cine-Substitution in the Thiophen Series; the Behaviour of 4-Nitro-3-thienyl Phenyl Sulphone towards Sodium Arenethiolates in Methanol

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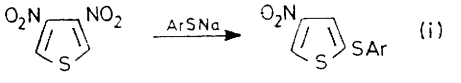
4-Nitro-3-thienyl phenyl sulphone (3) reacts with various sodium arenethiolates in methanol to give 5-arylthio-3-thienyl phenyl sulphones (4) (main products) and 2-arylthio-4-nitrothiophens (2). An anomalous addition–elimination mechanism is suggested to account for the formation of the *cine*-substitution products (2) and (4).

We have previously reported that 2,3-dinitrothiophen [1] and 3-nitro-2-thienyl and 2-nitro-3-thienyl phenyl sulphones [2] react with sodium arenethiolates in methanol to give the sulphides derived from normal substitution reactions, in analogy with similar *o*-nitrobenzene derivatives.[3] In the first case substitution of the nitro-group in either the 3- (preferred) or the 2-position occurs; in the other two cases only products derived from substitution of the phenylsulphonyl group were isolated.

In the case of another '*ortho*-like' disubstituted thiophen derivative,[4] *i.e.* 3,4-dinitrothiophen (1), a completely different behaviour towards sodium arenethiolates has been observed: 2-arylthio-4-nitrothiophens (2) were formed through a *cine*-substitution reaction [equation (i)].

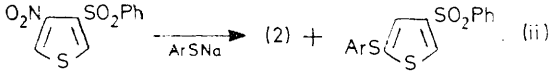


(1) (2) (i)

On the basis of this unexpected result it seemed of interest to study the reactivity of other 3-substituted 4-nitrothiophens towards nucleophiles. We report here the behaviour of 4-nitro-3-thienyl phenyl sulphone (3) towards a series of sodium *o*-, *m*-, and *p*-substituted benzenethiolates in methanol.

RESULTS AND DISCUSSION

A solution of compound (3) in methanol, treated with a large excess of substituted sodium benzenethiolate in the presence of the corresponding free arenethiol (see Experimental section and Table 1) gave a mixture of two



(3) (4) (ii)

a; 4—MeC_6H_4 e; 4—ClC_6H_4
b; 3—MeC_6H_4 f; 3—ClC_6H_4
c; 2—MeC_6H_4 g; 2—ClC_6H_4
d; Ph h; 2,4,6—$Me_3C_6H_2$

products. These were separated by column chromatography and identified through analytical and ^1H n.m.r.[4,5] data (Tables 2 and 3) as 5-arylthio-3-thienyl phenyl sulphones (4a—h) (main products) and 2-arylthio-4-nitrothiophens (2a—h) [equation (ii)]. In some instances [(2b and f) and (4c)] the sulphides were identified by

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[2] G. Guanti, C. Dell'Erba, and P. Macera, *J. Heterocyclic Chem.*, 1971, **8**, 537.
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[4] C. Dell'Erba, D. Spinelli, and G. Leandri, *Gazzetta*, 1969, **99**, 535.
[5] R. A. Hoffman and S. Gronowitz, *Arkiv Kemi*, 1960, **16**, 515, 563; L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, Oxford, 2nd edn., 1969.

oxidation by hydrogen peroxide in acetic acid to the corresponding sulphones [(2'b and f) and (4'c)] and in other cases by comparison with authentic samples obtained by reactions of the dinitrothiophen (1) with the same arenethiolates.[4] The total yield was high (>90%) in the majority of cases (Table 1). The lower yield observed for (4g and h) and (2g and h) can be explained by

TABLE 1

Reaction times and yields of *cine*-substitution products (2) and (4) in the reaction of 4-nitro-3-thienyl phenyl sulphone (3) with sodium arenethiolates in methanol

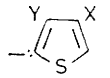
Arenethiolate	Reaction time [a] (days)	Yield (%) [b] (2)	(4)
4-MeC_6H_4SNa	7	13.5	76.5
3-MeC_6H_4SNa	10	6	87
2-MeC_6H_4SNa	14	12	78
PhSNa	14	12	78
4-ClC_6H_4SNa	21	10	84
3-ClC_6H_4SNa	31	13	83
2-ClC_6H_4SNa	1 [c]	9	66
2,4,6-$Me_3C_6H_2SNa$	0.4 [c]	5	47

[a] At room temperature unless otherwise noted. [b] Probable error ±5%; all experiments were carried out at least in duplicate. [c] At reflux.

partial decomposition, as ascertained independently, of the products under the conditions (reflux) required for the reactions of (3) with 2-chloro- and 2,4,6-trimethylbenzenethiolate. In all cases lower yields were obtained by carrying out the reactions under reflux, *e.g.* with sodium 2-methylbenzenethiolate the combined yield of (2) and (4) fell to 53.4%.

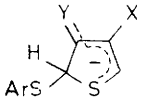
As previously found for the dinitrothiophen (1),[4] these results indicate that even in this case *cine*-substitution [6] instead of the expected normal substitution occurs. From the data of Table 1 the following further points emerge. (*a*) The ratio of the yields of (4) and (2), always greater than unity, indicates that in the *cine*-substitutions studied the nitro-group is the preferred leaving group. (*b*) The same ratios are essentially independent of the substituent in the sodium arenethiolate as well as of the experimental conditions. The ratios fluctuate between 5 : 1 and 15 : 1 in a way which cannot be rationalized in terms of substituent effects. (*c*) The reaction times (determined by t.l.c. analysis) are affected by the substituent in sodium arenethiolate: an electron-withdrawing group in the *meta*- or *para*-position decreases the rate, and the opposite effect is observed for electron-releasing groups. (*d*) The reaction rate is influenced by steric effects: the *ortho*-substituted benzenethiolates are less reactive than the *meta*- and *para*-isomers.

Two mechanisms may be invoked to explain the formation of the sulphides (2) and (4): an elimination–addition (*EA*) mechanism *via* a heteroaryne intermediate, or an anomalous addition–elimination (AE_a) mechanism.[6b,7] Neither the effect of the substituent in the arenethiolate on the reaction rate nor the values of the yield ratios help in choosing between these mechanisms. The lower electronic density at the α-position adjacent to the nitro-group in (3) could favour both nucleophilic attack at this carbon atom and proton abstraction from this position. However, an *EA* mechanism is unlikely for several reasons (*e.g.* experimental conditions,* absence of methoxy-derivatives among reaction products), especially the following. (*a*) Even though both nitro and phenylsulphonyl groups are easily replaced by nucleophiles *via* a normal aromatic substitution, neither is a good leaving group for the formation of arynes,[9,10] as demonstrated from the stability of *o*-nitro- [9a] and *o*-phenylsulphonyl-phenyl-lithium.[10] Moreover in an anionic intermediate like (5) or (6) the possibility of the



(5) X = NO_2, Y = $PhSO_2$

(6) X = $PhSO_2$, Y = NO_2



(7) X = NO_2, Y = $PhSO_2$

(8) X = $PhSO_2$, Y = NO_2

loss of group Y with its bonding electrons is greatly decreased [11] because of the electronic effects of both the neighbouring group X and the sulphur atom,[12] which inductively stabilize the negative charge. (*b*) Although five-membered heteroarynes have been proposed as reaction intermediates,[13] recent papers [14,15] have suggested these claims to be ' ambiguous '.[16]

It is therefore likely that in the reaction studied an AE_a mechanism is operative. This mechanism should involve in the first step nucleophilic attack of the arenethiolate anion at an α-position of (3) to give intermediates

* Methanol, a protonating agent for carbanion precursors of arynes, should inhibit the *EA* mechanism.[8]

[6] (*a*) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273; (*b*) F. Pietra, *Quart. Rev.*, 1969, **23**, 504.

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[11] Ref. 10, pp. 49, 50.

[12] Ref. 10, p. 290.

[13] R. Stoermer and B. Kahlert, *Chem. Ber.*, 1902, **35**, 1633; H. J. den Hertog and H. C. van der Plas, *Adv. Heterocyclic Chem.*, 1965, **4**, 121.

[14] G. Wittig and M. Rings, *Annalen*, 1968, **719**, 127; M. G. Reinecke and H. W. Adickes, *J. Amer. Chem. Soc.*, 1968, **90**, 511; D. A. de Bie, H. C. van der Plas, and G. Geurtsen, *Rec. Trav. chim.*, 1971, **90**, 594; M. G. Reinecke and T. A. Hollingworth, *J. Org. Chem.*, 1972, **37**, 4257; D. A. de Bie, H. C. van der Plas, G. Geurtsen, and K. Nijdam, *Rec. Trav. chim.*, 1973, **92**, 245; M. G. Reinecke, W. B. Mohr, H. W. Adickes, D. A. de Bie, H. C. van der Plas, and K. Nijdam, *J. Org. Chem.*, 1973, **38**, 1365.

[15] Ref. 10, p. 293; H. J. den Hertog and H. C. van der Plas in ' Chemistry of Acetylenes,' ed. H. G. Viche, Dekker, New York, 1969, p. 1149.

[16] M. G. Reinecke and J. G. Newsom, Abstracts, Fifth International Congress of Heterocyclic Chemistry, Lyublyana, 1975, p. C1.

like (7) and (8), which, after protonation (or proton-assisted transfer) on the adjacent β-carbon atom followed by elimination of nitrous or benzenesulphinic acid, can furnish the *cine*-substitution products (2) and (4), respectively. This pathway, completely different from that observed for 3-nitro-2-thienyl and 2-nitro-3-thienyl phenyl sulphones,[2] and similar to that suggested for the reaction of the dinitrothiophen (1) with arenethiolates,[4] can be related to the high degree of single-bond character[17] between C-3 and C-4 in the substrates (1) and (3). The higher yield of (4) can be related to the fact that the nitro-group delocalizes the negative charge in the transition states better than the phenylsulphonyl group,[18] favouring the formation of (8) with respect to (7). Moreover, steric factors could favour nucleophilic attack at C-5, since it is likely that the phenylsulphonyl group exerts a larger primary steric effect than the nitro-group.

EXPERIMENTAL

^{1}H N.m.r. spectra of solutions in $CDCl_3$ were measured with a Varian XL 100 instrument (Me_4Si as internal reference). Light petroleum had b.p. 30—50 °C.

4-Nitro-3-thienyl Phenyl Sulphone (3).—Oxidation of 4-nitro-3-thienyl phenyl sulphide (see below) with 30% hydrogen peroxide in glacial acetic acid gave the *sulphone*, m.p. 162° (from ethanol) (Found: N, 5.3; S, 23.8. $C_{10}H_7NO_4S_2$ requires N, 5.2; S, 23.8%); δ 8.50 (1 H, d, *J* 3.96 Hz), 8.36 (1 H, d, *J* 3.96 Hz), 7.96—8.14 (2 H, m), and 7.52—7.70 (3 H, m).

4-Nitro-3-thienyl Phenyl Sulphide.—This sulphide was prepared in one step (hydrolysis followed by decarboxylation) from methyl 4-nitro-3-phenylthio-2-thenoate [19] as follows. The ester (2 g), suspended in 9M-sulphuric acid (20 ml) was refluxed for 2 h, cooled, and poured into ice–water, and the product was extracted with ether. The extract was washed with water and 5% sodium carbonate solution, dried (Na_2SO_4), and evaporated to give a *solid* (1.1 g, 69%), which crystallized from light petroleum; m.p. 73° (Found: N, 5.85; S, 26.95. $C_{10}H_7NO_2S_2$ requires N, 5.9; S, 27.0%); δ 8.40 (1 H, d, *J* 3.92 Hz), 6.28 (1 H, d, *J* 3.92 Hz), and 7.38—7.70 (5 H, m).

Reactions of 4-Nitro-3-thienyl Phenyl Sulphone (3) *with Sodium Arenethiolates.*—A solution of compound (3) (0.5 g, 1.86 mmol), the sodium arenethiolate (18.6 mmol), and the arenethiol (18.6 mmol) in methanol (100 ml) was kept at room temperature or at reflux for the time indicated in Table 1. The methanol was evaporated off *in vacuo* and the residue extracted with benzene. The extract was washed with 5% sodium hydroxide solution (to remove the excess of arenethiol) and water, dried (Na_2SO_4), concentrated, and chromatographated on silica gel column (eluant 1 : 4 benzene–light petroleum). After the initial fractions (containing diaryl disulphide) the 2-arylthio-4-nitrothiophen (2) was obtained. Further elution with benzene yielded the 5-arylthio-3-thienyl phenyl sulphone (4). Mixed m.p.s of the sulphides (2a, c, d, g, and h) with the analogous compounds obtained from (1) as previously, [4] showed no depression. Compounds (2b and f) and (4c) were oils and were characterized as sulphones [(2′b and f) and (4′c)] obtained by oxidation with hydrogen peroxide in glacial acetic acid.

Further data are given in Tables 1—3.

TABLE 2

Physical and analytical data

Compd.*	Cryst. solvent †	M.p. (°C)	Calc. (%) [Found (%)]
(2′b)	B–LP [a]	83	N, 4.95; S, 22.6 [N, 5.0; S, 22.6]
(2e)	LP [b]	59	Cl, 13.1; N, 5.15; S, 23.55 [Cl, 13.25; N, 5.2; S, 23.35]
(2′f)	MeOH	107—109	Cl, 11.7; N, 4.6; S, 21.1 [Cl, 11.85; N, 4.65; S, 21.25]
(4a)	MeOH	77—78	C, 58.95; H, 4.05; S, 27.75 [C, 58.6; H, 4.05; S, 27.7]
(4b)	LP [c]	62	C, 58.95; H, 4.05; S, 27.75 [C, 59.05; H, 4.1; S, 27.75]
(4′c)	MeOH	125—126	C, 53.95; H, 3.7; S, 25.4 [C, 54.05; H, 3.65; S, 25.45]
(4d)	MeOH	120—121	C, 57.85; H, 3.6; S, 28.9 [C, 57.95; H, 3.65; S, 28.85]
(4e)	MeOH	141—142	Cl, 9.7; S, 26.2 [Cl, 9.8; S, 25.95]
(4f)	MeOH	88—89	Cl, 9.7; S, 26.2 [Cl, 9.75; S, 25.95]
(4g)	MeOH	93—94	Cl, 9.7; S, 26.2 [Cl, 9.8; S, 25.95]
(4h)	MeOH	121	C, 60.95; H, 4.8; S, 25.65 [C, 60.65; H, 4.8; S, 25.4]

[a] B.p. 60—80°. [b] B.p. 30—50°. [c] B.p. 80—100°.

* Primed numbers indicate the corresponding sulphones.
† B = benzene; LP = light petroleum.

TABLE 3

Chemical shifts (δ) and coupling constants

Compd.*	H-β (1 H, d)	H-α (1 H, d)	$J_{\alpha\beta}$/ Hz	Other
(2′b)	8.10	8.46	1.65	7.34—7.50 (2 H, m), 7.74—7.88 (2 H, m), 2.44 (3 H, s) ($MeC_6H_4{\cdot}SO_2$)
(2e)	7.74	8.30	1.61	7.16—7.32 (4 H, m) (ClC_6H_4S)
(2′f)	8.14	8.49	1.65	7.40—7.66 (2 H, m), 7.80—8.00 (2 H, m) ($ClC_6H_4{\cdot}SO_2$)
(4a)	7.40	8.08	1.52	7.48—7.68 (3 H, m), 7.90—8.05 (2 H, m) ($PhSO_2$); 7.02—7.30 (4 H, m), 2.34 (3 H, s) (MeC_6H_4S)
(4b)	7.44	8.10	1.50	7.50—7.64 (3 H, m), 7.90—8.06 (2 H, m) ($PhSO_2$); 6.96—7.24 (4 H, m), 2.30 (3 H, s) (MeC_6H_4S)
(4′c)	7.84	8.32	1.50	7.20—7.70 (6 H, m), 7.90—8.06 (2 H, m), 8.04—8.22 (1 H, m), 2.56 (3 H, s) ($PhSO_2$ and $MeC_6H_4{\cdot}SO_2$)
(4d)	7.43	8.10	1.50	7.48—7.62 (3 H, m), 7.88—8.04 (2 H, m) ($PhSO_2$); 7.15—7.30 (5H, m) (PhS)
(4e)	7.47	8.16	1.50	7.50—7.62 (3 H, m), 7.90—8.04 (2 H, m) ($PhSO_2$); 7.08—7.34 (4 H, m) (ClC_6H_4S)
(4f)	7.49	8.18	1.50	7.50—7.62 (3 H, m), 7.90—8.04 (2 H, m) ($PhSO_2$); 7.12—7.24 (4 H, m) (ClC_6H_4S)
(4g)	7.53	8.23	1.50	7.50—7.63 (3 H, m), 7.92—8.06 (2 H, m) ($PhSO_2$); 6.86—7.38 (4H, m) (ClC_6H_4S)
(4h)	7.08	7.82	1.50	7.46—7.62 (3 H, m), 7.86—8.02 (2 H, m) ($PhSO_2$); 6.96 (2 H, s), 2.27 (3 H, s), 2.41 (6 H, s) ($Me_3C_6H_2S$)

* Primed numbers refer to the corresponding sulphones.

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