadiazoles are fused heterocyclic derivatives showing various biological effects such as antifungal (13), antibacterial, hypotensive, and CNS depressant activities (14). For this reason, synthesis of several of the heterocyclic derivatives containing 1,2,3-triazole, 1,3,4-triazole, and 1,3,4-thiadiazole nuclei is very interesting because there has been no synthetic study on the title compounds of *s*-triazolo[3,4-b]-1,3,4-triazole containing a 1,2,3-triazole cycle in the literature up to now.

The title compounds were prepared according to the following method.

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and are uncorrected. Mass spectrum was performed on a HP-5988A spectrometer (EI at 70 eV). IR spectra were obtained in KBr discs using a Nicolet 170SX FT-IR spectrometer. ^{1}H NMR spectra were recorded at room temperature at 80.13 MHz on a Bruker FT-AC 80 instrument. 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 following methods in the literature (15) m.p. 182°–183°C (Lit. 182°–183°C) (16).

Esterification of 5-Methyl-1-(4-methylphenyl)-1,2,3-triazol-4-carboxylic Acid 1 with Absolute Ethanol

In a 150-mL flask, a mixture of 21.7 g (0.10 mol) of **1**, 46 g (59 mL, 1.0 mol) of absolute ethanol and 6 ml of concentrated sulfuric acid was refluxed gently for 10 h. The mixture was then cooled to room temperature, and refrigerated for 10–12 h. A white solid was obtained and filtered. The solid was washed with absolute ethanol and recrystallized from absolute ethanol. The yield of (**2**) (a white crystalline solid, m.p. 130–132°C) was 19.7 g (81%). ^{1}H NMR: δ 7.35 (s, 4H, Ar); 4.34–4.61 (q, 2H, J = 7.0 Hz, -OCH_2-); 2.58 (s, 3H, Ar-CH_3); 2.47 (s, 3H, -CH_3); 1.37–1.54 (t, 3H, J = 7.0 Hz, -CH_2CH_3).

5-Methyl-1-(4-methylphenyl)-1,2,3-triazol-4-carbonylhydrazine (**3**) was prepared from (**2**) following the procedure method in the literature (17).

A mixture of 0.1 mol of **2** and 0.15 mol (85% hydrazine hydrate) was refluxed in 200 mL of ethanol for 6 h. The ethanol, water, and excess hydrazine hydrate

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Table 1. Structures, Yields, Melting Points, and Elemental Analyses Data of 6-Aryl-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-*s*-triazolo[3,4-b]-1,3,4-thiadiazoles **6a–j**

Compound	Ar	Yield (%)	M.p. (°C)	Elemental Analyses (%) Calc (Found)		
				C	H	N
3		91	177–178	57.13 (57.45)	5.67 (5.59)	30.28 (30.52)
5		71	189–190	50.16 (50.39)	4.56 (4.52)	34.12 (34.38)
6a	o-ClC_6H_5	54	198–199	55.95 (56.40)	3.46 (3.36)	24.12 (24.51)
6b	m-ClC_6H_4	64	129–130	55.95 (56.34)	3.46 (3.41)	24.12 (24.48)
6c	p-ClC_6H_4	59	261–262	55.95 (56.22)	3.46 (3.44)	24.12 (24.31)
6d	m-$MeOC_6H_4$	58	220–221	59.54 (59.65)	4.25 (4.19)	24.30 (24.67)
6e	p-$MeOC_6H_4$	81	203–204	59.54 (59.76)	4.25 (4.15)	24.30 (24.75)
6f	m-MeC_6H_4	30	203–204	62.00 (62.45)	4.42 (4.39)	25.31 (25.58)
6g	p-MeC_6H_4	27	207–208	62.00 (62.33)	4.42 (4.37)	25.31 (25.63)
6h	α-$C_{10}H_7$	58	218–219	65.24 (65.41)	4.05 (3.98)	23.16 (23.54)
6i	5-methyl-1-(4-methylphenyl) -1,2,3-triazol-4-yl	64	248–249	58.96 (59.18)	4.30 (4.22)	29.89 (30.45)
6j	5-methyl-1-(4-chlorophenyl) -1,2,3-triazol-4-yl	68	255–256	54.04 (54.48)	3.50 (3.44)	28.65 (29.12)

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Table 2. IR Spectral Data of Compounds **6a–j**

	IR (cm^{-1}) (KBr disc)
3	3380, 3200, 3100, 1680, 1620
5	3290, 2920, 1625, 1565, 1485
6a	3047, 2921, 1614, 1578, 1518, 1446, 1378, 1273, 766, 713
6b	3062, 2920, 1616, 1570, 1518, 1457, 1378, 1277, 805, 720
6c	3025, 2922, 1614, 1592, 1517, 1457, 1373, 1266, 793, 713
6d	3040, 2932, 2836, 1606, 1578, 1516, 1463, 1375, 1268, 709
6e	3010, 2921, 1606, 1520, 1495, 1461, 1376, 1259, 710
6f	3022, 2923, 2857, 1612, 1520, 1454, 1371, 1253, 714
6g	3022, 2918, 1611, 1517, 1460, 1374, 1261, 710
6h	3042, 2904, 1613, 1515, 1449, 1378, 1269, 706
6i	3068, 2921, 2862, 1613, 1515, 1449, 1378, 1269, 719
6j	3068, 2922, 2857, 1611, 1519, 1463, 1381, 1269, 719

Table 3. ^{1}H NMR Spectral Data for Compounds[a]

Compound	^{1}H NMR ($CDCL_3$-*d*) δ (ppm), *J* (Hz)
3	7.34 (s, 4H, Ar_1), 4.80 (broad peak, 3H, N–H), 2.599 (s, 3H, $ArCH_3$), 2.46 (s, 3H, CH_3)
5	7.40 (s, 4H, Ar_1), 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	7.43 (s, 4H, Ar_1), 7.48–8.30 (m, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.76 (s, 3H, $ArCH_3$)
6b	7.44 (s, 4H, Ar_1), 7.49–8.06 (m, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.76 (s, 3H, $ArCH_3$)
6c	7.44 (s, 4H, Ar_1), 7.51–8.06 (q, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.75 (s, 3H, $ArCH_3$)
6d	7.43 (s, 4H, Ar_1), 7.06–7.53 (m, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.75 (s, 3H, $ArCH_3$), 3.93 (s, 3H, -OCH_3)
6e	7.44 (s, 4H, Ar_1), 7.00–8.04 (q, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.74 (s, 3H, $ArCH_3$), 3.93 (s, 3H, -OCH_3)
6f	7.44 (s, 4H, Ar_1), 7.47–7.87 (m, 4H, Ar_2), 2.50 (s, 3H, CH_3), 2.75 (s, 3H, Ar_1CH_3), 3.07 (s, 3H, Ar_2CH_3)
6g	7.43 (s, 4H, Ar_1), 7.28–7.91 (q, 4H, Ar_2), 2.49 (s, 3H, CH_3), 2.74 (s, 3H, Ar_1CH_3), 2.46 (s, 3H, Ar_2CH_3)
6h	7.44 (s, 4H, Ar_1), 7.28–8.89 (m, 7H, Ar_2), 2.51 (s, 3H, CH_3), 2.79 (s, 3H, $ArCH_3$)
6i	7.42 (s, 8H, Ar_1), 2.50 (s, 6H, CH_3), 2.77 (s, 3H, Ar_2CH_3), 2.80 (s, 3H, Ar_1, CH_3)
6j	7.43 (s, 4H, Ar_1), 7.44–7.71 (m, 4H, Ar_2), 2.51 (s, 3H, CH_3), 2.78 (s, 3H, Ar_2CH_3), 2.80 (s, 3H, Ar_1CH_3)

[a]All spectra were recorded at 297 K.

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

No	M^+	M/z (%)
6a	407(3)	379(27), 242(12), 213(55), 199(21), 181(9), 170(36), 169(62), 155(45), 111(22), 102(27), 91(92), 77(17), 65(84), 43(100)
6b	407(3)	379(40), 242(11), 213(70), 199(21), 181(11), 170(42), 169(77), 155(53), 137(22), 111(13), 102(31), 91(100), 77(13), 65(93), 43(10)
6c	407(5)	379(42), 242(10), 213(62), 199(23), 181(10), 170(36), 169(67), 155(57), 137(27), 111(19), 102(41), 91(100), 77(21), 65(81), 43(34)
6d	403(11)	375(100), 242(15), 213(80), 199(20), 170(46), 169(76), 151(50), 133(11), 107(4), 103(17), 92(10), 91(77), 77(16), 65(53)
6e	403(6)	375(51), 242(8), 213(45), 199(21), 170(38), 169(60), 151(79), 133(27), 107(4), 103(25), 92(11), 91(100), 77(19), 69(20), 65(85)
6f	387(11)	359(100), 242(15), 213(85), 199(20), 181(12), 170(46), 169(78), 155(11), 135(60), 117(15), 91(91), 77(12), 65(60)
6g	387(4)	359(50), 242(9), 213(44), 199(22), 181(8), 170(33), 169(54), 155(11), 135(52), 117(19), 91(100), 77(12), 65(79)
6h	423(15)	395(79), 242(15), 213(71), 199(29), 171(89), 170(58), 169(96), 153(63), 127(39), 91(100), 77(16), 65(74)
6i	468(3)	440(22), 242(3), 215(3), 213(23), 199(16), 181(6), 170(57), 169(75), 155(13), 91(100), 77(10), 65(70)
6j	488(1)	460(17), 242(6), 223(2), 213(49), 199(24), 181(12), 170(41), 169(73), 155(27), 111(63), 91(92), 77(15), 65(62), 44(100)

were removed in vacuo, and the residual solid recrystallized. It gave 21 g (91% yield) of product, m.p. 177°–178°C (other data shown in Tables 1–4).

1-Amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-1,3,4-triazole (**5**) was prepared from (**3**) via (**4**) following the method reported in the literature (18).

Carbon disulfide (0.14 mol) was added dropwise to an ice-cold solution of potassium hydroxide (0.15 mol) and 3-aryloxyacetic acid hydrazide (0.09 mol) in 150 mL absolute ethanol. The mixture was stirred at room temperature for 14 h. Dry ether (200 mL) was then added and the separated solid was filtered and washed with either (2 × 50 mL). The product (**4**) obtained in nearly quantitative yield was employed in the next reaction without further purification.

A suspension of (**4**) (about 0.08 mol) and hydrazine hydrate 85% (0.16 mol) in 50 mL of water was refluxed while stirring for 4 h. The color of the reaction mixture changed to green, hydrogen sulphide was evolved, and a homogeneous solution resulted. On dilution with 850 mL of cold water and acidification with concentrated HCl, a white solid was precipitated. The product was filtered, washed with water, and recrystallized from ethanol to give white flake of (**5**). It gave 18 g (71% yield) of product, m.p. 189°–190°C (see Tables 1–4).

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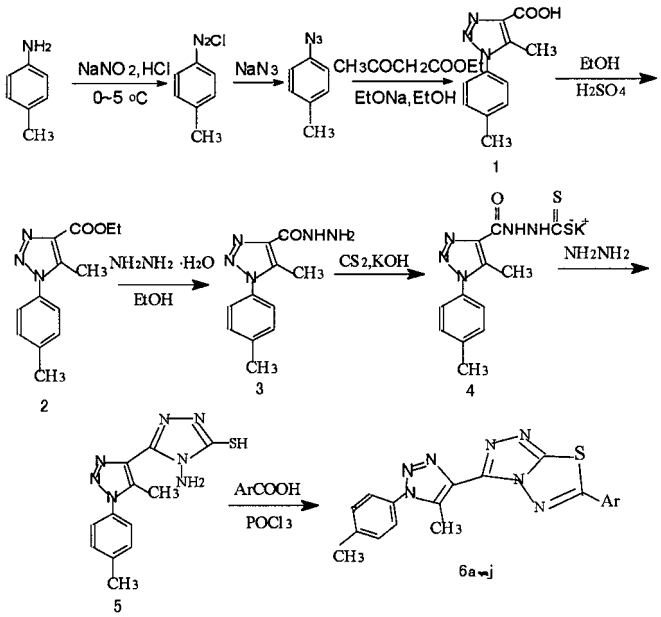
General Procedure of Preparation of 3-[5-Methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substitute-phenyl-*s*-triazolo[3,4-b]-1,3,4-thiadiazole Derivatives (6)

A mixture of 1-amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-1,3,4-triazole (**5**) (1 mmol), aromatic carboxylic acid (1 mmol) and $POCl_3$ (5 mL) was heated under reflux for 6 h. The cooled reaction mixture was poured into ice water and made alkaline by adding potassium hydroxide, then the resulting solid was filtered. It was recrystallized from ethanol to give the title compound (**6a**–**j**) (see Table 1).

RESULTS AND DISCUSSION

The novel 6-aryl-3-[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*-triazolo (**5**) with various aromatic carboxylic acids in the presence of phosphorus



Scheme 1.

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oxychloride. The structure of these compounds was characterized with ^{1}H NMR, IR, and MS spectroscopy, and results are given in Tables 1, 2, 3 and 4.

IR absorption peaks of **5** at 3270, 3167 and 2578 cm^{-1} are assigned to its NH_2 and SH groupings. When **5** converted **6**, the SH peak disappears but a new peak characteristic of $\nu_{c\text{-}s\text{-}c}$ appeared at 690 cm^{-1}. Like the allied system, compound **6** shows absorption peaks for N–N=C and N–N=N in the region of 1250–1290 cm^{-1} and for C=N in 1590–1680 cm^{-1}. In the mass spectra of **6**, the molecular ion peaks are very weak (relative intensities ~3–6%) and all the members of **6** exhibit some important ion peaks at m/z 242 (8–24%), 213 (45–70%), 170 (36–44%). Recently, we have established the crystal structure of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-(4-methylphenyl)-*s*-triazolo[3,4-b]-1,3,4-thiadiazole **6g** by x-ray diffraction (the manuscript will be submitted for revision). The crystal structure of **6g** agrees to the structure (Scheme 1).

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