Synthesis and properties of 1-alkyl-2-methyl-3-sulfonylpyrroles and 1-alkyl-2-methyl-3-sulfonylpyrrole-5-carboxylic acid derivatives

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1,2-Dialkyl-3-sulfonylpyrroles are versatile synthetic tools for obtaining related fused ring heterocycles, for instance, pyrrolothiazines. We have established a method for obtaining pyrrolic compounds with a variety of 3-sulfonyl moieties such as sulfones 4, sulfonates 5 and sulfonamides 6.

Several synthetic methods have been reported[1,2] for obtaining pyrrole-based fused-ring heterocycles, such as pyrrolo[3,2-*d*]-pyrimidines, which use the appropriate 3-substituted pyrrole as starting material. In a previous work[3] we reported the synthesis of 1,2-dialkyl-3-nitropyrroles **2** and studied the reactivity as a nucleophile of the benzylic type position on the side chain bound to carbon 2 of the pyrrole ring in these compounds. We described the reaction of 1-alkyl-2-methyl-3-nitropyrrole **2** with electrophiles (alkyl halides, aldehydes and acrylates to mention but a few) in the base–DMSO system, yielding the corresponding reaction product of nucleophilic attack of the deprotonated 2-methyl group to the electrophilic carbon of the reagent.

We now report the synthesis of 1-alkyl-2-methyl-3-sulfonylpyrrole-5-carboxylates **4–6** considering that these compounds could be suitable precursors of pyrrolothiazines,[4] analogues of known 1,2-benzothiazin-4-one 1,1-dioxides with antiinflammatory activity. The new synthesis makes this bioisostere of benzene readily available for conversion to various derivatives of biological interest,[5,6] such as antibacterial sulfonamides, diuretic agents and antiinflammatory agents.

Various methods have been described to synthesize compounds related to the 3-sulfonylpyrrole structure, such as acid-mediated isomerization of the easily available isomers[7,8] substituted at the 2-position with certain electrophiles. Unfortunately, this method is not appropriate for the synthesis of the desired 1,2-dialkyl-3-sulfonylpyrrole-5-carboxylates **4–6**, because it would require starting compounds unsubstituted at position 2 in order to obtain the 2-sulfonyl intermediate. Thus, we decided to extend the methodology applied for the synthesis of 1,2-dialkyl-3-nitropyrroles[3] to the 1,2-dialkyl-3-sulfonylpyrrole system, using a synthetic scheme equivalent to that described formerly by changing the electrophilic moiety (Scheme 1). In this method, compound **1** was treated with 70% nitric acid, yielding the corresponding compound **2**. Strict control of the reaction temperature was required (30 ± 1 °C) to obtain reasonable yields.

Position 5 of the pyrrole ring required protection as its reactivity towards electrophiles was higher than that of the desired position. The alkoxycarbonyl moiety was a suitable protecting group because, on one hand, it acted as the directing group for the electrophilic attack and, on the other hand, it could be easily removed by hydrolysis and decarboxylation.

In the present work, the electrophilic substitution step was performed by using chlorosulfonic acid as reagent. Chlorosulfonylpyrrole compounds **3** can easily be converted to a wide scope of pyrroles substituted with different sulfonyl derived groups in the position 3 (Scheme 1), such as sulfones **4,** sulfonates **5** and sulfonamides **6**.

We preliminarily compared the nucleophilic properties of the 2-methyl group in these systems with the reactivity observed in the nitropyrrole series.[3] The reactivity as a nucleophile of the 2-methyl group in compounds **2** was of considerable interest in order to increase the length of the chain bound to this position and to link functionalized residues.

Finally, we also report an efficient one-step process for eliminating the protecting group bound to position 5 of the pyrrole ring (Scheme 2), by refluxing the corresponding alkoxycarbonyl compound **4–6** with dilute HCl.

Results and discussion

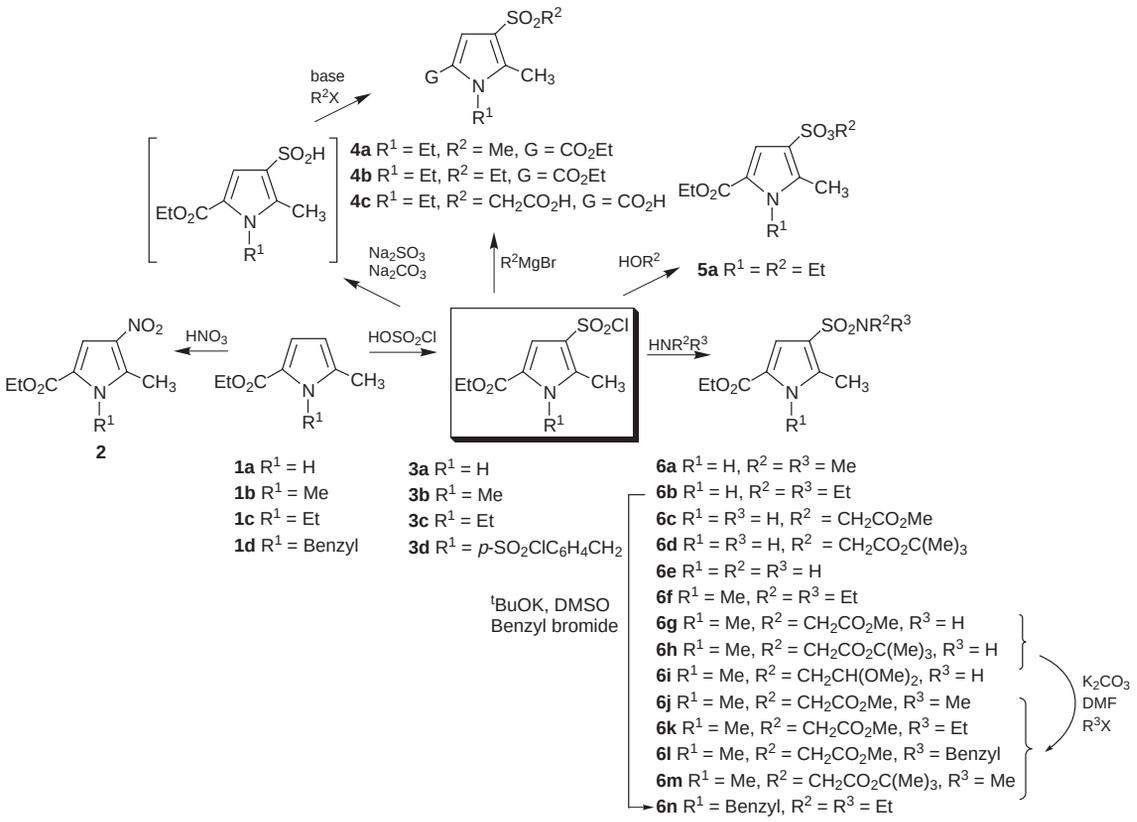
Compounds **1** were synthesized according to the established method.[3]

Treatment of compounds **1** with $HOSO_2Cl$ at 0 °C, following the method described by Clark *et al.*,[9] led to the corresponding chlorosulfonylpyrrole **3** with the exception of **1d** (R^1 = benzyl). Chlorosulfonation of this compound provided a 75% yield of the compound **3d** ($R^1 = p\text{-}SO_2Cl\text{-}C_6H_4CH_2$) doubly chlorosulfonated at the pyrrole and the benzene ring. Besides, yields for compounds **3** are higher when compared with the corresponding nitro compounds **2** (See Tables 1–3 for yields and other data).

Sulfones **4** were obtained by treatment of **3c** with Na_2CO_3–Na_2SO_3 following the method described by Feit.[10] The corresponding sulfinic acid obtained was not isolated and subsequent treatment with methyl iodide or chloroacetic acid provided sulfones **4a** (R^2 = Me) and **4c** ($R^2 = CH_2CO_2H$), respectively. Alternatively, sulfone **4b** (R^2 = Et) was obtained directly by treatment of **3c** with EtMgBr in ether at reflux temperature. It is noteworthy that the ester group bound to the position 5 of the pyrrole ring did not interfere with this reaction. Sulfonic ester **5a** was obtained following the procedure described,[11] by treating a solution of compound **3c** in ether with ethanol in the presence of pyridine at 0 °C. In a similar way, sulfonamides **6a–i** arose following the method described by Binder *et al.*[12] as a result of treatment of the chlorosulfonyl compound **3a** or **3b** with the hydrochloride of the corresponding primary or secondary amine in the presence of pyridine at room temperature.

Compounds **6j–m**, which contain a complex combination of alkyl residues bound to the amidic nitrogen, could be synthesized in good yield (77–94%) by alkylation of the corresponding primary sulfonamides **6g** and **6h** with alkyl halide (R^3X) in the presence of anhydrous K_2CO_3, using DMF as solvent (Scheme 1).

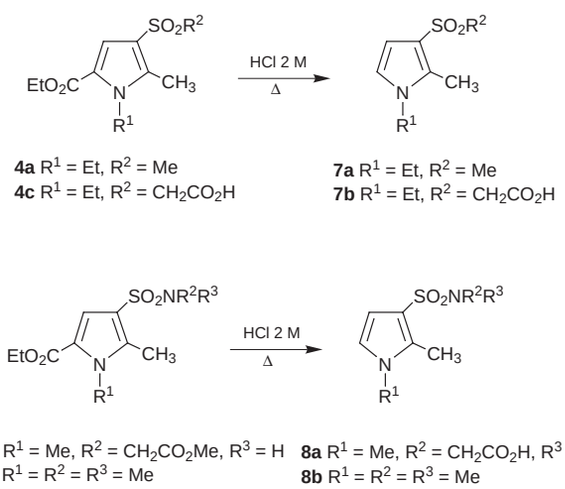
The nucleophilic properties of the 2-methyl group were



Scheme 1

preliminarily studied. Thus, in the alkylation of sulfonamides **6g** and **6h**, carried out in the above-mentioned conditions, we did not observe alkylation on the 2-methyl group. Moreover, treatment of compound **6c** ($R^1 = R^3 = H$, $R^2 = CH_2CO_2Me$) with a molar excess of methyl iodide as alkylating agent, using potassium *tert*-butoxide as base and DMSO as solvent, yielded (81%) the corresponding **6j** ($R^1 = R^3 = Me$). Again, no evidence of the 2-ethyl compound (C-alkylation in the 2-methyl group) was observed. These results suggest that hydrogens of the 2-methyl group in sulfonamide **6c** are much less acidic than the analogous protons in the related nitro compounds **2** previously studied.[3] Even if strong bases such as LDA and $NaNH_2$ were used, no C-alkylation occurred. Thus, treatment of sulfonamide **6f** ($R^1 = Me$, $R^2 = R^3 = Et$) with excess methyl iodide as alkylating agent, using $NaNH_2$ as base and DMF as solvent, under an argon atmosphere, gave no trace of the desired C-alkylated compound. Instead, some starting material was recovered. Furthermore, when **6f** dissolved in dry THF was treated with LDA 2 M and excess of methyl iodide or propionaldehyde as electrophiles, the desired alkylated product was not formed after 24 hours of reaction. Moreover, the starting sulfonamide **6f** compound was completely destroyed and a complex mixture was obtained. In spite of these negative results regarding the reactivity of the 2-methyl group, the alkylating procedure of the position 1 of the pyrrole ring could be considered an alternative for the synthesis of compounds **6**. As a result, the 1-alkyl group could be introduced in the last step by alkylation of sulfonamides **6a–d** with alkyl iodide using K^{t}BuO as base. This alternative method allowed the synthesis of sulfonamide **6n** (R^1 = Benzyl) by alkylation of **6b** with benzyl bromide, and gave **6n** in 88% yield.

Finally, the ethoxycarbonyl group in the 5 position (Scheme 2) can easily be cleaved by treatment of compounds **4–6** with HCl–ethanol at the refluxing temperature. Compounds **7** and **8** were obtained in good yields, with long reaction times (Table 1). We found that hydrolysis of the ester group bound to position 5 of the pyrrole ring was selective against the 3-aminosulfonyl



Scheme 2

moiety in compounds **6** (no sulfonic acids were detected). We also observed that decarboxylation of this group was selective against other carboxylic residues placed on the side chain in compounds **6c** ($R^2 = CH_2CO_2Me$) and **4c** ($R^2 = CH_2CO_2H$). These results disagree with those described by Brown[13] who treated aromatic systems related to alkylsulfonylbenzoic acids with a solution of HCl. In the above-mentioned conditions, this author observed cleavage of the carboxylic group placed on the sulfonylalkyl residue.

Experimental

IR Spectra were recorded on a Nicolet 5PC FT-IR spectrophotometer and are expressed as cm^{-1}. ^1H NMR Spectra were recorded on a Varian Gemini 200 spectrometer and δ values are expressed as ppm; J values are given in Hz. Chemical analyses were carried out by *Centre d'Investigació i Desenvolupament - C.S.I.C.* and by *Serveis Científico-Tècnics de la Universitat*

Table 1 Analytical data for 3-chlorosulfonylpyrroles **3**, 3-sulfonylpyrroles **4** and **5**, ethyl 1-alkyl-3-alkylaminosulfonyl-2-methylpyrrole-5-carboxylates **6** and for 1-alkyl-3-alkylsulfonyl-2-methylpyrroles **7** and 1-alkyl-3-alkylaminosulfonyl-2-methylpyrroles **8**

Compound (formula)	R^1	R^2	R^3	Yield (%)	ν_{max}/cm^{-1} (KBr)		Mp/°C	Found (%) (required)		
					CO	SO_2		C	H	N
3a ($C_8H_{10}ClNO_4S$)	H	Cl	—	81	1697[a]	1373, 1173	145–147	38.2 (38.17)	4.0 (4.00)	5.5 (5.56)
3b ($C_9H_{12}ClNO_4S$)	Me	Cl	—	80	1719	1385, 1158	104–106	40.6 (40.68)	4.4 (4.55)	5.2 (5.27)
3c ($C_{10}H_4ClNO_4S$)	Et	Cl	—	70	1718	1386, 1159	49–51	43.1 (42.93)	5.3 (5.04)	4.8 (5.00)
3d ($C_{15}H_{15}Cl_2NO_6S_2$)	*p*-$SO_2ClC_6H_4CH_2$	Cl	—	75	1712	1373, 1155	115–117	40.8 (40.92)	3.3 (3.43)	3.2 (3.18)
4a ($C_{11}H_{17}NO_4S$)	Et	Me	—	51	1711	1300, 1133	68–69	51.2 (50.94)	6.6 (6.60)	5.4 (5.46)
4b ($C_{11}H_{17}NO_4S$)	Et	Et	—	55	1717	1307, 1131	—[c]	52.9 (52.72)	7.1 (7.00)	5.0 (5.12)
4c ($C_{10}H_{13}NO_6S$)	Et	CH_2CO_2H	—	45	1712, 1678[b]	1317, 1131	203–204	43.7 (43.62)	4.6 (4.76)	4.8 (5.08)
5a ($C_{12}H_{19}NO_5S$)	Et	OEt	—	88	1713	1350, 1160	—[c]	50.0 (49.80)	6.8 (6.61)	4.6 (4.84)
6a ($C_{10}H_{16}N_2O_4S$)	H	Me	Me	67	1717	1324, 1155[d]	149–150	46.1 (46.13)	6.3 (6.19)	10.6 (10.76)
6b ($C_{12}H_{20}N_2O_4S$)	H	Et	Et	89	1681	1324, 1151[e]	132–133	50.0 (49.98)	7.1 (6.99)	9.6 (9.71)
6c ($C_{11}H_{15}N_2O_6S$)	H	CH_2CO_2Me	H	70	1755, 1687	1329, 1158[f]	137–138	43.4 (43.41)	5.3 (5.29)	9.0 (9.20)
6d ($C_{14}H_{22}N_2O_6S$)	H	$CH_2CO_2C(Me)_3$	H	72	1730, 1691	1330, 1166[g]	148–149	48.3 (48.54)	6.4 (6.45)	8.1 (8.08)
6e ($C_{11}H_{18}N_2O_4S$)	Me	Me	Me	70	1711	1324, 1143	99–100	48.1 (48.15)	6.7 (6.61)	10.1 (10.21)
6f ($C_{13}H_{22}N_2O_4S$)	Me	Et	Et	71	1711	1324, 1144	61–63	51.6 (51.63)	7.5 (7.33)	9.2 (9.26)
6g ($C_{12}H_{18}N_2O_6S$)	Me	CH_2CO_2Me	H	78	1736, 1723	1346, 1148[h]	100–101	45.2 (45.26)	5.7 (5.70)	8.8 (8.80)
6h ($C_{15}H_{24}N_2O_6S$)	Me	$CH_2CO_2C(Me)_3$	H	88	1721, 1710	1346, 1146[i]	125–127	49.9 (49.98)	6.9 (6.71)	7.7 (7.77)
6i ($C_{13}H_{22}N_2O_6S$)	Me	$CH_2CH(OMe)_2$	H	78 77[k]	1710	1325, 1148[j]	65–68	47.0 (46.69)	6.7 (6.63)	8.3 (8.37)
6j ($C_{13}H_{20}N_2O_6S$)	Me	CH_2CO_2Me	Me	81[l]	1756, 1716	1334, 1148	59–60	46.8 (46.84)	6.2 (6.35)	8.4 (8.40)
6k ($C_{14}H_{22}N_2O_6S$)	Me	CH_2CO_2Me	Et	83[k]	1753, 1706	1336, 1143	—[c]	48.8 (48.53)	6.6 (6.40)	7.9 (8.08)
6l ($C_{19}H_{24}N_2O_6S$)	Me	CH_2CO_2Me	Benzyl	94[k]	1709, 1750	1330, 1145	73–76	55.8 (55.86)	6.1 (5.92)	7.0 (6.85)
6m ($C_{16}H_{26}N_2O_6S$)	Me	$CH_2CO_2C(Me)_3$	Me	80[k]	1710, 1746	1326, 1144	83–84	51.3 (51.32)	7.1 (6.99)	7.5 (7.48)
6n ($C_{18}H_{24}N_2O_4S$)	Benzyl	Et	Et	88[m]	1708	1328, 1141	—[c]	59.5 (59.31)	6.7 (6.63)	7.4 (7.68)
7a ($C_8H_{13}NO_2S$)	Et	Me	—	75 (4 h)	—	1310, 1134	76–78	51.1 (51.31)	7.1 (6.99)	7.4 (7.48)
7b[n] ($C_9H_{13}NO_4S$)·1/5$C_4H_{10}O$	Et	CH_2CO_2H	—	78 (36 h)	1713	1310, 1149[b]	92–94	47.7 (47.80)	5.8 (6.14)	5.85 (5.68)
8a ($C_8H_{12}N_2O_4S$)	Me	CH_2CO_2H	H	48 (33 h)	1735	1320, 1143[c]	107–109	41.0 (41.36)	5.1 (5.20)	12.0 (12.06)
8b ($C_6H_8N_2O_4S$)	Me	Me	Me	55 (36 h)	—	1323, 1137	127–129	47.3 (47.50)	6.8 (6.97)	13.4 (13.85)

[a] Other: 3243 cm^{-1}; NH st. [b] Other: 2500–3500 (br OH st). [c] Compounds **4b**, **5a**, **6k** and **6n** were not solid at room temperature. IR were recorded on NaCl (film). [d] Other: 3278 cm^{-1}; NH st. [e] Other: 3266 cm^{-1}; NH st. [f] Other: 3250 cm^{-1}; NH st. [g] Other: 3243 cm^{-1}; NH st. [h] Other: 3273 cm^{-1}; NH **6h** respectively (see Experimental section). [i] Other: 3243 cm^{-1}; NH st. [j] Other: 3290 cm^{-1}; NH st. [k] Compounds **6j**–**m** were synthesized by alkylating the amidic nitrogen of compounds **6g** and **6h** respectively (see Experimental section). [l] Compound **6k** was also synthesized by double alkylation of compound **6c** with MeI in the K^{t}BuO–DMSO system. [m] Compound **6n** was synthesized by alkylating the pyrrolic nitrogen of compound **6b** using the K^{t}BuO–DMSO system (see Experimental section). [n] Compound **7b** was purified from ether and the elemental analysis gives the correct results for ($C_9H_{13}NO_4S$)·1/5$C_4H_{10}O$.

Table 2 ^{1}H NMR spectral data for 3-chlorosulfonylpyrroles **3**, 3-sulfonylpyrroles **4** and **5**, ethyl 1-alkyl-3-alkylaminosulfonyl-2-methylpyrrole-5-carboxylates **6**, 1-alkyl-3-alkylsulfonyl-2-methylpyrroles **7** and 1-alkyl-3-alkylaminosulfonyl-2-methylpyrroles **8**; δ_H (200 MHz; $CDCl_3$; Me_4Si)

Compound	CH_3CH_2O	CH_3CH_2O	H-4	$CH_3C(2)$	CH_xN	Others
3a	1.40	4.38	7.30 (d, *J* 2.5)	2.65	—	10–11 (br, NH)
3b	1.36	4.34	7.39	2.59	3.92 (3H, s)	—
3c	1.34	4.32	7.30	2.48	4.30 (2H, q, *J* 7)	1.31 (3H, t, *J* 7, CH_3CH_2N)
3d	1.33	4.26	7.52	2.55	5.81 (2H, s)	7.21 (2H, d, *J* 8), 8.03 (2H, d, *J* 8)
4a	1.30	4.25	7.31	2.51	4.42 (2H, q, *J* 7)	1.31 (3H, t, *J* 7, CH_3CH_2N)
4b	1.33	4.39	7.28	2.54	4.28 (2H, q, *J* 7)	1.33 (6H, CH_3CH_2N, $CH_3CH_2O_2S$)
4c[a]	—	—	7.05	2.44	4.33 (2H, q, *J* 7)	1.21 (3H, t, *J* 7, CH_3CH_2N), 4.25 (s, 2H, SO_2CH_2)
5a	1.35	4.40	7.29	2.52	4.29 (2H, q, *J* 7)	1.35 (3H, t, *J* 7, CH_3CH_2N)
6a	1.37	4.34	7.07 (d, *J* 2.6)	2.56	9.8 (br, NH)	2.71 [s, 6H, $(CH_3)_2SO_2$]
6b	1.37	4.33	7.08 (d, *J* 2.5)	2.54	9.8 (br, NH)	1.16 [t, 6H, *J* 7, $(CH_3CH_2)_2SO_2$], 3.23 [d, 4H, *J* 7, $(CH_3CH_2)_2SO_2$]
6c	1.37	4.33	7.13 (d, *J* 2.6)	2.53	10 (br, NH)	3.69 (s, 3H, CH_3CO_2), 3.81 (d, 2H, *J* 5.5, $SO_2NH–CH_2$), 5.19 (t, 1H, *J* 5.4, NH)
6d	1.35	4.32	7.12 (d, *J* 2.5)	2.53	9.7 (br, NH)	1.38 [s, 9H, $(CH_3)_3CO_2$], 3.68 (d, 2H, *J* 5.4, $SO_2NH–CH_2$), 5.08 (t, 1H, *J* 5.2, NH)
6e	1.32	4.25	7.14	2.48	3.86 (s, 3H, CH_3)	2.65 [s, 6H, $(CH_3)_2SO_2$]
6f	1.34	4.27	7.18	2.49	3.86 (s, 3H, CH_3)	1.16 [t, 6H, *J* 7, $(CH_3CH_2)_2SO_2$], 3.21 [d, 4H, *J* 7, $(CH_3CH_2)_2SO_2$]
6g	1.35	4.29	7.23	2.49	3.87 (s, 3H, CH_3)	3.68 (s, 3H, CH_3CO_2), 3.78 (d, 2H, *J* 5.5, $SO_2NH–CH_2$), 5.22 (t, 1H, *J* 5.5, NH)
6h	1.36	4.27	7.23	2.48	3.85 (s, 3H, CH_3)	1.36 [s, 9H, $(CH_3)_3CO_2$], 3.64 (d, 2H, *J* 5.6, $SO_2NH–CH_2$), 4.92 (t, 1H, *J* 5.2, NH)
6i	1.34	4.27	7.21	2.47	3.86 (s, 3H, CH_3)	3.02 [d, 2H, *J* 6, $CH_2CH(OMe)_2$], 3.36 (s, 6H, OCH_2), 4.40 [t, 1H, *J* 6, $CH_2CH(OMe)_2$], 4.61 (t, 1H, *J* 6, NH)
6j	1.36	4.26	7.20	2.48	3.88 (s, 3H, CH_3)	3.71 (s, 3H, CH_3CO_2), 2.88 (s, 3H, $SO_2N–CH_3$), 3.95 (s, 2H, $SO_2N–CH_2$)
6k	1.32	4.23	7.31	2.47	3.87 (s, 3H, CH_3)	1.25 (t, 3H, *J* 7, $SO_2NCH_2–CH_3$), 3.30 (q, 2H, *J* 7, $SO_2NCH_2–CH_3$), 3.69 (s, 3H, CH_3CO_2), 4.11 (s, 2H, $SO_2N–CH_2$)
6l[b]	1.35	4.28	7.27	2.47	3.88 (s, 3H, CH_3)	3.59 (s, 3H, CH_3CO_2), 3.90 (s, 2H, $SO_2N–CH_2$), 7.27 (m, 5H, H_{benzyl})
6m	1.34	4.27	7.20	2.48	3.86 (s, 3H, CH_3)	1.42 [s, 9H, $(CH_3)_3CO_2$], 2.88 (s, 3H, $SO_2N–CH_3$), 3.87 (s, 2H, $SO_2N–CH_2$)
6n[b]	1.30	4.22	7.30	2.41	5.66 (s, 2H, CH_2)	1.15 [t, 6H, *J* 7, $(CH_3CH_2)_2SO_2$], 3.24 [d, 4H, *J* 7, $(CH_3CH_2)_2SO_2$], 6.89–7.30 (m, 5H, H_{benzyl})
7a	—	—	6.46 (d, *J* 3)	2.48	3.88 (q, *J* 7, 2H, CH_2)	1.37 (t, *J* 7, 3H, CH_3), 3.01 [s, 3H, (SO_2CH_3)], 6.60 (d, *J* 3, H5)
7b	—	—	6.49 (d, *J* 3)	2.47	3.89 (q, *J* 7, 2H, CH_2)	1.38 (t, *J* 7, 3H, CH_3), 4.08 [s, 2H, $(SO_2CH_2CO_2H)$], 6.62 (d, *J* 3, H5)
8a	—	—	6.38 (d, *J* 3)	2.42	3.54 (s, 3H, CH_3)	3.79 (s, 2H, SO_2NCH_2), 5.0–5.4 (br, 2H, NH, CO_2H), 6.52 (d, *J* 3, H5)
8b	—	—	6.35 (d, *J* 3)	2.46	3.57 (s, 3H, CH_3)	2.66 [s, 6H, $SO_2NH(CH_3)_2$], 6.56 (d, *J* 3, H5)

[a] Recorded in DMSO-d_6. [b] Signals corresponding to H-4 and H_{benzyl} are overlapped.

Table 3 ^{13}C NMR spectral data for 3-chlorosulfonylpyrroles **3**, 3-sulfonylpyrroles **4** and **5**, ethyl 1-alkyl-3-alkylaminosulfonyl-2-methylpyrrole-5-carboxylates **6**, 1-alkyl-3-alkylsulfonyl-2-methylpyrroles **7** and 1-alkyl-3-alkylaminosulfonyl-2-methylpyrroles **8**; δ_C (50.3 MHz; $CDCl_3$; Me_4Si)

Compound	CH_3CH_2O	CH_3CH_2O	C2	C3	C4	C5	$CH_3C(2)$	CH_xN	CO	Others
3a	14.6	61.7	138.5	125.8	115.7	121.3	12.3	—	161.1	—
3b	14.1	60.6	139.5	124.1	116.8	122.5	10.8	33.0	159.8	—
3c										
3d	14.0	61.2	139.5	125.6	117.7	122.3	10.9	48.4	159.7	126.9, 127.7 (CHAr), 143.5, 143.7 (C Ar)
4a	13.9	60.0	137.1	120.0	117.6	121.2	9.9	40.3	159.7	15.3 (CH_3CH_2N), 45.2 (SO_2CH_3)
4b										
4c[a]	—	—	139.0	121.5	118.3	118.3	10.1	61.5	160.9	15.6 (CH_3CH_2N), 164.2 (CO)
5a	14.1	60.2	137.7	115.2	118.5	121.2	10.3	40.7	159.9	15.5 (CH_3CH_2N), 65.9 ($SO_3CH_2CH_3$)
6a	14.2	61.1	136.9	116.0	116.4	121.1	12.6	—	161.1	37.8 [$SO_2N(CH_3)_2$]
6b	14.2	61.0	136.0	120.7	115.9	120.9	12.4	—	161.2	14.1 [$SO_2N(CH_2CH_3)_2$], 41.8 [$SO_2N(CH_2CH_3)_2$]
6c[b]	14.0	60.8	136.7	119.1	116.2	120.8	11.9	—	160.8	43.7 (NCH_2CO_2), 52.3 (CO_2CH_3)$_3$, 169.7 (CO_2CH_3)
6d	14.2	61.1	136.8	119.7	116.3	120.7	12.2	—	161.2	27.7 [$(CH_3)_3C$], 44.7 (NCH_2CO_2), 82.8 [$(CH_3)_3C$], 168.3 [$CO_2C(CH_3)_3$]
6e	14.2	60.2	138.3	114.4	118.1	122.1	11.0	32.7	160.5	37.7 [$SO_2N(CH_3)_2$]
6f	14.2	60.2	137.3	119.5	117.6	121.8	10.9	32.7	160.6	14.1 [$SO_2N(CH_2CH_3)_2$], 41.7 [$SO_2N(CH_2CH_3)_2$]
6g	14.2	60.3	138.1	118.0	118.0	121.8	10.8	32.7	160.4	43.8 (NCH_2CO_2), 52.5 (CO_2CH_3), 169.5 (CO_2CH_3)
6h	14.2	60.2	138.1	118.0	118.0	121.7	10.8	32.7	160.4	27.7 [$(CH_3)_3C$], 44.6 (NCH_2CO_2), 82.6 [$(CH_3)_3C$], 168.0 [$CO_2C(CH_3)_3$]
6i	14.2	60.3	137.6	118.8	117.8	121.9	10.8	32.7	160.5	44.3 (SO_2NCH_2CH), 54.6 [$CH(OCH_3)_2$], 102.6 [$CH(OCH_3)_2$]
6j	14.2	60.2	138.1	117.1	118.0	121.1	10.8	32.7	160.5	35.4 (SO_2NCH_3), 50.7 (NCH_2CO_2), 52.0 (CO_2CH_3), 169.0 (CO_2CH_3)
6l	14.2	60.3	138.1	118.8	118.2	121.8	11.0	32.7	160.6	46.5 (SO_2NCH_3), 51.9 (NCH_2CO_2), 51.9 (CO_2CH_3), 127.9, 128.5, 128.6, 135.1 (phenyl), 169.0 (CO_2CH_3)
6m	14.2	60.2	138.0	118.1	117.8	121.8	11.0	32.7	160.5	27.8 [$(CH_3)_3C$], 35.3 (SO_2NCH_3), 51.4 ($SO_2NCH_2CO_2$), 81.9 [$C(CH_3)_3$], 167.6 [$CO_2C(CH_3)_3$]
6n[c]	14.1	60.3	136.6–137.7	127.9	118.1	120.3–121.7	10.8	48.4	160.3	13.9 [$SO_2N(CH_2CH_3)_2$], 41.6 [$SO_2N(CH_2CH_3)_2$], 48.4 (CH_2 benzylic), 125.6, 127.3, 128.7 (CH benzyl), 129.3, 130.9
7a	—	—	131.8	119.3	119.5	108.4	9.7	41.7	—	15.8 (CH_3CH_2), 45.6 (SO_2CH_3)
7b	—	—	134.0	116.7	120.2	109.5	10.0	42.2	—	15.8 (CH_3CH_2), 61.5 ($SO_2CH_2CO_2H$), 166.3 ($SO_2CH_2CO_2H$)
8a	—	—	132.8	116.4	121.3	108.5	9.9	33.9	—	43.7 (CH_2CO_2H), 171.4 (CH_2CO_2H)
8b	—	—	132.6	113.1	121.1	108.9	10.4	34.1	—	37.8 [$SO_2N(CH_3)_2$]

[a] Recorded in DMSO-d_6; [b] Recorded in $CDCl_3$ + CD_3OD; [c] two conformers are detected.

de Barcelona. Melting points were determined in a Büchi 510 apparatus and are uncorrected. All commercially available reagents and solvents were synthetic grade and used without further purification. Compounds **5** were synthesized following the method described in ref. 3.

Synthesis of ethyl 1-alkyl-3-chlorosulfonyl-2-methylpyrrole-5-carboxylates 3

Compound **1a** (2.0 g, 0.013 mol) was added portionwise to chlorosulfonic acid (*d* 1.753) (10 ml, 0.150 mol) at 0 °C. The stirred mixture was then allowed to stand at −10 °C for 24 hours, after which it was poured carefully dropwise into ice–water and extracted with chloroform. The organic phase was dried ($MgSO_4$), evaporated *in vacuo* to give a solid residue, and purified by chromatography on silica gel, yielding **3a** (2.66 g, 81%). Analytical and spectral data for compounds **3** are shown in Tables 1, 2 and 3.

The following compounds were obtained in a similar way by treating the corresponding compound **1** with $HOSO_2Cl$: ethyl 3-chlorosulfonyl-1,2-dimethylpyrrole-5-carboxylate **3b** (R^1 = Me); ethyl 3-chlorosulfonyl-1-ethyl-2-methylpyrrole-5-carboxylate **3c** (R^1 = Et); ethyl 3-chlorosulfonyl-1-(*p*-chlorosulfonylphenylmethyl)-2-methylpyrrole-5-carboxylate **3d** (R^1 = *p*-$SO_2ClC_6H_4CH_2$).

Synthesis of ethyl 1-ethyl-2-methyl-3-methylsulfonylpyrrole-5-carboxylate 4a

To a solution of ethyl 3-chlorosulfonyl-1,2-dimethylpyrrole-5-carboxylate **3b** (4.9 g, 17.5 mmol) in acetone (25 ml) we added a solution of Na_2SO_3 (4.4 g, 35 mmol) in H_2O (50 ml) stirred for 10 min at 70–80 °C (heating bath temperature). A solution of Na_2CO_3 (2.5 g, 23 mmol) in H_2O (50 ml) was then added. The mixture was refluxed for 2 h and after cooling, crude sulfinic acid was precipitated by addition of 2 M HCl to pH 2. After filtration the solid was dissolved in a mixture of H_2O (25 ml) and EtOH (25 ml) followed by addition of Na_2CO_3 until pH 10. MeI (*d* 2.28) (2.45 ml, 39 mmol) was then added and the mixture was refluxed for 2 h. After cooling, ethanol was evaporated *in vacuo* and H_2O (20 ml) was added followed by addition of conc. HCl until pH 2. The resulting white solid was filtered off and purified by column chromatography on silica gel using hexane–ethyl acetate as the eluent to give pure **4a** (2.3 g, 51%). Analytical and spectral data for compounds **4** are shown in Tables 1, 2 and 3.

Compound **4c** 3-carboxymethylsulfonyl-1-ethyl-2-methylpyrrole-5-carboxylic acid was obtained in a similar way, using a solution 50% NaOH as base. This compound was purified by recrystallization (ethanol–hexane).

Synthesis of ethyl 1-ethyl-3-ethylsulfonyl-2-methylpyrrole-5-carboxylate 4b

To a solution of ethyl 3-chlorosulfonyl-1-ethyl-2-methylpyrrole-5-carboxylate **3c** (1.0 g, 3.5 mmol) in ether (10 ml) under an inert atmosphere, a solution of EtMgBr (465 mg, 3.5 mmol) in ether (9 ml) was added. The mixture was refluxed for 1 h and a solution of 5% NH_4Cl (20 ml) was added after cooling. The layers were separated and the organic phase was washed with aq. $NaHCO_3$, dried ($MgSO_4$) and then concentrated by removal of solvent under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate as the eluent to give pure **4b** (0.21 g, 55%).

Synthesis of ethyl 1-ethyl-3-ethoxysulfonyl-2-methylpyrrole-5-carboxylate 5a

To a stirred mixture of pyridine (15 ml) and EtOH (15 ml) cooling with an ice-bath, a solution of ethyl 3-chlorosulfonyl-1-ethyl-2-methylpyrrole-5-carboxylate **3c** (1.8 g, 6.4 mmol) in ether (10 ml) was added. The mixture was stirred for 2 h at room temperature followed by addition of H_2O (25 ml) and extracted with ether. The ethereal phase was washed with 2 M HCl, dried ($MgSO_4$) and then concentrated by removal of solvent under reduced pressure to yield pure **5a** (1.65 g, 88%).

Synthesis of ethyl 1-alkyl-3-alkylaminosulfonyl-2-methylpyrrole-5-carboxylate 6a–i

Typical procedure: synthesis of ethyl 3-dimethylaminosulfonyl-2-methylpyrrole-5-carboxylate 6a (R^1 = H, R^2 = R^3 = Me). Dimethylamine hydrochloride (0.19 g, 2.4 mmol) was added to a stirred solution of ethyl 3-chlorosulfonyl-1,2-dimethylpyrrole-5-carboxylate **3b** (0.5 g, 2.0 mmol) in pyridine (2.5 ml). The mixture was stirred for 2.5 h at room temperature followed by addition of 2 M HCl until pH 2. The resulting white solid was filtered off and recrystallized from ethyl acetate–hexane yielding pure **6a** (0.345 g, 66.7%). Analytical and spectral data for compounds **6** is shown in Tables 1, 2 and 3.

The following compounds were obtained in a similar way by treating the corresponding compound **3** with different amine hydrochlorides: ethyl 2-methyl-3-(methoxycarbonylmethyl)-aminosulfonylpyrrole-5-carboxylate **6c** (R^1 = H, R^2 = CH_2CO_2-Me, R^3 = H); ethyl 2-methyl-3-(*tert*-butoxycarbonylmethyl)-aminosulfonylpyrrole-5-carboxylate **6d** [R^1 = H, R^2 = CH_2-$CO_2C(Me)_3$, R^3 = H]; ethyl 1,2-dimethyl-3-dimethylaminosulfonylpyrrole-5-carboxylate **6e** (R^1 = R^2 = R^3 = Me); ethyl 1,2-diethyl-3-diethylaminosulfonylpyrrole-5-carboxylate **6f** (R^1 = R^2 = R^3 = Et); ethyl 1,2-dimethyl-3-(methoxycarbonylmethyl)-aminosulfonylpyrrole-5-carboxylate **6g** (R^1 = Me, R^2 = CH_2-CO_2Me, R^3 = H); ethyl 1,2-dimethyl-3-(*tert*-butoxycarbonylmethyl)aminosulfonylpyrrole-5-carboxylate **6h** [R^1 = Me, R^2 = $CH_2CO_2C(Me)_3$, R^3 = H].

The following compounds were synthesized using the free amine as base and solvent, and no pyridine was added: ethyl 3-diethylaminosulfonyl-2-methylpyrrole-5-carboxylate **6b** (R^1 = H, R^2 = R^3 = Et); ethyl 1,2-dimethyl-3-(dimethoxyethyl)aminosulfonylpyrrole-5-carboxylate **6i** [R^1 = Me, R^2 = CH_2-$CH(OMe)_2$, R^3 = H].

Alkylation of sulfonamides 6c, 6g, 6h with K_2CO_3–DMF

Typical procedure: synthesis of ethyl 1,2-dimethyl-3-(methoxycarbonylmethyl)methylaminosulfonylpyrrole-5-carboxylate 6j (R^1 = Me, R^2 = CH_2CO_2Me, R^3 = Me). Compound **6g** (R^1 = Me, R^2 = CH_2CO_2Me) (1.75 g, 5.5 mmol) was added to a stirred mixture of potassium carbonate (3.8 g, 27 mmol) in DMF (30 ml) under an inert atmosphere. Methyl iodide (*d* 2.28) (0.37 ml, 5.8 mmol) was then added. After being stirred for 4 h at room temperature the slurry was quenched in ice–water and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$) and then concentrated by removal of solvent under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate as the eluent to give pure **6j** (1.39 g, 77%).

The following compounds were obtained in a similar way: ethyl 1,2-dimethyl-3-(methoxycarbonylmethyl)ethylaminosulfonylpyrrole-5-carboxylate **6k** (R^1 = Me, R^2 = CH_2CO_2Me, R^3 = Et); ethyl 1,2-dimethyl-3-(methoxycarbonylmethyl)-benzylaminosulfonylpyrrole-5-carboxylate **6l** (R^1 = Me, R^2 = CH_2CO_2Me, R^3 = Benzyl); ethyl 2-methyl-3-(*tert*-butoxycarbonylmethyl)methylaminosulfonylpyrrole-5-carboxylate **6m** [R^1 = H, R^2 = $CH_2CO_2C(Me)_3$, R^3 = Me].

Alkylation of 6c with methyl iodide using potassium *tert*-butoxide–DMSO: synthesis of ethyl 1,2-dimethyl-3-(methoxycarbonylmethyl)methylaminosulfonylpyrrole-5-carboxylate 6j (R^1 = Me, R^2 = CH_2CO_2Me, R^3 = Me)

Compound **6c** (R^1 = R^3 = H, R^2 = $CH_2CO_2CH_3$) (0.22 g, 0.7 mmol) was added to a stirred mixture of potassium *tert*-butoxide (0.20 g, 1.7 mmol) in DMSO (8 ml) under an inert atmosphere. Methyl iodide (0.25 ml, 4.0 mmol) was then added. After stirring for 2 h at room temperature the slurry was quenched in ice–water and extracted with ether. The organic

phase was washed with water, dried ($MgSO_4$) and then concentrated by removal of solvent under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate as the eluent to give pure **6j** (0.194 g, 81%).

Synthesis of ethyl 1-benzyl-3-diethylaminosulfonyl-2-methylpyrrole-5-carboxylate 6n with potassium *tert*-butoxide–DMSO

Compound **6b** (R^1 = H, $R^2 = R^3$ = Et) (0.10 g, 0.3 mmol) was added to a stirred mixture of potassium *tert*-butoxide (0.08 g, 0.7 mmol) in DMSO (4 ml) under an inert atmosphere. Benzyl bromide (0.14 ml, 0.21 g, 1.2 mmol) was then added. After stirring for 1.5 h at room temperature the slurry was quenched in ice–water, acidified with 2 M HCl and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$) and then concentrated by removal of solvent under reduced pressure. The residue was purified by column chromatography on silica gel using hexane–ethyl acetate as the eluent to give pure **6n** (0.095 g, 89%).

Cleavage of the ester group by acidic hydrolysis and subsequent decarboxylation

Typical procedure: synthesis of 1-ethyl-2-methyl-3-methylsulfonylpyrrole 7a (R^1 = Et, R^2 = Me). A mixture of **4a** (2.20 g, 7 mmol), ethanol (20 ml) and 2 M hydrochloric acid (20 ml) was heated to reflux temperature for 36 hours. The resulting slurry was allowed to cool, after which it was diluted with chloroform and the layers were separated. The organic phase was dried ($MgSO_4$) and evaporated to give a crystalline solid. Recrystallization (ethyl acetate–hexane) yielded pure **7a** (1.1 g, 78%). Analytical and spectral data for compounds **7** and **8** are shown in Tables 1, 2 and 3.

The following compounds were obtained in a similar way: 3-carboxymethylsulfonyl-1-ethyl-2-methylpyrrole **7b** (R^1 = Et, $R^2 = CH_2CO_2H$); 3-(carboxymethylaminosulfonyl)-1,2-dimethylpyrrole **8a** (R^1 = Me, $R^2 = CH_2CO_2H$, R^3 = H); 1,2-dimethyl-3-dimethylaminosulfonylpyrrole **8b** ($R^1 = R^2 = R^3$ = Me).

Compound **7b** was purified by column chromatography on silica gel using diethyl ether as the eluent.

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References

1 M.-I. Lim, R. S. Klein and J. J. Fox, *Tetrahedron Lett.*, 1980, **21**, 1013.
2 A. J. Elliot, J. A. Montgomery and D. A. Walsh, *Tetrahedron Lett.*, 1996, **37**, 4339.
3 A. M. Molins-Pujol, C. Moranta, C. Arroyo, M. T. Rodríguez, C. Meca, M. D. Pujol and J. Bonal, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 2277.
4 C. Moranta, Ph.D. Thesis, Universitat de Barcelona, Spain, 1997.
5 D. Lednicer, in *The Organic Chemistry of Drug Synthesis*, Wiley-Interscience Publication, 1995, vol. 5, pp. 64–75.
6 D. Lednicer, in *Strategies for Organic Drug Synthesis and Design*, Wiley-Interscience, 1998, pp. 42–46.
7 J. DeSales, R. Greenhouse and J. M. Muchowski, *J. Org. Chem.*, 1982, **47**, 3668 and references cited therein.
8 M. Kakushima and R. Frenette, *J. Org. Chem.*, 1984, **49**, 2025.
9 M. T. Clark, R. A. Coburn, R. T. Evans and R. J. Genko, *J. Med. Chem.*, 1986, **29**, 25.
10 P. W. Feit and O. B. T. Nielsen, *J. Med. Chem.*, 1976, **19**, 402.
11 O. R. Rogne, *J. Chem. Soc.* (*B*), 1971, 1334.
12 J. D. Binder, O. Hromatka, F. Geissler, K. Schmied, C. R. Noe, K. Burri, R. Pfister, K. Strub and P. Zeller, *J. Med. Chem.*, 1987, **30**, 678.
13 R. W. Brown, *J. Org. Chem.*, 1991, **56**, 4974.

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