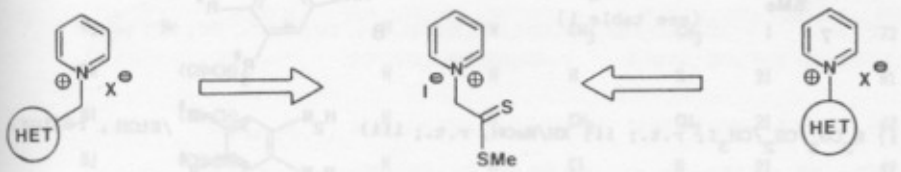
PREPARATION OF NEW BENZIMIDAZOLE DERIVATIVES FROM N-[(METHYLTHIO)THIOCARBONYLMETHYL]AZINIUM SALTS.

Ana M. Cuadro, Julio Alvarez-Builla*, and Juan J. Vaquero.

Departamento de Química Orgánica, Universidad de Alcalá de Henares. Madrid. Spain

Abstract- A series of new N-[(methylthio)thiocarbonylmethyl]azinium salts has been synthesized by reaction of carbon disulphide and methyl iodide with the corresponding phenacylazinium salt in a two-phase system followed by acid treatment of the ylide thus obtained. Condensation of dithioster derivatives with o-phenylenediamines gave N-(benzimidazolylmethyl)azinium salts in good yields.

Compounds containing the pyridinium moiety attached to heterocyclic systems are of current interest since they exhibit a wide range of biological activities[1-5]. In this respect we have been interested in the preparation of systems such as 2 and 3 by using the 1-[(methylthio)thiocarbonylmethyl]pyridinium iodide 1 as starting material[6] (Scheme 1) :



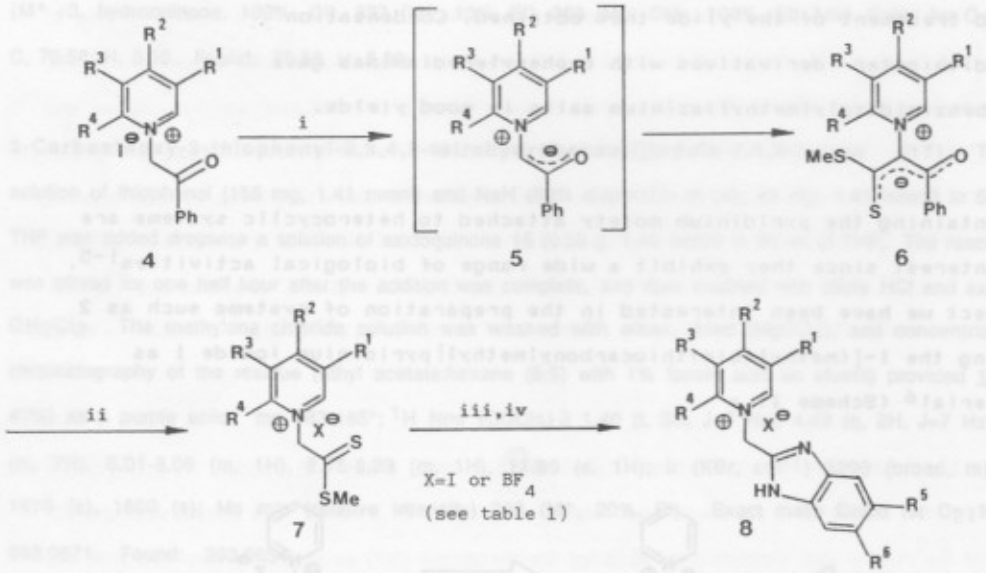
2 1 3

Scheme 1. HET=Heteroaromatic

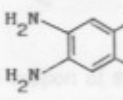
In recent papers[7,8] we reported the preparation of a series of compounds 2 which showed good activity as antibacterials[9]. Initial results stimulated us to try to obtain new series of unknown benzimidazolylmethylazinium salts 8 for biological screening.

The N-[(methylthio)thiocarbonylmethyl]azinium salts now chosen as starting materials were unknown but it was envisaged that they might be easily prepared following the procedure described by Kröhnke[6] to obtain the dithioester 7a. In this method, 1-phenacylpyridinium iodide reacts with carbon disulphide in methanolic sodium hydroxide solution followed by treatment with methyl iodide in methanol. However, this method proved to be unsuccessful when isoquinolinium, phenanthridinium or even some 3-substituted pyridinium salts were used as starting materials.

Therefore, we turned our attention to an alternative procedure developed by us[10] for the preparation of ylides **6**, in the expectation that these derivatives might be converted into the desired dithioesters 7 by removal of the benzoyl moiety.



4 5 6 7 8

Scheme 2. Reagents: i) $K_2CO_3/CS_2/CH_3I$, r.t.; ii) XH/MeOH, r.t.; iii)  /EtOH, reflux; iv) XH, r.t.

The ylides **6** here described were obtained in good yields by reaction of carbon disulphide/methyl iodide with the corresponding phenacyl derivative **4** in the presence of a non-nucleophilic base in a two-phase medium; conversion of ylides **6** into the dithioesters 7 was carried out by treatment with hydroiodic or tetrafluoroboric acid in methanol at room temperature (Scheme 2).

Table 1. Ylides 6, Dithioesters 7 and Benzimidazoles 8 Prepared

Compd. No.	R^1	R^2	R^3	R^4	R^5	R^6	X	Yield(%)[a]
6a	H	H	H	H	----	---	----	80
6b	H	C_6H_5	H	H	----	---	----	83
6c	$CONH_2$	H	H	H	----	---	----	65
6d	Br	H	H	H	----	---	----	64
6e	$(CH=CH)_2$		H	H	----	---	----	73
6f	$(CH=CH)_2$		$(CH=CH)_2$		----	---	----	36
7a	H	H	H	H	----	---	I	72
7b	H	C_6H_5	H	H	----	---	I	80
7c	$CONH_2$	H	H	H	----	---	BF_4	82
7d	Br	H	H	H	----	---	I	83
7e	$(CH=CH)_2$		H	H	----	---	I	80
8a	H	C_6H_5	H	H	H	H	2I	67
8b	H	C_6H_5	H	H	CH_3	CH_3	2I	67
8c	H	C_6H_5	H	H	Cl	H	2I	50
8d	$CONH_2$	H	H	H	H	H	$2BF_4$	62
8e	$CONH_2$	H	H	H	CH_3	CH_3	BF_4	73
8f	Br	H	H	H	H	H	2I	18
8g	Br	H	H	H	CH_3	CH_3	I	72
8h	$(CH=CH)_2$		H	H	H	H	2I	81
8i	$(CH=CH)_2$		H	H	CH_3	CH_3	2I	62
8j	$(CH=CH)_2$		H	H	Cl	H	2I	49

[a] Compounds 6a-c and e described in ref. 10; compound 7a described in ref 7.

Table 2. Physical and Spectroscopic Data of Ylides 6 and Dithioesters 7

Compd. No	mp (°C)	Molecular Formula[a]	Ir(KBr) ν (cm^{-1})	^1H-Nmr[b] δ (ppm)
6d	195	$C_{15}H_{12}BrNOS_2$ (366.3)	3400,3040,1615,1570,1475,1425, 1370,1310,1280,1255,1015,885 775	9.47 (s, 1H); 8.94 (d, J=7, 1H); 8.65 (d, J=7, 1H); 7.82 (t, J=7, 1H); 7.41 (s, 1H), 2.40 (s, 3H)
6f	230	$C_{23}H_{17}NOS_2$ (357.5)	3500,3300,3060,1625,1555,1445 1365,1200,1155,1005,970,890,830 795,780,760	9.20 (s, 1H); 8.5-7.1(m, 13H); 8.41 (m, 11H); 2.49 (s, 3H)
7b	165-166	$C_{14}H_{14}INS_2$ (387.3)	3000,2880,1635,1600,1555,1440 1435,1360,1295,1205,1195,1000,770 740	9.07 (d, J=7, 2H); 8.63 (d, J=7, 2H); 8.3 -7.4 (m, 5H); 6.20 (s, 2H); 2.77 (s, 3H)
7c	121-122	$C_9H_{11}BF_4N_2OS_2$ (314.1)	3270,3140,1690,1615,1380,1220, 1180,1070	9.46 (s, 1H); 9.09 (m, 2H); 8.8-7.8 (m, 3H); 6.24(s, 2H); 2.79(s, 3H)
7d	157	$C_{12}H_{12}INS_2$ (361.3)	3340,3000,2895,1640,1395 1280,1180,1160,980,815	10.16 (s, 1H); 8.7-7.7(m, 6H); 6.34 (s, 2H); 2.73 (s, 3H)
7e	152	$C_8H_8BrINS_2$ (390.1)	3030,2900,1615,1485,1455,1320, 1310,1215,1200,1160,1005,1025,905	9.45 (s, 1H); 9.04 (bs, 2H); 8.19 (t, J=6, 1H);6.13 (s, 2H); 2.79 (s, 3H)

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

[b] In DMSO-d_6, chemical shifts in ppm and coupling constants in Hz.

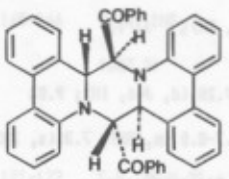
Table 3. Physical and Spectroscopic Data of Benzimidazoles 8

Compd. No	mp (°C)	Molecular Formula[a]	Ir (KBr) ν (cm^{-1})	^{1}H-Nmr[b] δ (ppm)
8a	187-188	$C_{19}H_{17}I_2N_3$ (541.2)	3460,3080-2670,1640,1505,1480 1225,1210,755	9.51 (bs, 2H); 9.27 (d, J=7, 2H); 8.72 (d, J=6, 2H); 8.37-7.27 (m, 9H); 6.46 (s, 2H)
8b	199-200	$C_{19}H_{21}I_2N_3$ (569.2)	3400,3060-2540,1640,1600,1555 1480,1440,1240,1210,860,795	11.52 (bs, 2H);9.3 (d, J=7, 2H); 8.76 (d, J=7, 2H); 8.3-7.4 (m, 7H); 6.51 (s, 2H); 2.41 (s, 6H)
8c	181-183	$C_{19}H_{16}ClI_2N_3$ (575.6)	3400,3060-2500,1640,1600,1480 1230,1210,820	10.23 (s, 2H); 9.23 (d, J=5.5, 2H); 8.65 (d, J=5.5, 2H); 8.3-7.0 (m, 8H); 6.33 (s, 2H)
8d	200-202	$C_{14}H_{14}B_2F_8N_4O$ (427.9)	3460-2600,1680,1610,1605 1445,1400,1305,1220,1090,860,	10.66 (bs, 2H); 9.62 (s, 1H); 9.28 (d, J=6, 1H); 9.06 (d, J=8, 1H); 8.7-7.2 (m, 7H); 6.36(s, 2H)
8e	188-190	$C_{16}H_{17}BF_4N_4O$ (368.1)	3440-2700,1705,1650,1505, 1480,1460,1440,1400,1310,1200	9.61 (bs, 1H); 9.28 (d, J=6, 1H); 9.03 (d, J=7, 1H); 8.7-8.0 (m, 3H); 7.31(s, 2H) 6.19 (s, 2H); 2.24 (s,6H)
8f	158-160	$C_{13}H_{12}BrI_2N_3$ (543.9)	3390,3005,1620,1475,1460,1450 1315,1170,815,750	9.63 (s, 1H); 9.20 (d, J=6, 1H); 8.97 (d, J=8.5, 1H); 8.18 (t, J=7, 1H); 7.6-7.1 (m, 4H); 6.17 (s, 2H); 3.6 (bs, 2H)
8g	172	$C_{15}H_{15}BrIN_3$ (441.1)	3370,2995,1620,1490,1455, 1310,1210,1190,1020,850,	9.48 (s, 1H); 9.2-7.5 (m, 3H); 7.17 (s, 2H); 6.96 (s, 2H); 3.30 (bs, 1H); 2.29 (s, 6H)
8h	165-166	$C_{17}H_{15}I_2N_3$ (515.2)	3340,3060-2520,1640,1620,1445 1390,1210,1175,1155,885,815, 770	10.32 (s, 1H); 8.9-8.1 (m, 6H); 7.8-7.3 (m, 4H); 6.83 (bs, 2H); 6.55 (s, 2H)
8i	192-193	$C_{19}H_{19}I_2N_3$ (543.2)	3380,3050-2550,1640,1550,1465, 1400,1230,1185,1040,810,790	10.36 (s, 1H); 9.85 (bs, 2H); 9.1-8.0 (m, 8H); 7.57 (s, 2H); 6.59 (s, 2H)
8j	172-173	$C_{17}H_{14}ClI_2N_3$. 1/2H_2O(430.7)	3350,3040-2540,1645,1510,1425 1400,1210,1190,930,820	10.34 (s, 1H); 9.92 (s, 2H); 9.0-7.2 (m, 9H); 6.49 (s, 2H)

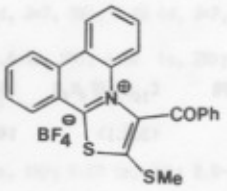
[a] Satisfactory microanalyses were obtained for all compounds described, within 0.4% error. [b] In DMSO-d_6.

It should be noted that neither this procedure nor literature method were successful with substrates carrying strong electron-withdrawing groups in 4-position of the pyridinium salt (e.g. CN, $COCH_3$) or with more π-deficient heterocycles (e.g. pyrazinium derivative). ^{1}H-Nmr experiments showed that such a type of salts are easily deprotonated, but the ylide 5 formed is unreactive towards carbon disulphide under different conditions. This fact can be explained in terms of the higher stability of these ylides, which in some cases have been isolated even though they slowly decompose[11,12] under exposure to air or heating.

It was also observed that the reaction of phenacylphenanthridinium iodide 4f, carbon disulphide and methyl iodide led to the formation of the ylide 6f and a new product, assigned as 9, formally a dimer of the monosubstituted ylide. Similar compounds have been described for isoquinolinium ylides.[13,14]



9



10

In contrast to the general behaviour of ylides 6, the ylide 6f was recovered unchanged after being treated with hydroiodic acid, but it was converted into the derivative 10 by heating in the presence of tetrafluoroboric acid. The formation of 10 is rationalised by attack of sulphur atom to the activated 6-position to give the corresponding dihydro derivative which is aromatized, presumably by aerial oxidation. A roughly similar process has been previously described[15]. Various other acids, conditions and media were also examined for the cleavage of the benzoyl moiety, but were all unsatisfactory. Finally, attempts were made to replace the benzoyl moiety with p-nitrobenzoyl group, but they failed in giving the desired ylide.

The benzimidazole derivatives 8 were easily prepared by condensation of the corresponding dithioester 7 with o-phenylenediamines in ethanol. Yields were not optimised, but in general, it was found that better yields were obtained when equimolar amounts of dithioester and diamine derivative were used and the reaction was carried out at reflux temperature.

Structures of all new compounds are supported by full spectroscopic data and by combustion analysis. The stereochemistry of new ylides 6 was assumed to be the one represented (the more thermodynamically stable isomer) in analogy with the structures previously established by X-Ray diffraction analysis of related ylides [10].

EXPERIMENTAL

Melting points were determined on a Buchi SMP-20 and are uncorrected. Ir spectra were recorded on Perkin Elmer 700 or 1310 Spectrophotometers. ^{1}H-Nmr spectra were obtained on Bruker WP 60 Wc and varian FT-80A instruments using TMS as internal reference.

Preparation of N-Phenacylderivatives 4. The 3-bromo-1-phenacylpyridinium bromide, 3-carbamoyl-1-phenacylpiridinium bromide and 1-phenacyl-4-phenylpiridinium bromide were prepared by the general procedure of Katritzky[16] and co-workers from the appropiate heterocycle derivative and phenacyl bromide. The 2-phenacylisoquinolinium bromide and 5-phenacylphenanthridinium bromide were obtained in a similar manner following the method reported by Stuckwisch[17].

Preparation of ylides 6; General procedure: The phenacyl derivative salt 4 (2 mmol) was added to a mixture of 50% potassium carbonate (20ml), carbon disulphide (20ml) and methyl iodide (4 mmol). The resulting suspension was vigorously stirred at room temperature for 20 h. At the end of that time the precipitate formed was filtered off and washed with water until neutral. After recrystallization from ethanol pure ylides 6a-e were obtained.

From the reaction of 5-phenacylphenanthridinium bromide a mixture of two compounds was observed by t.l.c. Chromatography of the mixture (silica gel, 60 Merck, 230-400 mesh) with acetone gave the ylide 6f, then, changing to methylene chloride, the dimer 9 was isolated (0.12 g, 20%), mp 178-180°C. Anal. Calcd for $C_{42}H_{30}N_2O_2$: C, 84.82; H, 5.08; N, 4.71. Found: C,85.03; H,4.95; N, 4.71);
Ir ν_{max} (KBr) : 3060, 2950, 1720, 1600, 1495, 1450, 1280, 1220 and 1180 cm^{-1};
^{1}H nmr δ ($CDCl_3$) : 6.24-7.81(m, 26H), 5.52(d, J=9, 2H), 5.18(d, J=9, 2H) ppm.
Ms m/z : 297(42), 296(100), 268(39), 179(49), 105(35) and 77(35).

Preparation of Dithioesters 7; General Procedure: To a suspension of **6a-e** (2 mmol) in methanol (30 ml), hydroiodic acid (57%, 2.2 mmol) or tetrafluoroboric acid (54%, 4.4 mmol) was added, and the reaction mixture was stirred at room temperature for 40 h. The resulting solution was evaporated and the residual oil was triturated with ethanol-ethyl acetate (1:1). Recrystallization from methanol gave the dithioesters **7a-e**.

After heating the ylide **6f** for 48 h at 60-70°C in the presence of tetrafluoroboric acid, the analysis of the crude by ^{1}H-nmr spectroscopy suggested that there was a mixture of two compounds. Chromatography on silica gel with methylene chloride gave 0.26 g of untransformed ylide and changing to acetone, 0.22 g (23 %) of cyclized product **10** were isolated, mp (EtOH-H_2O) 255-256°C. Anal. Calcd for $C_{23}H_{16}B_4FNSO_2$: C,58.36; H,3.40; N,2.95. Found C, 58.36; H, 3.78; N,3.25.

Ir ν_{max} (KBr) : 3400, 3060, 1665, 1595, 1475, 1415, 1325, 1285, and 1065 cm^{-1}; ^{1}H nmr δ (DMSO d_6) : 2.85 (s,3H), 7.56-8.93 (m,13H) ppm.

Preparation of Benzimidazole Derivatives 8; General Procedure: A mixture of the dithioester **7** (10 mmol) and the corresponding o-phenylenediamine (10 mmol) was heated under reflux in methanol (30 ml) for 10 h. The reaction mixture was then allowed to cool to room temperature, the solvent was evaporated and the residual oil was treated with an excess of acid (hydroiodic or tetrafluoroboric). The solid thus obtained was recrystallized from ethanol.

ACKNOWLEDGEMENTS

Authors wish to thank Comisión Asesora de Investigación Científica y Técnica (C.A.I.C.Y.T.) for financial support.

REFERENCES

1. W. Sliwa and G. Matusiak, Heterocycles, 1985,23, 1513.
2. W. Sliwa, Heterocycles, 1986, 24, 181.
3. P. Actor, E. L. Anderson, and D. I. Dimollo, Nature (London), 1967, 215, 321.

4. C. Baeder, H. Bahr, and D. Christ, Experientia, 1974, 30, 573.
5. P. Langcake, P. J. Kuhn, and H. Wade, "Progress in Pesticide Biochemistry and Toxicology" eds. by H. D. Hutson, and J. R. Roberts, 1983, Vol. 3, pg.1-88.
6. F. Kröhnke and K. Gerlach, Chem.Ber., 1962, 95, 1108.
7. J. Alvarez-Builla, F. Sanchez-Trillo, and G. Quintanilla, J. Chem. Soc. Perkin Trans I, 1984, 2693.
8. A. M. Cuadro, J. Alvarez-Builla, and Juan J. Vaquero. Heterocycles, 1988, 27, 1233.
9. C. Nombela, unpublished results.
10. J. Alvarez-Builla, E. Galvez, A. M. Cuadro, F. Florencio, and S. Garcia Blanco, J. Heterocyclic Chem., 1987, 24, 917.
11. W. G. Phillips and K. W. Ratts, J. Org. Chem. 1970, 35 ,3144.
12. I. C. Calder, Q. N. Porter, and C. M. Richards, Aust. J. Chem., 1972, 25, 345.
13. H. Ahlbrecht, J. Fröhlich, U. Habermalz, and F. Kröhnke, Tetrahedron Lett., 1967, 3649.
14. B. E. Landberg and J. W. Lown, J. Chem. Soc. Perkin Trans. I, 1975, 1326.
15. F. Kröhnke and H. H. Steuernagel, Chem. Ber. 1964, 97,1180.
16. A. R. Katritzky, N. E. Grzeskowiak, and J. Alvarez-Builla, J. Chem. Soc. Perkin Trans. 1, 1981, 1180.
17. C. G. Stuckwisch, Synthesis, 1973, 469.

Received, 7th April, 1988