Synthesis of Some 7*H*-*s*-Triazolo[3,4-b]-1,3,4-thiadiazine Derivatives

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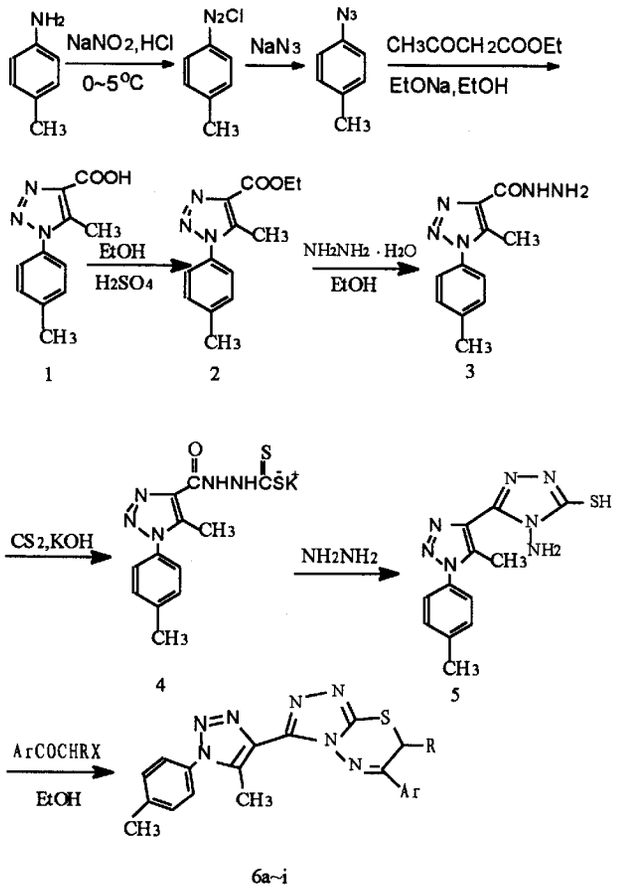
The cyclization of 1-amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-1,3,4-triazole with various α-haloketone in absolute ethanol yields 7*H*-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazines and their structures are established by elemental analysis, MS, IR and ^{1}H NMR spectral data.

INTRODUCTION

In continuation of previous research in the synthesis of pharmacologically active 7*H*-*s*-triazolo[3,4-b]-1,3,4-thiadiazine,[1] it is reported that a 1,3,4-triazole nucleus possesses fungicidal,[2] insecticidal,[3] antimicrobial,[4] bactericidal,[5] properties and a 1,2,3-triazole nucleus possesses antibacterial,[6] antifungal,[7] antiviral,[8] anti-inflammatory and analgesic[9] properties. Recently some new 1,3,4-triazole derivatives have been reported as possible anticonvulsants,[10] antidepressants, and plant growth regulators[11] and 1,2,3-triazole derivatives have been reported to inhibit tumor proliferation, invasion, and metastasis.[12] Likewise a 1,3,4-thiadiazole nucleus which incorporates an N-C-S linkage exhibits a large number of biological activities.[13] The fused 1,3,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives show various biological effects, such as antifungal,[14] antibacterial, hypotensive and CNS depressant activities.[15] 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. Therefore, it was planned to investigate a system which combines these three biologic components in a ring and to study their biological activities. Accordingly, we wish to report herein the synthesis of condensed 7*H*-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazine which possesses a chemically important nitrogen heterocyclic nucleus with a view to achieve better antimicrobial activity.

Scheme I



RESULTS AND DISCUSSION

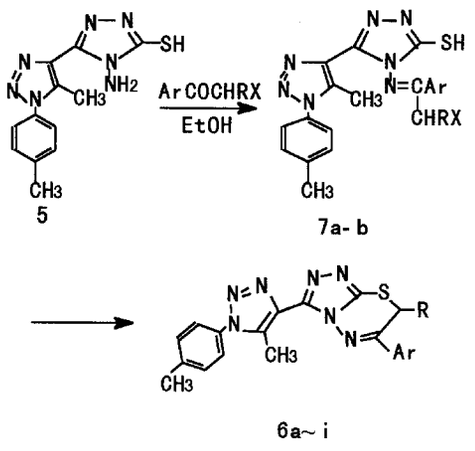
Refluxing the triazoles (**5**) in absolute ethanol with α-haloketone such as bromoacetone and phenacyl bromide followed by neutralisation with potassium carbonate afforded 7*H*-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-*s*-triazolo[3,4-b]-1,3,4-thiadiazines **6a-i** in 10-65% yields. The analytical and spectral data are in accordance with the structures assigned.

The IR spectra of these class of compounds were devoid of characteristic stretching frequencies of >C=N-groups. The

vibration bands of N-N=C and N-N=N were in the region 1206-1280cm^{-1} and 963-972 cm^{-1}, C=N was in the region 1590-1680 cm^{-1}. These data were very similar to previous reports.[16] The ^{1}H NMR spectra of **6a-i** revealed a singlet at δ 3.01-4.17 ppm due to -S-CH_2- groups, respectively. In the mass spectra the molecular ion is confirmed at 1-26%, but base peaks were at m/z 91, 65 or 44. All compounds had M-28 peaks. Satisfactory microanalyses were obtained for all the compounds. The spectral data of these compounds is given in Tables 2, 3 and 4.

We isolated two uncyclized products **7a** and **7b** when most of these reactions yield the cyclized products under neutral reaction conditions. We claim that the reaction mechanism is the following formation under the neutral reaction conditions.

Scheme II



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 spectrometer. 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**) were prepared by the method reported in the literature.[17]

The esterification of 5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-carboxylic acid (**1**) was achieved with absolute ethanol. In a 150-mL round bottomed flask was placed a mixture of (**1**) (21.7 g, 0.10 mol), absolute ethanol (46 g, 59-mL, 1.0 mol) 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). ^{1}H NMR: δ 7.35 (s, 4H, Ar); 4.34-4.61 (q, 2H, J = 7.0Hz, -OCH_2-); 2.58 (s, 3H, Ar-CH_3); 2.47 (s, 3H, -CH_3); 1.37-1.54 (t, 3H, J = 7.0Hz, -CH_2CH_3).

5-Methyl-1-(4-methylphenyl)-1,2,3-triazol-4-carbonyl hydrazine (**3**) was prepared from the procedure in the literature.[18]

A mixture of **2** (0.1 mol) and hydrazine hydrate (0.15 mol, 85%) in 200-mL of ethanol was refluxed for six hours. The ethanol, water and excess hydrazine hydrate were removed in vacuo, and the residual solid recrystallized. It gave 21 g. (91% yield) of product, m.p. 177-178 °C. IR: 3380, 3100-3200, 1680, 1620; ^{1}H NMR: 7.34 (s, 4H, Ar), 4.80 (broad peak, 3H, N-H), 2.59 (s, 3H, $ArCH_3$), 2.46 (s, 3H, CH_3).

1-Amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-1,3,4-triazole (**5**) was prepared by the method in the literature.[19]

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.

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

Compound	Ar	R	Yield(%)	M.p.(°C)	Compound	Ar	R	Yield(%)	M.p.(°C)
6a	H	H	40	194-195	**6g**	p-BrC_6H_4	H	63	276-277
6b	-$CH_2CH_2CH_2$-		65	229-230	**6h**	6-$MeOC_{10}H_7$-2-yl	H	10	154-155
6c	-$CH_2CH_2CH_2CH_2CH_2$-		65	207-208	**6i**	CH_3	H	6	89-90
6d	C_6H_5	H	41	256-257	**7a**	p-NO2C_6H_4C(Me)=N-		40	254-255
6e	p-MeC_6H_4	H	26	239-240	**7b**	6-$MeOC_{10}H_7C$(Et)=N-		56	167-168
6f	p-ClC_6H_4	H	53	245-246					

Satisfactory microanalyses were obtained for all the compounds.

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

Compound[a]	^{1}H NMR($CDCl_3$-*d*) δ (ppm)
6a	7.49(m,4H,p-MeC_6H_4), 7.76-7.87(t,1H,=CH-), 3.64-3.69(d,2H,-CH_2-S-), 2.65(s,3H,CH_3), 2.47(s,3H,$C_6H_4CH_3$)
6b	7.48(s,4H,p-MeC_6H_4), 3.83-4.03(t,1H,CH), 2.98-2.65(m,2H,-CH_2-), 2.65(s,3H,CH_3), 2.48(s,3H,$C_6H_4CH_3$), 1.98-2.04[m,6H,-$(CH_2)_3$-]
6c	7.39(m,4H,p-MeC_6H_4), 3.89-4.01(m,1H,CH), 2.89-3.01(m,2H,CH_2), 2.61(s,3H,CH_3), 2.48(s,3H,$C_6H_4CH_3$), 1.98-2.04[m,8H,-$(CH_2)_4$-]
6d	7.49-8.05(m,5H,Ph), 7.43(s,4H,p-MeC_6H_4), 4.04(s,2H,CH_2S), 2.68(s,3H,CH_3), 2.50(s,3H,$C_6H_4CH_3$), 2.44(s,3H,CH_3)
6e	7.28-7.93(q,4H,Ph), 7.42(s,4H,p-MeC_6H_4), 4.07(s,2H,CH_2S), 2.68(s,3H,CH_3), 2.49(s,3H,$C_6H_4CH_3$), 2.49(s,3H,$C_6H_4CH_3$)
6f	7.43-8.00(q,4H,Ph), 7.43(s,4H,p-MeC_6H_4), 4.04(s,2H,CH_2S), 2.70(s,3H,CH_3), 2.50(s,3H,$C_6H_4CH_3$)
6g	7.60-7.94(q,4H,Ph), 7.43(s,4H,p-MeC_6H_4), 4.04(s,2H,CH_2S), 2.69(s,3H,CH_3), 2.50(s,3H,$C_6H_4CH_3$)
6h	7.28-8.30(m,6H,Ar), 7.45(s,4H,p-MeC_6H_4), 4.19(s,2H,CH_2S), 4.10(s,3H,-OCH_3), 2.71(s,3H,CH_3), 2.51(s,3H,$C_6H_4CH_3$)
6i	7.41(s,4H,p-MeC_6H_4), 3.58(s,2H,CH_2S), 2.65(s,3H,CH_3), 2.49(s,3H,$C_6H_4CH_3$), 1.78(s,3H,CH_3)
7a	7.28-8.30(m,6H,Ar), 7.44(s,4H,p-MeC_6H_4), 4.51-4.78(q,1H,J=7.22Hz,CH), 4.08(s,3H,-OCH_3), 2.70(s,3H,CH_3), 2.50(s,3H,$C_6H_4CH_3$), 1.63-1.72(d,3H,J=7.22Hz,CH_3)
7b	7.41-8.03(m,6H,Ar), 7.44(s,4H,p-MeC_6H_4), 4.51-4.78(q,1H,J=7.22Hz,CH), 4.08(s,3H,-OCH_3), 2.70(s,3H,CH_3), 2.50(s,3H,$C_6H_4CH_3$), 1.63-1.72(d,3H,J=7.22Hz,CH_3)

Table 3. MS Spectral Data for Compounds **6a-i**

No	M$^+$	*m/z*(%)
6a	311(20)	283(8),257(8),256(45),228(10),227(9),223(10),213(4),198(6),196(13),195(45),181(14),172(4),171(16),170(41),169(68),144(17),143(21),128(17),116(12),114(10),102(11),91(98),77(18),65 (100),51(26)
6b	351(8)	323(15),290(9),269(22),244(9),213(11),199(11),196(3),195(4),181(11),172(6),171(26),170(51),169(68),156(15),144(15),143(13),128(12),116(10),114(6),102(9),91(91),77(14),65(100),51(24)
6c	365(10)	337(23),283(2),269(16),244(10),213(14),199(15),196(3),195(4),181(10),172(6),171(31),170(51),169(61),156(18),144(15),143(15),128(14),116(10),114(5),102(10),91(100),77(26),65(88),51(23)
6d	387(10)	359(24),256(26),228(14),227(10),223(11),213(7),198(7),196(14),195(54),181(11),172(3),171 (11),170(41),169(80),156(12),155(14),144(14),143(17),128(14),117(23),116(11),103(62),102(1),91(100),77(89),65(74),51(49)
6e	401(3)	373(8),256(10),255(8),244(5),243(6),228(99),227(5),223(5),213(7),199(11),196(8),195(25),181(9),172(3),171(9),170(31),169(40),156(10),144(10),143(11),131(16),128(9),118(16),117(30),116(19),115(30),102(9),91(100),77(13),65(63),51(14)
6f	421(1)	393(3),272(2),256(6),255(4),244(1),228(4),223(3),213(2),199(4),196(4),195(15),181(4),171(4),170(12),169(18),156(18),156(4),155(6),144(5),143(6),137(10),128(4),118(2),117(4),116(5),115 (5),111(11),102(11),97(10),91(35),77(8),75(12),65(22),51(10),44(100)
6g	465(2)	437(6),256(20),255(13),241(5),228(11),223(8),213(5),199(9),197(7),196(11),195(42),181(19),171(9),170(30),169(46),157(10),156(9),155(18),144(10),143(12),134(11),128(10),117(7),116 (10),115(10),102(45), 91(68),77(16),65(51),51(19),44(100)
6h	467(2)	439(5),261(3),256(4),255(3),244(2),198(8),182(3),171(5),170(7),169(10),157(5),156(4),155(6),144(4),143(5),139(5),128(5),118(4),117(5),116(5),15(7),111(5),102(4),97(9),91(20),77(8),65 (15),51(7),44(100)
6i	325(4)	297(6),256(17),255(7),241(3),228(6),227(5),223(5),213(2),195(20),181(7),171(6),170(18),169 (32),156(6),155(8),144(7),143(9),128(9),118(2),117(6),116(5),115(6),111(7),97(12),91(52),77 (12),65(41),51(13),44(100)
7a	561(1)	543(1),533(2),346(1),335(1),321(1),292(2),291(4),290(5),289(4),288(5),276(4),275(3),271(11),270(57),269(21),264(5),263(6),261(5),255(6),244(7),243(4),237(4),228(3),227(2),220(13),218 (12),213(5),196(11),195(6),181(10),171(12),170(32),169(40),156(9),155(8),153(18),152(16),144(11),143(14),139(10),128(11),127(6),117(6),116(6),115(9),113(12),91(51),77(11),65(40),51(11),44(100)

Dry ether (200-mL) was then added and the separated solid was filtered and washed with ether (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 refluxed while stirring for 4 h. The color of the reaction mixture changed to green, hydrogen sulphide was evolved, and a homogeneous

Table 4. IR Spectral Data for Compounds **6a-i**

No.	ν_{Ar-H}	ν_{R-H}	$\delta_{benzene\ ring}$	$\nu_{C=N}$	δ_{CH_3}	$\nu_{N-N=C}$	$\delta_{Ph\ CH}$	$\nu_{N-N=N}$	ν_{-S-H}
6a	3032	2922	1517,1451,1413	1603	1369	1206	1169,1114,1089,821	963	
6b	3039	2935	1518,1448,1420	1607	1369	1268	1097,1043 822	969	
6c	3039	2937	1519,1446	1606	1374	1265	1180,1114,1040,823	967	
6d	3054	2922	1518,1449	1601	1369	1262	1154,1114,1090,818	966	
6e	3041	2920	1518,1453	1598	1368	1267	1116,1090,1037,816	967	
6f	3034	2921	1519,1454,1416	1591	1369	1280	1172,1117,1092,817	966	
6g	3032	2919	1518,1456,1415	1584	1368	1278	1173,1117,1074,819	968	
6h	3034	2919	1520,1451	1598	1354	1275	1180,1114,1064,818	966	
6i	3054	2921	1519,1453	1617	1383	1276	1181,1114,1038,812	971	
7a	3054	2930	1519,1485,1448	1623	1353	1275	1180,1116,1065,822	967	2240
7b	3054	2921	1519,1453	1618	1382	1276	1181,1114,1038,811	972	2243

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. IR: 3290, 2920, 1625, 1565, 1485; ^{1}H NMR: 7.40 (s, 4H, Ar), 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).

General procedure of preparation of 3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl] derivatives 6a-i

A mixture of 1-amino-2-mercapto-5-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-1,3,4-triazole (1 mmol), and α-haloketone (1 mmol) such as bromoacetone and phenacyl bromide was refluxed in absolute ethanol and neutralized by potassium carbonate, to afford 7*H*-3-[5-methyl-1-(4-methylphenyl)-1,2,3-triazol-4-yl]-6-substituted-*s*-triazolo [3,4-b]-1,3,4-thiadiazine. The crude solid was recrystallized from ethanol to give the title compound. The results are given in Table 1.

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Key Words

7*H*-*s*-Triazolo[3,4-b]-1,3,4-thiadiazine; 1,2,3-Triazole; Synthesis; Identification.

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