Synthesis of 10-(4-Methyl-1-piperazinyl)thieno[3,2-*b*][1,5]benzoxazepines

Carlos Corral*, Jaime Lissavetzky and Ana M. Valdeolmillos

Instituto de Química Médica (C.S.I.C), Juan de la Cierva 3,
28006 Madrid, Spain

Received February 25, 1985

A series of the title compounds has been synthesized starting from methyl 3-hydroxythiophene-2-carboxylate. Its condensation with 2,4-dinitrochlorobenzene provides through compound **4e** a way to introduce 7-substituents by means of diazonium salts reactions.

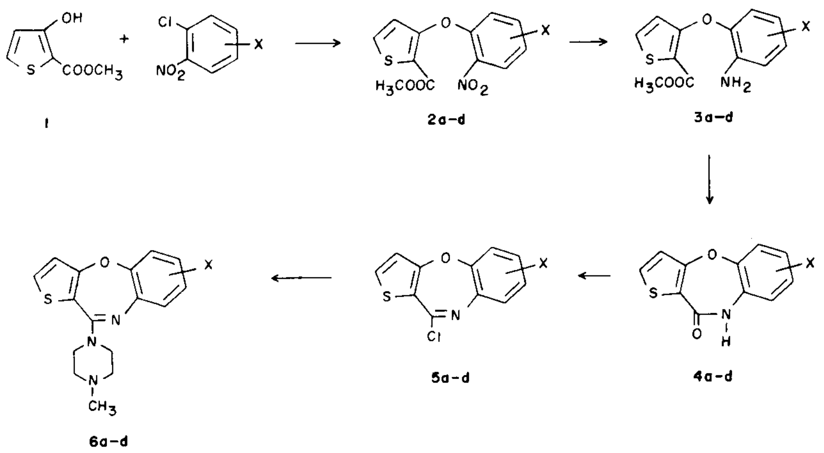
J. Heterocyclic Chem., **22**, 1349 (1985).

The synthesis of a representative series of the title compounds has been carried out in order to study the effect on potential neurological activity of the exchange of sulfur by oxygen in a previously synthesized series of 10-(4-methyl-1-piperazinyl)thieno[3,2-*b*][1,5]benzothiazepines [1].

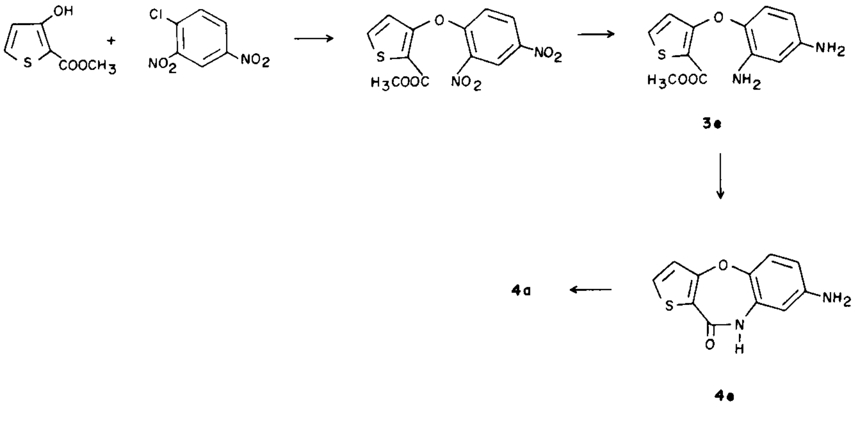
The general synthetic route to this series is outlined in Scheme 1.

Arylthienyl ethers **2** (Table 1) were obtained in acceptable yields, except for **2a**, by reaction of methyl 3-hydroxythiophene-2-carboxylate (**1**) with the corresponding *o*-chloronitrobenzene in dimethylsulfoxide at 100° in the presence of anhydrous potassium carbonate. The poor yield obtained for compound **2a** was doubled by ultrasonic irradiation under the same reaction conditions. The palladium on charcoal catalytic hydrogenation in ethanolic solution at room temperature of nitro compounds **2** gave essentially quantitative yields of the corresponding aminoethers **3** (Table 2). The oxazepinones **4** (Table 3) were prepared by intramolecular cyclization of the corresponding aminoethers **3** by heating them with sodium methyl-

Scheme 1



Scheme 2

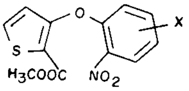


sulfinylmethanide in dimethylsulfoxide as described by Chakrabarti *et al* [2]. Finally, the crude iminochlorides **5** obtained from reaction of compounds **4** with phospohrus pentachloride in phosphorus oxychloride as solvent were reacted at room temperature with *N*-methylpiperazine in toluene to yield compounds **6**.

An indirect route (Scheme 2), which was used to obtain in an excellent overall yield of compound **4a**, provides a method to introduce a variety of substituents in position 7 of the thienobenzoxazepine nucleus through diazotization reactions. The starting compound, 2,4-dinitrochlorobenzene reacted very smoothly with compound **1** to give the dinitroether **2e** (96% yield). This was reduced by hydrogen to the diaminoether **3e** (92% yield), which was cyclized to

Table 1

Methyl 3-(2-Nitrophenoxy)thiophene-2-carboxylates

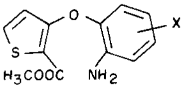


Compound	X	Reaction time (hours)	Yield (%) (Method)	Mp (°C) [a]	Molecular formula	Analysis % Calcd./Found C	H	N
2a	H	22	17 (A)	131-132	$C_{12}H_9NO_5S$	51.61	3.24	5.01
			34 (B)			51.91	3.45	5.18
2b	4Cl	20	59	125-126	$C_{12}H_8ClNO_5S$	45.96	2.57	4.46
						46.12	2.57	4.37
2c	6Cl	20	57	115-116	$C_{12}H_8ClNO_5S$	45.96	2.57	4.46
						45.69	2.52	4.74
2d	$4CF_3$	3	84	112-113	$C_{13}H_8F_3NO_5S$	44.95	2.30	4.03
						44.87	2.25	4.00
2e	$4NO_2$	0.5	96	111-112	$C_{12}H_8N_2O_7S$	44.45	2.48	8.64
						44.40	2.49	8.82

[a] Recrystallized from methanol. All these compounds showed the following common ir and ^{1}H-nmr spectroscopic data: ir (nujol): ν 1710 (C=O), 1550, 1340 (NO_2); ^{1}H-nmr (deuteriochloroform): δ 3.7-3.9 (s, 3H, CH_3), 7.0 (d, J = 5 Hz, 1H, H-4 thiophene), 7.6 (d, J = 5 Hz, 1H, H-5 thiophene), 6.9-7.7 (m, 2 or 3H, benzene protons), 8.1-8.5 (m, 1H, H-3 benzene proton).

Table 2

Methyl 3-(2-Aminophenoxy)thiophene-2-carboxylates

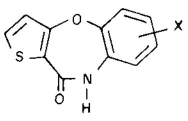


Compound	X	Yield (%)	Mp (°C) [a]	Molecular formula	Analysis % Calcd./Found C	H	N
3a	H	96	103-104	$C_{12}H_{11}NO_3S$	57.82	4.44	5.62
					57.80	4.20	5.43
3b	4Cl	94	116-117	$C_{12}H_{10}ClNO_3S$	50.82	3.55	4.97
					50.75	3.73	4.93
3c	6Cl	91	123-124	$C_{12}H_{10}ClNO_3S$	50.82	3.55	4.97
					51.01	3.64	4.89
3d	$4CF_3$	90	97-98	$C_{13}H_{10}F_3NO_3S$	49.21	3.15	4.41
					49.40	3.16	4.40
3e	$4NH_2$	92	168-169	$C_{12}H_{12}N_2O_3S$	54.37	4.57	10.59
					54.10	4.39	10.77

[a] Recrystallized from methanol/water. All these compounds showed the following common ir and ^{1}H-nmr spectroscopic data: ir (nujol): ν 3480, 3370 (NH_2), 1710-1690 (C=O); ^{1}H-nmr (deuteriochloroform): δ 1.5-3.6 (s, 2H, exchangeable with deuterium oxide, NH_2), 3.9 (s, 3H, CH_3), 6.5-6.8 (d, J = 5 Hz, 1H, H-4 thiophene), 6.7-7.1 (m, 3 or 4H, benzene protons), 7.3-7.5 (d, J = 5 Hz, 1H, H-5 thiophene).

Table 3

9*H*-10-Oxothieno[3,2-*b*][1,5]benzoxazepines

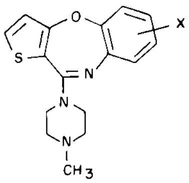


Compound	X	Yield (%)	Mp (°C) [a]	Molecular formula	Analysis % Calcd./Found		
					C	H	N
4a	H	76	219-220	$C_{11}H_7NO_2S$	60.83	3.24	6.45
					60.56	3.34	6.47
4b	7Cl	80	282-283	$C_{11}H_6ClNO_2S$	52.52	2.40	5.56
					52.67	2.21	5.71
4c	5Cl	82	249-251	$C_{11}H_6ClNO_2S$	52.52	2.40	5.56
					52.32	2.31	5.78
4d	$7CF_3$	86	212-213	$C_{12}H_6F_3NO_2S$	50.53	2.10	4.91
					50.27	2.02	4.93
4e	$7NH_2$	87	220-221	$C_{11}H_8N_2O_2S$	56.89	3.45	12.07
					56.61	3.31	11.88

[a] Recrystallized from ethyl acetate. All these compounds showed the following common ir and ^{1}H-nmr spectroscopic data: ir (nujol): ν 3220-3080 (NH), 1670-1660 (C=O); ^{1}H-nmr (dimethylsulfoxide-d_6): δ 6.8-7.0 (d, J = 5 Hz, 1H, H-4 thiophene), 6.8-7.4 (m, 3 or 4H, benzene protons), 7.8-7.9 (d, J = 5 Hz, 1H, H-5 thiophene), 10.2-10.4 (s, 1H, exchangeable with deuterium oxide, NH).

Table 4

10-(4-Methyl-1-piperazinyl)thieno[3,2-*b*][1,5]benzoxazepines



Compound	X	Yield (%)	Mp (°C) [a]	Molecular formula	Analysis % Calcd./Found		
					C	H	N
6a	H	45	oil [b]	$C_{16}H_{17}N_3OS_2 \cdot C_3H_8O$	63.68	6.70	11.73
					63.77	6.63	11.65
6b	7Cl	76	126-127	$C_{16}H_{16}ClN_3OS$	57.57	4.80	12.59
					57.50	5.01	12.63
6c	5Cl	53	110-111	$C_{16}H_{16}ClN_3OS$	57.57	4.80	12.59
					57.53	4.83	12.51
6d	$7CF_3$	66	161-162	$C_{17}H_{16}F_3N_3OS$	55.58	4.36	11.44
					55.55	4.42	11.34

[a] Recrystallized from 2-propanol. All these compounds showed the following common ^{1}H-nmr spectroscopic data: ^{1}H-nmr (carbon tetrachloride): δ 2.2-2.3 (s, 3H, CH_3), 2.3-2.6 (t, 4H, H-3 and H-5, piperazine), 6.7-6.9 (d, J = 5 Hz, 1H, H-4 thiophene), 6.8-7.2 (m, 3 or 4H, benzene protons), 7.4 (d, J = 5 Hz, 1H, H-5 thiophene). [b] Isolated with one 2-propanol molecule

the 7-aminothienobenzoxazepinone **4e** (87% yield). The diazonium salt of **4e** gave **4a** by treatment with hypophosphorus acid in 89% yield.

From the reaction of **1** with 2,4-dichloronitrobenzene a mixture of two compounds was obtained that could not be separated either by recrystallization or column chromatography.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrometer. Proton nuclear magnetic resonance spectra were recorded on a Varian EM-390 (90 MHz) spectrometer with TMS as internal reference. For ultrasonic irradiation a sonifier cell disruptor W 350 (Branson 300 W) was used.

Methyl 3-hydroxythiophene-2-carboxylate [3] was obtained according to the literature. All the other starting products were obtained from Fluka A.G.

Methyl 3-(2-Nitrophenoxy)thiophene-2-carboxylates **2a-e**.

Method A.

Anhydrous potassium carbonate (6.9 g, 0.05 mole) was added at 65° to a stirred solution of the corresponding *o*-chloronitrobenzene (0.05 mole) and methyl 3-hydroxythiophene-2-carboxylate (**1**) (7.9 g, 0.05 mole) in dimethylsulfoxide (40 ml). The reaction mixture was heated at 100° for the time indicated in Table 1 and once cooled poured into ice-water and the resulting mixture was extracted repeatedly with ether. The ethereal extracts were washed with water, dried over magnesium sulfate, evaporated to dryness and the residue was crystallized from methanol to yield yellow solids. Properties and yields of compounds **2a-e** are shown in Table 1.

Methyl 3-(2-Nitrophenoxy)thiophene-2-carboxylate (**2a**).

Method B.

This compound was synthesized in the same manner as described above using a reaction flask which was provided with a rubber-stopper with the suitable diameter for adapting the sonifier, which was directly immersed in the reaction medium. This compound was identical in all respects with that described above.

Methyl 3-(2-Aminophenoxy)thiophene-2-carboxylates **3a-e**.

To a suspension of compounds **2a-e** (3 g) in methanol (300 ml) was added palladium on charcoal (10%) (300 mg) as catalyst and the mixture was hydrogenated at 60 psi. The catalyst was filtered off, the solvent was evaporated to dryness and the residue was crystallized from methanol-water to yield colorless solids. Properties and yields of compounds **3a-e** are shown in Table 2.

9*H*-10-Oxothieno[3,2-*b*][1,5]benzoxazepines **4a-e**.

Sodium methylsulfinylmethanide (0.17 mole) was prepared by treating sodium hydride (9.1 g, 0.17 mole) with dimethylsulfoxide (100 ml) at 70° (until evolution of hydrogen ceased). The corresponding aminoester **3a-e** (0.059 mole) in dimethylsulfoxide (50 ml) was added slowly, the temperature of the exothermic reaction being kept below 80°. The mixture was stirred for 15 minutes and then was poured onto ice-water. The precipitate was filtered off, washed with water and dried. Crystallization from ethyl acetate gave the pure lactams **4a-e**. Properties and yields of compounds **4a-e** are shown in Table 3.

10-(4-Methyl-1-piperazinyl)thieno[3,2-*b*][1,5]benzoxazepines **6a-d**.

A mixture of the corresponding lactam **4a-d** (0.01 mole), phosphorus pentachloride (5.2 g, 0.025 mole) and phosphorus oxychloride (15 ml) was stirred and heated at 120° for 4 hours, and once cooled the resulting reaction mixture was poured into *n*-hexane-ice. The hexane layer was immediately separated to avoid the hydrolysis of the iminochloride, dried over magnesium sulfate and evaporated to dryness to yield the corresponding iminochlorides **5a-d** as yellow solids. These compounds showed good chromatographic purity and were not crystallized to avoid hydrolysis to the oxazepinones **4a-d**.

N-Methylpiperazine (5 ml) was added to a solution of the corresponding iminochlorides in anhydrous toluene. On leaving the reaction mixture overnight at room temperature, the *N*-methylpiperazine hydrochloride precipitated. The solvent was removed and the residue was treated with ether and water. The ethereal extracts were dried over magnesium sulfate and evaporated to dryness to yield compounds **6a-d** as yellow solids, which were crystallized from isopropylic alcohol. Properties and yields of compounds **6a-d** are shown in Table 4.

9*H*-10-Oxothieno[3,2-*b*][1,5]benzoxazepine (**4a**).

7-Amino-9*H*-10-oxothieno[3,2-*b*][1,5]benzoxazepine (**4e**) (2 g, 0.0086 mole) was added gradually to a vigorously stirred 6*M* hydrochloric acid solution (10 ml). The reaction mixture was stirred at room temperature for 30 minutes and once cooled below 0° (ice-salt bath). It was diazotised with sodium nitrite (0.59 g, 0.0086 mole) in water (2 ml). The resulting diazonium salt was stirred another hour at this temperature and was poured at once onto a well stirred 30% solution of hypophosphorus acid (14.7 ml, 0.086 mole). The reaction mixture was stirred at room temperature until evolution of nitrogen had ceased and the solid formed was filtered, washed with water and recrystallized from ethyl acetate to yield 1.7 g (89%) of **4a**, mp 219-220°. This compound was identical in all respects with that described in Table 3.

Acknowledgements.

We are indebted to our Department of Analyses and Instrumental Techniques for all the analytical and spectroscopic data.

REFERENCES AND NOTES

[1] C. Corral, A. Lasso, J. Lissavetzky and A. M. Valdeolmillos, *J. Heterocyclic Chem.*, **22**, (1985).

[2] J. K. Chakrabarti, T. A. Hicks, T. M. Hotten and D. E. Tupper, *J. Chem. Soc., Perkin Trans. I*, 937 (1978).

[3] P. R. Huddleston and J. M. Barker, *Synth. Commun.*, **9**, 731 (1979).