Synthesis of 6-Aryl-3-methylthio-1*H*-*s*-triazolo[4,3-*b*]-*s*-triazole Derivatives

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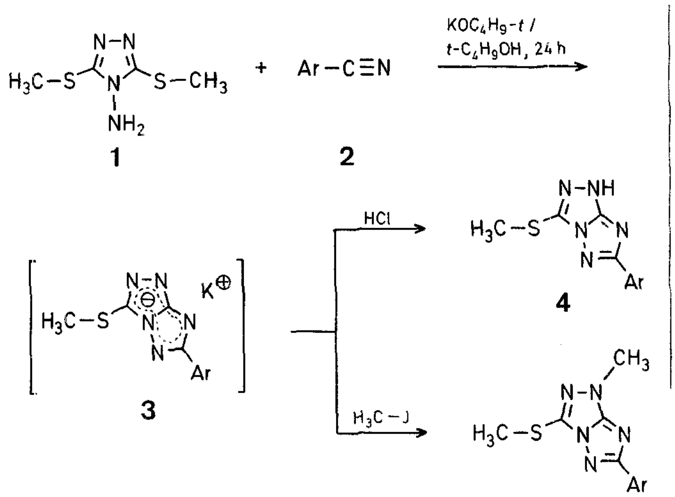
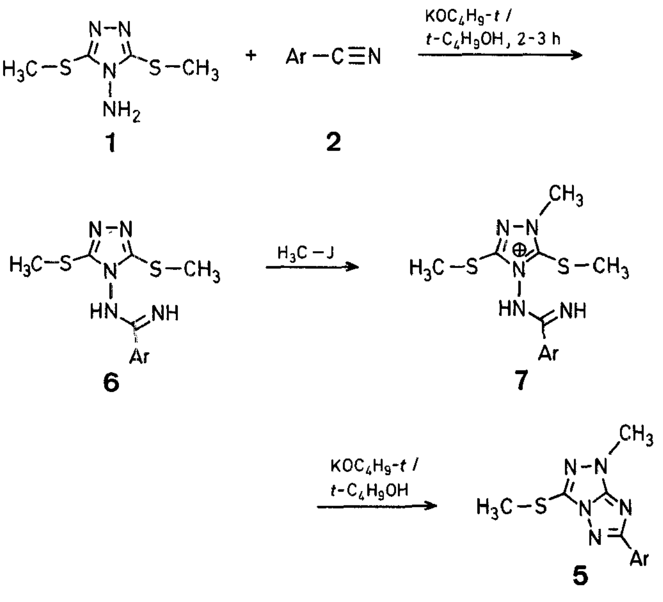
The 1,2,4-triazole moiety has recently been incorporated into H_1/H_2 histamine receptor blockers[1], cholinesterase-active agents[2], CNS stimulants[3], anti-anxiety agents[4], and sedatives[5]. The fusion of two triazole nuclei results in several isomeric ring systems and in this communication we describe the ready synthesis of derivatives of one of them: 1*H*-*s*-triazolo[4,3-*b*]-*s*-triazole, which has been classified as azapentalene type B with one ring junction nitrogen atom[6]. In spite of much work on the synthesis of the *s*-triazolo[4,3-*b*]-*s*-triazole ring system, no generally useful procedure for the preparation of 1*H*-derivatives has hitherto been reported; it has only been briefly mentioned[7] that 1*H*-*s*-triazolo[4,3-*b*]-*s*-triazoles may be obtained in 5% yield by cyclization of triazolylhydrazidic bromides with acetic acid.

We report here a convenient one-pot preparation of 6-aryl-1-methyl-3-methylthio-1*H*-*s*-triazolo[4,3-*b*]-*s*-triazoles and 6-aryl-3-methylthio-1*H*-*s*-triazolo[4,3-*b*]-*s*-triazoles in synthetically useful yields, by reaction of 4-amino-3,5-bis[methylthio]-1,2,4-triazole (**1**; readily available from thiocarbohydrazide, carbon disulfide and methyl iodide[8]) with aromatic nitriles **2** under basic conditions.

When treated with one equivalent of potassium *t*-butoxide and one equivalent of nitrile **2** in *t*-butanol under reflux for 24 h, the *N*-aminoheterocycle **1** is directly converted into the corresponding salt **3**, which undergoes electrophilic attack at the 1-position[9] by the action of hydrochloric acid or methyl iodide to give **4** or **5**, respectively, in good yields (Table 1). Structural elucidation of **4** and **5** is accomplished on the basis of spectral and microanalytical data. The ^{1}H-N.M.R. spectra of all triazolo-triazoles **5** show a singlet at $\delta = 3.92$ ppm attributable to N—CH$_3$, which is in good agreement with the reported value for this type of compounds[9].



An alternative route to triazolo-triazoles **5** is based on the reaction of **1** with nitriles **2** in the presence of potassium *t*-butoxide in *t*-butanol for 2-3 h to give the amidinotriazoles **6** as crystalline solids in good yields. Sequential treatment of compounds **6** with methyl iodide and potassium *t*-butoxide leads to **5** in moderate yields.



The conversion **6**→**5** involves quaternization of the 1,2,4-triazole ring followed by cyclization and elimination of methanethiol to give **5**. In some cases examined the intermediates **7** have been isolated as crystalline solids.

6-Aryl-3-methylthio-1*H*-*s*-triazolo[4,3-*b*]-*s*-triazoles 4; General Procedure:

A mixture of 4-amino-3,5-bis[methylthio]-1,2,4-triazole[8] (**1**; 1.76 g, 10 mmol), the appropriate aromatic nitrile **2** (10 mmol), potassium *t*-butoxide (1.12 g, 10 mmol), and *t*-butanol (50 ml) is refluxed until evolution of methanethiol ceases (~24 h). After cooling, the solvent is evap-

Table 1. Compounds 4 and 5 prepared

Compound No.	Ar	Yield[a] [%]	m.p.[b] [°C]	Molecular formula[c]	I.R. (Nujol)[d] ν [cm^{-1}]	^{1}H-N.M.R.[e] δ [ppm]	M.S. (70 eV)[f] *m/e* (rel. int. %)
4a	C_6H_5	86	237-240°	$C_{10}H_9N_5S$ (231.3)	3060, 1610, 1600, 1440, 1280, 1215, 1090, 835, 730, 705, 690	7.4-8.1 (m, 5H); 2.75 (s, 3H)	231 (24); 230 (71); 198 (6); 144 (10); 128 (11); 118 (8); 103 (100); 77 (17)
4b	4-Cl—C_6H_4	92	226-228°	$C_{10}H_8ClN_5S$ (265.7)	3060, 1610, 1600, 1440, 1425, 1280, 1210, 1115, 1090, 1010, 840, 740	7.4-7.9 (m, 4H); 2.75 (s, 3H)	267 (14); 265 (42); 232 (5); 196 (12); 194 (33); 165 (6); 163 (8); 139 (32); 138 (37); 137 (100); 102 (16)
4c	4-H_3C—C_6H_4	80	210-211°	$C_{11}H_{11}N_5S$ (245.3)	3060, 1610, 1505, 1450, 1430, 1300, 1110, 1090, 980, 840, 830, 745	7.3-8.1 (m, 4H); 2.75 (s, 3H); 2.40 (s, 3H)	245 (95); 212 (8); 174 (53); 158 (9); 143 (15); 132 (20); 117 (100); 90 (45)
4d	2-H_3C—C_6H_4	77	170-171°	$C_{11}H_{11}N_5S$ (245.3)	3060, 1620, 1500, 1460, 1305, 1270, 1210, 1100, 1080, 840, 780, 740	7.4-8.0 (m, 4H); 2.75 (s, 3H); 2.65 (s, 3H)	245 (100); 230 (49); 212 (5); 198 (21); 174 (12); 131 (10); 117 (18); 116 (19); 91 (8)
4e	2,4-di-H_3C—C_6H_3	79	173-175°	$C_{12}H_{13}N_5S$ (259.3)	3060, 1610, 1530, 1490, 1440, 1295, 1200, 1105, 840, 830, 755, 730	7.0-8.0 (m, 3H); 2.75 (s, 3H); 2.65 (s, 3H); 2.40 (s, 3H)	259 (100); 244 (58); 226 (16); 212 (41); 188 (30); 186 (24); 172 (22); 145 (45); 131 (83); 130 (91); 116 (78); 103 (56)
4f	2-Cl—C_6H_4	81	215-216°	$C_{10}H_8ClN_5S$ (265.7)	3070, 1610, 1600, 1510, 1480, 1450, 1310, 1210,, 1130, 1100, 770, 750, 730	7.2-8.0 (m, 4H); 2.75 (s, 3H)	267 (32); 265 (100); 232 (6); 230 (41); 194 (28); 163 (14); 139 (22); 137 (87); 102 (17)

Table 1. (Continued)

Compound No.	Ar	Yield[a] [%]	m.p.[b] [°C]	Molecular formula[c]	I.R. (Nujol)[d] ν [cm^{-1}]	^{1}H-N.M.R.[e] δ [ppm]	M.S. (70 eV)[f] m/e (rel. int. %)
5a	C_6H_5	82	147-148°	$C_{11}H_{11}N_5S$ (245.3)	1630, 1515, 1475, 1450, 1275, 1180, 980, 950, 790, 740, 705	7.4-8.1 (m, 5H); 3.91 (s, 3H); 2.75 (s, 3H)	245 (63); 212 (14); 174 (29); 128 (16); 118 (12); 117 (12); 103 (100); 77 (37)
5b	4-Cl—C_6H_4	68	184-185°	$C_{11}H_{10}N_5ClS$ (279.8)	1625, 1475, 1400, 1430, 1270, 1180, 1100, 1090, 1010, 950, 850, 750	7.4-7.9 (m, 4H); 3.92 (s, 3H); 2.75 (s, 3H)	281 (32); 279 (95); 248 (6); 246 (18); 210 (15); 208 (45); 165 (13); 163 (18); 139 (33); 137 (100); 128 (14); 102 (51)
5c	4-H_3C—C_6H_4	83	160-161°	$C_{12}H_{13}N_5S$ (259.3)	1625, 1480, 1450, 1430, 1280, 1180, 1105, 1030, 950, 840, 745	7.4-8.1 (m, 4H); 3.90 (s, 3H); 2.75 (s, 3H); 2.40 (s, 3H)	259 (94); 226 (17); 188 (29); 132 (23); 128 (13); 118 (25); 117 (100); 116 (48); 102 (8); 91 (29)
5d	2-H_3C—C_6H_4	61	74-75°	$C_{12}H_{13}N_5S$ (259.3)	1625, 1475, 1450, 1320, 1230, 1190, 1080, 970, 780, 740, 730	7.4-8.1 (m, 4H); 3.91 (s, 3H); 2.75 (s, 3H); 2.65 (s, 3H)	259 (94); 244 (34); 226 (7); 212 (33); 185 (37); 158 (22); 146 (28); 117 (100)
5e	2,4-di-H_3C—C_6H_3	74	130-131°	$C_{13}H_{15}N_5S$ (273.4)	1625, 1570, 1550, 1420, 1230, 1190, 1080, 990, 850, 760, 730	7.1-8.0 (m, 3H); 3.92 (s, 3H); 2.75 (s, 3H); 2.65 (s, 3H); 2.40 (s, 3H)	273 (100); 258 (40); 240 (8); 226 (35); 202 (32); 199 (24); 172 (29); 159 (26); 157 (21); 131 (82); 116 (71); 105 (28); 101 (35)
5f	2-Cl—C_6H_4	70	118-119°	$C_{11}H_{10}ClN_5S$ (279.8)	1630, 1470, 1420, 1320, 1220, 1190, 990, 950, 770, 740, 710	7.3-8.1 (m, 4H); 3.91 (s, 3H); 2.75 (s, 3H)	281 (33); 279 (100); 246 (23); 244 (51); 210 (16); 208 (48); 163 (20); 152 (22); 139 (28); 137 (84); 128 (21); 105 (31); 102 (52)
5g	4-O_2N—C_6H_4	59	235-237°	$C_{11}H_{10}N_6O_2S$ (290.3)	1630, 1520, 1470, 1350, 1180, 1100, 870, 740, 710	7.5-8.0 (m, 4H); 3.92 (s, 3H); 2.75 (s, 3H)	290 (100); 260 (12); 257 (17); 219 (73); 176 (14); 148 (16); 118 (20); 102 (67)

[a] Yield of isolated pure product.

[b] Uncorrected.

[c] The microanalyses were in good agreement with the calculated values (C ±0.24, H ±0.25, N ±0.27, S ±0.26).

[d] Recorded on a Perkin-Elmer 457 spectrometer.

[e] Recorded at 80 MHz a Varian FT-80 spectrometer with TMS as internal standard. Spectra of compounds **4** were run in DMSO-d_6 solution, and spectra of **5** in $CDCl_3$ solution. The NH signal in compounds **4** appears in all the cases as a broad singlet at δ=9.40-11.10 ppm.

[f] Recorded at 70 eV in a Hewlett-Packard 5980A.

orated under reduced pressure, the crude potassium salt **3** is dissolved in water (60 ml), insolubles are removed by filtration, and the aqueous basic solution is neutralized by slow addition of dilute hydrochloric acid (~10 ml). The white solid which separates out is filtered, dried, and crystallized from ethanol to give **4** as crystalline solids (Table 1).

6-Aryl-1-methyl-3-methylthio-1*H*-*s*-triazolo[4,3-*b*]-*s*-triazoles 5; General Procedure:

A mixture of 4-amino-3,5-bis[methylthio]-1,2,4-triazole[8] (**1**; 1.76 g, 10 mmol), the appropriate aromatic nitrile **2** (10 mmol), potassium *t*-butoxide (1.12 g, 10 mmol), and *t*-butanol (50 ml) is refluxed until evolution of methanethiol ceases (~24 h). After cooling, the solvent is evaporated under reduced pressure, the crude potassium salt **3** is dissolved in water (60 ml), and insolubles are removed by filtration. To this solution, methyl iodide (2.13 g, 15 mmol) and ethanol (15 ml) are added and the resulting reaction mixture is stirred at room temperature for 24 h. Evaporation of the solvent under reduced pressure and crystallization of the residue from ethanol yield **5** as crystalline solids (Table 1).

Amidinotriazoles 6; General Procedure:

A mixture of 4-amino-3,5-bis[methylthio]-1,2,4-triazole[8] (**1**; 1.76 g, 10 mmol), the appropriate aromatic nitrile **2** (10 mmol), potassium *t*-butoxide (1.12 g, 10 mmol), and *t*-butanol (50 ml) is refluxed until evolution of methanethiol at the head of the condenser is detected (2-3 h). After cooling, the solvent is evaporated under reduced pressure and the solid residue is washed with water, filtered, dried, and crystallized from ethanol to give **6** as crystalline solids (Table 2).

Compounds 5 from Amidinotriazoles 6; Typical Procedure:

Amidinotriazole **6a** (2.79 g, 10 mmol) and methyl iodide (1.70 g, 12 mmol) are refluxed in dry methanol (70 ml) for 7 h. After cooling, the solvent is removed under reduced pressure, the residue is dissolved in *t*-butanol (60 ml), potassium *t*-butoxide (1.12 g; 10 mmol) is added, and the resulting reaction mixture is refluxed for 20 h. After cooling, the solvent is removed under reduced pressure and the solid residue is washed with water, filtered, dried, and crystallized from ethanol to give **5a** as white needles; yield: 1.62 g (66%); m.p. 147-148 °C.

Amidinotriazolium Iodides 7; General Procedure:

A mixture of amidinotriazole **6** (10 mmol), methyl iodide (1.70 g, 12

Table 2. Amidinotriazoles **6** prepared

Compound No.	Ar	Yield[a] [%]	m.p.[b] [°C]	Molecular formula[c]	I.R. (Nujol)[d] ν [cm^{-1}]	^{1}H-N.M.R.[e] (DMSO-d_6/TMS) δ [ppm]	M.S. (70 eV)[f] m/e (rel. int. %)
6a	C_6H_5	89	264–265°	$C_{11}H_{13}N_5S_2$ (279.4)	3290, 3120, 1670, 1650, 1550, 1450, 1420, 1190, 980, 850, 790, 700, 675	7.3–7.9 (m, 7H); 2.53 (s, 6H)	279 (22); 278 (69); 231 (8); 119 (51); 104 (100); 77 (84)
6b	4-Cl—C_6H_4	96	243–245°	$C_{11}H_{12}ClN_5S_2$ (313.8)	3280, 3120, 1675, 1650, 1590, 1550, 1450, 1420, 1090, 1020, 860, 780, 710	7.4–7.9 (m, 6H); 2.55 (s, 6H)	315 (10); 314 (21); 313 (29); 312 (63); 265 (5); 198 (6); 197 (18); 196 (18); 155 (62); 153 (57); 138 (100); 111 (50); 102 (41)
6c	4-H_3C—C_6H_4	84	250–251°	$C_{12}H_{15}N_5S_2$ (293.4)	3300, 3130, 1670, 1650, 1590, 1550, 1450, 1420, 1190, 980, 830, 740, 710	7.3–8.1 (m, 6H); 2.55 (s, 6H); 2.40 (s, 3H)	293 (35); 292 (93); 245 (10); 177 (15); 162 (38); 161 (28); 133 (73); 118 (100); 102 (24); 91 (79)
6d	2-H_3C—C_6H_4	78	243–244°	$C_{12}H_{15}N_5S_2$ (293.4)	3310, 3160, 1650, 1570, 1450, 1420, 1310, 970, 765, 745, 680	7.4–8.0 (m, 6H); 2.65 (s, 3H); 2.55 (s, 6H)	293 (100); 246 (45); 245 (41); 177 (10); 162 (42); 161 (31); 133 (34); 132 (26); 118 (25); 116 (52); 102 (22); 91 (24)
6e	2,4-di-H_3C—C_6H_3	81	254–255°	$C_{13}H_{17}N_5S_2$ (307.4)	3300, 3140, 1645, 1570, 1450, 1420, 1230, 1180, 990, 970, 810, 705	7.4–8.1 (m, 5H); 2.65 (s, 3H); 2.53 (s, 6H); 2.40 (s, 3H)	307 (77); 260 (62); 191 (19); 162 (100); 147 (58); 146 (62); 132 (97); 117 (32); 102 (49); 91 (28); 79 (32); 77 (45)
6f	2-Cl—C_6H_4	92	250–252°	$C_{11}H_{12}ClN_5S_2$ (313.8)	3320, 3180, 1645, 1600, 1580, 1540, 1470, 1450, 1220, 1050, 980, 850, 770, 680	7.4–7.9 (m, 6H); 2.55 (s, 3H)	315 (12); 313 (37); 278 (22); 265 (5); 199 (6); 197 (18); 155 (41); 153 (44); 140 (33); 138 (100); 102 (59)
6g	4-O_2N—C_6H_4	97	247–249°	$C_{11}H_{12}N_6O_2S_2$ (324.4)	3360, 3330, 3140, 1655, 1575, 1530, 1420, 1350, 980, 875, 845, 770	7.4–7.9 (m, 6H); 2.53 (s, 6H)	324 (100); 276 (53); 208 (30); 205 (61); 178 (26); 176 (63); 160 (52); 149 (95); 118 (39); 103 (31); 102 (32)

[a] Yield of isolated pure product.

[b] Uncorrected.

[c] The microanalyses were in good agreement with the calculated values (C ±0.25, H ±0.24, N ±0.23, S ±0.20).

[d] Recorded on a Perkin-Elmer 457 spectrometer.

[e] Recorded at 80 MHz a Varian FT-80 spectrometer.

[f] Recorded at 70 eV in a Hewlett-Packard 5980A.

mmol) and dry methanol (70 ml) is refluxed for 7 h. After cooling, the solvent is evaporated under reduced pressure and the remaining solid is crystallized from methanol/diethyl ether to give **7** as crystalline solids. The following compounds **7** have been prepared:

4-Benzamidino-1-methyl-3,5-bis[methylthio]-1,2,4-triazolium Iodide: yield: 2.86 g (68%); colourless prisms; m.p. 212–214 °C.

$C_{12}H_{16}N_5JS_2$	calc.	C 34.21	H 3.82	N 16.62	S 15.22
(421.3)	found	34.08	3.81	16.54	15.11

I.R. (Nujol): ν=3320, 3290, 3170, 1635, 1545, 1475, 1420, 1310, 1195, 970, 790, 705 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ=2.65 (s, 6H); 4.05 (s, 3H); 7.5–8.3 ppm (m, 7H).

4-(4'-Chlorobenzamidino)-1-methyl-3,5-bis[methylthio]-1,2,4-triazolium Iodide: yield: 3.28 g (72%); colourless prisms; m.p. 224–227 °C.

$C_{12}H_{15}N_5ClJS_2$	calc.	C 31.62	H 3.31	N 15.36	S 14.07
(455.8)	found	31.70	3.25	15.31	14.13

I.R. (Nujol): ν=3310, 3290, 3160, 1635, 1595, 1540, 1470, 1420, 1310, 1100, 1015, 860, 845, 825, 740 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ=2.75 (s, 6H); 4.10 (s, 3H); 7.5–8.2 ppm (m, 6H).

4-(4'-Methylbenzamidino)-1-methyl-3,5-bis[methylthio]-1,2,4-triazolium Iodide: yield: 2.78 g (64%); colourless prisms; m.p. 174–175 °C.

$C_{13}H_{18}N_5JS_2$	calc.	C 35.86	H 4.16	N 16.08	S 14.7
(435.4)	found	35.88	4.09	16.15	14.6

I.R. (Nujol): ν=3320, 3300, 3180, 1635, 1600, 1540, 1480, 1420, 1310 1200, 990, 840, 730 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ=2.70 (s, 6H); 4.05 (s, 3H); 7.3–8.3 ppm (m 6H).

When a mixture of triazolium iodides **7**, equimolecular amounts of potassium *t*-butoxide, and *t*-butanol is refluxed for 24 h, compounds **5** are obtained in almost quantitative yields by similar work-up as described above.

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