PYRAZOLO[5,1-c]-1,2,4-TRIAZOLES FROM 1,2,4-TRIAZOLIUM SALTS AND SUBSTITUTED ACETONITRILES

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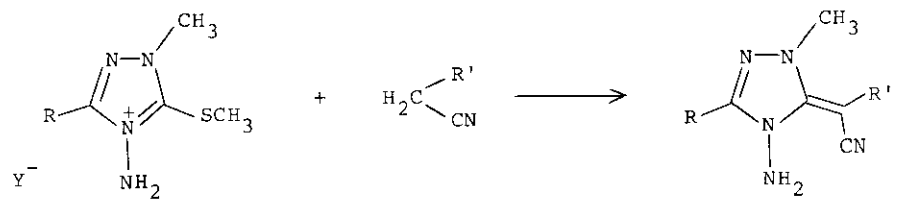
Abstract - 3-Substituted 4-amino-1-methyl-5-methylthio-1,2,4-triazolium salts react with acetonitriles activated by another electron-delocalizing group to give enamines which undergo cyclization by action of hydrogen chloride to give pyrazolo[5,1-c]-1,2,4-triazole derivatives.

The synthesis of fused heterocycles which contain the 1,2,4-triazole moiety has been of interest because of the biological activity they possess. In this context we have reported the preparation of 1,2,4-triazolo[1,5-a]pyridines[1,2,3]; 1,3,4-triazolo[3,2-a]pyridines[4]; 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles[5]; 1,2,4-triazolo[5,1-c]-1,2,4-triazines[6] and 1,2,4-triazolo[4,3-b]-1,2,4-triazoles[7,8,9]. We now describe a new general method for the synthesis of otherwise not readily accesible pyrazolo[5,1-c]-1,2,4-triazole derivatives.

The methods described for the preparation of the pyrazolo[5,1-c]-1,2,4-triazole ring system can be classified in two groups. One starts from pyrazole derivatives such as 3-hydrazino[10,11,12,13] or 3-diazonium salts[14,15]. The other involves cyclisative condensation reactions of 3,4-diamino-1,2,4-triazoles[16] or 4-amino-5-thioxo-1,2,4-triazole derivatives[17].

The method here reported is based in the reaction of the N-amino heterocycles 4-amino-1-methyl-3,5-bis(methylthio)-1,2,4-triazolium iodide 1a, readily available from 4-amino-3,5-bis(methylthio)-1,2,4-triazole and methyl iodide[18], and 4-amino-1,3-dimethyl-5-methylthio-1,2,4-triazolium trifluoromethanesulfonate 1b, with acetonitriles 2 activated by another electron-delocalizing group such as an ester, amide, hydrazide or a second nitrile group.

When treated with 1 equivalent of pyrrolidine and 1 equivalent of nitrile 2 in ethanol at room temperature for 24 h , the 4-amino-1,2,4-triazolium cations 1a and 1b underwent elimination of methanethiol to give the corresponding functionalized enamines 3 which were isolated as crystalline solids. The yields of the reaction were found to depend on the nature of the R' substituent in the nitrile 2. They were good for R'= CN, COOEt and COOMe, and moderate for R'= $CONH_2$ and $CONHNH_2$. In these latter cases the tetrazine 5 was isolated as the main product. Compounds 3 (R'= CN, COOEt, COOMe) undergo cyclization by action of dry hydrogen chloride at room temperature to give the corresponding pyrazolo[5,1-c]-1,2,4-triazoles 4 . The short reaction time for this reagent is remarkable. Howewer, attempted cyclization of compounds 3 (R'= $CONH_2$, $CONHNH_2$) failed to give 4. When enamine 3 (R'= CN) was treated with sodium methoxide the corresponding pyrazolo[5,1-c]-1,2,4-triazole 4 was isolated in moderate yield. Howewer, for 3 (R'= COOEt, COOMe) the corresponding compounds 4 were isolated in very low yield and for 3 (R'= $CONH_2$, $CONHNH_2$) the cyclization reaction failed to give 4 .

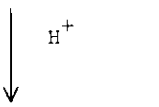


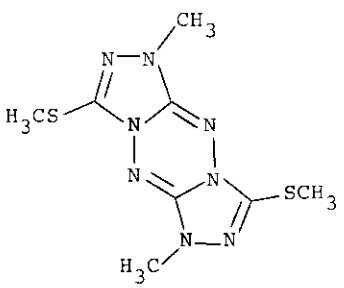
1a R=CH_3S Y=I

1b R=CH_3 Y=CF_3SO_3

2

3





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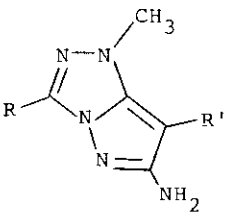

4

TABLE 1. Preparation of Enamines 3 .

Entry	R	R'	Mp(°C)	Yield	Crystal Form	Recryst. Solvent	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	CH_3S	CN	173-175	73	Needles	Ethanol	40.41	3.80	40.29	$C_7H_8N_6S$	40.37	3.87	40.35
b	CH_3S	$COOC_2H_5$	144-146	63	Prisms	Ethanol	42.22	5.06	27.31	$C_9H_{13}N_5O_2S$	42.34	5.13	27.43
c	CH_3S	$COOCH_3$	201-203	62	Needles	Ethanol	39.85	4.47	28.91	$C_8H_{11}N_5O_2S$	39.82	4.59	29.03
d	CH_3S	$CONH_2$	210-212	20	Prisms	Ethanol	37.09	4.36	37.06	$C_7H_{10}N_6OS$	37.16	4.45	37.14
e	CH_3S	$CONHNH_2$	193-195	30	Needles	Methanol	34.79	4.60	40.57	$C_7H_{11}N_7OS$	34.85	4.59	40.63
f	CH_3	CN	182-184	68	Plates	Ethanol	47.68	4.58	47.58	$C_7H_8N_6$	47.72	4.57	47.70
g	CH_3	$COOC_2H_5$	116-118	65	Prisms	Benzene/ hexane	48.38	5.79	31.30	$C_9H_{13}N_5O_2$	48.42	5.87	31.37
h	CH_3	$COOCH_3$	140-142	72	Needles	Benzene/ hexane	45.81	5.15	33.36	$C_8H_{11}N_5O_2$	45.93	5.30	33.47

TABLE 2. Preparation of Pyrazolo[5,1-c]-1,2,4-triazole Derivatives 4 .

Entry	R	R'	Mp(°C)	Yield	Crystal Form	Recryst. Solvent	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	CH_3S	CN	275-276	80	Needles	Methanol	40.19	3.77	40.40	$C_7H_8N_6S$	40.37	3.87	40.35
b	CH_3S	$COOC_2H_5$	186-187	73	Prisms	Ethanol	42.31	5.07	27.37	$C_9H_{13}N_5O_2S$	42.34	5.13	27.43
c	CH_3S	$COOCH_3$	190-191	74	Needles	Ethanol	39.72	4.45	28.98	$C_8H_{11}N_5O_2S$	39.82	4.59	29.03
d	CH_3	CN	245-247	83	Prisms	Ethanol	47.80	4.52	47.67	$C_7H_8N_6$	47.72	4.57	47.70
e	CH_3	$COOC_2H_5$	165-167	83	Prisms	Ethanol	48.33	5.80	31.28	$C_9H_{13}N_5O_2$	48.42	5.87	31.37
f	CH_3	$COOCH_3$	184-186	76	Prisms	Ethanol	45.88	5.32	33.40	$C_8H_{11}N_5O_2$	45.93	5.30	33.47

TABLE 3. Spectral data of compounds 3 and 4.

Compound No.	IR ν (cm^{-1})	^{1}H-NMR[a] δ (ppm)	MS[b] m/e(%)
3a	3365,3245,3110,2200, 2170,1665,1630,1575, 1510,1310,1280,1245, 1130,990,855,680.	6.30(2H,s) 3.95(3H,s) 2.65(3H,s)	208(M^+,44),193(5),192 (8),134(6),123(12), 107(12),106(100),80 (13),79(21),42(38).
3b	3285,3190,2185,1645, 1562,1506,1450,1415, 1310,1275,1180,1150, 1065,995,970,837, 765,700,680,650.	5.70(2H,s) 4.35(2H,q) 3.95(3H,s) 2.65(3H,s) 1.30(3H,t)	255(M^+,25),210(19), 183(42),167(25),158 (37),125(13),123(10), 109(22),107(31),101 (15),81(34),29(100).
3c	3279,3171,2197,1625, 1557,1500,1438,1370, 1342,1268,1200,1172, 1132,1075,1019,968, 832,752.	5.55(2H,s) 3.95(3H,s) 3.80(3H,s) 2.60(3H,s)	241(M^+,100),210(54), 209(19),194(12),193 (11),183(23),167(18), 158(27),139(11),107 (48),80(33),43(35).
3d	3400,3310,3190,3090, 2180,1650,1620,1590, 1545,1500,1420,1405, 1275,1150,1040,840, 780,700.	6.55(4H,m) 3.90(3H,s) 2.60(3H,s)	226(M^+,100),210(30), 209(65),193(46),167 (11),136(25),135(31), 124(13),107(67),81(47), 66(23),44(52).
3e	3210,3137,2175,1680, 1602,1545,1500,1370, 1335,1275,1150,1105, 980,795.	5.50(3H,m) 3.90(3H,s) 3.55(3H,s) 2.55(3H,s)	241(M^+,18),226(5),183 (16),173(18),167(10), 158(14),129(25),111(10), 109(9),99(35),84(17), 43(50),42(100).
3f	3350,3260,3110,2200, 2170,1665,1625,1570, 1315,1250,1215,1155, 1040,1020,940,820, 690.	6.30(2H,s) 4.00(3H,s) 2.60(3H,s)	176(M^+,68),160(3),135 (9),118(7),109(7),107 (10),106(100),91(25), 79(26),64(10),52(10), 43(25),42(56).
3g	3273,3188,2185,1638, 1545,1440,1364,1285, 1190,1166,1013,973, 877,758.	5.55(2H,s) 4.25(2H,q) 3.85(3H,s) 2.40(3H,s) 1.30(3H,t)	223(M^+,93),195(12),178 (71),177(15),151(100), 135(18),126(40),123(15), 109(33),107(29),81(31), 69(23),42(62).
3h	3276,3179,2190,1630, 1556,1439,1344,1284, 1205,1156,1078,1041, 975,914,860,757.	5.65(2H,s) 3.90(3H,s) 3.80(3H,s) 2.50(3H,s)	209(M^+,100),178(82), 177(20),153(7),151(36), 135(12),126(21),123(11), 107(25),80(19),69(16), 42(36).

TABLE 3 . Cont.

4a	3360,3305,3200,2210, 1636,1530,1490,1160, 1120,1025,985,970, 910,715.	6.15(2H,s) 3.80(3H,s) 2.60(3H,s)	208(M^+,62),191(9),175 (12),161(5),136(11), 121(17),109(8),108(7), 107(9),106(11),83(10), 80(16),66(23),42(100).
4b	3435,3280,3175,1675, 1620,1495,1465,1363, 1330,1275,1165,1105, 1020,770,695.	5.45(2H,s) 4.40(2H,q) 4.15(3H,s) 2.70(3H,s) 1.40(3H,t)	255(M^+,56),210(29),209 (60),183(14),166(15), 156(9),155(8),137(12), 136(18),125(15),110(12), 107(9),83(11),82(67), 81(100),80(68),66(32).
4c	3455,3290,3175,1680, 1620,1520,1490,1440, 1340,1280,1165,1105, 910,775,690.	5.35(2H,s) 4.20(3H,s) 3.95(3H,s) 2.75(3H,s)	241(M^+,93),210(30),209 (80),208(16),192(10), 166(16),163(10),142(18), 139(12),137(16),110(16), 107(11),83(12),82(68), 81(100),80(84),79(21), 68(25),66(25),42(32).
4d	3375,3335,3215,2215, 1650,1557,1523,1500, 1320,1257,1223,1109, 1040,939,719.	5.70(2H,s) 3.90(3H,s) 2.45(3H,s)	177(11),176(M^+,100), 149(5),106(5),91(6), 83(5),80(5),66(8), 42(25),28(5).
4e	3443,3280,3194,1681, 1630,1557,1523,1489, 1342,1285,1240,1108, 1019,951,787,707.	5.25(2H,s) 4.25(2H,q) 4.15(3H,s) 2.55(3H,s) 1.40(3H,t)	223(M^+,74),178(45), 177(100),151(14),136 (6),123(7),82(6),81 (14),80(9),66(6),42 (5),29(8).
4f	3449,3296,3188,1687, 1625,1557,1517,1489, 1347,1285,1240,1189, 1109,945,775,707.	5.40(2H,s) 4.15(3H,s) 3.95(3H,s) 2.55(3H,s)	209(M+,69),178(36), 177(100),151(5),136 (5),123(7),82(6),81 (13),80(10),66(6), 42(5),28(5).

[a] Obtained as solutions in $CDCl_3$, except for compounds 3a, 3d, 3e, 3f, 4a and 4d which were obtained in DMSO-d^6 .

[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 60 MHz spectrometer. Mass spectra were recorded on a Hewlett-Packard 5993 C spectrometer. Elemental analyses were performed with a Perkin-Elmer 240 C instrument.

4-Amino-1,3-dimethyl-5-methylthio-1,2,4-triazolium Trifluoromethanesulfonate 1b . 4-Amino-1,3-dimethyl-1,2,4-triazole-5H-thione (1.44 g, 10 mmol), methyl trifluoromethanesulfonate (1.64 g, 10 mmol) and dry dichloromethane (30 ml) were stirred at room temperature for 24 h . Elimination of solvent under reduced pressure and addition of ether (20 ml) to the residual material gave a solid which was filtered, dried and recrystallised from ethanol-ether (1:1) to give 1b (2.36g , 76%) as colourless prisms, mp 56-57°C (Found : C, 23.23; H, 3.48; N, 18.09; S, 20.65. $C_6H_{11}F_3N_4O_3S_2$ requires C, 23.37; H, 3.59; N, 18.17; S, 20.80%). ν max. (Nujol) 3320, 3275, 3225, 1625, 1260, 1165, 1030, 958, 850, 640 ; δ ($CDCl_3$) 5.95 (2H,s,broad), 4.05 (3H,s), 2.75 (3H,s), 2.55 (3H,s).

General Procedure for the Formation of Enamines 3 . Procedure A . To a solution of triazolium iodide 1a (1.59 g, 5 mmol) and pyrrolidine (0.36 g, 5 mmol) in ethanol (20 ml) the corresponding nitrile 2 (5 mmol) was added. The resultant mixture was stirred at room temperature for 24 h (evolution of methanethiol was clearly detected). The precipitated solid was collected by filtration and recrystallised from the appropriate solvent (see Table 1). Procedure B . Triazolium trifluoromethanesulfonate 1b (1.54 g, 5 mmol), pyrrolidine (0.36 g, 5 mmol) and the corresponding nitrile 2 (5 mmol) were stirred in ethanol (20 ml) at room temperature for 24 h . Elimination of the solvent under reduced pressure gave a solid residue which was dissolved in chloroform (30 ml) and washed with water (2x10 ml). The dried ($MgSO_4$) organic layer was evaporated under reduced pressure to yield the crude product which recrystallised from the appropriate solvent yielded 3 as crystalline solids (see Table 1).

General Procedure for the Formation of Pyrazolo[5,1-c]-1,2,4-triazoles 4 . A stream of dry hydrogen chloride gas was passed through a well-stirred solution

of enamine 3 (5 mmol) in dry dioxane (25 ml) for 30 min . The solution was concentrated under reduced pressure, the precipitate obtained was filtered off and recrystallised from the adequate solvent to give 4 (see Table 2).

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