SYNTHESIS OF 6-ARYL-1,3-DIMETHYL-1H-1,2,4-TRIAZOLO[4,3-b]-[1,2,4]TRIAZOLES

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Abstract - *The synthesis of various 1H-1,2,4-triazolo[4,3-b]-[1,2,4]triazoles has been achieved by reaction of 4-amino-1,3-dimethyl-5-thioxo-4,5-dihydro-1,2,4-triazole with aromatic nitriles in the presence of potassium t-butoxide.*

Our interest in the preparation of bridgehead nitrogen heterocycles has encouraged us to look for specific routes to derivatives of 1H-1,2,4-triazolo[4,3-b]-[1,2,4]triazole. In spite of many works on the synthesis of the 1,2,4-triazolo-[4,3-b][1,2,4]triazole ring system, no generally useful procedure for the preparation of 1H-derivatives has hitherto been reported; it has only briefly mentioned that 1H-1,2,4-triazolo[4,3-b][1,2,4]triazoles may be obtained in 5% yield by cyclization of triazolylhydrazidic bromides with acetic acid[1]. In this context we have reported the preparation of 6-aryl-1-methyl-3-methylthio-1H-1,2,4-triazolo-[4,3-b][1,2,4]triazoles from 4-amino-3,5-bis(methylthio)-1,2,4-triazole and aromatic nitriles under basic conditions[2], and the preparation and characterization of mesoionic compounds derived from the 1,2,4-triazolo[4,3-b][1,2,4]triazole ring system[3,4].

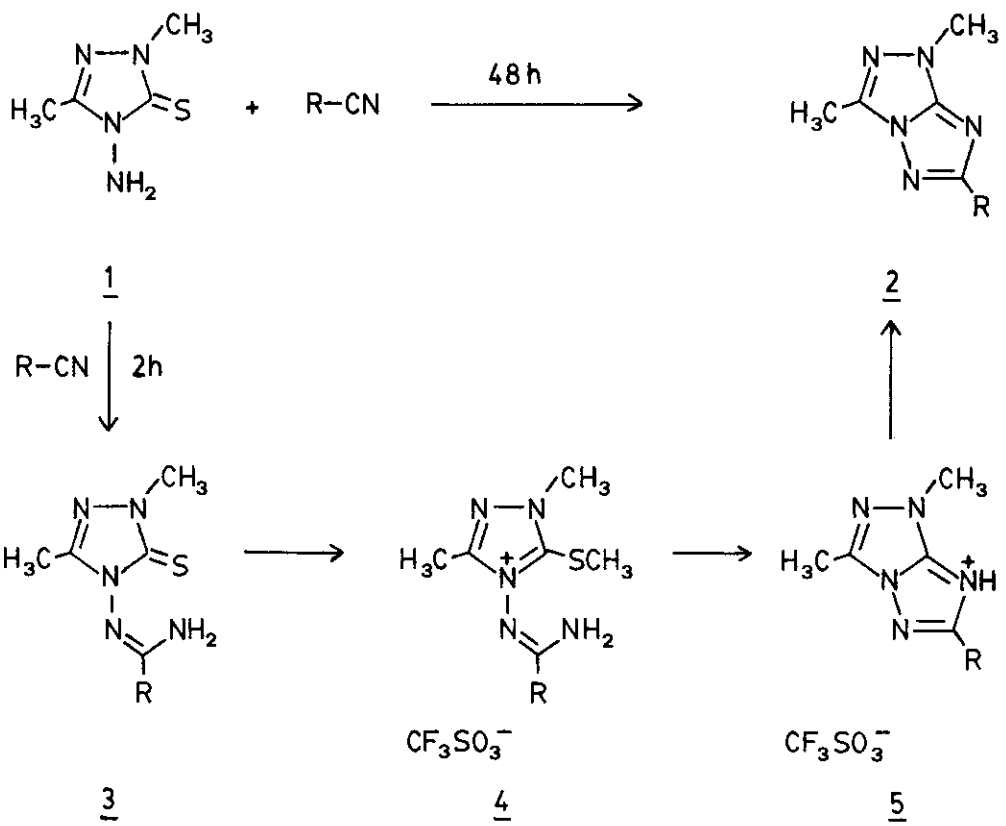
We report here a convenient one-pot preparation of 6-aryl-1,3-dimethyl-1H-1,2,4-triazolo[4,3-b][1,2,4]triazoles 2 in synthetically useful yields. Our approach is based on the reaction of nitriles with 4-amino-1,3-dimethyl-5-thioxo-4,5-dihydro-1,2,4-triazole 1, readily available from N-methylthiocarbohydrazide and acetic acid[5].

When treated with excess of potassium t-butoxide and one equivalent of nitrile in t-butanol under reflux for 48 h, the N-amino heterocycle 1 is directly converted into the corresponding 6-aryl-1,3-dimethyl-1H-1,2,4-triazolo[4,3-b][1,2,4]triazole 2 in moderate to good yields (50-84%). The reaction appears to be quite gene-

ral for aromatic nitriles; however attempts to apply the method to aliphatic nitriles were unsuccessful. When 2-cyanofuran or 2-cyanothiophene were used a mixture of the corresponding triazolotriazole 2 and amidinotriazole 3 was obtained in very low yield.

An alternative route to triazolotriazoles 2 is based on the reaction of compound 1 with a nitrile in the presence of one equivalent of potassium t-butoxide in t-butanol at reflux temperature for 2 h to give the amidinotriazole 3 as a crystalline solid in good yield. Reaction of 3 with methyl trifluoromethanesulphonate in dry dichloromethane at room temperature leads to the amidinotriazolium salt 4 which by heating in ethanolic solution undergoes cyclization to give 5; further treatment of compound 5 with aqueous potassium hydroxide leads to 2 in good yield.

Structural elucidation of 2 is accomplished on the basis of spectral and microanalytical data. In the ^{1}H-NMR spectra of all triazolotriazoles 2 the chemical shifts of N-CH_3 and C_3-CH_3 groups are characteristics at δ 3.85-4.05 and δ 2.55-2.65 ppm respectively, which are in good agreement with the reported values for this type of compounds[6]. In addition, the carbon atoms of the N-CH_3 and C_3-CH_3 methyl groups show up characteristically at δ 35.13 and 10.13 ppm respectively in the ^{13}C-NMR spectrum of compound 2b, as do the quaternary carbons C_3, C_6 and C_{7a} at δ 135.84, 169.57 and 156.48 ppm respectively[4,7].



1 2 3 4 5

TABLE 1. Preparation of 1H-1,2,4-Triazolo[4,3-b][1,2,4]triazoles 2 .

Entry	R	Mp(°C)	Yield (%)	Crystal form	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	C_6H_5	138-140	66	Prisms	61.91	5.22	32.73	$C_{11}H_{11}N_5$	61.96	5.20	32.84
b	4-H_3C-C_6H_4	173-174	59	Needles	63.31	5.65	30.77	$C_{12}H_{13}N_5$	63.42	5.77	30.81
c	3-H_3C-C_6H_4	122-125	56	Needles	63.39	5.70	30.73	$C_{12}H_{13}N_5$	63.42	5.77	30.81
d	4-Cl-C_6H_4	207-209	52	Needles	53.22	3.96	28.14	$C_{11}H_{11}ClN_5$	53.34	4.07	28.27
e	4-H_3CO-C_6H_4	145-147	84	Prisms	59.19	5.88	28.64	$C_{12}H_{13}N_5O$	59.25	5.93	28.79
f	3-H_3CO-C_6H_4	144-146	65	Prisms	59.13	5.81	28.73	$C_{12}H_{13}N_5O$	59.25	5.93	28.79
g	4-Pyridyl	162-163	53	Needles	55.94	4.61	39.19	$C_{10}H_{10}N_6$	56.07	4.70	39.23
h	3-Pyridyl	136-138	50	Needles	56.02	4.73	39.12	$C_{10}H_{10}N_6$	56.07	4.70	39.23

TABLE 2. Spectral Data for Compounds 2

Compound No.	IR ν (cm^{-1})	^{1}H-NMR[a] δ (ppm)	MS[b] m/z (%)
2a	1631,1552,1467,1421,1336 1240,1104,1059,787,736, 707,657.	8.6-8.4 (2H,m) 7.9-7.6 (3H,m) 4.00 (3H,s) 2.65 (3H,s)	213(M^+,100), 212(25), 144(5), 129(10),118(7), 104(9),103(77),77(16), 76(26),70(42),67(28).
2b	1631,1608,1557,1461,1443, 1331,1234,1104,843,747, 631.	8.2-7.9 (2H,m) 7.4-7.1 (2H,m) 3.85 (3H,s) 2.55 (3H,s)	227(M^+,100),226(23), 213(7),158(9),143(12), 132(8),117(25),116(16), 90(7),70(8),67(5).
2c	1631,1552,1461,1410,1325, 1241,1212,1081,1059,800, 747,654.	8.2-7.9 (2H,m) 7.6-7.2 (2H,m) 3.95 (3H,s) 2.60 (3H,s) 2.40 (3H,s)	227(M^+,100),226(25), 213(8),212(7),158(10), 143(18),117(21),116(15), 90(12),89(11),70(5), 67(5).
2d	1631,1602,1552,1449,1426, 1104,1095,1086,852,750.	8.4-8.2 (2H,m) 7.7-7.5 (2H,m) 4.00 (3H,s) 2.65 (3H,s)	249(33),247(M^+,100), 246(19),178(5),163(10), 139(20),137(60),102(15), 75(5),70(5),67(5).
2e	1631,1608,1580,1552,1461, 1427,1331,1245,1172,1161, 1036,855,753.	8.5-8.2 (2H,m) 7.4-7.1 (2H,m) 4.05 (3H,s) 4.00 (3H,s) 2.65 (3H,s)	243(M^+,100),228(16), 200(5),159(12),134(10), 133(57),118(9),103(17), 90(37),70(23),67(20).
2f	1636,1625,1580,1557,1461, 1410,1325,1223,1042,877, 866,787,747.	8.1-7.1 (4H,m) 4.05 (3H,s) 4.00 (3H,s) 2.65 (3H,s)	243(M^+,100),242(49), 213(18),159(6),134(6), 133(39),121(5),104(7), 103(26),90(22),70(15), 67(13).

TABLE 2. Continued

2g	1631,1552,1461,1427,1240, 1059,1030,838,747,651.	9.2-9.0 (2H,m) 8.4-8.2 (2H,m) 4.00 (3H,s) 2.65 (3H,s)	215(14),214(M^+,100), 213(19),130(6),104(7), 65(5).
2h	1631,1591,1552,1455,1410, 1342,1302,1240,1121,1025, 826,742,719,657.	9.50 (1H,m) 8.9-8.4 (2H,m) 7.6-7.3 (1H,m) 3.95 (3H,s) 2.60 (3H,s)	215(18),214(M^+,100), 213(23),145(6),130(11), 119(10),105(17),104(80), 77(49),76(23),70(23), 67(45).

[a] $CDCl_3$ as solvent; [b] Recorded at 70 eV .

EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. IR spectra were run using NaCl plates on a Nicolet FT-5DX spectrophotometer in Nujol emulsions. ^{1}H NMR spectra were obtained on a Varian EM-360A spectrometer at 60 MHz. Mass spectra were recorded on a Hewlett-Packard 5993 C spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 C instrument.

General Procedure for the Formation of 6-Aryl-1,3-dimethyl-1H-1,2,4-triazolo-[4,3-b][1,2,4]triazoles 2. A mixture of 4-amino-1,3-dimethyl-5-thioxo-4,5-dihydro-1,2,4-triazole 1 (1.44 g, 10 mmol), the appropriate aromatic nitrile (10 mmol), potassium t-butoxide (2.24 g, 20 mmol) in t-butanol (50 ml) was refluxed for 48 h. After cooling, the solvent was evaporated under reduced pressure, the crude product was washed with cold water (50 ml), separated by filtration, dried and recrystallised from ethanol to give 2 as crystalline solids (see Table 1).

Typical Procedure for the Formation of Amidinotriazole 3. A mixture of 4-amino-1,3-dimethyl-5-thioxo-4,5-dihydro-1,2,4-triazole 1 (1.44 g, 10 mmol), benzonitrile (1.03 g, 10 mmol), potassium t-butoxide (1.12 g, 10 mmol) in t-butanol (50 ml) was refluxed for 2 h. After cooling, the solvent was evaporated under reduced pressure and the solid residue was washed with water, dried and crystallised from ethanol to give 3(R=C_6H_5) (1.97 g, 80%) as colourless prisms, mp 220-221°C (Found : C, 53.36; H, 5.32; N, 28.22. $C_{11}H_{13}N_5S$ requires C, 53.42; H, 5.30; N, 28.31); IR ν max. (Nujol) 3313, 3216, 1647, 1557, 1342, 1268, 1200, 781, 690 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 8.5-7.6 (7H,m), 3.75 (3H,s), 2.20 (3H,s); m/z(%) 247(M^+, 100), 232(6), 214(13), 205(5), 204(6), 177(5), 144(22), 130(14), 129(33), 127(20), 119(24), 104(41), 77(29).

Typical Procedure for the Formation of Amidinotriazolium Salt 4. To a solution of amidinotriazole 3(R=C_6H_5) (0.5 g, 2 mmol) in dry dichloromethane (25 ml), methyl trifluoromethanesulphonate (0.43 g, 2.6 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure at room temperature and the crude solid was recrystallised from methanol/ether (1:1 v:v) to give 4(R=C_6H_5) (0.5 g, 60%) as colourless prisms, mp 135-137°C (Found : C, 37.87; H, 3.81; N, 16.90. $C_{13}H_{16}N_5F_3O_3S_2$ requires C, 37.95; H, 3.92; N, 17.02); IR ν max. (Nujol) 3383, 3345, 3221, 1663, 1597, 1562, 1285, 1245, 1227, 1172, 1030, 758, 702 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 8.1-7.0 (7H,m), 4.20 (3H,s), 2.70 (3H,s), 2.40 (3H,s); m/z(%) 262(3), 214(19), 213(100), 212(27), 129(11), 103(77), 77(21).

Typical Procedure for the Formation of Triazolo[4,3-b][1,2,4]triazole 2a. A solution of amidinotriazolium salt 4(R=C_6H_5) (0.35 g, 8.5 mmol) in ethanol (15 ml) was refluxed for 14 h. After cooling, the solvent was removed under reduced pressure and the solid residue was recrystallised from ethanol/ether (1:1 v:v) to give 5(R=C_6H_5) (0.3 g, 97%) as colourless prisms, mp 178-180°C (Found : C, 39.59; H, 3.26; N, 19.16. $C_{12}H_{12}N_5F_3O_3S$ requires C, 39.67; H, 3.33; N, 19.27); IR ν max. (Nujol) 3211, 1693, 1682, 1297, 1240, 1223, 1178, 1149, 1030, 718, 691 cm^{-1}. When compound 5(R=C_6H_5) (0.36 g, 1 mmol) was treated with 1N potassium hydroxide (15 ml) and the resultant mixture was stirred for 15 min, the triazolotriazole 2a was isolated as colourless prisms in 74% yield.

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