Nucleophilic Substitution in Five-membered Rings. Influence of Steric Interactions in the Reaction Area on Activation by a Nitro-group

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The reactivity of some 2-L-3-nitro-4-R-5-X-thiophens (L = Br or SO_2Ph; R = H or Me; X = H or NO_2) with various nucleophiles (sodium methoxide and benzenethiolate, aliphatic, cyclic, and aromatic amines) has been measured in methanol. The results obtained have been interpreted in the light of the electronic and steric effects of the nucleophiles. The k_H/k_{Me} values calculated confirm the data previously obtained with piperidine, *i.e.*, absence of a secondary steric effect (s.s.e). and presence of a small s.s.e. for bromine and phenylsulphonyl, respectively, as leaving groups. The special behaviour of *N*-methylaniline is discussed.

RECENTLY we have shown [1] the absence of kinetic secondary steric effects (s.s.e.) in heteroaromatic nucleophilic substitutions of halogens by piperidine in thiophen derivatives. However when the leaving group is phenylsulphonyl, there is a small s.s.e.[1c] In order to obtain more complete information about the influence of the leaving group on the s.s.e., we have now extended our study to the reactions of compounds (I)—(IV) with various neutral (*p*-toluidine, aniline, *o*-toluidine, 2,6-dimethylaniline, *N*-methylaniline, and diethylamine) and

(I) R = H, X = NO_2
(II) R = Me, X = NO_2
(III) R = H, X = H
(IV) R = Me, X = H

(V)
a; L = Br
b; L = SO_2Ph

anionic nucleophiles (sodium benzenethiolate and methoxide).

[1] (*a*) D. Spinelli, C. Dell'Erba, and G. Guanti, *J. Heterocyclic Chem.*, 1968, **5**, 323; (*b*) D. Spinelli, G. Consiglio, and A. Corrao, *J.C.S. Perkin II*, 1972, 1866; (*c*) D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *ibid.*, 1974, 1632.

RESULTS AND DISCUSSION

Products.—Compounds (I)—(IV) gave the correspond ing substitution products with nucleophiles in methanol, in almost quantitative yields as shown by t.l.c. or u.v.–visible (200—450 nm) analysis of the reaction mixtures. The relevant physical and analytical data are collected in Table 1.

TABLE 1

Physical and analytical data for 2-Nu-3-nitro-4-R-5-X-thiophens (V)

			Crystallization	M.p.	Found (%)				Required (%)				
X	R	Nu	solvent	(°C)	C	H	N	Formula	C	H	N	$\lambda_{max.}$/nm [a]	log ε [a]
NO_2	H	$NHC_6H_4Me(p)$ [b]										404	4.23
NO_2	H	NHPh [b]										402	4.24
NO_2	H	NEt_2	Ligroin–benzene	68	38.8	4.5	17.1	$C_8H_{11}N_3O_4S$	39.2	4.5	17.1	414	4.19
NO_2	H	NMePh	Ethanol	122	47.7	3.3	15.3	$C_{11}H_9N_3O_4S$	47.3	3.2	15.0	404	4.26
NO_2	H	$NHC_6H_4Me(o)$	Ethanol	168	47.0	3.3	14.9	$C_{11}H_9N_3O_4S$	47.3	3.2	15.0	404	4.20
NO_2	H	$NHC_6H_3Me_2(o,o')$	Ethanol	154	48.5	3.7	14.0	$C_{12}H_{11}N_3O_4S$	49.1	3.8	14.3	404	4.22
NO_2	Me	$NHC_6H_4Me(p)$	Ethanol–dioxan	188	49.8	3.8	14.0	$C_{12}H_{11}N_3O_4S$	49.1	3.8	14.3	404	4.25
NO_2	Me	NHPh	Ethanol–dioxan	210	47.2	3.2	14.8	$C_{11}H_9N_3O_4S$	47.3	3.2	15.0	404	4.25
NO_2	Me	NEt_2	Ligroin–benzene	72	41.9	5.0	16.4	$C_9H_{13}N_3O_4S$	41.7	5.0	16.2	416	4.26
NO_2	Me	NMePh	Ethanol	144	49.2	3.6	14.5	$C_{12}H_{11}N_3O_4S$	49.1	3.8	14.3	412	4.31
NO_2	Me	$NHC_6H_4Me(o)$	Ethanol–dioxan	185	48.9	3.6	14.1	$C_{12}H_{11}N_3O_4S$	49.1	3.8	14.3	404	4.22
NO_2	Me	$NHC_6H_3Me_2(o,o')$	Ethanol	182	50.5	4.2	13.5	$C_{13}H_{13}N_3O_4S$	50.8	4.3	13.7	404	4.23
H	H	OMe [b]										328 [c]	3.70 [c]
H	Me	SPh	Light petroleum	76	52.9	3.6	5.7	$C_{11}H_9NO_2S_2$	52.6	3.6	5.6	375	3.74
H	Me	OMe	Methanol	95	41.8	4.2	8.2	$C_6H_7NO_3S$	41.6	4.1	8.1	338 [d]	3.50 [d]

[a] In methanol. [b] C. D. Hurd and K. L. Kreuz, *J. Amer. Chem. Soc.*, 1952, **74**, 2965. [c] The wavelength chosen for readings was 345 nm (log ε 3.63). [d] The wavelength chosen for readings was 355 nm (log ε 3.42).

TABLE 2

Rate constants and activation parameters for the reactions of 2-bromo-3-nitro-5-X-thiophens (Ia) and (IIIa) with nucleophiles in methanol

X	Nucleophile	10^3k/l mol^{-1} s^{-1} (at various °C) [a]	$\Delta H^{\ddagger}$ [b]/ kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c]/ cal mol^{-1} K^{-1}	Reagent rate ratios [d]
NO_2	Piperidine [e]	1 060 (10.82), 1 990 (20.06), 3 780 (30.02)	10.7	20.6	47
NO_2	*p*-Toluidine [f]	44.0 (0.05), 83.1 (10.08), 141 (20.05)	8.7	32.7	3.4
NO_2	Aniline [f]	12.2 (0.02), 23.0 (10.02), 41.9 (20.05)	9.2	33.4	1
NO_2	Diethylamine	11.4 (9.98), 24.0 (20.05), 50.1 (30.10)	12.0	25.0	0.58
NO_2	*N*-Methylaniline	19.9 (20.05), 33.6 (29.98), 56.2 (40.04)	8.9	36.0	0.47
NO_2	*o*-Toluidine	3.49 (19.95), 6.36 (30.02), 11.0 (39.98)	9.9	35.9	0.084
NO_2	2,6-Dimethylaniline	0.0778 (20.04), 0.155 (29.99), 0.293 (39.98)	11.5	37.9	0.0019
H	Sodium benzenethiolate	47.7 (10.06), 116 (20.02), 253 (30.00)	13.8	15.8	2 900
H	Piperidine [g]	0.114 (20.00), 0.268 (30.00), 0.958 (46.33)	14.4	27.2	2.9
H	Sodium methoxide	0.0398 (20.05), 0.122 (29.95), 0.382 (39.95)	20.1	10.0	1

[a] The rate constants are accurate to within ±3%. [b] At 20°; the probable error is 0.5 kcal mol^{-1}. [c] At 20°. [d] Calculated at 20°; for X = NO_2, relative to aniline = 1; for X = H, relative to sodium methoxide = 1. The maximum error is ±6%. [e] D. Spinelli, G. Guanti, and C. Dell'Erba, *J. Heterocyclic Chem.*, 1968, **5**, 323. [f] D. Spinelli, G. Consiglio, and R. Noto, meeting of the Società Chimica Italiana, Messina, 1974. [g] D. Spinelli, G. Consiglio, and A. Corrao, *J.C.S. Perkin II*, 1972, 1866.

Kinetic Data.—Rate constants and activation parameters are reported in Tables 2—5. The reactions studied are bimolecular, and thus proceed through a two-step mechanism with fast decomposition of the intermediate complex.[2] Compounds (I) and (II) react too fast with sodium benzenethiolate and a simple spectrophotometric technique cannot be used. Moreover, upon treatment with sodium methoxide they do not give the expected substitution products in high yield.[3] Nevertheless, information on the behaviour of these nucleophiles can be obtained by measuring their reactivity with compounds (III) and (IV).[1c]

Reactivity of Compounds (I) *and* (II).—The observed order of reactivity of compounds (Ia) and (IIa) is piperidine > *p*-toluidine > aniline > diethylamine ≃ *N*-methylaniline > *o*-toluidine > 2,6-dimethylaniline, as foreseen. In fact, anilines show the sequence expected on the basis of electronic and steric effects exerted by the methyl group(s);[4] the different reactivity between piperidine and diethylamine, which have much the same basicity, is linked to the much greater steric hindrance of the latter.[5]

The order of reactivity of compounds (Ib) and (IIb) is similar to that observed for (Ia) and (IIa), but in this case *N*-methylaniline is less reactive than *o*-toluidine. An inspection of molecular models [1a,c] helps us to appreciate that a suitable arrangement of the *N*-methyl-(phenyl), phenylsulphonyl, and 3-nitro-groups in the transition state is very difficult to achieve because of the steric repulsions among them. So, going from aniline to *N*-methylaniline, the reactivity of (Ia) diminishes 2-fold whereas that of (Ib) drops 200-fold (Tables 2 and 4).

[2] (*a*) J. F. Bunnett, E. W. Garbisch, and K. M. Pruitt, *J. Amer. Chem. Soc.*, 1957, **79**, 385; (*b*) D. Spinelli, C. Dell'Erba, and A. Salvemini, *Ann. Chim.* (*Italy*), 1962, **52**, 1156; (*c*) L. Chierici, C. Dell'Erba, A. Guareschi, and D. Spinelli, *ibid.*, 1967, **57**, 632.

[3] C. D. Hurd and K. L. Kreuz, *J. Amer. Chem. Soc.*, 1952, **74**, 2965.

[4] N. B. Chapman, D. K. Chaudbury, and J. Shorter, *J. Chem. Soc.*, 1962, 1975; J. Miller, 'Aromatic Nucleophilic Substitution,' Elsevier, Amsterdam, 1968, chs. 6 and 8.

[5] O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 1950, 507.

TABLE 3

Rate constants and activation parameters for the reactions of 2-bromo-3-nitro-4-methyl-5-X-thiophens (IIa) and (IVa) with nucleophiles in methanol

X	Nucleophile	10^3k/l mol^{-1} s^{-1} (at various °C) [a]	$\Delta H^{\ddagger}$ [b]/ kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c]/ cal mol^{-1} K^{-1}	Reagent rate ratios [d]
NO_2	Piperidine [e]	563 (10.82), 991 (20.06), 2 000 (30.02)	10.7	21.9	27
NO_2	*p*-Toluidine	69.3 (9.96), 125 (20.08), 202 (29.95)	8.5	33.5	3.4
NO_2	Aniline	20.5 (9.93), 36.3 (20.05), 59.4 (29.96)	8.4	36.2	1
NO_2	Diethylamine	12.7 (20.05), 25.1 (30.05), 47.3 (40.12)	11.4	28.2	0.35
NO_2	*N*-Methylaniline	18.2 (19.98), 30.2 (29.95), 47.8 (40.00)	8.2	38.4	0.51
NO_2	*o*-Toluidine	2.42 (20.00), 4.35 (30.04), 7.47 (39.98)	9.7	37.3	0.068
NO_2	2,6-Dimethylaniline	0.0493 (20.04), 0.0948 (30.02), 0.184 (40.10)	11.4	39.3	0.0014
H	Sodium benzenethiolate	46.4 (20.08), 102 (29.98), 217 (40.08)	13.5	18.5	3900
H	Piperidine [e]	0.0584 (20.00), 0.138 (30.00), 0.306 (40.00)	14.5	28.3	4.9
H	Sodium methoxide	0.0119 (20.10), 0.0409 (29.95), 0.125 (39.95)	21.0	9.3	1

[a–d] As Table 2. D. Spinelli, G. Consiglio, and A. Corrao, *J.C.S. Perkin II*, 1972, 1866.

TABLE 4

Rate constants and activation parameters for the reactions of 2-phenylsulphonyl-3-nitro-5-X-thiophens (Ib) and (IIIb) with nucleophiles in methanol

X	Nucleophile	10^3k/l mol^{-1} s^{-1} (at various °C) [a]	$\Delta H^{\ddagger}$ [b]/ kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c]/ cal mol^{-1} K^{-1}	Reagent rate ratios [d]
NO_2	Piperidine [e]	2 430 (0.02), 4 140 (10.02), 6 800 (20.03)	7.6	28.8	58
NO_2	*p*-Toluidine	171 (0.10), 269 (9.98), 436 (20.08)	6.8	36.7	3.6
NO_2	Aniline	70.6 (10.00), 120 (20.03), 185 (29.96)	7.6	36.6	1
NO_2	Diethylamine	36.1 (20.00), 72.2 (30.05), 126 (40.35)	10.6	28.7	0.31
NO_2	*N*-Methylaniline	0.591 (20.05), 0.979 (29.98), 1.49 (40.02)	7.8	46.4	0.0051
NO_2	*o*-Toluidine	5.61 (20.02), 9.37 (30.03), 15.5 (39.98)	8.7	39.1	0.047
NO_2	2,6-Dimethylaniline	0.133 (20.05), 0.245 (30.00), 0.450 (40.00)	10.5	40.3	0.0011
H	Sodium benzenethiolate [f]	1 070 (0.00), 2 220 (10.00), 4 400 (20.02)	10.7	19.1	11 000
H	Piperidine [e]	0.0592 (20.05), 0.148 (30.10), 0.288 (40.10)	13.8	30.5	0.15
H	Sodium methoxide	0.409 (20.05), 1.20 (29.95), 3.00 (39.95)	17.7	13.7	1

[a–d] As Table 2. [e] D. Spinelli, G. Consiglio, R. Noto, and A. Corrao, *J.C.S. Perkin II*, 1974, 1632. [f] G. Guanti, C. Dell'Erba, and P. Macera, *J. Heterocyclic Chem.*, 1971, **8**, 537.

TABLE 5

Rate constants and activation parameters for the reactions of 2-phenylsulphonyl-3-nitro-4-methyl-5-X-thiophens (IIb) and (IVb) with nucleophiles in methanol

X	Nucleophile	10^3k/l mol^{-1} s^{-1} (at various °C) [a]	$\Delta H^{\ddagger}$ [b]/ kcal mol^{-1}	$-\Delta S^{\ddagger}$ [c]/ cal mol^{-1} K^{-1}	Reagent rate ratios [d]
NO_2	Piperidine [e]	257 (0.02), 485 (10.00), 878 (20.03)	9.3	27.5	42
NO_2	*p*-Toluidine	39.3 (9.91), 65.4 (20.08), 100 (29.95)	7.4	38.8	3.1
NO_2	Aniline	20.9 (20.08), 32.8 (30.05), 52.7 (41.33)	7.4	40.9	1
NO_2	Diethylamine	5.00 (20.05), 8.90 (29.98), 15.9 (40.35)	9.8	35.5	0.24
NO_2	*N*-Methylaniline	0.0373 (20.05), 0.0611 (29.95), 0.104 (40.06)	8.7	49.0	0.0018
NO_2	*o*-Toluidine	0.941 (19.93), 1.70 (30.05), 3.01 (39.98)	10.0	38.2	0.045
NO_2	2,6-Dimethylaniline	0.0226 (20.04), 0.0455 (30.00), 0.0865 (40.06)	11.6	40.0	0.0011
H	Sodium benzenethiolate	687 (20.08), 1 290 (29.60), 2 470 (40.10)	11.1	21.4	29 000
H	Piperidine [e]	0.007 66 (20.02), 0.0212 (30.00), 0.0444 (40.05)	15.4	29.1	0.33
H	Sodium methoxide	0.0242 (20.10), 0.0840 (29.95), 0.272 (39.95)	21.6	5.7	1

[a–e] As Table 4.

Reactivity of Compounds (III) *and* (IV).—The observed order of reactivity of compounds (IIIa) and (IVa) is sodium benzenethiolate $\gg$ piperidine > sodium methoxide, while with compounds (IIIb) and (IVb) it is sodium benzenethiolate $\gg$ sodium methoxide > piperidine. These two different reactivity patterns arise from a combination of factors, (i) the differences in softness (or hardness) of nucleophiles, (ii) the different polarizability of the leaving groups, and (iii) steric interactions in the reaction area.

Thus, the highly polarizable sodium benzenethiolate is the most reactive nucleophile with all the aromatic substrates studied, the highly polarizable phenylsulphonyl enhances, with respect to bromine, the difference of reactivity between the two anionic nucleophiles, and the apparent inversion of nucleophilicity between piperidine and sodium methoxide is connected with the higher steric requirements of the former, a factor which is particularly unfavourable for a leaving group as bulky as phenylsulphonyl.

Reactivity Ratios.—The k_H/k_{Me} values (Table 6) for the reactions with bromine as leaving group allow us to extend our observation of the absence of s.s.e. in piperidinodebromination,[1] to all the nucleophiles studied. The effect of the methyl group inserted at C-4 between the two activating nitro-groups or adjacent to a nitro-group at C-3 is, in fact, the normal electronic one, whatever the arrangement in space of the alkyl groups in amines and however bulky the nucleophile.

On the other hand, the k_H/k_{Me} values (Table 6), for the reactions of compounds with phenylsulphonyl as leaving group, duplicate the situation observed in piperidino-substitution, *i.e.* occurrence of a small kinetic s.s.e.[1c]

It is now worthwhile to consider the $(k_H/k_{Me})_b/(k_H/k_{Me})_a$

ratios (Table 6) which, probably, are a more precise index of s.s.e. All the nucleophiles studied except *N*-methylaniline display much the same value, whereas

TABLE 6

Reactivity ratios k_H/k_{Me} for the reactions of 2-L-3-nitro-4-R-5-X-thiophens with nucleophiles in methanol

X	Nucleophile	$(k_H/k_{Me})_a$ [a]	$(k_H/k_{Me})_b$ [a]	$(k_H/k_{Me})_b/(k_H/k_{Me})_a$ [b]
NO_2	Piperidine	1.9	7.8	4.1
NO_2	*p*-Toluidine	1.2	5.6	4.7
NO_2	Aniline	1.2	5.7	4.8
NO_2	Diethylamine	1.9	7.4	3.9
NO_2	*N*-Methylaniline	1.1	16	15
NO_2	*o*-Toluidine	1.4	5.9	4.2
NO_2	2,6-Dimethylaniline	1.6	5.8	3.6
H	Sodium benzenethiolate	2.5	6.4	2.6
H	Piperidine	1.9	7.7	4.1
H	Sodium methoxide	3.3	17	5.2

[a] Calculated at 20°. The maximum error is ±6%. [b] Calculated at 20°. The maximum error is ±12%.

the ratio for this nucleophile is quite high. We think that the *N*-methyl group introduces variations (see above) in the reaction area which increase the steric inhibition of the 3-nitro-group and make the kinetic s.s.e. more pronounced.

EXPERIMENTAL

Synthesis and Purification of Compounds.—2-Bromo-3,5-dinitrothiophen (Ia),[6] 2-bromo-3,5-dinitro-4-methylthiophen (IIa),[1a] 3,5-dinitro-2-phenylsulphonylthiophen (Ib),[2b] 3,5-dinitro-4-methyl-2-phenylsulphonylthiophen (IIb),[1c] 2-bromo-3-nitrothiophen (IIIa),[7] 2-bromo-3-nitro-4-methylthiophen (IVa),[1b] 3-nitro-2-phenylsulphonylthiophen (IIIb),[8] 3-nitro-4-methyl-2-phenylsulphonylthiophen (IVb),[1c] 2-methoxy-3-nitrothiophen,[3] *N*-(3,5-dinitro-2-thienyl)aniline,[3] and *N*-(3,5-dinitro-2-thienyl)-*p*-toluidine[3] were prepared and purified according to the methods reported. Methanol,[1b] piperidine,[1b] and benzenethiol [9] were purified as previously described. Commercial samples of amines were purified by distillation under reduced pressure.

The other substitution products (V) were prepared by refluxing for suitable periods (5 min—3 h) a solution of 2-bromo-3-nitro-4-methylthiophen or 2-bromo-3,5-dinitro-4-R-thiophen (R = H or Me) and the appropriate nucleophile in methanol: the reaction mixtures were evaporated at reduced pressure and the residue washed with water and purified by crystallization. M.p.s, crystallization solvents, and analytical data are reported in Table 1.

Kinetic Measurements.—The kinetics were followed spectrophotometrically as previously described.[2b,9] The concentrations employed were 10^{-3}M for substrates and 6×10^{-3}—4×10^{-1}M for amines as a function of their nucleophilicity; 10^{-3} and 2×10^{-1}M respectively for substrates and sodium methoxide; * 10^{-4} and 10^{-4}M for substrates and sodium benzenethiolate.

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* 2-Methoxy-3-nitrothiophen gives a Meisenheimer-type adduct with sodium methoxide.[10] For this reason, the kinetics of methoxy-substitution of compounds (III) and (IV) were followed under pseudo-first-order conditions and the samples of the reaction solutions were diluted by acidified methanol before the spectrophotometric determinations.

[6] R. Motoyama, K. Sato, and E. Imoto, *Nippon Kagaku Zhassi*, 1957, **78**, 779.
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[10] D. Spinelli, V. Armanino, and A. Corrao, *J. Heterocyclic Chem.*, 1970, **7**, 1441.