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TETRAHEDRON

Synthesis of (4-Chlorophenyl)-(1-oxo-1λ^4-benzo[b]thien-2-yl)methanone and study of its reactivity towards sulfur- and oxygen-containing nucleophiles.

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Abstract: (4-Chlorophenyl)-(1-oxo-1λ^4-benzo[b]thien-2-yl)methanone **2a** was synthesized by oxidation of the corresponding benzo[b]thiophene derivative **2** with the oxidative system H_2O_2/TFA. This benzo[b]thiophene sulfoxide undergoes Michael-type nucleophilic addition of sulfur- and oxygen-containing nucleophiles either under *basic* conditions leading to 2,3-dihydro-3-substituted-benzo[b]-thiophene 1-oxides or in *acidic* media leading then to rearomatized 3-substituted-benzo[b]thiophenes. This method provides an easy two-step functionalization of 2-acyl-benzo[b]thiophene derivatives.

Keywords: benzothiophenes; oxidation; sulfoxides; Michael reactions.

INTRODUCTION

In the last years, several biological studies have shown that thiophene- and benzo[b]thiophene 1-oxides can be formed as primary electrophilic metabolites *in vivo* and *in vitro* [3-7]. This has been recently extended to thiazole 1-oxides [8]. In addition, a number of 2-aroyl thiophenes are hydroxylated *in vivo* and *in vitro* in position 5 of the thiophene ring leading to the corresponding 5-hydroxy thiophene derivatives [9-14]. In particular, tienilic acid (TA) the metabolism of which has been thoroughly studied in our laboratory, is mainly transformed in 5-hydroxy tienilic acid (5-OHTA). The mechanism of this 5-hydroxylation has not yet been completely elucidated. Three different pathways can be proposed (scheme 1): (i) direct aromatic hydroxylation [15], (ii) classical arene oxide pathway involving primary epoxidation followed by rearrangement [16] or (iii) formation of an intermediate sulfoxide followed by nucleophilic attack of water in the activated 5-position of the thiophene ring, and final dehydration 4 (scheme 2).

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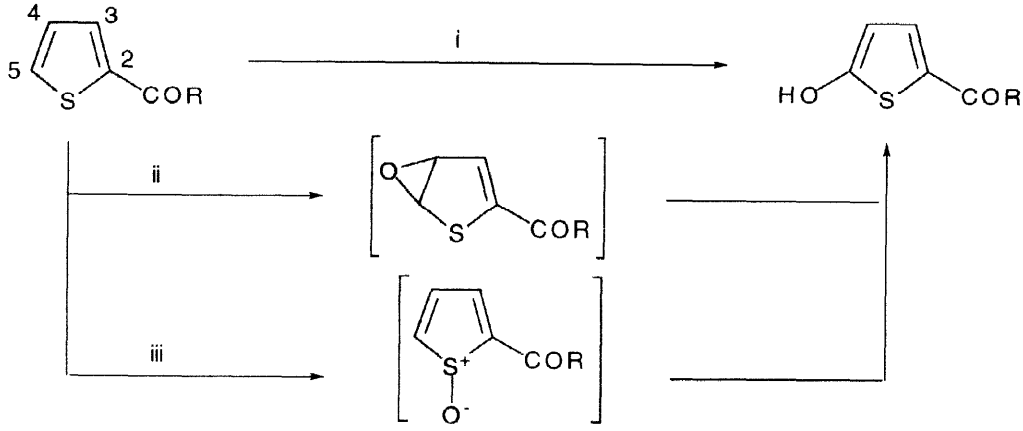
Scheme 1

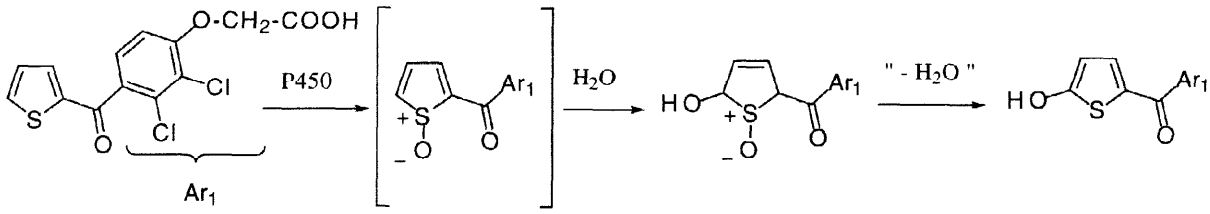
Different pathways which could account for the metabolic transformation of 2-aroylthiophenes into their corresponding 5-hydroxy derivatives.



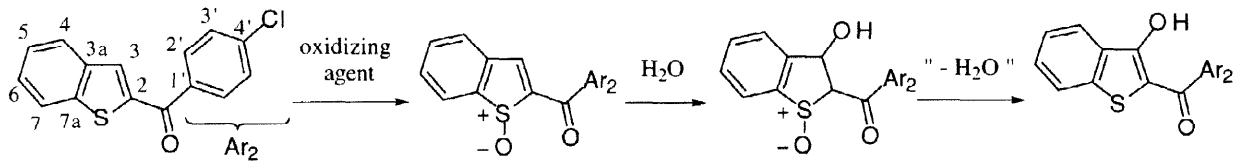
Moreover, the toxic effects of tienilic acid as well as its ability to act as a suicide substrate of P450 2C9 have been attributed to the intermediate formation of a thiophene 1-oxide. [4,17]

Scheme 2

• Hypothetical mechanism for the formation of 5-OHTA



• Model study



Preparation and isolation of thiophene 1-oxides are difficult mainly because of the following two reasons: (i) monocyclic thiophene 1-oxides readily dimerize in a Diels-Alder manner, and (ii) they are easily further oxidized to the corresponding 1,1-dioxides. So far, only a few thiophene 1-oxides have been described. [18-24]. All of them bear bulky substituents on the thiophene ring to reduce its ability to over react *via* the two pathways stated above. However, no thiophene 1-oxide bearing electroattracting substituents has ever been isolated and characterized. Moreover, according to the study published on the metabolism of the isomer of tienilic acid, bearing the aroyl group in position 3 of the thiophene ring [6], intermediate **1a** would probably be very reactive

and thus difficult to isolate (see scheme 2).

In contrast, substituted benzothiophene 1-oxides which were reported to be more stable than the corresponding thiophene 1-oxides, have been more studied in the past years [25-28].

In order to investigate whether the mechanism proposed for the 5-hydroxylation of tienilic acid has a chemical basis, we decided to carry out a model study using a benzothiophene derivative bearing an aroyl subtituent in position 2 (scheme 2).

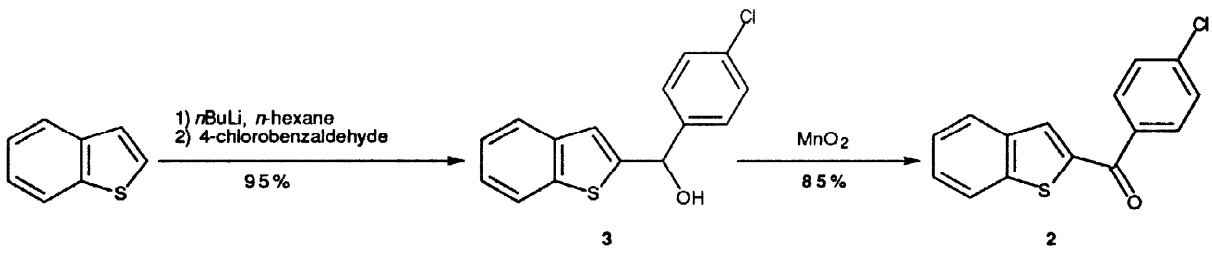
We report here the preparation of model compound 2 and its reactivity towards various sulfur- and oxygen-containing nucleophiles.

RESULTS

Synthesis and oxidation of 2.

The new benzo[b]thiophene derivative 2 was synthesized from commercially available benzo[b]thiophene in two steps (scheme 3): (i) synthesis of intermediate 3 from reaction of 2-lithiobenzo[b]thiophene formed *in situ* with 4-chlorobenzaldehyde; (ii) selective oxidation of the benzylic alcohol function with MnO_2 [29].

Scheme 3



3 2

Overall yield 80%

The oxidation of compound 2 was then attempted by several chemical methods. When we started our research in 1992, only one study had been reported on the oxidation of benzo[b]thiophene derivatives in which *meta*-chloroperbenzoic acid and *tert*-butyl hypochlorite was used as oxidants [25-27]. However, no benzo[b]thiophene 1-oxide bearing an electronwithdrawing group at the 2-position could be synthesized *via* these methods.

The results we obtained are summarized in table 1. In all cases, the corresponding 1-oxide and 1,1-dioxide were the only products formed. As already reported in the literature [30], dimethyl dioxirane (DMD) confirmed to be a very mild and selective reagent to convert a thiophene derivative to the corresponding 1,1-dioxide. Among the oxidative methods tested, the best to prepare 1-oxide **2a** was H_2O_2/TFA, in the presence of excess H_2O_2 (3 equivalents), at 0°C for one hour. Prolonging the oxidation at room temperature with the same proportions of reagents also gave 1,1-dioxide **2d** in good yield (scheme 4).

Like thiophene 1-oxides, benzo[b]thiophene 1-oxides were reported to react mainly *via* cycloaddition reactions [31] and in particular *via* Diels-Alder-type dimerizations [32]. During the course of our study, we did not observe such a reactivity. In our model compound **2a**, the C(2)-C(3) bond is doubly activated by the electron withdrawing carbonyl and sulfinyl groups in position 2. Hence we studied the Michael addition of nucleophiles on 1-oxide **2a**. This type of reactivity has already been observed with benzo[b]thiophene 1,1-dioxides [33], and

has been suggested to explain the formation of 2,3-dichloro-2,3-dihydrobenzo[b]thiophene 1-oxide obtained

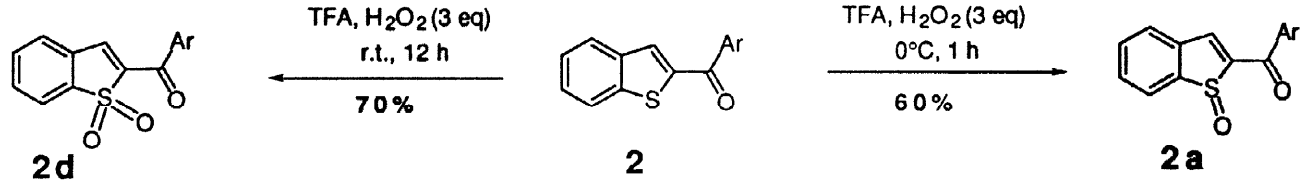
Table 1 : Oxidation of 2.

Oxidizing system	Conversion of 2	2a	2d
TFA/H_2O_2, 1 h, 0°C	100%	**100%**	0%
TFA/ H_2O_2, 12 h, r.t.	100%	0%	**100%**
$NaIO_4$ a)	no reaction	0%	0%
m-CPBA b)	40%	40%	60%
DMD (1eq.) c)	25%	50%	50%
DMD (3eq.) c)	100%	0%	100%

m-CPBA: meta-chloroperbenzoic acid; DMD: dimethyl dioxirane. a) $NaIO_4$ (1 eq.), CH_2Cl_2/CH_3CN (1/1) or H_2O ([2] =9 mM), r.t., 72 h. b) *m*-CPBA (1 eq.), CH_2Cl_2 ([2] = 8 mM), r.t., 24 h. c) DMD, CH_2Cl_2 ([2] = 5 mM), r.t., 5 min.

during the oxidation of benzo[b]thiophene by tertiobutyl hypochlorite [34]. However, no experimental evidence had been reported.

Scheme 4



In our study, 2-mercaptoethanol was chosen as a simple sulfur-containing nucleophile as it has commonly been used to mimic biological thiols such as glutathione or cysteine.

Reactivity of 2a towards sulfur- and oxygen-containing nucleophiles, under basic conditions [35]

In the presence of 2-mercaptoethanol, under *basic* conditions, 1-oxide **2a** was rapidly converted into a mixture of two products which could be isolated in 95% yield. These two products could not be separated for stability reasons. However, the proton NMR analysis of the mixture showed the presence of two sets of signals corresponding to the same protons. Considering the spectral data, the products were thus identified as a mixture of diastereo-isomers **4a** and **4b** ((30:70), scheme 5 [36]. These compounds derived from the nucleophilic attack of 2-mercaptoethanol on position 3 of the C(2)-C(3) bond.

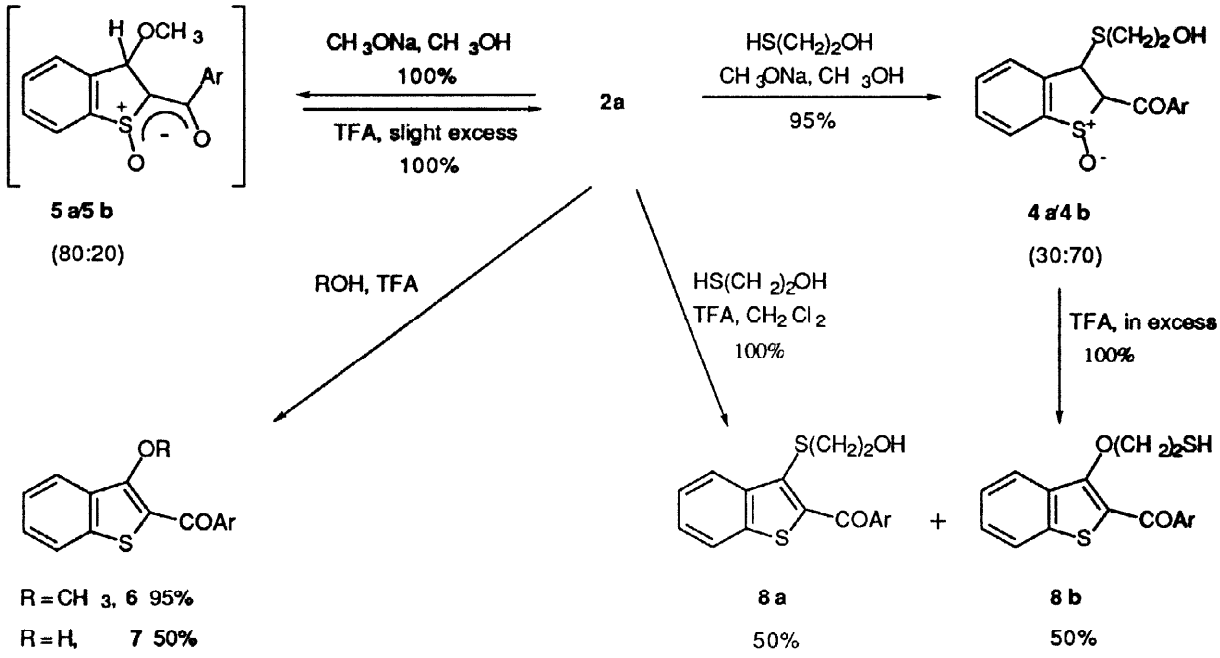
Compound **2a** was also reacted with sodium methoxide. However, in this case, no product could be isolated. We then carried out the reaction in the presence of deuterated sodium methoxide in deuterated methanol, and monitored it by ^1H and ^{13}C NMR. Compound **2a** was rapidly converted; the aromatic protons were shifted upfield and three new singlets appeared at 5.99, 5.42 and 3.30 ppm.

The disappearance of 1-oxide **2a** was confirmed by HPLC analysis of the crude reaction mixture, the new product(s) formed having the same polarity as **2a** but showing a different UV-visible spectrum (e.g. experimental). The spectral characteristics showed by the new product(s) were similar to the ones obtained for compounds **4a/4b**. Therefore, we proposed that a mixture of diastereoisomers **5a** and **5b** was obtained (80:20),

(scheme 5). Moreover, the analysis of the ^{13}C NMR spectrum as well as a HMQC COSY indicated that, in the conditions of the reaction, carbon C(2) of the benzo[b]thiophene ring was not deuterated since the signals at 108.5 and 106.6 ppm corresponding to the carbons C(2) appeared as singlets and not as triplets.

Scheme 5

Summary of the reactivity of 1-oxide **2a** towards sulfur- and oxygen-containing nucleophiles under *basic* and *acidic* conditions.



This was in accordance with the presence of only two singlets at 5.99 and 5.42 ppm in the proton NMR spectrum which likely correspond to the proton H(3) of the two diastereoisomers. However, we could not isolate compounds **5a/5b**. After acidic work-up, we only recovered the starting 1-oxide **2a** which probably result from the elimination of methanol.

Reactivity of 2a towards sulfur- and oxygen-containing nucleophiles, under acidic conditions. [35]

In the presence of trifluoroacetic acid (50 eq/2a), in methanol, 1-oxide **2a** was quantitatively transformed in compound **6**. Formally, the formation of 3-methoxy-2-substituted-benzo[b]thiophene **6** corresponds to dehydration of compounds **5a/5b**. The reaction was slow (14 h) and was considerably slowed down as the concentration of acid was decreased; no reaction occurred after one month in the absence of acid. The same reaction took place in the presence of other Bronsted acids ($HClO_4$, HCl, HBr), Lewis acids ($BF_3.OEt_2$, $FeCl_3$, $AgBF_4$), and even iron porphyrins, biomimetic models of cytochromes P450 [20]. Qualitative kinetic studies performed by UV-visible spectroscopy indicated that, for the same concentration of acid, the reaction was a little faster with $HClO_4$ or $BF_3.OEt_2$ than with TFA. The reaction also occurred with HCl or HBr. However, in these cases, there was also formation of compound **2**, probably from the reduction of 1-oxide **2a** by HCl or HBr [37]. With acetic acid, there was almost no reaction even after one week. Interestingly, a similar reaction was observed with water as nucleophile. Compound **7** was isolated in 50% yield (scheme 5)

For 2-mercaptoethanol, 1-oxide **2a** was quantitatively converted into a (50:50) mixture of compounds **8a** and **8b**. The same final (50:50) mixture of **8a/8b** was also obtained when the mixture of compounds **4a/4b** was treated in acidic conditions. Compound **8a** was isolated and completely characterized. Compound **8b** was not

stable and readily isomerized to compound **8a**. Therefore, its structure was proposed on the basis of its NMR data, compared with those obtained for compound **8a**. In acidic conditions, compound **8a** isomerized to a mixture of compounds **8a/8b**. Therefore, compounds **8a** and **8b** seemed to be in equilibrium. The detailed conditions of this equilibrium and the difference in behaviour between these two compounds are still under investigation. All the results described above are summarized in scheme 5.

Study of the protonation of 1-oxide 2a in the presence of excess TFA.

It is known that the sulfinyl function can be protonated in highly acidic media e. g. concentrated sulfuric acid [38]. By proton NMR, we studied the influence of excess trifluoroacetic acid on the chemical shifts of compounds **2**, **2a** and **2d**. In the presence of TFA in excess, we observed for the three components a global downfield shift, the most strongly shifted signal being that corresponding to proton H(3). However, in the case of 1-oxide **2a**, this shift was almost twice as large (0.26 ppm) as that observed for compounds **2** and **2d** (0.14 ppm). Moreover, this shift was reversible. When the mixtures were neutralized, the spectra of starting compounds **2**, **2a** and **2d** were obtained back. The additional shift observed for 1-oxide **2a** could therefore be attributed to the reversible protonation of the sulfinyl function.

DISCUSSION

The first goal of our study was to synthesize 1-oxide **2a**. Among the oxidative methods we tested, the only one to give cleanly 1-oxide **2a** was H_2O_2/TFA in the presence of an excess H_2O_2 at 0°C for one hour. With this H_2O_2/TFA oxidation system, we had already synthesized benzo[b]thiophene 1-oxide [3] which had never been obtained before, and also 2,5-diphenylthiophene 1-oxide [20]. When they gave a reaction, the other oxidative systems led either selectively to 1,1-dioxide **2d** (DMD, 3 equivalents/**2**) or gave mixtures of compounds **2a** and **2d** (*m*CPBA, DMD 1 equivalents/**2**). These last results indicate that, in these experimental conditions, the second oxidation of the sulfur atom leading to 1,1-dioxide **2d** is as fast as or even faster than the first oxidation, giving 1-oxide **2a**. As confirmed by the proton NMR study of the behaviour of 1-oxide **2a** in excess TFA, it is likely that under the acidic conditions of oxidation of **2** with H_2O_2/TFA (TFA was used as the solvent of the reaction), the formed 1-oxide **2a** is protonated at the oxygen atom. This protonation which would decrease the electronic density around the sulfur atom, slowing down the second oxidation of sulfur, could therefore account for the selectivity observed with this oxidative system.

We then showed that 1-oxide **2a** behaves as a Michael acceptor which can undergo the addition of various sulfur- and oxygen-containing nucleophiles.

First, we investigated the reactivity of 1-oxide **2a** in nucleophilic media (*basic* conditions), the usual conditions for Michael-type additions. The 3-substituted 2,3-dihydrobenzo[b]thiophene 1-oxides obtained derived from the attack of the sulfur- or oxygen-containing nucleophile used on position 3 of the C(2)-C(3) bond. In the presence of 2-mercaptoethanol, under *basic* conditions, 1-oxide **2a** was converted into a mixture of diastereoisomers **4a/4b** (30:70). These two compounds could not be separated, and so their stereochemistry could not be unambiguously determined. Nevertheless, on the basis of results reported in the literature on related 2,3-dihydrobenzo[b]thiophene 1-oxides, we propose the following elements for the interpretation of the structures. The crystal structure of 2-(1-oxo-2,3-dihydro-1λ^4-benzo[b]thien-3-yl)sulfanylethanol obtained by X-ray diffraction revealed that, in the major diastereoisomer, the oxygen atom of the sulfinyl function and the sulfanyl group in position 3 were on the same side (*syn*) of the mean plane of the benzo[b]thiophene ring [39]. If the addition of nucleophile is *syn* to oxygen of the sulfoxide, then the formation of only 2 diastereoisomers observed by NMR in the case of compounds **4a/4b**, instead of the eight possible, shows that the protonation of

the intermediate anion must be totally diastereospecific. We compared the NMR constants obtained for the ^3J coupling between protons H(2) and H(3) with those reported for 2,3-disubstituted 2,3-dihydrobenzo[b]thiophene 1-oxides and 1,1-dioxides [25]. Accordingly, we propose that minor compound **4a** could be the *cis* isomer (J = 6.5 Hz) and major compound **4b** could be the *trans* one (J = 7.5 Hz).

In the case of compounds **5a/5b**, the NMR spectra showed that position C2 was not protonated, thus was most probably a carbanion localized at C2 or its enolate form. Thus to account for the presence of two sets of signals in the proton NMR spectrum the addition of methanol must be stereospecific (80/20), similarly to the addition of mercaptoethanol which is slightly less stereospecific (70/30). However, in the absence of further data, we cannot provide any likely structural interpretation.

Second, we looked at the reactivity of 1-oxide **2a** under *acidic* conditions as it has been reported that 2-substituted 2,5-dihydrothiophene 1-oxide [3, 6] or substituted 2,3-dihydrobenzo[b]thiophene 1-oxide [40, 41] are susceptible to undergo dehydration in acidic media. The 3-substituted benzo[b]thiophenes obtained formally derived from the nucleophilic attack of the sulfur- or oxygen-containing nucleophile used on position 3 of the C(2)-C(3) bond followed by dehydration. In the presence of a large excess of trifluoroacetic acid, compounds **5a/5b** and **4a/4b** were quantitatively converted respectively to compound **6** and a mixture of compounds **8a/8b**. Formally, these conversions correspond to a dehydration. The same 3-substituted benzo[b]thiophene derivatives were obtained when 1-oxide **2a** was treated under *acidic* conditions in the presence of either methanol or 2-mercaptoethanol. With methanol as nucleophile, we followed the process by proton NMR. The following information was obtained : (i) adduct **5** formed under *basic* conditions was not stable; (ii) when the excess sodium methylate was neutralized, compound **5** was converted back to the starting 1-oxide **2a**; finally (iii) when **5a/5b** or **2a** were treated with an excess trifluoroacetic acid, they were slowly transformed into compound **6**. There are several possible protonation sites in molecule **5**, the oxygen atom of the sulfinyl group being the less basic one. We propose that: (i) when we just neutralize the excess base, being in slightly acidic conditions, the oxygen atom of the methoxy group is protonated; the elimination of a molecule of methanol then occurs, leading to the starting 1-oxide **2a**; (ii) when compounds **5** or **2a** are treated under more acidic conditions and longer reaction times, the oxygen atom of the sulfinyl function is also protonated, driving the reaction towards final "rearomatization" (scheme 6).

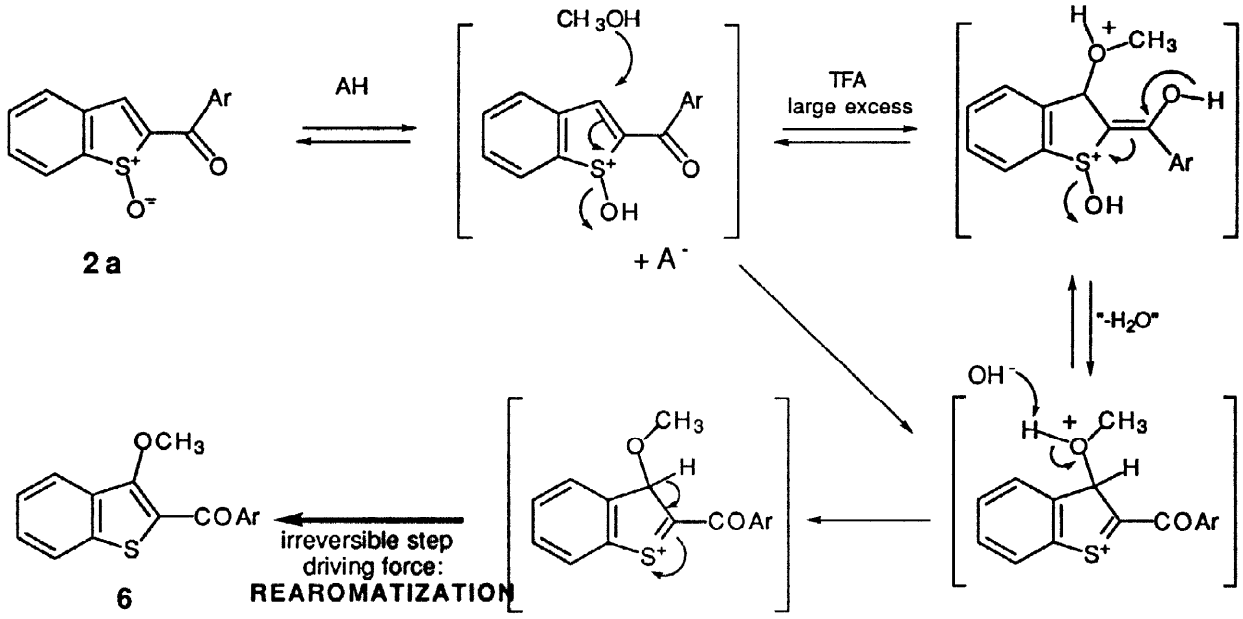
This last irreversible step is the *driving force* of the reaction; (iii) alternatively protonation of the sulfoxide to the sulfinic acid in pseudo-Pummerer reaction, and attack of the nucleophile followed by loss of water affords a sulfonium intermediate which upon deprotonation leads to the final aromatic product. The rate of this reaction was increased when the concentration of acid was increased or when a stronger acid than TFA like $HClO_4$ was used. This indicated that the protonation of the sulfinyl function may be the rate limiting step. We confirmed by proton NMR that protonation of the sulfinyl function can occur in the presence of excess TFA. However, this protonation is not very efficient as indicated by the small difference in chemical shifts observed for proton H(3) (0.14 ppm), compared for example with that reported for the tetrafluoroborate salt of 1-methylbenzo[b]thiophenium (0.6 ppm for proton H(3)) [42].and may explain why the conversion of 1-oxide **2a** to compound **5** is slow. The conclusions for the acid catalyzed reaction are summarized in scheme 6.

From the synthetical point of view, the sequence of sulfoxidation, nucleophilic attack and rearomatization provides an easy two-step functionalization of 2-acyl-benzo[b]thiophene derivatives as efficient as other existing methods. For example, compounds **6** and **7** were obtained with respective overall yields of 45% and 80% with the method presented here, compared with 60-70% for reported syntheses [43]. Also, the 3-hydroxyl derivative was obtained when the methyl ester of benzo[b]thien-2-yl-methanoic acid was treated following the sequence sulfoxidation, reaction with water under *acidic* conditions [44], indicating that the substituent in position 2 can be varied. Recently, various 3-alkoxy-2-benzo[b]thiophene-carboxamide 1-oxides have been shown to be inhibitors of neutrophiles adhesion, potentially useful as anti-inflammatory agents [28]. The method

described above could then provide an alternative way to synthesize for exemple this kind of compounds.[45]

Scheme 6

Proposed mechanism for the conversion of 1-oxide 2a in compound 6 under *acidic* conditions. The intermediates are indicated to suggest a possible pathway. However, there is no direct evidence for their existence. A concerted mechanism is also possible.



The aforementioned results provide a clear evidence that, on a chemical basis, the mechanism proposed in scheme 2 to account for the 5-hydroxylation of tienilic acid (scheme 2) is possible.The intermediate 1-oxide 2a can be converted to the corresponding 3-hydroxy compound 2c which is the vinylogous analog of 5-OHTA.

EXPERIMENTAL SECTION

Melting points were determined with a Kofler bank and are uncorrected. Mass spectra were recorded on a Nermag R10-10 spectrometer at the Ecole Normale Supérieure de Paris. Infra-red spectra were recorded on a Perkin Elmer 783 spectrophotometer. The intensity of each vibration is indicated between brackets using the following abbreviations: w (weak), m (medium), s (strong). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker ARX 250 spectrometer. Chemical shifts are reported in δ relative to the signal of TMS taken as an internal standard. The ^{1}H detected ^{1}H, ^{13}C HMQC spectrum was recorded at 300 K (1/2 J = 3.5 ms). The ^{1}H detected ^{1}H, ^{13}C HMBC spectrum 40 (PGF - HMBC, pulse gradient field heteroatom nuclear multiple - quantum correlation) was recorded at 300 K (1/2J = 50 ms). The assignments were made using one-dimensional ^{1}H and ^{13}C (^{1}H decoupled and DEPT-135) spectra and heteronuclear shift correlations. UV-visible spectra were recorded on a Kontron-Uvikon 810 (or 820) spectrophotometer. High-pressure liquid chromatography (hplc) was performed on an Altex gradient system using a C8 5μm MOS Hypersil column (1 mL/min flow rate) with two elution gradients: gradient A (solution C: 0.1 M ammonium acetate, pH 4.6; solution D: acetonitrile/water, 90/10 v/v; 60-100% D in C 15 min) and gradient B (solution C: 0.1 M ammonium acetate, pH 4.6; solution D: acetonitrile/water, 90/10 v/v; 50-100% D in C 20 min). UV and visible spectra were recorded on-line using a Spectra-Focus system (Spectra-Physics). Benzo[b]thiophene was

purchased from Aldrich, trifluoroacetic acid from Janssen Chimica and hydrogen peroxide (30% in water) from Prolabo.

Synthesis of benzo[b]thien-2-yl-(4-chlorophenyl)methanone (2).

To an ice-cooled ether solution of of benzo[b]thiophene (2.0 g (15.0 mmoles) in 10 ml) were added dropwise 7.5 ml (18.6 mmoles, 1.3 eq.) of a *n*BuLi solution in *n*-hexane (2.5 N). No change of color was observed. The resulting mixture was refluxed until the evolution of gas stopped (approximately 1.5 h). The mixture was cooled to room temperature and then to 0°C. 2.6 g (18.6 mmoles, 1.3 eq.) of 4-chloro-benzaldehyde in 10 ml of ether were added dropwise and the mixture was stirred at room temperature for 1.5 h (the reaction was monitored by tlc (silica, dichloromethane: Rf = 0.7 (4-chloro-benzaldehyde); Rf = 0.5 (3))). 20 ml of a saturated solution of ammonium chloride were then added. The aqueous layer was extracted with 20 ml of ether. The ether layer was then washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. 4.0 g (95%) of pure 3 were obtained as a pale brown powder . This crude product was recrystallized in hot isopropylic alcohol. 3.5 g (80%) of a white powder was obtained, mp 97°. ^{1}H NMR (CD_2Cl_2): 7.80 (d, J = 7.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.60 - 7.20 (m, 2H, H(5) and H(6)), 7.45 (d, J = 7.5 Hz, 2H, H(2')), 7.35 (d, J = 7.5 Hz, 2H, H(3')), 7.15 (s, 1H, H(3)), 6.10 (d, J = 3.5 Hz, 1H, CH-OH), 2.75 (d, J = 3.5 Hz, 1H, exchanged with D_2O, -OH); ^{13}C NMR (CD_2Cl_2): 148.8 (s), 141.7 (s), 140.2 (s), 139.7 (s), 134.1 (s), 129.0 (x2, d), 128.2 (x2, d), 124.8 (x2, d), 124.0 (d), 122.7 (d), 121.7 (d), 72.5 (-CH-OH); MS: (70 eV, EI) m/z 274/276 (M^+, 20/7), 257/259 ($(M-OH)^+$, 4/1), 135 (100); IR (KBr): ν 3500 (s, O-H); UV (CH_3CN): λ (ε) 300 (2300), 288 (2600), 264 (11000), 260 (15000). *Anal.* Calcd. for $C_{15}H_{11}ClOS$: C, 65.57; H, 4.03; S, 11.67; Cl, 12.90. Found: C, 65.52; H, 4.46; S, 11.04; Cl, 12.71.

To an ether solution of 3 (3.9 g (14.2 mmoles) in 50 ml) were added 6.2 g (71 mmoles, 5 eq.) of manganese dioxide. The mixture was stirred at room temperature and the reaction monitored by tlc (silica, dichloromethane: Rf = 0.8 (2); Rf = 0.5 (3)). After 2.5 h another 6.2 g of manganese dioxide was added. After 4.5 h, the precipitate was filtered and washed with 3x30 ml of ether and 30 ml of methanol. The organic layer was washed with 20 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure. 3.3 g (85%) of 2 were obtained. This crude solid was recrystallized in hot isopropyl alcohol. 1.2 g (30%) of a white powder was obtained, mp 140-141°. After flash chromatography (silica, dichloro-methane/hexane (60/40)) of the mother liquor 1.1 g (30%) of pure 2 was obtained. ^{1}H NMR (d_6-DMSO): 8.13 (s, 1H, H(3)), 8.05 (m, 2H, H(4) and H(7)), 7.93 (d, J = 9 Hz, 2H, H(2')), 7.67 (d, J = 9 Hz, 2H, H(3')), 7.53 (m, 2H, H(5) and H(6)); ^{13}C NMR ($CDCl_3$): 188.1 (carbonyl), 142.6 (x2, s), 138.9 (x2, s), 136.0 (s), 132.0 (d), 130.6 (x2, d), 128.8 (x2, d), 127.5 (d), 126.0 (d), 125.1 (d), 122.8 (d); MS: (70 eV, EI) m/z 272/274 (M+, 80/20), 161 (100); IR (KBr): ν 1630 (s, large, C-); UV (CH_3CN): λ (ε) 230 (28000), 260 (22000), 310 (33000). *Anal.* Calcd. for $C_{15}H_9ClOS$: C, 66.06; H, 3.32. Found: C, 66.15; H, 3.16.

Synthesis of (4-chlorophenyl)-(1-oxo-1λ^4-benzo[b]thien-2-yl)methanone (2a).

500 mg (1.8 mmoles) of 2 was dissolved in 15 ml (0.2 moles, 109 eq.) of trifluoroacetic acid. The solution immediately turned black. The mixture was cooled to 0°C. 0.625 ml (5,5 mmoles, 3 eq.) of an aqueous solution of hydrogen peroxide (30%) was then added. The solution slowly faded to bright yellow. The reaction was monitored by tlc (silica, dichloromethane/methanol (16:1): Rf = 0.6 (2a), Rf = 0.8 (2)). After 1h, 300 ml of a saturated solution of sodium hydrogencarbonate was added. The aqueous layer was extracted with 2x150 ml of dichloromethane. The combined organic layers were washed with 2x150 ml of brine, dried over magnesium sulfate and concentrated under reduced pressure, without heating. 516 mg of a crude solid were obtained containing traces of 2. Compound 2a was then purified by flash chromatograhy (silica, dichloromethane/methanol (16/1)). 440 mg (85%) of pure 2a was obtained and recrystallized in a mixture of

dichloromethane/hexane. 319 mg (60%) of a yellow powder was finally obtained, mp 158 - 159°. Compound **2a** decomposes in solution over a few days but can be stored in substance at 0°C for years. ^{1}H NMR (d_6-DMSO): 8.18 (s, 1H, H(3)), 8.11 (m, 1H), 7.87 (m, 1H), 7.97 (d, J = 9 Hz, 2H, H(2')), 7.72 (m, 2H, H(5) and H(6)), 7.66 (d, J = 9 Hz, 2H, H(3')); 1H NMR (d_4-CH_3OH): 8.06 (s, 2H), 7.96 (d, J = 7.5 Hz, 2H, H(2')), 7.89 - 7.81 (m, 1H), 7.77 - 7.70 (m, 2H), 7.60 (d, J = 7.5 Hz, 2H, H(3')); ^{13}C NMR ($CDCl_3$): 187.3 (carbonyl), 152.0 (s), 146.9 (s), 141.7 (d), 140.0 (s), 135.7 (s), 135.5 (s), 132.9 (d), 131.9 (d), 130.9 (x2, d), 129.4 (x2, d), 128.0 (d), 126.8 (d); MS: (chemical ionization, ammonia) m/z 306/308 ($(M+NH_4)^+$, 30/10), 290/292 (30/10), 273/275 (100/35); IR (KBr): 1065 (s, S-O), 1050 (s, S-O); UV (CH_3CN): λ (ε) 230 (21000), 266 (14000), 324 (12000); uv (methanol): λ (ε) 207 (55000), 230 (shoulder), 245 (31000), 263 (26000), 330 (17000). *Anal.* Calcd. for $C_{15}H_9ClO_2S$: C, 62.40; H, 3.14; S, 11.10; Cl, 12.28. Found: C, 62.23; H, 3.25; S, 10.89; Cl, 12.34.

Synthesis of (4-chlorophenyl)-(1,1-dioxo-1λ^4-benzo[b]thien-2-yl)methanone (2d).

The same experimental protocol as described above for the synthesis of 1-oxide **2a** was used. The reaction was monitored by tlc (silica, dichloromethane: Rf = 0 (**2a**), Rf = 0.4 (**2d**), Rf = 0.7 (**2**); dichloromethane/methanol (16:1): Rf = 0.6 (**2a**), Rf = 0.7 (**2d**), Rf = 0.8 (**2**)). The reaction was stirred overnight at room temperature. Starting from 500 mg (1.8 mmoles) of **2**, 470 mg (85%) of crude pure 1,1-dioxide **2d** was obtained and recrystallized in a mixture of dichloromethane/hexane. 380 mg (70%) of a pale yellow powder was finally obtained, mp 191 - 192°. Compound **2d** decomposes in solution over a few days but can be stored in substance at 0°C for years. ^{1}H NMR (d_6-DMSO): 8.40 (s, 1H, H(3)), 7.95 (m, 1H), 7.95 (d, J = 9 Hz, 2H, H(2')), 7.82 (m, 3H), 7.67 (d, J = 9 Hz, 2H, H(3')); ^{13}C nmr ($CDCl_3$): 185.2 (carbonyl), 150.2 (s), 139.8 (s), 138.5 (s), 135.7 (d), 134.4 (d), 133.9 (d), 130.6 (x2, d), 129.6 (x2, d), 128.3 (d), 127.3 (s), 122.0 (d), 121.4 (s); MS: (70 eV, EI) m/z 304/306 (M^+, 60/20), 139/141 (100/35); IR (KBr): ν 1150 (s, S-O); UV (CH_3CN): λ (ε) 240 (18000), 322 (11000). *Anal.* Calcd. for $C_{15}H_9ClO_3S$: C, 59.12; H, 2.97; S, 10.52; Cl, 11.63. Found: C, 59.25; H, 3.19; S, 10.54; Cl, 11.62.

Conversion of 2a into (4-chlorophenyl)-[3-(2-hydroxyethylsulfanyl)-1-oxo-2,3-dihydro-1λ^4-benzo[b]thien-2-yl]methanone (4a/4b).

To 5 ml of a methanol solution of sodium methylate (0.023 g (0.42 mmoles, 2.4 eq.)) were added 0.016 ml (0.21 mmole, 1.2 eq.) of 2-mercaptoethanol. The yellow solution was stirred for about 30 minutes. A solution of 50 mg (0.18 mmole, 1 eq.) of **2a** in 5 ml of methanol was added dropwise. The mixture was stirred at room temperature and monitored by tlc (silica, dichloromethane/methanol (24:1): Rf = 0.6 (**2a**), Rf = 0.5 and 0.3 (**4a** and **4b**)) and hplc (gradient A: tr = 4.6 min and tr = 4.9 min (265, **4a** and **4b**), 5.2 min (265 and 335, **2a**). After 2 hours, the crude reaction mixture was filtered over silica (dichloromethane/methanol (16:1)). 61 mg (95%) of a yellow oil was obtained. By proton NMR, this oil proved to be a (30:70) mixture of compounds **4a** and **4b**. ^{1}H NMR ($CDCl_3$): 8.20 - 7.40 (m, 16H), *isomer 4a*: 5.58 (d, J = 5.5 Hz, 1H, H(2), slowly exchanged with D_2O), 5.20 (d, J = 5.5 Hz, 1H, H(3)), 3.52 (t, J = 5 Hz, 2H, -SCH_2CH_2OH), 2.65 (t, J = 5 Hz, 2H, -SCH_2CH_2OH), 2.20 (s, 1H, -OH), *isomer 4b*: 5.70 (d, J = 5.5 Hz, 1H, H(3)), 5.12 (d, J = 5.5 Hz, 1H, H(2), slowly exchanged with D_2O), 3.77 (t, J = 5 Hz, 2H, -SCH_2CH_2OH), 2.79 (t, J = 5 Hz, 2H, -SCH_2CH_2OH), 2.50 (s, 1H, -OH); ^{13}C NMR ($CDCl_3$): 188.7 (carbonyl), 144.0 (s), 133.7 (d), 133.4 (d), 130.8 (d), 130.2 (d), 130.0 (d), 129.6 (d), 129.5 (s), 127.4 (d), 127.0 (d), 126.5 (d), the missing aromatic carbons could not be attributed, 82.0 (C(2), isomer **4a** or **4b**), 75.2 (C(2), isomer **4a** or **4b**), *isomer 4a*: 48.3 (C(3)), 62.0 (-SCH_2CH_2OH), 33.9 (-SCH_2CH_2OH), *isomer 4b*: 48.0 (C(3)), 61.3 (-SCH_2CH_2OH), 34.8 (-SCH_2CH_2OH); MS: (chemical ionization, ammonia) m/z 384/386 ($(M+NH_4)^+$, 3/1), 367/369 ($(M+H)^+$, 10/3), 349/351 (5/2), 290/292 (50/20), 273/275 (100/35); IR (film): ν 3400 (s, broad, O-H), 1090 (s), 1065 (m, broad), 1040 (s, broad), 1010 (s).

Conversion of 2a into (4-chlorophenyl)-(3-methoxy-1-oxo-2,3-dihydro-λ⁴-benzo[b]thien-2-yl)methanone (5a/5b).

To a solution of **2a** (29 mg, 0.1 mmole in 2.4 ml) in deuterated methanol were added 0.25 ml (1.0 mmole, 10 eq.) of a freshly prepared solution of deuterated sodium methylate in deuterated methanol (4 M). The solution turned orange. The reaction was then monitored by nmr and hplc (gradient B: tr = 5 min (206, 245, 263, 330, **2a**), tr = 5.5 min (210, 260, 307, **5a/5b**)). Compound **2a** was quantitatively converted into a new product which could not be isolated; when the crude mixture was neutralized, only 1-oxide **2a** was isolated. The analysis of the nmr spectra of the reaction mixture indicated the presence of a mixture of compounds **5a** and **5b** (80:20). ^{1}H NMR (d_4-CH_3OH): 7.80 - 7.60 (m, 4H), 7.69 (d, J = 7.5 Hz, 4H, H(2')), 7.57 - 7.42 (m, 4H), 7.38 (d, J = 7.5 Hz, 4H, H(3')), 5.99 (s, 1H, H(3), isomer **5a**), 5.42 (s, 1H, H(3), isomer **5b**), 3.35 (s, broad, 6H, -OCH_3); ^{13}C NMR (d_4-CH_3OH): *isomer 5a*. 182.9 (carbonyle), 147.9 (s), 144.1 (s), 143.6 (s), 135.5 (s), 132.0 (d), 130.8 (x2, d), 130.6 (d), 128.9 (x2, d), 127.8 (x2, d), 126.9 (d), 108.5 (C(2)), 82.8 (C(3)), *isomer 5b*: 186.0 (carbonyle), 147.8 (s), 144.0 (s), 143.6 (s), 135.3 (s), 130.2 (d), 130.8 (d), 127.5 (d), 127.1 (d) (the missing tertiary carbons could not be attributed), 106.6 (C(2)), 82.2 (C(3)); HMQC COSY (d_4-CH_3OH): correlation spots between the proton signals at 5.99 and 5.42 ppm and the carbon signals at 82.2 and 82.8 ppm; HMBC COSY (d_4-CH_3OH): correlation spots between the proton resonances at 5.99 and 5.42 ppm and carbon signals at 53 and 50 ppm (-OCH_3).

Conversion of 2a into (4-chlorophenyl)-(3-methoxybenzo[b]thien-2-yl)methanone (6).

To a methanolic solution of **2a** (50 mg, 0.17 mmole in 10 ml) were added dropwise 0.668 ml (8.7 mmoles, 50 eq.) of trifluoroacetic acid. The resulting slightly yellow solution was stirred at room temperature. The reaction was monitored by tlc (silica, dichloromethane/methanol (49:1): Rf = 0.5 (**2a**), Rf = 0.9 (**6**)) and hplc (gradient A: tr = 5 min (**2a**), tr = 12 min (**6**)). After 12 hours, 10 ml of a saturated solution of sodium hydrogencarbonate were added. The aqueous layer was extracted with 2x10 ml of dichloromethane. The organic layer was then dried over magnesium sulfate and concentrated under reduced pressure. 50 mg (95%) of crude pure **6** was obtained as a brownish oil. Compound **6** was identified by comparing its spectroscopic characteristics with those of an authentic sample prepared by another method [43]. ^{1}H NMR (CD_2Cl_2): 7.93 - 7.85 (m, 1H), 7.87 (d, J = 8 Hz, 2H, H(2')), 7.81 (m, 1H), 7.55 - 7.40 (m, 2H), 7.50 (d, J = 8 Hz, 2H, H(3')), 3.77 (s, 3H, -OCH3); ^{1}H NMR (d_4-CH_3OH): 7.87 (m, 1H), 7.84 (d, J = 7.5 Hz, 2H, H(2')), 7.82 (m, 1H), 7.51 (d, J = 7.5 Hz, 2H, H(3')), 7.46 (m, 1H), 7.40 (m, 1H) 3.75 (s, 3H, -OCH_3); ^{13}C NMR (CD_2Cl_2): 188.2 (carbonyle), 155.4 (s), 139.3 (x2, s), 137.3 (s), 134.0 (s), 132.1 (s), 131.1 (x2, d), 128.9 (x2, d), 128.5 (d), 125.1 (d), 123.5 (d), 123.4 (d), 63.2 (-OCH_3); MS: (70 eV, EI) m/z 302/304 (M+, 100/35); UV (CH_3CN): λ (ε) 261 (15000), 310 (10000), 343 (4000).

Conversion of 2a into (4-chlorophenyl)-(3-hydroxybenzo[b]thien-2-yl)methanone (7).

The same experimental protocol as that decribed above for the synthesis of compound **6** was carried out in a (1/1) mixture of water/dioxane. The reaction was monitored by tlc (silica, dichloromethane/methanol (49:1): Rf = 0.5 (**2a**), Rf = 0.9 (yellow spot, **7**)). The reaction was stirred overnight at room temperature. After one night, a yellow suspension was formed. Starting from 25 g (0.09 mmole) of **2a**, 12 mg (50%) of crude pure **7** was obtained as a bright yellow powder, mp = 151° (lit 150° [43]). Compound **7** was identified by comparing with an authentic sample [43]. ^{1}H NMR (CD_2Cl_2): 13.37 (s, 1H, exchanged with D_2O, no dilution effect, -OH), 8.03 (m, 1H), 8.01 (d, J = 9 Hz, 2H, H(2')), 7.77 (m, 1H), 7.59 (m, 1H), 7.52 (d, J = 9 Hz, 2H, H(3')), 7.45 (m, 1H); ^{13}C NMR (CD_2Cl_2): 190.9 (carbonyl), 166.1 (C(3)), 141.2 (C(7a)), 139.5 (C(4')), 137.1 (C(1')), 131.0 (C(6)), 130.7 (C(3a)), 130.4 (C(2')), 129.6 (C(3')), 125.5 (C(5)), 124.4 (C(4)), 123.6 (C(7)), 109.8 (C(2)); ms:

(70 eV, electron impact) m/z 288/290 (M^+, 70/25), 176 (100); IR (KBr): ν 3450 (w, O-H), 1590 (s, carbonyl); UV (CH_3CN): λ (ε) 265 (20000), 318 (15000), 378 (8000), 430 (shoulder).

Conversion of 2a into (4-chlorophenyl)-[3-(2-hydroxyethylsulfanyl)benzo[b]thien-2-yl]methanone (8a) and (4-chlorophenyl)-[3-(2-sulfanylethoxy)benzo[b]thien-2-yl]methanone (8b).

0.668 ml (8.7 mmoles, 50 eq.) of trifluoroacetic acid and 0.121 ml (1.7 mmoles, 10 eq.) of 2-mercaptoethanol were added dropwise to 10 ml of a methanol solution of **2a** (50 mg (0.17 mmole)). The solution instantly turned bright red. The reaction was monitored by tlc (silica, dichloromethane/methanol (49:1): Rf = 0.5 (**2a**), Rf = 0.7 (**8a**), Rf = 0.9 (**8b**)) and hplc (gradient A: tr = 5 min (265, 330, **2a**), tr = 8 min (260, 310), tr = 12 min (275 (shoulder), 305 (shoulder)), tr = 16 min (260, 310)). After 48 hours, 10 ml of a saturated solution of sodium hydrogencarbonate was added; the solution immediately faded. The aqueous layer was extracted with 10 ml of dichloromethane. The organic layer was then washed with 2x10 ml of water, dried over magnesium sulfate and concentrated under reduced pressure. 62 mg (95%) of a mixture of compounds **8a** and **8b** was obtained. The two products were separated by flash chromatography (silica, dichloromethane/methanol (49:1)). 30 mg (50%) of **8a** and 30 mg (50%) of **8b** were obtained as yellow oils. Compound **8b** was not stable and spontaneously gave compound **8a**. Compound **8a** crystallized , mp 73 - 76°. *Isomer 8a*: ^{1}H NMR (CD_2Cl_2): 8.20 - 8.10 (m, 1H), 8.00 - 7.90 (m, 1H), 7.87 (d, J = 9 Hz, 2H, H(2')), 7.60 - 7.50 (m, 2H), 7.49 (d, J = 9 Hz, 2H, H(3')), 3.51 (td, J = 10 Hz, J = 8 Hz, 2H, -SCH_2CH_2OH), 2.98 (t, J = 8 Hz; 2H, -SCH_2CH_2OH), 3.05 (t, J = 10 Hz, 1H, exchanged with D_2O, -OH); ^{13}C NMR (CD_2Cl_2): 190.2 (carbonyl), 142.5 (s), 140.6 (s), 140.4 (s), 140.1 (s), 136.8 (s), 132.0 (x2, d), 129.9 (s), 129.2 (x2, d), 127.7 (d), 126.1 (d), 124.9 (d), 123.3 (d), 60.6 (-CH_2OH), 39.5 (-SCH_2-); MS: (chemical ionization, ammonia) m/z 366/368 ($(M+NH_4)^+$, 55/20), 349/351 ($(M+H)^+$, 100/35); IR (KBr): ν 3400 (m, O-H); UV (CH_3CN): λ (ε) 263 (8000), 306 (17000). *Anal.* Calcd. for $C_{17}H_{13}ClO_2S_2$: C, 58.53; H, 3.75. Found: C, 58.02; H, 3.79. *Isomer 8b*: ^{1}H NMR (CD_2Cl_2): 8.20 - 8.10 (m, 1H), 8.00 - 7.90 (m, 1H), 7.83 (d, J = 9 Hz, 2H, H(2')), 7.64 - 7.53 (m, 2H), 7.49 (d, J = 9 Hz, 2H, H(3')), 4.30 (t, J = 5 Hz, 2H, -OC H_2CH_2SH), 3.15 (t, J = 5 Hz; 2H, -OCH_2CH_2SH), 1.54 (s, 1H, exchanged with D_2O, -SH); ^{13}C NMR (CD_2Cl_2): 189.4 (carbonyl), 143.9 (s), 140.5 (s), 140.0 (s), 136.8 (s), 129.0 (s), 128.4 (s), 131.7 (x2, d), 129.3 (x2, d), 127.7 (d), 126.2 (d), 124.6 (d), 123.3 (d), 66.7 (-CH_2OH), 34.4 (-SCH_2-).

Conversion of 4a/4b into a mixture of 8a/8b.

10 mg (0.03 mmole) of the mixture of **4a/4b** (30:70) was dissolved in 2 ml of dichloromethane. 0.104 ml (1.4 mmoles, 50 eq.) of trifluoroacetic acid was then added. The solution slowly turned bright red. After one night the mixture was worked up as described above. A (50:50) mixture of compounds **8a** and **8b** was obtained and identified by proton nmr.

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35. To simplify the presentation of the following result/discussion sections, we differentiated between ***basic*** and *acidic* conditions. ***Basic*** conditions refer to experiments pursued in the presence of a base to form the thiolate or methylate nucleophilic species. Experiments carried under *acidic* conditions were done in the presence of a large excess of an acid, (in general trifluoroacetic acid TFA).
36. Noteworthy, the same mixture of compounds **4a** and **4b** was also obtained when **2a** was treated with 2-mercaptoethanol without any addition of base.
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44. The methyl ester of (3-hydroxybenzo[b]thien-2-yl)methanoic acid was synthesized via the sulfoxide of the methyl ester of (benzo[b]thien-2-yl)methanoic acid in 50% yield (after flash chromatography on silica) following the method already described for the synthesis of compound **7**. The final compound was identified by comparison with the commercial compound purchased from Lancaster. The intermediate methyl ester of (1-oxo-1λ^4-benzo[b]thien-2-yl)methanoic acid was obtained as already described for the preparation of **2a** in 60% yield after a single recrystallization in CH_2Cl_2/pentane, mp 120 - 121°. ^{1}H NMR (d_6-DMSO): 8.28 (s, 1H, H(3)), 8.05 - 8.04 (m, 1H), 7.87 - 7.83 (m, 1H), 7.71 - 7.68 (m, 2H), 3.87 (s, 3H, -CH_3); ^{13}C NMR ($CDCl_3$): 161.6 (carbonyle), 146.8 (s), 143.2 (s), 142.5 (d), 135.2 (s), 132.5 (d), 131.6 (d), 127.0 (d), 126.9 (d), 53.0 (-CH_3); MS: (70 eV, EI) m/z 208 (M^+, 15), 192 ($(M-O)^+$, 45), 161 ($(M-O-OCH_3)^+$, 100); IR (KBr): ν 1035 (s, S-O). *Anal.* Calcd. for $C_{10}H_8O_3S$: C, 57.68; H, 3.87. Found: C, 57.59; H, 3.92.
45. We checked that isopropanol could be added to 1-oxide **2a**. Following the same procedure as that described for the synthesis of compound **6**, (4-chloro-phenyl)-(3-isopropyl-benzo[b]thien-2-yl)-methanone was obtained after 3 days at 50°C in TFA containing isopropanol (90%). ^{1}H NMR ($CDCl_3$): 7.89 - 7.78 (m, 4H), 7.56 - 7.37 (m, 4H), 4.22 - 412 (dq, J = 5 Hz, J = 7.5 Hz, -CH-(CH_3)$_2$), 0.96 (d, J = 7.5 Hz, methyl); ^{13}C NMR ($CDCl_3$): 188.8 (carbonyl), 153.05 (s), 139.6 (s), 139.2 (s), 136.9 (s), 135.5 (s), 131.6 (x2, d), 128.8 (x2, d), 128.4 (d), 126.7 (s), 125.17 (d), 123.9 (d), 123.5 (d), 80.3 (-CH-(CH_3)$_2$), 22.3 (methyl).
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