FUSED THIAZOLES FROM 3-AMINO-THIAZOLINE-2-THIONES: SYNTHESIS OF PYRAZOLO[5,1-b]THIAZOLE AND THIAZOLO[2,3-b]-1,3,4-THIADIAZINE DERIVATIVES

Pedro Molina*, Antonio Arques, Maria de los Desamparados Velasco, and José Manuel Villalgordo

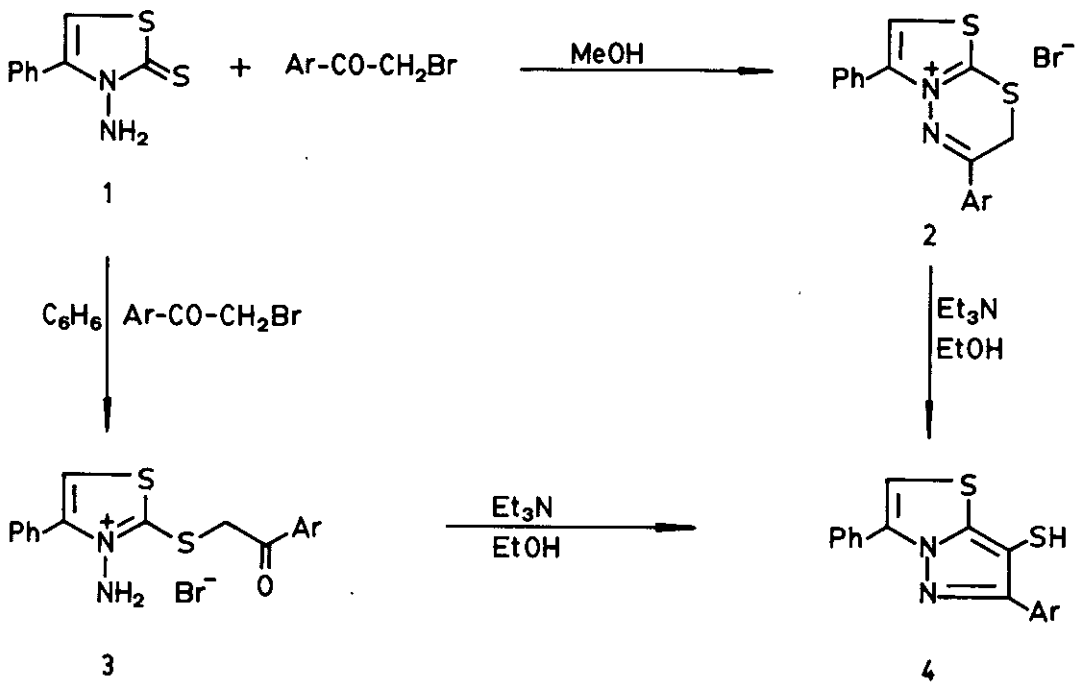
Departamento de Química Orgánica, Facultad de Ciencias,
Universidad de Murcia, 30001, Murcia, Spain

Abstract - Two approaches for the preparation of a number of pyrazolo[5,1-b]thiazoles are reported. The first involves reaction of 3-amino-4-phenyl-thiazoline-2-thione 1 with phenacyl bromides to give thiazolo[2,3-b]-1,3,4-thiadiazines 2 which by action of triethylamine are converted into the pyrazolo[5,1-b]thiazoles 4. The second is based on the reaction of 3-amino-2-methylthio-4-phenylthiazolium cation 5 with activated acetonitriles to give 7-substituted 6-amino-3-phenylpyrazolo[5,1-b]thiazoles 7.

In the last few years we were involved in a program aiming to develop synthetic approaches for nitrogen-bridgehead heterocycles utilising readily obtainable N-amino heterocycles or pyrylium cations as starting materials[1]. In this contex, we have reported the preparation of fused pyrazoles e.g. pyrazolo[1,5-a]pyridines[2,3,4], pyrazolo[5,1-c]-1,2,4-triazoles[5,6], pyrazolo[1,5-c]-1,3-oxazines[7], pyrazolo[2,3-d]-1,2,4-triazepines[8] and fused thiazoles e.g. thiazolo[3,2-a]pyridines[9], thiazolo[3',2':1,5]-1,2,4-triazolo[3,4-b]-1,3,4-thiazine[10] and thiazolo[3,2-c]quinazolines[11]. We now describe two general methods for the preparation of the otherwise not readily available pyrazolo[5,1-b]thiazole ring system which contain the pyrazolo and thiazole moieties.

No general method for the preparation of derivatives of the pyrazolo[5,1-b]thiazole ring system has hitherto been reported, it has only been mentioned that the reaction of pyrazoline-5-thiones with α-halocarbonyl compounds[12,13] or cyclization of 3-aminothiazolium salts by action of acetic anhydride/sodium acetate[14] lead to pyrazolo[5,1-b]thiazole derivatives. We now report here two apparently

widely applicable synthesis of derivatives of the pyrazolo[5,1-b]thiazole ring in synthetically useful yields. The first approach is based on the sequential treatment of 3-amino-4-phenylthiazoline-2-thiones 1, readily available from phenacyl hydrazinodithioformate[15], with phenacyl bromides and triethylamine. The N-amino heterocycle 1 reacts with phenacyl bromides in dry methanol to give the corresponding 6-aryl-3-phenyl-7H-thiazolo[2,3-b]-1,3,4-thiadiazin-3-ium bromides 2 in excellent yields (64-86%). However, when the reaction is carried out in dry benzene compound 1 undergoes alkylation on the exocyclic sulfur atom to give the corresponding 3-amino-2-phenacylthio-4-phenylthiazolium bromides 3 (60-88%). When ethanolic solutions of 2 or 3 are treated with equimolecular amounts of triethylamine pyrazolo[5,1-b]thiazole derivatives are obtained in excellent yields (67-98%). We believe that the conversion 2 ⟶ 4 is similar to the suggested[16] for the base-catalyzed rearrangement of 6H-1,3,4-thiadiazines into pyrazoles.



Structural elucidation of 2, 3 and 4 is accomplished on the basis of spectral and microanalytical data. The ir spectra of all thiazolo[2,3-b]-1,3,4-thiadiazinium bromides 2 show a strong absorption band in the region 1600 cm^{-1} attributable to the C=N bond; bands due to the NH_2 group are absent, while the presence of the NH_2 group in compounds 3 is confirmed by the absorption bands in the region 3370-3100 cm^{-1}; furthermore the carbonyl group in 3 appears near to 1670 cm^{-1}. In the ^{1}H-nmr spectra of 2 and 3 the chemical shift of methylene group is characteristic at δ 4.5-4.6 ppm while in the ^{1}H-nmr spectra of compounds 4 this signal is absent. Mass spectra of compounds 4 show the expected molecular ion, peaks are also found at m/z [M^+- Ar-CN], [M^+- Ar-CN - H], Ar-CN, 134 and 102.

Table 1. Preparation of 7H-Thiazolo[2,3-b]-1,3,4-thiadiazinium Bromides 2.

Entry	Ar	Mp(°C)	Yield (%)	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	C_6H_5	217-218	64	52.28	3.49	7.28	$C_{17}H_{13}N_2BrS_2$	52.44	3.36	7.19
b	4-Br-C_6H_4	235-236	76	43.79	2.41	6.13	$C_{17}H_{12}N_2Br_2S_2$	43.60	2.58	5.98
c	4-Cl-C_6H_4	216-217	86	47.93	2.61	6.41	$C_{17}H_{12}N_2BrClS_2$	48.18	2.85	6.61
d	4-O_2N-C_6H_4	233-234	86	46.92	2.85	9.73	$C_{17}H_{12}N_3BrO_2S_2$	47.01	2.78	9.67
e	4-C_6H_5-C_6H_4	214-215	75	59.47	3.83	5.84	$C_{23}H_{17}N_2BrS_2$	59.35	3.68	6.01

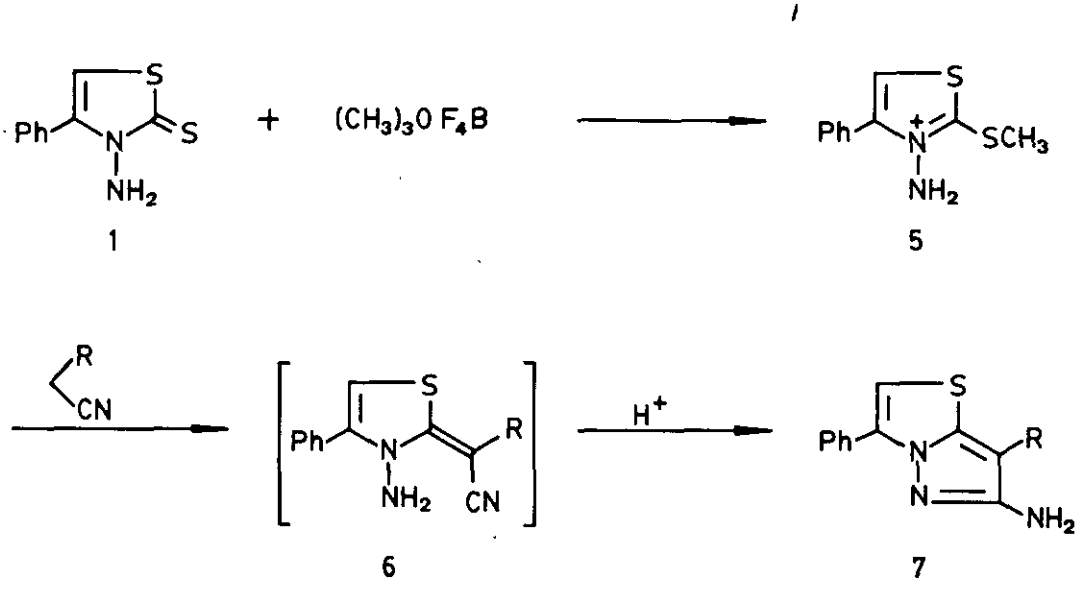
Table 2 .Preparation of 3-Amino-4-phenyl-2-phenacylthio-thiazolium Bromides 3.

Entry	Ar	Mp (°C)	Yield (%)	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
a	C_6H_5	219-220	67	49.93	3.89	6.73	$C_{17}H_{15}N_2BrOS_2$	50.12	3.71	6.87
b	4-Br-C_6H_4	145-146	60	42.17	2.78	5.52	$C_{17}H_{14}N_2Br_2OS_2$	41.99	2.90	5.76
c	4-Cl-C_6H_4	215-216	82	46.37	2.95	6.51	$C_{17}H_{14}N_2BrClOS_2$	46.21	3.19	6.34
d	4-O_2N-C_6H_4	206-207	61	45.26	3.27	9.36	$C_{17}H_{14}N_3BrO_3S_2$	45.13	3.12	9.29
e	4-C_6H_5-C_6H_4	210-211	88	56.98	4.63	5.91	$C_{27}H_{19}N_2BrOS_2$	57.14	4.79	5.79

Table 3. Preparation of Pyrazolo[5,1-b]thiazole Derivatives 4 and 7.

Compound N°	Ar/R	Mp (°C)	Yield (%) Method A	Yield (%) Method B	Found C	Found H	Found N	Molecular Formula	Required C	Required H	Required N
4a	C_6H_5	187-188	67	56	62.02	3.84	8.90	$C_{17}H_{12}N_2S_2$	62.20	3.92	9.08
4b	4-Br-C_6H_4	190-191	73	66	52.84	2.93	7.09	$C_{17}H_{11}N_2BrS_2$	52.71	2.86	7.23
4c	4-Cl-C_6H_4	192-193	74	70	59.55	3.23	8.17	$C_{17}H_{11}N_2ClS_2$	59.25	3.18	7.87
4d	4-O_2N-C_6H_4	269-270	98	82	57.70	3.03	12.07	$C_{17}H_{11}N_3O_2S_2$	57.77	3.13	11.88
4e	4-C_6H_5-C_6H_4	194-195	73	71	72.02	4.10	7.08	$C_{23}H_{16}N_2S_2$	71.84	4.19	7.28
7a	CN	189-191	43		60.18	3.41	23.19	$C_{12}H_8N_4S$	59.98	3.36	23.32
7b	COOEt	139-140	47		58.42	4.67	14.51	$C_{14}H_{13}N_3O_2S$	58.52	4.56	14.62
7c	COOMe	134-135	51		57.32	3.91	15.53	$C_{13}H_{11}N_3O_2S$	57.17	4.06	15.39

The second approach is based on the reaction of the N-aminoazonium salt 3-amino-2-methylthio-4-phenylthiazolium tetrafluoroborate 5, available from 1 and trimethyloxonium tetrafluoroborate, with acetonitriles activated by another electron-delocalizing group. Compound 5 reacts with activated acetonitriles in the presence of an excess of pyrrolidine to give the corresponding functionalized enamines 6, which can be used without purification in the next step. In only one case was the enamine isolated: 6 (R = CN) was obtained as crystalline product in 42% yield. Enamines 6 undergo cyclization by action of dry hydrogen chloride at room temperature to give the corresponding pyrazolo[1,5-b]thiazoles 7 (43-51%).



1 5 6 7

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 5993C spectrometer. Elemental analyses were performed with a Perkin-Elmer 240C instrument.

Improved Procedure for the Preparation of 3-Amino-4-phenylthiazoline-2-thione 1. To a solution of phenacyl hydrazinodithioformate[15] (2.26 g, 10 mmol) in dry isopropanol (30 ml) aqueous hydrochloric acid (11 N, 4 ml) was added. The mixture was stirred at reflux temperature for 3 h. After cooling, the solution was poured into ice-water (100 ml) and it was held at 4°C overnight. The precipitated solid was separated by filtration, washed well with water (2x50), 1N sodium hydroxide (2x50) and water until pH=7. The crude product recrystallized from ethanol gave 1 (1.17 g, 57%) as creamy flakes, mp 146-147°C [Lit. mp 146-147°C][15].

Table 4. Spectral Data of Compounds 2, 3, 4 and 7.

Compound No.	Ir (cm^{-1})	^{1}H-Nmr[a] (ppm)	MS[b] m/z (%)
2a	1613, 1591, 1574, 1489, 1342, 1160, 1030, 911, 793, 770, 751, 690.	8.2-7.3 (11H, m) 4.52 (2H, s)	308(6), 277(23), 276 (100), 275(17), 206(4) 205(17), 193(30), 160(4) 134(4), 103(6), 102(45).
2b	1585, 1549, 1490, 1447, 1412, 1315, 1185, 1072, 1007, 917, 823, 754, 685.	8.1-7.55 (10H, m) 4.60 (2H, s)	390(2), 389(3), 388(14), 383(3), 386(12), 358(6), 357(20), 356(100), 355 (29), 354(92), 192(3), 102(6).
2c	1591, 1553, 1492, 1459, 1444, 1412, 1320, 1183, 1093, 1020, 931, 915, 826, 753, 685.	8.1-7.3 (10H, m) 4.58 (2H, s)	345(2), 344(6), 343(6), 342(16), 313(8), 312(39) 311(25), 310(100), 205 (5), 134(5), 102(8).
2d	1610, 1583, 1562, 1523, 1472, 1455, 1347, 1336, 1319, 1155, 917, 860, 803, 769, 704, 688, 685.	8.65-7.35 (10H, m) 4.68 (2H, s)	354(3), 353(13), 322 (24), 321(100), 292(7), 291(29), 275(10), 274 (7), 205(9), 193(4), 134(8), 102(13).
2e	1591, 1563, 1489, 1444, 1319, 1200, 1155, 1007, 917, 849, 769, 747, 725, 696.	8.3-7.5 (15H, m) 4.55 (2H, s)	353(29), 352(100), 195 (59), 194(14), 193(69), 192(18), 181(44), 180 (93), 179(19), 153(24), 152(79), 134(74), 102 (53), 82(18), 80(16).
3a	3370, 3103, 1670, 1596, 1574, 1489, 1450,1397, 1325, 1206, 1172, 1098, 1002, 905, 770, 752, 690.	8.2-7.45 (11H, m) 4.6 (2H, s)	308(2), 276(4), 209 (13), 208(100), 200(6) 198(6), 148(7), 134(34), 105(81), 102(7), 77(20).
3b	3374, 3183,1693,1585, 1489, 1313, 1200, 1070, 979, 815, 764, 696 .	8.1-7.45 (10H, m) 4.55 (2H, s)	357(4), 356(12), 355 (4), 354(12), 280(13), 278(28), 276(13), 209 (13), 208(100), 185(73), 183(74), 157(12), 155 (12), 134(17), 102(4).

Table 4. (continuation).

3c	3194, 3069, 1687, 1585, 1568, 1488, 1398, 1364, 1297, 1200, 1166, 1088, 1013, 986, 866, 820, 798, 764, 696.	8.2-7.4 (10H, m) 4.6 (2H, s)	312(2), 310(6), 236(1), 234(4), 232(3), 209(7), 208(57), 141(33), 139 (100), 134(23), 113(6) 111(17), 102(5).
3d	3200, 3081, 1693, 1602, 1518, 1342, 1195, 990, 860, 843, 760, 696.	7.42-8.71 (10H, m) 4.68 (2H, s)	322(4), 321(16), 320 (8); 291(4), 245(3), 243 (3), 209(13), 208(100) 150(77), 134(26), 104 (19), 102 (6).
3e	3155, 3092, 1670, 1608, 1489, 1444, 1404, 1302, 1211, 1194, 1166, 996, 962, 832, 759, 725, 697.	8.40-7.45 (15H, m) 4.58 (2H, s)	353(2), 352(5), 276 (7), 274(7), 209(8), 208(62), 182(14), 181 (100), 153(12), 152(27) 134(12).
4a	3120, 3092, 1580, 1557, 1495, 1450, 1347, 1297, 1161, 1059, 821, 776, 742, 702, 690.	8.25-7.30 (10H, m) 6.90 (1H,s)	308(M^+, 27), 307(49), 206 (16), 205(58), 204(97), 160(6), 135(11), 134 (100), 103(9), 102(41), 89(14), 77(21).
4b	3120, 1597, 1552, 1494, 1448, 1404, 1247, 1291, 1161, 1070, 1008, 832, 770, 736, 720, 707.	8.11-7.99 (2H, m) 7.60-7.35 (5H,m) 7.22-7.05 (2H,m) 6.85 (1H, s)	388(M^++2, 6), 386(M^+, 6) 356(61), 355(8), 354 (62), 353(8), 366(13), 205(29), 204(30), 172 (13), 134(77), 128(13), 102(100), 77(16).
4c	3120, 1597, 1552, 1494, 1450, 1342, 1291, 1162, 1091, 1015, 830, 770, 721, 705.	8.40-8.10 (2H,m) 7.83 (2H, d, J=8.5 Hz), 7.70-7.45 (3H, m), 7.21 (2H, d, J=8.5 Hz) 7.0 (1H, s)	344(M^++2, 12), 343(14), 342(M+, 28), 341(20), 313(5), 312(22), 311 (15), 310(56), 306 (27), 205(83), 204 (100), 172(9), 160(8), 137(7), 134(66), 102(43)
4d	3115, 1602, 1518, 1460, 1342, 1109, 1020, 855, 747, 708, 691.	8.6-7.3 (9H, m) 7.0 (1H, s)	353(M^+, 14), 321(87), 275(15), 247(15), 205, (49), 204(53), 135(16),

Table 4. (continuation).

			134(80), 103(15), 102 (100), 89(14).
4e	1597, 1557, 1500, 1472, 1449, 1342, 1297, 1161, 1008, 917, 844, 764, 725, 706, 696.	8.30-7.25 (14H, m) 6.85 (1H, s)	384(M^+, 25), 383(20), 352(25), 351(5), 205 (90), 204(100), 179(30), 178(15), 172(6), 160(9), 153(11), 152(27), 134 (63), 102(31).
7a	3432, 3313, 3205, 3126, 2214, 1636, 1538, 1546, 1506, 1421, 1386, 1030, 919, 764, 726, 705, 692.	8.5-8.15 (2H, m) 7.75-7.50 (3H, m) 6.85 (1H, s) 5.05 (2H, s)	240(M^+, 100), 213(5), 187(16), 186(5), 161 (20), 134(9), 102(39).
7b	3465, 3318, 3208, 3118, 1703, 1626, 1507, 1493, 1450, 1360, 1307, 1126, 777, 756, 709.	7.98-7.86 (2H, m) 7.44-7.35 (3H, m) 6.76 (1H, s) 4.68 (2H, s) 4.31 (2H, q, J=7.1 Hz), 1.37 (3H, t, J=7.1 Hz)	287(M^+, 66), 259(5), 243(11), 242(46), 241 (100), 215(10), 187(19), 186(8), 134(16), 102(12).
7c	3455, 3304, 3138, 3047, 1694, 1610, 1534, 1501, 1493, 1451, 1329, 1192, 1125, 783, 750, 723, 696.	8.6-8.2 (2H, m) 7.85-7.5 (3H, m) 6.90 (1H, s) 5.13 (2H, s) 3.88 (3H, s)	273(M^+, 99), 242(42), 241(100), 187(25), 186 (17), 134(21), 102(16).

[a] Obtained as solutions in $CDCl_3$+TFA, except for compounds 4a, 4b, 4c, 4e and 7b which were obtained in $CDCl_3$; compounds 7a and 7e were obtained in DMSO-d_6.

[b] Recorded at 70 eV.

General Procedure for the Formation of 7H-Thiazolo[2,3-b]-1,3,4-thiadiazinium Bromides 2. To a solution of 3-amino-4-phenyl-thiazoline-2-thione 1 (0.416 g, 2 mmol) in dry methanol (15 ml) the appropriate phenacyl bromide (2 mmol) was added. The reaction mixture was stirred at reflux temperature for 24 h. On cooling, the precipitated solid was collected by filtration, dried and recrystallized from methanol to give 2 as yellow prisms (see Table 1).

General Procedure for the Formation of 3-Amino-2-phenacylthio-4-phenylthiazolium Bromides 3. To a solution of 1 (0.416 g, 2 mmol) in dry benzene (15 ml) the appropriate phenacyl bromide (2 mmol) was added. The resultant solution was refluxed for 2 h. After cooling, the precipitated solid was filtered, washed with benzene and recrystallized from benzene to give 3 as colourless needles (see Table 2).

General Procedure for the Formation of 6-Aryl-3-phenyl-7-mercaptopyrazolo[5,1-b]thiazoles 4. To a solution of the appropriate 7H-thiazolo[2,3-b]-1,3,4-thiadiazinium bromide 2 (2 mmol) (Method A) or 3-amino-2-phenacylthio-4-phenylthiazolium bromide 3 (2 mmol) (Method B) in absolute ethanol (15 ml), triethylamine (2 mmol) was added. The reaction mixture was stirred at reflux temperature for 4 h. After cooling, the precipitated solid was separated by filtration, dried and recrystallized from ethanol to give 4 as yellow prisms (see Table 3).

3-Amino-2-methylthio-4-phenylthiazolium Tetrafluoroborate 5. 3-Amino-4-phenylthiazoline-2-thione 1 (0.416 g, 2 mmol), trimethyloxoniun tetrafluoroborate (0.296 g, 2mmol) and dry dichloromethane (15 ml) were stirred under nitrogen at room temperature for 3 h. Elimination of solvent under reduced pressure and addition of ether (10 ml) to the residual material gave a solid which was filtered, dried and recrystallized from dichloromethane/ether (1:1) to give 5 (0.54 g, 87%) as colourles prisms, mp 103-105°C (Found: C, 38.55; H, 3.69; N, 8.83. $C_{10}H_{11}N_2BF_4S_2$ requires C, 38.73; H, 3.57; N, 9.03). $\nu_{max.}$(Nujol) 3381, 3296, 3144, 1613, 1494, 1421, 1325, 1302, 1285, 1228, 1200, 1070, 968, 934, 911, 843, 781, 764, 701; ($CDCl_3$+TFA) 7.9-7.4(5H, m), 7.1(1H, s), 2.9(3H, s).

General Procedure for the Formation of 7-Substituted 6-Amino-3-phenylpyrazolo[5,1-b]thiazoles 7. The appropriate activated acetonitrile (6 mmol), pyrrolidine (6 mmol) and absolute ethanol (15 ml) were stirred under nitrogen at room temperature for 20 min, then a solution of 5 (6 mmol) in absolute ethanol (15 ml) was added dropwise. The resultant mixture was stirred at room temperature for 15 h (evolution of methanethiol was clearly detected). A stream of dry hydrogen chloride was passed through the solution for 1 h. Elimination of solvent under reduced pressure leads to a crude product which recrystallized from ethanol yielded 7 as a crystalline solid (see Table 3).

Enamine 6 (R = CN). Malononitrile (0.66 g, 10 mmol), triethylamine (10 mmol) in dry acetonitrile (20 ml) were stirred under nitrogen at room temperature for 20 min, then a solution of 5 (10 mmol) in the same solvent (20 ml) was added. The reaction mixture was stirred at room temperature for 12 h. Elimination of solvent under reduced pressure and addition of cold ethyl acetate (10 ml) to the residual material gave a solid which was filtered and recrystallized from ethyl acetate to give 6 (R = CN) (0.20 g, 42%) as brown prisms, mp 197-198°C (Found: C, 60.18; H, 3.41; N, 23.19. $C_{12}H_8N_4S$ requires C, 59.92; H, 3.39; N, 23.22). ν_{max} (Nujol) 3358, 3262, 2202, 2180, 1619, 1517, 1497, 1364, 1291, 1138, 911, 769, 735, 696;

m/z 240(M^+, 100), 213(4), 187(17), 186(6), 161(25), 134(12), 102(65).

ACKNOWLEDGEMENT

The authors are indebted to Comisión Asesora de Investigación Científica y Técnica for financial support, project number 2019/83.

REFERENCES

1. P. Molina, Bull. Soc. Chim. Belg., 1986, 95, 973.
2. A. Arques, H. Hernandez, P. Molina and M.J. Vilaplana, Synthesis, 1981, 910.
3. P. Molina, A. Arques and A. Ferao, Synthesis, 1982, 645.
4. P. Molina, A. Arques and H. Hernandez, Synthesis, 1983, 1021.
5. P. Molina, M. Alajarín and M.J. Vilaplana, Heterocycles, 1985, 23, 641.
6. M. Alajarín, P. Molina, M.J. Pérez de Vega, M.C. Foces-Foces, F.H. Cano, R.M. Claramunt and J. Elguero, Chem. Scripta, 1985, 25, 230.
7. P. Molina, A. Tárraga, E. Romero and M. Lorenzo Peña, Synthesis, 1984, 71.
8. P. Molina, A. Tárraga and C. Serrano, Tetrahedron, 1984, 40, 4901.
9. P. Molina, M. Alajarín and M.J. Pérez de Vega, Synth. Commun., 1983, 13, 933.
10 P. Molina and M.J. Vilaplana, J. Chem. Res. (S), 1986, 70.
11. P. Molina, A. Arques and M.V. Vinader, Liebigs Ann. Chem., (in press).
12. K. Peseke, Z. Chem., 1976, 16, 52.
13. K. Peseke, C. Vogel, J. Blaesche and K.H. Kollhof, J. Prakt. Chem., 1982, 324, 639.
14. H. Koga, M. Hirobe and T. Okamoto, Chem. Pharm. Bull., 1974, 22, 482.
15. J. Sandstrom, Arkiv. Kemi., 1954, 7, 249.
16. R.R. Schmidt and H. Huth, Tetrahedron Lett., 1975, 33.

Received, 30th January, 1987