FULL PAPER

5-Substituted Benzothiophenes: Synthesis, Mechanism, and Kinetic Studies

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The kinetics of the reaction of 4-methoxythiophenoxyacetaldehyde diethyl acetal, 4-nitrothiophenoxyacetaldehyde diethyl acetal, and 3-methoxythiophenoxyacetaldehyde diethyl acetal in polyphosphoric acid has been explained. The kinetic behavior has been explained on the basis of aided simulation and on the basis of density functional theory calculations showing a different pathway for 4-nitrothiophenoxyacetaldehyde diethyl acetal and for 4-methoxythiophenoxyacetaldehyde diethyl acetal. In this last case, a very fast competing reaction to the dimerization product was observed.

Keywords: 5-Substituted benzothiophenes, Synthesis, Kinetics, DFT Calculations, Mathematical simulation.

Introduction

Heteroarenes are widely known in many fields of organic chemistry; in particular, medicinal chemistry is intimately associated with heterocyclic compounds and most known chemicals used in medicine are based on heterocyclic frameworks [1].

There are two main sources of heteroarenes: they are abundance in nature, often in complex form; and they can also be prepared in research laboratories by different synthetic approaches. Here, we focus on the benzothiophene (*Fig. 1*) nucleus that shows a wide spectrum of biological activities [2] as well as useful properties in material science [3]. Thus, the development of efficient and selective methodologies for the construction of diversely functionalized benzothiophenes is of considerable importance in organic chemistry.

A large number of methods to synthesize heterocycles containing benzothiophene ring have been reported in recent years [4], most of which involve the cyclization of benzenethiol derivatives. However, facile and versatile methods to access multisubstituted benzothiophenes are still limited. Furthermore, catalytic cyclization approaches using transition metals for the construction of the benzothiophene skeleton, which would provide a more efficient and practical route, are extremely rare in literature, presumably due to catalyst poisoning by sulfur. Only few recent reports are known [5] and the described methodology is not applicable to the synthesis of all the substituted benzothiophenes.

Moreover, mechanistic aspects in heterocyclic ring formation are still of large interest in scientific community. In this paper, we will discuss synthetic and mechanistic aspects, in particular, about the 5-substituted benzothiophene due to its importance for many biological active compounds, for example, raloxifene [6] (*Fig. 2*) which is an oral selective estrogen receptor modulator that has estrogenic actions on bone and antiestrogenic actions on the uterus and breast.

Furthermore, it is important to analyze the reaction from a kinetic point of view with the aim to predict its possible applicability on a large scale.

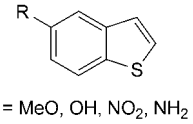

Fig. 1. Benzothiophene derivatives.

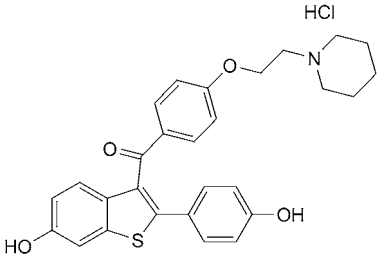

Fig. 2. Raloxifene.

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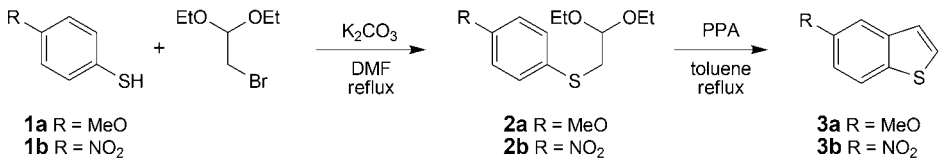
Scheme 1. Synthesis of 5-substituted benzothiophenes.



1a R = MeO
1b R = NO_2

2a R = MeO
2b R = NO_2

3a R = MeO
3b R = NO_2

Results and Discussion

Synthetic Aspects/Studies

In our long research in heterocyclic chemistry [7], we are interested in obtaining 4- and 5-substituted heteroarenes as suitable precursors for compounds active either against HIV protease [4] or against BACE-1 in *Alzheimer* disease [**2b**]. Furthermore, 4- and 5-aminobenzothiophenes, and 4- and 5-hydroxybenzothiophenes have been revealed as the most useful compounds in medicinal chemistry, but their synthesis has still a discussed approach: actually, cyclization starting from a suitable benzenethiol represents the best methodology, even if the total chemical yields appear unsatisfactory.

In particular, we recently reported the application of *Smiles* rearrangement for the synthesis of 4-aminobenzothiophene [8], starting from the 4-hydroxy precursor easily obtained as just known [9]. With the aim to obtain 5-hydroxy- and 5-aminobenzo[*b*]thiophene by *Smiles* rearrangement, we first prepared 5-methoxybenzothiophene; but during these studies, we noted a particular trend of the reaction.

The used synthetic approach to prepare 5-substituted benzo[*b*]thiophenes is based on a classical methodology [10], and it is still widely applied [11], consists of two steps as shown in *Scheme 1*.

In the first step, the nucleophilic substitution product (**2a** or **2b**) is obtained starting from the *p*-substituted benzenethiol (commercial and cheap) and bromoacetaldehyde diethyl acetal under basic conditions.

This step proceeds with an excellent yield without any formation of byproducts (**2a** 86% yield; **2b** 99% yield), but the second step represents an important downfall of yields; in fact, we obtained only 48% for **3a** and 35% for **3b**, respectively. This reaction consists of a cyclization and aromatization process, typically conducted with polyphosphoric acid in toluene, as well-known in literature just from 1935 [10]. During our attempts to obtain **3a**, we detected the formation of different intermediate species including non-aromatic compounds (**4a** and **5a**, see *Fig. 3*) and a disulfide (**6**, see *Fig. 3*) along with the desired 5-methoxybenzothiophene, so we began to understand a possible mechanism and decided to explore the potential electronic effect of the substituent group (MeO-, -NO_2). It is noteworthy that all the discussed intermediates were not isolated, in particular, for the compounds **4a** and **5a** reported in *Fig. 3*,

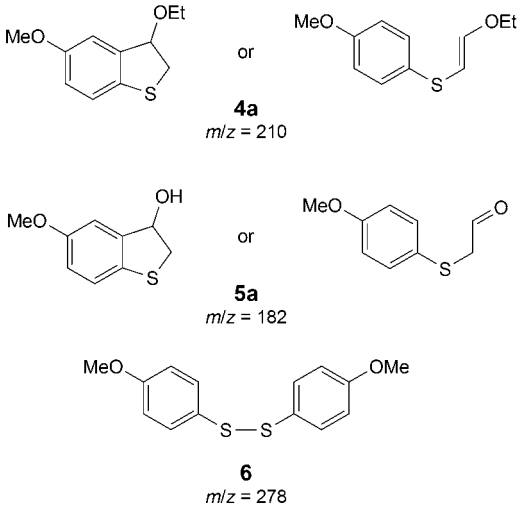


Fig. 3. Structures of intermediates and disulfide in the synthesis of 5-methoxybenzothiophene.

it has not been possible to assign one of the two proposed structures (it is assumed that it can be either one or the other).

We operated with 4-methoxybenzenthiol and decided to monitor the reaction by the GC/MS analysis (the visible species are reported in *Fig. 2*) with a sequence of sampling in a period of about 2 h, with the aim to understand the pathway; the obtained data are reported in *Fig. 4*.

The same protocol was repeated to prepare 5-nitrobenzothiophene **3b** which is a known compound synthesized by different methodologies; in particular, it was easily obtained by ring-opening/ring-closing procedure described in several papers by *Dell'Erba et al.* [12].

Also in this case, the reaction was followed by GC/MS with a sequence of sampling at regular time intervals in a period of about 4 h; the results are reported in *Fig. 5*.

From the MS data, it is possible to emphasize the formation of four main compounds and the evolution appears clear; compound **2b** rapidly decreases to transform first to compound **4b** with *m*/*z* 225 and subsequently to compound **5b** with *m*/*z* 197 (*Fig. 6*). At this moment, two routes are possible and the kinetic studies confirm that these are in competition; one gives the desired **3b**, while the second gives compound **7** with *m*/*z* 271.[1])

[1]) As regards intermediate **7,** despite having the same *m*/*z* of compound **2b,** its fragmentation and retention time are different.

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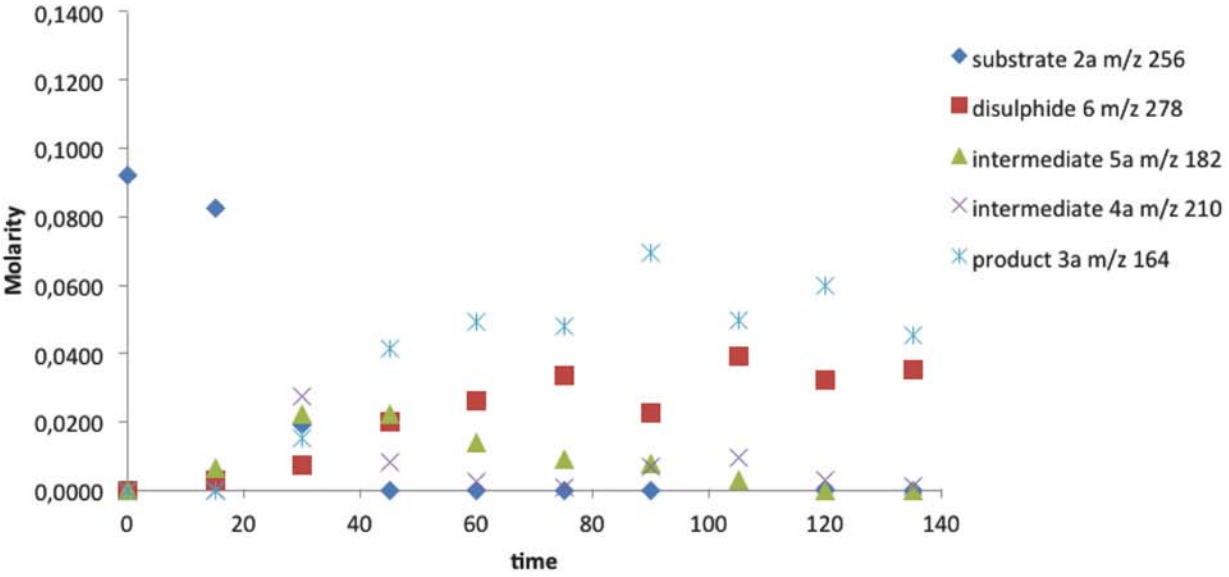

Fig. 4. Kinetics of the reaction **2a** → **3a**.

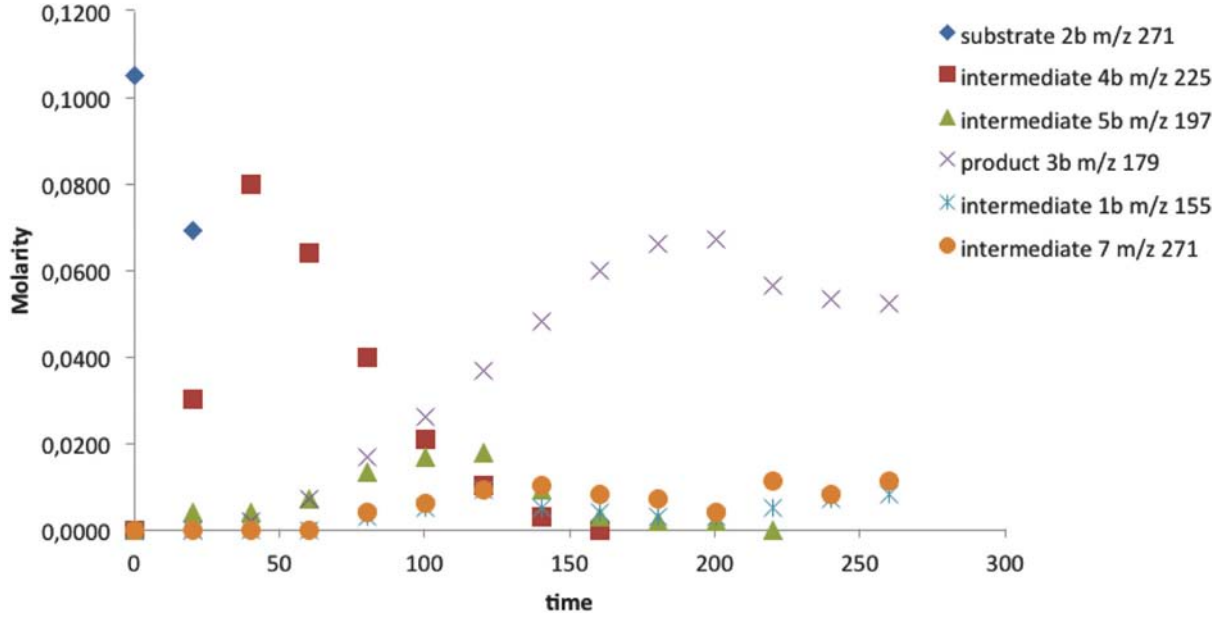

Figure 5. Kinetics of the reaction **2b** → **3b**.

Also in this case, with regard to intermediates **4b** and **5b**, in *Fig. 6* we reported the two possible structures.

Furthermore, we also examined the behavior of the reaction in the synthesis of 4-methoxybenzothiophene[2]) although it is clear that, in this case, two cyclization products, 4- and 6-methoxybenzothiophene (**3c**, **4c**) starting from 3-methoxybenzenethiol **1c**, (*Scheme 2*) were possible. Our idea was that, in this case, the disulfide will be not present because the substituent on benzenethiol precursor was in *meta*-position.

The reaction with the yields and the GC/MS data are reported in *Scheme 2* and *Fig. 7*: it appears immediately that the absence of the disulfide byproduct confirming the hypothesis of a relevant electronic effect on the course of cyclization; no other intermediates were visible to GC/MS.

[2]) The synthesis of 4-methoxybenzothiophene in good yield is well-known (as reported in: L. F. Fieser, R. G. Kennelly, *J. Am. Chem. Soc.* **1935**, *57*, 1611 – 1616; R. P. Napier, H. A. Kaufman, P. R. Driscoll, L. A. Glick, C. Chu, H. M. Foster, *J. Heterocycl. Chem.* **1970**, *7*, 393 – 394; A. Bekaert O. Provot, O. Rasolojaona, M. Alami, J. -D. Brion, *Tetrahedron Lett.* **2005**, *46*, 4187 – 4191; D. T. Drewry, R. M. Scrowston, *J. Chem. Soc. C* **1969**, 2750 – 2754; P. Dall, J. V. Johnson, C. E. Cook, *J. Org. Chem.* **1979**, *44*, 1421 – 1424).

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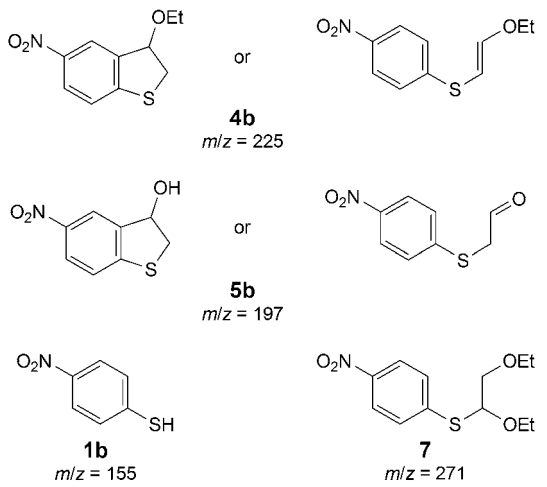


Fig. 6. Structures of the intermediates in the synthesis of 5-nitrobenzothiophene.

Kinetic Studies

To test our hypotheses on the mechanism, we performed some calculations on the kinetic results.

Although the above system can be solved analytically, we preferred to carry out a numerical integration with *Wolfram* Mathematica 9 [13] in order to take advantage of the remarkable arithmetic and graphics capabilities of this software.

The model equation has been coded in the Mathematica language and the solution was obtained by the NDSolve numerical integrator of ordinary differential equation. The code was performed in order to obtain a graphical output. The values of the constant $k_1 \ldots k_5$ are continuously varied, in a suitable range, using the Manipulate dynamic function of the Mathematica notebook: five sliders are defined, one for each constant, to set the numerical values of the k's and to see in real time the corresponding integral curves superimposed to the experimental data: an example of the output window is reported in *Fig. 8*.

With regard to the synthesis of 5-methoxybenzothiophene (**3a**), we have considered a kinetic model with the branched-chain mechanism, *i.e.*, a first-order linear sequence:

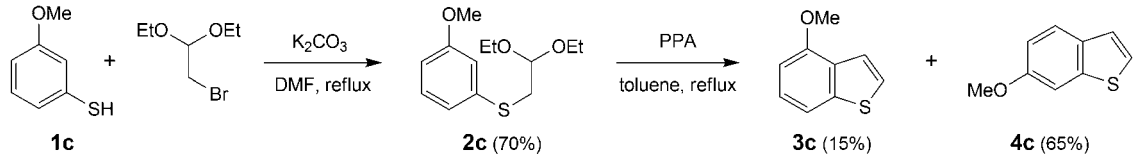
A → **B** → **C** → **D**

followed by a second-order dimerization side reaction:

2**C** → **E**

where **A**, **B** ... **E** stand for the compounds whose *m*/*z* values are 256 (**2a**), 210 (**4a**), 182 (**5a**), 164 (**3a**), and 278 (**6**), respectively.

Scheme 2. Synthesis of **3c** and **4c**.



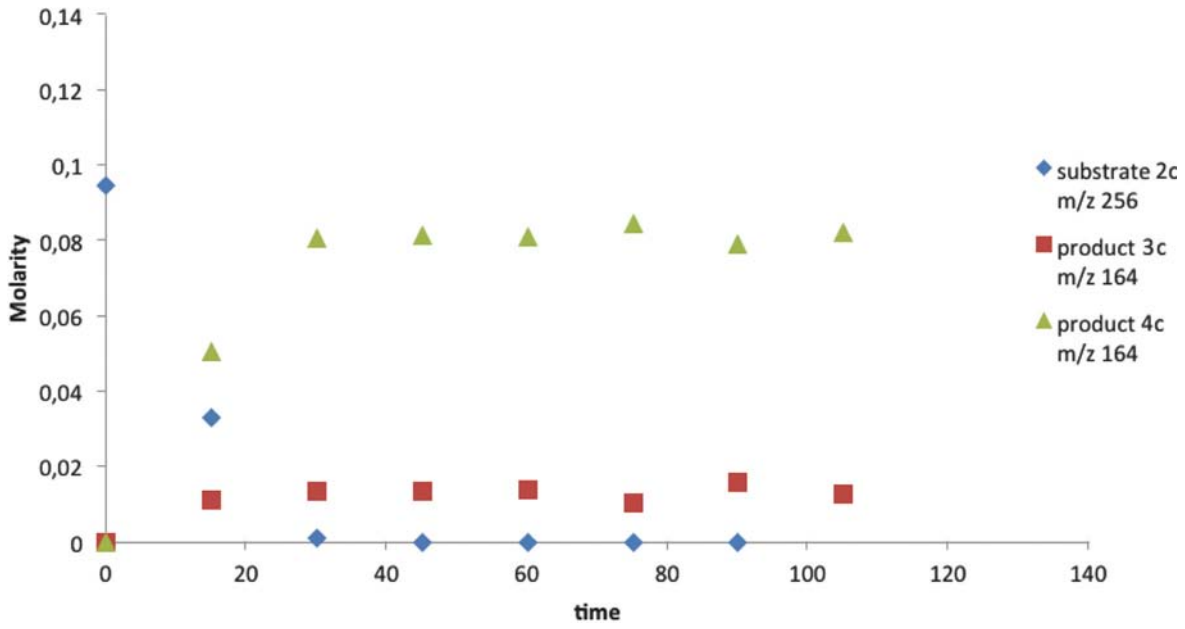


Fig. 7. Kinetics of the reaction **2c** → **3c** + **4c**.

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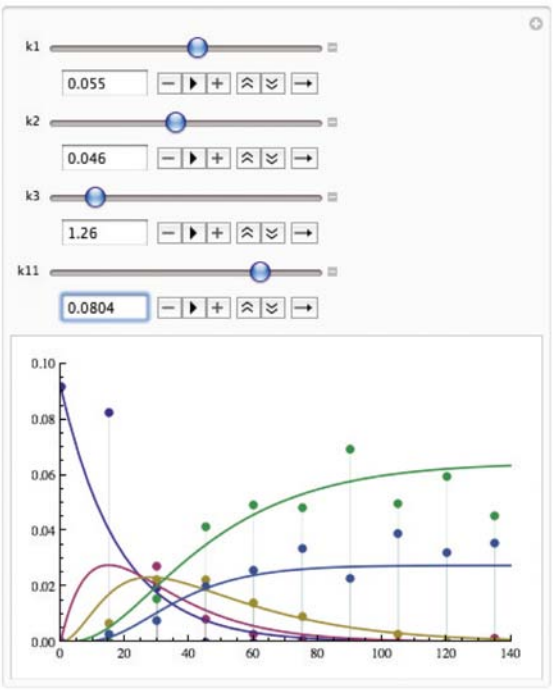


Fig. 8. A screenshot of the Mathematica notebook with the experimental (dots) and calculated (solid) kinetics.

The time evolution of the model can be represented by the following system of nonlinear first-order differential equations:

$$\mathbf{A}' = -k_1\mathbf{A}$$

$$\mathbf{B}' = k_1 A - k_2\mathbf{B}$$

$$\mathbf{C}' = k_2\mathbf{B} - k_3\mathbf{C} - k_4\mathbf{C}^2$$

$$\mathbf{D}' = k_3\mathbf{C}$$

$$\mathbf{E}' = k_4\mathbf{C}^2$$

where $\mathbf{A}'$, $\mathbf{B}'$... $\mathbf{E}'$ are the time derivatives of the molar concentration of the corresponding species **A**, **B**... **E**, and k_1... k_4 are the kinetic constants of the 1st... 4th reaction of the chain.

The initial concentration at $t = 0$ were 0.092M for **A** and zero for the remaining species, in agreement with the experimental setup. The computer simulation of the model was carried out with the Mathematica software, and the kinetic constants were optimized accordingly. The obtained values were the following: $k_1 = 9.53 \times 10^{-4}$/s, $k_2 = 1.38 \times 10^{-3}$/s, $k_3 = 7.83 \times 10^{-4}$/s, and $k_4 = 2.77 \times 10^{-2}$/M s.

In the synthesis of 5-nitrobenzothiophene (**3b**), we used a kinetic model where the irreversible consecutive first-order chemical reactions involving four species are considered:

$$\mathbf{A} \rightarrow \mathbf{B} \rightarrow \mathbf{C} \rightarrow \mathbf{D}$$

followed by a side reaction:

$$\mathbf{B} \rightarrow \mathbf{E}$$

where **A** ... **E** stand for the compounds whose *m*/*z* values are 271 (**2b**), 225 (**4b**), 197 (**5b**), 179 (**3b**), and 271 (**7a**), respectively.

The time evolution of the model can be represented by the following system of ordinary differential equations:

$$\mathbf{A}' = -k_1\mathbf{A}$$

$$\mathbf{B}' = k_1\mathbf{A} - k_2\mathbf{B} - k_4\mathbf{B}$$

$$\mathbf{C}' = k_2\mathbf{B} - k_3\mathbf{C}$$

$$\mathbf{D}' = k_3\mathbf{C}$$

$$\mathbf{E}' = k_4\mathbf{B}$$

where $\mathbf{A}'$ ... $\mathbf{E}'$ are the time derivatives of the molar concentration of the corresponding species **A** ... **E**, and k_1 ... k_5 are the kinetic constants of the 1st ... 4th reaction of the chain.

Starting from the initial concentration of **A** at $t = 0$ (in our case 0.1050M), the solution of the system gives the evolution of the concentration of the six chemical species as a function of time. Our problem is to match the theoretical values with the experimental ones in order to get the best fit for the kinetic constants.

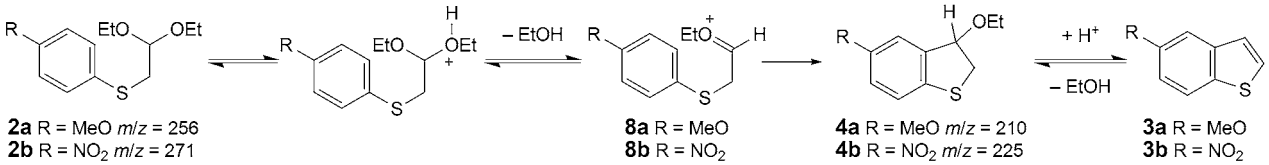
The kinetic constants are then optimized by changing the parameters until the computed curves match the data points. The best fit is obtained by visual inspection. The obtained kinetic constants were $k_1 = 1.01 \times 10^{-3}$/s, $k_2 = 1.75 \times 10^{-4}$/s, $k_3 = 7.0 \times 10^{-4}$/s, and $k_4 = 2.5 \times 10^{-5}$/s.

The order of magnitude of the results has been confirmed by a *Monte Carlo* optimization of the kinetic constants. We tried up to a million of different random values for the rate constants, and we have minimized the sum of the squared differences between the experimental concentrations and those estimated by the model. The results, calculated by Mathematica *Wolfram*, show a reasonable agreement with the values previously obtained.

Mechanistic Studies/Aspects

On the basis of kinetic results, the following mechanism can be proposed (*Scheme 3*). The proposed mechanism

Scheme 3. Proposed reaction mechanism.



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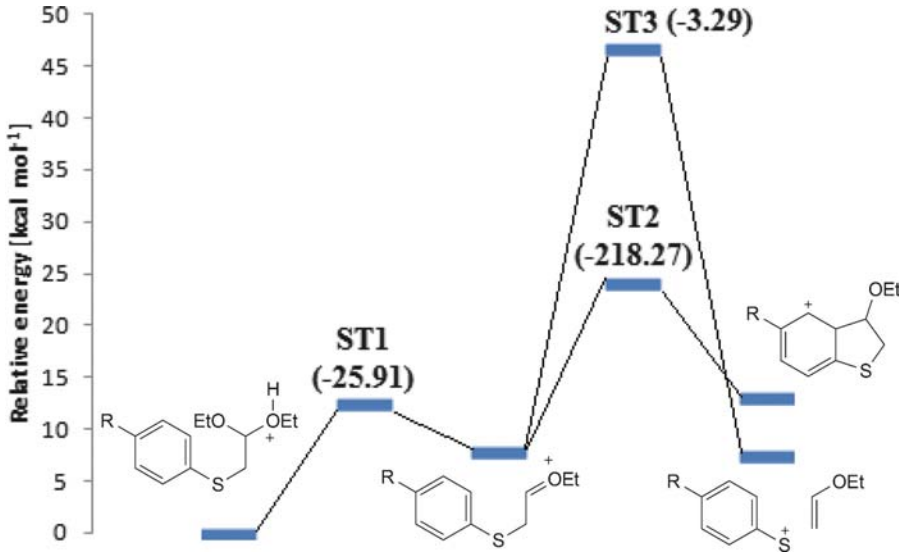

Fig. 9. Relative energy of some intermediates and transition states in the reaction **2a** → **3a**. In the brackets, the negative frequency in the calculated infrared spectra.

consists of an electrophilic aromatic substitution induced by the electrophiles (**8a – b**), followed by an aromatization step due to the loss of EtOH.

To test this mechanism, we performed some density functional theory (DFT) calculations at B3LYP/6-311G++(2d,p) level on *Gaussian* 09 [14]. Starting from the protonated form of compound **2a**, it can lose EtOH to give **8a** (*Scheme 3*). The following step is an electrophilic aromatic substitution reaction with activation energy of 16.1 kcal/mol to give the transition state **ST2** and, then, the cyclized product (*Fig. 9*). It is noteworthy that **8a** can undergo an elimination reaction to give ethyl vinyl ether and the thiol. In this case, the reaction occurred with a transition state (**ST3**) with energy of 38.9 kcal/mol. This is in agreement with the observed kinetic behavior.

Electrophilic aromatic substitution occurred on a substrate where the thioether function directs the reaction on the *ortho*-positions. These positions are in *meta* considering the MeO group. The substituents did not direct the reaction in the same position. On the contrary, when the reaction is performed on **2b**, the activating thioether and the deactivating nitro group directed the reaction on the same positions on the aromatic ring. In this case, the calculated transition state was 14.2 kcal/mol in agreement with the higher reactivity of this substrate in comparison with **2a**.

In this case, a description of the reactivity on the basis of the interaction between HOMO and LUMO of the reagents is not sufficient to describe the system. In *Fig. 10*, we reported the HOMO and LUMO of **8a** and **8b**. The HOMO is mainly localized in the aromatic part

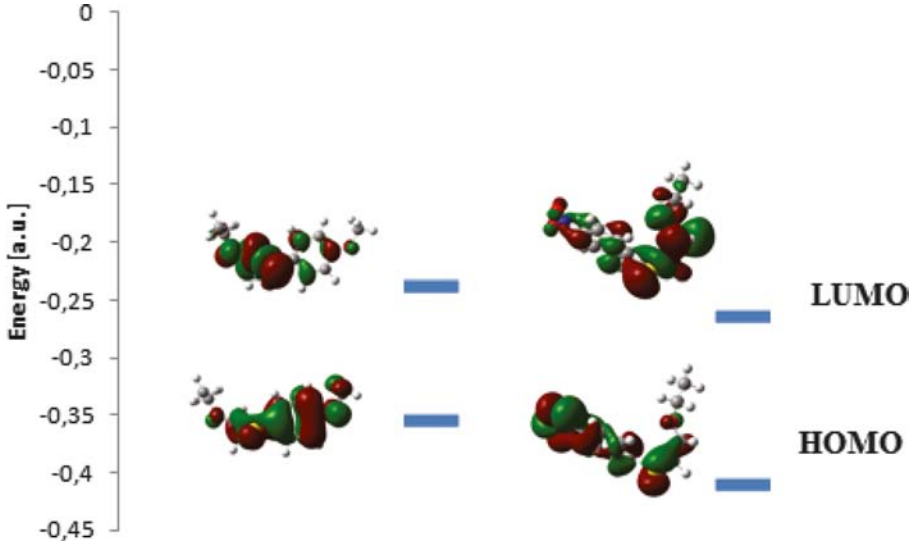

Fig. 10. HOMO and LUMO in **8a** (left) and **8b** (right).

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of the molecule, while the LUMO is mainly localized on the cationic side chain. The energy difference between HOMO and LUMO increased in **8b** in contrast with the experimental results. We can suppose, in this case, that the role of polar component in *Klopman–Salem* equation [15] is relevant if compared with the role of frontier orbitals.

Conclusions

The reaction of 4-methoxythiophenoxyacetaldehyde diethyl acetal, 4-nitrothiophenoxyacetaldehyde diethyl acetal, and 3-methoxythiophenoxyacetaldehyde diethyl acetal in polyphosphoric acid showed a complex kinetic behavior. Both computer-aided kinetic simulation and DFT calculations allowed to explain the observed behavior. In particular, the electronic effect of the substituent groups seems crucial in directing the cyclization and aromatization step. As suggested by the analysis of the experimental data and as confirmed by calculations, methoxy-substituted and nitro-substituted derivatives follow different reaction paths which are directed by activating/deactivating nature of these groups and their relative position to the thioether function in the intermediates **8a** and **8b**. Moreover, these effects influence the conversion of the intermediates into the final main products, *i.e.*, the disulfide **6** starting from 4-methoxythiophenoxyacetaldehyde diethyl acetal and 5-nitrobenzothiophene **3b**, starting from 4-nitrothiophenoxyacetaldehyde diethyl acetal.

In 3-methoxythiophenoxyacetaldehyde diethyl acetal, disulfide formation is not observed confirming the importance of substituent position relative to the intermediate: in this case, in fact, the thioether function and the MeO group lead the reaction in the same direction (on the *ortho-para* positions with prevalence of **4c** product formation).

In summary, in this work, starting from the experimental kinetic data in agreement with computer simulations and DFT calculations, a hypothesis about the mechanism in the synthesis of 5-substituted benzothiophenes from the corresponding thiophenoxyacetaldehyde diethyl acetals has been formulated.

In particular, in 4-nitrothiophenoxyacetaldehyde diethyl acetal, the rate determining step was $k_2 = 1.75 \times 10^{-4}$/s, corresponding to an electrophilic reaction. In the case of 4-methoxythiophenoxyacetaldehyde diethyl acetal, the rate determining step was $k_3 = 7.83 \times 10^{-4}$/s, corresponding to the same type of reaction. Furthermore, in this work for the first time, the application of the *Wolfram* Mathematica 9 to the kinetic parameters estimation of a complex chemical system is described.

We gratefully acknowledge the *University of Basilicata* for their financial support.

Experimental Part

General

CH_2Cl_2 was dried by distillation over anh. $CaCl_2$ in an inert atmosphere; Et_2O and THF were dried using Na/benzophenone. Dry DMF, toluene, and chlorobenzene were commercially available. Thin-layer chromatography (TLC) was carried out on precoated silica gel *60* plates (0.2 mm thickness) with the indicated solvents, and the plates were scanned under ultraviolet light at 254 and 365 nm. Column chromatography was carried out on *Merck* (Darmstadt, Gemany) silica gel *60* (70 – 230 mesh *ASTM*). Petroleum ether (PE) refers to the boiling range 40 – 60°. When a solvent gradient was used, the increase in polarity was done gradually from PE to mixtures of Et_2O/PE or AcOEt/PE. All the intermediates were not isolated but exclusively analyzed by GC/MS so their characterization is not reported. M.p.: *Mell-Temp-II* apparatus (Sigma-Aldrich. Milan, Italy); uncorrected. ^{1}H- and ^{13}C-NMR spectra: *Varian INOVA* 400 and 500 MHz instruments (Palo Alto, California, USA), in $CDCl_3$ soln. at room temperature with TMS as an internal reference; the chemical shifts are reported in ppm of TMS in δ units, and the J values are given in Hertz (Hz). MS: *Hewlett–Packard* GC/MS *6890-5973* (Agilent, Santa Clara, California, USA).

1-[(2,2-Diethoxyethyl)sulfanyl]-4-methoxybenzene (**2a**). In a reaction flask, in an inert atmosphere, commercial 4-methoxybenzenethiol (**1a**) (2.31 g, 16.5 mmol) was dissolved in anhydrous DMF, then potassium carbonate (5.01 g, 36.3 mmol) and bromoacetaldehyde diethyl acetal (= 2-bromo-1,1-diethoxyethane; 3.4 ml, 19.8 mmol) were added and the mixture was brought to reflux (153°). During the heating phase, the following color changes were observed: the mixture turned from milky white to pale yellow; and after 6 h of reflux, when the reaction was stopped, the mixture appeared brown and clear.

The quench involved about 100 ml of distilled water and three extractions with Et_2O. The organic layers were washed with a saturated solution of NH_4Cl, water, brine, finally dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The dark red oil obtained was purified by chromatographic column packed with silica and eluted with hexane/Et_2O (9:1), giving 3.63 g (yield 86%) of pure product (**2a**) (yellow thick oil; R_f 0.4 with hexane/Et_2O 9:1). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.21 – 1.18 (*t*, 6 H); 3.04 – 3.02 (*m*, 2 H); 3.53 – 3.51 (*m*, 2 H); 3.79 – 3.54 (*m*, 2 H); 3.80 (*s*, 3 H); 4.60 (*t*, 1 H); 6.85 – 6.83 (*d*, 2 H); 7.40 – 7.38 (*d*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 15.21; 55.90; 61.06; 66.02; 102.69; 114.23; 114.56; 127.54; 127.98; 128.13; 157.10 ppm. MS (EI, 70 eV): 256 (27) [M^+], 165 (22), 139 (44), 103 (100), 75 (52), 47 (31).

1-Benzothiophen-5-yl Methyl Ether (**3a**). To a reaction flask containing the polyphosphoric acid (2.58 g, 11.34 mmol) in anhydrous toluene (70 ml), 1-[(2,2-

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diethoxyethyl)sulfanyl]-4-methoxybenzene (**2a**) (2.42 g, 9.45 mmol) was added and the mixture is refluxed for 17 h in an inert atmosphere. After this time, a check on TLC (8:2 hexane/Et_2O) showed the disappearance of the substrate, so the reaction was stopped. For the quench, a solution of 4M KOH was added dropwise to the reaction mixture until neutrality. Extractions with Et_2O provided the organic phases that were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude dense and dark red oil was purified on chromatographic column packed with silica and eluted with hexane/Et_2O (8:2), to afford 372 mg (yield 24%) of 1-benzothiophen-5-yl methyl ether (**3a**) (thick fragrant yellow oil; R_f 0.7 with hexane/Et_2O (8:2) and 744 mg (yield 48%) of bis(4-methoxyphenyl) disulfide (**6a**) (thick yellow oil; R_f 0.4 with hexane/Et_2O 8:2). Data of 1-benzothiophen-5-yl methyl ether (**3a**): M.p.: 44 – 45°. ^{1}H-NMR (500 MHz, $CDCl_3$): 3.81 (*s*, 3 H); 6.93 (*d*, *J* = 5 Hz, 1 H); 7.22 – 7.20 (*m*, 2 H); 7.37 (*d*, *J* = 5 Hz, 1 H); 7.67 (*d*, *J* = 10 Hz, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 55.5; 105.5; 114.6; 123.1; 123.6; 127.5; 132.1; 140.6; 157.4. MS (EI, 70 eV): 164 (100) [M^+], 149 (64), 121 (62). Bis(4-methoxyphenyl) disulfide (**6a**): ^{1}H-NMR (400 MHz, $CDCl_3$): 3.76 (*s*, 3 H); 6.83 – 6.85 (*m*, 4 H); 7.42 – 7.44 (*m*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 55.1; 114.4; 128.1; 132.4; 159.7. MS (EI, 70 eV): 278 (56) [M^+], 139 (100).

1-[(2,2-Diethoxyethyl)sulfanyl]-3-methoxybenzene (**2c**). In a reaction flask, in an inert atmosphere, commercial 3-methoxybenzenethiol (**1c**) (400 mg, 2.85 mmol) was dissolved in anhydrous DMF, then potassium carbonate (860 mg, 6.22 mmol) and diethyl bromoacetal (0.5 ml, 3.38 mmol) were added, and the mixture was refluxed. During the heating phase, the following color changes were observed: after 15 min, the mixture turned from white to yellow; and after 1 h of reflux, the mixture appeared brown/greenish. After 150 min, the reaction was stopped, treated with distilled water and extracted with Et_2O. The organic layers were washed with a saturated solution of NH_4Cl, water, brine, finally dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The dark oil obtained was purified by chromatographic column packed with silica and eluted with hexane/Et_2O (8:2), giving 485 mg (yield 67%) of pure product (**2c**) (colorless thick oil; R_f 0.4 with 9:1 hexane/Et_2O). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20 (*t*, *J* = 7.2 Hz, 6 H); 3.14 (*d*, *J* = 5.6 Hz, 2 H); 3.53 – 3.57 (*m*, 2 H); 3.66 – 3.79 (*m*, 2 H); 3.80 (*s*, 3 H); 4.66 (*t*, *J* = 5.6 Hz, 1 H); 6.72 (*dd*, *J* = 8.2 Hz, 1 H); 6.94 (*m*, 2 H); 7.19 (*t*, *J* = 8.0 Hz, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.2; 37.3; 55.3; 62.2; 101.7; 111.8; 114.3; 121.3; 129.6; 137.9; 159.8. MS (EI, 70 eV): 256 [M^+].

1-Benzothiophen-4-yl methyl ether (**3c**) *and* **1-Benzothiophen-6-yl methyl ether** (**4c**). To a reaction flask containing the polyphosphoric acid (508 mg, 2.22 mmol), **1-[(2,2-diethoxyethyl)sulfanyl]-3-methoxybenzene** (**2c**) (485 mg, 1.89 mmol) was added in anhydrous toluene (20 ml) and the mixture was refluxed for 3 h in an inert atmosphere. After this time, a check on TLC (9:1 hexane/Et_2O) showed the disappearance of the substrate, so the reaction was stopped. For the quench, a solution of 4M KOH was added dropwise to the reaction mixture until neutrality. Extractions with Et_2O provided the organic phases that were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude oil was purified on chromatographic column packed with silica and eluted with hexane/CH_2Cl_2 (7:3), to afford 47 mg (yield 15%) of 1-benzothiophen-4-yl methyl ether (**3c**) (thick yellow oil; R_f 0.7 with hexane/CH_2Cl_2 7:3) and 203 mg (yield 65%) of 1-benzothiophen-6-yl methyl ether (**4c**) (thick fragrant yellow oil; R_f 0.4 with hexane/CH_2Cl_2 7:3). Data of 1-benzothiophen-4-yl methyl ether (**3c**): ^{1}H-NMR (500 MHz, $CDCl_3$): 3.98 (*s*, 3 H); 6.77 (*d*, *J* = 7.2 Hz, 1 H); 7.31 (*d*, *J* = 7.5 Hz, 1 H); 7.35 (*dd*, *J* = 6.5 Hz, 1 H); 7.48 (*d*, *J* = 7.5 Hz, 1 H); 7.52 (*d*, *J* = 5 Hz, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 55.39; 103.75; 114.82; 120.51; 124.57; 125.24; 130.42; 141.29; 155.04. MS (EI, 70 eV): 164 (100) [M^+], 149 (95), 121(65), 77 (14). Data of 1-benzothiophen-6-yl methyl ether (**4c**): ^{1}H-NMR (500 MHz, $CDCl_3$): 3.90 (s, 3 H); 7.06 (*dd*, *J* = 9 Hz, 1 H); 7.28 (*m*, 2 H); 7.38 (*d*, *J* = 2 Hz, 1 H); 7.73 (*dd*, *J* = 8.5 Hz, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 55.50; 104.74; 114.35; 123.34; 123.61; 124.04; 133.60; 141.13; 157.33. MS (EI, 70 eV): 164 [M^+].

1-[(2,2-Diethoxyethyl)sulfanyl]-4-nitrobenzene (**2b**)**.** In a reaction flask, in an inert atmosphere, commercial 4-nitrobenzenethiol (**1b**) (1.10 g, 7.1 mmol) was dissolved in anhydrous DMF, then potassium carbonate (2.36 g, 17.1 mmol) and bromoacetaldehyde diethyl acetal (1.4 ml, 9.3 mmol) were added, and the mixture was refluxed for 2 h. During the heating phase, the mixture turned from yellow to red. The quench was conducted with about 200 ml of distilled H_2O and three extractions with AcOEt. The organic layers were washed with a saturated solution of NH_4Cl, water, brine, finally dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The dark red oil obtained was purified by chromatographic column packed with silica and eluted with hexane/Et_2O (8:2), giving 1.88 g (yield 99%) of pure product (**2b**) (yellow thick oil; R_f 0.3 with hexane/Et_2O 8: 2). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.19 – 1.16 (*t*, 6 H); 3.22 – 3.20 (*d*, 2 H); 3.57 – 3.53 (*q*, 2 H); 3.70 – 368 (*q*, 2 H); 4.68 (*t*, 1 H); 7.40 – 7.37 (*d*, 2 H); 8.07 – 8.06 (*d*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.12; 35.76; 62.64; 101.46; 123.69; 126.45; 145.02; 147.28. MS (EI, 70 eV): 271 [M^+], 226 (13), 103 (100), 75 (49), 47 (42).

5-Nitro-1-benzothiophene (**3b**). To a reaction flask containing the polyphosphoric acid (6.38 g, 28 mmol) in anhydrous toluene (65 ml), 1-[(2,2-diethoxyethyl)sulfanyl]-4-nitrobenzene (**2b**) (1.88 g, 6.94 mmol) was added and the mixture was refluxed for 4 h in an inert atmosphere. After this time, a check on TLC (9:1 hexane/Et_2O) showed the disappearance of the substrate, so the reaction was stopped. For the quench, a solution of 4M KOH was added dropwise to the reaction mixture until

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neutrality. The mixture was extracted with Et_2O and washed with brine. The combined organic extracts were dried with Na_2SO_4 and concentrated under vacuum. The crude dense and dark brown oil was purified on chromatographic column packed with silica and eluted with hexanes/Et_2O (9:1), to afford 434 mg (yield 35%) of 5-nitro-1-benzothiophene (**3b**) (yellow solid; R_f 0.5 with hexane/Et_2O 9:1). M.p.: 135 – 137°. ^{1}H-NMR (400 MHz. $CDCl_3$): 7.41 – 7.40 (*d*, 1 H); 7.57 – 7.56 (*d*, 1 H); 7.89 – 7.87 (*d*, 1 H); 8.10 – 8.08 (*d*, 1 H); 8.61 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 118.48; 119.22; 122.93; 124.64; 129.95; 131.05; 139.24; 145.47. MS (EI, 70 eV): 179 (100) [M^+], 149 (11), 133 (71), 121 (22), 89 (51).

Theoretical Calculations

All the calculations were performed by using the *Gaussian* 09 program, Revision A.02. Molecular structures were optimized by using the *Kohn–Sham*'s DFT [16] with the *Becke*'s three-parameter hybrid exchange-correlation functional known as B3LYP [17]. The 6-31+G(d,p) basis set was applied for all the calculations as implemented in the *Gaussian* 09 program. All the optimized geometries were obtained by using the standard thresholds for self-consistent field computations and geometry optimizations. Analytical evaluation of the energy second derivative matrix (*Hessian* matrix) with respect to *Cartesian* coordinates at the same level of approximation confirmed the nature of minima and transition structures of the energy surface points associated to the optimized structures. All the computations have been performed by using the *Gaussian* 09 standard approach which considers the molecule in vacuum.

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