

Thiophene Series. XV (I). The Effect of Leaving Groups on the Reactivity of Nitro-Activated Thiophene Derivatives with Sodium Thiophenoxide

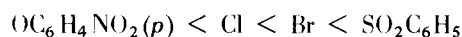
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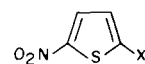
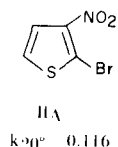
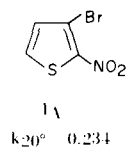
The effect of leaving groups on the reactivity of 3-X-2-nitrothiophene (I), 2-X-3-nitrothiophene (II) and 2-X-5-nitrothiophene (III) (X = Cl, Br, I, OC₆H₄NO₂(*p*), SO₂C₆H₅) with sodium thiophenoxide has been examined.

The results show that the reactivity ratio k_{III}/k_{II} is always greater than unity and is relatively uninfluenced by changing leaving groups compared to the ratio k_I/k_{II} . The ratio k_I/k_{II} is greater or smaller than unity, according to following patterns of leaving groups:



Examination of the reactivity of the three series of compounds having Cl, Br, I and C₆H₄NO₂(*p*) as leaving groups showed the absence of an "element effect" which indicates that in the transition states of these displacement reactions there is little breaking of the bond to the group being displaced.

Previous research (2) on the reactivity of bromonitrothiophenes I_A and II_A toward nucleophilic reagents re-



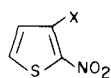
Series III

X = Cl, Br, I, OC₆H₄NO₂(*p*), SO₂C₆H₅

The results obtained in these two "ortho-like" series where the nitro group is bound to the carbon atom adjacent to the reaction center are compared with those of the series III in which the activating group is in a "para-like" position with respect to the reaction center.

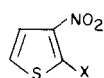
vealed that bromine is displaced by sodium thiophenoxide in methanol with an almost doubled velocity when the reaction site is at the β- rather than at the α-position ($k_{I_A}/k_{II_A} \cong 2$).

In order to determine whether or not, in nucleophilic substitutions, the leaving group affects the relative reactivity of β- and α-displacement in the nitro-activated thiophene derivatives, we have measured the reaction rates of the following thiophene derivatives with sodium thiophenoxide.



Series I

X = Cl, Br, I, OC₆H₄NO₂(*p*), SO₂C₆H₅



Series II

Discussion.

Tables I and II report the rate constants and activation parameters of the reaction of the various substrates with sodium thiophenoxide.

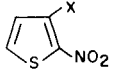

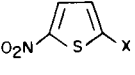
In the case of 2-iodo-3-nitrothiophene the rate constant of the thiophenoxy-deiodination reaction could not be measured. This substrate reacted differently from the other halogen-nitrothiophenes using the same reaction conditions to give a low yield of phenyl-2-(3-nitro)thienyl-sulphide. Research is in progress on the anomalous behavior of this substrate.

Table II reports the reactivity ratios k_I/k_{II} and k_{III}/k_{II} for each leaving group.

These ratios indicate that:

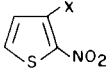

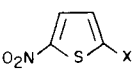
a) the reactivity of compounds of series III is always greater than that of the isomeric series II; it may also be pointed out that the reactivity ratios k_{III}/k_{II} are close

TABLE I
Rate Constants for the Reactions of
Thiophene Derivatives with Sodium Thiophenoxide

Substrate	T	X					SO ₂ -C ₆ H ₅
		OC ₆ H ₄ NO ₂ (p)	Cl	Br (a)	I		
 I	0°	—	—	—	—	11.04	
	10.00°	0.101	0.057	—	0.071	22.41	
	20.02°	0.238	0.136	0.234	0.169	43.42	
	30.00°	0.528	0.308	—	0.376	—	
 II	0°	—	—	—	—	1.07	
	10.00°	0.200	0.040	—	—	2.22	
	20.02°	0.460	0.092	0.116	—	4.40	
	30.00°	0.976	0.200	—	—	—	
 III	0°	—	—	—	—	3.59	
	10.00°	0.395	—	—	—	7.23	
	20.02°	0.826	0.126 (a)	0.136	0.088 (a)	13.90	
	30.00°	1.640	—	—	—	—	

(a) See reference (2).

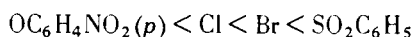
TABLE II
Activation Parameters and Reactivity Ratios at 20.02° for the Reactions
of the Thiophene Derivatives with Sodium Thiophenoxide

Substrate		X					SO ₂ -C ₆ H ₅
		O-C ₆ H ₄ -NO ₂ (p)	Cl	Br	I		
 I	k _I (a)	0.238	0.136	0.234	0.169	43.42	
	ΔH [‡] (b)	13.5	13.8	13.6	13.6	10.3	
	-ΔS [‡] (c)	15.2	15.3	14.9	15.6	15.8	
 II	k _{II} (a)	0.460	0.092	0.116	—	4.40	
	ΔH [‡] (b)	12.7	13.1	13.8	—	10.7	
	-ΔS [‡] (c)	16.6	18.3	15.8	—	19.1	
 III	k _{III} (a)	0.826	0.126	0.136	0.088	13.90	
	ΔH [‡] (b)	11.5	14.2	14.2	14.6	10.1	
	-ΔS [‡] (c)	19.4	14	13.9	13.6	18.6	
	k _I /k _{II}	0.52	1.5	2.0	—	9.9	
	k _{III} /k _{II}	1.8	1.4	1.2	—	3.2	

(a) k_I, k_{II} and k_{III} are expressed in l mol⁻¹ sec⁻¹ and point out respectively the rate constants of the reactions towards sodium thiophenoxide of the thiophene derivatives of series I, II and III. The probable error is ± 4%. (b) In kcal mol⁻¹. At 20°. The probable error is ± 0.3 kcal mol⁻¹. (c) In e.u. At 20°.

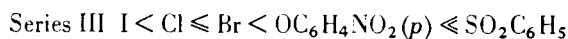
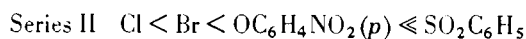
to unity and are relatively unaffected by the type of leaving group. The results indicate that the reactivity with sodium thiophenoxide is affected by variations in size and polarizability of the leaving group in both the compounds of series III (*para*-activation) and of series II (*ortho*-activation).

b) k_I/k_{II} ratios can be greater or smaller than unity depending on the type of leaving group and they vary according to the following pattern:



As can be seen, the variation of the k_I/k_{II} ratio is a function of the leaving group, and although not being very great, (the variation of k_I/k_{II} ratio is about 20 changing from $\text{OC}_6\text{H}_4\text{NO}_2(p)$ to $\text{SO}_2\text{C}_6\text{H}_5$) points out that the velocity of β - and α -displacement on the nitro-activated thiophene derivatives can be reversed depending on the group being displaced.

Data in Tables I and II show the following order of mobility of the leaving groups in each of the three series of reaction:

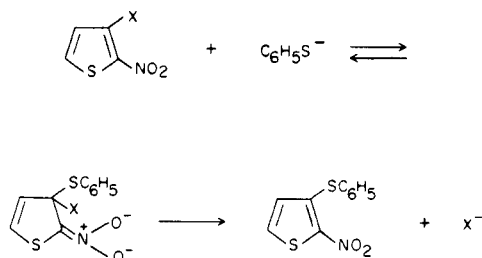


From the sequences of reactivity the following points can be noted:

1) In all three series of reactions, the $\text{SO}_2\text{C}_6\text{H}_5$ group, as found in other aromatic substrates (3), is the most easily displaced by sodium thiophenoxide.

2) Concerning the reaction mechanism of nucleophilic substitutions in series I, II and III, the examination of reactivity of compounds having as leaving groups Cl, Br, I, $\text{OC}_6\text{H}_4\text{NO}_2(p)$ is important. These groups are those used (4) to study the "element effect" in other aromatic nucleophilic substitutions.

Both order of mobility and low reactivity variation determined by the above leaving groups in the three series of reactions indicate that the nucleophilic substitutions with sodium thiophenoxide in compounds of the I, II and III series proceed with the two-step mechanism generally accepted (4) for aromatic nucleophilic substitutions in which the decomposition of the intermediate complex is not "rate-determining"; e.g. for series I:



Previous research (2,5) has shown that the most important resonance forms describing the electronic distribution of the reaction intermediate in the nucleophilic substitutions in bromonitroactivated thiophenic derivatives are those with the negative charge on the nitro group.

EXPERIMENTAL

Solvent and Reagents.

Methanol was purified by a previously described method (2).

2-Chloro-5-nitrothiophene (6), 2-bromo-5-nitrothiophene (7), 2-iodo-5-nitrothiophene (8), 2-chloro-3-nitrothiophene (6), 2-bromo-3-nitrothiophene (9), 2-iodo-3-nitrothiophene (10), 2-nitro-3-bromothiophene (11), and 2-nitro-3-iodothiophene (8), were prepared by literature methods.

The sulphides were prepared as described in a previous paper (2).

The reaction procedure kinetics were followed by spectrophotometric methods described previously (2).

Products.

The remaining compounds were prepared in the following way.

4-Nitrophenyl 2-(3-Nitro)thienyl Ether (II, X = $\text{OC}_6\text{H}_4\text{NO}_2(p)$).

A mixture of 1 g. of 2-bromo-3-nitrothiophene (1 mole) and of 0.85 g. of potassium *p*-nitrophenoxide (1 mole) was heated at 170-180° for three hours. The cooled product was washed with water, filtered and purified by means of chromatography on a silica-gel column (elution with benzene). Crystallization from benzene/light petroleum (b.p. 60-80°) gave pale yellow crystals, m.p. 102-103°.

Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{N}_2\text{O}_5\text{S}$: C, 45.11; H, 2.27; N, 10.52; S, 12.04. Found: C, 45.8; H, 2.30; N, 10.66; S, 12.10.

Phenyl 2-(3-Nitro)thienyl Sulfone (II, X = $\text{SO}_2\text{C}_6\text{H}_5$).

This compound was prepared by peracetic acid oxidation of phenyl 2-(3-nitro)thienyl sulphide (2). The product, obtained after refluxing the mixture for one-half hour and dilution with water, was colorless and had a melting point of 132-133° after crystallization from alcohol.

Anal. Calcd. for $\text{C}_{10}\text{H}_7\text{NO}_4\text{S}_2$: C, 44.60; H, 2.62; N, 5.20; S, 23.81. Found: C, 44.50; H, 2.59; N, 5.23; S, 23.83.

2-Nitro-3-chlorothiophene (in I, X = Cl).

This compound was prepared from 2-nitro-3-aminothiophene (12) by the Sandmeyer reaction. The brown oil obtained from ether extraction of the mixture followed by evaporation of the solvent itself, was purified by chromatography on a silica gel column (elution with 1:5 (v/v) benzene/light petroleum (b.p. 60-80°) and crystallization from light petroleum (b.p. 30-60°) gave colorless needles, m.p. 59-60°.

Anal. Calcd. for $\text{C}_4\text{H}_2\text{ClNO}_2\text{S}$: C, 29.37; H, 1.23; Cl, 21.71; N, 8.56; S, 19.60. Found: C, 29.40; H, 1.21; Cl, 21.93; N, 8.56; S, 19.60.

4-Nitrophenyl-3-(2-Nitro)thienyl Ether (in I, X = $\text{OC}_6\text{H}_4\text{NO}_2(p)$).

This compound was prepared from 2-nitro-3-bromothiophene and potassium *p*-nitrophenoxide using the same conditions as for II, X = $\text{OC}_6\text{H}_4\text{NO}_2(p)$. The cooled product was purified by chromatography on a silica gel column (elution with benzene) and crystallized from benzene/light petroleum (b.p. 60-80°), m.p. 132-133°.

Anal. Calcd. for $C_{10}H_6N_2O_5S$: C, 45.11; H, 2.27; N, 10.52; S, 12.04. Found: C, 45.15; H, 2.29; N, 10.68; S, 12.20.

Phenyl 3-(2-Nitro)thienyl Sulfone (I, $X = SO_2C_6H_5$).

This compound was obtained by peracetic oxidation of phenyl 3-(2-nitro)thienyl sulphide (2) under the same conditions used for II, $X = SO_2C_6H_5$ to give a colorless product, m.p. 143° , after crystallization from ethanol.

Anal. Calcd. for $C_{10}H_7NO_4S_2$: C, 44.60; H, 2.62; N, 5.20; S, 23.81. Found: C, 44.58; H, 2.65; N, 5.28; S, 23.45.

4-Nitrophenyl 2-(5-Nitro)thienyl Ether (III, $X = OC_6H_4NO_2(p)$).

This compound was prepared from 2-bromo-5-nitrothiophene and potassium *p*-nitrophenoxide under the same conditions used for II, $X = OC_6H_4NO_2(p)$. The brown oil was washed with water, filtered, chromatographed on a silica gel column (elution with 10:1 (v/v) benzene/light petroleum b.p. $30-60^\circ$) and crystallized from light petroleum (b.p. $80-100^\circ$): a colorless compound, m.p. $101-102^\circ$ was obtained.

Anal. Calcd. for $C_{10}H_6N_2O_5S$: C, 45.11; H, 2.27; N, 10.52; S, 12.04. Found: C, 45.18; H, 2.30; N, 10.70; S, 11.69.

Phenyl 2-(5-Nitro)thienyl Sulfone (III, $X = SO_2C_6H_5$).

This compound was prepared by peracetic acid oxidation of phenyl 2-(5-nitro)thienyl sulphide (2) under the same conditions used for II, $X = SO_2C_6H_5$. The solid obtained after dilution of the reaction mixture with water was crystallized from light petroleum (b.p. $80-100^\circ$), m.p. $99-100^\circ$.

Anal. Calcd. for $C_{10}H_7NO_4S_2$: C, 44.60; H, 2.62; N, 5.20; S, 23.81. Found: C, 44.68; H, 2.65; N, 5.15; S, 23.19.

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