On the Reaction of 3-Bromo-2-nitrobenzo[*b*]thiophene ^{13}C-Labeled at C-2 with 3-(Trifluoromethyl)aniline: A Preliminary Insight into a Nucleophilic Substitution with Rearrangement

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The results of the title reaction have furnished proofs *against* a rearrangement of the carbon-atom skeleton and *for* a nitro group shift in the relevant nucleophilic substitution.

Recently we have shown[1,2] that 3-bromo-2-nitrobenzo[*b*]thiophene (**1**) reacts with some amines giving together with the expected products of *ipso*-substitution of bromine, *i.e.* the N-substituted 3-amino-2-nitrobenzo[*b*]thiophenes **2**,[3] and their unexpected *isomers* N-substituted 2-amino-3-nitrobenzo[*b*]thiophenes **3**. Although a number of pathways can be proposed[1] to rationalize the competitive formation of **2** and **3**, they essentially fall within two different classes (Scheme 1).

(i) The first kind of pathways proceeds through the attack of the amine onto C-3 of **1** followed by the formation, at some stage of the reaction, of an intermediate (*e.g.* **4**) in which C-2 and C-3 become in some way equivalent with respect to the sulfur atom. This may cause a rearrangement of the carbon-atom skeleton in the thiophene ring with substitution, so determining the formation of the isomers **2** and **3**$(C)_r$;[4] in the latter, the amino group would be linked to the rearranged carbon 2, *i.e.* to the carbon atom originally occupying the position 3 in the starting material **1**.

(ii) Alternatively, the reaction could occur through a multiple (*e.g.*, double) addition of the nucleophile to C-2 and C-3 while the nitro group becomes bonded to both the same carbon atoms 2 and 3, providing anchimeric assistance to the loss of the leaving group (Br^-). The resulting intermediate **5** can eventually eliminate a molecule of nucleophile, thus leading to products **2** and **3**$(NO_2)_r$.[4] Because in this case there is no skeletal rearrangement (but a nitro group shift), in the substitution products **2** and **3**$(NO_2)_r$ the amino group shall be linked to the carbon atoms that were C-3 and C-2 in the starting product **1**, respectively.

It must be remarked that all the pathways proposed hinge on the essentially *nonaromatic* character of the thiophene moiety of the benzo[*b*]thiophene system.[5]

As a matter of fact, also in other *aromatic* substitution reactions (*e.g.*, S_EAr processes) the behavior of condensed systems containing a five-membered ring (benzo[*b*]furan, benzo[*b*]pyrrole, and benzo[*b*]thiophene) can be parelleled to that of a C=C−Ẍ system, the heteroatom acting as an electron-donating substituent with respect to the adjacent *ethylenic* double bond.[6] This behavior can justify, for instance, the course of the electrophilic substitution at C-3 in benzo[*b*]thiophene.[7] Currently this kind of reactivity is interpreted on the grounds of the difference in the resonance energy between the two condensed rings (benzene and five-membered ring), which makes the electrophilic substitution energetically more favorable on the less aromatic ring through the formation of the more stable σ-complex (*i.e.*, the one corresponding to a lower loss of resonance energy and stabilized by a larger number of resonance structures retaining the aromatic character of the benzene ring).

Such a *nonaromatic* behavior is not confined to condensed heterocyclic systems, but it is also shared by the naphthalene ring as well as by the isolated thiophene ring, *e.g.* in some nitro derivatives. Thus, 2,3-dinitronaphthalene[8] and 1,4-dimethyl-2,3-dinitronaphthalene[9] can react with nucleophiles to give a *cine*- and a *tele*-substitution, respectively, paralleling a similar behavior of 3,4-dinitrothiophene[10] and of 2,5-dimethyl-3,4-dinitrothiophene.[11]

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(4) In order to distinguish the different pathways to the *N*-substituted 2-amino-3-nitrobenzo[*b*]thiophenes **3**, these isomers are identified as **3**$(C)_r$ (*i.e.* deriving from rearrangement of the carbon-atom skeleton) or as **3**$(NO_2)_r$ (*i.e.* deriving from a nitro group shift).

(5) Accordingly, one of us (Z.P.) has pointed out that activation parameters for the thermolysis of 3-azidobenzo[*b*]thiophene are different from those observed for aromatic azides but similar to those of vinyl azide (Toselli, M.; Spagnolo, P.; Zanirato, P. *Gazz. Chim. Ital.* **1989**, *119*, 411).

(6) A similar localized effect (i.e. restricted to the C=C−Ẍ system) has been recently evidenced studying the ^{13}C NMR behavior of some azidoindoles and -benzo[*b*]thiophenes (Foresti, E.; Di Gioia, M. T.; Nanni, D.; Zanirato, P. *Gazz. Chim. Ital.* **1995**, *125*, 151).

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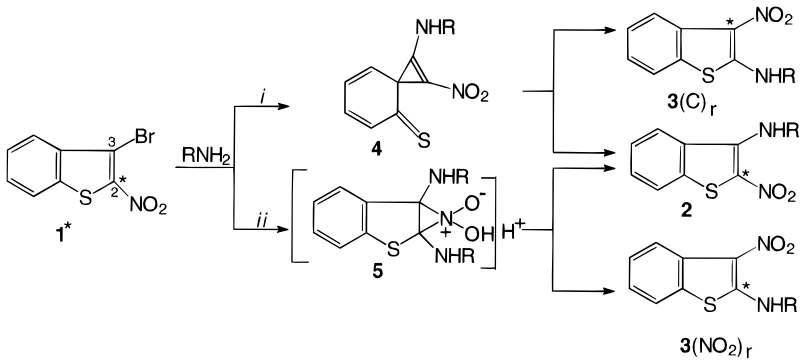
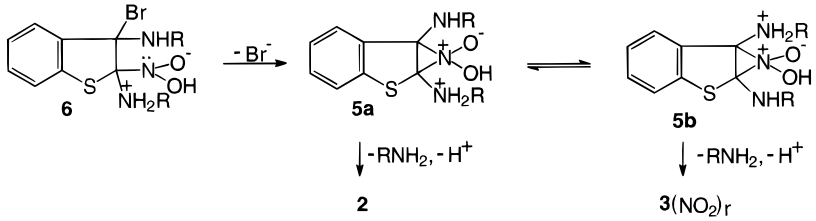
Scheme 1[a]



[a] In **1** the relevant carbon atoms of the thiophene ring are numbered according to the IUPAC rules and the labeled carbon is starred. Also in **2** and **3** the labeled carbon atoms are starred to evidence the occurrence [as in **3**$(C)_r$] or not [as in **3**$(NO_2)_r$] of a rearrangement of the carbon-atom skeleton.

Scheme 2



Results and Discussion

In order to gain deeper mechanistic informations on the novel and peculiar nucleophilic substitution of **1** with amines we report herein the results obtained from an experiment designed so as to allow us to make a choice between a skeletal rearrangement (type i pathway) and a nitro group shift (type ii pathway).

This goal can be easily achieved by reacting 3-bromo-2-^{13}C-2-nitrobenzo[*b*]thiophene **1*** (ca. 11% labeled) with 3-(trifluoromethyl)aniline in DMF in the experimetal conditions we have previously used.[1] The two isomeric labeled products can be separated by chromatography and analyzed by EI/MS and ^{13}C NMR spectrometry.

The mass spectra have confirmed in both the reaction products (**2*** and **3***) the same ^{13}C isotopic enrichment of **1*** (*ca.* 11%). An accurate analysis of ^{13}C NMR data has in turn indicated, beyond any reasonable doubt, that in the (2-nitrobenzo[*b*]thiophene-3-yl)(3-(trifluoromethyl)phenyl)amine **2*** (the *expected ipso*-substitution product) as well as in the (3-nitrobenzo[*b*]thiophene-2-yl)(3-(trifluoromethyl)phenyl)amine **3*** (the *unexpected* rearranged product) labeling exclusively occurs at C-2. Such an outcome definitely allows us to exclude any pathway which requires a rearrangement of the carbon-atom skeleton and to consider possible only pathways involving a nitro group migration.

On the grounds of both the experimental data collected and literature reports, some hypotheses on the reaction pathway can be advanced, admitting that the thiophene moiety of **1** could behave as a halonitroalkene unit.

As a matter of fact, it is well known that nitroalkenes react with oxygen, sulfur, nitrogen, and carbon nucleophiles giving addition products.[12] Moreover examples of nucleophilic addition to nitrothiophenes have been reported. For instance, 3,4-dinitrothiophene reacts with sulfur and nitrogen nucleophiles giving a *cine*-substitution[10] and a ring-opening reaction,[13] respectively: in both instances it has been ascertained that the first step of the reaction is represented by a Michael type nucleophilic addition to the α-carbon of the thiophene derivative which thus behaves as a nitroalkene.

Therefore in the reaction examined herein a stepwise double addition of amine can be envisaged (Scheme 2). The first addition would lead to the intermediate product **6a** which recalls the usual *σ*-adducts observed in S_NAr,[14] such as *e.g.* the Meisenheimer adduct obtained from 3-methoxy-2-nitrobenzo[*b*]thiophene and sodium methoxide.[2c] Such an adduct, when deriving from an aromatic system, can only revert to starting materials or evolve to products (likely via base-catalyzed pathways[14]). Because of the *low* aromatic character of the thiophene ring of the benzocondensed system, **6a** could directly furnish the *ipso*-substitution product **2** or add a second molecule of amine at the carbon−nitrogen double bond, thus leading to the zwitterionic intermediate **6b**. The latter can in turn evolve through an anchimerically assisted loss of Br^- to give the *N*-oxide of 1a,6a-dihydro-6-thia-1-azacyclopropan[*a*]inden-1-ol in its protonated forms **5a** and **5b**: these would eventually lead to **3**$(NO_2)_r$ and **2**, respectively.

It must be remarked that the formation of small ring intermediates has been hypothesized and/or proved in

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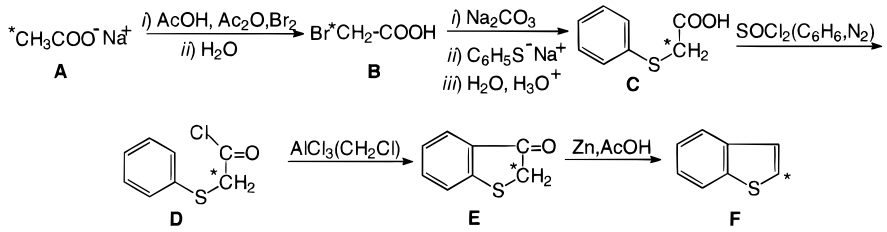
Scheme 3



many organic reactions. Two examples, in particular, seem akin to the transformation herein: (i) in electrophilic additions of sulfenyl derivatives to alkynes and alkenes as well as in the solvolysis of vinylic substrates with the participation of a β-group (sulfur, iodine, or aryl) the occurrence of cyclic triatomic ions as intermediates has been shown;[15] (ii) in the *cine*-substitution by the arenethiolate/arenethiol system on 3,4-dinitrothiophene strong evidence in favor of the formation of a bicyclo intermediate with a episulfonium ion structure condensed with a dihydrothiophene ring has been collected.[10c]

Moreover the base-catalyzed 1,2-nitro group shift in some conjugated nitroalkenes has been interpreted, admitting the formation of a three-membered nitrogen-ring intermediate on the basis of some kinetic evidence.[16]

Experimental Section

Melting points were determined on a Büchi 510 apparatus and are uncorrected. ^{1}H 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} DMSO-d_6 solutions on a switchable ^{1}H/^{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. The mass spectra were recorded on a VG70 70E mass spectrometer.

Chemicals. 3-Bromo-2-nitrobenzo[*b*]thiophene labeled at C-2 (**1***, labeling *ca*. 11%) was obtained from labeled benzo[*b*]thiophene **F** by bromination[17] followed by nitration[18] according to the literature.

The intermediate **F** was prepared from commercial sodium 2-^{13}C-acetate (**A**) through a multistep procedure (see Scheme 3) entailing its bromination and successive reaction of the sodium salt of the resulting bromoacetic acid (**B**) with sodium benzenethiolate. The (phenylthio)acetic acid (**C**) was converted into its acyl chloride (**D**) and cyclized to benzo[*b*]thiophen-3-one (**E**) by intramolecular ring-closure. Finally, the reduction of the latter ketone afforded the labeled benzo[*b*]thiophene (**F**). All the compounds obtained (**B**−**F**) were analyzed by EI/MS spectrometry in order to determine the percentage of labeling. Their structures were confirmed by ^{1}H and ^{13}C NMR spectrometry and by comparison with authentic samples of nonlabeled compounds. The single steps of Scheme 3 are described below.

Labeled Benzo[*b*]thiophene. F [mp 30−33 °C (lit. 32 °C)[19]] was obtained in 60% yield by reduction of **E** (15 g, 0.1 mol) with zinc dust (30 g) and acetic acid (113 mL) according to literature.[19] The crude **F** was purified by treatment of the oily residue with DDQ in refluxing *n*-hexane followed by chromatography on a silica column.

Labeled Benzo[*b*]thiophene-3-one (E). Labeled (phenylthio)acetic acid (**C**; 23.5 g, 0.14 mol) was converted into its acyl chloride **D** by refluxing (1.5 h) under nitrogen with freshly distilled thionyl chloride excess (20.3 mL, 33.2 g, 0.28 mol) in benzene (40 mL). The mixture was worked up as reported in literature.[19] A dichloromethane (60 mL) solution of the crude chloride (*ca*. 22.3 g, 0.12 mol, 86%) was converted into the title compound by the action of a suspension of anhydrous aluminum chloride (16 g, ca. 0.12 mol) in dry dichloromethane (150 mL). The mixture was worked up as reported in literature.[20] The crude labeled benzo[*b*]thiophene-3-one (80%) was quickly crystallized from light petroleum ether. Mp 66−68 °C (lit. 67−69 °C).[20]

Labeled (Phenylthio)acetic Acid (C). A water solution (150 mL) of labeled sodium bromoacetate (27.4 g, 0.17 mol) was added to a water solution (30 mL) of sodium benzenethiolate (0.17 mol) and the mixture, after heating (90−100 °C, 1.5 h), worked up according to literature.[21] The title compound (24.6 g, 86%) was crystallized from water. Mp 62−63 °C (lit. 62−63 °C).[21]

Labeled Bromoacetic Acid (B). A warm solution of acetic acid (17.2 mL, 0.30 mol), labeled sodium 2-^{13}C-acetate (**A**; 10 g, 0.12 mol; ^{13}C: 99%, Cambridge Isotope Laboratories), and acetic anhydride (5 mL, 0.053 mol) was treated with bromine (64 g, 0.40 mol) as rapidly as possible, but avoiding loss of bromine through the condenser (ca. 2 h). The solution was refluxed until it became colorless, cooled, and treated with water (2 mL) to destroy the acetic anhydride. The mixture was worked up as reported in literature.[22] The crude labeled bromoacetic acid (27.4 g, 90%, mp 50 °C) was used without further purification.

Reaction of Labeled 3-Bromo-2-nitrobenzo[*b*]thiophene 1* with 3-(Trifluoromethyl)aniline. The reaction was carried out in *N*,*N*-dimethylformamide (DMF) in the presence of triethylamine as previously reported.[1] The labeled (2-nitrobenzo[*b*]thiophene-3-yl)(3-(trifluoromethyl)phenyl)-amine **2*** and (3-nitrobenzo[*b*]thiophene-2-yl)(3-(trifluoromethyl)phenyl)amine **3*** obtained were first analyzed by EI/MS spectrometry (labeling *ca*. 11%) and then accurately by ^{1}H and ^{13}C NMR spectrometry. The NMR data have confirmed the structure designed and shown that in both the amines ^{13}C labeling exclusively occurs at C-2.

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