On the reaction between 3-bromo-2-nitrobenzo[*b*]thiophene and some amines: a novel aromatic nucleophilic substitution with rearrangement

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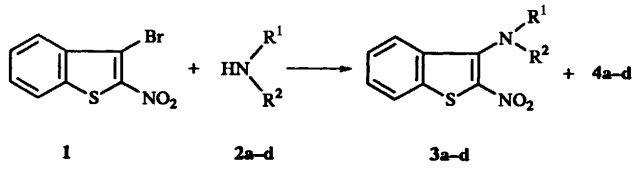
3-Bromo-2-nitrobenzo[*b*]thiophene reacted with some amines in *N*,*N*-dimethylformamide giving, together with the expected *N*-substituted 3-amino-2-nitrobenzo[*b*]thiophenes **3** deriving from aromatic nucleophilic substitution, their isomers **4**, whose unexpected structure of *N*-substituted 2-amino-3-nitrobenzo[*b*]thiophenes has been determined by means of spectroscopic techniques. As 2-bromo-3-nitrobenzo[*b*]thiophene gave tars with nucleophiles, the observed reaction could be of use for the synthesis of **4**. Some hypotheses on the mechanism of formation of **3** and **4** are suggested.

3-Bromo-2-nitrobenzo[*b*]thiophene **1** is known[1] to react with neutral and anionic nucleophiles giving the expected ipso-substitution products (presumably *via* the S_NAr mechanism). Recently some of us reported the pharmacologic properties of a series of *N*-substituted 3-amino-2-nitrobenzo[*b*]thiophenes **3**, which show interesting analgesic, antiexudative and anti-inflammatory activities.[2] A closer study of the synthesis of these compounds showed that in some instances the nucleophilic substitution between 3-bromo-2-nitrobenzo[*b*]thiophene **1** and amines **2** in DMF did not furnish a unique product; thus, together with the expected **3**, by-products **4** were isolated in 15–35% yield (Scheme 1).



1 **2a–d** **3a–d**

a R^1 = H, R^2 = $C_6H_4CF_3$-3
b R^1 = H, R^2 = $C_6H_4CF_3$-4
c R^1 = H, R^2 = CH_2CO_2Me
d R^1 = Pr, R^2 = CH_2CO_2Et

Scheme 1

Results

3-Bromo-2-nitrobenzo[*b*]thiophene **1** (purity degree >98%) reacted with 3- and 4-(trifluoromethyl)aniline, glycine methyl ester and *N*-propylglycine ethyl ester **2a–d** giving two reaction products **3a–d** (yield 85–65%) and **4a–d** (yield 15–35%), whose structures were investigated using spectroscopic techniques: a thorough discussion will be hereinafter carried out on the products **3a** and **4a** obtained with 3-(trifluoromethyl)aniline **2a**.

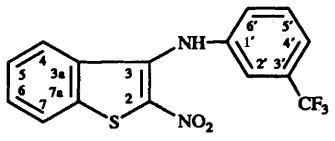
Analytical data (C, H, N, S and molecular weight) showed that both **3a** and **4a** had the molecular formula $C_{15}H_9F_3N_2O_2S$. As expected,[2b,3] the ^1H NMR spectrum of **3a** (the main product of the reaction) in [$^2H_6$]dimethyl sulfoxide ([$^2H_6$]DMSO) solution (see Table 1) showed the presence of the four protons of a 2,3-disubstituted benzo[*b*]thiophene moiety together with four protons with resonances in the range δ 7.45–7.60, relevant to the anilino moiety. On the other hand **4a** (the by-product of the reaction) also, although with different chemical shift values, interestingly enough showed proton resonances supporting the same overall substitution pattern. In both **3a** and **4a** a proton signal (exchangeable with deuterium oxide) in the low-field region confirmed the presence of a proton bound to a nitrogen atom.

Table 1 ^{13}C and ^1H NMR chemical shifts (in ppm) relative to internal TMS in [$^2H_6$]DMSO solutions for benzo[*b*]thiophenes **3a**, **b**, **4a**, **b** and **5**

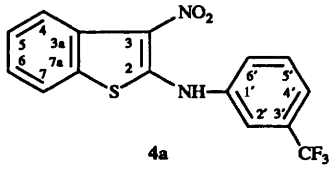
Compound	**3a**[a]	**4a**[a]	**3b**[a]	**4b**[a]	**5**
C-2(H)	127.95	161.48	129.94	160.22	136.00 (9.27)
C-3	139.88	120.75	138.58	121.44	141.38
C-3a	130.31	130.94	130.96	130.84	129.48
C-4(H)	125.73 (7.46)	121.38 (8.32)	125.76 (7.70)	121.59 (8.34)	122.91 (8.45)
C-5(H)	124.98 (7.34)	126.82 (7.48)	125.20 (7.41)	126.92 (7.48)	127.03 (7.67)
C-6(H)	130.72 (7.63)	124.91 (7.32)	130.69 (7.66)	125.08 (7.35)	126.27 (7.59)
C-7(H)	123.86 (8.01)	122.43 (7.81)	123.79 (8.03)	122.40 (7.79)	123.82 (8.20)
C-7a	137.09	125.03	136.87	125.20	138.41
(NH)	(10.38)	(11.34)	(10.32)	(11.05)	
C-1′	141.07	140.20	144.39	142.96	
C-2′(H)	118.43 (7.60)	121.55 (8.02)	120.60 (7.29)	124.22 (7.85)	
C-3′(H)	129.77	130.43	126.10 (7.67)	126.83 (7.89)	
C-4′(H)	120.85 (7.53)	123.96 (7.79)	123.82	127.29	
C-5′(H)	130.03 (7.59)	130.92 (7.77)	126.10 (7.67)	126.83 (7.89)	
C-6′(H)	125.54 (7.46)	128.50 (7.95)	120.60 (7.29)	124.22 (7.85)	
CF_3	123.96	123.66	124.47	123.37	

[a] Values for $^1J_{C,F}$ 272.6 ± 0.1, $^2J_{C,F}$ 32.0 ± 0.1 and $^3J_{C,F}$ 3.8 ± 0.1 Hz.

The proton fully decoupled ^{13}C NMR spectrum of **3a** showed signals corresponding to 15 carbon atoms, four of them (C-2′, C-3′, C-4′ and CF_3) as quartets with coupling constant values dependent on their differing interactions with the fluorine atoms. The coupled ^{13}C NMR spectrum, together with hetero-nuclear selective decoupling experiments, was consistent with structure **3a**, *i.e.* (2-nitrobenzo[*b*]thiophen-3-yl)(3-trifluoromethylphenyl)amine, the expected product of ipso-substitution from **1**.[2b] The assignments of the chemical shifts to the various nuclei are reported in Table 1. The ^{13}C NMR spectra (decoupled, coupled and heterocorrelated) of **4a** once more showed a similar substitution pattern, which is in agreement with a structure of (3-nitrobenzo[*b*]thiophen-2-yl)(3-trifluoromethylphenyl)amine, *i.e.* of an unexpected product possibly



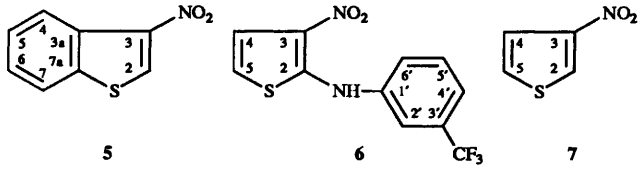
3a



4a

deriving from some rearrangement in the benzo[*b*]thiophene skeleton along with substitution. Thus, when comparing the ^{13}C NMR chemical shift values of **3a** and **4a** one observes that in **4a** the C-2 atom of the thiophene moiety is significantly deshielded with respect to **3a** because of the lack of an *ortho*-like effect from the anilino moiety that, in contrast, clearly influences the C-3 chemical shift of **4a**. Moreover C-7a is more shielded in **4a** than in **3a** because of the replacement of the *para*-like deshielding effect of the nitro group (effective in **3a**) with an opposite *para*-like shielding effect of the anilino group. In addition, the carbon atoms C-4 and C-6 of the benzo-condensed moiety, which are conjugated with the substituent at C-2, are significantly shielded ($\Delta\delta$ 4–6 ppm) by long range effects of the anilino group in **4a**, as compared with the deshielding due to the nitro group in **3a**. On the other hand, C-5 and C-7, which are not conjugated with the substituent at C-2, are hardly affected by a change in the substituent itself. Finally, the chemical shift values of C-1′, C-3′ and C-5′ of **4a** are strictly comparable with those of the corresponding carbon atoms of **3a** ($\Delta\delta$ < 1 ppm), whereas C-2′, C-6′ and C-4′ (*ortho* and *para* with respect to the amino group) are more deshielded ($\Delta\delta$ 3 ppm), thus indicating reduced electronic interactions between the aromatic ring and the amino group.

It is known [1d] that 2-bromo-3-nitrobenzo[*b*]thiophene is not able to give 3-nitro-2-piperidinobenzo[*b*]thiophene by action of piperidine, moreover De Santis and Stegel[1c] synthesized 2-methoxy-3-nitrobenzo[*b*]thiophene by nitration of 2-methoxybenzo[*b*]thiophene. Thus, with the aim of gaining further insight into the substituent effects on the chemical shift values of **4a** we also analysed the ^{13}C NMR spectra in [$^2H_6$]DMSO solutions of 3-nitrobenzo[*b*]thiophene **5**,[4] (3-nitro-2-thienyl)(3-trifluoromethylphenyl)amine **6** and 3-nitro-



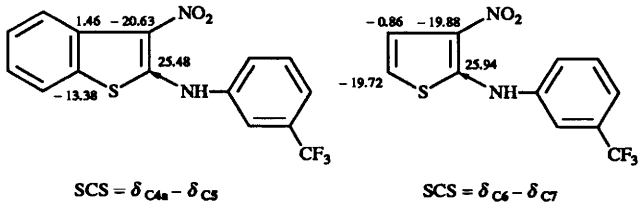
5 **6** **7**

thiophene **7**.[5] By comparing the ^{13}C chemical shifts of **4a** and **5** (Table 1) and those of **6** (Experimental section) and **7** † we calculated the substituent chemical shift (SCS) values determined by the introduction at C-2 of the (3-trifluoromethyl)-anilino group. An examination of the effects observed (see Scheme 2) shows that, while the SCS values at C-2 and C-3 are

† Data from ref. 5. δ_C(TMS–[$^2H_6$]DMSO) 129.76 (C-2), 148.01 (C-3), 122.15 (C-4) and 128.90 (C-5); δ_H(TMS–[$^2H_6$]DMSO) 8.76 (2-H), 7.74 (5-H) and 7.65 (4-H).

Table 2 ^{13}C and ^1H NMR chemical shifts (in ppm) relative to internal TMS in [$^2H_6$]DMSO solutions for benzo[*b*]thiophenes **3c**, **d** and **4c**, **d**

Compound	3c	4c	3d	4d
C-2	119.07	164.40	133.10	163.27
C-3	147.32	120.37	146.41	122.84
C-3a	128.57	131.27	134.33	132.05
C-4(H)	127.28	121.29	126.91	121.21
	(8.17)	(8.29)	(8.19)	(8.19)
C-5(H)	125.28	126.84	125.34	126.56
	(7.45)	(7.46)	(7.52)	(7.47)
C-6(H)	131.37	124.57	130.05	124.52
	(7.67)	(7.31)	(7.65)	(7.34)
C-7(H)	123.85	122.48	123.52	121.97
	(7.93)	(7.83)	(7.97)	(7.84)
C-7a	138.00	124.84	135.84	126.09
(NH)	(9.72)	(10.02)		
$C(H_2)CO_2R$	46.46	48.37	54.34	56.29
	(4.93)	(4.43)	(4.34)	(4.45)
CH_2CO_2R	169.70	168.40	169.61	168.40
$CH_2CO_2R(H)$	52.56	52.45	60.47	60.78
	(3.77)	(3.77)	(4.06)	(4.13)
			13.83	13.88
			(1.12)	(1.18)
$C(H_2)CH_2CH_3$			55.47	58.74
			(3.69)	(3.57)
$CH_2C(H_2)CH_3$			21.15	19.90
			(1.55)	(1.77)
$CH_2CH_2C(H_3)$			10.68	10.72
			(0.79)	(0.91)



SCS = $\delta_{C4a} - \delta_{C5}$ SCS = $\delta_{C6} - \delta_{C7}$

Scheme 2

comparable in the two couples of compounds, C-7a of **4a** experiences a lower shielding effect than C-5 of **6**. This peculiar behaviour may be related to the different nature of C-5 and of C-7a, the latter being, in fact, a junction carbon atom, whose properties must therefore depend on its participation in both a benzene and a thiophene ring.

NMR experiments on **3b–d** and **4b–d**, analogous to those reported above, allowed the assignment, for such derivatives, of structures similar to those of **3a** and **4a**, respectively. The relevant chemical shift values are collected in Tables 1 and 2.

The bulk of ^{13}C NMR data so far collected allow some general deductions on chemical shift attributions. For instance, different amino moieties cause (Tables 1 and 2) relatively small variations in the chemical shift of the carbon atoms of the benzo[*b*]thiophene skeleton within the **3a–d** or the **4a–d** series: this allows the use of some of the chemical shift values to characterize the products obtained. In particular, this approach is very effective in the analysis of compounds **4a–d**, which show characteristic resonances for the eight carbon atoms of the benzo[*b*]thiophene skeleton with minor variations of 3–4 ppm for C-2 and C-3 and 0.5–1 ppm for C-3a–C-7a.

The electron impact mass spectra (EI-MS) of **3a** and **4a** allowed the direct determination of the molecular formula by exact mass measurement (Found: 338.0330 and 338.0340, respectively, for **3a** and **4a**. $C_{15}H_9F_3N_2O_2$ requires 338.0337), confirming the data obtained by elemental analysis and molecular weight determination. In both **3a** and **4a** the molecular peak shows the highest relative intensity. Globally the two EI-MS show the same fragmentation pattern, although

with different relative intensities, in agreement with the proposed structures: in particular, the spectra show the characteristic fragmentations expected for nitro(hetero)-aromatics,[3] trifluoromethyl-containing molecules[3b] and benzo[*b*]thiophenes.[3a]

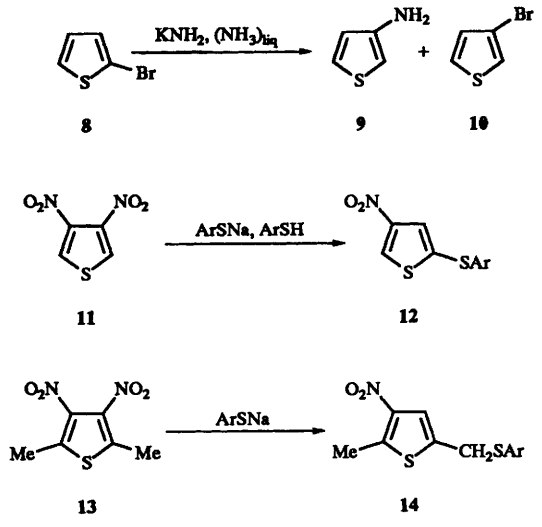
A further confirmation of the structure proposed for **4a** was obtained by comparing its UV–VIS spectrum in methanol with that of **3a**. The spectrum of **3a** is characterized by maxima at 331 and 443 nm (ε/dm^3 mol^{-1} cm^{-1} 9800 and 13 400, respectively) attributable to the chromophore O_2N–C=C–NR^1R^2, which is part of a heteroaromatic system. The presence of the same chromophore was clearly manifest also in the spectrum of **4a**, which showed a weak band at *ca.* 320–340 nm (ε/dm^3 mol^{-1} cm^{-1} 2900–3400), partially hidden by a band at 395 nm (ε/dm^3 mol^{-1} cm^{-1} 12 800). A similar trend was observed in the UV–VIS spectra of **4b–d** as compared with **3b–d**.

To gain a first insight into the real course of the process we followed by NMR the reaction between **1** and **2d** in [$^2H_6$]DMSO solution. While the zero time ^{1}H and ^{13}C NMR spectra of the mixture showed only the signals of the two starting products,‡ by monitoring the downfield (aromatic) region at regular intervals we observed the disappearance of **1** together with the corresponding parallel increase of the signals relevant to **3d** and **4d**. At any stage of the reaction the ^{1}H NMR spectra allowed the calculation of a constant ratio between the two **3d** and **4d** isomers (**3d**:**4d** = 65:35) and this could indicate their formation along competitive reaction pathways and the exclusion of rearrangements following the primary process.

Discussion

In the thiophene series many examples of 'anomalous' nucleophilic substitutions have been reported (Scheme 3).[6] Thus, 2-bromothiophene **8** with potassium amide in liquid ammonia gives a mixture of 3-amino- **9** and 3-bromo-thiophene **10** through a cine-substitution occurring *via* a BCHD (base-catalysed halogen dance) mechanism, 3,4-dinitrothiophene **11** with sodium arenethiolates and arenethiols in methanol furnishes 2-arylsulfanyl-4-nitrothiophenes **12** through a cine-substitution occurring *via* an ASE (addition–substitution–elimination) mechanism, while 2,5-dimethyl-3,4-dinitrothiophene **13** reacts with sodium arenethiolates in methanol to give 5-(arylsulfanylmethyl)-2-methyl-3-nitrothiophenes **14** through a tele-substitution *via* tautomerization followed by a S_N2'-like process.

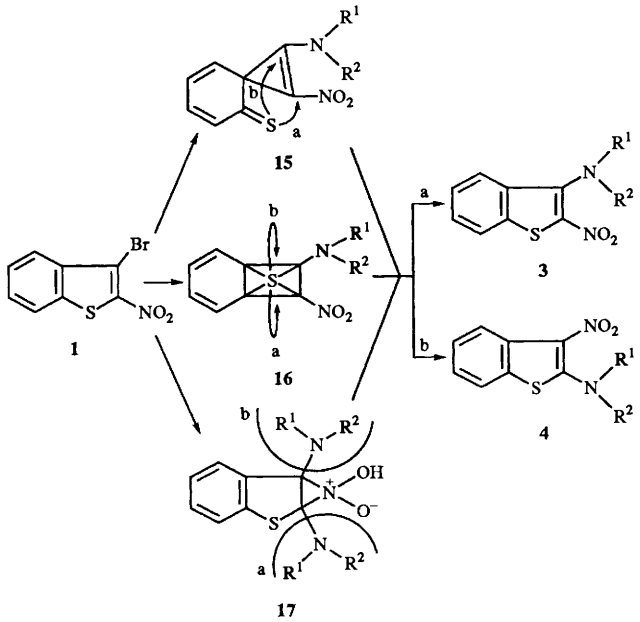
The results obtained in the present paper can hardly be accounted for in the framework of the examples of the known 'anomalous' (*i.e.* non-ipso) nucleophilic substitution reactions. Neither the BCHD mechanism (that requires the presence of an acidic hydrogen atom in the aromatic, or heteroaromatic ring involved, and is not characteristic of compounds containing strong electron-withdrawing groups) nor the usual cine-substitution mechanism [occurring *via* aryne or aryne-like (hetaryne) intermediates (EA mechanism) as well as *via* the ASE mechanism, the abnormal addition–elimination (EA_a) mechanism or the addition of nucleophile followed by ring opening and ring closure (ANRORC) mechanism] could be invoked. In



8 **9** **10** **11** **12** **13** **14**

Scheme 3

fact no example of 'anomalous' nucleophilic substitution reactions is known, which involves an apparent scrambling between the position of the nucleophilic attack and of the activating group (the nitro group, in the case). In our instance, the formation of the two reaction products requires, at some stage of the reaction, an intermediate in which carbon atoms 2 and 3 of the benzo[*b*]thiophene ring become in some way 'equivalent' with respect to the sulfur atom so determining the rearrangement in the benzo[*b*]thiophene skeleton along with the substitution. The behaviour of 3-bromobenzo[*b*]thiophene with piperidine[7] which gives beside the expected 3-piperidinobenzo[*b*]thiophene as major product also a small amount (1–5%) of the 2 isomer, does not help in understanding the behaviour of **1** with amines **2a–d**.



1 **15** **16** **17** **3** **4**

Scheme 4

At first sight some different pathways for the reactions shown in Scheme 1 seem possible: (*i*) an intermediate with a spiro[2.5]octa-1,5,7-triene-4-thione **15** (or spiro[2.5]octa-5,7-diene-4-thione) structure; (*ii*) an intermediate which is a thiophene valence bond isomer **16**; (*iii*) an intermediate with an *N*-oxide of 1a,6a-dihydro-6-thia-1-aza-cyclopropan[*a*]inden-1-ol structure **17**, deriving from a double nucleophilic addition

‡ Chemical shift values measured at zero time for the reaction mixture agree very well (to within ± 0.05 ppm) with those separately obtained for the two starting products. **1**, δ_C(TMS–[$^2H_6$]DMSO) 145.89 (C-2), 111.76 (C-3), 136.38 (C-3a), 126.22 (C-4), 127.19 (C-5), 130.64 (C-6), 123.70 (C-7) and 136.53 (C-7a); δ_H(TMS–[$^2H_6$]DMSO) 8.18 (7-H), 8.02 (4-H), 7.76 (6-H) and 7.67 (5-H). **2d**, δ_C(TMS–[$^2H_6$]DMSO) 48.36 ($CH_2CH_2CH_3$), 18.66 ($CH_2CH_2CH_3$), 10.89 ($CH_2CH_2CH_3$), 46.47 (CH_2CO_2), 166.60 (CO_2), 61.54 (OCH_2) and 13.91 (OCH_2CH_3); δ_H(TMS–[$^2H_6$]DMSO) 9.50 (NH), 4.19 (OCH_2), 3.91 (CH_2CO_2), 2.84 ($CH_2CH_2CH_3$), 1.66 ($CH_2CH_2CH_3$), 1.22 (OCH_2CH_3) and 0.88 ($CH_2CH_2CH_3$).

followed by an anchimerically assisted loss of Br^-.§ Scheme 4 shows examples of some possible intermediates. Experiments are in progress to ascertain the nature of the intermediates.

Despite the lack of reliable conclusions concerning its mechanism, the reported reaction can be used to obtain compounds **4**, whose synthesis from 2-bromo-3-nitrobenzo[*b*]thiophene does not seem to be possible.[1c,d]

Experimental

Melting points were determined on a Büchi 510 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer operating in FT mode at 250.13 and 62.90 MHz, respectively, in 0.1 mol dm^{-3} [$^2H_6$]DMSO solutions on a switchable $^1H/^{13}C$ 5 mm probe. Tetramethylsilane (TMS) was used as internal standard. ^{13}C NMR chemical shift values were measured in the proton fully decoupled spectra; proton coupled spectra were obtained in the 'gated decoupled' mode. Signal assignment was confirmed by both homonuclear and heteronuclear selective decoupling experiments. UV–VIS spectra in methanol were recorded on a Varian Cary 1E spectrophotometer. The mass spectra were recorded on a VG70 70E mass spectrometer.

(2-Nitrobenzo[*b*]thiophen-3-yl)(3-trifluoromethylphenyl)amine 3a and (3-nitrobenzo[*b*]thiophen-2-yl)(3-trifluoromethylphenyl)-amine 4a

A solution of 3-bromo-2-nitrobenzo[*b*]thiophene[1b,8] (2.58 g, 10 mmol), triethylamine (2.51 cm^3, 18 mmol) and 3-(trifluoromethyl)aniline (4.83 g, 30 mmol) in *N*,*N*-dimethylformamide (DMF; 30 cm^3) was refluxed for 15 min. The reaction mixture was poured into water–ice and then the precipitate was filtered off and washed with water. The crude mixture (yield 85%) was separated by chromatography on a silica gel column [70–230 mesh; eluent: benzene–cyclohexane (4:1)]. The two products were purified by crystallization from cyclohexane. **3a**, orange, mp 162–163 °C (lit.,[2b] mp 161–163 °C) **4a**, yellow, mp 177–178 °C (Found: C, 53.1; H, 2.7; N, 8.4; S, 9.6. $C_{15}H_9F_3N_2O_2S$ requires C, 53.26; H, 2.68; N, 8.28; S, 9.48%) **3a**:**4a** = 85:15.

(2-Nitrobenzo[*b*]thiophen-3-yl)(4-trifluoromethylphenyl)amine 3b and (3-nitrobenzo[*b*]thiophen-2-yl)(4-trifluoromethylphenyl)-amine 4b

The reaction was carried out as for the synthesis of **3a** and **4a**, starting from 4-(trifluoromethyl)aniline: the crude mixture (yield 85%) was separated and purified as above. **3b**, orange, mp 180–181 °C (lit.,[2b] mp 189–191 °C) **4b**, yellow, mp 167–168 °C (Found: C, 53.2; H, 2.6; N, 8.3; S, 9.6%) **3b**:**4b** = 85:15.

Methyl (2-nitrobenzo[*b*]thiophen-3-ylamino)acetate 3c and methyl (3-nitrobenzo[*b*]thiophen-2-ylamino)acetate 4c

To a solution of 3-bromo-2-nitrobenzo[*b*]thiophene (2.58 g, 10 mmol) in DMF (50 cm^3) were added potassium carbonate (4.15 g, 30 mmol) and glycine methyl ester hydrochloride (3.77 g, 30 mmol) dissolved in the minimum amount of water. The reaction mixture was stirred at room temperature for 8 h and then poured into water–ice. The precipitated product was filtered off, washed with water (yield 70%) and separated by flash chromatography on a silica gel column [70–230 mesh; eluent: cyclohexane–ethyl acetate (7:3)]. The two products were purified by crystallization from ethanol. **3c**, orange, mp 169–170 °C; **4c** (Found: C, 49.7; H, 3.8; N, 10.6; S, 12.1. $C_{11}H_{10}N_2O_4S$ requires C, 49.62; H, 3.79; N, 10.52; S, 12.04%) yellow, mp 177–178 °C (Found: C, 49.6; H, 3.8; N, 10.5; S, 12.0%) **3c**:**4c** = 65:35.

§ We thank a referee for his/her suggestion of this pathway.

Ethyl [*N*-(2-nitrobenzo[*b*]thiophen-3-yl)-*N*-propylamino]-acetate 3d and ethyl [*N*-(3-nitrobenzo[*b*]thiophen-2-yl)-*N*-propylamino]acetate 4d

The reaction was carried out as for the synthesis of **3c** and **4c**, using *N*-propylglycine ethyl ester hydrochloride (5.45 g, 30 mmol): the crude mixture (yield 70%) was separated by MPLC on a silica gel column [230–400 mesh; eluent: cyclohexane–chloroform (1:1)]. The two products were purified by crystallization from light petroleum (bp 35–60 °C) [**3d**, orange, mp 62–63 °C (Found: C, 55.9; H, 5.7; N, 8.8; S, 10.1. $C_{15}H_{18}N_2O_4S$ requires C, 55.88; H, 5.63; N, 8.69; S, 9.95%)] and from hexane [**4d**, yellow, mp 49–50 °C (Found: C, 55.9; H, 5.6; N, 8.7; S, 10.0%)], respectively; **3d**:**4d** = 65:35.

(3-Nitrothiophen-2-yl)(3-trifluoromethylphenyl)amine 6

To a solution of 2-bromo-3-nitrothiophene (0.21 g, 1 mmol) in ethanol (10 cm^3) were added sodium hydrogen carbonate (0.084 g, 1 mmol) and 3-(trifluoromethyl)aniline (0.161 g, 1 mmol). The reaction mixture was refluxed for 6 h and then the solvent was removed under reduced pressure. The residue, which contained a significant amount of unchanged 2-bromo-3-nitrothiophene, was washed with water and then purified by double flash chromatography on a silica gel column [70–230 mesh; using as eluents benzene–cyclohexane (3:2) and light petroleum–diethyl ether (5:1), respectively]. The so obtained **6** was purified by crystallization from ethanol; yellow, mp 97–98 °C; δ_C 155.70 (C-2), 128.13 (C-3), 121.29 (C-4), 109.18 (C-5), 141.38 (C-1'), 118.74 (C-2'), 130.22 (C-3'), 121.79 (C-4'), 130.72 (C-5'), 125.54 (C-6') and 123.74 (CF_3); δ_H 10.51 (NH), 7.89 (2'-H), 7.84 (6'-H), 7.69 (5'-H), 7.61 (4'-H), 7.32 (4-H) and 6.71 (5-H).

Acknowledgements

We thank CNR and MURST for financial support.

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Paper 4/07614A
Received 14*th December* 1994
Accepted 7*th February* 1995