Substituent Effects in Homolytic Substitution Reactions. The Phenylation of Some 3-Substituted Thiophens

By C. M. Camaggi, G. De Luca, and A. Tundo,* Istituto di Chimica Organica e di Chimica Industriale, Viale Risorgimento 4, 40136 Bologna, Italy

The homolytic phenylation of some 3-substituted thiophens has been investigated; in addition, isomer ratios and partial rate factors for the phenylation of thioanisole, methyl phenyl sulphone, 2-methylthiothiophen, and 2-methylsulphonylthiophen have been determined. The isomeric composition of the products and the partial rate factors obtained for the phenylation of 3-substituted thiophens indicate that the main effect of the substituent is to render the two α-positions (2- and 5-) non-equivalent, the former being activated, the latter generally deactivated with respect to an α-position of thiophen. Structure–reactivity relationships are discussed.

THE isomer ratios and partial rate factors for the homolytic phenylation of some 2-substituted thiophens have been previously rationalised [1] in terms of a particular stabilisation of the radical–substrate complex for attack of the phenyl radical at position 3, due to the presence of electron-withdrawing groups in position 2. An alternative explanation was based on the partial ' dienic character ' of thiophens substituted in position 2 by $-I$ or $-M$ groups.

We have now studied the homolytic phenylation of a number of 3-substituted thiophens, in order to determine the isomeric composition of the phenylated products and the partial rate factors. The same substituent groups were chosen as had been employed in the study of 2-substituted thiophens, with the exception that chlorothiophens were not investigated.

In addition, the effects of methylthio- and methylsulphonyl groups in both the 2- and the 3-position of thiophen were determined; for comparison, isomer ratios and partial rate factors for the phenylation of thioanisole and methyl phenyl sulphone were determined. For these substrates, no partial rate factors were available in the literature, and the isomer ratios determined by McVrigh [2] are probably incorrect owing to the experimental procedure employed.

Thioanisole is reported to react with benzoyl peroxide *via* a non-radical pathway; [3] we did not encounter a similar problem with *N*-nitrosoacetanilide, and by using this radical source we obtained high yields of phenylated products. Partial rate factors (k_{ortho}, k_{meta}, and k_{para}) reported in Table 1 are relative to a position of benzene and were calculated in the usual way,[4] as also was the total rate factor.

[1] C. M. Camaggi, G. De Luca, and A. Tundo, *J.C.S. Perkin II*, 1972, 412.
[2] P. McVrigh, *Diss. Abs.*, 1958, **19**, 1206.
[3] D. I. Davies, D. H. Hey, and B. Summers, *J. Chem. Soc.* (*C*), 1970, 2653.
[4] D. H. Hey, *Adv. Free Radical Chem.*, 1967, **2**, 47; G. H. Williams in ' Essays on Free Radical Chemistry,' *Chem. Soc. Special Publ.* No. 24, 1970, p. 25.

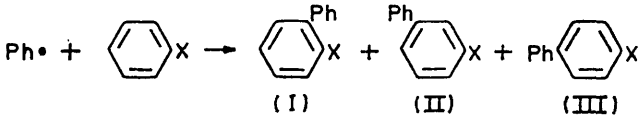
Tables 2 and 3 give the isomer ratios obtained for the phenylation of the substituted thiophens, together with the partial rate factors obtained in experiments in which phenyl radicals reacted with equimolecular quantities of thiophen and substituted thiophen. The reaction mixtures were analysed by g.l.c., and partial rate factors were obtained from the formulae indicated, similar to those employed for the phenylation of 2-substituted thiophens.[1]

Two methods of radical production were employed in these experiments: use of *N*-nitrosoacetanilide and aprotic diazotisation of aniline.[5] The data obtained with both reagents are the same within the limits of experimental error. The yields of phenylated products were in all cases satisfactory (40—70%).

The introduction of a substituent in position 2 of thiophen was observed to remove the high α : β selectivity found in the phenylation of the unsubstituted substrate.[1,6] This trend is still observable in the data for the phenylation of 2-methylthio- and 2-methylsulphonyl-thiophen, for which the ratios [α-substitution product] : [β-substitution products] are 2·6 and 0·74, respectively (for thiophen [6] this ratio is 13·3). In contrast, the α : β substitution products ratio obtained in the phenylation of 3-substituted thiophens is closer to that obtained in the phenylation of unsubstituted thiophen. The percentage of β-substitution product is in this case in the range 0—7·3%, whereas in the case of the corresponding 2-substituted thiophens the corresponding values are in the range 20·8% (for 2-methylthiophen) to 77% (for 2-nitrothiophen). The effect of the 3-substituent is more evident on the two free α-positions. Position 2 is activated, position 5 generally deactivated; in addition, the activation of position 2 is of the same order as that observed for an *ortho*-position in the corresponding monosubstituted benzene. Thus at this position the effects of the substituent and of the thiophen structure

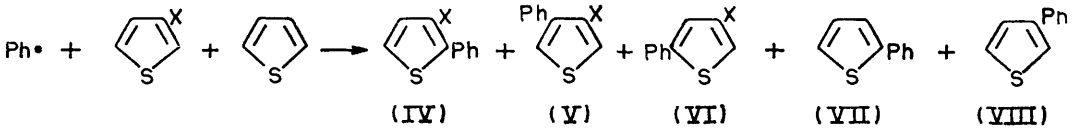
TABLE 1

Isomer ratios and partial rate factors for the homolytic phenylation of thioanisole and methyl phenyl sulphone



X	$\frac{X}{H}K$	% (I)	% (II)	% (III)	k_{ortho}	k_{meta}	k_{para}
SMe (*a*)	2·93	66·4	13·2	20·4	5·83	1·16	3·58
(*b*)		54	19	27			
SO_2Me (*a*)	1·72	46·6	26·5	26·9	2·40	1·36	2·72
(*b*)		28	49	23			

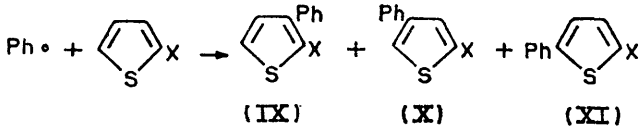
(*a*) This work. (*b*) Ref. 2.



$$k_2 = 2\frac{\text{mol (IV)}}{\text{mol (VII)}};\quad k_4 = 2\frac{\text{mol (V)}}{\text{mol (VII)}};\quad k_5 = 2\frac{\text{mol (VI)}}{\text{mol (VII)}}$$

TABLE 2

Homolytic phenylation of 2-methylthiophen and methyl 2-thienyl sulphone. Isomer ratios and partial rate factors (reactivity of an α-position of the unsubstituted thiophen = 1)



X	% (IX)	% (X)	% (XI)	k_3 *	k_4 *	k_5 *
SMe	26·5	1·6	71·9	0·83	0·05	2·25
SO_2Me	57·4		42·6	1·15		0·85

* For details of the calculation of partial rate factors, see ref. 1.

TABLE 3

Homolytic phenylation of 3-substituted thiophens; isomer ratios and partial rate factors

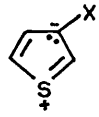
X	% (IV)	% (V)	% (VI)	k_2	k_4	k_5
Me	66·6	7·3	26·1	2·92	0·32	1·14
Br	80·3	2·2	17·5	2·57	0·07	0·56
CO_2Me	84·8		15·2	2·98		0·53
NO_2	99·0			3·80		
SMe	83·1	6·0	10·9	5·51	0·40	0·72
SO_2Me	74·2		25·8	2·98		0·53

[5] J. I. G. Cadogan, *J. Chem. Soc.*, 1962, 4257.
[6] C. M. Camaggi, R. Leardini, M. Tiecco, and A. Tundo, *J. Chem. Soc. (B)*, 1970, 1683.

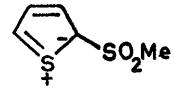
seem to be additive. The situation is different for position 5. As this is a *meta*-like position with respect to the substituent, it was expected either to be slightly activated or unaffected, but not deactivated as observed.

Non-additivity of substituent effects has also been observed in the phenylation of 2-substituted thiophens,[1] where the activation of position 3 is much larger than that expected, while position 5 is less activated or in some cases deactivated. In the phenylation of *para*-disubstituted benzenes the effect of the substituents is additive only if both groups have similar electronic properties; when they have opposite electronic properties the reactivity is lowered below that of the more reactive of the two corresponding monosubstituted benzenes.[7]

The experimental data indicate that the additivity of substituent effects does not apply if mutual conjugation between substituents (or between substituent and heteroatom) is present. In the case of 3-substituted thiophens the mutual conjugation is not so important as in the case of the 2-substituted heterocycle;[8] in fact, the substituent effect is here less marked, the non-additivity being evident only in the deactivation of position 5, a central atom of the ' dienic system ' (XII), which would be partially stabilised by an electron-withdrawing substituent.



(XII)



(XIII)

An additional comment concerns the effect of sulphur-containing substituents. It has been observed recently from hydrogen-abstraction studies that α-thio-radicals are particularly stabilised with respect to α-oxy-radicals.[9] We have found a similar effect in the phenylation of methylthio-substituted aromatic substrates. Recent determinations of the reactivity of anisole give the following partial rate factors:[7] k_{ortho}, 5·6—6·5; k_{meta}, 0·88—1·23; k_{para}, 1·86—2·31. The reactivity of the *ortho*-position of thioanisole (see Table 1) is not markedly different from that of anisole, and the difference between the two substrates is noticeable only in the reactivity of the *para*-position. Simamura and his co-workers[4] used *N*-nitrosoacetanilide as radical source in the phenylation of anisole and obtained k_{ortho} 3·56; k_{meta} 0·93; k_{para} 1·29. Comparison with these data, obtained with the same radical source as in the present work, shows the activating effect of the sulphur atom to be more pronounced than that of the oxygen atom.

The strong activating effect of the methylthio-group is also observable both in position 2 and in position 3 of thiophen.

In 2-methylthiothiophen position 5 is more reactive than position 3; the situation is reversed in 2-methylsulphonylthiophen. This result is consistent with the rationalisation previously proposed for the data obtained in the phenylation of other 2-substituted thiophens; the methylsulphonyl group is thought to stabilise a structure such as (XIII) more than the methylthio-group.

In order to provide a theoretical rationalisation of these experimental data, two kinds of structure–reactivity relationships could be invoked, involving either consideration of the relative stability of the intermediate σ-complexes or correlation with some ground-state property of the aromatic substrate.

At present the only ground-state ' reactivity index ' for homolytic substitution reactions is the ' free valence ' parameter, but this is a useful criterion for alternant hydrocarbons only.[10] Localisation energies (quantitative measures of the stability of σ-complexes), obtained from sophisticated SCFMO calculations, have recently proved useful in correlating reactivity patterns for electrophilic substitution reactions,[11] but these data are probably much less useful in the case of the corresponding homolytic substitutions, because the free radical σ-complex gives a poor picture of the transition state.[12] Furthermore, in the thiophen series, attack of the phenyl radical at the sulphur atom, followed by rearrangement of the intermediate thus formed, is not excluded.

EXPERIMENTAL

G.l.c. analyses were carried out with a Varian 1520 gas-chromatograph, equipped with flame ionisation detector. N.m.r. spectra were measured with a JEOL C 60 HL instrument.

Thiophen and 3-methylthiophen were commercial products purified in the usual way; methyl 3-thenoate was prepared by esterification of commercial 3-thenoic acid. 2-[13] and 3-[14] Methylthiophen, 2-[13] and 3-[14] methylsulphonylthiophen, 3-bromothiophen,[15] and 3-nitrothiophen[16] were prepared as reported and purified by several crystallisation or distillations; n.m.r. spectroscopy was used as a test for purity. 2-[17] and 3-[18] Phenylthiophen and the isomeric 3-methyl-phenylthiophens[19] were prepared as reported.

3-Bromo-2-phenylthiophen.—2,3-Dibromothiophen[20] (7·5 g) was added in ethereal solution to a solution of n-butyl-

[7] D. I. Davies, D. H. Hey, and B. Summers, *J. Chem. Soc.* (*B*), 1971, 2681.
[8] S. Gronowitz, *Adv. Heterocyclic Chem.*, 1963, **1**, 1.
[9] K. Uneyama, H. Namba, and S. Oae, *Bull. Chem. Soc. Japan*, 1968, **41**, 1928.
[10] M. J. S. Dewar, ' The Molecular Orbital Theory of Organic Chemistry,' McGraw-Hill, New York, 1969.
[11] G. R. Howe, *J. Chem. Soc.* (*B*), 1971, 984.
[12] M. J. Perkins, in ' Free Radicals,' ed. J. K. Kochi, Interscience, New York, vol. I, in the press.
[13] J. Cymerman-Craig and J. N. Loder, *J. Chem. Soc.*, 1954, 237.
[14] S. Gronowitz, *Arkiv Kem.*, 1958, **13**, 269.
[15] S.-O. Lawesson, *Arkiv Kem.*, 1957, **11**, 373.
[16] P. Reginando and R. Delaby, *Bull. Soc. chim. France*, 1955, 1614.
[17] V. Ramanathan and R. Levine, *J. Org. Chem.*, 1962, **27**, 1667.
[18] S. Gronowitz and N. Gjös, *Acta Chem. Scand.*, 1967, **21**, 2823.
[19] M. G. Voronkov and B. L. Goldstein, *Zhur. Obschei Khim.*, 1950, **20**, 1218; M. G. Voronkov and A. S. Braun, *J. Gen. Chem.* (*U.S.S.R.*), 1948, **18**, 70.
[20] S.-O. Lawesson, *Arkiv Kem.*, 1957, **11**, 317.

lithium in dry ether [from n-butyl bromide (4·2 g) and lithium (0·55 g)] at −70 °C. Cyclohexanone (3·05 g) was added and the temperature rose to −30 °C; the mixture was then allowed to warm to room temperature and hydrolysed, and the ethereal layer was concentrated. The oily residue was first distilled (b.p. 140—142 °C at 2 mmHg), then aromatised with *o*-chloroanil in boiling benzene. Chromatography on silica gel (light petroleum as eluant) gave 3-*bromo*-2-*phenylthiophen* (3 g), b.p. 143—144 °C at 2 mmHg (Found: C, 50·3; H, 2·9; Br, 33·55; S, 13·4. $C_{10}H_7BrS$ requires C, 50·2; H, 2·95; S, 13·3; Br, 33·55%).

By the same method were prepared 3-*bromo*-4-*phenylthiophen* from 3,4-dibromothiophen;[20] m.p. 68—70 °C (Found: C, 50·1; H, 3·0; Br, 34·0; S, 13·0%), and 4-*bromo*-2-*phenylthiophen*, from 2,4-dibromothiophen;[20] m.p. 70—71 °C (Found: C, 50·1; H, 2·9; Br, 33·65; S, 12·9%).

3-*Methylthio*-2-*phenylthiophen*.— 3-Bromo-2-phenylthiophen (3 g) was metallated with n-butyl-lithium [from n-butyl bromide (1·7 g) and lithium (0·2 g)] and dimethyl disulphide (1·2 ml) was added to the mixture at −70 °C. The mixture was allowed to warm to room temperature, then hydrolysed, and the ethereal phase was concentrated. The residue was chromatographated on silica gel [light petroleum (b.p. 40—60 °C) as eluant], then distilled; b.p. 132—134 °C at 2 mmHg (Found: C, 64·4; H, 4·9; S, 31·1. $C_{11}H_{10}S_2$ requires C, 64·05; H, 4·85; S, 31·05%).

By the same method were prepared 3-*methylthio*-4-*phenylthiophen*, from 3-bromo-4-phenylthiophen; m.p. 76—78 °C (Found: C, 64·2; H, 4·95; S, 31·6%), and 4-*methylthio*-2-*phenylthiophen*, from 4-bromo-2-phenylthiophen; m.p. 39—40 °C (Found: C, 64·3; H, 5·0; S, 31·25%).

From the oxidation of the corresponding sulphides with hydrogen peroxide in acetic acid were prepared 3-*methylsulphonyl*-2-*phenylthiophen*, m.p. 49—50 °C (Found: C, 55·85; H, 4·3; S, 27·0. $C_{11}H_{10}O_2S_2$ requires C, 55·45; H, 4·2; S, 26·9%), 3-*methylsulphonyl*-4-*phenylthiophen*, m.p. 112—113 °C (Found: C, 55·75; H, 4·35; S, 26·9%), and 4-*methylsulphonyl*-2-*phenylthiophen*, m.p. 85—86 °C (Found: C, 55·65; H, 4·3; S, 26·9%).

3-*Nitro*-2-*phenylthiophen*.—2-Bromo-3-nitrothiophen[21] (1 g) and iodobenzene (1·2 g) were preheated to 130 °C, and copper bronze (0·65 g) was added during 30 min while the temperature was raised to 190 °C. After 3 h at this temperature, the mixture was extracted with chloroform, then the extract was chromatographed on silica gel, with light petroleum–benzene (4 : 1) as eluant. An unidentified low-melting product was eluted first, followed by 3-nitro-2-phenylthiophen, m.p. 100—101 °C (lit.,[18] 101·5—102·5 °C) (Found: C, 58·6; H, 3·55; S, 15·7; N, 7·0. Calc. for $C_{10}H_7NO_2S$: C, 58·55, H, 3·4; S, 15·6; N, 6·8%).

3-*Nitro*-4-*phenylthiophen* was prepared similarly from 3-nitro-4-bromothiophen;[21] m.p. 115—116 °C (Found: C, 58·6; H, 3·5; S, 17·0; N, 7·0%).

4-*Nitro*-2-*phenylthiophen*.—4-Nitro-2-iodothiophen[22] (1·3 g) was photolysed in benzene for 24 h (Hanau PL 368 lamp). Chromatography of the reaction mixture allowed the separation of the *product*, m.p. 159—160 °C (Found: C, 58·7; H, 3·5; S, 15·8; N, 6·9%).

Methyl 2-*Phenyl*-3-*thenoate*.—2-Iodothiophen-3-carbaldehyde[23] (1·6 g) was irradiated (Hanau PL 368 high-pressure lamp) in benzene (200 ml) for 24 h. Chromatography of the mixture led to the separation of 2-phenylthiophen-3-carbaldehyde, m.p. 51—53 °C (1·22 g, 86%), which was directly oxidised [with silver nitrate (2·6 g) and sodium hydroxide (1·1 g) in water] to 2-phenyl-3-thenoic acid, m.p. 234—236 °C. The *methyl ester* was obtained by treatment with diazomethane; m.p. 79—80 °C (Found: C, 65·5; H, 4·6; S, 14·95. $C_{11}H_{10}O_2$ requires C, 66·05; H, 4·7; S, 14·7%).

Methyl 4-*Phenyl*-3-*thenoate*.—Methyl 4-iodo-3-thenoate (0·9 g; obtained by treatment of the acid[24] with diazomethane) was photolysed in benzene for 24 h. Chromatography on silica gel gave *methyl* 4-*phenyl*-3-*thenoate* (83%), m.p. 48—49 °C (Found: C, 66·3; H, 4·55; S, 14·95%).

Methyl 5-*Phenyl*-3-*thenoate* was similarly prepared from methyl 5-iodo-3-thenoate;[23] m.p. 91—92 °C (72%) (Found: C, 66·1; H, 4·8; S, 14·95%).

Phenylation Reactions.—Phenyl radicals were generated in mixtures of thiophen and substituted thiophen both by decomposition of *N*-nitrosoacetanilide and by aprotic diazotisation of aniline at 40 °C. The experimental procedure has been described previously.[1,6]

G.l.c. separations and analyses were performed with the following columns (1/8 in diam.): 5% FFAP on Varapart 30 (80—100 mesh) for phenylation of 3-bromo-, 3-methoxycarbonyl-, 3-methylthio-, and 3-methylsulphonyl-thiophen, thioanisole, and methyl phenyl sulphone; 5% polyphenyl ether (6 rings) on Varapart 30 (80—100 mesh) for phenylation of 3-methylthiophen; 5% SE 30 on Varapart 30 (80—100 mesh) for phenylation of 3-nitrothiophen.

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[21] R. Motoyama, S. Nishimura, and E. Imoto, *Nippon Kagaku Tosshi*, 1957, **78**, 788, 954.
[22] J. Tirouflet, P. Fournari, and J. P. Chané, *Compt. rend.*, 1956, **242**, 1799; 1957, **243**, 500.
[23] R. Guilard, P. Fournari, and M. Person, *Bull. Soc. chim. France*, 1967, **11**, 4124.
[24] W. Steinkopf, H. F. Schmith, and H. Fiedler, *Annalen*, 1937, **527**, 237.