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# On the reactivity of 3-bromo-2-nitrobenzo[*b*]thiophene with nucleophiles: elucidation of the base-catalysed mechanism with rearrangement

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**Abstract**—The reactivity of 3-bromo-2-nitrobenzo[*b*]thiophene (**1**) with several (anionic and neutral) nucleophiles has been examined. Only with neutral, weak nucleophiles (as anilines) **1** gives, in the presence of non-nucleophilic bases (triethylamine or potassium carbonate), together with the 'expected' 3-amino-2-nitrobenzo[*b*]thiophenes (**3**) also the 'unexpected' 2-amino-3-nitrobenzo[*b*]thiophenes (**4**). The composition of the final isomeric mixture depends on the base added (nature and quantity) and on the solvent used. The results demonstrate the relevance of base-catalysis and support a reaction pathway involving the formation of an anionic intermediate (**B**) which undergoes addition of a second molecule of nucleophile to give (**C**) in which migration of the nitro group occurs through a three membered ring (**D** or **E**) formed by loss of bromide ion. © 2001 Elsevier Science Ltd. All rights reserved.

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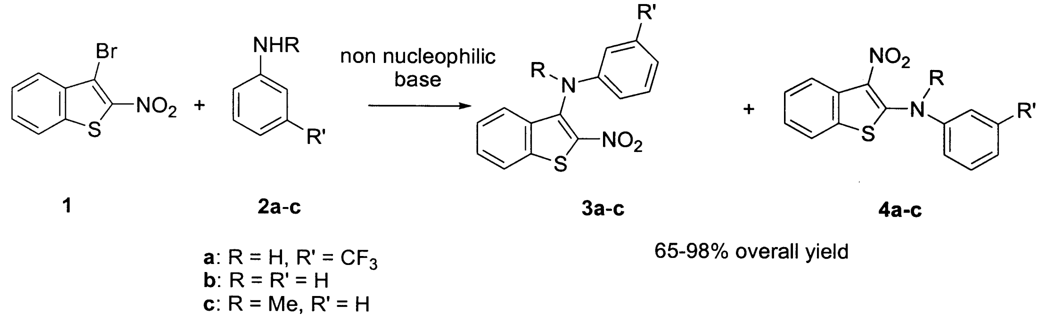
## 1. Introduction

In the framework of our interest in aromatic nucleophilic substitutions,[1–4] we have recently studied the behaviour of 3-bromo-2-nitrobenzo[*b*]thiophene (**1**) with nucleophiles, observing 'unexpected' results in the reaction with some amines.[5,6] Thus we observed, for example, that by refluxing in DMF for 15 min in the presence of $Et_3N$ (a non-nucleophilic base in the experimental conditions employed) **1** and 3-(trifluoromethyl)aniline (**2a**) gave a mixture of the isomeric 3-amino-2-nitro- (**3a**) and 2-amino-3-nitrobenzo[*b*]thiophene (**4a**) (i.e. the 'expected' and 'unexpected' product, respectively; (Scheme 1)) in the 85:15 relative ratio.[5] To enlighten the course of the reaction we studied the behaviour of the $^{13}$C-labelled **1** at C-2, collecting proof in favour of a reaction pathway involving a base-catalysed nitro group migration.[6]

The mechanistic study above originates from a drug-design project linked to the observation that *N*-substituted 3-amino-2-nitrobenzo[*b*]thiophenes show analgesic, anti-exudative and anti-inflammatory properties[7,8] together with very low mutagenicity[9] as measured through the Ames test: thus a way to a new potential class of drugs seems to have been disclosed.

The reactivity of **1** has already been investigated with some anionic (sodium hydroxide[10] and methoxide[11,12]) and



Scheme 1.

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*Keywords*: 3-bromo-2-nitrobenzo[*b*]thiophene; nucleophiles; aromatic nucleophilic substitutions.

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neutral nucleophiles (ammonia,[10] diethylamine,[10] aniline,[10] cyclohexylamine,[11] piperidine,[11,13] morpholine,[13,14] and several other aliphatic and aromatic amines[7,8]). In every case the exclusive formation of the expected *ipso*-substitution products had been claimed.

To gain further insight into the reaction and with the aim of finding experimental conditions favourable to the synthesis of **4a** and structurally similar compounds we have examined the influence of several factors on the reactivity of **1** towards nucleophiles.

## 2. Results

First we confirmed[8] that, in the absence of non-nucleophilic bases, **1** reacts with **2a** in refluxing DMF to give exclusively the 'normal' substitution product **3a**, thus suggesting that the formation of **4a** (the 'unexpected' product) requires catalysis by a base (e.g. $Et_3N$, $pK_B$ 2.99)[15a] stronger than the nucleophile itself (**2a**, $pK_B$ 10.51).[15b] To verify this hypothesis, by using our standard conditions[5] (substrate/nucleophile/added base=1:3:1.8) we have carried out the reaction in the presence of pyridine ($pK_B$ 8.75) or potassium carbonate ($pK_B$ 3.75), i.e. two possible catalysts of much weaker (the former) or comparable basicity (the latter) with respect to $Et_3N$: in the first instance only **3a** was obtained while, in contrast, a significant yield of **4a** (**3a**/**4a**=62:38) was observed with the carbonate. This result clearly indicates the significance of the added base, confirming the occurrence of some kind of base-catalysis for the formation of **4a**.

For a better understanding of the factors that could affect the course of this peculiar kind of nucleophilic substitution we have examined in more detail the influence of the nature of solvent, added base (as well as its concentration), nucleophile[16] and substrate (extending with this aim the study to 3-bromo-5-chloro-2-nitrobenzo[*b*]thiophene).

### 2.1. Influence of the solvent

In order to collect information on the role of the solvent we have chosen a set of solvents with relatively high boiling points (as a matter of fact the reaction occurred very slowly in low-boiling solvents such as methanol or ethanol) and with different properties[17a] such as: relative permittivity (dielectric constant, $\epsilon$) for the pure liquid at 25°C; donicity (normalized donor number, $DN^N$), i.e. an estimate of electron donor ability; solvatochromic solvent polarity [a good estimate of hydrogen-bond donor character (HBD): normalized constant, $E_T^N$]. The relevant values for DMF are bp 153°C, $\epsilon$ 36.71, $DN^N$ 0.69, $E_T^N$ 0.404.

**Table 1.** Results of the reaction of **1** with **2a** (3 mol. equiv.) by refluxing in the presence of $Et_3N$ (1.8 mol. equiv.) for 15 min (columns 1 and 2) or until disappearance of **1** (columns 4, 5, and 6) in various solvents (column 3)

| **3a**/**4a** (%) | Yield (%) | Solvent | **3a**/**4a** (%) | Yield (%) | Time |
|---|---|---|---|---|---|
| 85:15 | 82 | DMF | 75:25 | 90 | 2 h |
| 80:20 | 92 | DMSO | 80:20 | 92 | 15 min |
| 95:5 | 19 | Toluene | 93:7 | 90 | 24 h |
| 92:8 | 28 | 2-ButOH | 88:12 | 92 | 16 h |
| 100:0 | 22 | HFiP | 100:0 | 90 | 16 h |
| –[a] | 5 | ACN | 97:3 | 95 | 24 h |

All the reactions were carried out on a 1.5 mmol scale.

[a] The isomeric ratio could not be evaluated.

The solvents tested were toluene [bp 110.6°C, with a low dielectric constant (2.38) and a low $E_T^N$ (0.099)], 2-butanol [2-BuOH, bp 99.5°C, a protic polar solvent ($\epsilon$ 16.56, $E_T^N$ 0.506)], hexafluoroisopropanol [HFiP, bp 59°C, a protic solvent with significant acidic character ($pK_A$ 9.31, $\epsilon$ 16.7,[18] $E_T^N$ 1.068)], and two further dipolar solvents as DMSO (bp 189°C, $\epsilon$ 46.45, $DN^N$ 0.77, $E_T^N$ 0.444) and acetonitrile (ACN, bp 82°C, $\epsilon$ 35.94, $DN^N$ 0.36, $E_T^N$ 0.460). The last two solvents have different properties relative to the proton 'affinity', the first favouring and the second disfavouring (because of its protophobicity) proton transfer reactions.

All the experiments (Table 1) have been carried out in the standard conditions for a short time (15 min) as well as until complete disappearance of **1**. Both series of data evidence a reactivity sequence (DMSO>DMF>2-ButOH≅HFiP>toluene≅ACN) wherein high-boiling aprotic dipolar solvents rank highest, as expected for a nucleophilic substitution. In every case very good overall yields (≥90%) have been obtained.

We have also ascertained that no interconversion between **3a** and **4a** occurs in the reaction conditions: thus no rearrangement was observed by refluxing, even for long times, pure **3a** or **4a** in the presence of **2a** and $Et_3N$.

Concerning the isomeric (**3a**/**4a**) product composition, we can comment as follows: (a) in HFiP only **3a** could be obtained probably because of the acidic character of the solvent (see the reported $pK_A$ value and the $E_T^N$ value, monitoring a high HBD character), which prevents the effect of the base added (cf. the results obtained in DMF in the absence of $Et_3N$); (b) in ACN only a trace amount (3%) of **4a** has been observed, probably because of the protophobicity of the solvent; (c) in toluene as well as in 2-BuOH, both of low polarity and non-HBA (hydrogen-bond acceptor) solvents (hence of low efficiency both in promoting nucleophilic substitutions and in stabilizing polar intermediates) low absolute yields of **4a** have been

**Table 2.** Results for the reaction of **1** with **2a** in DMF in the presence of variable amounts of different non-nucleophilic bases, until disappearance of **1**

| Entry | Base | **1**/**2a**/base (molar ratio) | **3a**:**4a** (%) | Yield (%) |
|---|---|---|---|---|
| 1 | $Et_3N$ | 1:3:3 | 60:40 | 85 |
| 2 | $Et_3N$ | 1:3:1.8 | 75:25 | 90 |
| 3 | $Et_3N$ | 1:3:1 | 87:13 | 95 |
| 4 | $Et_3N$ | 1:3:0.5 | 91:9 | 98 |
| 5 | $Et_3N$ | 1:3:0.33 | 100:0 | 76 |
| 6 | $Et_3N$ | 1:3:0 | 100:0 | 82 |
| 7 | $C_5H_5N$ | 1:3:1.8 | 100:0 | 82 |
| 8 | $K_2CO_3$[a] | 1:3:3 | 50:50 | 68 |
| 9 | $K_2CO_3$[a] | 1:3:1.8 | 62:38 | 66 |
| 10 | $K_2CO_3$[a] | 1:3:1 | 57:43 | 84 |
| 11 | $K_2CO_3$[a] | 1:3:0.5 | 63:37 | 95 |

All the reactions were carried out on a 1.5 mmol scale.

[a] Solubilized in 0.5 mL of $H_2O$.

**Table 3.** Results for the reaction of **1** with **2b** in DMF in the presence of $Et_3N$ or $K_2CO_3$, until disappearance of **1**

| Entry | Base | **1**/**2b**/base (molar ratio) | **3b**/**4b** (%) | Yield (%) | Time (min) |
|---|---|---|---|---|---|
| 1 | $Et_3N$ | 1:3:1.8 | 100:0 | 90 | 45 |
| 2 | $Et_3N$ | 1:3:3 | 100:0 | 98 | 45 |
| 3 | $Et_3N$ | 1:3:10 | 80:20 | 86 | 15 |
| 4 | $K_2CO_3$[a] | 1:3:3 | 80:20 | 90 | 30 |
| 5 | $K_2CO_3$[b] | 1:3:5 | 75:25 | 92 | 15 |
| 6 | $K_2CO_3$[c] | 1:3:10 | 75:25 | 83 | 15 |

All the reactions were carried out on a 1.5 mmol scale.

[a] $K_2CO_3$ was solubilized in 0.5 mL of $H_2O$.

[b] $K_2CO_3$ was solubilized in 0.6 mL of $H_2O$.

[c] $K_2CO_3$ was solubilized in 2.3 mL of $H_2O$.

observed (6 and 11%, respectively); (d) best yields of **4a**, together with overall highest reactivity, have been found in DMSO and DMF, two aprotic (following Reichardt's recommendation[17b] this term should be more correctly replaced with nonhydroxylic or non-HBD) dipolar solvents both able to promote bimolecular nucleophilic substitutions, to solvate polar intermediates and to behave as HBA solvents: accordingly DMF has been chosen for all the experiments hereinafter.

## 2.2. Influence of base concentration and strength

The influence of the base concentration on the reaction outcome is well evidenced in entries 1–6 of Table 2, which show a direct dependence of the formation of **4a** on the quantity of $Et_3N$.

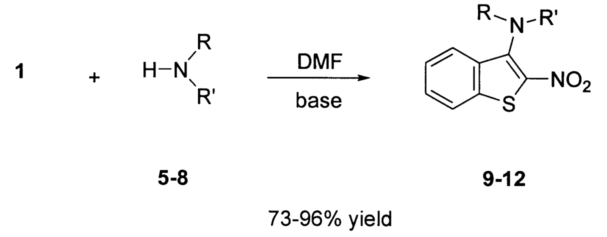
The base strength proves in turn to be a very important factor, as **3a** is the only reaction product in the presence of pyridine (Table 2; entry 7). On the other hand, with $K_2CO_3$ we observed that the relative percentage of **3a** and **4a** is only moderately affected by the quantity of the salt (entries 8 and 9).

## 2.3. Influence of nucleophile[19]

*A. Neutral nucleophiles*: We have tested several aliphatic and aromatic amines. With aniline (**2b**; $pK_B$ 9.37), which is significantly more nucleophilic than **2a**, in the presence of 1.8–3.0 mol equiv. of $Et_3N$ only the expected *N*-(2-nitrobenzo[*b*]thiophene-3-yl)aniline (**3b**) was formed (Table 3, entries 1 and 2), whereas in the presence of 3 equiv. of $K_2CO_3$ (Table 3, entry 4) we obtained (Scheme 1) a 80:20 mixture of **3b** and of the 'unexpected' isomer *N*-(3-nitrobenzo[*b*]thiophene-2-yl)aniline (**4b**), in excellent overall yield (90%).

A significant formation of **4b** in the presence of $Et_3N$ was observed only with a large (tenfold) excess of the catalyst (Table 3, entry 3). On the other hand, a further excess of $K_2CO_3$ (Table 3, entries 5 and 6) causes no significant effect on the **3b**/**4b** ratio.

When employing even stronger nucleophiles, (such as cyclohexylamine (**5**), diethylamine (**6**), piperidine (**7**) or dimethylamine (**8**), i.e.aliphatic amines in the 3–4 $pK_B$ range) only the 'expected' 3-amino-2-nitrobenzo[*b*]thiophenes were observed in the presence of $Et_3N$ as well as of $K_2CO_3$ (Scheme 2 and Table 4).



**Scheme 2.**

**Table 4.** Results for the reaction of **1** with aliphatic amines in DMF in the presence of $Et_3N$ or $K_2CO_3$, until disappearance of **1**

| Entry | Amine | Base | **1**/amine/base (molar ratio) | Product (yield %) |
|---|---|---|---|---|
| 1 | **5** | $Et_3N$ | 1:3:1.8 | **9** (96) |
| 2 | **6** | $Et_3N$ | 1:3:1.8 | **10** (93) |
| 3 | **7** | $Et_3N$ | 1:3:1.8 | **11** (76) |
| 4 | **7** | $K_2CO_3$[a] | 1:3:3 | **11** (73) |
| 5 | **8**[b] | $K_2CO_3$[a] | 1:3:3 | **12** (78) |

All the reactions were carried out on a 1.5 mmol scale.

[a] $K_2CO_3$ was solubilized in 0.5 mL of $H_2O$.

[b] Dimethylamine hydrochloride, neutralized with $K_2CO_3$.

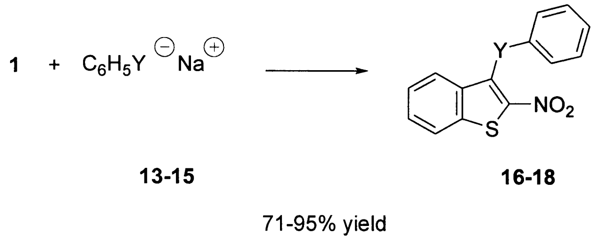
Compounds **9**,[11] **10**[10] and **11**[11,13] were already known and their structures were assigned by comparison with literature data: these, as well as unknown compounds, have been fully characterized by $^1H$ and $^{13}C$ NMR and mass spectra.

On the other hand with the arylaliphatic *N*-methylaniline (**2c**; $pK_B$ 9.15; Scheme 1) in the presence of $K_2CO_3$ as catalyst (**1**/**2c**/$K_2CO_3$=1:3:5) a 66:34 mixture of the isomeric **3c** and **4c** in a good overall yield (65%) was obtained.

*B. Anionic nucleophiles*: We have also tested the reactivity of **1** with some oxygen and sulphur anionic nucleophiles: sodium phenoxide (**13**), benzenethiolate (**14**) and benzensulfinate (**15**). In every case we obtained exclusively the 'expected' product of reaction (Scheme 3). Of course, considering the anionic nature of such nucleophiles, the addition of bases (as $Et_3N$ or $K_2CO_3$) has no meaning. Moreover we observed that $Et_3N$ decomposes 2-nitrobenzo[*b*]thiophen-3-yl phenyl sulfone (**18**) on refluxing in DMF.

## 2.4. Influence of substrate

Finally, we estimated the effect of a substituent in the



**Scheme 3.**

benzene ring of the substrate using the reaction between 3-bromo-5-chloro-2-nitrobenzo[*b*]thiophene (**19**) and the aniline **2a** under experimental conditions (**19**/**2a**/$Et_3N$=1:3:3) similar to those reported for compound **1** (entry 1 of Table 2). The resulting 45:55 mixture of the isomeric 5-chloro-2-nitro-*N*-[3-(trifluoromethyl)phenyl]-benzo[*b*]thiophen-3-amine (**20**) and 5-chloro-3-nitro-*N*-[3-(trifluoromethyl)phenyl]benzo[*b*]thiophen-2-amine (**21**) (65% overall yield) only shows a small, although significant, influence of the substituent on the reaction.

## 3. Discussion

On account of the results obtained the overall conclusion can be drawn that the nucleophilic substitution on 3-bromo-2-nitrobenzo[*b*]thiophene (**1**) gives ‘unexpected’ substitution products only with neutral weak nucleophiles such as anilines and in the presence of a base (e.g. $Et_3N$ or $K_2CO_3$) stronger than the nucleophile itself. This clearly indicates the need for base-catalysis for the occurrence of the ‘unexpected’ substitution pathway, and $K_2CO_3$ appears especially effective in this respect.

A deeper analysis of the data and some further considerations were necessary in order to ensure a complete understanding of the results obtained.

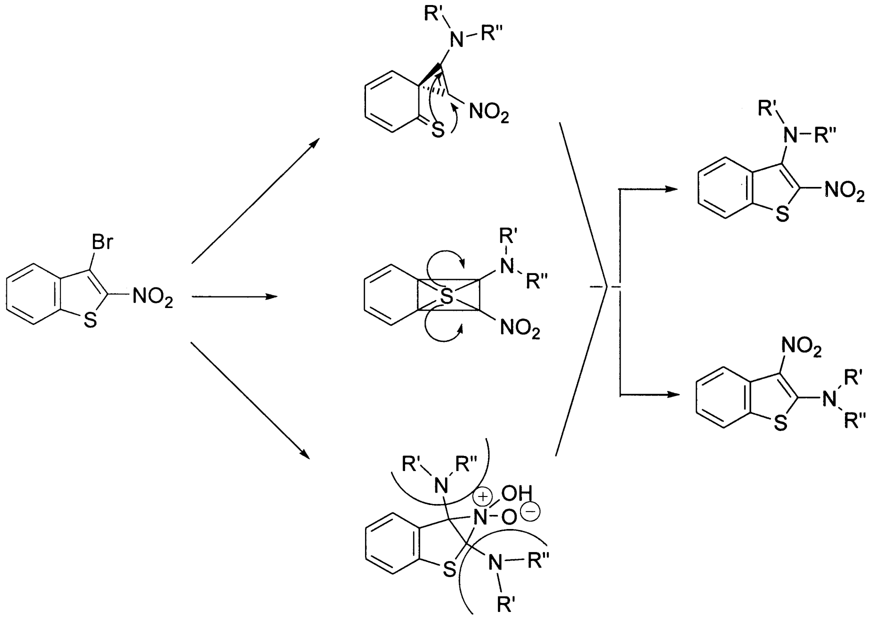
First of all, it must be recalled that in $S_NAr$ processes on benzene derivatives, the intermediate σ-adduct can either lose the nucleophile (going back to the starting materials) or the leaving group (giving the substitution product): in both cases the driving force is the regeneration of the aromatic ring and its resonance stabilization. The situation can be significantly different in heteroaromatic systems and especially in five-membered rings: as a matter of fact the lower resonance stabilization energy and the presence of a weak heteroatom–carbon bond discloses the way to new reaction pathways which are unavailable to ‘true’ aromatic systems.[20] The situation can be envisaged as even more complex in benzocondensed derivatives, as, for example, the thiophene ring can hardly be considered aromatic in benzo[*b*]thiophenes:[21] the reactivity of nitrobenzo[*b*]thiophene derivatives[24] could thus be best related to that of nitroalkenes (or of arylnitroalkenes),[25] i.e. **1** behaving as a nitroalkene-like system.

Concerning the mechanism of nucleophilic substitutions on 3-bromo-2-nitrobenzo[*b*]thiophene (**1**), we previously supposed[5] (Scheme 4) that the formation of the ‘unexpected’ substitution products could essentially depend on:

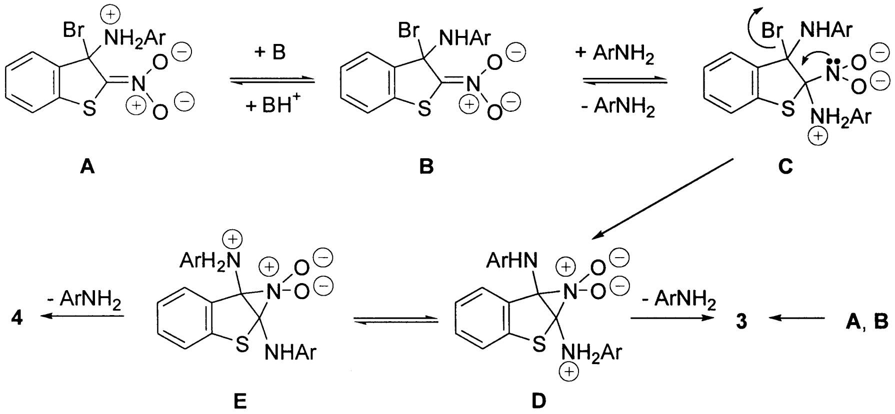
(a) the formation of an intermediate in which C-2 and C-3 become equivalent with respect to the sulphur atom (i.e. through some kind of skeletal rearrangement of the thiophene ring), or
(b) a base-catalysed addition of the nucleophile at both C-2 and C-3 with formation of a cyclic intermediate[26] and, eventually, a nitro-group shift from C-2 to C-3.

The results obtained with **1** $^{13}C$-labeled at C-2 allowed us to exclude hypothesis (a) providing instead evidence for a nitro-group shift (hypothesis b).[6]

A critical examination of the new results herein can help in the understanding of the reactivity of **1**. As a matter of fact we have studied four kinds of reactions: (1) reaction with



**Scheme 4.**



**Scheme 5.**

anionic (strong) nucleophiles; (2) reaction with strong neutral nitrogen nucleophiles ($pK_B<4$); (3) reaction with weak neutral nitrogen nucleophiles ($pK_B>9$); (4) reaction with the previous weak neutral nitrogen nucleophiles in the presence of non-nucleophilic strong bases ($pK_B<4$). As indicated above, the experimental data indicate that the formation of the 'unexpected' products of substitution occurs only in the last case, i.e. with weak nucleophiles and in the presence of non-nucleophilic strong bases.

Actually, cases 1 and 2 resemble the usual activated aromatic nucleophilic substitution,[1–3,27] with a fast and 'early'[28] σ-adduct formation followed by bromide ion elimination to the normal *ipso*-substitution product. In contrast, with weak nucleophiles (cases 3 and 4) the σ-adduct (**A**) formation should be 'late'.[28] In case 3 the base is weak (i.e. the excess nucleophile itself) and the formation of the anionic intermediate **B** is unfavoured and/or too slow to affect the course of the reaction: therefore the only product obtained is the 'normal' one after bromine loss from **A**. In case 4, however, (Scheme 5) the strong catalytic base present can be responsible for a fast proton abstraction. Here, though, because of the low contribution of the thiophene ring to the total resonance stabilization energy of the benzo[*b*]thiophene system, the following expulsion of the leaving group from **B** (restoring the thiophene ring and leading directly to **3**) can be in competition with the addition of a second molecule of the nucleophile at the carbon–nitrogen double bond, thus leading to the anionic intermediate **C**. The contemporary presence of two negative charges on the nitro group, making its nitrogen atom a strong nucleophilic centre, could well force **C** to evolve through an anchimerically assisted loss of bromide ion giving the cyclic intermediates **D** or **E**,[26] and hence **3** and **4**, respectively.

The formation of **B** from **A** by proton abstraction (the key step to the 'unexpected' product) can be related to the acidic character of the proton in the $-NH_2^+-Ar$ residue. As a matter of fact the intermediate **A** obtained from **2a–c** is much more acidic than the corresponding ones from the primary and secondary aliphatic amines (estimated $\Delta pK_a$ 6–8), and accordingly only with **2a–c** the formation of **B** is effective,[29] resulting in the formation of appreciable amounts of 3-nitro-2-arylaminobenzo[*b*]thiophenes; furthermore, as foreseeable on the grounds of such a rationalization **2a** leads to 'unexpected' product more easily and hence with higher yields than **2b** (estimated $\Delta pK_a$ ca. 1).

## 4. Conclusion

A detailed study of the peculiar reactivity of **1** with several nucleophiles has been carried out: the high purity of **1** (>98%) allows us to exclude the possibility that compounds **4a–c** could derive from 2-bromo-3-nitrobenzo[*b*]thiophene formed as by-product during the nitration of 3-bromobenzo[*b*]thiophene. Moreover we did not obtain **4**-like products in every instance, but only with anilines observing **3**/**4** ratios which depend on the experimental conditions (solvent, nature and quantity of the added base). However it is known[13] that 2-bromo-3-nitrobenzo[*b*]thiophene is not able to give 2-amino-3-nitrobenzo[*b*]thiophenes **4** by the action of amines.

In conclusion the obtained results prove that **1** gives **also** the 'unexpected' **4a–c only** with neutral, weak nucleophiles (e.g. anilines) and in the presence of added non-nucleophilic strong bases. Therefore we feel that enlighting the role of base-catalysis for the occurrence of the 'unexpected' pathway we have been able to give proof in favour of the formation of a three-membered ring intermediate[26] capable of rationalizing the C-2 to C-3 nitro-group shift.

## 5. Experimental

### 5.1. General

NMR spectra were recorded on a Varian Gemini 300 Instrument in the Fourier transform mode at 21±0.5°C in DMSO-$d_6$. $^1$H (300.07 MHz, 0.02 M) and $^{13}$C (75.43 MHz, 0.1 M) chemical shifts (δ) are in ppm relative to TMS as secondary internal reference; coupling constants are in Hz. Mass spectra were recorded on a VG70 70E apparatus. Melting points were measured using a Kofler apparatus and are uncorrected. Solvents were removed under reduced pressure. TLC: precoated silica gel (Merck $F_{254}$) or aluminum oxide neutral (Merck art. 5550) plates. Flash chromatography: silica gel 60 (ICN Silica 32–63) or aluminum oxide neutral (Merck art. 1097). Compound **1** was obtained in 98% purity according to a literature procedure.[30]

**5.1.1. General procedure for the evaluation of solvent's influence (Table 1).** *Method A*: **2a** (0.6 mL, 4.65 mmol) and $Et_3N$ (0.4 mL, 2.88 mmol) were successively added to a solution of **1** (0.400 g, 1.55 mmol) in the proper solvent (4.5 mL) and refluxed for 15 min. The mixture was cooled to room temperature, poured into ice/water and the precipitate was filtered and dried under vacuum. Compounds **3a** and **4a** were purified and separated from residual **1** by flash-chromatography on silica gel (toluene/cyclohexane=4:1 v/v as eluant) and identified as reported.[5]

*Method B*: The mixture was refluxed until disappearance of **1**, quantities and operating procedures being otherwise as described above.

**5.1.2. General procedure for the evaluation of the effect of base concentration and strength.** Compound **2a** (0.6 mL, 4.65 mmol) and the base (amounts as in Table 2) were successively added to a solution of **1** (0.400 g, 1.55 mmol) in DMF (4.5 mL) and the mixture was heated and kept at 120°C until disappearance of **1**. After cooling to room temperature and pouring into ice/water; the precipitate was filtered, dried under vacuum and then treated as described in method A in Section 5.1.1.

**5.1.3. General procedure for the reactions of 1 with aniline (2b).** Aniline (0.4 mL, 4.65 mmol) and the base (amounts as in Table 3) were successively added to a solution of **1** (0.400 g, 1.55 mmol) in DMF (4.5 mL). The mixture was heated and kept at 120°C until disappearance of **1**, then cooled to room temperature and poured into ice/water; the precipitate was filtered and dried under vacuum. Crystallization from EtOH gave compound **3b**. The mother liquor furnished, by flash-chromatography on aluminum oxide (ethyl acetate/petroleum ether=1:7 v/v as eluant), the remaining **3b** and **4b**, in order of elution.

*Compound* **3b**: Orange crystals from toluene; mp 218–219°C (lit.[8,10] 222–223 and 210–211°C, respectively); $^{1}H$ and $^{13}C$ NMR[8,31] as well as mass[32] spectra have been already reported. HRMS: 270.04676, $C_{14}H_{10}N_2O_2S$ requires 270.04630.

*Compound* **4b**: Orange crystals from toluene; mp 156–157°C; $^{1}H$ NMR $\delta$ 11.28 (s, exch., 1H, NH), 8.32 (dd, $^{3}J$=8.1 Hz, $^{4}J$=0.6 Hz, 1H, H-4), 7.78 (d, $^{3}J$=8.1 Hz, 1H, H-7), 7.61–7.45 (m, 5H, H–Ar), 7.44 (pt, $^{3}J$=8.1 Hz, 1H, H-5), 7.31 (pt, $^{3}J$=8.1 Hz, 1H, H-6); $^{13}C$ NMR $\delta$ 162.42 (C-2), 139.23 (C-1′), 130.94 (C-3a), 129.66 (C-3′ and C-5′), 127.68 (C-4′), 126.69 (C-5), 125.02 (C-7a), 124.74 (C-6), 124.60 (C-2′ and C-6′), 122.34 (C-7), 121.23 (C-4), 119.94 (C-3); M/S *m/z*(%) 270 ($M^+$, 100), 237 (12), 236 (29), 235 (37), 223 (14), 222 (25), 221 (11), 145 (10), 121 (11), 120 (13), 76 (29), 50 (18); HRMS: 270.04662, $C_{14}H_{10}N_2O_2S$ requires 270.04630. [Found: C, 62.32; H, 3.81; N, 10.24. $C_{14}H_{10}N_2O_2S$ requires C, 62.21; H, 3.73; N, 10.36].

**5.1.4. Reaction of 1 with *N*-methylaniline (2c).** *N*-Methylaniline (0.5 mL, 4.65 mmol) and $K_2CO_3$ (1.07 g, 7.75 mmol in 0.8 mL of $H_2O$) were successively added to a solution of **1** (0.400 g, 1.55 mmol) in DMF (7 mL) and the mixture kept at 120°C until disappearance of **1** (30 min). The mixture was then cooled to room temperature, poured into ice/water and extracted with toluene (4×60 mL). The extracts were dried over $Na_2SO_4$ and concentrated in vacuum, and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether=1:9 v/v as eluant). The faster running band afforded compound **3c** (0.19 g), the slower running band afforded compound **4c** (0.09 g) for an overall 65% yield.

*Compound* **3c**: Garnet red crystals from EtOH; mp 115–116°C; $^{1}H$ NMR $\delta$ 8.09 (d, $^{3}J$=8.1 Hz, 1H, H-7), 7.64 (ddd, $^{3}J$=8.1 Hz, $^{3}J$=6.7 Hz, $^{4}J$=1.6 Hz, 1H, H-6), 7.44–7.37 (m, 2H, H-5 and H-4), 7.25 (m, 2H, H-3′ and H-5′), 6.94–6.89 (m, 3H, H-2′, H-4′ and H-6′), 3.45 (s, 3H, $CH_3$); $^{13}C$ NMR $\delta$ 146.36 (C-3), 141.52 (C-1′), 140.03 (C-2), 135.94 (C-7a), 133.86 (C-3a), 130.04 (C-6), 129.23 (C-3′ and C-5′), 125.77 (C-4 or C-5), 125.65 (C-5 or C-4), 123.96 (C-7), 120.83 (C-4′), 116.14 (C-2′ and C-6′), 40.08 (N–$CH_3$); M/S *m/z* (%) 284 ($M^+$, 69), 267 (5), 255 (11), 237 (100), 223 (43), 210 (14), 161 (4), 146 (9), 134 (16), 121 (19), 119 (12), 104 (13), 91 (10), 89 (15), 77 (68), 63 (12), 51 (44); HRMS: 284.06158, $C_{15}H_{12}N_2O_2S$ requires 284.06195. [Found: C, 63.15; H, 4.26; N, 8.81. $C_{15}H_{12}N_2O_2S$ requires C, 63.36; H, 4.25; N, 8.95].

*Compound* **4c**: Yellow needles from EtOH; mp 99–100°C; $^{1}H$ NMR $\delta$ 8.18 (d, $^{3}J$=8.1 Hz, 1H, H-4), 7.89 (d, $^{3}J$=8.0 Hz, 1H, H-7), 7.45 (t, $^{3}J$=8.1 Hz, $^{3}J$=8.1 Hz, 1H, H-5), 7.48–7.32 (m, 5H, H–Ar), 7.24 (dd, $^{3}J$=8.1 Hz, $^{3}J$=8.0 Hz, 1H, H-6); $^{13}C$ NMR $\delta$ 160.53 (C-2), 146.79 (C-1′), 131.72 (C-3a), 129.69 (C-3′ and C-5′), 127.36 (C-7a), 126.71 (C-5), 125.97 (C-4′), 124.81 (C-6), 124.56 (C-3), 122.42 (C-7), 122.11 (C-2′ and C-6′), 121.29 (C-4), 44.98 (N–$CH_3$); M/S *m/z* (%) 284 ($M^+$, 51), 267 (34), 255 (19), 237 (100), 223 (31), 210 (4); 161 (17), 146 (12), 134 (18), 120 (12), 119 (12), 104 (11), 91 (21), 89 (9), 77 (41), 63 (7), 51 (26); HRMS: 284.06163, $C_{15}H_{12}N_2O_2S$ requires 284.06195. [Found: C, 63.21; H, 4.33; N, 8.79. $C_{14}H_{10}N_2O_2S$ requires C, 63.36; H, 4.25; N, 8.95].

**5.1.5. General procedure for the reactions of 1 with aliphatic amines 5–8.** The amine (4.65 mmol) and the base (amounts as in Table 4) were successively 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 crystallization or flash-chromatography on silica gel.

*Compound* **9**: Orange crystals from cyclohexane; mp 139–141°C (lit.[11] 139–140°C); $^{1}H$ NMR $\delta$ 9.53 (d, exch. $^{3}J$=8.1 Hz, 1H, NH), 8.19 (dd, $^{3}J$=8.4 Hz, $^{4}J$=0.8 Hz, 1H, H-4), 7.92 (dd, $^{3}J$=8.1 Hz, $^{4}J$=1.0 Hz, 1H, H-7), 7.68 (ddd, $^{3}J$=8.1 Hz, $^{3}J$=7.3 Hz, $^{4}J$=0.8 Hz, 1H, H-6), 7.49 (ddd, $^{3}J$=8.4, $^{3}J$=7.3 Hz, $^{4}J$=1.0 Hz, 1H, H-5), 4.41–4.34 (m, 1H, CH), 2.12–1.21 (m, 10H, 5×$CH_2$); $^{13}C$ NMR $\delta$ 147.49 (C-3), 138.39 (C-7a), 131.61 (C-6), 127.74 (C-3a), 127.69 (C-4), 125.67 (C-5), 124.07 (C-7), 119.55 (C-2), 52.69 (CH), 32.87 (2×$CH_2$), 24.72 ($CH_2$), 23.50 (2×$CH_2$); M/S *m/z* (%) 276 ($M^+$, 84), 242 (20), 241 (14), 194 (48), 178

(35), 177 (11), 164 (25), 161 (22), 160 (19), 149 (12), 148 (73), 147 (15), 146 (20), 136 (25), 135 (46), 134 (62), 121 (30), 103 (18), 102 (13), 99 (12), 89 (16), 83 (11), 81 (21), 77 (16), 76 (14), 55 (100); HRMS: 276.09356, $C_{14}H_{16}N_2O_2S$ requires 276.09325.

*Compound* **10**: Orange crystals from EtOH; mp 53°C (lit.[10] 54°C) from flash-chromatography (cyclohexane/benzene=1:4 v/v as eluant); $^1$H NMR $\delta$ 8.05 (dd, $^3J$=8.3 Hz, $^4J$=1.1 Hz, 1H, H-4), 7.89 (dd, $^3J$=8.1 Hz, $^4J$=1.1 Hz, 1H, H-7), 7.60 (ddd, $^3J$=8.1 Hz, $^3J$=7.2 Hz, $^4J$=1.1 Hz 1H, H-6), 7.45 (ddd, $^3J$=8.3 Hz, $^3J$=7.2 Hz, $^4J$=1.1 Hz 1H, H-5), 3.61 (q, $^3J$=7.1 Hz, 4H, 2×$CH_2$), 1.09 (t, $^3J$=7.1 Hz, 6H, 2×$CH_3$); $^{13}$C NMR $\delta$ 146.58 (C-3), 136.02 (C-7a), 134.30 (C-3a), 131.59 (C-2), 129.97 (C-6), 126.27 (C-4), 125.30 (C-5), 123.56 (C-7), 46.95 (2×$CH_2$), 13.62 (2×$CH_3$); M/S *m*/*z* (%) 250 ($M^+$, 16), 223 (13), 207 (14), 189 (16), 175 (14), 163 (17), 162 (17), 161 (100), 160 (20), 148 (14), 147 (15), 135 (27), 134 (72), 133 (14), 103 (12), 102 (11), 89 (31), 77 (10), 76 (16), 71 (15), 70 (10), 69 (42), 63 (14); HRMS: 250.07714, $C_{12}H_{14}N_2O_2S$ requires 250.07760.

*Compound* **11**: Orange crystals from EtOH; mp 119–121°C (lit.[13] 118–120°C); $^1$H NMR $\delta$ 8.07 (m, 1H, H-4), 7.90 (m, 1H, H-7), 7.62 (m, 1H, H-6), 7.47 (m, 1H, H-5), 3.56–3.52 (m, 4H, 2×$CH_2$), 1.77–1.68 (m, 6H, 3×$CH_2$); $^{13}$C NMR $\delta$ 147.39 (C-3), 136.37 (C-7a), 133.04 (C-3a), 130.10 (C-6), 128.58 (C-2), 126.43 (C-4), 125.31 (C-5), 123.66 (C-7), 53.40 (2×$NCH_2$), 26.18 ($CH_2$), 23.38 (2×$CH_2$); M/S *m*/*z* (%) 262 ($M^+$, 49), 245 (100), 228 (21), 227 (30), 217 (45), 214 (13), 200 (14), 190 (11), 188 (19), 187 (13), 186 (26), 175 (26), 174 (13), 173 (13), 163 (22), 162 (19), 161 (37), 160 (47), 149 (20), 148 (41), 147 (33), 146 (14), 135 (21), 134 (47), 133 (25), 121 (15), 116 (15), 102 (11), 89 (45), 85 (14), 69 (11), 67 (22), 57 (23), 55 (26); HRMS: 262.07743, $C_{13}H_{14}N_2O_2S$ requires 262.07760.

*Compound* **12**: Yellow crystals from EtOH; mp 107–109°C; $^1$H NMR $\delta$ 8.27 (m, 1H, H-4), 7.89 (m, 1H, H-7), 7.61 (m, 1H, H-6), 7.44 (m, 1H, H-5), 3.31 (s, 6H, 2×$CH_3$); $^{13}$C NMR $\delta$ 148.28 (C-3), 136.45 (C-7a), 132.53 (C-3a), 130.08 (C-6), 127.24 (C-4), 126.02 (C-2), 125.02 (C-5), 123.55 (C-7), 44.60 (2×$CH_3$); M/S *m*/*z* (%) 222 ($M^+$, 89), 205 (16), 193 (16), 177 (23), 176 (39), 175 (38), 174 (13), 163 (19), 162 (16), 161 (100), 160 (44), 150 (55), 149 (30), 148 (60), 147 (27), 146 (17), 135 (18), 134 (63), 133 (22), 121 (45), 117 (12), 116 (11), 102 (10), 90 (12), 89 (44), 76 (10), 69 (14), 67 (14), 62 (11); HRMS: 222.04590, $C_{10}H_{10}N_2O_2S$ requires 222.04630. [Found: C, 54.12; H, 4.51; N, 12.50. $C_{10}H_{10}N_2O_2S$ requires C, 54.04; H, 4.53; N, 12.60].

**5.1.6. 2-Nitro-3-phenoxybenzo[*b*]thiophene (16).** Sodium phenoxide trihydrate (**13**) (0.790 g, 4.65 mmol) was added to a solution of **1** (0.400 g; 1.55 mmol) in dioxane (25 mL); the resulting solution was stirred at room temperature for 33 h and then poured into ice/water. The precipitate was filtered, dried under vacuum (yield 71%) and identified as 2-nitro-3-phenoxybenzo[*b*]thiophene (**16**): yellow needles from EtOH/dioxane; mp 132–134°C; $^1$H NMR $\delta$ 8.18 (m, 1H, H-7), 7.73 (m, 1H, H-6), 7.62 (m, 1H, H-4), 7.50 (m, 1H, H-5), 7.41–7.36 (m, 2H, H-3′ and H-5′), 7.19–7.10 (m, 3H, H-2′, H-4′ and H-6′); $^{13}$C NMR $\delta$ 156.63 (C-1′), 144.66 (C-3), 137.30 (C-2), 134.86 (C-7a), 130.64 (C-6), 130.54 (C-3a), 130.07 (C-2′ and C-6′), 126.36 (C-5), 124.07 (C-4 and C-7), 123.75 (C-4′), 115.81 (C-3′ and C-5′); M/S *m*/*z* (%) 271 ($M^+$, 10), 224 (12), 179 (10), 178 (100), 162 (12), 152 (13), 136 (29), 134 (38), 121 (12), 120 (20), 108 (12), 106 (10), 104 (11), 77 (30), 76 (15), 69 (11), 65 (15), 51 (30), 50 (14); HRMS: 271.02984, $C_{14}H_9NO_3S$ requires 271.03031. [Found: C, 61.85; H, 3.52; N, 5.07. $C_{14}H_9NO_3S$ requires C, 61.98; H, 3.34; N, 5.16].

**5.1.7. 2-Nitro-3-phenylsulfanylbenzo[*b*]thiophene (17).** Sodium benzenethiolate (**14**) (0.614 g, 4.65 mmol) was added to a solution of **1** (0.400 g; 1.55 mmol) in dioxane (25 mL); the resulting solution was stirred at room temperature for 24 h and then concentrated in vacuum. The residue was treated with water and the solid filtered off and dried. By crystallization from MeOH 2-nitro-3-phenylsulphanylbenzo[*b*]thiophene (**17**) was obtained (yield 80%): yellow needles, mp 95–96°C; $^1$H NMR $\delta$ 8.17 (m, 1H, H-4 or H-7), 7.63 (m, 1H, H-5 or H-6), 7.48–7.34 (m, 7H, H–Ar); $^{13}$C NMR $\delta$ 148.41 (C-2), 137.19 (C-7a), 136.47 (C-1′), 132.75 (C-3a), 130.24 (C-3), 130.14 (C-2′ and C-6′), 129.75 (C-4′), 129.63 (C-3′ and C-5′), 128.04, 126.11, 125.99, 123.92; M/S *m*/*z* (%) 287 ($M^+$, 93), 241 (23), 240 (82), 223 (24), 222 (42), 208 (18); 195 (13), 194 (32), 165 (15), 164 (10), 152 (13), 146 (100), 136 (41), 121(19), 120 (53), 108 (16), 93 (10), 77 (35), 69 (19), 51 (20); HRMS: 287.00688, $C_{14}H_9NO_2S_2$ requires 287.01084. [Found: C, 58.48; H, 3.27; N, 4.76. $C_{14}H_9NO_2S_2$ requires C, 58.52; H, 3.16; N, 4.87].

**5.1.8. 2-Nitrobenzo[*b*]thiophen-3-yl phenyl sulfone (18).** A solution of **1** (0.400 g; 1.55 mmol) in EtOH (60 mL) was added of sodium benzenesulfinate (**15**) (0.327 g, 2.01 mmol) and warmed to 60°C for 15 min. On cooling, yellow crystals of **18** from EtOH/dioxane (mp 194°C; yield 95%) were obtained; $^1$H NMR $\delta$ 8.58 (m, 1H, H-4 or H-7), 8.28 (m, 1H, H-7 or H-4), 8.14 (m, 2H, H-2′ and H-6′), 7.81–7.68 (m, 5H, H-5, H-6, H-3′, H-4′ and H-5′); $^{13}$C NMR $\delta$ 153.47 (C-2), 139.35 (C-7a), 135.27 (C-1′), 134.74 (C-4′), 131.76 (C-3a), 129.80 (C-3′), 129.00 (C-6), 128.37 (C-3), 127.81 (C-4), 127.27 (C-2′), 125.29 (C-5), 123.99 (C-7); M/S *m*/*z* (%) 319 ($M^+$, 100), 226 (34), 208 (22), 165 (16), 162 (18), 136 (17), 134 (27), 125 (30), 91 (10), 77 (26), 51 (12); HRMS: 318.99799, $C_{14}H_9NO_4S_2$ requires 318.99730. [Found: C, 52.78; H, 2.98; N, 4.31. $C_{14}H_9NO_4S_2$ requires C, 52.65; H, 2.84; N, 4.39].

**5.1.9. Reaction of 19 with 3-trifluoromethylaniline (2a).** **2a** (0.6 mL, 4.65 mmol) and $Et_3N$ (0.4 mL, 4.65 mmol) were successively added to a solution of **19** (0.456 g, 1.55 mmol) in DMF (8 mL). The resulting solution was kept at 120°C until disappearance of **19** (45 min). Then the mixture was cooled at room temperature and poured onto ice water; the precipitate was filtered and dried under vacuum (yield 65%). Using flash-chromatography on silica gel (cyclohexane/toluene=1:4 v/v as eluant), compounds **20** and **21** were isolated in a 45:55 ratio (65% overall yield).

*Compound* **20**: Orange needles from EtOH; mp 183–185°C; $^1$H NMR $\delta$ 10.37 (br s, exch., 1H, NH), 8.07(d, $^3J$=8.5 Hz, 1H, H-7), 7.73 (dd, $^3J$=8.5 Hz, $^4J$=1.9 Hz, 1H, H-6), 7.67 (d, $^4J$=1.9 Hz, 1H, H-4), 7.58 (m, 1H, H-5′), 7.52 (m, 1H, H-2′), 7.51 (m, 1H, H-4′), 7.41 (m, 1H, H-6′); $^{13}$C NMR $\delta$ 140.99 (C-1′), 138.02 (C-3), 135.35 (C-7a), 132.24 (C-5), 130.68 (C-6), 130.03 (C-3a), 129.99 (C-5′), 129.59 (C-3′), 129.34 (C-2), 125.77 (C-7), 124.72 (C-6′), 124.70 (C-4), 123.99 ($CF_3$), 120.54 (C-4′), 117.59 (C-2′); M/S $m/z$ (%) 372 ($M^+$, 100), 338 (26), 325 (23), 313 (13), 292 (14), 291 (68), 290 (14), 271 (18), 257 (29), 222 (13), 189 (13), 168 (10), 145 (43), 133 (13), 125 (17), 119 (11), 95 (23), 75 (25), 69 (43), 63 (15); HRMS: 371.99400, $C_{15}H_8ClF_3N_2O_2S$ requires 371.99471. [Found: C, 48.27; H, 2.30; N, 7.12. $C_{15}H_8ClF_3N_2O_2S_2$ requires C, 48.33; H, 2.16; N, 7.52].

*Compound* **21**: Yellow needles from EtOH; mp 160–161°C; $^1$H NMR $\delta$ 11.39 (br s, exch., 1H, NH), 8.28 (d, $^4J$=2.1 Hz, 1H, H-4), 8.03 (m, 1H, H-2′), 7.95 (m, 1H, H-6′), 7.86 (d, $^3J$=8.5 Hz, 1H, H-7), 7.80–7.78 (m, 2H, H-4′ and H-5′), 7.39 (dd, $^3J$=8.5 Hz, $^4J$=2.1 Hz, 1H, H-6); $^{13}$C NMR $\delta$ 162.64 (C-2), 139.99 (C-1′), 132.40 (C-3a), 131.85 (C-5), 130.90 (C-5′), 130.35 (C-3′), 128.87 (C-6′), 124.53 (C-6), 124.26 (C-4′), 124.10 (C-7), 123.57 (C-7a), 123.56 ($CF_3$), 121.90 (C-2′), 120.39 (C-4), 119.76 (C-3); M/S $m/z$ (%) 372 ($M^+$, 100), 342 (19), 341 (12), 340 (18), 339 (26), 338 (26), 291 (24), 271 (20), 257 (15), 256 (11), 180 (18), 172 (12), 171 (21), 170 (11), 169 (20), 168 (15), 156 (12), 155 (20), 154 (15), 145 (49), 142 (10), 133 (16), 125 (16), 119 (29), 95 (17), 76 (10), 75 (22), 69 (22), 63 (11); HRMS: 371.99429, $C_{15}H_8ClF_3N_2O_2S_2$ requires 371.99471. [Found: C, 48.39; H, 2.28; N, 7.35. $C_{15}H_8ClF_3N_2O_2S_2$ requires C, 48.33; H, 2.16; N, 7.52].

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