Chlorosulphonation of Thiophene and Furan-2-Carboxanilides

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(Received 15th April, 1985)

Summary: Thiophene-2-carboxanilide, the p-chloro,bromo, nitro derivatives and N-(2'-pyridyl) thiophene-2-carboxamide reacted with chlorosulphonic acid to give the sulphonyl chlorides (I, VIII, XIV, XVI, XVIII). The yields were comparatively low when electron-withdrawing groups were present, e.g. nitro and 2-pyridyl. With the p-carboxy derivative only thiophene-2-carboxylic acid was isolated and the p-methyl derivative gave an unidentified product. Furan-2-carboxanilide with chlorosulphonic acid afforded the sulphonyl chloride (XXII). With the unsubstituted heterocyclic carboxanilides, sulphonation occurred in the phenyl ring to give (I, XXII) but with substituted anilides reaction occurred preferentially in the 4-position of the heterocyclic nucleus. The spectral data of the compounds are briefly discussed.

The work described forms part of our programme on the chemistry and biological activity of various types of aromatic sulphonyl compounds [1-5]; in particular it extends our studies [6-8] on thiophene sulphonyl derivatives.

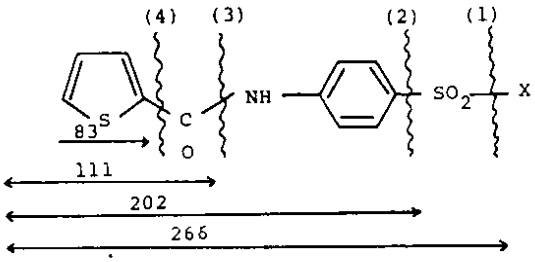
Sulphanilamide and its derivatives are well-established [9] antibacterial drugs some of which show anti-fungal properties [10].

Thiophene-2-carboxanilide [11] was obtained by reaction of thiophene-2-carboxylic acid with thionylchloride-dimethylformamide followed by condensation with aniline. Thiophene-2-carboxanilide, with excess chlorosulphonic acid (6 mols) at 40°, afforded an excellent yield (80%) of the 4'-sulphonylchloride (I).

Repetition at higher temperature caused carbon-nitrongen bond cleavage to give thiophene-2-carboxylic acid. The chloride (I) (Table 1) by treatment with dimethylamine, sodium azide and hydrazine gave II, III and IV respectively (Table 1). The letter was condensed with acetone and benzaldehyde to form the hydrazones (V,VI). The hydrazide (IV) by refluxing with acetylacetone gave the 3,5-dimethylpyrazole (VII).

Thiophene-2-carboxamide with chlorosulphonic acid is known [6] to give the 4-sulphonyl chloride. In contrast, chlorosulphonation of thiophen-2-carboxanilide occurs in the para-position of the phenyl ring to give (I) without any appreciable substitution in the heterocyclic nucleus. The orientation of sulphonation is presumably a reflection of the deactivating influence of the 2-carboxamido group on the thiophene ring making the phenyl ring the preferred site for electrophilic substitution. The proposed structures of the derivatives (II,V) were supported by the PMR spectra which clearly showed the AA'BB' pattern for the resonances

of the aromatic protons. In addition the mass spectra of II and III showed the molecular ions and fragmentation occurred in the order 1 2 3 4.



4'-Chlorothiophene-2-carboxanilide reacted with chlorosulphonic acid (6 mols) at 50° to give mainly the 4-sulphonyl chloride (VIII) (50%) together with a little of the 5-isomer (2 spots on TLC). At temperature 50° thiophene-2-carboxylic acid was obtained. The chloride (VIII) reacted with nucleophiles to give the 4-sulphonyl derivatives (IX-XIII). 4'-Bromothiophene-2-carboxanilide with chlorosulphonic acid under similar conditions gave the 4-sulphonyl chloride (XIV) (75%), characterized as the dimethylamide (XV). The PMR spectra of the dimethylamides (IX,XV) showed the thiophene 3 and 5 protons as doublets (δ 8.4 and 8.1, $J_{3,5}$ 1.2Hz), in agreement with previous results [12]. The 3 proton will be deshielded by the combined anisotropic effects of the carboxamide and sulphamoyl groups and therefore resonates at lower field than the 5 proton. The phenyl protons appeared as a multiplet (δ 7.8-7.35, J_{AB} 8Hz) showing a typical AA'BB' pattern indicative of p-disubstitution; the amidic proton appeared as a broad singlet (δ 9.8). The PMR spectra of the acetone hydrazones (V and XII) showed that the sulphamoyl (SO_2NH) group resonated at lower field (δ 10.5) than the amidic proton (CONH) (δ 9.8).

The mass spectra of 4'-chloro derivatives (VII-X) gave the molecular ions (M^+) and showed a base peak at 209 corresponding to the 2-carbonylthiophenesulphonyl chloride fragment confirming that sulphonation has occurred on the thiophene ring.

Chlorosulphonation of thiophene-2-carboxanilides containing the electron-withdrawing nitro and 2-pyridyl groups afforded comparatively low yields of the sulphonyl chlorides (XVI, XVIII); while the p-carboxy derivative with chlorosulphonic acid (6 mols, room temperature) gave thiophene-2-carboxylic acid. The results are not unexpected, since electron-withdrawing groups should weaken the amide bond facilitating carbon-nitrogen bond cleavage. A surprising observation was the failure of the p-methyl derivative to give the expected 4'-sulphonyl chloride. The product was an unidentified compound containing sulphur and chlorine which reacted with dimethylamine, but the IR spectrum did not show a carbonyl absorption and the analytical and PMR data were incorrect. N-(2'-Pyridyl)-thiophene-2-carboxamide reacted with a large excess of chlorosulphonic acid (15 mols) at 80° to give the sulphonyl chloride (XVII) (42%). Use of a mixture of chlorosulphonic acid (6 mols) and phosphorus pentachloride (1 mol) gave a similar yield but with chlorosulphonic acid (6 mols) alone the 4-sulphonic acid was obtained. The chloride (XVIII) was characterized as the derivatives (XIX-XXI) (Table 1).

Furan-2-carboxamide is reported [7] to react with chlorosulphonic acid to give the 4-sulphonyl chloride. In

Table-1: Physical data of thiophenecarboxamide sulphonyl derivatives

Compd. No.	MP °C	Yield %	Formula	Analysis % Found (Calc) C	H	N	MS M^+
IIa	159-161	78	$C_{13}H_{14}N_2O_3S_2$	54.0 (50.3)	4.7 (4.5)	9.1 (9.0)	310
III	130-132	88	$C_{11}H_8N_4O_3S_2$	43.3 (43.0)	2.8 (2.6)	18.5 (18.2)	308
IV	179-181	80	$C_{11}H_{11}N_3O_3S_2$	44.2 (44.4)	3.9 (3.7)	10.7 (10.6)	
V	195-196	76	$C_{14}H_{15}N_3O_3S_2$	49.5 (49.8)	4.4 (4.5)	12.5 (12.7)	-
VI	208-210	60	$C_{18}H_{15}N_3O_3S_2$	55.9 (56.1)	3.9 (3.9)	10.9 (10.9)	-
VII	157-158	59	$C_{16}H_{15}N_3O_3S_2$	52.8 (52.7)	4.2 (4.2)	11.6 (11.6)	-
IX	194-196	78	$C_{13}H_{13}ClN_2O_3S_2$	45.6 (45.3)	3.7 (3.8)	7.9 (8.0)	347
X	165-166	91	$C_{11}H_7ClN_4O_3S_2$	38.3 (38.5)	2.3 (2.0)	16.2 (16.4)	341
XI	155-156	81	$C_{11}H_{10}ClN_3O_3S_2$	40.0 (39.8)	3.1 (3.0)	12.8 (12.7)	-
XIIb	194-195	67	$C_{14}H_{14}ClN_3O_3S_2$	45.3 (45.2)	3.8 (3.7)	11.4 (11.3)	-
XIII	202	94	$C_{18}H_{14}ClN_3O_3S_2$	48.9 (48.7)	3.5 (3.3)	10.0 (10.0)	-
XV	206	64	$C_{13}H_{13}BrN_3O_3S_2$	40.0 (40.2)	3.4 (3.4)	6.9 (7.2)	389
XVII	208-210	39	$C_{13}H_{13}N_3O_5S_2$ $\frac{1}{2}H_2O$	42.9 (42.5)	3.6 (3.8)	11.2 (11.5)	355
XIXc	159	63	$C_{12}H_{13}N_3O_3S_2$	46.1 (46.3)	4.1 (4.2)	13.7 (13.5)	311
XX	144-145	51	$C_{10}H_{10}N_4O_3S_2$	40.1 (40.3)	3.2 (3.4)	18.6 (18.8)	-
XXI	193-194	63	$C_{13}H_{14}N_4O_3S_2$	46.0 (46.1)	3.9 (4.1)	16.3 (16.5)	-

(a) PRM (DMSO-d_6) 9.8* (1H,s,CONH), 8.3-7.5 (7H,m,phenyl and thiphene H), 2.8 (6H,s,NMe_2)

(b) PMR (acetone-d_6): 105.* (1H,s,SO_2NH), 9.8* (1H,s,CONH), 8.4-8.0 (2H,dd,thiophene-3,5H), 7.8-7.4 (4H, q,phenyl H), 2.8(6H,s,N=CMe_2).

(c) PMR ($CDCl_3$): 9.0 (1H, s, CONH), 8.4-7.0 (6H,m,ArH),2.8 (6H,s,NMe_2).

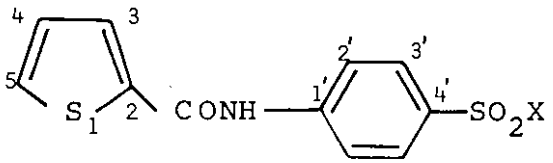
contrast, Furan-2-carboxanilide [13] like the thiophene analogue reacts with chlorosulphonic acid (6 mols) at room temperature to give the 4'-sulphonyl chloride (XXII, Table 2) contaminated with a little furan-2-carboxylic acid; at higher temperatures only the latter compound was isolated. It is surprising that in the presence of the highly reactive furan nucleus, preferential sulphonation still occurs in the phenyl ring. The chloride (XXII) was characterized as the compounds (XXIII-XXIX) (Table 2). The PMR spectra of the dimethylamide (XXIII) and the acetone hydrazone (XVII) showed a multiplet (δ 7.8) for the phenyl proton resonances with the AA'BB' splitting pattern confirming p-sulphonation in the phenyl ring. The mass spectra of (XXIII) and the azide (XXIV) provided

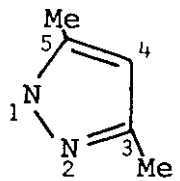
Table-2: Physical data for furnacarboxanilide sulphonyl derivative

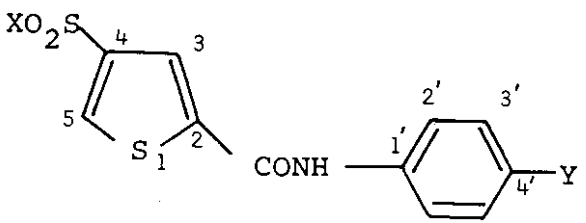
Compd No.	MP °C	Yield %	Formula	Analysis % Found C	H	(calc) N	MS M^+
XXIIIa	158	87	$C_{13}H_{14}N_2O_4S$	52.9 (53.1)	4.8 (4.8)	9.5 (9.5)	294
XXIV	110-112	93	$C_{11}H_8N_4O_4S$	45.5 (45.2)	2.9 (2.7)	18.9 (19.2)	292
XXV	65-66	56	$C_{17}H_{27}N_2O_7PS$	47.2 (47.0)	6.4 (6.2)	6.3 (6.5)	
XXVI	185-186	81	$C_{11}H_{11}N_3O_4S$	46.7 (47.0)	4.1 (3.9)	15.1 (14.9)	-
XXVIIb	206	87	$C_{14}H_{15}N_3O_4S$	52.4 (52.3)	4.7 (4.7)	13.0 13.1)	-
XXVIII	200	65	$C_{18}H_{15}N_3O_4S$	58.5 (58.5)	4.1 (4.1)	11.3 (11.4)	
XXIX	197	36	$C_{16}H_{15}N_3O_4S$	55.7 (55.6)	4.3 (4.3)	12.2 (12.2)	-

a) PMR($CDCl_3$): 8.6* (1H,s,CONH), 8.0-6.5 (7H, m, furan and phenyl H), 2.8 (6H, s, NMe_2)

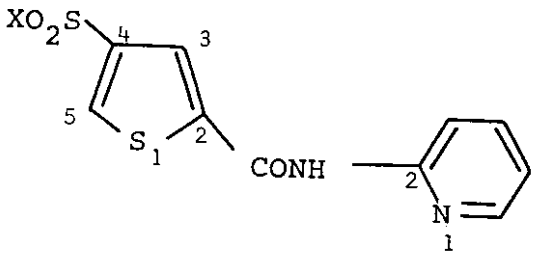
b) PMR (acetone-d_6): 10.0* (1H, s, SO_2NH), 8.8* (1H, s, CONH), 8.3-6.8 (7H, m, ArH), 2.2 (6H, s, $N{=}CMe_2$)



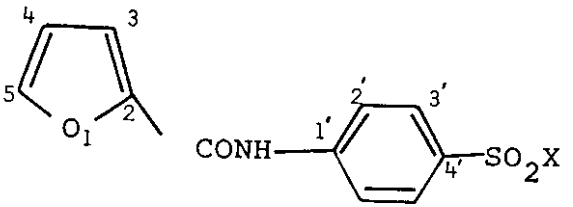
	X
(I)	Cl
(II)	NMe_2
(III)	N_3
(IV)	$NHNH_2$
(V)	$NHN{=}CMe_2$
(VI)	NHN=CHPh
(VII)	

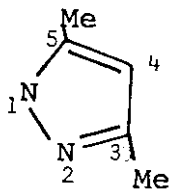


	X	Y
(VIII)	Cl	Cl
(IX)	NMe_2	Cl
(X)	N_3	Cl
(XI)	$NHNH_2$	Cl
(XII)	$NHN{=}CMe_2$	Cl
(XIII)	NHN=CHPh	Cl
(XIV)	Cl	Br
(XV)	NMe_2	Br
(XVI)	Cl	NO_2
(XVII)	NMe_2	NO_2



	X
(XVIII)	Cl
(XIX)	NMe_2
(XX)	$NHNH_2$
(XXI)	$NHN{=}CMe_2$



	X
(XXII)	Cl
(XXIII)	NMe_2
(XXIV)	N_3
(XXV)	$N{=}P(OEt)_3$
(XXVI)	$NHNH_2$
(XXVII)	$NHN{=}CMe_2$
(XXVIII)	NHN=CHPh
(XXIX)	

further support for the proposed structures. The mass spectra of the hydrazides and hydrazones did not show the molecular ions (M^+) but suffered extensive decomposition in agreement with previous observations [2].

Experimental

Melting points were obtained using a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded as nujol mulls with a Unicam SP 100 spectrophotometer. PMR spectra were determined with a Varian HA80 spectrometer using TMS as internal standard, an asterisk indicates resonances removed after treatment with D_2O. Mass spectra were obtained with a VG micromass spectrometer at 60eV. TLC carried out on Camlab silica gel plates sensitised to UV 264 nm.

Chlorosulphonation of thiophene-2-carboxanilide

Thiophene-2-carboxanilide (5 g) was gradually added to chlorosuphonic acid (17 g; 6 mols) at 0°. The solution was warmed (40°) for 45 min, and poured onto ice (100 g). The precipitate was filtered off, washed with water (2 x 50 ml) and dried to give the 4'-sulphonylchloride (I) m.p. 150-151°; yield 6g (80%)

IR; ν_{max} 3300 (NH), 1680 (C=O), 1600 (arom C=C), 1320, 1160 (SO_2) cm^{-1}. MS: 301 (M^+), 266 (M-Cl), 202 (M - SO_2Cl), 111 (M - $NHC_6H_4SO_2$ Cl), 83, 36, 28. TLC (EtOAc - pentane 2:3) showed one spot R_f 0.40.

Chlorosulphonation of 4'-chlorothiophene-2-carboxanilide

4'-Chlorothiophene-2-carboxanilide reacted with chlorosulphonic acid (6 mols) at 50° for 3 hr to give the sulphonyl chloride (VIII) as pale yellow crystals, mp 101-102°; yield 3.6 g (50%).

IR: ν_{max} 3200 (NH), 1690 (C = O), 1600 (arom C = C), 1340. 1160 (SO_2) cm^{-1}. MS: 336 (M^+), 302 (M-Cl), 211, 209, 91, 64, 28. TLC (EtOAc - cyclohexane 2:3) showed one spot, R_f0.60.

Chlorosulphonation of 4'-bromothiophene-2-carboxamide

Reaction under similar conditions gave the chloride (XIV) as yellow crystals, m.p. 90-92°; yield 4.2 g (75%) IR: ν_{max} 3200 (NH), 1690 (C = O) 1600 (arom C = C), 1340, 1160 (SO_2) cm^{-1}. MS: 381(M^+), 347 (M - Cl), 283 (M-SO_2Cl), 211, 209, 111, 91, 63, 45, 20. TLC (EtOAc-cyclohexane 2:3) showed one spot, R 0.60.

Chlorosulphonation of 4'-nitrothiophene-2-carboxamide

4'-Nitrothiophene-2-carboxanilide (2g) was heated with chlorosulphonic acid (5.6 g, 6 mols) at 60° for 6 hours to give the crude sulphonyl chloride (XVI) m.p. 84°-87°; yield 1.8 g. IR: ν_{max} 3300 (NH), 1680 (C = O), 1600 (arom C = C), 1520 (NO_2), 1340, 1160 (SO_2) cm^{-1}.

MS: 263 (M^+), 228 (M-Cl), 164 (M-SO_2Cl), 111,91, 68, 28. TLC (EtOAc-cyclohexane 1:1) showed 3 spots, R_F 0.60, 0.30 and 0.20. The first two spots are the 4- and 5-sulphonyl chlorides while the latter is thiophene-2-carboxylic acid.

Chlorosulphonation of N-(2'-pyridyl) thiophene-2-carboxamide

N-(2'-Pyridyl) thiophene-2-carboxamide (5g) was heated with chlorosulphonic acid (34g, 15 mol) at 80° for

3 hours to give the sulphonyl chloride (XVIII), m.p. 356-360°; yield 3.1g (42%). IR: ν_{max} 3300(NH), 1680 (C=O), 1600 (arom C = C), 1340, 1160 (SO_2) cm^{-1}. TLC (EtOAc -cyclohexane 2:3) showed 2 spots, R_f 0.45 and 0.20 (thiophene-2-carboxylic acid). Sodium fusion test was positive for N,S,Cl.

Attempted chlorosulphonation of 4'-methylthiophene-2-carboxamide

4'-Methylthiophene-2-carboxamide (5g) was stirred with chlorosulphonic acid (16 g, 6 mols) at room temperature for 6 hour to give a solid, m.p. 122-125°; yield 2.1 g. IR: ν_{max} 3200 (NH), 1600 (arom C=C) 1335, 1140, (SO_2) cm^{-1}. MS: 381, 379, 361, 280, 209, 191, 111, 76, 46, 28. Sodium fusion test was positive for N, S, Cl. TLC (EtOAc-cyclohexane 3:5) showed one spot, R_f 0.40. Treatment of the product with excess dimethylamine afforded a solid, m.p. 136-141°; yield 1.2 g. IR: ν_{max} 3200(NH), 1595 (arom C=C), 1360, 1140 (SO_2) cm^{-1}.

MS: 324 (M^+), 217, 129, 111, 97, 73, 69. TLC (EtOAc-cyclohexane showed one spot, R_f 0.60. PMR ($CDCl_3$): δ 7.9-7.0 (10 H, m, ArH), 2.3 (3H, s, Me). (Found: C, 32.5; H, 5.2; N, 14.6. $C_{14}H_{16}N_2O_3S_2$ requires: C, 51.9; H, 4.9; N, 8.6%). Sodium fusion test was positive for N, S and negative for Cl.

Chlorosulphonation of furan-2-carboxanilide

Furan-2-carboxanilide (5g) was stirred with chlorosulphonic acid (19 g, 6 mols) at room temperature for 1 hr to give the sulphonyl chloride (XXII), m.p. 130-131°; yield 4.8 g (60%). IR: ν_{max} 3300 (NH), 1680 (C = O), 1590 (arom C = C), 1340, 1160 (SO_2) cm^{-1}.

MS: 287 (M^+), 250 (M-Cl), 186 (M-SO_2 Cl), 95, 91, 67, 51, 50. TLC (EtOAc-cyclohexane 2:3) showed 2 spots, R_f 0.54, and 0.30 (furan-2-carboxylic acid). (Found: C, 45.8; H, 2.8; N, 5.1. $C_{11}H_8ClNO_4S$ requires C, 46.2; H, 2.8 N 4.9%).

General procedures for reactions of the carboxanilide sulphonyl chlorides with various nucleophilic reagents

(a) dimethylamine

The sulphonyl chloride (0.01 mol) was reacted with dimethylamine (0.02 mol) in methanol (15 ml) at room temperature (2hr). The solution was poured onto ice and the solid product purified by recrystallization from aqueous methanol.

(b) sodium azide

The sulphonyl chloride (0.1 mol) was treated with sodium azide (0.2 mol) in aqueous acetone (30 ml). The pure azide was obtained by addition of ice and recrystallization from acetone. The azide (XXIV) (0.005 mol) was refluxed with triethylphosphite (0.005 mol) in toluene (15 ml) for 2 hr to give the triethoxyphosphinimine (XXV)

(c) hydrazine

The sulphonyl chloride (0.01 mol) was stirred with hydrazine hydrate (0.04 mol) in 1:1 aqueous methanol (30 ml) for 3 hr. Addition of ice-water (150 ml) precipitated the hydrazide, which was characterized

as hydrazones. The hydrazide (0.005 mol) was heated (50°) with acetone (10 ml) or an ethanolic solution of benzaldehyde (0.005 mol) for ¼ hr, cooling gave the pure hydrazones. Treatment of the hydrazides (IV, XXVI) with acetylacetone in boiling ethanol (6 hr) afforded the 3,5-dimethylpyrazoles (VII, XXIX) respectively.

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