2-METHYLTHIO-1,3,4-THIADIAZOLIUM CATIONS AS USEFUL PRECURSORS FOR THE PREPARATION OF 2-AMINO-1,3,4-THIADIAZOLE DERIVATIVES AND AS DEHYDRATING REAGENTS OF ALDOXIMES

Pedro Molina*, Alberto Tárraga, and Arturo Espinosa

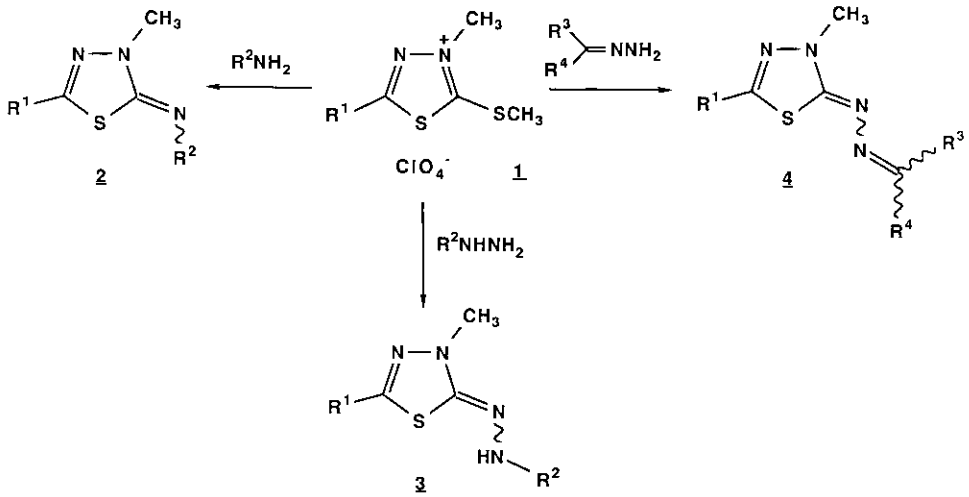
Departamento de Química Orgánica, Facultad de Ciencias Químicas y Matemáticas, Universidad de Murcia, Campus de Espinardo, 30071 Murcia, Spain

Abstract — The 2-methylthio-1,3,4-thiadiazolium perchlorates 1 react with primary amines, hydrazines, hydrazones and hydrazides to give the 2-amino-1,3,4-thiadiazole derivatives 2, 3 and 4 respectively. Similarly, 1 with diamino compounds leads to the corresponding bi-heterocycles 11, 12 and 13. The reaction of 1 with aldoximes leads directly to 1,3,4-thiadiazol-2-ones 16 and the corresponding nitriles in high yields.

Previously, we have studied the reaction of alkyl 2-methyldithiocarbazates with acyl chlorides to provide a convenient method for the preparation of novel 2-alkylthio-1,3,4-thiadiazolium cations in good yields.[1] Our interest in the synthesis and chemical properties of 2-functionalized 1,3,4-thiadiazole derivatives prompted us to investigate the reaction of 2-methylthio-1,3,4-thiadiazolium perchlorates 1 with several types of nucleophiles, mainly N-, O- and C-nucleophiles.

The present paper records investigation on the preparation of 2-amino-1,3,4-thiadiazole systems by reaction of the perchlorates 1 both with amines or hydrazines. These compounds have received much attention because they are biologically active compounds. They display antimicrobial,[2] antitumor,[3] hypoglycemic,[4] radioprotective,[5] anti-inflammatory,[6] antihistamine and anticholinergic[7] activities, in addition to uncouple oxidative phosphorylation in mitochondrias and photosynthetic phosphorylation in chloroplasts,[8] as well as they are used as pesticides,[9] dyes[10] and lubricants.[11] They have therefore attractive interest concerning their synthesis. So far, there are two main routes for the preparation of 2-amino-1,3,4-thiadiazoles. One starts from a 1,3,4-thiadiazole ring with a substituent, such as a halogen atom or an alkylsulphonyl group, which can be displaced by ammonia or an amine. This approach could be of value as a way of preparing 2-amino-1,3,4-thiadiazole corresponding to thiosemicarbazides which are not readily available. Thus 2-hydrazino-5-substituted 1,3,4-thiadiazoles have been prepared by hydrazinolysis of 2-methylsulphonyl[12] or 2-chloro-5-substituted 1,3,4-thiadiazoles.[13] Less common are methods using thiosemicarbazide derivatives as open chain precursors. Thus 2-alkylamino-1,3,4-thiadiazoles are prepared from 4-alkylthiosemicarbazides by reaction with carboxylic acids[14] or orthoformates.[15] The nature of the substituent in the 4-position of the thiosemicarbazide has a

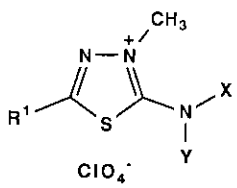
Scheme 1



Compound	R^1	R^2
1 a	CH_3	
1 b	C_6H_5	
1 c	4-$H_3C.C_6H_4$	
1 d	4-$H_3CO.C_6H_4$	
1 e	4-$O_2N.C_6H_4$	
2 a	4-$H_3CO.C_6H_4$	CH_3
2 b	4-$H_3CO.C_6H_4$	$C_6H_5.CH_2$
2 c	4-$H_3CO.C_6H_4$	1-Adamantyl
3 a	4-$H_3C.C_6H_4$	C_6H_5
3 b	4-$H_3CO.C_6H_4$	C_6H_5
3 c	4-$H_3CO.C_6H_4$	1-Adamantyl
3 d	4-$H_3CO.C_6H_4$	4-$H_3C.C_6H_4CO$
3 e	4-$H_3CO.C_6H_4$	4-$Br.C_6H_4.CO$
3 f	4-$H_3CO.C_6H_4$	4-$O_2N.C_6H_4.CO$

Compound	R^1	R^3	R^4
4 a	CH_3	H	C_6H_5
4 b	C_6H_5	H	C_6H_5
4 c	4-$H_3CO.C_6H_4$	H	C_6H_5
4 d	CH_3	CH_3	4-$Cl.C_6H_4$
4 e	C_6H_5	CH_3	4-$O_2N.C_6H_4$
4 f	4-$H_3C.C_6H_4$	CH_3	4-$Cl.C_6H_4$

5 - 10



Compound	X	Y
5	H	R^2
6	H	NH-R^2
7	H	N=CR^3R^4
8	-$(CH_2)_4$-	
9	CH_3	NH_2
10	CH_3	N=CHR^2

profound effect on its reactivity.

We now describe a general method for the preparation of some 2-amino derivatives of the 1,3,4-thiadiazole ring from 5-substituted 3-methyl-2-methylthio-1,3,4-thiadiazolium perchlorates 1 and amino compounds. The 1,3,4-thiadiazolium salts 1 react with primary alkylamines in the presence of triethylamine in methanol at reflux temperature for 5 h to give 5-substituted 2-alkylimino-3-methyl-2,3-dihydro-1,3,4-thiadiazoles 2 in excellent yields (Scheme 1). The establishment of these structures is based on their ^{1}H, ^{13}C nmr and mass spectra. ^{1}H Nmr spectra show as the only characteristic signal a singlet at δ = 3.54-3.68, corresponding to the N-methyl group, whereas the ^{13}C nmr spectra show signals at δ = 35.22-35.71 due to the N-methyl group, in addition to the signals at δ = 147.34-158.44 and 143.80-144.82 corresponding to the ring carbon atoms C-2 and C-5, respectively. The assignement of carbon shifts, and specially those of quaternary downfield carbons, has required proton coupled spectra, by means that the absolute value of the long range carbon-proton coupling constants and of the multiplicity characterizes each carbon signal *uniquely*.[16,17] *In this sense, undecoupled ^{13}C nmr spectrum of 2b provides a powerful tool for* distinguishing the two ring carbon atoms and the C-4 in the 5-substituent, because it shows the expected triplet ($^{3}J_{C=N-C-H}$= 8.53 Hz) x quadrouplet ($^{3}J_{C-N-C-H}$= 8.06 Hz) pattern for C-2 at δ = 158.34 and the triplet ($^{3}J_{C-C-C-H}$= 4.70 Hz) for C-5 at δ = 144.82, appearing the C-4 atom on the 5-substituent as a complex multiplet at δ = 160.91. Mass spectra show the expected molecular ion peaks in high intensity, appearing the base peak at m/z =[M^{+}-$R^{2}NCS$].

Similarly, compounds 1 react with phenylhydrazine, adamantylhydrazine and arylhydrazides in the presence of triethylamine in ethanol at room temperature for 2 h to give the corresponding 1,3,4-thiadiazoles 3 in excellent yields (Scheme 1). The ir spectra of compounds 3 show an absorption band at 3136-3375 cm^{-1} due to the amino group, and 3d-f show, in addition, a strong absorption band at 1635-1641 cm^{-1} attributable to the carbonyl group. In the ^{1}H nmr spectra of compounds 3, the N-methyl group appears characteristically at δ = 3.60-3.85 as it does in the ^{13}C nmr spectra at δ = 35.81-35.87; moreover, the ring carbons C-2 and C-5 appear at δ = 161.78-164.82 and δ = 145.48-145.90, respectively. Mass spectra show the expected molecular ion peaks, which are the base peaks for 3a-b.

Compounds 1 also react with hydrazones in the presence of equimolar amounts of triethylamine in ethanol at reflux temperature for 4 h to give the corresponding 1,3,4-thiadiazoles 4 in good yields (Scheme 1). In the ^{1}H nmr spectra of compounds 4, the N-methyl group appears at δ = 3.66-3.82 and, in addition, in compounds 4a-c (R^{3}=H), the aldiminic proton appears at δ = 8.36-8.67, whereas in compound 4d (R^{3}=CH_3), the C-methyl group occurs at δ = 2.47. The carbon chemical shifts of C-2 and C-5 for the imino structure 4c are δ = 166.30 and δ = 148.31, respectively. Mass spectra show the expected molecular ion peaks and the fragmentation patterns are in agreement with the proposed structures.

^{1}H Nmr and ^{13}C nmr chemical shift values in compounds 2-4 are in very good agreement with those reported for 2-imino-1,3,4-thiadiazoles.[16-19] Also, it is known that the coupling constants $^{1}J_{C-H}$ for N-benzyl methylene groups are related with the extent of charge delocalization on the nitrogen atom and have been used to establish the structure of some related 2-imino-1,3,4-thiadiazoles.[16] In the case of 2b, the value $^{1}J_{C-H}$= 133.97 Hz observed confirms the proposed structure.

The first step for all of these reactions described above should be the nucleophilic attack of the primary amino group to the 2-position in the thiadiazolium ring, followed by elimination of methanethiol to give the corresponding 2-amino-1,3,4-thiadiazolium cations 5-7, which under basic conditions are converted into the neutral species 2-4. In this sense we have found that

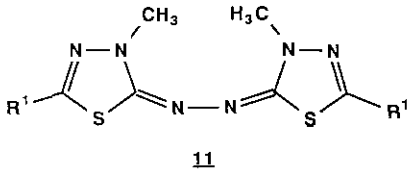
when those reactions were carried out without addition of base, the only products obtained were the salts 5-7. The salts 5-7 underwent deprotonation on treatment with triethylamine in ethanolic medium at room temperature.

By using secondary amino groups as nucleophiles, such as pyrrolidine, the reaction leads to the cationic specie 8 which was identified by microanalytical and spectral data. Similarly, methylhydrazine reacts with 1 under mild conditions to give the perchlorate 9, as the only product, isolated in moderate yield. Support for the formula 9 is clearly provided by the ir spectrum, which shows bands at 3320 and 3215 cm^{-1} due to the NH_2 group and by the fact that treatment with p-anisaldehyde in the presence of catalityc amounts of trifluoroacetic acid gave the aldimine 10.

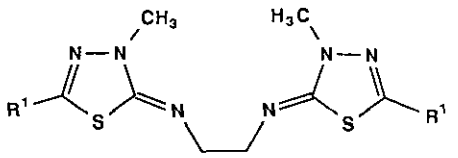
^1H And ^{13}C nmr spectra are useful in distinguishing between neutral and cationic species, because in the latter case the N-methyl group appears at δ = 3.93-4.38 in the ^1H nmr, while in the ^{13}C nmr it does at δ = 37.97-41.08, appearing C-2 and C-5 at δ = 165.08-171.65 and 152.86-154.73 respectively. Also, for compounds 5a-b is characteristic the expected coupling between the NH and the CH_2 ($^3J_{HNCH}$= 4.82 Hz) or CH_3 ($^3J_{HNCH}$= 5.00 Hz).

Salts 1 react with symmetrical diamino compounds, such as hydrazine, ethylenediamine and o-phenylenediamine to give the bi-heterocycles 11, 12 and 13 respectively as crystalline solids in excellent yields (Scheme 2). Analytical and spectral data support their structures.

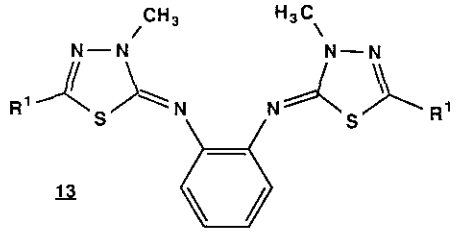
Scheme 2



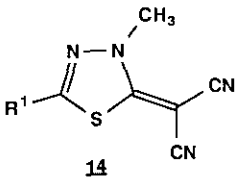
11



12



13



14

Compound	R^1
11 a	CH_3
11 b	4-$H_3C.C_6H_4$
12	4-$O_2N.C_6H_4$
13 a	4-$H_3C.C_6H_4$
13 b	4-$H_3CO.C_6H_4$
13 c	4-$O_2N.C_6H_4$
14	4-$H_3CO.C_6H_4$

1,3,4-Thiadiazolium salts 1 also react, in basic medium, with compounds possessing active methylene groups. Thus, the reaction of 1 with malononitrile in the presence of triethylamine in acetonitrile at room temperature leads to 2-dicyanomethylene-1,3,4-thiadiazole 14 in high yield (Scheme 2). The only method described so far, for the preparation of related compounds, lies in the reaction of acid chloride phenylhydrazones with thioketenes to provide a 3-phenylthiadiazoline with a difunctionalized group in the 5-position.[20]

Scheme 3

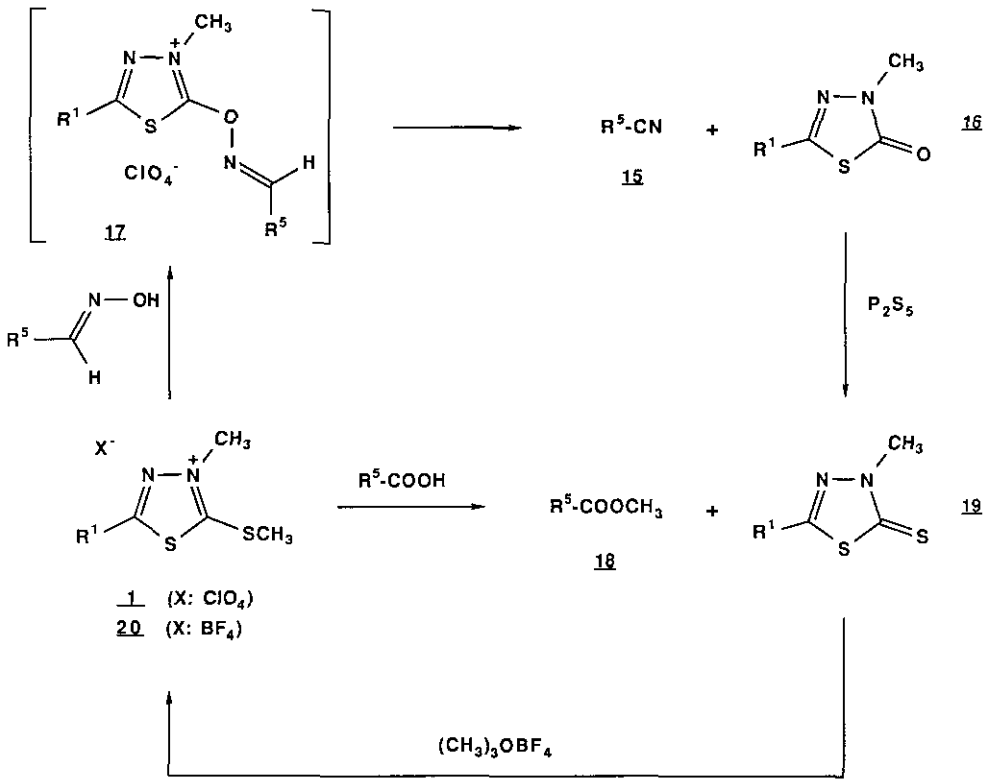


Table 1: Nitriles 15 and esters 18 prepared

Compound	R^5	Yield (%)	mp(°C) or bp(°C/Torr) Found	Reported[22]
15 a	C_6H_5	83	52 / 4	69 / 10
15 b	4-$H_3C.C_6H_4$	81	71 / 10	103-6 / 20
15 c	4-$H_3CO.C_6H_4$	85	60-62	61-62
15 d	3,4-$(H_3CO)_2.C_6H_3$	94	67	67-68
15 e	4-$O_2N.C_6H_4$	79	147-149	149
18 a	C_6H_5	87	199 / 760	96-8 / 24
18 b	4-$H_3C.C_6H_4$	80	217 / 760	222.5 / 760
18 c	3-$Cl.C_6H_4$	83	231 / 760	114 / 18
18 d	2-$O_2N.C_6H_4$	81	275 / 760	176 / 21

On the other hand, we also report here the reaction of 1 with oxygen-containing nucleophiles such as aldoximes and carboxylic acids.

It is expected that reaction of compounds 1 with aldoximes results in the displacement of methanethiolate ion to give O-substituted aldoximes. We consequently tested the expected reactivity of 1, the good leaving group ability of the thiadiazolones ring system and hence its behaviour as dehydrating agent. We now present an efficient method for the preparation of aromatic nitriles 15 from the corresponding aldoximes and an equimolar amount of 1 and triethylamine in dichloromethane at room temperature. Although the dehydration of aldoximes was carried out with several 5-substituted 1,3,4-thiadiazolium cations 1, the best results were obtained when R^1=4-$O_2N.C_6H_4$, which allow to separate easily the nitrile from the insoluble 5-(p-nitrophenyl)-1,3,4-thiadiazol-2-one 16d formed. We believe that the mechanism for this conversion involves the initial formation of the O-substituted aldoxime 17 as an intermediate, which undergoes elimination to give the corresponding nitrile 15 and the 1,3,4-thiadiazole 16 (Scheme 3)(Table 1).

The principal advantages of this method in contrast with the classical synthesis of nitriles from aldoximes using new mild dehydrating agents[21] are the single and easy procedure, high yields, mild reaction conditions, the convenient work up and the availability of the starting 1,3,4-thiadiazolium salts 1 which can also be regenerated as tetrafluoroborates 20 by sequential treatment of the resulting 16 with P_2S_5 and trimethyloxonium tetrafluoroborate.

However, compounds 1 react with aromatic carboxylic acids in the presence of potassium carbonate in chloroform at reflux temperature to give the corresponding methyl esters 18, identified by comparison with authentic pure samples, and 5-substituted 3-methyl-2-thioxo-2,3-dihydro-1,3,4-thiadiazoles 19 in excellent yields (Scheme 3)(Table 1).

Compounds 16, 19 and 20 have been characterized on the basis of their microanalytical and spectral data. Thiadiazolones 16 show an intense absorption band in the ir spectra at 1668-1669 cm^{-1} due to the carbonyl group. In the ^1H nmr, the N-methyl protons appear at δ = 3.59-3.69 while in the ^{13}C nmr for 16a this N-methyl carbon atom resonates at δ = 34.11, appearing the thiadiazole ring carbons at δ = 169.34 (C-2) and δ = 149.85 (C-5). On the other hand, in the thiadiazolethiones 19, the N-methyl group appears at δ = 3.90-3.92 in the ^1H nmr spectra, appearing this group's signal for 19b in the ^{13}C nmr at δ = 38.82. In the ^{13}C nmr spectrum is observed a large downfield chemical shift for C-2 at δ = 185.00, and a smaller shift in the same direction for C-5, at δ = 156.96. Tetrafluoroborates 20 display the same spectroscopical properties to those of the corresponding perchlorates.[1] Mass spectra show the molecular ion peaks as the base peak for compounds 16 and 19.

EXPERIMENTAL

Melting points were obtained in 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 recorded using a Varian EM-360 A (60 MHz) spectrometer or a Bruker AC-200 (200 MHz) using tetramethylsilane as internal reference. ^{13}C Nmr spectra, were determined on a Bruker AC-200 (50.3 MHz) spectrometer . The EI-mass spectra were obtained with a Hewlett-Packard 5993 C spectrometer at 70 eV. Elemental analyses were performed with a Perkin Elmer 240 C instrument. Nmr spectra for compounds **4e-f**, **7a-c**, and **13c** are not given because they are insoluble in the ordinary deuterated solvents.

Preparation of 3-Methyl-2-methylthio-5-substituted 1,3,4-thiadiazolium Perchlorates 1a-e. The title compounds were prepared following the general method described in previous paper.[1]

1e, R^1=4-$O_2N.C_6H_4$; (99%) white prisms; mp 255-256°C (from acetonitrile); (Found: C, 32.71; H, 2.81; N, 11.29. $C_{10}H_{10}ClN_3O_6S_2$ requires C, 32.66; H, 2.74; N, 11.43 %); ν_{max}(cm^{-1}) 1609, 1532, 1491, 1409, 1294, 1098, 926, 868, 855, 735, 708, 689; δ (^{1}H, 60 MHz)($CDCl_3$/TFA) 8.61 (2H,d,J=8.70Hz), 8.28 (2H,d,J=8.70Hz), 4.38 (3H,s), 3.23 (3H,s); m/z (%) 268 (M^+-ClO_4^-, 2), 253 (100), 177 (53), 149 (21), 122 (2), 105 (37), 103 (28), 76 (28), 73 (11), 47 (18).

General Procedure for the Preparation of 2-Imino-3-methyl-5-substituted 2,3-dihydro-1,3,4-thiadiazoles 2, 3 and 4. To a suspension of the corresponding 3-methyl-2-methylthio-1,3,4-thiadiazolium perchlorate **1** (5 mmol) in methanol (15 ml), equimolar amounts of the appropriate amino derivative (5 mmol) and triethylamine (0.51 g, 5 mmol) were added, and the mixture was refluxed for 5 h. On cooling, the solid formed is filtered off, dried and recrystallized from the adequate solvent.

2a, R^1=4-$H_3CO.C_6H_4$, R^2=CH_3; (1.06 g, 90%) yellow flakes; mp 112°C (from n-hexane); (Found: C, 56.03; H, 5.68; N, 17.82. $C_{11}H_{13}N_3OS$ requires C, 56.15; H, 5.57; N, 17.86 %); ν_{max}(cm^{-1}) 1643, 1605, 1506, 1404, 1347, 1300, 1254, 1176, 1016, 824, 721, 667; δ (^{1}H, 200 MHz)($CDCl_3$) 7.55 (2H,d, J=8.80Hz), 6.89 (2H,d,J=8.80Hz), 3.81 (3H,s,CH_3O), 3.58 (3H,s,endo CH_3N), 3.06 (3H,s,exo CH_3N); (^{13}C) 160.66, 158.44 (C-2), 144.20 (C-5), 126.85, 123.75, 114.08, 55.20 (CH_3O), 43.53 (exo CH_3N), 35.22 (endo CH_3N); m/z (%) 235 (M^+, 50), 221 (9), 163 (17), 162 (100), 161 (26), 147 (49), 134 (23), 133 (96), 119 (30), 107 (25), 102 (11), 73 (11).

2b, R^1=4-$H_3CO.C_6H_4$, R^2=$C_6H_5.CH_2$; (1.40 g, 90%) green prisms; mp 99°C (from n-hexane); (Found: C, 65.58; H, 5.53; N, 13.41. $C_{17}H_{17}N_3OS$ requires C, 65.57; H, 5.50; N, 13.49 %); ν_{max}(cm^{-1}) 1636, 1607, 1580, 1504, 1452, 1350, 1306, 1246, 1178, 1028, 923, 832, 740, 691; δ (^{1}H, 200 MHz)($CDCl_3$) 7.56 (2H,dd,J=6.81Hz,J=2.04Hz), 7.43-7.23 (5H,m), 6.90 (2H,dd,J=6.81Hz,J=2.04Hz), 4.40 (2H,s,CH_2), 3.81 (3H,s,CH_3O), 3.68 (3H,s,CH_3N); (^{13}C) 160.91, 158.34 (C-2), 144.82 (C-5), 139.59, 128.33, 127.48, 126.81, 123.53, 114.22, 60.66 (CH_2), 55.32 (CH_3O), 35.71 (CH_3N); m/z (%) 311 (M^+, 73), 234 (12), 163 (11), 162 (100), 161 (24), 147 (29), 134 (17), 133 (98), 119 (12), 108 (8), 91 (32), 77 (8).

2c, R^1=4-$H_3CO.C_6H_4$, R^2=$C_{10}H_{15}$ (1-adamantyl); (1.51 g, 85%) white needles; mp 161°C (from methanol); (Found: C, 67.54; H, 7.14; N, 11.78. $C_{20}H_{25}N_3OS$ requires C, 67.57; H, 7.09; N, 11.82 %);

ν_{max}(cm^{-1}) 1603, 1508, 1455, 1342, 1307, 1292, 1256, 1170, 1032, 822, 714, 672; δ (^{1}H, 200 MHz)($CDCl_3$) 7.56 (2H,dd,J=6.80Hz,J=2.11Hz), 6.89 (2H,dd,J=6.80Hz,J=2.11Hz), 3.81 (3H,s,CH_3O), 3.54 (3H,s,CH_3N), 2.12 (3H,broad s), 1.89 (6H,d,J=2.84Hz), 1.70 (6H,t,J=2.97Hz); δ (^{13}C) 160.48, 147.34 (C-2), 143.80 (C-5), 126.80, 124.15, 114.07, 55.27 (CH_3O), 53.25 (Ad,C-1), 40.75 (Ad, C-2), 36.62 (Ad,C-3), 35.64 (CH_3N), 29.71 (Ad,C-4); m/z (%) 355 (M^+,56), 340 (2), 222 (30), 220 (7), 193 (3), 163 (18), 162 (100), 161 (14), 151 (14), 149 (13), 135 (49), 133 (77), 119 (12), 107 (7).

3a, R^1=4-$H_3C.C_6H_4$, R^2=C_6H_5; (1.17 g, 79%) yellow prisms; mp 145-147°C (from methanol); (Found: C, 64.70; H, 5.57; N, 19.02. $C_{16}H_{16}N_4S$ requires C, 64.84; H, 5.44; N, 18.90 %); ν_{max}(cm^{-1}) 3244, 1606, 1575, 1494, 1406, 1293, 1186, 1151, 1030, 936, 816, 768, 731, 699; δ (^{1}H, 60 MHz)($CDCl_3$) 8.12-7.53 (9H,m), 3.85 (3H,s,CH_3N), 2.43 (3H,s); m/z (%) 296 (M^+, 100), 204 (25), 149 (13), 148 (13), 147 (16), 146 (28), 145 (37), 118 (70), 117 (38), 93 (15), 92 (17), 91 (33), 77 (26).

3b, R^1=4-$H_3CO.C_6H_4$, R^2=C_6H_5; (1.30 g, 83%) yellow prisms; mp 173°C (from methanol); (Found: C, 61.49; H, 5.18; N, 18.01. $C_{16}H_{16}N_4OS$ requires C, 61.52; H, 5.16; N, 17.93 %); ν_{max}(cm^{-1}) 3237, 1606, 1575, 1505, 1407, 1308, 1247, 1178, 1034, 935, 833, 768, 730, 693; δ (^{1}H, 60 MHz) 7.73 (2H,d, J=8.0Hz), 7.34 (2H,d,J=8.0Hz), 7.22-6.90 (5H,m); 3.80 (6H,s); m/z (%) 312 (M^+, 100), 220 (30), 165 (14), 163 (22), 162 (24), 161 (28), 148 (15), 147 (20), 134 (53), 133 (18), 107 (26), 93 (17), 92 (28), 91 (29), 77 (19).

3c, R^1=4-$H_3CO.C_6H_4$, R^2=$C_{10}H_{15}$ (1-adamantyl); (1.65 g, 89%) yellow prisms; mp 134°C (from methanol); (Found: C, 64.85; H, 7.03; N, 15.09. $C_{20}H_{26}N_4OS$ requires C, 64.83; H, 7.07; N, 15.12 %); ν_{max}(cm^{-1}) 3375, 1620, 1507, 1454, 1309, 1259, 1180, 1039, 819, 801, 721, 695; δ (^{1}H, 200 MHz)($CDCl_3$) 7.57 (2H,dd,J=6.75Hz,J=2.09Hz), 6.90 (2H,dd,J=6.75Hz,J=2.09Hz), 3.83 (3H,s,CH_3O), 3.60 (3H,s, CH_3N), 2.08 (3H,broad s), 1.74 (6H,d,J=2.41Hz), 1.66 (6H,broad s); δ (^{13}C) 161.78 (C-2), 160.66, 145.90 (C-5), 126.99, 124.01, 114.14, 55.31 (CH_3O), 55.02 (Ad,C-1), 41.93 (Ad,C-2), 36.78 (Ad,C-3), 35.82 (CH_3N), 29.55 (Ad,C-4); m/z (%) 370 (M^+, 57), 235 (46), 222 (18), 221 (54), 163 (15), 162 (22), 161 (34), 151 (24), 149 (19), 135 (100), 134 (29), 133 (82), 119 (12), 107 (23).

3d, R^1=4-$H_3CO.C_6H_4$, R^2=4-$Br.C_6H_4$.CO; (1.95 g, 93%) yellow needles; mp 268°C (from acetonitrile); (Found: C, 48.81; H, 3.55; N, 3.40. $C_{17}H_{15}BrN_4O_2S$ requires C, 48.70; H, 3.61; N, 13.36 %); ν_{max}(cm^{-1}) 3136, 1641, 1593, 1565, 1506, 1481, 1317, 1252, 1179, 1031, 851, 840, 745; δ (^{1}H, 200 MHz) (DMSO-d_6) 11.17 (1H,s,NH), 7.82 (2H,d,J=8.27Hz), 7.71 (2H,d,J=8.27Hz), 7.62 (2H,d,J=8.42Hz), 7.03 (2H,d,J=8.42Hz), 3.81 (3H,s,CH_3O), 3.66 (3H,s,CH_3N); δ(^{13}C) 164.74 (C-2), 161.37 (C=O), 160.88, 145.55 (C-5), 132. 68, 131.31, 129.28, 127.11, 124.86, 122.07, 114.59, 55.34 (CH_3O), 35.82 (CH_3N); m/z (%) 420 (M^++2, 15), 418 (M^+, 15), 235 (76), 185 (31), 183 (33), 162 (53), 161 (46), 157 (28), 155 (29), 147 (15), 134 (32), 133 (100), 119 (15), 108 (10).

3e, R^1=4-$H_3CO.C_6H_4$, R^2=4-$H_3C.C_6H_4$.CO; (1.67 g, 94%) yellow needles; mp 253°C (from methanol); (Found: C, 60.85; H, 5.19; N, 15.66. $C_{18}H_{18}N_4O_2S$ requires C, 61.00; H, 5.12; N, 15.81 %); ν_{max}(cm^{-1}) 3152, 1640, 1611, 1585, 1504, 1310, 1261, 1252, 1179, 1032, 841, 751, 735; δ (^{1}H, 200 MHz) (DMSO-d_6) 10.96 (1H,s,NH), 7.78 (2H,d,J=8.09Hz), 7.60 (2H,d,J=8.91Hz), 7.29 (2H,d,J=8.09Hz), 7.02 (2H,d,J=8.91Hz), 3.80 (3H,s,CH_3O), 3.65 (3H,s,CH_3N), 2.39 (3H,s); δ (^{13}C)

164.69 (C-2), 162.31 (C=O), 160.86, 145.48 (C-5), 141.06, 130.76, 128.80, 127.21, 127.09, 122.16, 114.59, 55.34 (CH_3O), 35.81 (CH_3N), 20.89; m/z (%) 354 (M^+, 32), 235 (90), 162 (38), 161 (40), 147 (11), 134 (24), 133 (70), 120 (11), 119 (100), 108 (7), 91 (55).

3f, R^1=4-$H_3CO.C_6H_4$, R^2=4-$O_2N.C_6H_4$.CO; (1.85 g, 96%) yellow needles; mp 257-258°C (from methanol); (Found: C, 53.11; H, 3.83; N, 18.02. $C_{17}H_{15}N_5O_4S$ requires C, 52.98; H, 3.92; N, 18.17 %); ν_{max}(cm^{-1}) 3150, 1635, 1577, 1518, 1349, 1264, 1180, 1024, 868, 854, 702; δ (^{1}H, 200 MHz)(DMSO-d_6) 11.38 (1H,s,NH), 8.34 (2H,d,J=8.71Hz), 8.10(2H,d,J=8.71Hz), 7.62 (2H,d,J=8.78Hz), 7.03 (2H,d, J=8.78Hz), 3.81 (3H, s,CH_3O), 3.67 (3H,s,CH_3N); δ (^{13}C) 164.82 (C-2), 160.94, 160.57 (C=O), 146.96, 145.69 (C-5), 139.28, 128.68, 127.15, 123.51, 122.00, 114.62, 55.36 (CH_3O), 35.87 (CH_3N); m/z (%) 385 (M^+, 20), 235 (68), 162 (79), 161 (55), 151 (26), 150 (36), 147 (19), 134 (39), 133 (100), 122 (8), 119 (18), 108 (13).

4a, R^1=CH_3, R^3=H, R^4=C_6H_5; (0.86 g, 74%) yellow prisms; mp 116-118°C (from ethanol); (Found: C, 56.61; H, 5.18; N, 24.30. $C_{11}H_{12}N_4S$ requires C, 56.87; H, 5.21; N, 24.12 %); ν_{max}(cm^{-1}) 1609, 1579, 1533, 1451, 1413, 1337, 1268, 1206, 1035, 762, 753, 694, 668; δ (^{1}H, 60 MHz) (DMSO-d_6) 8.63 (1H, s), 8.73-7.30 (5H,m), 3.84 (3H,s,CH_3N), 2.59 (3H,s); m/z (%) 232 (M^+, 51), 129 (18), 115 (60), 104 (100), 103 (47), 89 (51), 77 (83), 73 (15), 71 (32), 70 (21), 69 (35), 55 (40).

4b, R^1=C_6H_5, R^3=H, R^4=C_6H_5; (1.46 g, 99%) yellow needles; mp 121-122°C (from ethanol); (Found: C, 65.44; H, 4.60; N, 19.21. $C_{16}H_{14}N_4S$ requires C, 65.28; H, 4.79; N, 19.03 %); ν_{max}(cm^{-1}) 1609, 1577, 1545, 1445, 1404, 1337, 1250, 1043, 760, 712, 695; δ (^{1}H, 60 MHz)(DMSO-d_6) 8.67 (1H,s), 8.70-7.20 (10H,m), 3.82 (3H,s,CH_3N); m/z (%) 294 (M^+, 12), 190 (1), 177 (56), 135 (12), 132 (4), 131 (9), 104 (26), 103 (11), 90 (80), 89 (45), 77 (100).

4c, R^1=$H_3CO.C_6H_4$, R^3=H, R^4=C_6H_5; (1.51 g, 93%) yellow prisms; mp 118-119°C (from ethanol); (Found: C, 62.81; H, 4.93; N, 17.42. $C_{17}H_{16}N_4OS$ requires C, 62.94; H, 4.97; N, 17.27 %); ν_{max}(cm^{-1}) 1609, 1579, 1547, 1505, 1451, 1339, 1257, 1173, 1032, 942, 831, 756, 689; δ (^{1}H, 200 MHz) (DMSO-d_6) 8.36 (1H,s), 7.76-7.73 (2H,m), 7.65 (2H,d,J=8.57Hz), 7.45-7.42 (3H,m), 7.02 (2H,d, J=8.57Hz), 3.80 (3H,s,CH_3O), 3.66 (3H,s,CH_3N); δ (^{13}C) 166.30 (C-2), 160.89, 151.90 (N=C-H), 148.31 (C-5), 134.85, 129.54, 128.59, 127.21, 126.94, 122.27, 114.49, 55.29 (CH_3O), 36.01 (CH_3N); m/z (%) 324 (M^+, 29), 220 (7), 207 (79), 163 (19), 162 (34), 161 (25), 147 (29), 133 (33), 119 (5), 104 (54), 103 (26), 91 (24), 90 (100), 89 (37), 77 (13).

4d, R^1=CH_3, R^3=CH_3, R^4=4-Cl.C_6H_4; (1.36 g, 97%) yellow prisms; mp 96-98°C (from ethanol); (Found: C, 51.27; H, 4.40; N, 19.82. $C_{12}H_{13}ClN_4S$ requires C, 51.33; H, 4.67; N, 19.95 %); ν_{max}(cm^{-1}) 1594, 1539, 1489, 1442, 1397, 1302, 1276, 1208, 1013, 832, 766, 718; δ (^{1}H 60 MHz)(DMSO-d_6) 8.30-7.51 (4H,m), 3.72 (3H,s,CH_3N), 2.47 (6H,s); m/z (%) 282 (M^++2, 4), 280 (M^+, 12), 154 (4), 152 (10), 140 (34), 139 (15), 138 (100), 137 (35), 128 (6), 115 (39), 113 (9), 111 (23), 73 (34), 71 (14), 70 (10), 69 (18).

4e, R^1=C_6H_5, R^3=CH_3, R^4=4-$O_2N.C_6H_4$; (1.75 g, 99%) orange prisms; mp 181-182°C (from dimethyl sulfoxide); (Found: C, 57.83; H, 4.25; N, 19.70. $C_{17}H_{15}N_5O_2S$ requires C, 57.78; H, 4.28; N, 19.82 %); ν_{max}(cm^{-1}) 1589, 1538, 1489, 1407, 1346, 1287, 1073, 1015, 856, 752, 714, 687; m/z (%) 353 (M^+, 23), 190 (18), 176 (30), 163 (10), 149 (28), 148 (10), 136 (15), 135 (23), 132 (30), 122 (5), 104 (28), 103 (100), 77 (70).

4f, R^1=4-$H_3C.C_6H_4$, R^3=CH_3, R^4=4-$Cl.C_6H_4$; (1.59 g, 89%) *yellow prisms; mp* 209°C (from dimethyl sulfoxide); (Found: C, 60.47: H, 4.73; N, 15.82. $C_{18}H_{17}ClN_4S$ requires C, 60.58; H, 4.80; N, 15.70 %); ν_{max}(cm^{-1}) 1591, 1539, 1399, 1364, 1293, 1277, 1253, 1014, 831, 825, 767, 718; m/z (%) (358 (M^++2, 2), 356 (M^+, 6), 204 (20), 190 (13), 154 (15), 152 (46), 150 (5), 149 (15), 147 (13), 146 (20), 145 (12), 140 (12), 139 (16), 138 (34), 137 (33), 117 (8), 113 (31), 111 (100), 91 (6).

General Procedure for the Preparation of 2-Amino-3-methyl-5-substituted 1,3,4-thiadiazolium Perchlorates 5, 6, 7, 8 and 9. To a suspension of the appropriate 3-methyl-2-methylthio-5-substituted 1,3,4-thiadiazolium perchlorate **1** (5 mmol) in dry ethanol (20 ml), the corresponding amino derivative (5 mmol) was added, and the mixture was refluxed for 6 h. After cooling the crystals formed were collected by filtration, washed with n-hexane (2 x 15 ml), dried and recrystallized from the adequate solvent.

5a, R^1=4-$H_3CO.C_6H_4$, R^2=CH_3; (1.53 g, 91%) white needles; mp 223-225°C (from ethanol); (Found: C, 39.34; H, 4.16; N, 12.49. $C_{11}H_{14}ClN_3O_5S$ requires C, 39.35, H, 4.20; N, 12.51 %); ν_{max}(cm^{-1}) 3245, 1615, 1506, 1426, 1404, 1314, 1294, 1261, 1185, 1111, 1036, 930, 846, 725, 688; δ (^{1}H, 200 MHz) ($CDCl_3$/TFA) 7.69 (2H,dd,J=6.83Hz,J=2.00Hz), 7.03 (2H,dd,J=6.83Hz,J=2.00Hz), 3.93 (3H,s,CH_3N), 3.89 (3H,s,CH_3O), 3.29 (3H,d,J=4.82Hz,CH_3NH); δ (^{13}C) 168.35 (C-2), 163.20, 154.30 (C-5), 128.56, 119.39, 115.14, 55.61 (CH_3O), 37.69 (CH_3N), 36.33 (CH_3NH): m/z (%) 236 (M^+-ClO_4^-, 9), 235 (M^+-$HClO_4$, 61) 163 (11), 162 (100), 161 (27), 147 (37), 134 (16), 133 (82), 119 (14), 108 (10), 73 (17).

5b, R^1=4-$H_3CO.C_6H_4$, R^2=$C_6H_5.CH_2$; (1.81 g, 88%) *green prisms; mp* 182-184°C (from ethanol); (Found: C, 49.51; H, 4.49; N, 10.19. $C_{17}H_{18}ClN_3O_5S$ requires C, 49.58; H, 4.40; N, 10.20 %); ν_{max}(cm^{-1}) 3237, 1611, 1505, 1428, 1350, 1255, 1189, 1111, 1028, 932, 849, 768, 726, 693; δ (^{1}H, 200 MHz)($CDCl_3$/TFA) 8.93 (1H,t,J=5.00Hz,NH), 7.63 (2H,dd,J=6.94Hz,J=1.93Hz), 7.43-7.34 (5H,m), 7.00 (2H,dd,J=6.94Hz,J=1.93Hz), 4.65 (2H,d,J=5.00Hz,CH_2), 3.99 (3H,s,CH_3N), 3.87 (3H,s,CH_3O); δ (^{13}C) 167.06 (C-2), 163.36, 154.73 (C-5), 131.79, 129.59, 129.44, 128.60, 128.28, 119.14, 115.14, 55.56 (CH_3O), 53.36 (CH_2), 37.97 (CH_3N); m/z (%) 312 (M^+-ClO_4^-, 8), 311 (M^+-$HClO_4$, 39), 234 (11), 163 (10), 162 (100), 161 (22), 147 (26), 133 (94), 119 (13), 108 (8), 91 (30), 77 (8).

6a, R^1=4-$H_3C.C_6H_4$, R^2=C_6H_5; (1.83 g, 92%) yellow prisms; mp 182-184°C (from methanol); (Found: C, 48.58; H, 4.34; N, 14.01. $C_{16}H_{17}ClN_4O_4S$ requires C, 48.43; H, 4.32; N, 14.12 %); ν_{max}(cm^{-1}) 3283, 3171, 1635, 1504, 1426, 1292, 1237, 1188, 1103, 1053, 825, 772, 700; δ (^{1}H, 60 MHz)(DMSO-d_6) 7.89 (2H,d,J=8.5Hz), 7.73-7.02 (7H,m), 4.07 (3H,s,CH_3N), 2.49 (3H,s); m/z (%) 297 (M^+-ClO_4^-, 17), 296 (M^+-$HClO_4$, 100), 205 (14), 191 (10), 148 (14), 147 (28), 146 (35), 145 (42), 118 (65), 117 (22), 107 (9), 93 (36), 92 (20), 91 (28), 77 (24).

6b, R^1=4-$H_3CO.C_6H_4$, R^2=C_6H_5; (1.92 g, 93%) yellow prisms; mp 131-133°C (from methanol); (Found: C, 46.62; H, 4.08; N, 13.48. $C_{16}H_{17}ClN_4O_5S$ requires C, 46.55; H, 4.15; N, 13.57 %); ν_{max}(cm^{-1}) 3297, 3237, 1633, 1503, 1422, 1290, 1257, 1180, 1095, 1046, 900, 839, 767, 722, 694; δ (^{1}H, 60 MHz) ($CDCl_3$) 8.00-7.04 (9H,m), 3.95 (6H,s); m/z (%) 313 (M^+-ClO_4^-, 14), 312 (M^+-$HClO_4$, 100), 221 (20), 207 (8), 165 (15), 163 (26), 162 (30), 161 (30), 147 (18), 134 (50), 107 (34), 93 (20), 92 (22), 91 (30), 77 (18).

7a, R^1=CH_3, R^3=H, R^4=C_6H_5; (1.48 g, 89%) yellow prisms; mp 233-235°C (from ethanol); (Found: C, 39.66; H, 3.78; N, 16.91. $C_{11}H_{13}ClN_4O_4S$ requires C, 39.70; H, 3.94; N, 16.84 %); ν_{max}(cm^{-1}) 3243, 1623, 1553, 1424, 1351, 1239, 1113, 1056, 930, 767, 700, 672; m/z (%) 233 (M^+-ClO_4^-, 2), 232 (M^+-$HClO_4$, 19), 115 (90), 104 (16), 103 (2), 90 (100), 89 (42), 77 (15), 73 (16), 70 (6), 69 (15).

7b, R^1=4-$H_3CO.C_6H_4$, R^3=H, R^4=C_6H_5; (1.34 g, 63%) yellow needles; mp 229-231°C (from ethanol); (Found: C, 48.13; H, 4.20; N, 13.04. $C_{17}H_{17}ClN_4O_5S$ requires C, 48.06; H, 4.03; N, 13.19 %); ν_{max}(cm^{-1}) 3226, 1627, 1605, 1497, 1422, 1310, 1262, 1187, 1120, 1045, 931, 837, 760, 710, 692; m/z (%) 325 (M^+-ClO_4^-, 10), 324 (M^+-$HClO_4$, 33), 220 (9), 207 (42), 163 (23), 162 (42), 161 (30), 147 (15), 133 (40), 119 (2), 104 (67), 103 (19), 90 (100), 89 (30), 77 (26).

7c, R^1=CH_3, R^3=CH_3, R^4=4-Cl.C_6H_4; (1.20 g, 63%) white prisms; mp 148-150°C (from ethanol); (Found: C, 37.70; H, 3.59; N, 14.58. $C_{12}H_{14}Cl_2N_4O_4S$ requires C, 37.81; H, 3.70; N, 14.70 %); ν_{max}(cm^{-1}) 3247, 1610, 1555, 1429, 1363, 1211, 1092, 1013, 843, 832, 805, 766, 718; m/z (%) 283 (M^++2-ClO_4^-, 3), 282 (M^++2-$HClO_4$, 11), 281 (M^+-ClO_4^-, 10), 280 (M^+-$HClO_4$, 29), 154 (3), 152 (9), 140 (30), 138 (100), 125 (11), 123 (17), 115 (91), 113 (3), 111 (1), 73 (16), 69 (14).

7d, R^1=4-$H_3C.C_6H_4$, R^3=CH_3, R^4=4-Cl.C_6H_4; (1.76 g, 77%) yellow needles; mp 197-199°C (from ethanol); (Found: C, 47.43; H, 3.89; N, 12.40. $C_{18}H_{18}Cl_2N_4O_4S$ requires C, 47.27; H, 3.97; N, 12.25 %); ν_{max}(cm^{-1}) 3239, 1614, 1532, 1492, 1308, 1246, 1189. 1092, 1031, 843, 822, 764, 712; δ (^{1}H, 60 MHz)($CDCl_3$/TFA) 8.11-7.52 (8H,m), 4.29 (3H,s,CH_3N), 2.58 (3H,s), 2.51 (3H,s); m/z (%) 359 (M^++2- ClO_4^-, 3), 358 (M^++2-$HClO_4$, 13), 357 (M^+-ClO_4^-, 10), 356 (M^+-$HClO_4$, 40), 191 (41), 154 (4), 152 (8), 149 (12), 147 (23), 146 (18), 145 (21), 140 (34), 138 (100), 113 (4), 111 (11), 103 (56), 91 (14).

8, R^1=4-$H_3C.C_6H_4$; (1.60 g, 89%) white prisms; mp 195°C (from ethanol); (Found: C, 46.82; H, 5.01; N, 11.80. $C_{14}H_{18}ClN_3O_4S$ requires C, 46.73; H, 5.04; N, 11.68 %); ν_{max}(cm^{-1}) 1608, 1543, 1506, 1456, 1350, 1280, 1095, 1036, 912, 820, 719, 625; δ (^{1}H 200 MHz)(DMSO-d_6) 7.78 (2H,d,J=8.10Hz), 7.45 (2H,d,J=8.10Hz), 4.20 (3H,s,CH_3N), 3.92 (4H,t,J=6.43Hz), 2.43 (3H,s), 2.13 (4H,t,J=6.43Hz); δ (^{13}C) 165.08 (C-2), 152.86 (C-5), 142.78, 130.17, 126.40, 124.33, 54.89, 40.76 (CH_3N), 25.71, 21.00; m/z (%) 260 (M^+-ClO_4^-, 38), 245 (30), 190 (12), 149 (10), 147 (18), 146 (85), 145 (100), 131 (12), 118 (85), 117 (71), 91 (60), 74 (15), 73 (21), 70 (30).

9, R^1=4-$H_3C.C_6H_4$; (1.24 g, 74%) white prisms; mp 160-162°C (from methanol); (Found: C, 39.57; H, 4.63; N, 16.58. $C_{11}H_{15}ClN_4O_4S$ requires C, 39.47; H, 4.52; N, 16.74 %); ν_{max}(cm^{-1}) 3320, 3215, 1668, 1568, 1505, 1407, 1318, 1272, 1189, 1091, 913, 842, 725, 670; δ (^{1}H, 200 MHz)(DMSO-d_6) 7.72 (2H,d,J=8.11Hz), 7.38 (2H,d,J=8.11Hz), 6.71 (2H,s,NH_2), 4.10 (3H,s,endo CH_3N), 3.69 (3H,s, exo CH_3N), 2.39 (3H,s); δ (^{13}C) 171.65 (C-2), 154.51 (C-5), 142.53, 130.04, 126.32, 124.54, 44.14 (exo CH_3), 41.08 (endo CH_3), 20.97; m/z (%) 235 (M^+-ClO_4^-, 4) 220 (8), 219 (57), 147 (11), 146 (100), 145 (70), 118 (36), 117 (23), 102 (10), 91 (17), 73 (8).

Preparation of 3-Methyl-2-[2-(p-methoxybenzylidene)-1-methylhydrazino]-5-(p-tolyl)-1,3,4-thiadiazolium Perchlorate 10. To a suspension of 3-methyl-2-(1-methylhydrazino)-5-(p-tolyl)-1,3,4-thiadiazolium perchlorate **9** (0.33 g, 1 mmol), in dry toluene (10 ml), p-anisaldehyde (0.20 g, 1.5 mmol) and trifluoroacetic acid (0.02 g) were added. The mixture was stirred under reflux tem-

perature for 5 h and the solvent was then removed. The resultant material was scratched with ether/ethanol (1:1, 10 ml), and the solid formed was filtered off, washed with ether (5 ml) and crystallized from methanol to give **10** (0.18 g, 40%) as yellow prisms; mp 240-242°C; (Found: C, 50.27; H, 4.74; N, 12.40. $C_{19}H_{21}ClN_4O_5S$ requires C, 50.39; H, 4.67; N, 12.37 %); ν_{max}(cm^{-1}) 1624, 1607, 1515, 1317, 1258, 1172, 1091, 1030, 847, 822, 726, 701; δ (^1H, 60 MHz) 8.67 (1H,s), 8.17-7.10 (8H,m), 4.38 (3H,s,endo CH_3N), 4.01 (3H,s,exo CH_3N), 3.95 (3H,s,CH_3O), 2.48 (3H,s); m/z (%) 353 (M^+-ClO_4^-, 3), 219 (65), 191 (5), 162 (4), 147 (11), 146 (100), 145 (68), 134 (27), 133 (82), 118 (40), 117 (22), 107 (4), 103 (29), 91 (25), 73 (7).

General Procedure for the Preparation of 1,2-Bis-(3-methyl-5-substituted 2,3-dihydro-1,3,4-thiadiazol-2-ylidene)hydrazines 11. To a very well stirred suspension of the corresponding 3-methyl-2-methylthio-5-substituted 1,3,4-thiadiazolium perchlorate **1** (5 mmol) in dry ethanol (12 ml), a solution of anhydrous hydrazine (0.10 g, 3 mmol) and triethylamine (0.51 g, 5 mmol) in the same solvent (8 ml) was added dropwise and the mixture was allowed to stand at room temperature for 5 h. The resultant solid was collected by filtration and crystallized from methanol to give **11**.

11a, R^1=CH_3; (0.88 g, 69%) white prisms; mp 255°C; (Found: C, 37.39; H, 4.80; N, 32.77. $C_8H_{12}N_6S_2$ requires C, 37.48; H, 4.72; N, 32.78 %); ν_{max}(cm^{-1}) 1587, 1562, 1544, 1436, 1409, 1351, 1259, 1200, 1002, 760, 664; δ (^1H, 60 MHz)(DMSO-d_6) 3.83 (6H,s,CH_3N), 2.53 (6H,s); m/z (%) 256 (M^+, 12), 128 (8), 102 (10), 74 (6), 73 (100), 72 (26), 70 (6), 69 (12).

11b, R^1=4-$H_3C.C_6H_4$; (1.33 g, 65%) yellow prisms; mp 340°C; (Found: C, 58.96; H, 5.05; N, 20.44. $C_{20}H_{20}N_6S_2$ requires C, 58.80; H, 4.93; N, 20.57 %); ν_{max}(cm^{-1}) 1580, 1354, 1286, 1247, 1182, 1049, 1012, 924, 822, 713, 699; δ (^1H, 60 MHz)(DMSO-d_6) 7.82 (4H,d,J=8.2Hz), 7.41 (4H,d,J=8.2Hz), 3.85 (6H,s,CH_3N), 2.44 (6H,s); m/z (%) 408 (M^+, 20), 204 (10), 178 (4), 149 (100), 146 (19), 145 (19), 117 (59), 91 (27).

General Procedure for the Preparation of N,N'-Bis-(3-methyl-5-substituted 2,3-dihydro-1,3,4-thiadiazol-2-ylidene)-1,2-diamino derivatives 12 and 13. To a suspension of the corresponding 5-aryl-3-methyl-2-methylthio-1,3,4-thiadiazolium perchlorate **1** (5 mmol) in ethanol (30 ml), the appropriate 1,2-diamino derivative (5 mmol) and triethylamine (0.51 g, 5 mmol) were added, and the mixture was stirred at reflux temperature for 8 h. On cooling, the crystals formed were separated by filtration, dried and recrystallized from the adequate solvent.

12, R^1=4-$O_2N.C_6H_4$; (1.14 g, 91%) orange needles; mp 260-261°C (from acetonitrile); (Found: C, 48.30; H, 3.57; N, 22.41. $C_{20}H_{18}N_8O_4S_2$ requires C, 48.19; H, 3.64; N, 22.48 %); ν_{max}(cm^{-1}) 1647, 1625, 1591, 1523, 1342, 1291, 1257, 1013, 928, 849, 752, 684; δ (^1H, 200 MHz)(DMSO-d_6/TFA) 8.44 (4H,d,J=8.83Hz), 8.14 (4H,d,J=8.83Hz), 4.01 (6H,s,CH_3N), 3.96 (4H,s,CH_2); δ (^{13}C) 161.24 (C-2), 151.81 (C-5), 150.35, 133.76, 128.68, 125.48, 50.03 (CH_2), 39.26 (CH_3N); m/z (%) 498 (M^+, 2), 262 (10), 249 (100), 236 (9), 180 (16), 177 (9), 149 (87), 145 (22), 123 (33), 122 (18), 77 (78).

13a, R^1=4-$H_3C.C_6H_4$; (1.06 g, 88%) colourless prisms; mp 202-203°C (from dimethyl sulfoxide); (Found: C, 64.46; H, 5.06; N, 17.20. $C_{26}H_{24}N_6S_2$ requires C, 64.44; H, 4.99; N, 17.34 %); ν_{max} (cm^{-1}) 1608, 1574, 1308, 1257, 1115, 1041, 917, 815, 758, 718, 684; δ (^1H, 200 MHz)(DMSO-d_6) 7.64 (4H,d,J=8.13Hz), 7.57 (2H,dd,J=6.00Hz,J=3.44Hz), 7.45 (2H,dd,J=6.00Hz,J=3.44Hz), 7.30

(4H,d, J=8.13Hz), 3.92 (6H,s,CH_3N), 2.36 (6H,s); δ (^{13}C) 164.94 (C-2), 151.88 (C-5), 144.56, 139.76, 131.19, 129.23, 127.50, 127.02, 124.62, 39.08 (CH_3N), 21.78; m/z (%) 484 (M^+, 70), 339 (15), 307 (25), 294 (22), 280 (17), 242 (9), 149 (8), 146 (79), 145 (90), 135 (18), 118 (100), 117 (45), 103 (7), 91 (53), 90 (29), 77 (15).

13b, R^1=4-$H_3CO.C_6H_4$; (1.20 g, 93%) white prisms; mp 184°C (from dimethyl sulfoxide); (Found: C, 60.41; H, 4.74; N, 16.21. $C_{26}H_{24}N_6O_2S_2$ requires C, 60.45; H,4.68; N, 16.27 %); ν_{max}(cm^{-1}) 1602, 1574, 1506, 1308, 1251, 1177, 1036, 922, 832, 758, 690; δ (^1H, 60 MHz)(DMSO-d_6) 7.50 (4H,d,J=8.9Hz), 7.08 (4H,s), 6.83 (4H,d,J=8.9Hz), 3.77 (6H,s,CH_3O), 3.66 (6H,s,CH_3N); m/z (%) 516 (M^+, 38), 355 (10), 350 (19), 323 (14), 310 (14), 296 (10), 258 (6), 221 (3), 193 (4), 162 (51), 151 (13), 133 (100), 119 (22), 108 (10), 90 (20), 77 (7).

13c, R^1=4-$O_2N.C_6H_4$; (1.28 g, 94%) red prisms; mp 196°C (from dimethyl sulfoxide); (Found: C, 52.90; H, 3.21; N, 20.36. $C_{24}H_{18}N_8O_4S_2$ requires C, 52.74; H. 3.32; N, 20.36 %); ν_{max}(cm^{-1}) 1593, 1574, 1528, 1510, 1487, 1418, 1335, 1233, 1008, 848, 749, 687; m/z (%) 546 (M^+, 30), 369 (13), 365 (16), 337 (20), 325 (10), 311 (11), 250 (28), 178 (12), 177 (88), 176 (48), 149 (100), 148 (83), 134 (10), 122 (5), 103 (45), 102 (80), 90 (25), 77 (12), 76 (40).

Preparation of 2-Dicyanomethylene-5-(p-methoxyphenyl)-3-methyl-2,3-dihydro-1,3,4-thiadiazole 14.
To a solution of 5-(p-methoxyphenyl)-3-methyl-2-methylthio-1,3,4-thiadiazolium perchlorate **1d** (2.14 g, 5 mmol) in dry acetonitrile (15 ml), equimolar amounts of malononitrile (0.33 g, 5 mmol) and triethylamine (0.51 g, 5 mmol) were added, and the mixture was stirred at room temperature for 12 h. The solvent was then removed off, and the residue was triturated with ethanol (10 ml). The resultant solid was filtered off, dried and recrystallized from chloroform to give **14** (1.15 g, 85%) as white prisms; mp 188-190°C; (Found: C, 57.60; H, 3.81; N, 20.75. $C_{13}H_{10}N_4OS$ requires C, 57.76; H, 3.73; N, 20.73 %); ν_{max}(cm^{-1}) 2204, 2165, 1606, 1546, 1504, 1456, 1413, 1319, 1260, 1179, 1020, 926, 842, 723; δ (^1H, 60 MHz)($CDCl_3$/TFA) 7.84 (2H,d,J=8.8Hz), 7.18 (2H,d,J=8.8Hz), 4.23 (3H,s,CH_3N), 3.98 (3H,s,CH_3O); m/z (%) 270 (M^+, 100), 255 (8), 230 (17), 165 (10), 151 (75), 134 (16), 133 (85), 122 (17), 119 (6), 108 (13), 90 (29).

Reaction of 1 with Aldoximes. General Procedure.
To a well stirred solution of 3-methyl-2-methylthio-5-substituted 1,3,4-thiadiazolium salt **1** (10 mmol) in dichloromethane (20 ml), equimolecular amounts of the appropriate aldoxime (10 mmol) and triethylamine (1.01 g, 10 mmol) were added, and the mixture was allowed to stand at room temperature for 3 h. The solvent was then removed under reduced pressure at room temperature, and the residual material was extracted with n-hexane (4 x 20 ml). Removal of the solvent under vacuum, at room temperature, yield the crude nitrile, which was purified either by sublimation, distillation under reduced pressure, or by column chromatography using n-hexane/dichloromethane (2:1) as eluent. The pure nitriles obtained were all known and were characterized by comparison of their ir and ^1H nmr spectra with those of pure samples. Yields are given for the reactions in which **1e** was used (Table 1). The unextracted residue was triturated with water (10 ml), filtered off, washed with n-hexane (10 ml) and crystallized from ethanol to give the corresponding 3-methyl-2-oxo-2,3-dihydro-1,3,4-thiadiazole **16**.
Compounds **16** were also prepared in near quantitative yields by treatment of the starting **1** with catalitic amounts of triethylamine in aqueous methanol at reflux temperature for 0.5 h.

16a, R^1=4-$H_3C.C_6H_4$; (83-94%) white needles; mp 118-120°C; (Found: C, 58.15; H, 5.00; N, 13.60. $C_{10}H_{10}N_2OS$ requires C, 58.23; H, 4.89; N, 13.58 %); ν_{max}(cm^{-1}) 1669, 1615, 1495, 1408, 1345, 1287, 1251, 1024, 843, 818, 701, 634; δ (^1H, 200 MHz)($CDCl_3$) 7.52 (2H,dd,J=6.33Hz,J=1.77Hz), 7.20 (2H,dd,J=6.33Hz,J=1.77Hz), 3.59 (3H,s,CH_3N), 2.37 (3H,s); δ (^{13}C) 169.34 (C=O), 149.85 (C-5), 140.93, 129.48, 127.84, 125.57, 34.11 (CH_3N), 21.26; m/z (%) 206 (M^+, 100), 149 (8), 147 (60), 146 (92), 145 (84), 118 (32), 117 (15), 91 (50), 90 (10).

16b, R^1=4-$O_2N.C_6H_4$; (83-95%) yellow needles; mp 183-185°C; (Found: C, 45.59; H, 2.88; N, 17.82. $C_9H_7N_3O_3S$ requires C, 45.57; H, 2.97; N, 17.71 %); ν_{max}(cm^{-1}) 1668, 1607, 1530, 1407, 1350, 1285, 1254, 1019, 854, 753, 686, 637; δ (^1H 60 MHz)(DMSO-d_6) 8.50 (2H,d,J=8.6Hz), 8.09 (2H,d,J=8.6Hz), 3.69 (3H,s,CH_3N); m/z (%) 237 (M^+, 100), 178 (8), 177 (83), 149 (27), 122 (2), 104 (3), 103 (24), 89 (4), 77 (3).

Reaction of 1 with Carboxylic Acids. General Procedure. To a suspension of the corresponding 3-methyl-2-methylthio-1,3,4-thiadiazolium salt **1** (10 mmol) in chloroform (50 ml), anhydrous potassium carbonate (5.53 g, 40 mmol) and equimolar amount of the appropriate carboxylic acid (10 mmol) were added, and the resulting mixture was stirred at reflux temperature for 9 h. The warm solution was separated by filtration, the solvent was removed under reduced pressure, and the residual material was extracted with n-hexane (4 x 20 ml). Removal of the solvent afforded the corresponding methyl ester **18**, which was purified either by column chromatography using n-hexane/dichloromethane (2:1) as an eluent, or by distillation under reduced pressure. The pure methyl esters obtained are all known and were characterized by comparison of their ir and ^1H nmr with those of pure samples. Yields are given for the reactions in which **1e** was used (Table 1). Trituration of the unextracted residue with water (10 ml) and subsequent filtration of the solid formed, allows the isolation of the corresponding 3-methyl-2-thioxo-2,3-dihydro-1,3,4-thiadiazoles **19**, which were crystallized from ethanol.

19a, R^1=C_6H_5; (83-85%); mp 127-129°C.[23]

19b, R^1=4-$H_3C.C_6H_4$; (76-81%); yellow needles; mp 129°C; (Found: C, 53.97; H, 4.60; N, 12.49. $C_{10}H_{10}N_2S_2$ requires C, 54.03; H, 4.53; N, 12.60 %); ν_{max}(cm^{-1}) 1610, 1495, 1417, 1349, 1298, 1248, 1135, 1117, 1025, 906, 817, 723; δ (^1H, 200 MHz)($CDCl_3$) 7.53 (2H,dd,J=6.37Hz,J=1.78Hz), 7.24 (2H,dd,J=6.37Hz,J=1.78Hz), 3.92 (3H,s,CH_3N), 2.39 (3H,s); δ (^{13}C) 185.00 (C=S), 156.96 (C5), 141.99, 129.77, 126.23, 125.83, 38.82 (CH_3N), 21.39; m/z (%) 222 (M^+, 100), 149 (24), 147 (6), 146 (32), 145 (31), 132 (26), 118 (71), 117 (24), 105 (51), 103 (8), 91 (21), 76 (14), 73 (7).

19c, R^1=4-$H_3CO.C_6H_4$; (78-80%); yellow needles; mp 139-141°C; (Found: C, 50.50; H, 4.28; N, 11.70. $C_{10}H_{10}N_2OS_2$ requires C, 50.40; H, 4.23; N, 11.75 %); ν_{max}(cm^{-1}) 1604, 1499, 1422, 1356, 1307, 1294, 1263, 1177, 1034, 838, 722; δ (^1H, 60 MHz) 7.70 (2H,d,J=9.2Hz), 7.08 (2H,d,J=9.2Hz), 3.97 (3H,s,CH_3O), 3.91 (3H,s,CH_3N); m/z (%) 238 (M^+, 100), 223 (16), 165 (13), 163 (26), 162 (42), 161 (44), 134 (60), 133 (30), 119 (12), 107 (15), 73 (23).

19d, R^1=4-$O_2N.C_6H_4$; (76-83%); orange prisms; mp 185-186°C; (Found: C, 42.61; H, 2.79; N, 16.62. $C_9H_7N_3O_2S_2$ requires C, 42.68; H, 2.79; N, 16.59 %); ν_{max}(cm^{-1}) 1603, 1520, 1425, 1343, 1297, 1250, 1151, 1026, 852, 735, 706, 687; δ (^1H, 60 MHz) ($CDCl_3$) 8.61 (2H,d,J=9.3Hz), 8.14 (2H,d,J=9.3Hz), 3.90 (3H,s,CH_3N); m/z (%) 253 (M^+, 100), 177 (27), 176 (17), 149 (24), 148 (3),

134 (13), 122 (2), 105 (80), 103 (30), 91 (12), 76 (34), 73 (15), 64 (25).

Reaction of 3-Methyl-5-substituted 2-oxo-1,3,4-thiadiazole 16 with Phosphorus Pentasulfide. General Procedure. To a suspension of the apropriate **16** (5 mmol) in toluene (50 ml), phosphorus pentasulfide (3.33 g, 15 mmol) was added, and the reaction mixture was heated under reflux temperature for 48 h. The warm solution was filtered, and the solvent was partially removed under reduced pressure. The crystals formed were collected by filtration, and recrystallized from ethanol to give **19b** and **19d** in 71% and 79% yield, respectively.

General Procedure for the Preparation of 3-Methyl-2-methylthio-5-substituted 1,3,4-thiadiazolium Tetrafluoroborates 20. To a solution of the corresponding 3-methyl-5-substituted 2-thioxo-2,3-dihydro-1,3,4-thiadiazole **19** (5 mmol) in dry dichloromethane (15 ml), an equimolar amount of trimethyloxonium tetrafluoroborate (0.74 g, 5 mmol) was added, and the mixture was stirred at reflux temperature for 4 h. On cooling, the separated solid was collected by filtration, washed with ether (2 x 5 ml) and recrystallized from suitable solvents to give **20**. Spectral datas were in complete agreement with those of the corresponding perchlorates **1**.[1]

20a, R^1=4-$H_3C.C_6H_4$; (1.44 g, 89%); white prisms; mp 165-167°C (from dichloromethane); (Found: C, 40.77; H, 4.08; N, 8.59. $C_{11}H_{13}BF_4N_2S_2$ requires C, 40.76; H, 4.04; N, 8.64 %).

20b, R^1=4-$O_2N.C_6H_4$; (1.47 g, 83%); white prisms; mp 235-237°C (from acetonitrile); (Found: C, 33.78; H, 2.90; N, 11.91. $C_{10}H_{10}BF_4N_3O_2S_2$ requires C, 33.82; H, 2.84; N, 11.83 %).

ACKNOWLEDGEMENT

The authors are indebted to Dirección General de Investigación Científica y Técnica for financial support, Project number PB86-0039.

REFERENCES

1. P. Molina, A. Tárraga, and A. Espinosa, Synthesis, 1988, 690.
2. W.A. Remers, G.J. Gibs, and M.J. Wiess, J. Heterocycl. Chem., 1969, 6, 835.
3. K. Lu and T. Loo, Cancer Chemother. Pharmacol., 1980, 4, 275.
4. F. Kurzer, Org. Compd. Sulphur, Selenium, Tellurium, 1973, 2, 725.
5. M. Davis, Org. Compd. Sulphur, Selenium, Tellurium, 1979, 5, 440.
6. Reckitt and Colman Products Ltd., Ger. Patent 2727146, 1978 (Chem Abstr., 1978, 88, 105357).
7. F. Kurzer, Org. Compd. Sulphur, Selenium, Tellurium, 1977,4, 431.
8. G. Schaefer, A. Trebst, and K.H. Buechel, Z. Naturforsch (C), 1975, 30, 183.
9. Inst. Phys. Chem. Res., Jpn. Kokai 7725028, 1977 (Chem. Abstr., 1977, 87, 147054).
10. Eastman Kodak Co., U.S. Patent 3493556, 1970 (Chem. Abstr., 1970, 73, 36555).
11. Lubrizol Corp., U.S. Patent 4246126, 1981 (Chem. Abstr., 1981, 94, 142505).
12. K. Fujii, H. Yoshikawa, and M. Yuasa, J. Pharm. Soc. Jpn., 1954, 74, 1056.
13. M. Kanoaka, J. Pharm. Soc. Jpn., 1955, 75, 1149.
14. E.U.P. Tao and C.F. Christie Jr., Org. Prep. Proced. Int., 1975, 7, 179.
15. R.A. Corburn, B. Bhooshan, and R.A. Glennon, J. Org. Chem., 1973, 38, 3974.

16. G. L'abbé, G. Verhelst, L. Huybrechts, and S. Toppet, J. Heterocycl. Chem., 1977, 14, 515.
17. D. Leppard and H. Sauter, J. Heterocycl. Chem., 1980, 17, 1469.
18. G. L'abbé, G. Verhelst, S. Toppet, G.S.D. King, and J. Briers, J. Org. Chem., 1976, 41, 3403.
19. J. Motoyoshiya, M. Nishijima, I. Yamamoto, H. Gotoh, Y. Katsube, Y. Ohshiro, and T. Agawa, J. Chem. Soc. Perkin Trans. I, 1980, 574.
20. K. Dikoré and R. Wegler, Angew. Chem. Int. Ed. Engl., 1966, 5, 970.
21. a) G. Sosnovsky and M. Konieczny, Z. Naturforsch. (B), 1978, 33, 1033. b) G. Sosnovsky and J.A. Krogh, Synthesis, 1978, 703. c) G.A. Olah and Y.D. Vankar, Synthesis, 1978, 702. d) H. Suzuki, T. Fuchita, A. Iwasa, and T. Mishina, Synthesis, 1978, 905. e) A. Carotti, F. Campagna and R. Ballini, Synthesis, 1979, 56. f) G.A. Olah, S.C. Narang, and A. García-Luna, Synthesis, 1980, 659.
22. Handbook of Chemistry and Physics, Ed. by R.C. West, 52nd Edn., Chemical Rubber Co., Cleveland, Ohio, 1972-1973.
23. R. Fusco and C. Musante, Gazz. Chim. Ital., 1938, 68, 147.

Received, 22nd June, 1989