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Benzothiophene-*S*-oxides – an Overview

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In this review on the class of benzothiophene-*S*-oxides the preparation, the structural and physical properties as well as the reactivity of these molecules are presented. Moreover, their importance as intermediates into the microbial transformation of environmentally harmful benzothiophenes is highlighted. Possible technical applications are also discussed.

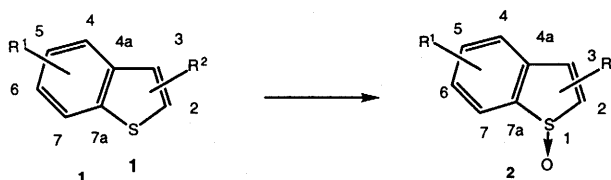
Introduction

This overview is the second of a series of three reviews on the preparation, the physical properties and the chemical reactivity of benzothiophene-*S*-oxides, dibenzothiophene-*S*-oxides^[1] and thiophene-*S*-oxides.

Preparation

Benzothiophene-*S*-oxides are much less stable than dibenzothiophene-*S*-oxides,^[1] the latter of which can be regarded as bridged diarylsulfoxides rather than diareno annelated thiophene-*S*-oxides. Especially the parent compound benzo[*b*]thiophene-*S*-oxide itself and benzothiophene-*S*-oxides unsubstituted at C-2 and C-3 are not very stable at higher concentrations in solution. They readily undergo cycloaddition reactions to form the formal [4+2]-dimerisation products. Accordingly, the methods of preparing benzothiophene-*S*-oxides are much less varied, often give poor yields and can be applied only to a narrow scope of benzothiophene-*S*-oxides. Until 1975, there have been only sporadic reports^[2-5] on this class of molecules. P. Geneste et al.^[6-8] have prepared a number of benzo[*b*]thiophene-*S*-oxides from the corresponding benzothiophenes by oxidation with nitroperoxybenzoic acid (see also ref. 31), while D. Mansuy et al.^[9] could prepare the corresponding benzothiophene-*S*-oxides from benzo[*b*]thiophene-*S*-oxide and 2-(4-chlorobenzoyl)-benzo[*b*]thiophene-*S*-oxide in yields of 90% and 40% respectively, using the oxidizing system H₂O₂/CF₃CO₂H^[10] (see Scheme 1, Table 1). Here, the actual oxidant is the peroxytrifluoroacetic acid, which is known to be a convenient reagent for the preparation of sulfoxides. The latter has been utilized by A. D. Palkowitz et al.^[11] in their synthesis of a raloxifene analog. The reaction temperature and reaction time in this transformation are of importance; at 0°C the benzo[*b*]thiophene-*S*-oxide could

be isolated, at rt mainly the benzo[*b*]thiophene-*S*,*S*-dioxide formed. The use of *m*-CPBA as sole oxidant leads mainly to the benzothiophene-*S*,*S*-dioxides, however, the presence of BF₃-etherate in the reaction mixture also leads to benzothiophene-*S*-oxides at low temperatures^[12] in acceptable yields. This is strongly reminiscent of the situation in the preparation of simple thiophene-*S*-oxides, where *m*-CPBA alone leads to the formation of thio-



H ₂ O ₂ , CF ₃ CO ₂ H	BT (BTO only stable under dilution, 40%)		Mansuy 1995
H ₂ O ₂ , CF ₃ CO ₂ H	2-(<i>p</i> -Cl-Ph)CO-BT	60% (0°C, 1h)	Mansuy, Dansette 1998
H ₂ O ₂ , CF ₃ CO ₂ H	3-Br-6-MeO-2-(MeO-Ph)-BT	80% (2h)	Palkowitz 1997
H ₂ O ₂ , HOAc	3- <i>i</i> PrO-5-MeO-BT-2-CONH ₂	23% (rt, 8h)	Boschelli 1995
H ₂ O ₂ , SeO ₂	3- <i>i</i> PrO-5-MeO-BT-2-CONHR	53% (R=Et, rt, 14h)	Boschelli 1995
Oxaziridine	3- <i>i</i> PrO-5-MeO-BT-2-COOH	53% (rt, 20h)	Boschelli 1995
Oxaziridine	5-HO-3- <i>i</i> PrO-BT-2-CONH ₂	62% (rt, 48h)	Boschelli 1995
<i>m</i> -CPBA/BF ₃	2-Me-BT	72% (24h, -18°C)	Arima 2000
Bu ^t OCl, ^t BuOH	BT (product = 2-Cl-BTO)	25%	Geneste 1977
Bu ^t OCl, MeOH	3-Br-BT	80% (-70°C)	Geneste 1975
Bu ^t OCl, MeOH	2-Br-BT	30% (-70°C)	Geneste 1975
Bu ^t OCl, MeOH	3-Me-BT	60% (-70°C)	Geneste 1975
<i>P. putida</i> UV4	2-Me-BT	26% (56% ee)	Boyd 1996

Scheme 1 and Table 1. Preparation of BTOs from BTs by Oxidation of benzothiophene-*S*,*S*-dioxides and the addition of BF₃-etherate in the reaction mixture halts the oxidation at the level of the thiophene-*S*-oxides.^[13,14] This may be attributed to two factors: BF₃ itself may catalyze the oxidation of the peracid and it may complex to oxygen of the thiophene-*S*-oxide (or benzo[*b*]thiophene-*S*-oxide) formed, thus decreasing the electron density on the sulfur and making it less prone towards a second oxidation to the corresponding thiophene-*S*,*S*-dioxide (benzo[*b*]thiophene-*S*,*S*-dioxide). The same may hold true for the system H₂O₂/CF₃CO₂H (or CF₃CO₃H/CF₃CO₂H). On the other hand the

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nitroperoxybenzoic acid may be reactive enough and the nitrobenzoic acid acidic enough not to need an additional acid/Lewis acid. Some 3-alkoxy-substituted BTs have been transformed to BTOs by the use of $\text{H}_2\text{O}_2/\text{SeO}_2$. An interesting oxidation method of BTs uses (\pm)-*trans*-2-phenyl-sulfonyl-3-phenyloxaziridine.^[15] Thus far, however, the use of this method has been limited to the oxidation of 3-alkoxy substituted BTs. *tert*-Butylhypochlorite in *tert*-butanol, in *tert*-butanol/water, in methanol and in methanol/water^[6-8] has also been used in the preparation of benzothiophene-*S*-oxides. This system is less recommendable as *tert*-butylhypochlorite also acts as a chlorinating agent. Dimethyldioxirane (DMD), which is known to oxidize thiophenes to thiophene-*S,S*-dioxides,^[16] has been shown to give dibenzothiophene-*S*-oxide as well, but in very poor yield. Some other oxidants such as NaIO_4 do not give any BTOs.

Microbial oxidation of benzothiophenes, dibenzothiophenes and thiophenes themselves has elicited interest, especially in view of possible use in detoxification of soil and upgrading of fuel by conversion of the sulfur containing heterocyclic components. It is known that toluene dioxygenase (TDO) and naphthalene dioxygenase (NDO) from a number of strains of *Pseudomonas putida* catalyze the oxidation of organic sulfides.^[17,18] Of preparative interest is the sulfoxidation of benzo[*b*]thiophenes using intact cells of *P. putida*. In the case of the conversion of 2-methylbenzothiophene with NCIMB 8859 (wild-type bacterium) the corresponding (1*S*)-2-methylbenzo[*b*]thiophene-*S*-oxide (**2b**) could be isolated in 26% yield and 56% ee.^[19] Using *P. putida* UV4 (1*R*)-**2b** was isolated as a minor metabolite (2% yield) of high enantiopurity (>98% ee). This enantiocomplementary behavior is quite often exhibited by NDO/TDO. It must be noted, however, that the main metabolites of benzo[*b*]thiophenes using *P. putida* are the dihydroxylated products. Moreover, it is not always easy to predict the outcome of the reactions. Thus, 3-methylbenzo[*b*]thiophene (**1h**) is not oxidatively transformed by *P. putida* to yield 3-MeBTO (**2a**). Unsubstituted BTO (**2k**) is formed in the reaction of benzo[*b*]thiophene itself, but dimerizes readily to give the typical sequioxides.

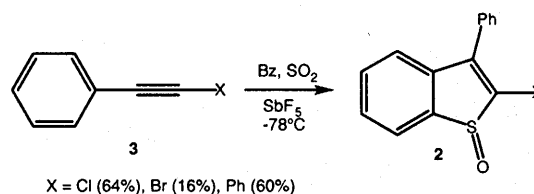
Earlier experiments concerning the viability of cytochrome C as a biocatalyst for thiophenes had shown that BTO can be isolated when oxidizing BT with cytochrome C and H_2O_2 .^[20,21] A later report states, however, that difficulties had been encountered upon scale-up of the procedure (i.e., for the transformation of 94 mg of BT) – here not only BTO and BTO_2 could be isolated but also a number of other sulfur-containing metabolites, among them benzo[*b*]naphtho[1,2-*d*]thiophene, formed by self-condensation of BTO (**2k**, see

Scheme 13, below).

Enantiomerically enriched BTO-2-COOHs have also been prepared by classical resolution using (*R*)- and (*S*)- α -methylbenzylamine, respectively. The configuration of the sulfur for the individual enantiomers has been determined by X-ray crystal structural analysis of the methylbenzylammonium salts.^[22]

Studies have been carried out on the stepwise oxidation of thiophenes and benzothiophenes by hydrogen peroxide catalysed by methyltrioxorhenium(VII).^[23] Methyltrioxorhenium (VII) [MTO]^[24] has proved to be an effective catalyst for the oxidation of many types of substrates by hydrogen peroxide. The kinetics of the reaction has been probed for a number of benzothiophenes. It was found that the oxidation to the benzothiophene-*S*-oxide is about four times faster for 2-methylbenzothiophene than for the unsubstituted molecule.^[23] Also in the case in the peracid oxidation of thiophenes a substituent at C-2 (and/or C-5) has a significant effect on the oxidability of the sulfur, where electron-donors at those positions favor the oxidation and electron-withdrawing substituents impede the oxidation. Interestingly, a methyl substituent at C-3 leads to a higher rate constant in the oxidation. This is explained by enhancement of nucleophilicity of the sulfur using resonance stabilization arguments.^[23]

A totally different access to certain BTOs was found by R.



Scheme 2

R. L. Fan et al.^[9]

Fan and S. I. Miller.^[25] A number of phenylethyne **3** could be converted to BTOs **2** by reaction with antimony pentafluoride in liquid sulfur dioxide in the presence of benzene (Scheme 2). Very likely intermediates in this reaction are the 2,2-diphenylvinylsulfonic acids. In the case of 1-bromo-2-phenylethyne the above reaction gave the corresponding BTO as the minor product the sulfonic acid as the major product. The sulfonic acid could be converted to the BTO under mild Lewis acid conditions (ZnCl_2 , CS_2).^[25]

Structural and Physical Properties

Substituted benzothiophene-*S*-oxides have been adequately characterized by spectroscopic methods. ^{13}C NMR spectroscopic data has been reported in detail. It was found that the signals of C-2, C-3, C-4, C-5, C-7 and C-7a in substituted BTOs are all shifted down-field when compared to the corresponding carbon values of correspondingly substituted benzothiophenes, while C-3a

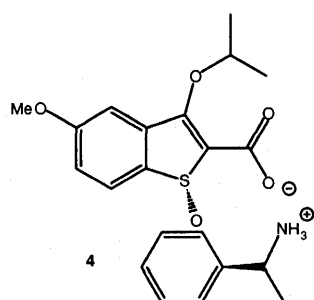
shows only a small shift towards higher field.^[26]

When the C-NMR values of the benzo-unit in substituted 2,3-dihydrobenzothiophene-*S*-oxides are compared to those of accordingly substituted BTOs it is evident that they experience a deshielding. This is also the case in the 2,3-dihydrobenzothiophenes (as compared to the benzothiophenes), but much less evident in the case of substituted 2,3-dihydrobenzothiophene-*S,S*-dioxides (as compared to the corresponding benzothiophene-*S,S*-dioxides). This has led to the assumption that the bond C2-C3 in benzothiophene-*S,S*-dioxides is much more of an ethylenic character than the corresponding bond in the benzothiophene-*S*-oxides, which would mean that the heterocycle in BTOs would show more delocalisation (*i.e.*, aromaticity) than in the BTO₂s. This reminiscent of the situation of thiophenes-thiophene-*S*-oxides-thiophene-*S,S*-dioxides, where clearly the thiophene-*S,S*-dioxide has the highest diene character^[27] and thus shows the least aromaticity of the three classes of compounds.

The SO stretching frequencies of 2-Me-BTO (**2b**) have been measured to be 1025, 1065 cm⁻¹ (vs. 1026, 1072 cm⁻¹ for dibenzothiophene-*S*-oxide, 1020, 1037, 1088 cm⁻¹ for diphenylsulfoxide and 1020 (sh) and 1065 cm⁻¹ for DMSO).^[28] It must be noted, however, that large 'environmental' shifts are observed for all sulfoxides. Because of this it would be advisable to compare calculated data with data gathered from gas-phase measurements. So far these, however, do not exist for all the molecules cited.

Mass spectrometry has been used in many studies of BTO and its derivatives in the microbial transformation of BTs of natural origin (see below).

An X-ray crystal structure has been published for 2-methylbenzo[*b*]thiophene-*S*-oxide. X-ray crystal structural analysis were also prepared of (*R*)-5-Methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic acid 1-oxide (*S*)- α -methylbenzylamine salt and of (*S*)-5-methoxy-3-(1-methylethoxy)benzo[*b*]thiophene-2-carboxylic acid 1-oxide (*R*)- α -methylbenzylamine salt (**4**) (Fig.



Boschelli et al. 1995 Fig. 1

1).^[22]

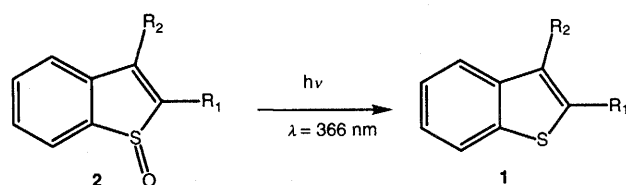
The accessibility of enantiopure benzo[*b*]thiophene-*S*-oxide has led to the study of the barrier of the inversion at

the pyramidally configured sulfur. By dynamic proton NMR the inversion barrier for 2-methylbenzo[*b*]thiophene-*S*-oxide (**2b**) was calculated to be $\Delta G^\ddagger = 25.1$ kcal/mol.^[19] This is lower than that calculated by methods.^[28]

Reactivity

a.) Reduction/Deoxygenation: BTOs can be reductively deoxygenated to BTs by the reaction with LiAlH₄ (see Scheme 8).^[11] Some BTOs substituted at C-2 undergo photoreduction (see Scheme 3). P. Geneste has studied the reduction of BTOs to BTs with a number of catalysts (*e.g.*, on cobalt(III)oxide-molybdenum(VI)oxide alumina).^[29,30]

b.) Photoreactivity: The photoreactivity of substituted benzothiophene-*S*-oxides has been studied extensively by P. Geneste et al.^[31-33] BTOs carrying various substituents at positions C-2 and C-3 have been irradiated in benzene in the presence of benzophenone as a sensitizer. The outcome of the reaction depended heavily on the substitution pattern of the starting material. Halogenated, *i.e.* brominated or chlorinated BTOs for the most part gave an inseparable mixture of products. This has also been found in the photoirradiation of halogenated thiophene-*S*-oxides, where a number of compounds were formed in the

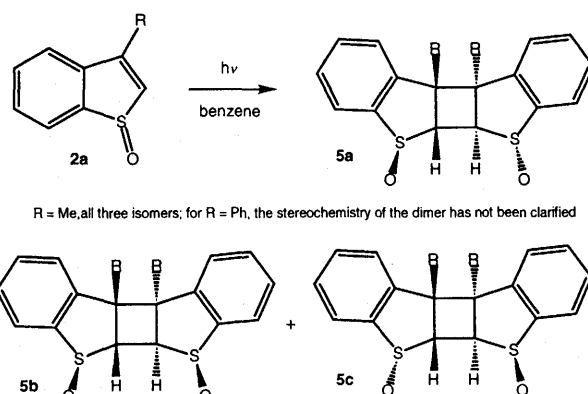


for: a.) R₁ = Me, R₂ = H; b.) R₁ = Ph, R₂ = H; and c.) R₁ = Me, R₂ = Me

P. Geneste et al. 1981

Scheme 3

photoirradiation of the starting material in CH₂Cl₂ in the absence of an added photosensitizer.^[34] In these cases, however, the products could be separated and it was found



R = Me, all three isomers; for R = Ph, the stereochemistry of the dimer has not been clarified

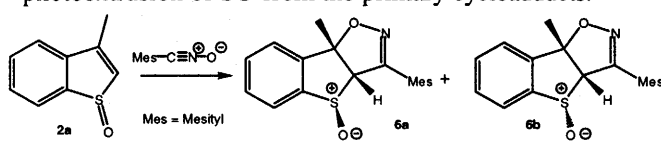
P. Geneste et al. 1981

Scheme 4

that the C-X bond cleaves in the photoirradiation leading to halo-radicals which subsequently lead to the products formed.^[34] BTOs with alkyl- or aryl-substituents at C-3

photodimerize (Scheme 4). Thus, 3-Me-BTO (**2a**) gives two dimers, **5a** and **5b**, in 40% yield upon photoirradiation in benzene at $\lambda = 313$. When benzophenone added as a sensitizer the photoirradiation of 3-Me-BTO at $\lambda = 366$ nm again results in the same dimers, albeit in higher yield. Dimer **5a** can be epimerized to **5b** and **5c** (THF/HCl), a third dimer which could potentially have formed but did not form in the photoreaction. BTOs with alkyl- or aryl-substituents at C-2 undergo a photodeoxygenation in benzene (Scheme 3) upon irradiation at $\lambda = 313$ nm and at $\lambda = 366$ nm in the presence of benzophenone as a sensitizer. In the latter case only very small amounts of a dimerisation product could be isolated upon photoirradiation of the 2-methylbenzothiophene-*S*-oxide (**2b**).

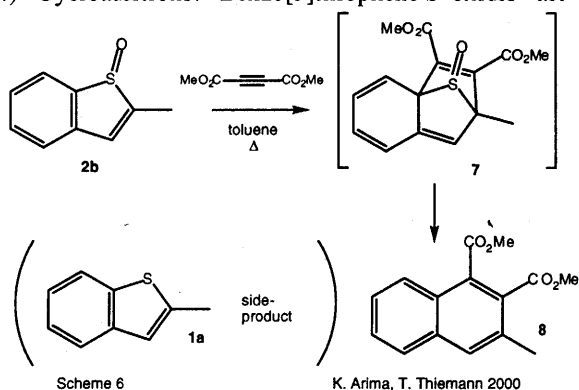
Little is known of the photochemistry of unsubstituted BTO itself, as it is not easy to isolate in sufficient quantities and as it is not sufficiently inert under dark conditions. Interestingly, however, the photooxidation of BT has already been studied a long time ago.^[35,36] Here, benzo[*b*]naphtho[1,2-*d*]thiophenes are formed, most likely by dimerisation of transient BTO and subsequent photoextrusion of SO from the primary cycloadducts.^[37]



Scheme 5

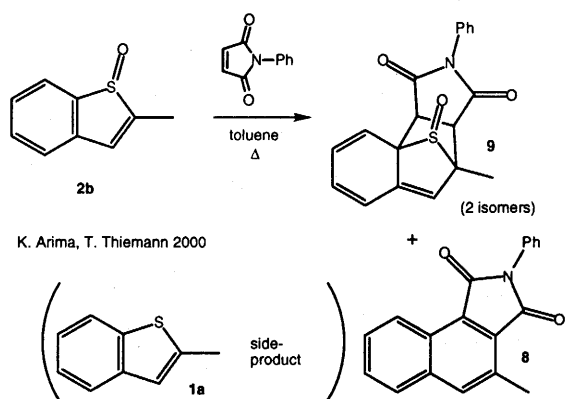
P. Geneste et al. 1979

c.) Cycloadditions: Benzo[*b*]thiophene-*S*-oxides act as



Scheme 6

K. Arima, T. Thiemann 2000



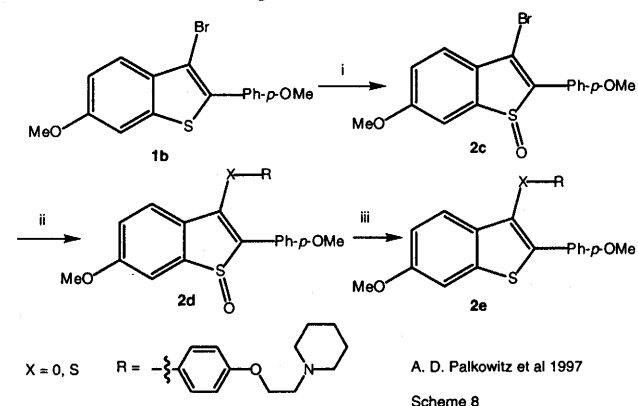
Scheme 7

K. Arima, T. Thiemann 2000

ene-component in dipolar [3+2] cycloaddition reactions. Thus, P. Geneste et al.^[38] could show that 3-methylbenzo[*b*]thiophene-*S*-oxide (**2a**) (Scheme 5) reacts well mesitronitrile oxide to give in a regioselective manner a 1:1 mixture of *syn*- and *anti* isomers of 3-(2,4,6-trimethylphenyl)-8b-methylbenzo[*b*]thieno[2,3-*d*]isoxazoline 4-oxide, **6a** and **6b**.^[39,40]

The use of BTOs as diene components in Diels-Alder type reactions, although clearly postulated by a number of authors, has not been studied very thoroughly up to this date. Nevertheless, BTOs such as 2-methyl-BTO (**2b**), react with acetylenes to form substituted naphthalenes (e.g., **8**, Scheme 7).^[41] Interestingly, side products in this reaction are the benzo[*b*]thiophenes (BTs, e.g., **1a**) themselves. That is to say that BTOs are reduced under thermal conditions. While the formation of BTs as side products is a nuisance, they can be recycled back to BTOs and thus are not lost in the process. Although no competitive experiments have been carried out thus far, it seems that BTOs are less reactive towards alkynes than similarly substituted thiophene-*S*-monoxides. The reason for this clearly is that the aromaticity of the annelated ring is broken in the intermediate. It is restored, however, by the subsequent extrusion of SO. The bridged thiabicyclo[2.2.1]-heptadienes **7** cannot be isolated,^[41] just as they cannot in the cycloaddition reactions of the thiophene-*S*-oxides.^[13,14,42] BTOs are more reactive towards alkynes than the corresponding benzothiophene-*S,S*-dioxides (BTO₂s), the cycloaddition reactions of which have already been diligently studied.

The reaction of BTOs with alkenes as dienophiles leads to a more complex range of products, depending on the conditions used (Scheme 7). In contrast to [4+2]-cycloaddition reactions of thiophene-*S*-oxides, which typically are totally stereocontrolled,^[13,14,42] in the case of the BTOs (e.g., with *N*-phenylmaleimide) more than one isomer of the primary cycloadduct **9** forms,^[41] although one is clearly dominant. Additionally, a small amount of aromatized product **8** and of diene form. The



A. D. Palkowitz et al 1997

Scheme 8

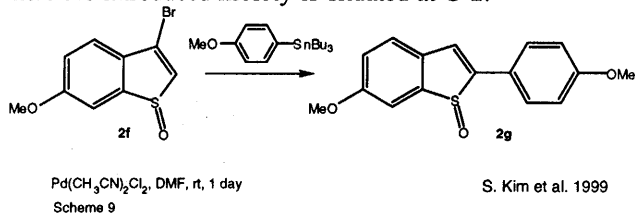
i. H₂O₂, CF₃COOH, CH₂Cl₂, 2h; ii. RXH, NaH, DMF; iii. LiAlH₄, THF, 0°C

latter is also seen in many of the cycloaddition reactions

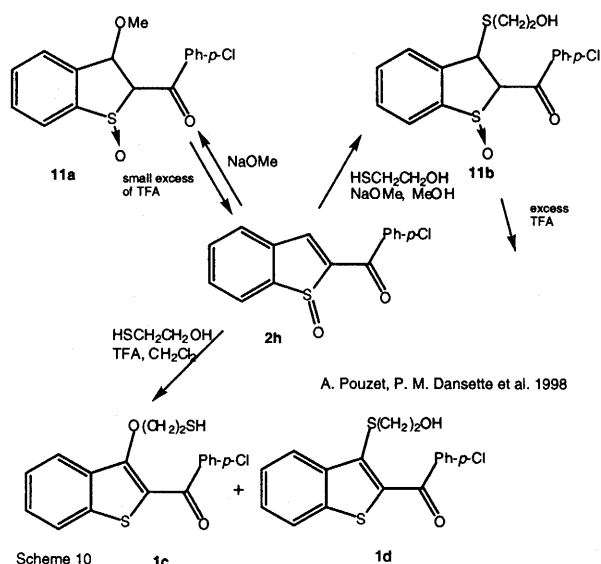
carried out with the thiophene-*S*-oxides. Moreover, BT (1a) is also found (as a simple reduction product of BTO)^[41] as already mentioned for the cycloaddition of BTOs with alkynes (see above).

d.) Michael Reactions and Miscellaneous Reactions at C-2: The oxidation of 3-bromo-DBT (1b) to 3-bromo-DBTO (2c) activates the molecule towards nucleophilic displacement of the bromo-functionality at C-3 (Scheme 8). Thus, substituted phenols and thiophenols could be added to C-3.^[11] The BTOs were then reduced to give back the benzothiophenes,^[11] which were then used in a study of raloxifene analogs for use as selective estrogen receptor modulators (SERM; see ref. 49).

Interestingly, a C-C bond forming reaction at the same position (C-3) under Stille conditions (Scheme 9) leads to a rearranged product 2g, where the group *de facto* is introduced at C-2. Suzuki-Kumada type couplings of aryl boronic acids of the corresponding 3-bromo and 3-iodobenzothiophenes also lead to rearranged products where the introduced moiety is situated at C-2.^[43]



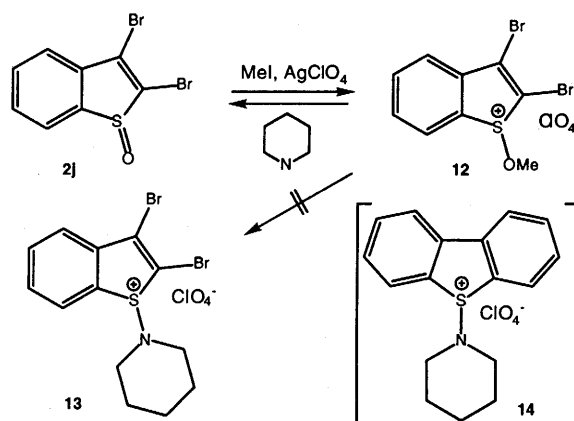
Michael type reactions have been carried out on 2-aryl substituted benzo[*b*]thiophene-*S*-oxide 2h (Scheme 10).^[44,45] The reaction of 2h with 2-mercaptoethanol under basic conditions yielded the formal Michael-adduct 11b. It



must be kept in mind, however, that the aryl-moiety at C-2 is an excellent electron withdrawing group. Whether oxidation state of the sulfur in 2h only contributes in this reaction in diminishing the aromaticity of the molecule or whether the sulfoxy-moiety also contributes as a Michael acceptor is not clear. Interestingly, under acidic conditions, either in the presence of a Lewis acid or a Brønsted acid, nucleophiles such as alcohols, thiols and even water were

added at C-3; under the reaction conditions, however, thiophenes of type 1c/1d were isolated, which formally are the dehydration products of the primary Michael-adducts. In the absence of an added acid the reactions did not proceed.^[44] The reactions could, however, also be catalysed by iron porphyrins, valued by the authors P. Pouzet, P. M. Dansette et al. as biomimetic models of cytochrome P450.^[45] The chlorinated side products found in the oxidation of benzo[*b*]thiophene may in part also be due to a Michael addition.^[7,8]

The oxygen of the sulfoxy-moiety in benzo[*b*]thiophene-*S*-oxides can be alkylated (e.g., 2j to 12). This has been shown by R. M. Acheson and J. K. Stubbs (Scheme 11).^[46] The alkoxy-group can, however, not be displaced by a nucleophile like it has been carried out with corresponding dibenzothiophene-*S*-oxides, where an alkoxy group could be displaced by an amino group (e.g., by piperidine to give 14). If 1-methoxy 2,3-



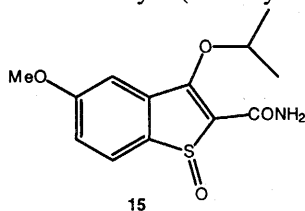
dibromobenzo[*b*]thiophenium perchlorate (12) is reacted with piperidine, only 2,3,-dibromobenzo[*b*]thiophene-*S*-oxide (2j) can be isolated.

While benzo[*b*]thiophene-*S*-oxides are often labile under reductive and/or acidic conditions, a number of reactions can be performed with 2,3-disubstituted BTOs without transforming the thiophene-*S*-oxide unit. A good example may be seen in the reaction of some 3-alkoxybenzo[*b*]thiophene-*S*-oxide 2-carboxylates to the corresponding amides. Reaction conditions involve the presence of a strong (albeit non-nucleophilic) base (NaH), the preparation of an acid chloride with thionyl chloride and the addition of amines (benzylamine, aniline, ammonia) – the thiophene-*S*-oxide unit remains unharmed.^[22]

Applications and Use

3-Alkoxy-2-benzo[*b*]thiophenecarboxamide *S*-oxides have been forwarded as inhibitors of neutrophils adhesion, potentially useful as anti-inflammatory agents.^[22] One of the key steps in the pathogenesis of acute inflammation is the adherence of neutrophils to the

vascular endothelium. The neutrophils then migrate to surrounding tissues resulting in tissue damage and pain. E-Selectin, ICAM-1, and VCAM-1 are the proteins which act upon cell adhesion and whose expression on endothelial cells is upregulated by inflammatory stimuli. Cell adhesion can be prevented by inhibiting the upregulation of the inducible adhesion molecules on the endothelium. 5-Methoxy-3-(1-methylethoxy)benzo[*b*]-



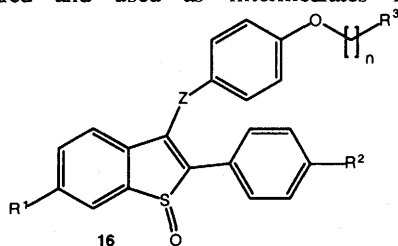
PD-144795 (D. H. Boschelli et al. 1995)

Fig. 2

thiophene-2-carboxamide 1-oxide [PD 144795, **15**, Fig. 2] was found to inhibit E-Selectin, ICAM-1 and VCAM-1 mediated cell adhesion.^[22,47,48] *In vivo* and *in vitro* activity of PD 144795 was particularly strong for the (*S*)-Enantiomer. A 93% inhibition of cell adhesion at an oral dose of 10mg/kg (male outbred Charles River Labs Wistar rats) as determined by RPAR^[49] was reported.^[22] Other, differently substituted benzo[*b*]thiophene-*S*-oxides were found to be much less active.^[22] PD 144795 has been tested *in vivo* and has been found to inhibit swelling induced by *Mycobacterium butyricum* caused footpad edema. Moreover, it was effective against adjuvant-induced polyarthritis (AIP) in rats,^[48] which is used as a model for chronic inflammations. The compound was tested in a wide-range *in vitro* screen and did not show any activity against other enzymes/proteins, specifically it is not an inhibitor of cyclooxygenase or of 5-lipoxygenase.^[22]

3-Phenylbenzo[*b*]thiophene-*S*-oxides have been patented as pesticides (acaricides).^[51]

Benzo[*b*]thiophene-*S*-oxides of type **16** (Fig. 3) have been prepared and used as intermediates for substituted



R¹ = H, OR, OH; R² = H, Hal, OH, OR; R³ = Pip, Pyr, Morph.; n = 2,3; Z = O, S
A. D. Palkowitz et al. (Eli Lilly and Company, USA) US Pat. 1995

Fig. 3

benzothienopyridines, which have been forwarded as being useful in the treatment of various medical conditions associated with post-menopausal syndrome (see also above and ref. 50). The syndromes listed are osteoporosis, uterine fibroid disease, endometriosis and aortal smooth muscle cell proliferation.^[11, 52-61]

D. Mansuy, P. M. Dansette et al.^[62, 64], (see also ref. 63 and ref. 44, 45) have carried out seminal work on the oxidative metabolism of thiophenes in organisms. Special importance of these results stems from the fact that a diuretic drug, tienilic acid (**17**, Fig. 4), leads to immunoallergic hepatitis in 0.01% of patients treated.

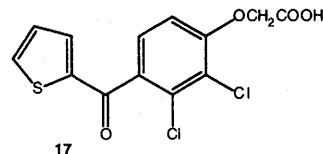


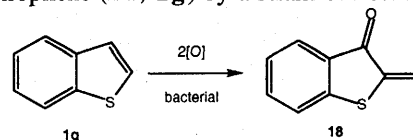
Fig. 4 Tienilic acid

The metabolic cytochrome P450 mediated oxidation of tienilic acid (**17**) apparently leads to the formation of electrophilic metabolites that covalently bind to hepatic proteins. The nature of the intermediate of tienilic acid after further reactions of the oxidated species was not readily known. Studies that have been carried out with thiophenes as well as benzothienopyridines, however, strongly suggest that thiophene-*S*-oxides are viable intermediates in the metabolism. These may then react *in vivo* with glutathione with the eventual formation of mercapturic acid or, in adverse cases, they may react with liver proteins. Analogous reactions *in vitro* are shown in Scheme 10.

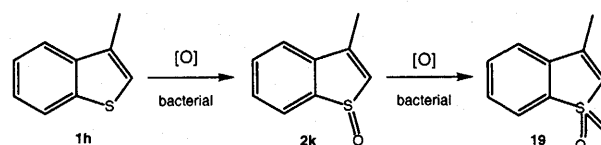
A thermal conversion of high petroleum fractions and oil residues in the presence of thiophene-*S*-oxides or benzothienopyridine-*S*-oxides has been forwarded.^[65]

Environmental Importance

A major concern for the oil industry and the public in general is the presence of organosulfur compounds in crude oil and other fuel sources. Large amounts of time and financial resources have been devoted to extraction methods of sulfur compounds from petroleum. Although hundreds of different organosulfur compounds have been found in crude oils, it is mostly the benzothienopyridines and dibenzothienopyridines and their derivatives where most of the attention lies.^[66-75] Especially their alkylated derivatives present problems. Alkylbenzothienopyridines and dibenzothienopyridines as well as thiolanes and thianes are susceptible to biodegradation, however. Early reports by F. Sagardia et al.^[66] have discussed the degradation of benzothienopyridine (BT, **1g**) by a strain of *Pseudomonas* (*P.*



Metabolic Pathway mostly followed by 2,3-non-substituted BTs.



Metabolic Pathway mostly followed by 2-, 3-, substituted and 2,3-disubstituted BTs.

Scheme 12

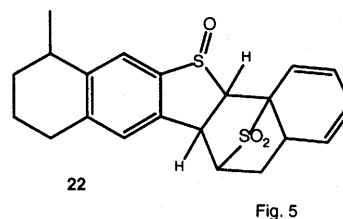
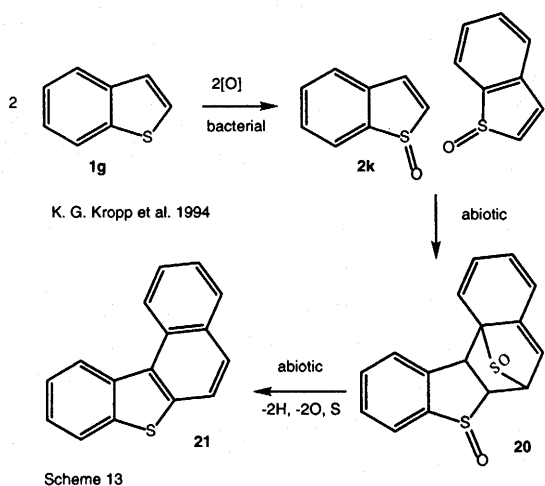
Fedorak, Grbic-Galic 1991

aeruginosa) in the soil in an oil-aqueous environment. In this case, the *Pseudomonas* strain did not use BT as its sole carbon source, *i.e.*, other organic compounds were metabolized as well. Naphthalene has been found as one such source of carbon.^[67] It could be shown that one of the metabolites in the transformation of BT is BTO as well as 2,3-dihydro-BT-2,3,-diol and BT-2,3-dione (**18**) (see also Scheme 12).^[68] Early identification of the metabolites was undertaken by gas chromatography-mass spectrometry analysis. P. M. Fedorak and D. Gbric-Galic subjected benzothiophene (BT, **1g**) and 3-methylbenzothiophene (3-BT, **1h**) to an aerobic cometabolism^[69] (using either 1-methylnaphthalene, glucose or peptone as a further energy source). The experiments provided the following results: a.) addition of BT to a culture of *Pseudomonas sp.* strain BT1, grown on 1-methylnaphthalene, in fact inhibited the further growth of the culture for some time (5 days); the addition of 3-methyl-BT (**1h**) had a similar but much less pronounced effect; b.) the main metabolite found BT was benzothiophene-2,3-dione (BT-2,3-dione, **18**), no BTO was observed; c.) the main metabolites of 3-Me-BT (**1h**) were found to be 3-Me-BTO (**2k**) and 3-Me-BTO₂ (**19**); with time the ratio of 3-Me-BTO₂ to 3-Me-BTO increased, indicating that 3-Me-BTO₂ (**19**) is formed by microbial oxidation of 3-Me-BTO (**2k**); d.) none of these metabolites were found when BT or 3-Me-BT was added to the incubation extract without an added energy source. Unfortunately an experiment of microbially transforming BT (**1g**) or 3-Me-BT (**1h**) in a 'real' crude oil (Prudhoe Bay crude oil) failed, as the detection of natural BT and 3-Me-BT was difficult to perform. Adding 3-Me-BT (**1h**) to the crude oil in the presence of the incubation extract did yield small amounts of 3-Me-BTO (**2k**). The addition of BT to the mixture did not yield any isolable BT-2,3-dione (**18**). The authors state, however, that it is extremely difficult to isolate BT-2,3-dione (**18**) from a mixture containing Prudhoe Bay crude oil.

It was predicted that benzothiophenes with an alkyl substituent on the thienyl unit, *i.e.* at C-2 or C-3 (*e.g.*, **1a** and **1h**), would preferentially be oxidized at the thienyl

sulfur, *i.e.*, to the corresponding BTOs (*i.e.*, **2a** and **2b**) and BTO₂s. Benzothiophenes lacking substituents at these positions would preferentially oxidized at C-2 and/or C-3, yielding BT-2,3-diones (*e.g.*, **18**). Later experiments have proven this to be true, also for 4-, 5- and 6-Me-BTs. Interestingly 7-Me-BT has been reported to yield 7-Me-BT-2,3-dione as well as 7-Me-BTO and 7-Me-BTO₂. Later, however, other *Pseudomonas* strains have been reported to produce both products oxidized at the sulfur as well as at C-2 and/or C-3. Moreover, K. G. Kropp et al.^[73] also observed high-molecular weight products formed through metabolism of BT or of benzo-methylated BT. Later experiments have shown these high weight products to be benzo[*b*]naphtho[1,2-*d*]thiophenes (*e.g.*, **21**). The products were identified by GC-MS spectroscopy. To distinguish among possible isomers, the species isolated was subjected to a desulfurization mediated by nickel boride and the desulfurized metabolite was identified by comparison with known samples (*e.g.*, with 1-phenylnaphthalene). The proposed mechanism of formation of the benzo[*b*]naphtho[1,2-*d*]thiophenes **21** is the known dimerisation of BTOs (*e.g.*, of **2k**, Scheme 13). Interestingly, the benzo[*b*]naphtho[1,2-*d*]thiophenes **21** have also been isolated from the photooxidation of BT (see above). These dimerisation products formed in the metabolism not only of BT itself but also of 4-, 5-, 6- and 7-Me-BTs in cultures of *Pseudomonas* isolates SB(G), W1 and F.^[73]

It has been found that benzo[*b*]thiophenes and some of their derivatives and reaction products may be responsible for gasoline deposit formation in engine induction systems (EIS).^[76-81] Thus, P. Martin and A. Mendez have isolated arenothiophene oxides from FCC (Fluid Catalytic Cracking) naphtha. These were then reacted with a mixture of benzothiophene, 1-octene, toluene, cyclopentane and anilines under reflux conditions. Reaction samples were taken after certain time periods and analysed by GC-MS spectroscopy.^[78] A number of products identified were dimerisation products of benzo[*b*]thiophene-*S,S*-dioxides or of benzo[*b*]thiophene-*S,S*-dioxides and benzo[*b*]thiophenes. However, products such as **22** (Fig. 5),^[77] which may stem from the reaction of a benzo[*b*]thiophene-*S*-oxide and a benzo[*b*]thiophene-*S,S*-dioxide, have also been isolated. The formation of these higher weight components have been linked to the formation of deposits in EIS.



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