

Analysis of substituent effects: the reactions of some 2-L-5-nitro-3-X-thiophenes with primary and secondary amines in methanol

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Received (in Cambridge, UK) 18th December 2001, Accepted 7th March 2002

First published as an Advance Article on the web 4th April 2002

The kinetics of the reactions of some 2-L-5-nitro-3-X-thiophenes with primary and secondary amines in methanol at various temperatures have been studied with the aim of obtaining information about the proximity effects of 3-X *ortho*-like substituents. The results obtained have shown that for all the substituents considered, except for X = Br, the proximity effects of steric nature are of little relevance with respect to the electronic ones. Thus, it has been possible to establish a set of *ortho* sigma constants which account well for the electronic effects of 3-X substituents and to obtain excellent linear free energy *ortho*-correlations.

Introduction

After the authoritative review and book published by J. F. Bunnett¹ and J. Miller,² respectively, many papers and reviews concerning the field of nucleophilic aromatic substitutions (S_N-Ar) have been published. Among these, it is worthwhile mentioning the outstanding reviews written by C. F. Bernasconi³ and F. Terrier.⁴

The subject of S_N-Ar reactions continues to attract the interest of many research workers. For example, some recent work has been dealing with the regioselectivity in polynitroarene anionic σ-adduct formation,⁵ with the first isolation of a π-complex precursor in Meisenheimer complex formation, and with base catalysis in aromatic nucleophilic substitutions.⁶

Compared with the overwhelming quantity of papers concerning the application of the Hammett equation to benzene compounds, after the review published by Tomasik and Johnson⁷ the corresponding studies on heterocyclic compounds have received less and only occasional attention.

In this and in the following paper⁸ we report a kinetic study of the reactions of some 2-L-5-nitro-3-X-thiophenes 1–3 with some primary and secondary amines in methanol and in benzene (Scheme 1).

This study was aimed at obtaining information about the overall effect of *ortho*-like substituents in S_N-Ar reactions of thiophene substrates and at exploring the possibility of carrying out linear free energy *ortho*-correlations.

The substrates used present an activating nitro group fixed at

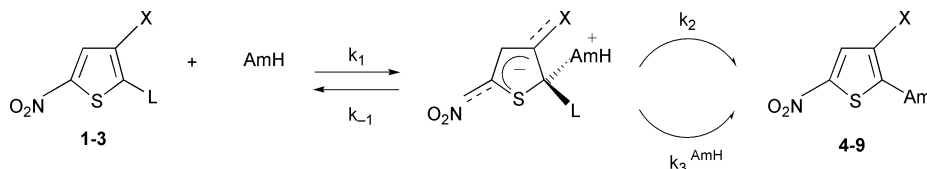
C-5 and a variable substituent at C-3, that is, at an *ortho*-like position with respect to the reaction centre at C-2.

The 3-substituents chosen are: i) hydrogen (X = H) as a landmark, even though the corresponding substrate has to be considered as just being "not substituted"; ii) methyl and bromine, two "*ortho*"-substituents with a similar van der Waals' encumbrance⁹ but very different firmness and solidity; iii) some sp² groups (X = CONH₂, CO₂Me, COMe) with the same geometry around the carbonyl carbon atom but with different "external" and "internal" conjugative interactions and different steric encumbrance; iv) methylsulfonyl substituent (X = SO₂Me), a group with electronic effects comparable¹⁰ to those of the acetyl group (X = COMe) but with a tetrahedral geometry much more "compressive" with respect to the adjacent reaction centre; v) the cyano group (X = CN), a strong electron-withdrawing substituent with a "linear" geometry; and finally vi) the nitro group (X = NO₂), with a nearly "planar" geometry.¹¹

The presence of a substituent in an "*ortho*" position with respect to the reaction centre can influence the reaction pathway as a function of three main factors:

a) the activation degree of the substrate; b) the primary¹² and secondary¹³ kinetic steric effects as a function of the features of nucleophile and nucleofuge; c) the eventual anchimeric assistance¹⁴ in the intermediate decomposition as a function of nucleophile, nucleofuge and the solvent.

The nucleophiles chosen for this study are three secondary cyclic amines, pyrrolidine (PYRH), piperidine (PIPH) and



AmH = pyrrolidine (PYRH), piperidine (PIPH), morpholine (MORH), *N*-benzylmethylamine (BMAH), *n*-butylamine (BuAH), benzylamine (BzAH)

1: L = Br, 2: L = OC₆H₅, 3: L = OC₆H₄NO_{2-p}

a: X = CH₃, b: X = H, c: X = Br, d: X = CONH₂, e: X = CO₂CH₃, f: X = COCH₃, g: X = SO₂CH₃, h: X = CN, i: X = NO₂

4: Am = PYR, 5: Am = PIP, 6: Am = MORF, 7: Am = BMA, 8: Am = BuA, 9: Am = BzA

Scheme 1

morpholine (MORH) for which different structural and conformational peculiarities are expected,¹⁵ two primary amines, *n*-butylamine (BuAH) and benzylamine (BzAH); and an acyclic secondary amine, *N*-benzylmethylamine (BMAH), which together with benzylamine forms a homogeneous secondary-primary pair.

The leaving groups or nucleofuges chosen are bromine, classically considered as a “good” leaving group¹⁶ and phenoxy and *p*-nitrophenoxy groups, a homogeneous pair of nucleofuges possessing a different leaving group ability in connection with a different intrinsic basicity. The two oxygenated groups are traditionally considered¹⁷ “poor” leaving groups in S_NAr reactions and, therefore, in the reactions of such substrates with neutral nucleophiles, especially with amines of low basicity, it is likely that base catalysis would be observed.⁶

The solvents used are methanol and benzene. The first one is a polar, protic, ionizing solvent, able to favour the decomposition of the zwitterionic intermediate. It has been chosen, indeed, to exclude any possible incidence of eventual catalytic phenomena and to confine the mechanistic observations to the first part of the reaction pathway, that is, where the first transition state is formed.⁴

In contrast, benzene is an aprotic, apolar and scarcely polarizable solvent, which represents an “ideal” medium to promote the “need” for base catalysis for the intermediate decomposition.^{6,15,17,18} In this paper we will deal with the reactions of compounds 1–3 (L = Br, OC₆H₅ and OC₆H₄NO₂-*p*) with amines in methanol and we will show that it is possible to obtain sets of substituent constants for *ortho*-like substituents which account well for the behaviour of the various series of substituted compounds, as a function of the nucleofuge.

In the following paper, we report on the results of an analogous study applied to the substrates with bromine as leaving group, in benzene solvent. By applying the same procedure as for the reactions in methanol, it will be shown that also in benzene there is the possibility of obtaining linear free energy *ortho*-correlations. *Inter alia*, the method used allows one to estimate k_1 values for the apparently base-catalysed systems.

Results and discussion

Reactions of 2-bromo-3-X-5-nitrothiophenes with primary and secondary amines in methanol

Rate constants and activation parameters for the title reactions are reported in Table 1. All the reactions proved to be first order both in substrate and in nucleophile; therefore, they follow the universally accepted attachment-detachment mechanism¹ with the overall reaction rate determined by the rate of formation of the reaction intermediate ($k_A = k_1$).

When the logarithms of relative kinetic constants [$\log(k_X/k_H)$] for the reactions of 2-bromo-3-X-5-nitrothiophenes with a given amine are plotted against σ_p^- substituent constants¹⁹ (Table 2) statistically significant linear *ortho*-correlations are obtained (Table 3, columns 2–5), provided that the data relative to X = SO₂Me are excluded from the calculations. In fact, it is well known that the σ_p^- constant for the methylsulfonyl substituent does not describe adequately the behaviour of this substituent in the thiophene series.²⁰

The confidence level of each single correlation is more than acceptable,²¹ bearing in mind that the σ_p^- constants used, obtained for *para*-like substituents¹⁹ could be rather inadequate to describe correctly the behaviour of *ortho*-like substituents. In order to improve the correlations and to obtain a set of σ constants more “adherent” to the heteroaromatic system considered, we have utilized Brown’s method, that is, the so-called “Extended Selectivity Treatment (EST)”²²

Thus, by plotting the $\log(k_X/k_H)$ values for a given X substituent and for the six reactions studied against the ρ values of “first approximation”, calculated as above, and by including in the correlations the point (0, 0), one obtains the “secondary”

($\sigma_{X,Br}$)_M values reported in Table 2, second line. In order to obtain a range of sigma values “homogeneous” with that of the σ_p^- substituent constant, these ($\sigma_{X,Br}$)_M parameters have been “anchored” to $\sigma_{NO_2^-} = 1.23$, as derived from the acidity constant of *p*-nitroanilinium ion¹⁹ and the resulting parameters have been reported in Table 2 as ($\sigma_{o,T}$)_{Br}.

The correlations of $\log(k_X/k_H)$ values with ($\sigma_{o,T}$)_{Br} constants for each amine nucleophile afford the new values ρ reported in Table 3, column 6, and this time the quality of correlations is more than satisfactory. This is not a trivial result in that the necessary condition to obtain good cross-correlations of this kind is that the proximity effects of the various substituents do not change significantly with changing nucleophile and, inversely, the success of such correlations represents important evidence that this is, at least as a first approximation, the case.

Among the amines studied *N*-benzylmethylamine is the one which in theory should show the greatest difficulty in forming the bond with the C-2 carbon atom, *i.e.*, the reaction centre, and indeed the worst correlation pertains to this amine (Table 3).

A comparison of ($\sigma_{o,T}$)_{Br} constants, obtained by the simultaneous use of the data relative to the six reactions series with the corresponding thiophene substituent constants optimized for *para*-like substituents [($\sigma_{p,T}$)_{Br}, Table 2]²³ allows one to claim that for all the substituents studied, except for X = Br, the proximity effects of steric nature are of little relevance with respect to the electronic ones.

This result is quite surprising, if one considers the behaviour of analogous benzene systems,⁴ and depends on the favourable geometry²⁴ of the thiophene ring which allows an extremely good arrangement of substituents by which the steric effects are minimized.

The “*ortho*” substituent which displays the greatest difference ($\sigma_{p,T} - \sigma_{o,T}$) is, as expected, bromine which is unfavoured by its steric encumbrance and altogether by its incapacity to form the hydrogen bonding of the “built-in” solvation.¹⁴ On account of this latter factor, the *ortho*-substituent CN also turns out rather disadvantaged.

Reaction of 2-phenoxy- and 2-*p*-nitrophenoxy-3-X-5-nitrothiophenes with primary and secondary amines in methanol

Rate constants and activation parameters for the title reactions are reported, respectively in Tables 4 and 5. All the reactions are second order overall, *i.e.*, first order in substrate and first order in nucleophile.

When the logarithms of relative kinetic constants [$\log(k_X/k_H)$] for the reactions of either 2-phenoxy-3-X-5-nitrothiophenes or 2-*p*-nitrophenoxy-3-X-5-nitrothiophenes with a given amine are plotted against σ_p^- substituent constants (Table 2) statistically significant linear *ortho*-correlations are obtained (Tables 6 and 7, columns 2–5) provided that the data relative to X = SO₂Me are excluded from the calculations (*cf.* above for L = Br).

The confidence level of each single correlation is good;²¹ however, it is possible to better the correlations by the method used above for the reactions involving bromine as leaving group.

Thus, by plotting the [$\log(k_X/k_H)$] values for a given X substituent and for the six or five reactions studied against the “first approximation” ρ values and by including in the correlations the point (0, 0) one obtains the “secondary” (σ_{X,OC_6H_5})_M and ($\sigma_{X,OC_6H_4NO_2-p}$)_M values reported in Table 2, lines 5 and 6. The substituent constants obtained by anchoring (σ_{X,OC_6H_5})_M and ($\sigma_{X,OC_6H_4NO_2-p}$)_M to $\sigma_{NO_2^-} = 1.23$ are reported in Table 2 under ($\sigma_{o,T}$)_{OC₆H₅} and ($\sigma_{o,T}$)_{OC₆H₄NO_{2-p}}, respectively.

The correlations of $\log(k_X/k_H)$ for the two leaving groups with ($\sigma_{o,T}$)_{OC₆H₅} and ($\sigma_{o,T}$)_{OC₆H₄NO_{2-p}}, respectively, give the new ρ values reported in Tables 6 and 7, columns 6–9.

Also in these cases, the success of correlations represents important evidence that the proximity effects do not change significantly with changing nucleophile.

Table 1 Logarithmic kinetic constants and activation parameters^a for the reaction of 2-bromo-3-X-5-nitrothiophenes **1** with primary and secondary amines in methanol

X	PYRH	PIPH	MORH	BMAH	BuAH	BzAH
Me	-4.9843 14.4; -32	-5.3671 13.6; -36	-6.0307 14.6; -36	-6.2284 13.9; -39	-6.9965 16.3; -35	-7.3496 17.9; -31
H	-4.5881 14.8; -29	-4.7925 15.3; -28	-5.3583 15.3; -31	-5.5055 14.8; -33	-6.4411 15.0; -37	-6.7065 16.1; -34
Br	-3.7309 12.1; -34	-4.1126 13.5; -31	-4.7620 14.0; -32	-5.1207 12.9; -38	-5.6271 15.1; -33	-5.9603 16.4; -30
CONH ₂	-2.1550 11.9; -28	-2.5555 12.4; -28	-3.1850 13.7; -26	-3.2579 11.1; -36	-3.9024 13.2; -31	-4.2019 13.4; -32
CO ₂ Me	-1.6940 10.4; -31	-2.0350 12.1; -27	-2.6049 11.2; -32	-3.1552 11.2; -35	-3.5086 12.3; -32	-3.7692 12.1; -34
COMe	-1.1780 11.0; -26	-1.4445 10.8; -28			-2.9244 11.3; -33	-3.2670 13.2; -28
SO ₂ Me	-1.0589 10.5; -27	-1.3665 11.4; -26	-2.0341 11.4; -29	-2.2803 10.2; -34	-2.7549 13.0; -27	-3.1148 13.3; -27
CN	-1.2961 10.9; -27	-1.3900 10.4; -29	-2.1462 11.6; -29	-2.3704 10.3; -34	-3.1026 12.9; -29	-3.4160 14.1; -26
NO ₂	0.6345 ^b	0.2979 10.7; -21	-0.3036 8.5; -31	-0.5203 9.2; -30	-1.2721 11.4; -25	-1.5229 10.9; -28

^a For each couple X-amine the number on the first line represents log *k* calculated at 20 °C from activation parameters; the numbers on the second line are, respectively, $\Delta H^\ddagger/\text{kcal mol}^{-1}$ at 20 °C, and $\Delta S^\ddagger/\text{cal mol}^{-1} \text{K}^{-1}$ at 20 °C. The kinetic constants, *k*/l mol⁻¹ s⁻¹, measured in the range 0–40 °C, were reproducible to within $\pm 3\%$; the maximum error of ΔH^\ddagger is $\pm 0.5 \text{ kcal mol}^{-1}$; the maximum error of ΔS^\ddagger is $\pm 2 \text{ cal mol}^{-1} \text{K}^{-1}$. ^b Value directly measured at 20 °C.

Table 2 Substituent constants

	Me	H	Br	CONH ₂	CO ₂ Me	COMe	SO ₂ Me	CN	NO ₂
σ_p^{-a}	-0.10	0.00	0.30	0.62	0.74	0.82	1.05	0.99	1.23
$(\sigma_{X,\text{Br}})_M$	-0.15	0.00	0.17	0.58	0.69	0.84	0.86	0.81	1.26
$(\sigma_{o,\text{T}})_{\text{Br}}$	-0.15	0.00	0.17	0.57	0.68	0.82	0.84	0.79	1.23
$(\sigma_{p,\text{T}})_{\text{Br}}$		0.00	0.35	0.51	0.65	0.80	0.83	0.87	1.23
$(\sigma_{X,\text{OC}_6\text{H}_5})_M$		0.00		0.48	0.68	0.71	0.76	0.76	1.34
$(\sigma_{X,\text{OC}_6\text{H}_4\text{NO}_2\text{-}p})_M$		0.00		0.61	0.76	0.81	0.76	0.84	1.31
$(\sigma_{o,\text{T}})_{\text{OC}_6\text{H}_5}$		0.00		0.44	0.62	0.65	0.70	0.70	1.23
$(\sigma_{o,\text{T}})_{\text{OC}_6\text{H}_4\text{NO}_2\text{-}p}$		0.00		0.57	0.71	0.76	0.71	0.79	1.23

^a Ref. 21.

Table 3 Susceptibility constants and other statistical data^a for the reactions of 2-bromo-3-X-5-nitrothiophenes **1** with amines in methanol

Amine	ρ^b	<i>i</i>	<i>r</i>	<i>n</i>	ρ^c	<i>i</i>	<i>r</i>	<i>n</i> ^d
PYRH	4.03	-0.10	0.989	8	4.09	0.12	0.999	9
PIPH	4.07	-0.22	0.991	8	4.12	0.00	0.999	9
MORH	4.01	-0.29	0.990	7	4.11	-0.07	0.999	8
BMAH	3.96	-0.37	0.983	7	4.08	-0.15	0.997	8
BuAH	4.12	-0.15	0.990	8	4.21	0.07	0.999	9
BzAH	4.14	-0.20	0.988	8	4.22	0.02	0.999	9

^a ρ , reaction constant; *i*, intercept of the regression line with the ordinate ($\sigma = 0$); *r*, correlation coefficient; *n*, number of data points. ^b Values obtained by using σ_p^- constants (Table 2). ^c Values obtained by using $(\sigma_{o,\text{T}})_{\text{Br}}$ constants (Table 2). ^d Data for X = SO₂CH₃ included throughout.

Conclusions

When the X substituent is the same, the reactivity order observed is invariably PYRH > PIPH > MORH > BMAH > BuAH > BzAH. The greater nucleophilicity of secondary with respect to primary amines can be attributed to the favourable interactions ion-induced dipole in the reaction intermediate, between the positively charged 'ammonium' nitrogen and the polarizable alkyl chains bonded to it and for each of the two classes of amines reflects, at least partially, the differences in basicity.²⁵

It is worth noting the inversion in reactivity with respect to the basicity order, in the pair morpholine-*N*-methylbenzylamine. As a matter of fact in the formation of the aromatic carbon atom-nucleophilic nitrogen bond, BMAH is sterically more hindered than MORH, and although more basic,²⁵ turns out less reactive.

The close resemblance of the "optimized" sigma constants for the substituents CO₂Me, COMe, SO₂Me and CN arises from the fact that the reactivity sequence for these substituents, as determined by the nucleophile, present some overlap.

In fact, each reactivity sequence comes out from the different proximity interactions which occur in the reaction area as a function of the position of the rate determining transition state along the reaction coordinate.

For example, in the reactions of phenoxy derivatives (Y = H) with pyrrolidine and piperidine, which are likely to imply early transition states¹⁰ and where the prevailing extraconjugative relationship occurs between the reaction centre and the nitro group at C-5,¹⁰ the two substituents CO₂Me and COMe behave as if they possessed only inductive effects and thus turn out practically "equivalent" as regards the electronic effects.

Table 4 Logarithmic kinetic constants and activation parameters^a for the reaction of 2-phenoxy-3-X-5-nitrothiophenes **2** with primary and secondary amines in methanol

X	PYRH	PIPH	MORH	BMAH	BuAH	BzAH
H	-3.5855 13.3; -30	-3.7083 13.1; -31	-4.2737 13.1; -33	-4.4428 12.1; -38	-5.3946 13.9; -36	-5.6707 13.9; -37
CONH ₂	-2.1231 12.2; -27	-2.3573 11.7; -29	-2.7826 11.1; -33	-2.9907 12.1; -31	-3.6354 13.1; -30	-3.9651 13.2; -32
CO ₂ Me	-1.3777 11.2; -26	-1.6364 10.4; -30	-2.2306 10.4; -33	-2.3788 10.7; -33	-3.0259 12.9; -28	-3.2146 12.7; -30
COMe	-1.5046 11.3; -27	-1.7119 11.1; -28	-2.0353 10.4; -32	-2.0520 10.5; -32	-2.8478 12.7; -28	-3.1090 12.0; -32
SO ₂ Me	-1.1807 9.7; -31	-1.6665 8.4; -37	-2.1503 9.7; -35	-2.2109 9.9; -35	-2.4982 12.9; -26	-2.8569 12.2; -30
CN	-1.0604 11.2; -25	-1.2183 9.2; -33	-1.1915 9.6; -34	-2.1547 10.1; -34	-2.7592 12.4; -29	-2.9802 12.0; -31
NO ₂	0.6313 8.2; -28	0.2612 10.6; -21	0.0817 9.9; -24	-0.0345 9.9; -25	-0.8028 11.4; -23	-1.0317 11.4; -24

^a For each couple X-amine the number on the first line represents log *k* calculated at 20 °C from activation parameters; the numbers on the second line are, respectively, $\Delta H^\ddagger/\text{kcal mol}^{-1}$ at 20 °C, and $\Delta S^\ddagger/\text{cal mol}^{-1} \text{K}^{-1}$ at 20 °C. The kinetic constants, *k*/l mol⁻¹ s⁻¹, measured in the range 0–40 °C were reproducible to within ± 3%; the maximum error of ΔH^\ddagger is ± 0.5 kcal mol⁻¹; the maximum error of ΔS^\ddagger is ± 2 cal mol⁻¹ K⁻¹.

Table 5 Logarithmic kinetic constants and activation parameters^a for the reaction of 2-*p*-nitrophenoxy-3-X-5-nitrothiophenes **3** with primary and secondary amines in methanol

X	PIPH	MORH	BMAH	BuAH	BzAH
H	-3.3822 12.9; -30	-4.0439 12.6; -34	-4.3741 11.3; -40	-5.1248 14.0; -34	-5.2701 13.9; -35
CONH ₂	-1.3773 9.7; -32	-1.9038 11.4; -28	-2.0157 9.4; -36	-2.9201 12.2; -30	-3.2410 13.5; -27
CO ₂ Me	-0.7711 7.5; -37	-1.4453 10.8; -28	-1.5858 6.7; -43	-2.3000 12.0; -28	-2.5428 15.5; -17
COMe	-0.5866 8.7; -32	-1.2484 10.1; -30	-1.3889 7.7; -39	-2.1768 11.7; -28	-2.4113 14.1; -21
SO ₂ Me	-0.8396 5.4; -44	-1.6812 10.2; -31	-1.8059 7.0; -43	-2.0077 12.0; -27	-2.2207 11.2; -31
CN	-0.2916 9.5; -27	-1.0972 9.4; -31	-1.2299 8.3; -36	-2.2432 15.7; -15	-2.4717 14.1; -22
NO ₂	1.1926 8.9; -23	0.6078 9.3; -24	0.5142 6.4; -34	-0.6676 13.6; -15	-0.8150 13.2; -17

^a For each couple X-amine the number on the first line represents log *k* calculated at 20 °C from activation parameters; the numbers on the second line are, respectively, $\Delta H^\ddagger/\text{kcal mol}^{-1}$ at 20 °C, and $\Delta S^\ddagger/\text{cal mol}^{-1} \text{K}^{-1}$ at 20 °C. The kinetic constants, *k*/l mol⁻¹ s⁻¹, measured in the range 0–40 °C were reproducible to within ± 3%; the maximum error of ΔH^\ddagger is ± 0.5 kcal mol⁻¹; the maximum error of ΔS^\ddagger is ± 2 cal mol⁻¹ K⁻¹.

Table 6 Susceptibility constants and other statistical data^a for the reactions of 2-phenoxy-3-X-5-nitrothiophenes **2** with amines in methanol

Amine	ρ^b	<i>i</i>	<i>r</i>	<i>n</i>	ρ^c	<i>i</i>	<i>r</i>	<i>n</i> ^d
PYRH	3.18	-0.25	0.964	6	3.44	-0.01	0.998	7
PIPH	3.04	-0.25	0.970	6	3.24	0.02	0.993	7
MORH	3.22	-0.28	0.953	6	3.51	-0.09	0.996	7
BMAH	3.25	-0.29	0.947	6	3.56	-0.09	0.995	7
BuAH	3.44	-0.21	0.967	6	3.74	0.08	0.997	7
BzAH	3.49	-0.22	0.967	6	3.79	0.06	0.999	7

^a ρ , reaction constant; *i*, intercept of the regression line with the ordinate ($\sigma = 0$); *r*, correlation coefficient; *n*, number of data points. ^b Values obtained by using σ_p^- constants (Table 2). ^c Values obtained by using $(\sigma_{o,T})_{\text{OC,H}}$ constants (Table 2). ^d Data for X = SO₂CH₃ included throughout.

Table 7 Susceptibility constants and other statistical data^a for the reactions of 2-*p*-nitrophenoxy-3-X-5-nitrothiophenes **3** with amines in methanol

Amine	ρ^b	<i>i</i>	<i>r</i>	<i>n</i>	ρ^c	<i>i</i>	<i>r</i>	<i>n</i> ^d
PIPH	3.56	-0.10	0.990	6	3.75	-0.04	0.998	7
MORH	3.51	-0.04	0.988	6	3.76	-0.06	0.997	7
BMAH	3.73	-0.04	0.984	6	3.95	-0.01	0.997	7
BuAH	3.42	-0.04	0.980	6	3.65	0.14	0.989	7
BzAH	3.41	-0.02	0.978	6	3.65	0.07	0.990	7

^a ρ , reaction constant; *i*, intercept of the regression line with the ordinate ($\sigma = 0$); *r*, correlation coefficient; *n*, number of data points. ^b Values obtained by using σ_p^- constants (Table 2). ^c Values obtained by using $(\sigma_{o,T})_{\text{OC,H,NO}_2-p}$ constants (Table 2). ^d Data for X = SO₂CH₃ included throughout.

Moreover, since COMe is slightly disfavoured from a steric point of view, the sequence CO₂Me > COMe ($k_{\text{CO}_2\text{Me}}/k_{\text{COMe}}$ 1.2–1.3) is observed.

As the nucleophilicity of the amine decreases, the transition state becomes later and later,²⁶ the “competition” of the 3-X substituent with the 5-nitro group acquires some relevance

Table 8 Characterisation data for compounds **2f**, **2g**, **2h**, **6**, **7**, **8** and **9**

	δ (DMSO- d_6 , 300 MHz)	HRMS Calculated/found	Calculated/found		
			% C	% H	% N
2f	8.23 (H-4); 7.65–7.47 (Ar-H) ^b ; 2.59 (COCH ₃)	263.025357/263.025230	57.74/57.60	3.44/3.60	5.32/5.25
2g	8.15 (H-4); 7.66–3.48 (CH ₂ O) ^b ; 3.44 (SO ₂ CH ₃)	298.992744/298.992216	44.14/44.30	3.03/3.20	4.68/4.55
2h	8.62 (H-4); 7.65–7.48 (Ar-H) ^b	246.010229/246.009914	53.65/53.40	2.46/2.30	11.38/11.50
6a	7.90 (H-4); 3.76–3.72 (CH ₂ O) ^b ; 3.23–3.21 (CH ₂ N) ^b ; 2.14 (CH ₃)	228.056977/228.056864	47.36/47.50	5.30/5.20	12.27/12.50
6b	7.93 (H-4) ^a ; 6.37 (H-3) ^a ; 3.75–3.70 (CH ₂ O) ^b ; 3.46–3.40 (CH ₂ N) ^b	214.041411/214.041214	44.85/45.00	4.70/4.80	13.08/12.90
6c	7.95 (H-4); 3.75–3.71 (CH ₂ O) ^b ; 3.48–3.40 (CH ₂ N) ^b	291.951725/291.951695	32.78/32.90	3.09/3.15	9.56/9.45
6d	8.14 (H-4); 7.87 (NH ₂); 7.42 (NH ₂); 3.75–3.71 (CH ₂ O) ^b ; 3.42–3.38 (CH ₂ N) ^b	257.047275/257.047028	42.02/42.20	4.31/4.50	16.33/16.20
6e	8.11 (H-4); 3.78–3.31 (CH ₂ O, CO ₂ CH ₃) ^b ; 3.49–3.44 (CH ₂ N) ^b	272.046838/272.046693	44.11/44.00	4.44/4.20	10.29/10.30
6g	8.17 (H-4); 3.79–3.75 (CH ₂ O) ^b ; 3.57–3.54 (CH ₂ N) ^b ; 3.38 (SO ₂ CH ₃)	292.018899/292.018765	36.98/37.10	4.14/4.20	9.58/9.70
6h	8.37 (H-4); 3.78–3.75 (CH ₂ O) ^b ; 3.73–3.68 (CH ₂ N) ^b	239.036615/239.036463	45.18/45.30	3.79/4.00	17.56/17.40
6i	8.38 (H-4); 3.80–3.78 (CH ₂ O) ^b ; 3.55–3.50 (CH ₂ N) ^b	259.026473/259.026292	37.07/37.20	3.50/3.40	16.21/16.40
7a	7.90 (H-4); 7.40–7.27 (Ar-H) ^b ; 4.76 (CH ₂); 3.16 (N-CH ₃); 2.18 (CH ₃)	262.077600/262.078200	59.52/59.65	5.38/5.30	10.68/10.45
7b	7.90 (H-4) ^a ; 7.38–7.27 (Ar-H) ^b ; 6.28 (H-3) ^a ; 4.74 (CH ₂); 3.19 (CH ₃)	248.061950/248.062161	58.05/58.20	4.87/5.00	11.28/11.20
7c	7.92 (H-4); 7.42–7.28 (Ar-H) ^b ; 4.75 (CH ₂); 3.13 (CH ₃)	325.972461/325.972885	44.05/44.25	3.39/3.45	8.56/8.45
7d	8.04 (H-4); 7.93 (NH ₂); 7.42–7.25 (Ar-H, NH ₂) ^b ; 4.79 (CH ₂); 3.13 (CH ₃)	291.067763/291.067893	53.60/53.50	4.50/4.60	14.42/14.60
7e	8.07 (H-4); 7.38–7.24 (Ar-H) ^b ; 4.83 (CH ₂); 3.72 (CO ₂ CH ₃); 3.15 (CH ₃)	306.067429/306.067742	54.89/54.80	4.61/4.60	9.14/9.10
7f	8.40 (H-4); 7.37–7.20 (Ar-H) ^b ; 4.78 (CH ₂); 3.11 (CH ₃); 2.43 (COCH ₃)	290.072514/290.072688	57.92/58.00	4.86/4.80	9.65/9.70
7g	8.15 (H-4); 7.40–7.29 (Ar-H) ^b ; 4.92 (CH ₂); 3.40 (SO ₂ CH ₃); 3.28 (CH ₃)	326.039501/326.039865	47.84/48.00	4.32/4.40	8.58/8.50
7h	8.36 (H-4); 7.42–7.30 (Ar-H) ^b ; 4.95 (CH ₂); 3.40 (CH ₃)	273.057199/273.057334	57.13/57.40	4.06/4.00	15.37/15.30
8a	8.75 (NH); 7.75 (H-4); 3.20–3.10 (CH ₂ -1) ^b ; 2.31 (CH ₃); 1.68–1.62 (CH ₂ -2) ^b ; 1.40–1.30 (CH ₂ -3) ^b ; 0.90 (CH ₃)	214.077600/214.077320	50.45/50.60	6.59/6.50	13.07/13.15
8b	8.80 (NH); 7.81 (H-4) ^a ; 6.07 (H-3) ^a ; 3.22–3.15 (CH ₂ -1) ^b ; 1.60–1.50 (CH ₂ -2) ^b ; 1.40–1.30 (CH ₂ -3) ^b ; 0.90 (CH ₃)	200.061950/200.062068	47.98/48.10	4.32/4.30	8.58/8.50
8c	8.70 (NH); 7.90 (H-4); 3.22–3.12 (CH ₂ -1) ^b ; 2.31 (CH ₃); 1.70–1.60 (CH ₂ -2) ^b ; 1.42–1.36 (CH ₂ -3) ^b ; 0.90 (CH ₃)	277.972461/277.972642	34.42/34.50	3.97/3.90	10.03/10.10
8f	8.50 (NH); 8.05 (H-4); 3.20–3.12 (CH ₂ -1) ^b ; 2.45 (COCH ₃); 1.72–1.60 (CH ₂ -2) ^b ; 1.40–1.36 (CH ₂ -3) ^b ; 0.92 (CH ₃)	242.072514/242.072805	49.57/49.69	5.82/5.95	11.56/12.10
8g	8.45 (NH); 8.02 (H-4); 3.30–3.20 (SO ₂ CH ₃ , CH ₂ -1) ^b ; 1.66–1.55 (CH ₂ -2); 1.39–1.28 (CH ₂ -3) ^b ; 0.90 (CH ₃)	278.039501/278.039641	38.84/38.90	5.07/5.00	10.06/10.10
8h	9.55 (NH); 8.30 (H-4); 3.31–3.23 (CH ₂ -1) ^b ; 1.61–1.57 (CH ₂ -2); 1.35–1.28 (CH ₂ -3) ^b ; 0.89 (CH ₃)	225.057199/225.057455	47.99/48.10	4.92/5.00	18.65/18.50
9a	9.18 (NH); 7.90 (H-4); 7.38–7.30 (Ar-H) ^b ; 4.48 (CH ₂); 2.25 (CH ₃)	248.061950/248.062080	58.05/58.25	4.87/5.05	11.28/11.20
9b	9.22 (NH); 7.84 (H-4) ^b ; 7.42–7.38 (Ar-H); 6.13 (H-3) ^b ; 4.45 (CH ₂)	234.046299/234.046379	56.40/56.50	4.30/4.20	11.96/12.10
9c	9.43 (NH); 7.92 (H-4); 7.39–7.30 (Ar-H) ^b ; 4.46 (CH ₂)	311.956811/311.956555	42.18/42.45	2.90/2.95	8.94/8.90
9f	10.3 (NH); 8.40 (H-4); 7.38 (Ar-H); 4.60 (CH ₂); 2.46 (COCH ₃)	276.056864/276.057045	56.51/56.40	4.38/4.50	10.14/10.20
9g	9.95 (NH); 8.25 (H-4); 7.45–7.38 (Ar-H) ^b ; 4.60 (CH ₂); 3.42 (SO ₂ CH ₃)	312.023851/312.023678	46.14/46.50	3.87/5.60	8.97/8.90
9h	10.1 (NH); 8.05 (H-4); 7.48–7.42 (Ar-H) ^b ; 4.65 (CH ₂)	271.041548/271.041705	57.55/57.50	3.34/3.30	15.49/15.30

^a Double peak. ^b Multiplet.

and the COMe group thus becomes more efficient than CO₂Me ($k_{\text{CO}_2\text{Me}}/k_{\text{COMe}}$ 0.6–0.8) in stabilizing the reaction intermediate.

The methylsulfonyl group normally shows a set of electronic effects^{10,19} comparable with that of the acetyl group but at the same time displays a less favourable geometry for the formation of the hydrogen bonding of the built-in solvation and due to its bulk, comparatively greater than that of the other substituents, can exert a significant retarding primary steric effect.^{11,12} Of course, this latter effect is as much lesser as is the transition state later along the reaction coordinate. Finally, the cyano group, whose geometry is not very favourable for the formation of the hydrogen bonding, will assume a more and more “feeble” importance in the reactivity sequence, as this factor becomes more and more decisive.

The σ constants calculated for the case L = OC₆H₅ (Table 2, line 7) are smaller than the corresponding values for L =

OC₆H₄NO₂-*p* (Table 2, line 8). This fact is in accord with the observation that the phenoxy group, which is more electron-donating than the *p*-nitrophenoxy group, exerts a levelling effect on the electronic effects of the 3-X substituent, especially in the starting compound but also in the transition state.

Experimental

Synthesis and purification of compounds

Compounds **1a–e**, **g–i**,²⁷ **1f**,²⁸ **2b**,²⁹ **2d**,^{e,18d} **2i**,³⁰ **3**,³¹ **4a–i**,³² **5a–e**,^{g–i},²⁷ **5f**,³³ **7i**,^{17b} **8d**,^{e,18b} **8i**,^{18b} **9d**,^{e,18d} **9i**^{17b} were prepared and purified by the methods reported. Compounds **2f**, **2g** and **2h** were prepared by reacting the corresponding 2-bromo-3-X-5-nitrothiophenes with potassium phenoxide (**2f**, mp 99–100 °C from MeOH; **2g**, mp 104–105 °C from MeOH; **2h**, mp 99–100 °C from ligroin-benzene. All the new compounds gave

Table 9 Physical and spectroscopic data for compounds **4–9**

Am	PYP		MOR		BMA		BuA		BzA	
	$\lambda_{\max}/\text{nm}^a$ log ϵ	PIP $\lambda_{\max}/\text{nm}^a$ log ϵ	Mp/ $^{\circ}\text{C}$ Solvent	$\lambda_{\max}/\text{nm}^a$ log ϵ	Mp/ $^{\circ}\text{C}$ Solvent	$\lambda_{\max}/\text{nm}^a$ log ϵ	Mp/ $^{\circ}\text{C}$ Solvent	$\lambda_{\max}/\text{nm}^a$ log ϵ	Mp/ $^{\circ}\text{C}$ Solvent	$\lambda_{\max}/\text{nm}^a$ log ϵ
Me	460 ^b	440 ^c	132–133	414	186	450	183–184	442	144–145	449
	4.553	4.161	Methanol	4.065	Methanol	4.310	Methanol–water	4.452	Methanol	4.261
H	460 ^b	448 ^c	169–170	435	105–106	437	75–77	438	163–164	438
	4.555	4.500	Methanol	4.350	Methanol	4.462	Methanol	4.457	Methanol	4.463
Br	455 ^b	428 ^c	110–111	408	Oil	435	81–82	443	151	440
	4.428	4.140	Methanol	4.073		4.287	Methanol	4.411	Ligroine	4.388
CONH ₂	435 ^b	432 ^c	187	417	142–143	430		426 ^f		422 ^h
	4.350	4.210	Methanol	4.139	Toluene	4.328		4.375		4.361
CO ₂ Me	425 ^b	420 ^c	167	404	80–81	416		415 ^f		410 ^h
	4.348	4.220	Methanol	4.156	Methanol	4.271		4.354		4.328
COMe	425 ^b	420 ^d	123	409	98–99	420	78–80	415	200–201	412
	4.34	4.199	Methanol	4.117	Methanol	4.263	Methanol	4.204	Methanol	4.332
SO ₂ Me	413 ^b	404 ^c	153–154	390	79–80	404	113–114	404	141–142	400
	4.338	4.120	Methanol	4.046	Ligroine	4.210	Light petroleum	4.288	Methanol	4.297
CN	420 ^b	418 ^c	150–151	408	109–110	415	131–132	415	130–132	410
	4.352	4.301	Methanol	4.241	Methanol	4.326	Methanol	4.331	Methanol	4.301
NO ₂	420 ^b	380 ^c	107–108	378		403 ^e		415 ^g		410 ⁱ
	4.215	4.199	Light petroleum	4.176		4.190		4.250		4.229

^a In menthol. ^b Ref. 32. ^c Ref. 29. ^d Ref. 33. ^e Ref. 17b. ^f Ref. 18d. ^g Ref. 18b. ^h Ref. 18d. ⁱ Ref. 17b.

correct analysis and NMR spectra, see data in Table 8). Compounds **1–3** gave the expected amino derivatives **4–9** on treatment with amines in methanol, in high yields (> 95%) as indicated by TLC and UV–Vis (200–450 nm) spectral analysis of the mixtures obtained after complete reaction. The relevant physical data of unknown compounds **4–9** are shown in Table 9. All ¹H NMR spectra were recorded on a Varian Gemini 300 instrument in the Fourier transform mode at 21.0 ± 0.5 °C in DMSO-*d*₆. Mass spectra were recorded on a VG70 70E apparatus. All melting points were obtained with a Reichert Termovar apparatus.

Kinetic data

Optical density measurements were carried out, after dilution with acidified methanol, by using a Zeiss PMQ II UV–Vis spectrophotometer. The wavelength and log ϵ values for UV spectral measurements are shown in Table 9. The concentrations used were from 5.0 × 10⁻⁵ to 1.5 × 10⁻⁵ M for substrates and from 1.0 × 10⁻³ to 1.0 × 10⁻¹ M for the amines.

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