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On the reaction of 3-bromo-2-nitrobenzo[*b*]thiophene with some *ortho*-substituted anilines: an analysis of the products of reaction and of their NMR and MS properties

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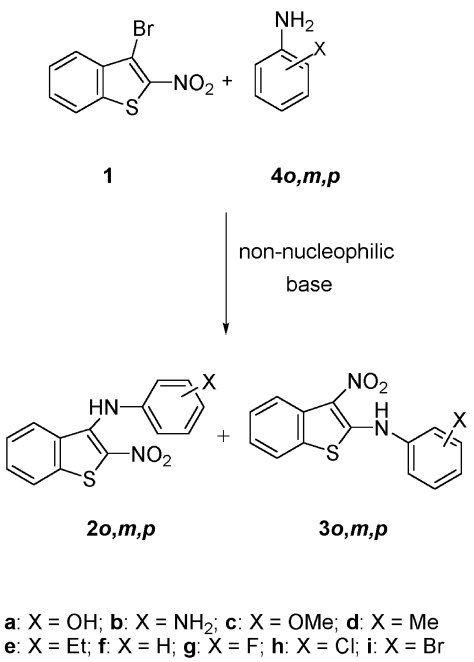
Abstract—The title reaction, carried out in DMF in the presence of triethylamine or potassium carbonate, has furnished the 'expected' 3-amino-2-nitrobenzo[*b*]thiophenes **2*o*** together with the 'unexpected' 2-amino-3-nitrobenzo[*b*]thiophenes **3*o***, thus recalling the situation observed with other weak nucleophiles in the presence of non-nucleophilic bases. The effects (electronic as well as steric) of the *ortho*-substituent (OH, NH_2, OMe, Me, Et, F, Cl and Br) on the course of the reaction have been investigated, determining their influence on yields and product ratios (**2*o*/3*o***). An analysis of ^{13}C NMR and MS spectra of **2*o*** and **3*o*** has been carried out. *Ab initio* computations on **2*o*f**, **2*o*i**, **3*o*f** and **3*o*i** at DFT level have furnished informations on their geometry and stability in the gas phase, thus allowing to assign a role to their stability on the course of the reaction as well as on some EI-MS results.

1. Introduction

In the framework of our investigations on the nucleophilic reactivity of halogenonitroheterocycles[1–3] we have observed that 3-bromo-2-nitrobenzo[*b*]thiophene (**1**) reacts with weak nucleophiles (for example, anilines) in the presence of non-nucleophilic bases (triethylamine or potassium carbonate) giving beside the expected **2*m*** and **2*p*** also the unexpected **3*m*** and **3*p***, deriving from a novel kind of nucleophilic substitution with rearrangement (Scheme 1).[4–6] Moreover we have been interested for a long time in the study of chemico-physical and biological properties of nitroheterocyclic compounds showing pharmacological activity.[7–10] Actually, a number of *N*-substituted 3-amino-2-nitrobenzo[*b*]thiophenes **2** show analgesic, anti-exudative and/or anti-inflammatory activities. In particular, some (**2*m*** and **2*p***) show high anti-inflammatory activity[11,12] (probably affecting the bio-synthesis of the prostaglandines or of the autacoids related to them) and present, at the same time, only a low mutagenic activity (as shown by the Ames test)[9] notwithstanding the presence of the nitrogroup: thus, they can be indicated as promising anti-inflammatory drugs. These facts further strengthen the well recognised observation that the thiophene ring is a structural element in a number of pharmacologically active compounds (chemotherapeutics as well as radiosensitizers).[13,14]



a: X = OH; **b**: X = NH_2; **c**: X = OMe; **d**: X = Me
e: X = Et; **f**: X = H; **g**: X = F; **h**: X = Cl; **i**: X = Br

Scheme 1.

Keywords: nucleophilic aromatic substitution; rearrangements in S_NAr; 3-bromo-2-nitrobenzo[*b*]thiophene; ^{13}C NMR; EI-MS.

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Therefore, we have now extended our interest to the reactivity of **1** with a series of *ortho*-substituted anilines (**4*o***: X=OH, NH_2, OMe, Me, Et, F, Cl, Br) with the two main aims of (i) gaining further informations about the influence of the structure of the nucleophile on the course of the reaction, and then on the relevant **2*o*/3*o*** ratios, and (ii) attaining, through the synthesis of new amines characterised by the benzo[*b*]thiophene skeleton, a better knowledge on structure/activity relationships in thiophenes and benzo[*b*]thiophenes.

Furthermore, following our investigation of the ^{13}C NMR[15] and MS[16] properties of the corresponding **2*m*** and **2*p***, we herein report on both the ^{13}C SCS (substituent-induced chemical shift) and MS behaviour of **2*o***, in order to make a comparison of substituent effects and an estimation of the influence of proximity effects in such compounds. A comparison of substituent effects in the two series of *ortho*-substituted compounds obtained (**2*o*** and **3*o***) has also been possible.

2. Results and discussion

2.1. Reactivity of 1 with *ortho*-substituted anilines: synthesis of 2*o* and 3*o*

The title reactivity and the influence of the electronic and proximity effects of the *ortho*-substituent on the course of the reaction have been evaluated by carrying out the reaction between **1** and various **4*o*** in DMF at reflux until complete disappearance of **1**, in the presence of triethylamine. As we have previously pointed out[4,6] the best results (in terms of both yields and reaction times) are obtained carrying out the reaction in DMF [a solvent with a high hydrogen-bond donor (HBD) character][17] and using a 1:3:3 substrate to aniline to Et_3N ratio. For the sake of comparison with previous results[11,12] the reactivity of **1** has been tested, with two model *ortho*-substituted anilines (**4*o*b–*o*c** X=NH_2 and OMe), also in the absence of non-nucleophilic bases obtaining, as expected,[6] only the relevant **2*o*** in excellent yields (93 and 99%, respectively).

The obtained data, collected in Table 1, allow some considerations on both the reaction times necessary to complete the reaction and the **2*o*/3*o*** ratios. It must be remembered that *ortho*-substituted anilines, because of the mixing of the operating proximity effects (electronic and steric), are always less nucleophilic and basic than the corresponding *para*-substituted derivatives. This agrees with the well known observation that *para*-substituted anilines are usually more reactive as nucleophiles than *ortho*-substituted anilines at least by a factor of ten (for example, in substrates such as halogenonitrothiophenes, which are relatively not very sensitive to steric effects),[18] also because of the lower basicity of the latter (differences ranging between 0.5 and 1.8 pK_a units).[19]

First of all it must be remarked that, in the experimental conditions adopted, no nucleophilic substitution occurred with *ortho*-substituted anilines containing strong electron-withdrawing groups such as CF_3 or NO_2. According to the general behaviour observed in the anilino-debromination reaction,[1–3] a relation between the reaction time and the electronic effects of the substituent present in the aniline has been observed: thus, reaction times vary from 30 min for X=*ortho*-OMe to *ca.* 3 h for X=*ortho*-Cl. The case of the reaction with *ortho*-bromoaniline appears interesting, as a reaction time much longer (10 h) than that required by all the other *ortho*-substituted anilines is associated with a low global yield (20%), probably due to a significant time-dependent decomposition of the reactants and/or products.

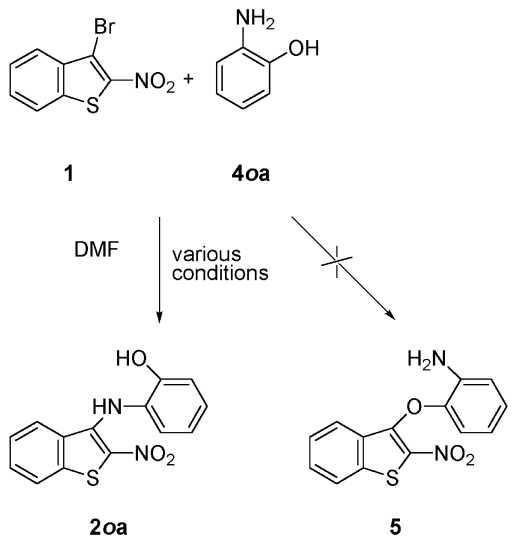
A comment on the trend of the **2*o*/3*o*** ratios, calculated by ^1H NMR analysis of the final reaction mixtures is also possible, e.g. as a dependence on the substituent electronic effects (measured by the Hammett *para*-substituted constants):[20] with regard to the resonance effects, in first approximation an *ortho*-substituent can be assimilated to a *para* one. Thus, anilines containing electron-repelling or donating substituents (X=Et, Me, or OMe) furnish predominantly (**2*o*/3*o***, 3.2–8.1) or exclusively (X=OH and NH_2; note that *ortho*-phenylenediamine is the strongest base/nucleophile we have used) the relevant **2*o***, while *ortho*-chloro and *ortho*-bromoaniline give a prevalence of the relevant **3*o*** (**2*o*/3*o***, 0.7–0.9). Interestingly *ortho*-fluoroaniline, as foreseeable on the basis of the Hammett *para*-substituent constant, shows an intermediate behaviour (**2*o*/3*o***, 1.4).

For the sake of comparison we have also studied the reaction of **1** with *para*-chloroaniline in the presence of a non-nucleophilic base to gain information on the effect of the position of the substituent in the arylamino ring. We have thus observed that *para*-chloroaniline reacts with **1** faster

Table 1. Reaction of 3-bromo-2-nitrobenzo[*b*]thiophene (**1**) with *ortho*-substituted anilines (**4o**) in DMF (120°C) in the presence of Et_3N until disappearance of starting product **1**

Compounds	X	Time (min)	Yield (%)	%**2*o***–%**3*o***	Mixture separation
a	OH	60[a]	30	100:0	Crystallization from ethanol
b	NH_2	65	19	100:0	Ethyl acetate–petroleum ether=1:4 on SiO_2
c	OMe	30	82	89:11	Fractional crystallization from ethanol
d	Me	90	84	77:23	Ethyl acetate–petroleum ether=1:8 on Al_2O_3
e	Et	120	73	76:24	Ethyl acetate–petroleum ether=1:9 on Al_2O_3
g	F	150	83	58:42	Ethyl acetate–petroleum ether=1:6 on Al_2O_3
h	Cl[b]	175	46	47:53	Ethyl acetate–petroleum ether=1:7 on Al_2O_3
i	Br	600	20	42:58	Ethyl acetate–petroleum ether=1:7 on Al_2O_3

[a] Temperature 50°C; see text and experimental.
[b] In comparable experimental conditions the reaction with *para*-chloroaniline goes to completion into 80 min with high yield (90%) and a high **2/3** ratio (4.9). **2*p*h** (see Ref. 12); **3*p*h**, mp 234°C from ethanol, ^1H NMR (δ): 7.31 (1H, dd, *J*=8.0, 7.3 Hz, H6), 7.47 (1H, dd, *J*=8.0, 7.3 Hz, H5), 7.61 (m, 4H, H2′, H3′, H5′, H6′), 7.77 (1H, d, *J*=7.8 Hz, H7), 8.31 (1H, d, *J*=8.0 Hz, H4), 11.24 (1H, s exch, NH); HRMS: found 304.00721, calcd 304.00733.



Scheme 2. Conditions and yields: (i) rt, 5 days (63%); (ii) 50°C, 90 min (30%); (iii) 50°C, Et_3N, 60 min (30%); (iv) 50°C, K_2CO_3, 30 min (41%); (v) 50°C, K_2CO_3 (large excess), 15 min (25%).

than *ortho*-chloroaniline (reaction time, 80 min vs 3 h) and gives a higher **2/3** ratio (4.9 vs 0.7). These results are well in line with previsions: in fact, on going from *ortho*- to *para*-chloroaniline both the basicity (ΔpK_a ca. 1.3)[19] and the nucleophilicity (for example, in simple thiophene systems the reactivity ratios with the two anilines are about 10^2)[18] increase, thus largely favouring the normal S_NAr pathway with respect to the base-catalysed nucleophilic substitution with rearrangement.

The reaction of **1** with *ortho*-aminophenol (**4*o*a**) has been deeply investigated. This aniline is a bidentate nucleophile which could, at least in principle, behave as a nitrogen- as well as an oxygen-nucleophile. A choice between the two different possibilities should be possible by changing the experimental conditions: in the absence of bases the aminogroup should be effective, while in the presence of bases the ionised phenolic hydroxyl could be the nucleophilic species. Some complications could be dependent on the fact that with a substrate such as **1** the added bases could affect the course of the reaction with a weak amine (Scheme 2).

Interestingly it must be remarked that operating at room temperature as well as at 50°C (at higher temperature, e.g. 80°C, only tar formation has been observed) in the absence or in the presence of added bases (Et_3N or K_2CO_3) the only observed product has been **2*o*a**: neither **3*o*a** nor the relevant ether **5** has been observed. Perhaps a fast Smiles-like rearrangement[21] would prevent the detection of any formed **5**. The detected highest yield in **2*o*a** has been observed at room temperature (63%, no base added), the increase of either temperature (50°C) or concentration of the added bases causing a significant yield reduction.

In conclusion the systematic study of the reaction of **1** with several *ortho*-substituted anilines has shown a strong dependence of the reactivity as well as of the **2*o*/3o** ratio on the proximity (steric and electronic) effects of the *ortho*-substituent.

2.2. Analysis of ^{13}C NMR data of 2*o* and 3*o* in DMSO-d_6 and $CDCl_3$ solutions

Anisotropy, resonance and inductive effects affect ^{13}C chemical shifts (c.s.'s) of carbon atoms of aromatic and heteroaromatic rings: the superimposition of these effects[22] usually prevents the occurrence of mono- (Hammett) or bi-parametric (DSP, dual substituent parameter)[23] linear free-energy relationships (lfer's) for the relevant SCS values, when substituent and probe carbon atom are in the same ring. In contrast, the effect of a substituent not directly linked to the ring containing the probe carbon atom leads to SCS values (possibly small) that can be correlated by means of mono- or bi-parametric lfer's.[7,15,24,25]

Thus, investigating the ^{13}C NMR data of several **2*m*** and **2*p*** in DMSO-d_6 solutions we have evidenced the occurrence of an alternate polarisation, which can involve carbons C-3, C-2, C-3a, C-7a, C-4 and C-5 of the 2-nitrobenzo[*b*]thiophen-3-yl moiety. A DSP treatment of the ^{13}C SCS indicates a large and a low resonance contribution for aryl *para*- and *meta*-substituents, respectively, while the inductive component remains constant throughout.[15]

However in compounds **2*o*** and **3*o*** some further complication could be expected considering the proximity effects that the substituent could exert.

2.2.1. ^{13}C NMR data in DMSO-d_6. In Tables 2 and 3 ^{13}C SCS data of **2*o*** and **3*o*** in DMSO-d_6 are collected. Notwithstanding the absence of compounds containing strong electron-withdrawing substituents (see above) a significant set of substituents has been investigated (ranging from OH, NH_2 and OMe to halogens). A rough examination

Table 2. ^{13}C NMR substituent-induced chemical shifts (SCSs) for 3-anilino-2-nitrobenzo[*b*]thiophenes (**2*o***) in DMSO-d_6

Compounds	X	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
f	H	124.42	142.71	129.35	126.19	124.59	130.72	123.78	137.49	139.26	124.19	129.18	126.21	129.18	124.19
a	OH	−2.53	2.70	−0.21	−0.40	0.13	0.30	−0.03	0.08	−13.90	28.07	−12.74	2.66	−9.73	3.23
b	NH_2	−2.65	2.40	−0.51	0.25	0.18	0.42	−0.02	0.52	−16.87	22.27	−13.67	3.09	−13.01	3.85
c	OMe	−1.89	1.95	−0.29	−0.57	0.15	0.33	0.07	0.05	−12.67	29.51	−16.86	2.56	−8.44	2.59
d	Me	−2.55	2.47	−0.57	−0.38	0.24	0.32	0.16	0.46	−1.69	10.76	1.80	2.03	−2.09	3.18
e	Et	−2.53	2.72	−0.76	−0.05	0.12	0.35	0.19	0.57	−2.37	16.30	0.22	2.38	−2.09	3.44
g	F	−0.22	0.18	0.16	−1.03	0.50	0.20	0.16	−0.25	−12.10	32.24	−12.90	2.40	−4.13	3.51
h	Cl	−0.75	0.82	−0.23	−0.81	0.54	0.33	0.29	0.05	−2.88	6.02	0.98	2.89	−0.62	4.12
i	Br	−0.98	0.89	−0.41	−0.71	0.44	0.30	0.23	0.07	−1.57	−3.13	4.06	3.20	−0.33	4.52
	ΔSCS[a]	2.65	2.72	0.92	1.28	0.54	0.42	0.32	0.82	16.87	35.37	20.92	3.20	13.01	4.52

[a] ΔSCS range of substituent effect on chemical shifts.

Table 3. ^{13}C NMR substituent-induced chemical shifts (SCS's) for 2-anilino-3-nitrobenzo[*b*]thiophenes (**3*o***) in DMSO-d_6

Compounds	X	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
f	H	162.42	119.94	130.94	121.23	126.69	124.74	122.34	125.02	139.23	124.60	129.66	127.68	129.66	124.60
c	OMe	−0.79	0.10	−0.26	0.15	0.17	0.16	0.13	0.24	−11.83	27.33	−17.17	0.91	−8.72	−1.25
d	Me	1.75	−0.77	0.13	0.02	0.00	−0.16	0.09	0.24	−0.73	9.94	1.71	1.11	−2.25	1.83
e	Et	2.08	−0.72	0.37	0.01	0.01	−0.13	0.07	0.22	−1.43	15.61	0.05	1.41	−2.27	2.10
g	F	0.14	0.07	−0.05	0.00	−0.03	−0.12	−0.11	−0.01	−12.29	31.34	−13.05	2.19	−4.36	2.72
h	Cl	0.41	−0.15	0.11	0.17	0.21	0.10	0.22	0.25	−2.64	5.30	0.94	2.28	−0.86	3.22
i	Br	0.45	−0.25	0.04	0.11	0.16	0.05	0.16	0.25	−1.17	−3.91	4.05	2.56	−0.30	3.36
	ΔSCS[a]	2.87	0.87	0.63	0.17	0.24	0.32	0.33	0.26	12.29	35.25	21.22	2.56	8.72	4.61

[a] ΔSCS range of substituent effect on chemical shifts.

of data evidences the absence of the expected substituent effects on SCS: for example, in the **2*o*** series both electron-withdrawing and -repelling substituents cause shielding and deshielding of C-2 and C-3 (the carbon carrying the anilino moiety), respectively. Also in the case of **3*o*** the SCS variations can not be related to the electronic effects of the substituents, essentially paralleling the situation observed for **2*o***.

In contrast, the cross-correlations for the *ipso*- (C-2′), *ortho*- (C-1′ and C-3′) and *para*-carbons (C-5′) of the anilino moiety of **2*o*** gave good or excellent statistical results versus the relevant SCS of the *ortho*-substituted anilines (*s* 0.84–1.21, *r* 0.987–0.999; data in Table 4, lines 6–9) or of monosubstituted benzenes (data not reported). The same excellent statistical results have been obtained for the corresponding carbon atoms of **3*o*** (*s* 0.80–1.13, *r* 0.990–0.999; data in Table 4, lines 10–13).

2.2.1.1. ^{13}C NMR Data in $CDCl_3$. In order to lower the proximity effects caused by the solvent used we have also collected ^{13}C c.s. values of **2*o*** and **3*o*** in $CDCl_3$ solutions (data in Tables 5 and 6), that is in a solvent with a completely different ability to behave as HBD solvent.[17] In this solvent, though, **2*o*a** is so little soluble that we have not recorded its spectrum.

In the **2*o*** series electron-withdrawing and -repelling substituents cause shielding and deshielding of C-3 (ΔSCS 3.27 ppm), respectively, while the usual inverted effect can be evidenced for C-2 (ΔSCS 2.74 ppm). The relevant SCS values give good mono-parametric correlations (*r* 0.97 and 0.92, respectively; data in Table 4, lines 1 and 2)[26] vs. σ_p^-, with susceptibility constants (ρ^- −6.13 and 5.12, respectively) of the same order of those calculated for the *para*-isomer (**2*p***).[15] This result can be related to the absence of the specific solute–solvent

Table 4. Statistical data for the single-parameter analysis of SCS values of carbon atom of **2*o*** and **3*o*** and for the cross-correlation with anilines (**4*o***)

Line	Solvent	Probe atom	Series	$\rho\pm s_\rho$ (or $\beta\pm s_\beta$)	Substituent constant[a] or SCS of probe atom	Series	$i\pm s_i$	*n*	*r*	CL>%
1	$CDCl_3$	C-2	**2*o***	5.12±0.71	σ_p^-		−0.17±0.14	8	0.924	99.9
2	$CDCl_3$	C-3	**2*o***	−6.13±0.56	σ_p^-		0.07±0.11	8	0.974	99.9
3	$CDCl_3$	C-7*a*	**2*o***	−0.96±0.30	σ_p^-		−0.15±0.06	8	0.781	99.0
4	$CDCl_3$	C-2	**3*o***	−9.40±1.09	σ_p^-		0.48±0.19	6	0.982	99.9
5	$CDCl_3$	C-3	**2*o***	0.74±0.04	C-2	**3*o***	−0.12±0.06	6	0.995	99.9
6	DMSO-d_6	C-1′	**2*o***	1.21±0.07	C-1	**4*o***	1.06±0.52	8	0.987	99.9
7	DMSO-d_6	C-2′	**2*o***	0.84±0.05	C-2	**4*o***	3.11±0.95	8	0.989	99.9
8	DMSO-d_6	C-3′	**2*o***	0.98±0.02	C-3	**4*o***	0.76±0.17	8	0.999	99.9
9	DMSO-d_6	C-5′	**2*o***	1.16±0.03	C-5	**4*o***	0.64±0.18	8	0.997	99.9
10	DMSO-d_6	C-1′	**3*o***	1.13±0.07	C-1	**4*o***	1.34±0.47	7	0.990	99.9
11	DMSO-d_6	C-2′	**3*o***	0.80±0.05	C-2	**4*o***	2.42±1.00	7	0.990	99.9
12	DMSO-d_6	C-3′	**3*o***	0.98±0.02	C-3	**4*o***	0.72±0.16	7	0.999	99.9
13	DMSO-d_6	C-5′	**3*o***	1.12±0.04	C-5	**4*o***	0.42±0.14	7	0.997	99.9

ρ, susceptibility constant for the single-parameter analysis; β, slope of the cross correlation; *i*, intercept; s_ρ and s_β standard deviations; *n*, number of points; *r*, correlation coefficient; CL, confidence level.
[a] Substituent constants from Ref. 20.

Table 5. ^{13}C NMR substituent-induced chemical shifts (SCSs) for 3-anilino-2-nitrobenzo[*b*]thiophenes (**2*o***) in $CDCl_3$

Compounds	X	C-2	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
f	H	125.00	144.26	128.78	127.17	124.33	130.61	123.49	138.87	138.60	125.42	129.73	127.41	129.73	125.42
b	NH_2	−1.06	1.71	0.02	−0.39	0.46	0.24	−0.15	0.04	−14.98	17.74	−13.46	2.26	−10.77	2.75
c	OMe	−0.59	0.36	0.17	−0.60	−0.03	0.04	−0.18	−0.31	−11.78	27.98	−17.99	0.97	−9.04	0.43
d	Me	−1.51	1.19	−0.04	−0.64	0.28	0.18	−0.03	0.08	−1.68	9.36	1.66	0.95	−2.48	1.51
e	Et	−1.47	1.35	−0.12	−0.35	0.16	0.14	−0.01	0.18	−2.18	15.09	0.02	1.18	−2.58	1.73
g	F	0.74	−0.69	0.13	−1.07	0.33	0.05	0.04	−0.34	−11.99	31.46	−12.89	1.35	−4.89	1.80
h	Cl	1.09	−1.52	0.08	−0.83	0.31	−0.02	0.01	−0.46	−2.57	4.26	0.79	0.56	−2.08	0.92
i	Br	1.23	−1.56	0.07	−0.69	0.30	−0.04	0.07	−0.38	−1.07	−5.46	3.99	0.86	−1.41	1.09
	ΔSCS[a]	2.74	3.27	0.29	1.07	0.49	0.28	0.25	0.64	14.98	36.92	21.98	2.26	10.77	2.75

[a] ΔSCS range of substituent effect on chemical shifts.

Table 6. ^{13}C NMR substituent-induced chemical shifts (SCSs) for 2-anilino-3-nitrobenzo[*b*]thiophenes (**3*o***) in $CDCl_3$

Compounds	X	C-2	C-3	C-3*a*	C-4	C-5	C-6	C-7	C-7*a*	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
f	H	160.92	121.75	131.06	122.64	127.06	125.22	121.49	125.28	138.28	122.49	129.98	127.32	129.98	122.49
c	OMe	−2.05	0.26	−0.24	−0.12	−0.06	−0.11	0.06	0.16	−10.70	28.04	−18.62	−0.32	−9.14	−2.88
d	Me	1.72	1.20	0.34	−0.04	−0.02	−0.07	0.11	0.25	−1.11	10.42	1.73	0.93	−2.51	1.16
e	Et	2.08	1.17	0.28	−0.16	−0.09	−0.10	0.11	0.19	−1.74	16.31	0.00	1.26	−2.58	1.45
g	F	−0.86	0.65	−0.03	0.15	0.18	0.14	0.11	0.11	−11.55	32.47	−13.18	0.90	−4.95	0.44
h	Cl	−2.01	0.71	−0.23	0.05	0.13	0.14	0.06	0.08	−2.62	4.74	0.64	0.16	−1.97	−0.74
i	Br	−1.65	0.59	−0.17	0.02	0.11	0.13	0.08	0.00	−1.24	−4.81	3.90	0.70	−1.28	−0.19
	ΔSCS[a]	4.13	1.20	0.58	0.31	0.27	0.25	0.11	0.25	11.55	37.28	22.52	1.58	9.14	4.33

[a] ΔSCS range of substituent effect on chemical shifts.

interactions that, in contrast, characterise the c.s.'s in DMSO-d_6.

Concerning the **2*o*** series the small ΔSCS values (0.3–1.1 ppm) and the occurrence of some scattered behaviour for the other carbons of the benzo[*b*]thiophene moiety discourages the search for lfer's, except for C-7a. In this instance only a rough correlation has been observed by means of a mono-parametric lfer treatment (ρ^- −0.96, *r* 0.78; data in Table 4, line 3). Interestingly a dissociation of electronic effects in their components (inductive and resonance contributions) strongly improves the statistical results (ρ_I −1.17 and ρ_R^- −0.29, *R* 0.94_5): this occurrence can be related to the peculiar ρ_R^-/ρ_I ratio observed (λ ca. 0.25), unusually low for conjugated systems. As a matter of fact the λ value calculated recalls the figure observed in *meta*-substituted compounds,[15] indicating that anyhow some significant steric hindrance operates, thus lowering the resonance effects.

For compounds of the **3*o*** series a somewhat different behaviour has been observed: only the C-2 c.s. shows the expected substituent effects. As a matter of fact, electron-withdrawing and -repelling substituents cause shielding and deshielding on c.s. (ΔSCS 4.15 ppm), giving good mono-parametric correlations (*r* 0.98; data in Table 4, line 4) vs. σ_p^- with a susceptibility constant (ρ^- −9.40) comparable with that calculated for C-3 of **2*o***. Therefore a good cross-correlation (*s* 0.74, *r* 0.995; data in Table 4, line 5) can be evidenced between the SCS's of C-3 of **2*o*** and of C-2 of **3*o***, that is between the SCS's of the two carbon atoms directly linked to the anilino moiety.

Anyhow, also in $CDCl_3$ the cross-correlations of the SCS's for the *ipso*- (C-2′), *ortho*- (C-1′ and C-3′) and *para*-carbons (C-5′) of the anilino moiety of **2*o*** and **3*o*** gave good or excellent statistical results versus the relevant SCS's of *ortho*-substituted anilines or of monosubstituted benzenes (data not reported), paralleling the situation observed in DMSO.

The whole of the ^{13}C NMR results furnishes a new interesting example of lfer concerning *ortho*-substituted compounds, which strictly recalls that observed in the case of *ortho*-substituted 5-nitro-3-thiophenecarboxanilides previously studied by us.[7]

2.3. Analysis of MS of 2*o* and 3*o*

The main peaks of the 70 eV mass spectra of compounds **2*o*** and **3*o*** are reported in Table 7. Chloro and bromo derivatives are considered as effectively monoisotopic species, i.e. the relative abundance of halogen-containing ions has been calculated by summing up all isotopic contributions.

The molecular ion is always responsible for the base peak of the mass spectra except for **2*o*b** and **2*o*i** (X=NH_2 and Br, respectively). In the case of **2*o*i** this should be related to the presence of the feeble C_{Ar}–Br bond: as a matter of fact in both **2*o*i** and **3*o*i** all the $-Br^{\cdot}$ peaks ($[M-NO_2X]^{+\cdot}$, $[M-HNO_2X]^+$, $[M-OHX]^{+\cdot}$) show high relative abundance (see after).

The following fragmentation pathways have been observed: (a) loss of $NO^{\cdot}$, (b) loss of $NO_2^{\cdot}$ and HNO_2, (c) loss of $OH^{\cdot}$, (d) loss of $X^{\cdot}$ and (e) formation of $XC_6H_4O^+$. These pathways are reported in Scheme 3 and strictly recall those observed for the previously studied **2*m*** and **2*p***.

Some considerations can be made on the results obtained.

2.3.1. Loss of $NO^{\cdot}$. The nitro to nitrite isomerization followed by loss of $NO^{\cdot}$ is a well-established process in EI-MS of nitro-aromatic or -heteroaromatic compounds. A comparison between the two series (**2*o*** and **3*o***) gives an interesting information: the $[M-NO]^+$ peak is usually of low intensity and more abundant in **3*o*** than in the relevant **2*o***, except than for **2*o*c** (X=OMe), for which a significant fragmentation occurs (30%).

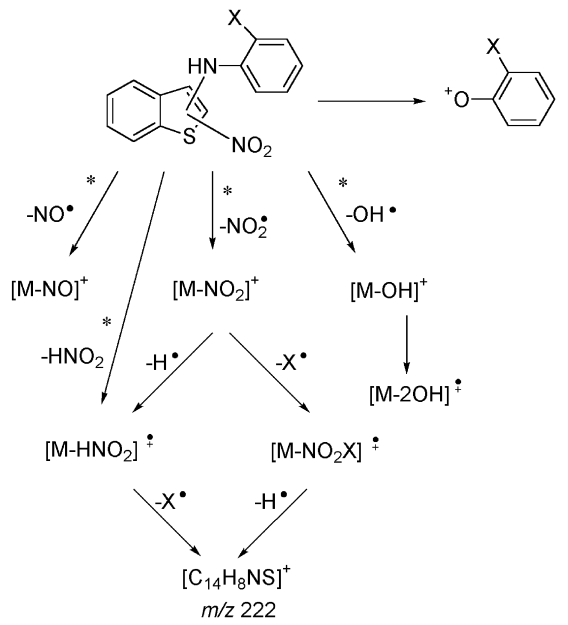
2.3.2. Loss of $NO_2^{\cdot}$ and HNO_2. The peaks for the relevant two ions are present in all the examined compounds but in **2*o*i** (X=Br). The sum of the two peaks is more abundant in **2*o*** than in the corresponding **3*o*** except for **2*o*i** (X=Br), where all the peaks related to $-X^{\cdot}$ are prevalent, and once more again for **2*o*c** (X=OMe). In the case of **2*o*b** (X=NH_2) $[M-NO_2]^+$ is the base peak. Considerations concerning the HNO_2 loss have been previously discussed and a 10*H*-[1]benzothieno[3,2-*b*]indole structure for the formed cation has been proposed.[16]

The loss of $X^{\cdot}$ together with $NO_2^{\cdot}$ and HNO_2 will be discussed hereinafter.

2.3.3. Loss of $OH^{\cdot}$. The loss of $OH^{\cdot}$ causes the formation of $[M-OH]^+$ and $[M-2OH]^{+\cdot}$: the second being more abundant than the first one. In some cases the $[M-2OH]^{+\cdot}$ ion is responsible for a peak with a relative abundance higher than 33% (**3*o*d**, ***o*f**–***o*h**: X=Me, H, F, Cl; **2*o*d**: X=Me).

Table 7. Significant peaks of the mass spectra of **2*o*>** and **3*o*>**

	X	M	$M-NO_2$	$M-HNO_2$	$M-NO_2X$	$M-HNO_2X$	M−OH	M−2OH	M−NO	$C_6H_4X^+$	$XC_6H_4O^+$	Other peaks
2*o*a	OH	286 (100)	240 (49.3)	239 (32.5)	223 (8.7)	222 (4.9)	269 (3.1)	252 (38.6)	256 (−)	93 (−)	109 (7.0)	238 (43.8)
2*o*b	NH_2	285 (59.2)	239 (100)	238 (74.7)	223 (21.9)	222 (19.2)	268 (3.1)	251 (27.4)	255 (−)	92 (18.6)	108 (17.7)	252 (11.7)
2*o*c	OMe	300 (100)	254 (7.1)	253 (11.2)	223 (21.9)	222 (6.3)	283 (2.0)	266 (12.6)	270 (30.0)	107 (−)	123 (9.3)	210 (27.4)
3*o*c	OMe	300 (100)	254 (14.3)	253 (18.3)	223 (<1)	222 (−)	283 (−)	266 (5.3)	270 (<1)	107 (−)	123 (8.6)	210 (16.0)
2*o*d	Me	284 (100)	238 (53.6)	237 (39.7)	223 (49.5)	222 (21.0)	267 (2.5)	250 (39.3)	254 (3.3)	91 (36.3)	107 (6.4)	65 (50.8)
3*o*d	Me	284 (100)	238 (27.0)	237 (27.2)	223 (28.5)	222 (4.9)	267 (4.4)	250 (62.8)	254 (4.1)	91 (26.8)	107 (8.6)	65 (48.8)
2*o*e	Et	298 (100)	252 (96.5)	251 (13.0)	223 (53.4)	222 (6.5)	281 (−)	264 (11.3)	268 (−)	105 (6.1)	121 (33.9)	288 (11.5)
3*o*e	Et	298 (100)	252 (43.3)	251 (6.5)	223 (11.0)	222 (13.9)	281 (3.1)	264 (13.3)	268 (0.7)	105 (1.8)	121 (5.1)	263 (20.8)
2*o*f	H	270 (100)	224 (40.6)	223 (78.7)	223 (78.7)	222 (9.4)	253 (−)	236 (29.4)	240 (−)	77 (55.9)	93 (−)	121 (21.0)
3*o*f	H	270 (100)	224 (14.3)	223 (24.6)	223 (24.6)	222 (10.8)	253 (4.6)	236 (36.9)	240 (8.7)	77 (29.1)	93 (2.0)	121 (10.7)
2*o*g	F	288 (100)	242 (9.8)	241 (57.9)	223 (9.6)	222 (3.1)	271 (13.1)	254 (19.7)	258 (2.9)	95 (9.2)	111 (1.1)	139 (19.3)
3*o*g	F	288 (100)	242 (11.4)	241 (19.4)	223 (2.1)	222 (5.1)	271 (8.9)	254 (44.4)	258 (8.8)	95 (15.9)	111 (1.2)	139 (4.1)
2*o*h	Cl	304/306 (100)	258/260 (4.2)	257/259 (8.9)	223 (71.3)	222 (39.4)	287/289 (2.0)	270/272 (23.0)	274/276 (1.8)	111/113 (10.6)	127/129 (−)	75 (10.4)
3*o*h	Cl	304/306 (100)	258/260 (7.6)	257/259 (7.5)	223 (34.4)	222 (30.8)	287/289 (6.1)	270/272 (40.8)	274/276 (11.5)	111/113 (21.4)	127/129 (4.9)	75 (47.4)
2*o*i	Br	348/350 (44.6)	302/304 (7.8)	301/303 (−)	223 (100)	222 (51.0)	331/333 (−)	314/316 (7.8)	318/320 (−)	155/157 (−)	171/173 (−)	76 (30.7)
3*o*i	Br	348/350 (100)	302/304 (−)	301/303 (4.9)	223 (45.9)	222 (41.3)	331/333 (−)	314/316 (21.1)	318/320 (4.6)	155/157 (27.9)	171/173 (2.3)	76 (35.9)



Scheme 3. Main fragmentation pathways of compounds **2*o*** and **3*o***.

The formation of these two ions reflects a typical *ortho*-effect observed in the mass spectra of several classes of *ortho*-nitro-aromatic (or -heteroaromatic) amines: well known examples are those of *ortho*-nitrodiarylamines,[27–29] *ortho*-nitroanilines,[29–31] *ortho*-nitroaminopyridines[32] and aryl(2-nitrobenzo[*b*]thiophene-3-yl)amines.[16] Studies performed by using substrates labelled with deuterium at the nitrogen of the amino group as well as at the phenyl ring or at the alkyl group linked to the aminogroup evidenced a significant preference of OH· loss from the hydrogen of the amino group, the preference being enhanced in the metastable decomposition. Anyhow the loss of two OH· gave the same final ion[16,28] for which a [1]benzothieno[2,3-*b*]quinoxaline structure has been proposed.[16]

2.3.4. Loss of X·. The formation of several ions deriving from this loss has been observed, the most common being $[M-NO_2X]^{+\cdot}$, $[M-HNO_2X]^+$, $[M-OHX]^{+\cdot}$. The direct occurrence of significant $[M-X]^+$ peaks has been observed only in the case of **2*o*i** (5.5%) and **3*o*i** (ca. 1%), according with the peculiar weakness of the $C_{Ar}-Br$ bonds.

The formation of the $[M-NO_2X]^{+\cdot}$ ion by further fragmentation from the $[M-NO_2]^+$ one competes with formation of the $[M-HNO_2]^{+\cdot}$ ion. The relative abundance of the $[M-HNO_2]^{+\cdot}$ and $[M-NO_2X]^{+\cdot}$ ions might be related to the $C_{Ar}-X$ bond strength: in the fluoro and amino derivatives the formation of the $[M-HNO_2]^{+\cdot}$ ion largely prevails, while in the chloro, bromo and ethyl derivatives the formation of the $[M-NO_2X]^{+\cdot}$ ion is overwhelming. Methyl and methoxy derivatives show non-homogeneous behaviours: prevalent formation of $[M-HNO_2]^{+\cdot}$ and $[M-NO_2X]^{+\cdot}$ has been observed for **2*o*c** and **3*o*c** (X=OMe), respectively, while in **2*o*d** and **3*o*d** (X=Me) a slight preference of $[M-NO_2X]^{+\cdot}$ and similar quantities of the two ions could be detected, respectively. Concerning the $[M-HNO_2X]^+$ ion, its formation, always observed but for **3*o*c**, is particularly important in chloro and bromo derivatives (31–51%).

In the formation of the $[M-OHX]^{+\cdot}$ ions a situation similar to that seen in the case of the $[M-NO_2X]^{+\cdot}$ ions has been observed.

2.3.5. Formation of $[XC_6H_4O]^+$. The formation of significant amounts of this ion has been recently observed in compounds bearing a strong electron-repelling or donating substituent in the *para*-position of the anilino moiety.[16] Its formation results from an oxygen migration from the *ortho*-nitro group to other parts of the molecule and characterises several EI-induced fragmentations. Replacements of an aromatic or heteroaromatic nitrogen by oxygen from other sources such as carbonyl groups have been similarly observed.[33–35] The driving force for such rearrangements appears to be the stabilisation of the *ortho*- or *para*-quinoid structure.[16,33]

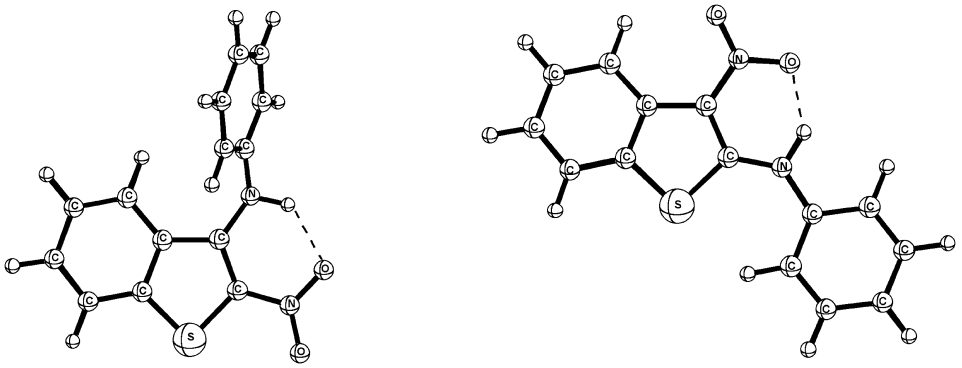
As a matter of fact significant amounts of these ions have been observed when methyl, ethyl, methoxy and amino groups are present.

The whole of the obtained results (loss of $NO^{\cdot}$, $NO_2^{\cdot}$, $OH^{\cdot}$ and $2OH^{\cdot}$, $X^{\cdot}$ and the formation of $[ArO]^+$) strongly supports the results of the EI-induced fragmentation evidenced in **2*m*** and **2*p*** compounds.

Interestingly, ab-initio computations can help in understanding some EI-MS results. If we look at the behaviour of **2*o*f** and **3*o*f** we can observe that fragmentations of the former are higher than those of the latter (for example, compare formation of $M-NO_2^+$ and of $M-HNO_2^{+\cdot}$): this can depend, at least in part, on the higher stability of **3*o*f** with respect to **2*o*f** (ΔE 16.8 kJ mol^{-1}, see after). The higher stability of **3*o*** with respect to **2*o*** causes even larger effects in the case of the **2*o*i/3*o*i** couple: for example the molecular ion (45%) of **2*o*i** is not responsible for the base peak, in contrast with what happens with **3*o*i** (molecular ion 100%). The behaviour of **2*o*b** can be related to the same factor.

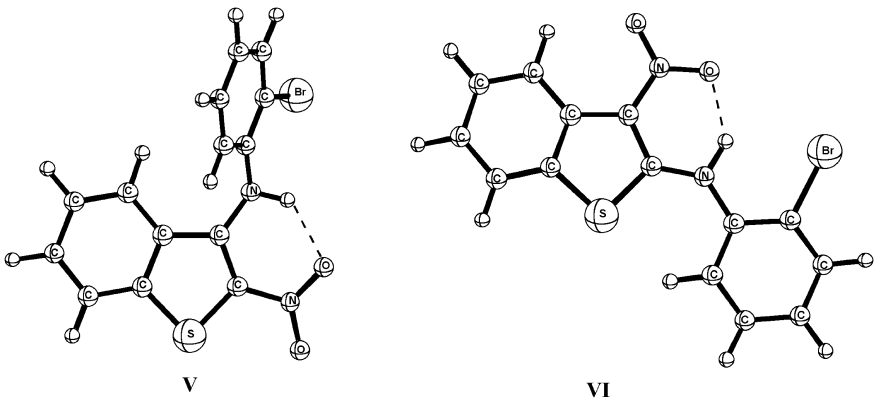
2.4. Ab initio calculations of the stability and the geometry of some 2*o* and 3*o* compounds

The course of the reaction of **1** with weak nucleophiles in the presence of non-nucleophilic bases with formation of an unexpected substitution product (**3**) together with the expected one (**2**) raises an intriguing question. Because bromine is a good leaving group, the reaction of nitroactivated bromoaromatic (or heteroaromatic) substrates would give only the expected product of reaction (that is the *ipso*-substitution product);[36] then the question is: why does **1** show this unexpected behaviour? That is, which is the *driving force* that induces this unexpected behaviour? In an attempt to reply to this question we have carried out an ab initio computation to gain information on the geometry and the stability of **2*o*f** and **3*o*f** (the parent compounds of the two series) in the gas phase. For the sake of comparison we have also carried out the same calculations on the **2*o*i** and **3*o*i** couple, that is on the anilino compounds containing a bulky and electron-withdrawing substituent linked to the phenyl ring with a feeble C_{Ar}-Br bond (i.e. factors which could



I **III**

Figure 1. Optimised geometries for **2*o*f** and **3*o*f** (conformers **I** and **III**).



V **VI**

Figure 2. Optimised geometries for **2*o*i** and **3*o*i** (conformers **V** and **VI**).

Table 8. Bond lengths (Å) for **I**, **III**, **V** and **VI** calculated using DZVP basis set in the gas phase and for **VII**[39]

	I	III	V	VI	VII
S/C-2	1.758	1.753	1.757	1.756	1.754
C-2/C-3	1.399	1.414	1.396	1.411	1.355
C-2/NO_2	1.408		1.412		
C-3/NO_2		1.414		1.418	
C-3/NH	1.368		1.372		
C-2/NH		1.351		1.358	
C-3/C-3*a*	1.458	1.454	1.456	1.454	1.446
C-3*a*/C-4	1.412	1.410	1.412	1.411	1.423
C-4/C-5	1.389	1.395	1.389	1.395	1.368
C-5/C-6	1.410	1.404	1.410	1.404	1.397
C-6/C-7	1.391	1.396	1.391	1.396	1.379
C-7/C-7*a*	1.402	1.395	1.402	1.395	1.396
C-3*a*/C-7*a*	1.418	1.412	1.418	1.411	1.399

Table 9. Bond angles (°) for **I**, **III**, **V** and **VI** calculated using a DZVP basis set in the gas phase and for **VII**[39]

	I	III	V	VI	VII
S/C-2/C-3	115.3	111.1	115.3	110.6	112.4
S/C-2/NO_2	118.0		118.0		[a]
S/C-2/NH		124.2		124.3	
C-2/C-3/NH	123.4		123.6		[b]
C-2/C-3/NO_2		122.5		122.6	
C-2/C-3/C-3*a*	110.0	113.9	110.1	114.1	112.4
C-3/C-3*a*/C-7*a*	111.9	111.2	111.9	111.0	112.9
C-3*a*/C-4/C-5	119.7	119.5	119.7	119.5	117.9
C-4/C-5/C-6	120.7	121.4	120.7	121.5	123.1
C-5/C-6/C-7	120.7	120.1	120.7	120.0	119.6
C-6/C-7/C-7*a*	118.7	118.2	118.7	118.1	118.5
C-7/C-7*a*/C-3*a*	121.4	122.8	121.4	123.1	122.1
C-7*a*/C-3*a*/C-4	118.8	117.9	118.9	117.8	118.7
C-7*a*/S/C-2	89.2	92.0	89.3	92.2	91.7

[a] S/C-2/CH_3 118.4°.
[b] C-2/C-3/CH_3 123.8°.

affect the **2*o*/3*o*** ratios as well as the course of the EI-MS fragmentations).

2.4.1. Geometry and stability of 2*o*f, 3*o*f, 2*o*i and 3*o*i. Ab initio computations have been carried out at the density functional theory (DFT) level[37,38] in order to consider electronic correlations. The results obtained are collected in Figures 1–2 and in Tables 8 and 9, where bond lengths and angles for the most stable conformers **I**, **III**, **V** and **VI** are reported. For both **2*o*f** and **3*o*f** we have addressed our attention to the study of conformers (possibly planar) with two opposite geometries: the first one with the proton of the phenylamino group [N(H)], the second with the phenyl directed towards the nitro group, respectively. Let us now consider the results obtained for the optimised structures.

First of all it must be remarked that in all the studied conformers the individual five- and six-membered rings are by their selves planar, but the benzo[*b*]thiophene system as a whole always shows a (small) deviation from planarity (not higher than 2°).

An interesting outcome is that only in conformer **III** of **3*o*f** the phenylamino and the thienyl groups are coplanar: **III** shows a strong hydrogen bond (1.784 Å) between the proton of the phenylamino group [N(H)] and one of the two oxygens of the nitro group and comes out as the most stable one. In contrast, conformer **IV** of **3*o*f**, with the phenyl group directed towards the nitro group, is much less stable (ΔE 41.9 kJ mol^{-1}) as it can not form any hydrogen bond; moreover the phenylamino and the thienyl group are not coplanar because of the repulsion between the phenyl and the nitro group (dihedral angle between thienyl and phenylamino rings 42°, with the nitro group rotated of 11° and moreover 7° out of the plane with respect to the thienyl ring). Looking at **2*o*f** we observe that it cannot be planar because of steric requirements: in the more stable conformer (**I**), with the proton of the phenylamino group [N(H)] directed towards one of the two oxygens of the nitro group (a hydrogen bond weaker than in **III** is present: 1.922 Å), the coplanarity is prevented by the repulsive interactions between the C–4(H) and the C–2′(H) protons, that force the phenylamino ring to be rotated with respect to the thienyl one of about 35°. Therefore every attempt to calculate the energy content for a stable coplanar structure (see above) of **2*o*f** fails, because a planar structure would requires a big deviation of bond angles from their normal values, making this conformation energetically and then geometrically 'impossible'. In conformer **I** the distance between the two protons above is 2.889 Å, i.e. higher than the contact distance between two protons, leading to a lower stability of the conformer **I** with respect to **III** (ΔE 16.8 kJ mol^{-1}).

In conformer **II**, the least stable among the four considered, the interaction between the phenylamino ring and the nitro group prevents molecular coplanarity (see above, the phenylamino ring appear rotated with respect to the thienyl one of about 44°), and the repulsive interactions between the C–4(H) and the N(H) protons appear less important (distance between the two protons 2.151 Å). In this case, as in **IV**, no hydrogen bond is present. Surely the absence in **II** and **IV** of a more or less strong hydrogen bond causes the highest energy content (that is the lowest stability); their energy contents are similar (ΔE 4.6 kJ mol^{1}) and both conformers are non-planar.

In conclusion **III** represents the most stable conformer (ΔE 16.8, 41.9 and 46.5 kJ mol^{-1} with reference to **I**, **IV** and **II**, respectively), because of the occurrence of the strongest hydrogen bond and of the best conjugative interactions between phenylamino and nitro groups. This second factor could be responsible for the length of the C-2/C-3 bond of **III** (1.414 Å) being higher than in **I** (1.399 Å), **IV** (1.393 Å) and **II** (1.391 Å) and at the same time of the length of the C_{Th}–N(H) bond of **III** (1.351 Å) being lower than in **I** (1.368 Å), **IV** (1.370 Å) and **II** (1.377 Å).

The other bonds show only small variations in the different conformers and their values are consistent with those determined by X-rays measurements for the 5-bromo-2,3-dimethylbenzo[*b*]thiophene (**VII**),[39] which is again a 2,3-disubstituted benzo[*b*]thiophene as **I**–**VI**. For the sake of comparison, also the experimentally determined[39] bond lengths and angles of **VII** are collected in Tables 8 and 9, respectively.

On the basis of the results obtained with **2*o*f** and **3*o*f** we have taken into account, for the **2*o*i** and **3*o*i** couple, only the two most stable conformers, that is those with the proton of the arylamino group [N(H)] directed towards one of the two

oxygens of the nitro group. Once more conformer **VI** (**3*o*i**) is more stable (ΔE 11.4 kJ mol^{-1}) than **V** (**2*o*i**): it shows a strong hydrogen bond (1.804 Å), the arylamino and the thienyl groups are coplanar and a good arrangement is achieved for bromine, which seems able to interact with the proton of the arylamino group [N(H)]. As matter of fact the calculated distance in the NH…Br system is 2.506 Å, while the sum of the Van der Waals radii is not lower than 3.1 Å. The conformer **V** (**2*o*i**) is less stable, has a hydrogen bond weaker than **VI** (1.954 Å), and, as in **I**, the arylamino and the thienyl groups are not coplanar, the arylamino ring being rotated with respect to the thienyl one of about 39°. Again the more stable **VI** has a C-2/C-3 bond longer than **V** (1.411 and 1.396 Å, respectively) and a shorter C_{Th}–N(H) bond (1.358 and 1.372 Å, respectively).

2.4.2. Insight into the reaction mechanism. Ab initio computations can be of help in understanding the course of the reaction of **1** with weak nucleophiles. Recently, we have deeply discussed some data on the reactivity of **1** with several nucleophiles in different experimental conditions:[6] the proposed mechanisms are collected in Scheme 4. We have pointed out that the peculiar energetic situation of benzocondensed heterocycles, in which the heterocyclic ring can be hardly considered aromatic, is probably responsible for the occurrence of two independent reaction pathways: 1) the normal S_NAr reaction (the exclusive reaction pathway with strong nucleophiles or with weak nucleophiles in the absence of added non-nucleophilic bases; presumably one of the reaction pathways with weak nucleophiles also in the presence of added non-nucleophilic bases), which gives only the 'expected' substitution product; 2) a base-catalysed reaction pathway,[1–3,40,41] that occurs only in the presence of non-nucleophilic bases and whose contribution increases with their concentration, whereby effective deprotonation of A leads to B, and hence to the anionic intermediate C: the latter evolves towards cyclic intermediates eventually furnishing the 'unexpected' substitution products and, less probably, also the 'expected' one.

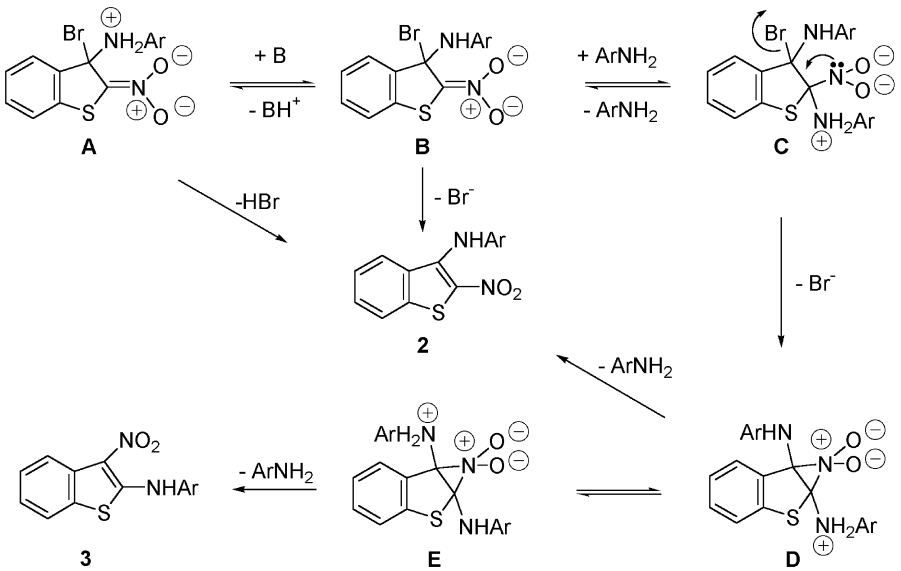
The ab initio computations herein, providing information about the 'relative' stability of the two isomers, better enlighten the driving forces of the reaction. The two energetically favoured conformers of **2*o*f** and **3*o*f** show a significantly different energy content (ΔE 16.8 kJ mol^{-1}) and the formation from **D**/**E** of the 'unexpected' isomer would be preferred with respect to that of the less stable 'expected' one. Moreover the different **2*o*/3*o*** ratios as a function of the strength of the weak nucleophile used (that is, the more efficient the nucleophile, the higher the ratio) seem to confirm that the partition between the two reaction pathways depends on the nature of the nucleophile: good nucleophiles do not require base-catalysis and then favour the normal S_NAr pathway.[6]

3. Conclusions

A coordinated synthetic, spectrometric (^{13}C NMR and EI-MS) and theoretical study on the reactivity of **1** with some *ortho*-substituted anilines and on the relevant reaction products has been carried out.

The whole of reactivity results has allowed to ascertain the influence of the nature of the substituent in the aniline on the course of the nucleophilic displacement (reactivity as well as **2*o*/3*o*** ratio). An accurate analysis of ^{13}C and EI-MS spectra of the obtained **2*o*** and **3*o*** has also been carried out.

Finally, ab initio computations at DFT level in the gas phase have furnished useful informations on the different geometry and stability of the **2*o*** and **3*o*** isomers and of their conformers. The results obtained have given further support to the reaction mechanism proposed by us,[4–6] ascribing a role to the different stability of the two isomers **2*o*** and **3*o*** (for example, **3*o*f** is 16.8 kJ mol^{-1} more stable than **2*o*f**) on the course of the reaction. Such a stability difference could also be responsible of some EI-MS results.



Scheme 4. Reaction pathways proposed for the formation of the substitution products.

Table 10. Melting point, crystallisation solvent, colour, IR and HRMS of **2*o*a**-***o*e**, ***o*g**-***o*i** and **3*o*c**-***o*e**, ***o*g**-***o*i**

Compounds	X	**2*o***: mp (°C); crystallisation solvent; colour; IR ν (cm^{-1})[a]	HRMS	**3*o***: mp (°C); crystallisation solvent colour; IR ν (cm^{-1})	HRMS
a	OH	224–226; ethanol; red; 3384.3, 3278.9, 3014.2, 1575.6, 1402.7	Found: 286.04085, calcd: 286.04121	–	–
b	NH_2	205–206; ethanol; red; 3486.8, 3393.4, 3248.1, 3009.4, 1570.6, 1539.6, 1482.5, 1404.7, 1311.3	Found: 285.05698, calcd: 285.05720	–	–
c	OMe	141–141.5; ethanol; red; 3268.9, 3009.4, 1575.9, 1539.6, 1407.7, 1311.3	Found: 300.05709, calcd: 300.05686	212–213; ethanol; yellow; 3258.5, 3019.8, 1555.2, 1498.1, 1384.0	Found: 300.05725, calcd: 300.05686
d	Me	160.5–161; ethanol; orange; 3248.3, 3009.6, 1570.8, 1544.9, 1482.6, 1404.8, 1316.3	Found: 284.06221, calcd: 284.06195	116–117; cyclohexane; yellow; 3248.3, 3009.6, 1550.1, 1477.4, 1441.1, 1384.0, 1332.1	Found: 284.06226, calcd: 284.06195
e	Et	121–122; cyclohexane; orange; 3248.1, 3009.4, 1575.9, 1544.8, 1482.5, 1404.7, 1316.5	Found: 298.07767, calcd: 298.07760	147–148; cyclohexane; yellow; 3248.1, 3009.4, 1555.8, 1472.2, 1446.2, 1384.0, 1337.3	Found: 298.07782, calcd: 298.07760
g	F	174–175; ethanol; orange; 3265.4, 3011.7, 1575.8, 1542.9, 1491.3, 1402.0, 1317.5	Found: 288.03668, calcd: 288.03688	173–174; ethanol; yellow, 3227.4, 3009.4, 1560.4, 1456.6, 1441.8, 1384.0, 1337.3	Found: 288.03715, calcd: 288.03688
h	Cl	192–193; ethanol; pale orange; 3268.9, 3018.8, 1575.9, 1539.6, 1472.2, 1404.7, 1320.0	Found: 304.00764[b], calcd: 304.00733	161.5–162.5; ethanol; garnet red; 3248.1, 3019.8, 1550.0, 1441.0, 1384.0, 1332.1	Found: 304.00716[b], calcd: 304.00733
i	Br	196.5–197.5; ethanol; pale orange; 3268.9, 3009.4, 1575.9, 1539.0, 1472.2, 1404.7, 1319.7	Found: 347.95653[c], calcd: 347.95681	158–158.5; ethanol; garnet red; 3258.5, 3009.4, 1550.0, 1461.6, 1441.0, 1384.0, 1337.3	Found: 347.95699[c], calcd: 347.95681

[a] In $CHCl_3$ solution.
[b] ^{35}Cl isotope.
[c] ^{79}Br isotope.

Table 11. ^{1}H NMR spectral data of compounds **2*o*** in DMSO-d_6

Compounds	X	^{1}H NMR
a	OH	6.93 (1H, dd, *J*=7.8, 7.5 Hz, H5′); 7.00 (1H, d, *J*=8.0 Hz, H3′); 7.05 (1H, d, *J*=8.5 Hz, H4); 7.17 (1H, dd, *J*=8.5, 7.0 Hz, H5); 7.28 (1H, dd, *J*=8.0, 7.5 Hz, H4′); 7.34 (1H, d, *J*=7.8 Hz, H6′); 7.57 (1H, dd, *J*=8.1, 7.0 Hz, H6); 7.92 (1H, d, *J*=8.1 Hz, H7); 10.00 (1H, s exch, OH); 10.31 (1H, s exch, NH).
b	NH_2	5.40 (2H, s exch, NH_2); 6.62 (1H, dd, *J*=7.4, 7.4 Hz, H5′); 6.85 (1H, d, *J*=8.2 Hz, H4); 6.94 (1H, d, *J*=8.5 Hz, H3′); 7.11–7.20 (3H, m, H5, H4′, H6′); 7.56 (1H, dd, *J*=8.2, 7.4 Hz, H6); 7.90 (1H, d, *J*=8.2 Hz, H7); 10.19 (1H, s exch, NH).
c	OMe	3.70 (3H, s, OMe); 7.02–7.09 (2H, m, H4, H5′); 7.10–7.22 (2H, m, H5, H3′); 7.39–7.45 (2H, m, H4′, H6′); 7.58 (1H, dd, *J*=7.8, 7.1 Hz, H6); 7.94 (1H, d, *J*=7.8 Hz, H7); 10.29 (1H, s exch, NH).
d	Me	2.23 (3H, s, Me); 6.63 (1H, d, *J*=8.3 Hz, H4); 7.11 (1H, dd, *J*=8.3, 7.8 Hz, H5); 7.31–7.46 (4H, m, H3′, H4′, H5′, H6′); 7.56 (1H, dd, *J*=7.8, 7.8 Hz, H6); 7.93 (1H, d, *J*=8.0 Hz, H7); 10.51 (1H, s exch, NH)
e	Et	1.10 (3H, t, *J*=7.5 Hz, CH_3); 2.63 (2H, q, *J*=7.5 Hz, CH_2); 6.62 (1H, d, *J*=8.4 Hz, H4); 7.10 (1H, dd, *J*=8.4, 7.3 Hz, H5); 7.31–7.37 (2H, m, H5′, H6′); 7.44–7.47 (2H, m, H3′, H4′); 7.55 (1H, dd, *J*=8.0, 7.3 Hz, H6); 7.93 (1H, d, *J*=8.0 Hz, H7); 10.56 (1H, s exch, NH).
g	F	7.12 (1H, d, *J*=8.3 Hz, H4); 7.23–7.47 (4H, m, H5, H4′, H5′, H6′); 7.52 (1H, dd, *J*=8.0, 8.0 Hz, H3′); 7.61 (1H, dd, *J*=8.0, 7.7 Hz, H6); 7.98 (1H, d, *J*=8.0 Hz, H7); 10.32 (1H, s exch, NH).
h	Cl	6.77 (1H, d, *J*=8.0 Hz, H4); 7.20 (1H, dd, *J*=8.0, 7.7 Hz, H5); 7.45–7.49 (2H, m, H4′, H5′); 7.54–7.69 (3H, m, H6, H3′, H6′); 7.97 (1H, d, *J*=8.0 Hz, H7); 10.39 (1H, s exch, NH).
i	Br	6.77 (1H, d, *J*=8.0 Hz, H4); 7.19 (1H, dd, *J*=8.5, 8.0 Hz, H5); 7.40–7.62 (4H, m, H6, H4′, H5′, H6′); 7.84 (1H, d, *J*=8.0 Hz, H3′); 7.97 (1H, d, *J*=8.5 Hz, H7); 10.48 (1H, s exch, NH).

Table 12. ^{1}H NMR spectral data of compounds **3*o*** in DMSO-d_6

Compounds	X	^{1}H NMR
c	OMe	3.89 (3H, s, OMe); 7.13 (1H, dd, *J*=7.8, 7.0 Hz, H5′); 7.25–7.44 (3H, m, H6, H3′, H4′); 7.49 (1H, dd, *J*=7.8, 7.8 Hz, H5); 7.62 (1H, d, *J*=7.7 Hz, H6′); 7.81 (1H, d, *J*=7.3 Hz, H7); 8.33 (1H, d, *J*=7.8 Hz, H4); 11.33 (1H, s exch, NH).
d	Me	2.29 (3H, s, Me); 7.28 (1H, dd, *J*=8.0, 7.8 Hz, H6); 7.37–7.53 (5H, m, H5, H3′, H4′, H5′, H6′); 7.72 (1H, d, *J*=8.0 Hz, H7); 8.31 (1H, d, *J*=7.8 Hz, H4); 11.14 (1H, s exch, NH).
e	Et	1.14 (3H, t, *J*=7.4 Hz, CH_3); 2.65 (2H, q, *J*=7.4 Hz, CH_2); 7.28 (1H, dd, *J*=7.7, 7.2 Hz, H6); 7.37–7.52 (5H, m, H5, H3′, H4′, H5′, H6′); 7.72 (1H, d, *J*=7.2 Hz, H7); 8.30 (1H, d, *J*=7.6 Hz, H4); 11.17 (1H, s exch, NH)
g	F	7.31 (1H, dd, *J*=7.8, 7.6 Hz, H6); 7.36–7.54 (4H, m, H5, H4′, H5′, H6′); 7.70 (1H, dd, *J*=8.2, 7.7 Hz, H3′); 7.77 (1H, d, *J*=7.6 Hz, H7); 8.31 (1H, d, *J*=7.8 Hz, H4); 11.11 (1H, s exch, NH).
h	Cl	7.32 (1H, dd, *J*=7.8, 7.3 Hz, H6); 7.46–7.58 (3H, m, H5, H4′, H5′); 7.73–7.79 (3H, m, H-7, H3′, H6′); 8.32 (1H, d, *J*=7.5 Hz, H4); 11.28 (1H, s exch, NH)
i	Br	7.31 (1H, dd, *J*=8.4, 7.3 Hz, H6); 7.40–7.50 (2H, m, H5, H4′); 7.59 (1H, dd, *J*=8.7, 7.6 Hz, H5′); 7.73–7.79 (2H, m, H7, H6′); 7.89 (1H, d, *J*=7.9 Hz, H3′); 8.32 (1H, d, *J*=7.9 Hz, H4); 11.26 (1H, s exch, NH)

4. Experimental

Melting points were determined using a Kofler apparatus and are uncorrected. NMR spectra were recorded on a Varian Gemini 300 Instrument in the Fourier transform mode at 21±0.5°C in DMSO-d_6 and in $CDCl_3$. ^{1}H (300.07 MHz, 0.02M) and ^{13}C (75.43 MHz, 0.1 M) chemical shifts (δ) are in ppm relative to TMS as secondary internal reference. High resolution mass spectra (HRMS) were recorded on a VG70 70E apparatus. IR spectra were obtained with a Perkin–Elmer Spectrum RX IFT-IR System in $CHCl_3$ solution. Solvents were removed under reduced pressure. TLC: precoated silica gel (Merck F_{254}) or aluminium oxide neutral (Merck art. 5550) plates. Flash chromatography: silica gel 60 (ICN Silica 32–63) or aluminium oxide neutral (Merck art. 1097). All new compounds gave good C, H, N and S analysis. The substrate (**1**) was obtained in 98% purity according to a literature procedure.[42]

4.1. General Procedure for the reactions of 1 with Anilines 4*o*b–*o*i

The appropriate aniline (4.65 mmol) and Et_3N (4.65 mmol) were added to a solution of **1** (0.400 g, 1.55 mmol) in DMF (4.5 mL) and the mixture kept at 120°C until disappearance of **1**. The mixture was then cooled to room temperature, poured into ice/water and the precipitate filtered, dried under vacuum and purified by crystallisation or flash-chromatography on silica gel. Reaction times, yields, isomeric ratios and separation method are reported in Table 1. Crystallisation solvent, melting point, colour, IR and HRMS are reported in Table 10 and ^{1}H NMR in DMSO-d_6 are collected in Tables 11 and 12, respectively.

4.2. Procedure for the reactions of 1 with anilines 4*o*b–*o*c in the absence of Et_3N

The appropriate aniline (4.65 mmol) was added to a solution of **1** (0.400 g, 1.55 mmol) in DMF (4.5 mL) and the mixture kept at 120°C until disappearance of **1**. The mixture was then cooled to room temperature, poured into ice/water and the precipitate filtered, dried under vacuum and crystallised from EtOH to give **2*o*** as the exclusive product (**2*o*b**: 1 h; 93%. **2*o*c**: 30 min; 99%).

4.3. Reactions of 1 with *ortho*-Aminophenol (4*o*a)

Method i. *ortho*-Aminophenol (4.65 mmol) was added to a solution of **1** (0.400 g, 1.55 mmol) in DMF (4.5 mL) and the mixture kept at room temperature until disappearance of **1** (5 days). The mixture was then poured into ice/water and the precipitate filtered, dried under vacuum and purified by crystallisation from ethanol to give 63% of **2*o*a**. Physical data are reported in Tables 10–12.

Method ii. Operating as above, but at 50°C, after 90 min compound **2*o*a** was obtained in 30% yield.

Method iii. *ortho*-Aminophenol (4.65 mmol) and triethylamine (4.65 mmol) were added to a solution of 1 (0.400 g, 1.55 mmol) in DMF (4.5 mL) and the mixture kept at 50°C until disappearance of 1 (1 h). The mixture was then cooled to room temperature, poured into ice/water and the precipitate filtered, dried under vacuum and purified by crystallisation from ethanol to give **2*o*a** (30%).

Method iv. Operating as above, but with K_2CO_3 (4.65 mmol in 0.5 mL of H_2O), after 30 min compound **2*o*a** was obtained in 41% yield.

Method v. Operating as above, but with K_2CO_3 (15.55 mmol in 2.3 mL of H_2O), after 15 min compound **2*o*a** was obtained in 25% yield.

4.4. Computational methods

All DFT molecular structures were fully optimised with the gradient method available in the GAUSSIAN 98[37,38] program package and rigorously characterised as minima according to the number of imaginary mode by applying a second-order derivative calculation. DFT level geometry were performed using the non-local hybrid Becke's three-parameter exchange functional denoted as B3LYP,[37,38] using the DZVP[38] basis set which is a local spin density (LSD)-optimised basis set of double-ζ quality in the valence shell plus polarisation functions.

Further computational details including Cartesians coordinates and computed total energies of optimised structures are available by request to Corresponding Author.

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