HETEROCYCLES, Vol. 29, No. 10, 1989

HETEROARYL STABILISED AZINIUM YLIDES. 1,3,4-THIADIAZOLE AS STABILISING GROUP

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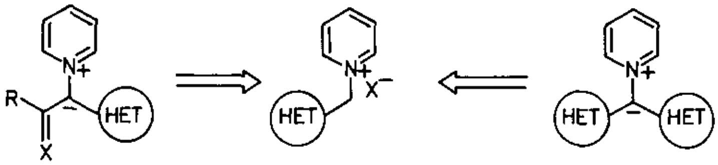
Abstract- Reaction of 1-[(1,3,5-thiadiazol-2-yl)]-methylpyridinium derivatives with diverse electrophiles produced disubstituted heteroarylmethylpyridinium ylides. Only with phenyl isothiocyanate 1,3-dipolar cycloaddition was observed.

Azinium ylides are highly interesting compounds for their reactivities, biological properties and applications[1,2,3]. Usually, simple electron-attracting groups, as carbonyl, ester, cyano etc., have been used to delocalize the anion moiety, but the possibility of using heteroaryl groups as stabilisers has been much less exploited. In recent years, we have been interested in the preparation of systems such as 2 and 3, by using 1-heteroarylmethylpyridinium salts 1 as starting materials[4,5] (Scheme 1) :

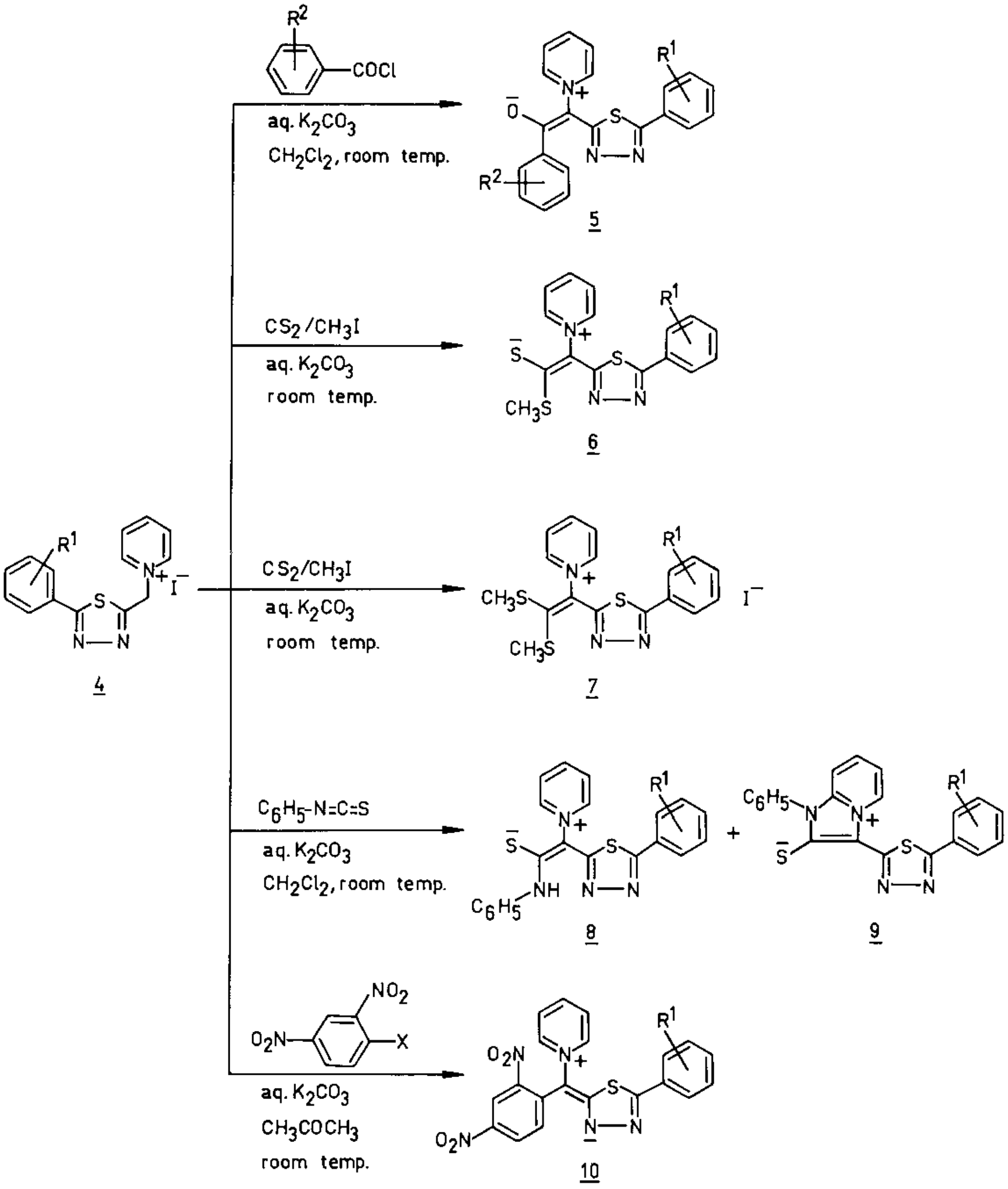


2 1 3

HET= Heteroaryl ring
X= S,O

Scheme 1

Both derivatives 2 and 3 would behave as stable dipoles with negatively charged heterocyclic moieties, from which there is no precedent, except for tetrazolyl derivatives described by Katritzky and coworkers[6].


R2
COCl
aq. K2CO3
CH2Cl2, room temp.
5
CS2/CH3I
aq. K2CO3
room temp.
6
R1
N+
I−
S
N
N
4
CS2/CH3I
aq. K2CO3
room temp.
CH3S
CH3S
7
C6H5-N=C=S
aq. K2CO3
CH2Cl2, room temp.
NH
C6H5
8
+
9
NO2
O2N
X
aq. K2CO3
CH3COCH3
room temp.
10

Scheme 2

In a recent paper[6], we reported the preparation of pyridinium salts of **1** and **2** types bearing a benzimidazole moiety, which are being tested as antibacterials[7]. Initial results stimulated us to develop new series of ylides and we wish to report here the preparation of some pyridinium ylides stabilised by 1,3,4-thiadiazole rings. All results are shown in Scheme 2.

The starting (thiadiazolylmethyl)pyridinium iodides **4** were prepared by a previously published method[5], using 1-methylthiothiocarbonylmethylpyridinium iodide and the corresponding arylhydrazides.

When the corresponding monosubstituted ylide, generated in situ from the pyridinium iodide **4** in 50% aqueous K_2CO_3, reacted at room temp. with aroyl halides, disubstituted ylides **5** were formed, all of them showing strong ir absorption around 1620 cm^{-1} characteristic of a carbonyl-stabilised ylide[8].

On treatment of **4** with 50% aqueous K_2CO_3 and CS_2/CH_3I as organic phase, using 2 equivalents of methyl iodide[8], ylides **6** were isolated in almost quantitative yield, after vigorous stirring at room temperature, for 20 h. ^1H-Nmr spectra of crude **6** showed no sign of the corresponding cycloadduct[9]. When the process was conducted by increasing the amount of methyl iodide to a 25-fold excess, Ketene dithioacetal iodides **7** were isolated after 9 days.

When the ^1H-nmr spectra of **7** were compared with those of ylides **6** it could be observed a low field shift for all the pyridinium resonances (approx. 0.2 ppm) showing the disappearance of anionic moiety influence.

In the reaction of **4** with phenyl isothiocyanate in a two-phase medium[10], the formation of two products was observed. After separation by column chromatography, they were identified as the ylides **8** and the pyrido[1,2-a]-imidazolium-2-tiolate derivatives **9** produced by oxidation of the initial cycloadduct. Using biphasic techniques, the reaction of pyridinium ylides with heterocumulenes usually gives disubstituted ylides[6,8,10], 1,3-dipolar cycloaddition being observed only with very reactive azinium systems like phenantridinium derivatives[9].

The ^1H-nmr spectra for compounds **9** showed a clear disappearance of the pyridinium proton signals, due to the dipolar character of the products. The structure was confirmed by X-ray crystallography of **9c**, represented in the scheme 3. All data are given in Tables 3-7.

Several experiments were carried out to prepare pyridinium ylides with two heteroaromatic sustituents, like **3** (scheme 1), by nucleophilic displacement with an aryl halide[11]. Initially, 2- and 4-chloropyridines were used, but **4** was recovered untransformed in more than 80-85% yields. The same was observed with 2- and 4-nitrochlorobenzene, and only 2,4-dinitrohalobenzenes produced ylides **10**, the fluorine derivative giving the higher yield. Alternative

Table 1. New Pyridinium Derivatives Prepared

Compd. No.	R^1	R^2	X	Reaction Time (h)	Yield (%)[a]
4a	H	–	–	6	76[5]
4b	2-Cl	–	–	6	99
4c	4-Cl	–	–	6	99
5a	H	H	–	1	64
5b	H	4-NO_2	–	1	62
5c	H	4-Cl	–	1	68
6a	H	–	–	24	99
6b	2-Cl	–	–	24	93
7a	H	–	–	216	62
7b	2-Cl	–	–	216	30
8a	H	–	–	1.5	36
8b	2-Cl	–	–	1.5	21
8c	4-Cl	–	–	1.5	41
9a	H	–	–	1.5	14
9b	2-Cl	–	–	1.5	31
9c	4-Cl	–	–	1.5	41
10a	H	–	F	14	85
10a	H	–	Cl	14	73

[a] Yields in isolated pure products. Compounds 8 and 9 were produced as mixtures in the same process.

Table 2. Physical and Spectroscopic Data of Compounds 4 to 10

Compd. No	mp (°C)	Molecular Formula[a]	^1H-Nmr[b] (ppm)
4a	191-193	$C_{14}H_{12}N_3SI$[c]	
4b	175-176	$C_{14}H_{11}N_3SClI$	9.24 (d, J=5.5 Hz, 2H); 8.69 (t, J=7.8 Hz, 1H); 8.30-8.01 (m, 3H); 7.64-7.39 (m, 3H); 6.48 (s, 1H)
4c	214-215	$C_{14}H_{11}N_3SClI$	9.21 (d, J=5.5 Hz, 2H); 8.68 (t, J=7.8 Hz, 1H); 8.29-7.44 (m, 6H); 6.43 (s, 2H)
5a	228-230	$C_{21}H_{15}N_3OS$	9.02 (d, J=5.4 Hz, 2H); 8.46 (t, J=7.2 Hz, 1H); 8.05-7.82 (m, 4H); 7.50-7.42 (m, 3H); 7.17 (br s, 5H)
5b	237-239	$C_{21}H_{14}N_4O_3S.2/3H_2O$	9.03 (d, J=5.6 Hz, 2H); 8.46 (t, J=7.3 Hz, 1H); 8.05-7.78 (m, 6H); 7.44-7.33 (m, 5H)
5c	267-268	$C_{21}H_{14}N_3OSCl.H_2O$	9.01 (d, J=5.5 Hz, 2H); 8.46 (t, J=7.4 Hz, 1H); 8.05-7.98 (m, 4H); 7.47-7.38 (m, 2H); 7.18 (br s, 5H)
6a	226-227	$C_{16}H_{13}N_3S_3$	9.10 (d, J=5.4 Hz, 2H); 8.76 (t, J=7.0 Hz, 1H); 8.24 (t, J=7.0 Hz, 2H); 7.91-7.79 (m, 2H); 7.47-7.39 (m, 3H); 2.45 (s, 3H)
6b	212-214	$C_{16}H_{12}N_3S_3Cl$	9.11 (d, J=6.1 Hz, 2H); 8.76 (t, J=7.4 Hz, 1H); 8.23 (t, J=7.2 Hz, 2H); 8.04-7.87 (m, 1H); 7.62-7.35 (m, 3H); 2.46 (s, 3H)

[a] Satisfactory microanalyses were obtained for all new compounds described, within 0.4% error.

[b] In DMSO-d_6

[c] Described in ref.[5].

Table 2 (Cont.). Physical and Spectroscopic Data of Compounds 4 to 10

Compd. No	mp (°C)	Molecular Formula[a]	^{1}H-Nmr[b] (ppm)
7a	217-218	$C_{17}H_{16}N_3S_3I$	9.35 (d, J=5.5 Hz, 2H); 8.92 (t, J=7.6 Hz, 1H); 8.43 (t, J=7.4 Hz, 2H); 8.06-7.95 (m, 2H); 7.60-7.53 (m, 3H); 2.71 (s, 3H); 2.54 (s, 3H)
7b	210-212	$C_{17}H_{15}N_3S_3ClI$	9.36 (d, J=5.6 Hz, 2H); 8.93 (t, J=7.3 Hz, 1H); 8.44 (t, J=7.0 Hz, 2H); 8.16-8.05 (m, 1H); 7.70-7.48 (m, 3H); 2.71 (s, 3H); 2.54 (s, 3H).
8a	200-203	$C_{21}H_{14}N_4S_2.H_2O$	9.05 (d, J=5.5 Hz, 2H); 8.63 (t, J=7.1 Hz, 1H); 8.15 (t, J=6.8 Hz, 2H); 7.85-7.74 (m, 2H); 7.63-7.15 (m, 9H)
8b	134-135	$C_{21}H_{15}N_4S_2Cl.H_2O$	8.98 (d, J=5.7 Hz, 2H); 8.54 (t, J=7.4 Hz, 1H); 8.15-7.84 (m, 3H); 7.64-6.87 (m,9H)
8c	116-117	$C_{21}H_{15}N_4S_2Cl.H_2O$	9.03 (d, J=5.7 Hz, 2H); 8.21 (t, J=7.5 Hz, 1H); 8.13-6.93 (m, 12H)
9a	304-306	$C_{21}H_{14}N_4S_2$	10.20 (d, J=6.2 Hz, 1H); 8.07-7.80 (m, 2H); 7.69-7.21 (m, 11H)
9b	273-275	$C_{21}H_{13}N_4S_2Cl$	10.05 (d, J=6.2 Hz, 1H); 8.04-7.06 (m, 14H)
9c	310-312	$C_{21}H_{13}N_4S_2Cl.2/3Cl_2CH_2$	10.15 (d, J=6.1 Hz, 1H); 8.05-7.15 (m, 14H)
10a	180-182	$C_{20}H_{13}N_4OS$	9.10 (d, J=5.5 Hz, 2H); 8.64-8.55 (m, 2H), 8.19 (t, J=6.8 Hz, 2H); 7.92-7.72 (m, 3H); 7.57-6.71 (m, 4H)

[a] Satisfactory microanalyses were obtained for all new compounds described, within 0.4% error.

[b] In DMSO-d_6

Table 3. Structure of Compound **9c**. Atomic Parameters for Non-Hydrogen Atoms. Coordinates and Thermal Parameters as $U_{EQ} = (1/3)\ (U_{ij}a_i^{*}a_j^{*}a_ia_j\cos(a_i,a_j)).10^3$

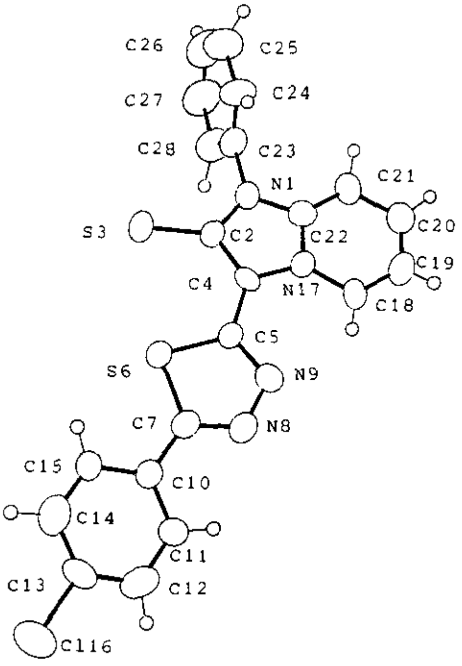
Atom	x	y	z	U_{EQ}
N1	0.7362(7)	-0.0830(7)	0.3173(8)	42(3)
C2	0.7061(8)	-0.0242(7)	0.2582(9)	39(3)
S3	0.8192(3)	-0.0490(2)	0.0893(3)	53(1)
C4	0.8373(8)	0.0597(7)	0.3671(9)	37(3)
C5	0.8958(9)	0.1539(7)	0.3549(9)	39(3)
S6	0.9329(2)	0.1727(2)	0.2023(2)	42(1)
C7	0.9876(8)	0.2937(7)	0.2952(9)	40(3)
N8	0.9766(8)	0.3111(7)	0.4272(8)	51(4)
N9	0.9244(9)	0.2318(7)	0.4628(9)	55(4)
C10	1.0493(8)	0.3649(8)	0.2418(9)	40(4)
C11	1.0958(9)	0.3258(8)	0.1238(10)	44(4)
C12	1.1584(9)	0.3925(9)	0.0809(11)	55(4)
C13	1.1718(10)	0.5003(9)	0.1516(12)	51(4)
C14	1.1255(10)	0.5412(9)	0.2675(12)	58(5)
C15	1.0682(10)	0.4711(8)	0.3127(10)	47(4)
Cl16	1.2496(3)	0.5857(3)	0.0959(4)	76(2)
N17	0.8037(7)	0.0460(6)	0.4872(7)	37(3)
C18	0.8278(9)	0.1030(8)	0.6260(10)	45(4)
C19	0.7818(11)	0.0715(9)	0.7231(11)	58(5)
C20	0.7139(11)	-0.0153(10)	0.6922(11)	58(5)
C21	0.6935(10)	-0.0747(9)	0.5520(11)	53(4)
C22	0.7404(9)	-0.0403(8)	0.4565(10)	47(4)
C23	0.6750(10)	-0.1784(9)	0.2491(11)	51(4)
C24	0.7411(11)	-0.2948(9)	0.2833(14)	64(5)
C25	0.6773(14)	-0.3825(11)	0.2161(17)	79(8)
C26	0.5582(13)	-0.3524(14)	0.1243(16)	87(7)
C27	0.4892(11)	-0.2340(12)	0.0874(15)	73(6)
C28	0.5492(10)	-0.1456(10)	0.1470(13)	63(5)
Cl29	0.4904(0)	0.2077(0)	0.2756(0)	144(0)
Cl30	0.4894(0)	0.3370(0)	0.5214(0)	193(0)
C31	0.5300(0)	0.3402(0)	0.3683(0)	177(0)

Table 4. Structure of Compound 9c. Atomic Parameters for Hydrogen Atoms. Coordinates and Thermal Parameters as $\exp(-8\pi^2U(\sin 0/\lambda)^2).10^3$

Atom	x/a	y/b	z/c	U
H11	1.083	0.256	0.088	44
H12	1.185	0.627	-0.004	51
H14	1.109	0.627	0.278	50
H15	1.051	0.475	0.398	45
H18	0.866	0.162	0.636	45
H19	0.822	0.091	0.817	61
H20	0.666	-0.042	0.749	56
H21	0.650	-0.143	0.544	53
H24	0.840	-0.318	0.356	62
H25	0.677	-0.449	0.264	91
H26	0.505	-0.379	0.074	82
H27	0.396	-0.216	0.017	81
H28	0.512	-0.050	0.111	69
H311	0.483	0.417	0.306	170
H312	0.623	0.340	0.392	170

Table 5. Structure of Compound 9c. Bond Distances (Å)

N1 - C2	1.369(13)	N1 - C22	1.368(11)
N1 - C23	1.451(12)	C2 - S3	1.677(9)
C2 - C4	1.401(10)	C4 - C5	1.459(13)
C4 - N17	1.387(12)	C5 - S6	1.715(10)
C5 - N9	1.320(10)	S6 - C7	1.729(8)
C7 - N8	1.308(12)	C7 - C10	1.461(14)
N8 - N9	1.342(13)	C10 - C11	1.408(13)
C10 - C15	1.376(11)	C11 - C12	1.360(16)
C12 - C13	1.383(13)	C13 - C14	1.383(16)
C13 - Cl16	1.733(12)	C14 - C15	1.367(17)
N17 - C18	1.397(10)	N17 - C22	1.341(12)
C18 - C19	1.350(16)	C19 - C20	1.374(16)
C20 - C21	1.436(13)	C21 - C22	1.361(16)
C23 - C24	1.335(12)	C23 - C28	1.377(11)
C24 - C25	1.376(16)	C25 - C26	1.313(16)
C26 - C27	1.364(17)	C27 - C28	1.371(17)
Cl29- C31	1.783	Cl30- C31	1.703



Scheme 3

Table 6. Structure of Compound **9c**. Bond Angles

C22 - N1 - C23	121.6(7)	C2 - N1 - C23	127.5(7)
C2 - N1 - C22	110.9(7)	N1 - C2 - C4	105.0(7)
N1 - C2 - S3	125.7(6)	S3 - C2 - C4	129.2(7)
C2 - C4 - N17	107.8(7)	C2 - C4 - C5	127.8(7)
C5 - C4 - N17	124.2(7)	C4 - C5 - N9	122.2(7)
C4 - C5 - S6	123.7(6)	S6 - C5 - N9	114.1(7)
C5 - S6 - C7	87.0(4)	S6 - C7 - C10	125.0(6)
S6 - C7 - N8	112.8(6)	N8 - C7 - C10	122.1(7)
C7 - N8 - N9	114.3(7)	C5 - N9 - N8	111.8(7)
C7 - C10 - C15	119.1(8)	C7 - C10 - C11	121.9(7)
C11 - C10 - C15	119.0(8)	C10 - C11 - C12	119.9(8)
C11 - C12 - C13	119.7(9)	C12 - C13 - C116	119.4(7)
C12 - C13 - C14	121.3(9)	C14 - C13 - C116	119.3(7)
C13 - C14 - C15	118.4(8)	C10 - C15 - C14	121.6(8)
C4 - C17 - C22	109.1(6)	C4 - C17 - C18	130.7(7)
C18 - N17 - C22	120.2(7)	N17 - C18 - C19	117.9(8)
H18 - C18 - C19	127.1(9)	C18 - C19 - C20	122.6(8)
C19 - C20 - C21	119.0(9)	C20 - C21 - C22	116.2(9)
N17 - C22 - C21	123.9(8)	N1 - C22 - C21	129.0(8)
N1 - C22 - N17	107.2(7)	N1 - C23 - C28	117.7(8)
N1 - C23 - C24	120.5(9)	C24 - C23 - C28	121.8(9)
C23 - C24 - C25	118.0(10)	C24 - C25 - C26	121.5(11)
C25 - C26 - C27	121.3(13)	C26 - C27 - C28	118.8(11)
C23 - C28 - C27	118.6(10)	C129- C31 - C130	100.1

Table 7. Structure of Compound **9c**. Torsion Angles

C2 - N1 - C22 - N17	-0.6(10)	C2 - N1 - C22 - C21	-179.9(9)
C22 - N1 - C2 - C4	-0.5(9)	C22 - N1 - C2 - S3	-179.3(7)
N1 - C2 - C4 - N17	1.4(9)	C2 - C4 - N17 - C22	-1.8(9)
S6 - C5 - N9 - N8	0.7(10)	N9 - C5 - S6 - C7	-0.8(7)
C5 - S6 - C7 - N8	0.7(7)	S6 - C7 - N8 - N9	-0.5(10)
C7 - N8 - N9 - C5	-0.2(11)	C11 - C12 - C13 - C116	-179.2(8)
C4 - N17 - C22 - N1	1.5(9)	C4 - N17 - C18 - C19	179.9(9)
C20 - C21 - C22 - N1	178.8(9)		

Table 8. Microanalyses

Calcd (%)
Found (%)

Compound	C	H	N	S	
4b	40.43	2.65	10.11		
	40.40	2.50	10.02		
4c	40.43	2.65	10.11		
	40.20	2.98	10.43		
5a	70.56	4.23	11.76		
	70.48	4.33	11.65		
5b	60.87	3.70	13.50		(2/3 H_2O)
	60.68	3.89	13.50		
5c	61.54	3.91	10.26		(H_2O)
	61.29	3.97	10.23		
6a	55.98	3.79	12.24		
	56.10	4.10	11.96		
6b	50.86	3.18	11.13		
	50.57	3.34	10.89		
7a	42.06	3.30	8.66		
	42.21	3.49	8.88		
7b	39.27	2.89	8.08		
	39.57	3.09	8.18		
8a	62.07	4.43	13.79		(H_2O)
	62.42	4.29	13.58		
8b	57.21	3.86	12.71		(H_2O)
	57.50	3.87	12.42		
8c	57.21	3.86	12.71		(H_2O)
	57.64	3.79	12.54		
9a	65.28	3.62	14.51		
	65.12	3.84	14.55		
9b	59.93	3.09	13.32	15.22	
	59.55	3.55	13.49	14.89	
9c	54.49	3.00	11.74	13.42	(2/3 CH_2Cl_2)
	54.25	3.27	11.97	13.69	
10a	57.28	3.10	16.71		
	57.14	3.06	16.59		

recovered untransformed in more than 80-85% yields. The same was observed with 2- and 4-nitrochlorobenzene, and only 2,4-dinitrohalobenzenes produced ylides 10, the fluorine derivative giving the higher yield. Alternative approaches to 3 are being developped.

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 and are uncorrected. Ir spectra were recorded on Perkin Elmer 883 or 1310 spectrophotometers. ^{1}H-Nmr spectra were obtained on Bruker WP 60 Wc and Varian FT-80A instruments using TMS as internal reference. All 1-(2′-(5′-phenyl)thiadiazolylmethyl)pyridinium iodides **4** were prepared as in ref. [5], from 1-(methylthiothiocarbonylmethyl)pyridinium iodide and the corresponding phenylhydrazide.

Preparation of Ylides 5 and 8. General procedure: To a well stirred suspension of the corresponding pyridinium salt **4** (1 mmol) in 50% aqueous potassium carbonate (10 ml) and dichlorometane (10 ml), the corresponding electrophile (1.2 mmol) was added. After vigorous stirring at room temperature for the time given in Table 1, the reaction mixture was extracted with dichloromethane, and the organic solution was dried over $MgSO_4$, concentrated and chromatographed (silica gel 60 Merck, 230-400 mesh) with dichloromethane-acetone (1:1) as eluent.

In the reaction of **4** with phenyl isothiocyanate two main products were detected, and the residue from dichloromethane extract was chromatographed (silica gel 60 Merck, 230-400 mesh) with hexane-ethyl acetate (7:3) to give **9**, and then with dichloromethane-acetone (1:1) to give **8**. All compounds **9** were recrystallised from ethanol. However, recrystallization of **8** in the same way always caused partial conversion into **9**. Finally, they were purified by two runs through a chromatographic column as described, using dichloromethane-acetone (1:1) as eluent.

Preparation of Ylides 6. To a well stirred suspension of the corresponding pyridinium salt **4** (1 mmol) in 50% aqueous potassium carbonate (10 ml), a solution of methyl iodide (2 mmol) in carbon disulphide (10 ml) was added. After stirring at room temperature for 24 h, ylides **6** were collected as a precipitate which was recrystallised from ethanol.

Preparation of Ketene Dithioacetals 7. The process was the same for compounds 6, but using a larger excess of methyl iodide (25 mmol). After stirring at room temperature for 9 days, the reaction mixture was extracted with dichloromethane, and the extract was dried over $MgSO_4$, concentrated, and the residue was recrystallised from methanol, yielding the corresponding **7** as described in Table 1.

Preparation of Ylide 10. To a stirred mixture of potassium carbonate (6 mmol) in water (2 ml) and acetone (10 ml), **4a** (3 mmol) was added. After 10 min, the 2, 4-dinitrohalobenzene (3 mmol) was added dropwise (the fluoride) or in small portions (the chloride) to the deep yellow solution. The reaction mixture was stirred overnight at room temperature. The crude ylide was extracted with dichloromethane, the extract was dried over $MgSO_4$, concentrated and chromatographed (silica gel 60 Merck, 230-400 mesh) with dichloromethane-acetone (1:1) as eluent.

Crystal data. Compound **9c**. $C_{21}H_{13}N_4S_2Cl$. 2/3 CH_2Cl_2. $a = 11.460(4)$, $b = 11.514(5)$, $c = 9.596(3)$ Å, $\alpha = 95.31(3)$, $\beta = 111.62(2)$, $\gamma = 73.10(3)°$, $V = 1126.1(8)$ Å^3, $M = 505.866$, $Z = 2$, $Dc = 1.492$ g/cm^3, $F(000) = 516$, $\mu = 6.036$ cm^{-1}, space group P-1.

Crystallographic Measurements. Symmetry independent reflections of a prismatic crystal (0.20x0.10x0.40 mm) were collected on an Enraf-Nonius CAD4 four-circle diffractometer with graphite-monochromated Mo $K\alpha = 0.7170$ Å radiation. 6530 reflections were measured but only 2393 were considered as observed applying the conditions $I > 2\sigma(I)$ and included in the refinement. Intensity data up to $\theta = 30°$, ($-16<h<16$, $-16<k<16$, $0<l<12$), $\omega/2\theta$ scan mode.

X-Ray Structure Analysis. The MULTAN 80 [12] computer program was initially used and revealed a part of the molecule, which was used as input of the DIRDIF program [13]. This showed the complete molecule and other three peacks belonging to a solvating CH_2Cl_2, having a high thermal agitation. Isotropic cycles and one anisotropic cycle of least squares refinement were applied to all atoms and progressive refinements were made with the fixed CH_2Cl_2 molecule. Positions of H atoms were found from ΔF and geometrical considerations and were non refined. The final agreement parameter R was 0.085 (Δ/σ max = 0.09). The maximum height in final F synthesis was 0.20 out the around of the CH_2Cl_2 atoms, due to their disordered character. Scattering and anomalous dispersion factors have been taken from International Tables for X-Rays Crystallography [14]. Calculations have been performed with the X-Ray 76 System [15]. Scheme 3 shows a view of the molecule with the atomic numbering used in the crystallographic study.

ACKNOWLEDGEMENTS

Authors wish to thank the Comisión Interministerial de Ciencia y Tecnología (C.I.C.Y.T.) for financial support, the Ministerio de Educación y Ciencia (M.E.C.) for a grant to one of us (R.C.M.), and ALTER S. A. for a generous gift of chemicals.

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Received, 17th January, 1989