A NEW SYNTHETIC APPROXIMATION TO THIAZOLES WITH A VERSATILE PERSUBSTITUTION AND/OR PERFUNCTIONALIZATION

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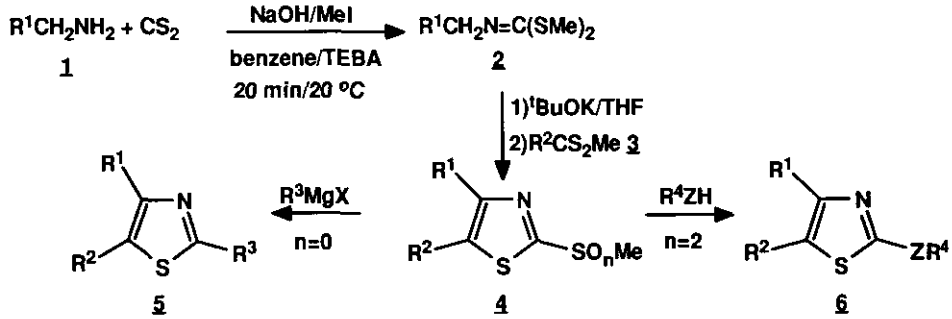
Abstract-A new synthetic approach to 2-alkyl-, 2-aryl-, and 2-N-alkylaminothiazoles has been carried out. This strategy is based on the high versatility of synthons derived from 2-methylthiothiazoles.

The preparation of a number of thiazoles with a broad biologic activity and hetero substituents at C2 position of ring has been carried out by the Hantzsch method from an α-halo carbonyl or α-halo nitrile compound and thiocarbamates or ureas.[1-3] Other synthetic routes have aimed to the formation of thiazole C4-C5 bond using acyl- and cyanoiminothiocarbonates as precursors.[4] A suitable choice of these starting materials allows for the introduction of a variety of substituents in C2, C4, and C5 positions. Other syntheses of C2-substituted thiazoles have been reported by van Leusen,[5] Vandenberghe,[6] and several other authors.[7] Some of these methods have been reviewed.[8]

We have reported an alternative method that allows for selection in the nature of the substituents on C4 and C5 positions of 2-methylthiothiazoles.[9-11] This route has shown to be an useful approach to the synthesis of thiazoles because the 2-methylsulfenyl group can be replaced by carbon- and heteroatomic nucleophiles. Thus, thiazoles of type (4) (Scheme 1) have been obtained from readily available precursors such as alkylamines (1) and dithioesters (3) via the dimethyl N-(alkylimino)dithiocarbonates (2) (Scheme 1).[11]



Scheme 1

The nature of C4 and C5 substituents may be varied with a suitable selection of the alkylamine and dithioester. A subsequent replacement of the 2-methylthio group may be accomplished by two alternative paths: a C-substitution to

thiazoles (5) by a cross-coupling reaction with Grignard reagents or a reaction with heteroatomic reagents to yield thiazoles (6). In the latter case, a previous oxidation of 2-methylthio group is required to obtain the best results.

In this paper, the scope of this new strategy has been broadened by investigating the cross-coupling and N-substitution reactions on a typical substrate (5-phenyl-2-methylthio-4-thienylthiazole (4a)).

RESULTS AND DISCUSSION

The synthesis of (4a) has been carried out in 70% yield from dimethyl N-(2-thienyl)iminodithiocarbonate (2a) (unpublished data) and methyl dithiobenzoate (3a).[11] We have selected the thiazole (4a) as starting material because its structure resembles several other heterocyclic compounds with antiinflamatory and cytostatic activities.[12,13]

Cross-coupling Reactions

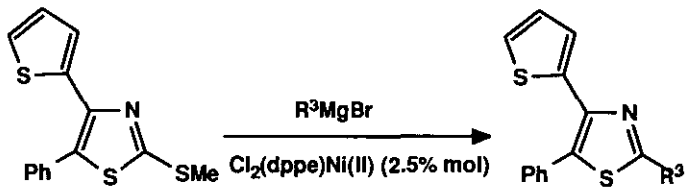
The cross-coupling reactions of 4a with aryl and alkyl Grignard reagents in ether and a catalytic amount (2.5% mol) of dichloro[bis(diphenylphosphino)ethane]nickel(II) complex, Ni(dppe)Cl_2, may be accomplished after the method described by Pridgen[14] (Scheme 2). The results are collected in Table 1.

Table 1. Cross-coupling reactions of 4a with Grignard reagents (R^3MgBr) in Et_2O catalyzed by Ni(dppe)Cl_2

Run	R^3	Compound	Yield (%)	mp (°C)
1	Ph	5a	90[a]	60-61
2	p-$MeOC_6H_4$	5b	95[b]	130-131
3	m-MeC_6H_4	5c	87	105-107
4	n-Pr	5d	93	oil
5	Me	5e	16[c]	oil
6	cyclo-C_5H_9	5f	36	oil
7	Bu^tCH_2	5g	--[d]	--
8	Bu^t	5h	--[d]	--

[a]42% (THF). [b]34% (THF). [c]MeMgI was used. [d]No reaction.

The yields are strongly dependent on the nature of the Grignard reagent. The best results have been observed with aryl and primary alkyl substituents (Table 1; runs 1-4). ß-Substituents in the alkyl groups lead to a significant decrease of the yields (Table 1; run 4 vs. 7). Likewise, sec-alkyl derivatives are less reactive than the primary alkyl compounds (Table 1; run 4 vs. 6), and the reaction failed with neopentyl and tert-alkyl reagents (Table 1; runs 7 and 8). Furthermore, a negative influence of the replacement of bromine for iodide has been observed (Table 1; run 4 vs. 5). This fact may be attributed to an important self-coupling of the Grignard reagent (radical reaction path) with an alkylmagnesium iodide whereas an oxidative addition-reductive elimination may be the preferred reaction path with other Grignard reagent.[15]



4a 5a-f

R^3: a, Ph; b, p-$MeOC_6H_4$; c, m-MeC_6H_4; d, n-Pr; e, Me; f, cyclo-C_5H_9 (16-95%)

Scheme 2

The reaction mechanism probably starts from the reduction of Cl_2(dppe)Ni(II) by the alkylmagnesium halide to produce a Ni(0) complex that is the true catalyst, and leads to a Ni(II) complex by an oxidative addition to the C2-S bond of thiazole (4a). Transmetallation of this complex with the Grignard reagent originates a new complex that leads to the final product (5) through a reductive elimination step with regeneration of the Ni(0) complex and completion of the catalytic cycle.

N-Substitution reactions

The N-substitution reactions with hydrazine, morpholine, and cyclohexylamine have been carried out on the 2-methylsulfonyl derivative (4c) obtained by oxidation of 4a. We have tested the use of potassium permanganate and m-chloroperbenzoic acid as oxidants.[16-18] The results are collected in Table 2.

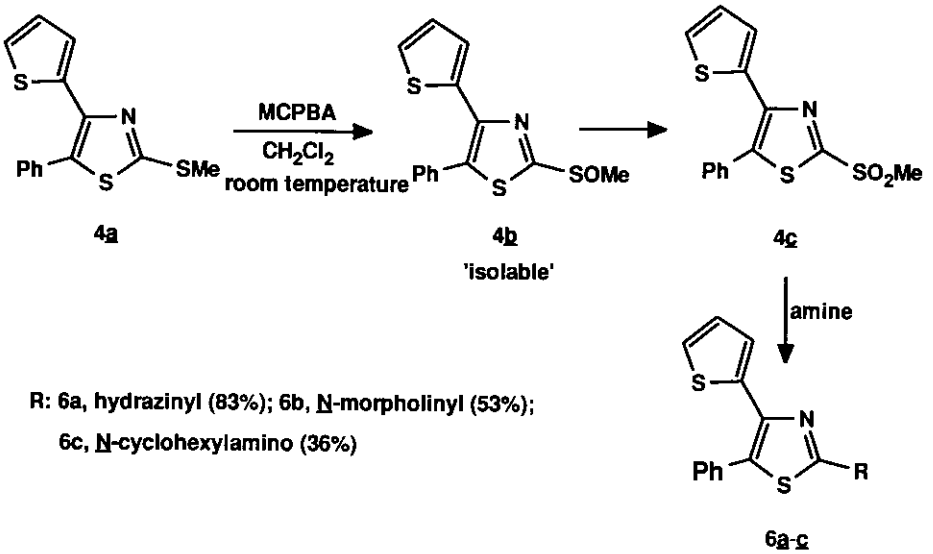
Table 2. Observed yields in the oxidation reactions of 4a to 2-methylsulfonyl-5-phenyl-4-(2-thienyl)thiazole (4c)

Run	Reaction conditions	4c, yield(%)	Reference
1	$KMnO_4/H_2O$-CH_2Cl_2/TEBA/52 h/20°C	36	16
2	$KMnO_4/H_2O$-CH_2Cl_2/Bu_4N^+,I^-/52 h/20°C	38	16
3[a]	$KMnO_4$/AcOH/0.5 h/42°C	57	17
4	MCPBA/CH_2Cl_2/4 h/20°C	98	18

[a]In this reaction the 2-methylsulfinyl-5-phenyl-4-(2-thienyl)thiazole (4b) was isolated in 14% yield.

The best result was achieved with m-chloroperbenzoic acid. The reaction was followed by tlc and the 2-methylsulfinyl derivative (4b) could be observed as an intermediate compound that quantitatively yields 4c in 4 h (Scheme 3).

The methylsulfonyl group was selected instead of the methylsulfenyl group because the former is a better leaving group than the second one. Likewise, Willms[19] has recently used 2-methylsulfonylbenzothiazoles for O-nucleophilic substitution reactions by phenols in good yields, and Hortsmann[20] has obtained 2-hydrazinylbenzothiazoles by reaction of 2-methylsulfonylbenzothiazoles with hydrazine in water-ethanol.



R: 6a, hydrazinyl (83%); 6b, N-morpholinyl (53%); 6c, N-cyclohexylamino (36%)

Scheme 3

The reaction of **4a** with N-nucleophiles in water-ethanol led to low yields. Therefore, the N-substitution of the methylsulfonyl group was performed by reaction with the amine at reflux in absence of solvent. In these conditions the compounds (**6a-6c**) were obtained in moderate-good yields.

All the prepared compounds were characterized by combustion analysis and their structures have been established from their ir, ^{1}H-nmr, and ^{13}C-nmr data. The most important features of the ^{13}C spectra are collected in Table 3.

The most significative results for the structural elucidation are related to ^{13}C-nmr signals of thiazole carbons in the 2C- (**5a-h**), 2S- (**4a-c**), and 2N-substituted derivatives (**6a-c**) (Figure 1).

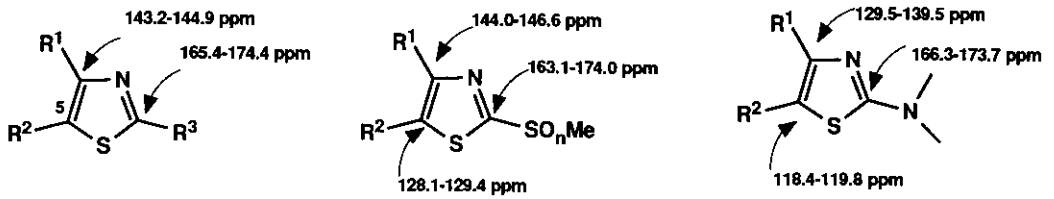


Figure 1

The assignment of signals to thiazole carbons follows from comparison of these results with the spectroscopic data reported for 4,5-diphenyl-2-methylthiothiazole (δ : 170.5 (C2), 149.1 (C4), 134.9 (C5) (unpublished data). The most relevant observation is the significant shielding observed for the C5 carbon in the C2-N-substituted derivatives (**6a-c**) in relation to the similar compounds of series (**4**) and (**5**). A similar effect has been observed for the C4 signal of thiazole in a series of 5-aminothiazoles[21] with respect to the 5C-substituted analogues.[11] In both cases, this shielding may be accounted from an electron-releasing mesomeric effect of the N-heteroatom on C2 and C5 carbons, respectively (Figure 2).

Table 3. ^{13}C-nmr data of thiazoles (4a-4c), (5a-5f), and (6a-6c) in $CDCl_3$.

Compd.	R^3	C2	C4	C5
4a	SMe	164.3	144.0	128.1
4b	SOMe	174.0	146.2	129.4
4c	SO_2Me	163.1	146.6	129.2
5a	Ph	165.4	144.9	--[b]
5b	p-$MeOC_6H_4$	165.4	144.5	--[b]
5c	m-MeC_6H_4	165.7	144.8	--[b]
5d	n-C_7H_7	169.3	143.4	127.9
5e	Me	164.5	143.4	127.6
5f	cyclo-C_5H_9	174.4	143.2	129.8
6a[a]	NH_2-NH-	173.7	139.5	118.4
6b	N-morpholinyl	168.5	138.5	119.8
6c	N-cyclohexylamino	166.3	129.5	118.8

[a]In DMSO-d_6. [b]Unobserved signals in the spectra.

An unequivocal assignment of thiophene and phenyl carbon signals has been followed from 2D heteronuclear correlation (HETCOR) spectra[22] while the remaining signals were assigned from reported data for model compounds.[9-11,21,23]

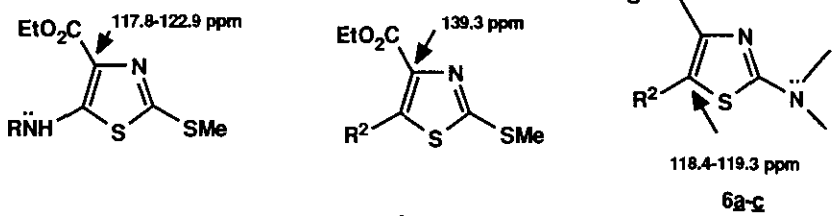


Figure 2

EXPERIMENTAL

Benzyltriethylammonium chloride, potassium tert-butoxide, magnesium, m-chloroperbenzoic acid, and cyclohexylamine were purchased from Merck; 2-aminomethylthiophene, morpholine, haloalkyl and haloaryl derivatives and dichloro[bis(diphenylphosphino)ethane]nickel(II) from Aldrich; bromobenzene from Doesder, and hydrazine hydrate (80%) were from Scharlau. The tlc plates (silica gel 60 F_{254}, of 0.20 mm thickness), and the powdered silica gel (23-400 mesh, 60 F_{254}) for flash chromatography were purchased from Merck.

The melting points were measured on a Gallemkapf apparatus and are uncorrected. Combustion microanalysis were performed in the 'Centro de Investigación y Desarrollo' (C.S.I.C.), Barcelona (Spain). Ir spectra were obtained with a Perkin Elmer 781 spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were recorded on a Varian VXR 300S spectrometer of the 'Servicio de Resonancia Magnética Nuclear', Universidad Complutense, Madrid (Spain) (^{1}H: 300 MHz; ^{13}C: 75 MHz), in $CDCl_3$ as solvent and 298^{0}K. The chemical shifts are quoted as δ values from TMS as internal reference.

Dimethyl N-(2-thienyl)iminodithiocarbonate 2a. This compound was prepared in 88% yield by the reported procedure (unpublished data) from 2.03 g (10 mmol) of 2-aminothiophene. The crude product is obtained with a high purity (>98%), and this was tested by tlc chromatography on silica gel (hexane/ethyl acetate: 95/5 v/v), and ^{1}H-nmr. Ir(film): 3110, 1585, 920, 710 cm^{-1}. ^{1}H-Nmr, δ (ppm): 2.44 (s, 3H, SMe), 2.57 (s, 3H, SMe), 4.80 (s, 2H, CH_2), 6.95 (m, 2H, H2 and H3 of thiazole ring), 7.10 (m, 1H, H4 of thiazole ring). ^{13}C-Nmr, δ (ppm): 14.5 (SMe), 14.6 (SMe), 51.5 (CH_2), 123.3 (C3), 123.8 (C4), 126.4 (C5), 144.1 (C2), 159.9 (C=N).

Methyl dithiobenzoate 3a. This compound was obtained in 82% yield by the reported procedure.[24] (Lit.[24]: 85%), 145^{0}C/12 torr. The crude product was purified by distillation under reduced pressure, and this purity was tested by tlc chromatography on silica gel (hexane/ethyl acetate: 95/5 v/v), and ^{1}H-nmr. Ir (film): 3080, 2910, 2000, 1605, 1580, 1495, 1455, 1325, 1240, 890, 770, 695 cm^{-1}. ^{1}H-Nmr, δ (ppm): 2.76 (s, 3H, SMe), 7.34-7.40 (m, 2H, m-H), 7.49-7.53 (m, 1H, p-H), 7.98-8.01 (m, 2H, o-H). ^{13}C-Nmr, δ (ppm): 21.0 (SMe), 127.0 (m-C), 128.6 (o-C), 129.0 (ipso-C), 132.5 (p-C), 195.3 ($\underline{C}S_2Me$).

2-Methylthio-5-phenyl-4-(2-thienyl)thiazole 4a. This compound was prepared by the reported procedure[11] from 2.56 g (12 mmol) of **2a**, 2.67 g (24 mmol) of potassium tert-butoxide in 50 ml of dry THF, and 2.24 g (13 mmol) of **3a** in 7 ml of dry THF. Yield: 97% (3.36 g). The purity of crude was tested by tlc chromatography on silica gel (hexane/ethyl acetate: 95/5 v/v), and was purified by recrystallization from n-pentane (white needles). mp 91-92^{0}C. Ir (KBr): 3090, 3020, 2950, 1610, 1590, 1560, 1490, 865, 850, 710 cm^{-1}. ^{1}H-Nmr, δ (ppm): 2.74 (s, 3H, SMe), 6.87 (dd, ^{3}J= 5.25 Hz, ^{3}J= 3.9 Hz, 1H, H8), 7.03 (dd, ^{3}J=3.9 Hz, ^{4}J= 1.2 Hz, 1H, H7), 7.19 (dd, ^{3}J= 5.25 Hz, ^{4}J= 1.2 Hz, 1H, H9), 7.39-7.47 (m, 5H, Ph). ^{13}C-Nmr, δ (ppm): 16.5 (SMe), 125.6 (C9), 125.7 (C7), 127.1 (C8), 128.1 (C5), 128.8 (C13), 128.9 (C11), 130.1 (C12), 131.2 (C6), 137.5 (C10), 144.0 (C4), 164.3 (C2). Anal. Calcd for $C_{14}H_{11}NS_3$: C, 58.09; H, 3.84; N, 4.84. Found: C, 57.92; H, 3.75; N, 4.77.

General Procedure to the cross-coupling reactions of 4a with Grignard reagents. To a stirred solution of **4a** (0.400 g, 1.384 mmol) in dry ether (15 ml) was added a solution of Grignard reagent (1.85 mmol) in dry ether (4 ml) and Cl_2(dppe)Ni(II) (18 mg, 0.035 mmol). The reaction mixture was stirred at room temperature for 16 h, and was then quenched by pouring into a saturated aqueous ammonium chloride solution (15 ml), and extracted with ether (3 x 15 ml). The combined ethereal extracts were dried on $MgSO_4$ (12 h), and the solvent was evaporated to dryness. The product

was purified by a flash chromatography on silica gel (compounds **5a**, **5d**, **5e**, **5f**) using hexane/dichloromethane (1/1 v/v) as eluent, or by recrystallization from the suitable solvent (compounds **5b** and **5c**).

2,5-Diphenyl-4-(2-thienyl)thiazole 5a. Yield: 90%. This compound was isolated as a solid by flash chromatography and recrystallized from pentane. mp 60-61°C. Ir (KBr): 1610, 1530, 1490, 1470, 1450, 930, 870, 850, 700 cm^{-1}. ^{1}H-Nmr, δ (ppm): 6.88 (dd, ^{3}J= 3.9 Hz, ^{3}J= 5.1 Hz, 1H, H8), 7.08 (dd, ^{3}J= 3.9 Hz, ^{4}J= 1.2 Hz, 1H, H7), 7.20 (dd, ^{3}J= 5.1 Hz, ^{4}J= 1.2 Hz, 1H, H9), 7.40 (m, 6H, Ph), 7.50 (m, 2H, Ph), 7.99 (m, 2H, Ph). ^{13}C-Nmr, δ (ppm): 125.5 (C9), 125.6 (C7), 126.3 (C16), 127.0 (C8), 128.6 (C13), 128.75 (C15), 128.7 (C12), 129.9 (C11), 130.9 (C17), 131.3 (C6), 133.1 (C14), 137.8 (C10), 144.9 (C4), 165.4 (C2). Anal. Calcd for $C_{19}H_{13}NS_2$: C, 71.44; H, 4.10; N, 4.38. Found: C, 71.02; H, 3.98; N, 4.41.

5-Phenyl-4-(2-thienyl)-2-(p-methoxyphenyl)thiazole 5b. Yield: 95%. This compound was isolated as a white crystalline solid. mp 130-131°C (recrystallized from ether). Ir(KBr): 1610, 1585, 1490, 1470, 1380, 840, 760 cm^{-1}. ^{1}H-Nmr, δ (ppm): 3.83 (s, 3H, OMe), 6.89 (dd, ^{3}J=5.1 Hz, ^{3}J= 3.9 Hz, 1H, H8), 6.94 (AA' submultiplet of an AA'XX' spin system, 2H, H15), 7.07 (dd, ^{3}J= 3.9 Hz, ^{4}J= 1.2 Hz, 1H, H7), 7.21 (dd, ^{3}J= 5.1 Hz, ^{4}J= 1.2 Hz, 1H, H9), 7.39-7.51 (m, 5H, Ph at C5), 7.92 (XX' submultiplet of an AA'XX' spin system, 2H, H16). ^{13}C-Nmr, δ (ppm): 55.2 (OMe), 114.8 (C16), 125.4 (C9), 125.6 (C7), 126.1 (C14), 127.1 (C8), 127.8 (C15), 128.5 (C13), 128.7 (C12), 129.8 (C11), 131.5 (C6), 144.5 (C4), 161.1 (C17), 165.4 (C2). Anal. Calcd for $C_{20}H_{15}NOS_2$: C, 68.73; H, 4.33; N, 4.01. Found: C, 68.22; H, 4.28; N, 3.86.

5- Phenyl-4-(2-thienyl)-2-(m-tolyl)thiazole 5c. Yield: 87%. This compound was isolated as a white crystalline solid. mp 105-107°C (recrystallized from n-pentane). Ir (KBr): 1610, 1450, 845, 795, 770 cm^{-1}. ^{1}H-Nmr, δ (ppm): 2.41 (s, 3H, SMe), 6.89 (dd, ^{3}J= 5.25 Hz, ^{3}J= 3.9 Hz, 1H, H8), 7.08 (dd, ^{3}J= 3.9 Hz, ^{4}J= 1.2 Hz, 1H, H7), 7.21 (dd, ^{3}J= 5.1 Hz, ^{4}J= 1.2 Hz, 1H, H9), 7.39-7.41 (m, 3H, Ph at C5), 7.49-7.52 (m, 2H, Ph at C5), 7.21 (br s, 1H, H17), 7.31 (t, ^{3}J= 7.8 Hz, 1H, H18), 7.77-7.78 (br d, ^{3}J= 7.8 Hz, 1H, H19), 7.28 (br s, 1H, H15). ^{13}C-Nmr, δ (ppm): 21.3 (Me), 123.5 (C19), 125.5 (C9), 125.7 (C7), 126.8 (C18), 127.1 (C8), 128.5 (C13), 128.6 (C15), 128.7 (C11), 129.9 (C12), 130.8 (C17), 131.4 (C6), 133.0 (C16), 137.8 (C14), 144.8 (C4), 165.7 (C2). Anal. Calcd for $C_{19}H_{15}NS_2$: C, 70.99; H, 4.70; N, 4.36. Found: C, 70.90; H, 4.62; N, 4.22.

5-Phenyl-2-propyl-4-(2-thienyl)thiazole 5d. Yield: 93%. This compound was isolated as an oil. Ir(film): 1590, 1490, 1380, 750, 690 cm^{-1}. ^{1}H-Nmr, δ (ppm): 1.06 (t, ^{3}J= 7.3 Hz, 3H, $C\underline{H}_3CH_2CH_2$), 1.85 (quartet of triplets, ^{3}J= 7.3 Hz, ^{3}J= 7.6 Hz, 2H, $CH_3C\underline{H}_2CH_2$), 2.98 (t, ^{3}J= 7.6 Hz, 2H, $CH_3CH_2C\underline{H}_2$), 6.85 (dd, ^{3}J= 5.1 Hz, ^{3}J= 3.6 Hz, 1H, H8), 6.99 (dd, ^{3}J= 3.6 Hz, ^{4}J= 1.2 Hz, 1H, H7), 7.17 (dd, ^{3}J= 5.1 Hz, ^{4}J= 1.2 Hz, 1H, H9), 7.36-7.46 (m, 5H, Ph). ^{13}C-Nmr, δ (ppm): 13.7 (C16), 23.3 (C15), 35.3 (C14), 125.3 (C9), 125.5 (C7), 127.1 (C8), 127.9 (C5), 128.4 (C13), 128.7 (C12 or C11), 130.0 (C11 or C12), 131.8 (C6), 137.9 (C10), 143.4 (C4), 169.3 (C2). Anal. Calcd for $C_{16}H_{15}NS_2$: C, 67.33; H, 5.30; N, 4.91. Found: C, 67.09; H, 5.15; N, 4.83.

2-Methyl-5-phenyl-4-(2-thienyl)thiazole 5e. Yield: 16%. This compound was isolated as an oil. Ir(film): 1590, 1380, 710 cm^{-1}. ^{1}H-Nmr, δ (ppm): 2.76 (s, 3H, Me), 6.89 (dd, ^{3}J= 5.1 Hz, ^{3}J= 3.6 Hz, 1H, H8), 7.02 (dd, ^{3}J= 3.6 Hz, ^{4}J= 1.1 Hz, 1H, H7), 7.20 (dd, ^{3}J= 5.1 Hz, ^{4}J= 1.1 Hz, 1H, H9), 7.36-7.44 (m, 5H, Ph). ^{13}C-Nmr, δ (ppm): 29.7 (Me), 125.6 (C9), 125.9 (C7), 127.2 (C8), 127.6 (C5), 128.7 (C13), 128.9 (C12 or C11), 130.1 (C11 or C12), 130.6 (C6 or C10), 131.5 (C10 or C6), 143.4 (C4), 164.5 (C2). Anal. Calcd for $C_{14}H_{11}NS_2$: C,65.33; H, 4.31; N, 5.44. Found: C, 65.43; H, 4.19; N, 5.32.

2-Cyclopentyl-5-phenyl-4-(2-thienyl)thiazole 5f. Yield: 36%. This compound was isolated as an oil. Ir(film): 1600, 1520, 780, 700 cm^{-1}. ^{1}H-Nmr, δ (ppm): 1.66-1.92 (m, 8H, cyclopentyl ring), 3.40-3.50 (m, 1H, H14), 6.87 (dd, ^{3}J= 3.7 Hz, ^{3}J= 5.1 Hz, 1H, H8), 7.00 (dd, ^{3}J= 3.7 Hz, ^{4}J= 1.2 Hz, 1H, H7), 7.18 (dd, ^{3}J=5.1 Hz, ^{4}J= 1.2 Hz, 1H, H9), 7.37-7.47 (m, 5H, Ph). ^{13}C-Nmr, δ (ppm): 25.4 (C16), 34.4 (C15), 44.1 (C14), 125.3 (C9), 125.5 (C7), 127.1 (C8), 128.4 (C13), 128.7 (C12 or C11), 129.8 (C5), 130.1 (C11 or C12), 131.9 (C6), 138.0 (C10), 143.2 (C4), 174.4 (C2). Anal. Calcd for $C_{18}H_{17}NS_2$: C, 69.41; H, 5.50; N, 4.50. Found: C, 69.33; H, 5.38; N, 4.17.

2-Methylsulfinyl-5-phenyl-4-(2-thienyl)thiazole 4b. To a solution of **4a** (0.350 g, 1.2 mmol) in acetic acid (9 ml) at 42^{0}C was slowly added during 0.30 h a solution of potassium permanganate (0.38 g, 2.4 mmol) in distilled water (9 ml). The reaction mixture was then cooled at room temperature with a bath of water and quenched with 0.2 ml of a saturated solution of sodium bisulphite and 4.5 ml of a solution of ammonium hydroxide/water (80/20 v/v). The reaction mixture was extracted with ethyl acetate (3 x 5 ml). The combined organic layers were washed with water (2 x 5 ml) and dried ($MgSO_4$) and evaporated to dryness. A flash chromatography on silica gel (hexane/ethyl acetate: 70/30 v/v) of the crude (0.357 g) allowed the isolation of two compounds that were identified as 2-methylsulfinyl-5-phenyl-4-(2-thienyl)thiazole (**4b**) (0.055 g; yield: 14%) and 2-methylsulfonyl-5-phenyl-4-(2-thienyl)thiazole (**4c**) (0.220 g; yield: 57%) from their ir, ^{1}H-, and ^{13}C-nmr spectra.

4b. This compound was isolated as oil. Ir(film): 1570, 1400, 1325, 1195, 1020, 890, 810 cm^{-1}. ^{1}H-Nmr, δ (ppm): 3.09 (s, 3H, SOMe), 6.90 (dd, ^{3}J= 5.1 Hz, ^{3}J= 3.6 Hz, 1H, H8), 7.05 (dd, ^{3}J= 3.6 Hz, ^{4}J= 1.2 Hz, 1H, H7), 7.24 (dd, ^{3}J= 5.1 Hz, ^{4}J= 1.2 Hz, 1H, H9), 7.46 (m, 5H, Ph). ^{13}C-Nmr, δ (ppm): 43.2 (SOMe), 126.2 (C9), 126.4 (C7), 127.2 (C8), 128.9 (C12), 129.4 (C5), 129.9 (C13), 130.2 (C11), 135.4 (C10), 136.4 (C6), 146.2 (C4), 174.0 (C2).

2-Methylsulfonyl-5-phenyl-4-(2-thienyl)thiazole 4c. To a solution of **4a** (0.255 g, 0.881 mmol) in dry methylene chloride (4.0 ml) was slowly added m-chloroperbenzoic acid (0.415 g, 2.4 mmol). The evolution of reaction mixture was followed by tlc (hexane/ethyl acetate: 80/20 v/v), and after 1 h the compound (**4a**) was unobserved and the principal compound of reaction mixture was the sulfoxide (**4b**). After 3 h at room temperature the sulfoxide (**4b**) was quantitatively transformed in the sulfone (**4c**). The reaction mixture was then diluted with ether (50 ml) and successively washed with solutions of Na_2SO_3 (5%, 2x10 ml), $NaHCO_3$ (5%, 2 x 10 ml), and water (2 x 5 ml). The organic layer was dried ($MgSO_4$) and evaporated to dryness. The crude was purified by recrystallization from methanol. Yield: 98%. mp 135-136^{0}C.

Ir(KBr): 1610, 1590, 1560, 1490, 1450, 1340, 865, 850 cm^{-1}. ^{1}H-Nmr, δ (ppm): 3.41 (s, 3H, SO_2Me), 6.91 (dd, ^3J= 3.6 Hz, ^3J= 5.1 Hz, 1H, H8), 7.11 (dd, ^3J= 3.6 Hz, ^4J= 1.2 Hz, 1H, H7), 7.26 (dd, ^3J= 5.1 Hz, ^4J= 1.2 Hz, 1H, H9), 7.48 (m, 5H, Ph). ^{13}C-Nmr, δ (ppm): 43.2 (SO_2Me), 126.8 (C9), 127.1 (C7), 127.2 (C8), 129.0 (C12), 129.2 (C5), 129.8 (C13), 129.9 (C11), 135.4 (C10), 137.4 (C6), 146.6 (C4), 163.1 (C2). Anal. Calcd for $C_{14}H_{11}NO_2S_2$: C, 58.11; H, 3.83; N, 4.84. Found: C, 58.23; H, 3.61; N, 4.97.

General procedure for the nucleophylic substitution reactions of 4c with amines. In a dried nitrogen-filled round-bottomed flask fitted with magnetic stirrer and a rubber septum **4c** (0.5 g, 1.56 mmol) was dissolved in the amine (5.33 mmol). The solution was then heated at the boiling point of the amine for 4.5 h, and then was allowed to reach the room temperature. The reaction mixture was then hydrolyzed with a solution of 5N NaOH up to reach a pH 9. Ether was added (25 ml) and the organic layer was decanted, washed with water (20 ml) until pH 7, and dried ($MgSO_4$). The solvent was evaporated and the crude products (**6a**-**6c**) were purified by a flash chromatography on silica gel (hexane/ethyl acetate: 80/20 v/v).

2-Hydrazinyl-5-phenyl-4-(2-thienyl)thiazole 6a. This compound was obtained from 0.50 g (1.56 mmol) of **4c** and 12 ml of hydrazine hydrate (80%). The crude product (0.438 mg) was purified by a flash chromatography and recrystallization from methanol. Yield: 0.354 g (83%). mp 148-149°C. Ir(KBr): 3200, 1645, 1610, 1525, 895, 765, 710 cm^{-1}. ^{1}H-Nmr (DMSO-d_6), δ (ppm): 4.06 (br s, 2H, NH_2), 5.97 (d, ^3J= 3.0 Hz, 2H, H7 and H8), 6.43-6.52 (m, 6H, Ph and H9), 7.83 (br s, 1H, NH). ^{13}C-Nmr, δ (ppm): 118.4 (C5), 124.1 (C9), 125.2 (C7), 127.2 (C8), 127.8 (C13), 128.9 (C11), 129.8 (C12), 132.7 (C6), 133.0 (C19), 139.5 (C4), 173.7 (C2). Anal. Calcd for $C_{13}H_{11}N_3S_2$: C, 57.11; H, 4.06; N, 15.37. Found: C, 57.29; H, 3.95; N, 15.01.

2-N-Morpholinyl-5-phenyl-4-(2-thienyl)thiazole 6b. This compound was obtained from 0.50 g (1.56 mmol) of **4c** and 0.46 g (5.33 mmol) of morpholine. The crude product (0.544 g) was purified by a flash chromatography and recrystallization from methanol. Yield: 0.272 g (53%). mp 150-151°C. Ir(KBr): 1575, 1540, 1520, 895, 745, 690 cm^{-1}. ^{1}H-Nmr, δ (ppm): 3.40-3.82 (AA'XX' system, 8H, X: 3.49 ppm; A: 3.81 ppm; $J_{AA'}$=0.87 Hz, J_{AX}= 6.82 Hz, $J_{XX'}$= 0.87 Hz, $J_{A'X'}$= 3.07 Hz, morpholine ring), 6.84 (dd, ^3J= 3.6 Hz, ^3J= 5.1 Hz, 1H, H8), 6.99 (dd, ^3J= 3.6 Hz, ^4J= 1.2 Hz, 1H, H7), 7.14 (dd, ^3J= 5.1 Hz, ^4J= 1.2 Hz, 1H, H9), 7.32-7.42 (m, 5H, Ph). ^{13}C-Nmr, δ (ppm): 48.2 (C14), 66.1 (C15), 119.8 (C5), 125.1 (C9), 125.2 (C7), 127.1 (C8), 128.0 (C13), 128.7 (C11), 130.1 (C12), 132.1 (C6), 138.5 (C4), 140.3 (C10), 168.5 (C2). Anal. Calcd for $C_{17}H_{16}N_2OS_2$: C, 62.16; H, 4.91; N, 8.53. Found: C, 61.97; H, 4.82; N, 8.37.

2-(N-Cyclohexylamino)-5-phenyl-4-(2-thienyl)thiazole 6c. This compound was obtained from 0.5 g (1.56 mmol) of **4c** and 0.528 g (5.33 mmol) of cyclohexylamine. The crude product (0.520 g) was purified by a flash chromatography and recrystallization from hexane. Yield: 0.190 g (36%). mp 140-141°C.. Ir (KBr): 3160, 1560, 1510, 880, 750, 705 cm^{-1}. ^{1}H-Nmr, δ (ppm): 1.30 (m, 5H, cyclohexyl ring), 1.61 (m, 1H, cyclohexyl ring), 1.74 (m, 2H, cyclohexyl ring), 2.08 (m, 2H,

cyclohexyl ring), 3.25 (m, 1H, H14), 5.37 (d, ^3J= 7.8 Hz, 1H, NH), 6.84 (dd, ^3J= 5.1 Hz, ^3J= 3.6 Hz, 1H, H7), 6.97 (dd, ^3J= 3.6 Hz, ^4J= 1.2 Hz, 1H, H8), 7.14 (dd, ^3J= 5.1 Hz, ^4J= 1.2 Hz, 1H, H9), 7.34 (m, 3H, Ph), 7.44 (m, 2H, Ph). ^{13}C-Nmr, δ (ppm): 24.5 (C16), 25.3 (C17), 32.8 (C15), 118.8 (C5), 124.7 (C9), 125.0 (C7), 126.9 (C8), 127.6 (C13), 128.5 (C12), 129.3 (C12), 129.5 (C4), 132.3 (C6), 138.3 (C11), 166.3 (C2). Anal. Calcd for $C_{19}H_{20}N_2S_2$: C, 67.02; H, 5.92; N, 8.23. Found: C, 67.12; H, 5.85; N, 8.35.

Acknowledgements

This work has been supported by the Comision Interministerial de Ciencia y tecnologia (CICYT; No. FAR 88-0514), Ministerio de Educacion y Ciencia, Madrid (SPAIN). E. M. gratefully acknowledges the Ministry of Education for a F. P. I. grant.

REFERENCES

1. W. Klose, U. Niedballa, K. Schwarz, and I. Boettcher, Arch. Pharm., 1983, 316, 941.
2. R. Maeda, E. Ohsugi, T. Fujioka, and K. Hirose, Chem. Pharm. Bull., 1983, 31, 3424.
3. W. Davies, J. A. Maclaren, and L. R. Wilkinson, J. Chem. Soc., 1950, 3491.
4. M. Augustin, M. Richter, and S. Salas, J. Prakt. Chem., 1980, 322, 55; R. Gompper, M. Gang, and F. Saygin, Tetrahedron Lett., 1966, 1885; G. D. Krapivin, A. Jurasek, J. Kovac, and V. G. Kul'nevich, Coll. Czech. Chem. Commun., 1984, 49, 2285.
5. A. M. van Leusen, H. J. Jeuring, J. Wildeman, and S. P. J. M. van Nispen, J. Org. Chem., 1981, 46, 2069.
6. J. F. Willems and A. Vandenberghe, Bull. Soc. Chim. Belg., 1960, 69, 517; J. F. Willems and A.Vandenberghe, Ibid., 1961, 70, 745.
7. V. Metzger, 'Thiazole and its Derivatives' in 'The Chemistry of Heterocyclic Compounds', John Wiley, New York, 1979, Vol. 34, p. 284; R. Gompper and H. Herlinger, Chem. Ber., 1956, 89, 2816; R. Gompper, Ibid., 1956, 89, 1762; A. Takamizawa, H. Hirai, T. Ishida, and Y. Matsumoto, Chem. Pharm. Bull., 1967, 15, 731; G. Orellana, C. Alvarez-Ibarra, and M. L. Quiroga, Bull. Soc. Chim. Belg., 1988, 97, 731.
8. C. Alvarez-Ibarra and M. L. Quiroga, An. Quím., 1990, 86, 418.
9. C. Alvarez-Ibarra, E. Dávila, A. Mateo, P. Ortiz, and M. L. Quiroga, Tetrahedron Lett., 1987, 28, 6667.
10. C. Alvarez-Ibarra, M. Gil, P. Ortiz, and M. L. Quiroga, Heterocycles, 1988, 27, 2177.
11. G. Alonso, C. Alvarez-Ibarra, G. Orellana, and M. L. Quiroga, Bull. Soc. Chim Belg., 1989, 98, 215.
12. J. Uhlendorf, P. Kuhl, and S. Leyck, Ger. Offen. DE 3.601.411 (1987) (Chem. Abstr., 1987, 107, 154328c); T. Kawakita, M. Sano, M. Yasumoto, K. Oshuga, and K. Haga, Eur. Pat. Appl. EP 183.191 (1986) (Chem. Abstr., 1986, 105, P115056b.

13. V. K. Ahluwalia, N. Kaila, and S. Bala, Indian J. Chem., Sect. B, 1986, 25B, 502; V. K. Ahluwalia, K. K. Arora, and G. Kaur, Indian J. Pharm. Sci., 1986, 48, 95.

14. L. N. Pridgen, Synthesis, 1984, 1047; L. N. Pridgen and L. B. Killmer, J. Org. Chem., 1981, 46, 5402.

15. M. Kumuda, Pure Appl. Chem., 1980, 52, 669; J. K. Ochi, 'Organometallic Mechanism and Catalysis', Academic Press, New York, 1978.

16. G. W. Gokel, H. M. Gerdes, and D. M. Dishong, J. Org. Chem., 1980, 45, 3634.

17. J. Bourdais, J. Heterocyc. Chem., 1976, 13, 491.

18. S. Florio, C. J. M. Sterling, and J. L. Leng, Ibid., 1982, 19, 237.

19. L. Willms, R. Handte, and H. Mildenberger, Eur. Pat. Appl., 1982, EP 44.497 (Chem. Abstr., 1982, 96, 199676k).

20. W. Horstmann, Ger. Offen., 1987, DE 3.524.866 (Chem. Abstr., 1987, 106, 215508q).

21. The assignment of signals of C5 and C4 carbons are changed in reference 10.

22. A. Bax, J. Magn. Reson., 1983, 53, 517.

23. E. Breitmaier and W. Voelter, 'Carbon-13 NMR Spectroscopy', Verlag Chemie, 3rd Ed., 1987, p. 254, 281.

24. J. Meijer, P. Vermeer, and L. Brandsma, Recl. Trav. Chim. Pays Bas, 1973, 92, 601.

Received, 5th July, 1991