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Abstract

Thiophene S-oxides constitute a class of molecules that have been studied in more detail only recently. Their existence as intermediates in the peracid mediated oxidation of thiophenes to thiophene S,S-dioxides, however, has been known over some time. Over the last 20 years, a larger number of thiophene S-oxides have been prepared and isolated in pure form. Thiophene S-oxides have been found to be good dienes in [4 + 2]-cycloaddition reactions, where they react with electron-poor, electron-neutral and electron-rich dienophiles with high syn π-facial stereoselectivity. Thiophene S-oxides have been found to be metabolites of thienyl-containing pharmaceuticals such as the anti-platelet drugs ticlopidine and clopidogrel. The chapter gives an overview of the preparation and reactivity of this class of compounds.

Keywords: thiophenes, selective oxidation, cycloaddition, functionalized arenes, drug metabolites

1. Early history of oxidation reactions of thiophenes: cycloaddition reactions of thiophene S-oxides prepared in situ in absence of Lewis acids

In the first half of the 20th century, considerable effort was devoted to the oxidation of the heteroaromatic thiophene (1) with the understanding that the oxidation of thiophene to thiophene S,S-dioxide (2) (Figure 1) would be accompanied by the loss of aromaticity [1, 2]. The non-substituted thiophene S,S-dioxide (1) is not very stable in the pure state [3], but undergoes a slow dimerization with concurrent extrusion of SO₂ from the primary cycloadduct (4) [4], leading to 5 (Scheme 1). Only much later were the properties and reactivity of pure, isolated non-substituted thiophene S,S-dioxide (2) described [5].
Much of the early work on the oxidation of thiophenes to thiophene S,S-dioxides involved hydrogen peroxide (H$_2$O$_2$) as oxidant, later *meta*-chloroperoxybenzoic acid (m-CPBA). That thiophene S-oxide was an intermediate in such oxidation reactions [6–8] was evident from the isolation of so-called sesquioxides as dimerization products of thiophene S-oxides [9–12]. Here, the thiophene S-oxide acted as diene with either another molecule of thiophene S-oxide or thiophene S,S-dioxide acting as ene [9–12] to give cycloadducts 6–8 (Figure 2). Thiophene S-monoxide (3) as an intermediate in the oxidation process of thiophene (1) to thiophene S,S-dioxide (2) could not be isolated under the conditions.

Nevertheless, the idea that a thiophene S-oxide intermediate could be reacted with an alkene of choice led Torssell [13] oxidize methylated thiophenes with m-CPBA in the presence of quinones such as *p*-benzoquinone (12). This gave cycloadducts 13 and 14 (Scheme 2) [13]. Further groups [11, 12, 14–19] used this strategy to react thiophene S-oxides such as 11, prepared *in-situ* with alkenes and alkynes in [4 + 2]-cycloadditions (Schemes 3 and 4). In the reaction with alkenes, 7-thiabicyclo[2.2.1]heptene S-oxides such as 13 were obtained, while the reaction of thiophene S-oxides with alkynes led to cyclohexadienes and/or to aromatic products, where the initially formed, instable 7-thiabicyclo[2.2.1]hepta-2,5-diene S-oxide system 21 extrudes its SO bridge spontaneously (Scheme 4). A number of synthetic routes to multifunctionalized cyclophanes 32 [17], aryl amino acids 25 [16] and to crown ethers 29 [15] (Scheme 5).
have used the cycloaddition of thiophene S-oxides 19, created in-situ, as a key step. The formation of the 7-thiabicyclo[2.2.1]heptene S-oxides (such as 13, 18) proceeds with stereocontrol. The cycloadditions yield predominantly endo-cycloadducts, with the oxygen of the sulfoxide bridge directed towards the incoming dienophile, exhibiting the \( \text{syn-} \pi \)-facial stereoselective nature of the reaction (see below for further discussion of the stereochemistry of the cycloadducts). Thiophene S,S-dioxides 2 possess an electron-withdrawing sulfone group, which leads both to a polarization and to a reduction of the electron density in the diene [20]. This results in a decrease of the energy of the HOMO as compared to identically...
substituted cyclopentadienes [20]. Thiophene $S,S$-dioxides are sterically more exacting than C$_5$ non-substituted cyclopentadienes, with the lone electron pairs on the sulfone oxygens leading to adverse non-bonding interactions with potentially in-coming dienophiles of high $\pi$-electron density. Thus, thiophene $S,S$-dioxides often require higher temperatures [21, 22] in cycloaddition reactions than identically substituted cyclopentadienes. Recent frontier molecular orbital calculations at the HF/6-311++G(d,p)//M06-2X/6-31+G(d) level theory have shown that both HOMO (by 0.5 eV) and LUMO (by 0.4 eV) in thiophene $S$-oxide (3) are slightly higher in energy than in thiophene $S,S$-dioxide (2) [23]. Oxidation of the thienyl-unit in 33 leads to an intramolecular cycloaddition, where indanones 34 are obtained (Scheme 6) [24].

Scheme 5. Cycloaddition of thiophene $S$-oxides prepared in situ—applications in the synthesis of functionalized aminocarboxylic acids 25, crown ethers 29 and cyclophanes 32.

Scheme 6. Intramolecular cycloaddition of $in situ$ prepared thiophene $S$-oxide 34.
2. Cycloaddition reactions of thiophene S-oxide prepared in situ in the presence of Lewis acids: thiophene S-oxides are isolated

Yields of cycloadducts have been found to be much higher, when oxidative cycloaddition reactions of thiophenes are carried out with meta-chloroperoxybenzoic acid (m-CPBA) or with H₂O₂ at lower temperatures such as at −20°C in the presence of a Lewis acid catalyst such as BF₃·Et₂O [11, 12, 25, 26] (Scheme 7) or of trifluoroacetic acid (CF₃CO₂H) [27]. Electron-poor dienophiles such as tetracyanoethylene, acetylene dicarboxylates, quinones, maleimides and maleic anhydride and mono-activated enes such as cyclopentenone and acrolein were used in these reactions.

Scheme 7. Oxidative cycloaddition of thiophene 36 to naphthoquinone (37) in the presence of BF₃·Et₂O.

Scheme 8. Preparation of multifunctionalized cyclophane 41 by oxidative cycloaddition of thiophenophane 39 in the presence of BF₃·Et₂O.

Scheme 9. Preparation of aethiosides A–C (44a–c) by oxidative cycloaddition of thienosteroidal sapogenin 42.
Under the conditions m-CPBA/BF$_3$/C$_2$H$_5$O, the cycloadditive transformation of thiophene S-oxides, prepared in situ, was used in the synthesis of new cyclophanes such as 39 (Scheme 8) [25]. A series of 2,3-bis(hydroxyphenyl) substituted 7-thiabicyclo[2.2.1]hept-2-ene S-oxides as potential estrogen receptor ligands were prepared by oxidative cycloaddition of 3,4-bis(hydroxyphenyl)thiophenes in the presence of BF$_3$/C$_2$H$_5$O [28]. Also the key step in Yu et al.’s [27] synthesis of steroidal saponins 44, closely related to the E-ring areno containing natural products aethiosides A–C, is a BF$_3$/C$_2$H$_5$O catalyzed oxidative cycloaddition of the thieno-containing steroidal saponin 42 (Scheme 9) [26]. Furthermore, Zeng and Eguchi [29] were able to functionalize C$_6$0 (46) by cycloaddition with in-situ produced 2,5-dimethylthiophene S-oxide (45) [29, 30] (Scheme 10). Nevertheless, sterically hindered thiophenes are more difficult to be subjected to the oxidative cycloaddition reactions (Figure 3).

3. Preparation and isolation of pure thiophene S-oxides

Thiophene S-oxides could be isolated in pure form as side-products in a number of oxidative cycloaddition reactions using alkylated thiophenes as substrates run with m-CPBA in the presence of BF$_3$/C$_2$H$_5$O [11, 12]. Nevertheless, the first ascertained thiophene S-oxide (51) isolated in pure form came from the oxidation of the sterically exacting 2,5-bis-tert-butylthiophene (50) in absence of a Lewis acid or an added protic acid. 2,5-Bis-tert-butylthiophene S-oxide (51) could be isolated in 5% yield [32] (Scheme 11).

Previous to the isolation of thiophene S-oxides in pure form, based on UV-spectroscopic measurements, Procházka [33] had claimed that the parent thiophene S-oxide (3) could be
prepared by double elimination from 3,4-dimesyloxy-2,3,4,5-tetrahydrothiophene S-oxide (53) and studied in solution. While subsequently the latter part of the assertion was thrown into doubt, the isolation of sesquioxides \(7/8\) from the reaction indicated at least the presence of thiophene S-oxide under these conditions [33] (Scheme 12).

Interestingly, a toluene solution of \(\eta^5\)-ethyltetramethylcyclopentadienyl-\(\eta^4\)-tetramethylthienyl rhodium complex \([\text{Cp}^*\text{Rh}(\eta^4\text{-TMT})]\) (54) can be oxidized with dry oxygen to \([\text{Cp}^*\text{Rh(TMTO)}]\) (56), which features a \(\eta^4\)-coordinated thiophene S-oxide ligand. Complex 56 was isolated and an X-ray crystal structure was carried out. Alternatively, \([\text{Cp}^*\text{Rh}(\eta^4\text{-TMT})]\) (54) can be oxidized electrochemically to \([\text{Cp}^*\text{Rh}(\eta^4\text{-TMT})]^{2+}\) (55), which can also be obtained by protonation of \([\text{Cp}^*\text{Rh(TMTO)}]\) (56). Reaction of \([\text{Cp}^*\text{Rh}(\eta^4\text{-TMT})]^{2+}\) (55) with potassium methylsilanolate (KOSiMe\(_3\)) leads back to \([\text{Cp}^*\text{Rh(TMTO)}]\) (56) [34] (Scheme 13).

The reaction of the cationic transitory ruthenium complex \([\text{Ru}(\text{C}\(_6\)\text{R}\(_6\))(\text{C}\(_4\)\text{R}\(_4\)\text{SO})]^+\) (57) with hydroxyl anion (OH\(^-\)) gives \([\text{Ru}(\text{C}\(_6\)\text{H}\(_6\))(\text{C}\(_4\)\text{R}\(_4\)\text{SO})]\) (58) [35] (Scheme 14). Here, in contrast to the complex \([\text{Cp}^*\text{Rh(TMTO)}]\) (56), the thiophene S-oxide ligand in \([\text{Ru}(\text{C}\(_6\)\text{H}\(_6\))(\text{C}\(_4\)\text{R}\(_4\)\text{SO})]\) (58) is not

Scheme 11. Isolation of 2,5-bis-tert-butylthiophene S-oxide 51 by simple thiophene oxidation with meta-chloroperoxybenzoic acid (m-CPBA) [32].

Scheme 12. In situ preparation of parent thiophene S-oxide (3) by an elimination reaction [33].

Scheme 13. Oxidation of \([\text{Cp}^*\text{Rh}(\eta^4\text{-TMT})]\) (54) to \([\text{Cp}^*\text{Rh(TMTO)}]\) (56) [34].
stable, but opens to an acetylpropenethiolate. Stable osmium thiophene S-oxide complexes of type (cymene)Os(C₄Me₄S=O) have also been prepared [36]. In neither of the cases, was it tried to decomplex the thiophene S-oxide ligand.

In the 1990s, two main synthetic methodologies were developed to prepare thiophene S-oxides 63. The first involves the reaction of substituted zirconacyclopentadienes 62 with thionyl chloride (SOCl₂), developed by Fagan et al. [37, 38] and by Meier-Brocks and Weiss [39]. Typically, tetraarylzirconacyclopentadienes 62a can be synthesized easily by reacting CpZrCl₂ (59), n-BuLi and diarylethynyl (61a) in one step (Scheme 15). This strategy was followed by Tilley et al. [40, 41] in their synthesis of substituted thiophene S-oxides. Miller et al. published results for a synthesis of 2,5-diarylthiophene S-oxides (63b) along the same lines, using ethynylarene (61b) [42].

The other methodology involves an oxidation of a thiophene with either a peracid in the presence of a Lewis acid such as titanium tetrachloride (TiCl₄) [43] or boron trifluoride etherate (BF₃·Et₂O) [44, 45] or with hydrogen peroxide in the presence of a protonic acid such as trifluoroacetic acid [46, 47] (Scheme 16). Also, the use of the reaction system H₂O₂ in presence of NaFe(III) ethylenediaminetetraacetate/Al₂O₃ has been reported [48, 49] (Scheme 16) as has been the use of the reaction system [(C₁₈H₃₇)₂(CH₃)₂N]₃[SiO₄H(WO₅)₃] [50]. The thiophene S-oxides 65, suitably substituted, can be isolated by column chromatography and can be held in substance for a number of weeks without appreciable degradation, when in crystallized form and when kept in the dark. It is supposed that the Lewis acid not only activates the

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**Scheme 14.** Base hydrolysis of [Ru(C₆R₆)(C₄R₄S)]⁺ (57) [34].

**Scheme 15.** Synthesis of tetraarylthiophene S-oxides 63a/b by reaction of tetraarylzirconacyclopentadienes 62a/b with SOCl₂.
peracid, but also coordinates to the oxygen in the formed thiophene S-oxide, thus reducing the electron-density on the sulfur of the thiophene S-oxide, making it less prone to undergo a second oxidation to the thiophene S,S-dioxide.

It has been shown that in a molecule, such as 66 or 67, with two thienyl cores, both can be oxidized to thienyl-S-oxides with m-CPBA, BF₃·Et₂O/CH₂Cl₂, −20°C [11, 17]. Under these conditions, the second thiophene unit can compete successfully with a thiophene S-oxide for the oxidant (Figure 4).

4. Reactions of thiophene S-oxides

4.1. [4 + 2]-cycloaddition reactions

Even before thiophene S-oxides could be isolated in pure form, it was evident that thiophene S-oxides are good dienes in cycloaddition reactions, as “trapping” by cycloaddition reaction was one of the standard techniques to gauge the presence of thiophene S-oxide intermediates and provided a versatile preparative entry to 7-thiabicyclo[2.2.1]heptenes 68. These in turn could be converted to substituted arenes 71 by either pyrolysis [15], photolysis [51], or PTC-catalyzed oxidative treatment with KMnO₄ [15] or electrochemical oxidation [18] or 7-thiabicyclo[2.2.1]heptenes (70) by reaction of 68 with PBr₃ [52]. Reaction of 68 with tributyltin hydride gives cyclic dienes such as 72 \(-\text{R} \equiv X \equiv \text{X} \equiv \text{(CO)N} \equiv \text{Ph(CO)} \equiv\). Base catalyzed cleavage of the sulfoxyl bridge of 1,4-dihalo-7-thiabicyclo[2.2.1]heptene S-oxides 68 (R¹ = Cl or Br) leads to the generation of diaryl disulfides such as 69 (Scheme 17).
With the possibility of isolating the thiophene S-oxides, it became possible to carry out cycloaddition reactions with alkenes that themselves react with m-CPBA. Thiophene S-oxides such as 73 have been found to react equally well with electron-rich alkenes such as enol ethers (74) [53], with electron neutral alkenes such as with cyclopentene (76) [53, 54] and with electron-poor alkenes such as with cyclopentenone or with maleic anhydride [11, 54] (Scheme 18). Also, thiophene S-oxides react with bicyclopropylidene (82) [55] under high pressure (10 kBar, Scheme 19), with allenes [56] (such as 79, Scheme 19), with cyclopropylideneketone [55] (Scheme 20) and with benzene (90) [56], both formed in-situ (Scheme 21). The reaction of tetrachlorocyclopropene (93) with 3,4-bis-tert-butylthiophene S-oxide (73) led to 6,7-bis-tert-butyl-2,3,4,4-tetrachloro-8-thiabicyclo[3.2.1]octa-2,6-diene 8-oxide (95), resulting from a ring opening of the primary cycloadduct 94 with a concomitant migration of a chloro atom [57] (Scheme 22). The ability of the thiophene S-oxides to undergo cycloadditions with alkenes, regardless of the electron demand of the reaction, has made Houk et al. say that thiophene 1-oxide cycloadditions warrant their classification as click reactions [23].

Scheme 17. 7-Thiabicyclo[2.2.1]heptene S-oxides 68 as versatile precursors to arenes.

Scheme 18. 3,4-Bis-tert-butylthiophene S-oxide (73) cycloadding to electron-rich and electron-neutral alkenes.
Scheme 19. Thiophene S-oxides cycloadd to allenes and to bicyclopropylidene (82) under high pressure.

Scheme 20. One pot Wittig reaction—Diels Alder reaction with thiophene S-oxide 87 as diene.


Scheme 22. Cycloaddition of thiophene S-oxide (73) with tetrachlorocyclopropene (93).
Thiophene S-oxides are good precursors for the preparation of heavily substituted arenes such as 100 [58] (Scheme 23). Often, tetraarylcyclopentadienones 97 are used to synthesize oligoaryl benzenes by cycloaddition reaction. However, tetraphenylthiophene S-oxide (96) is the more reactive diene when compared to tetraphenylcyclopentadienone (97) as can be seen in the competitive cycloaddition of 96 and 97 with N-phenylmaleimide (98), where at room temperature only tetraphenylthiophene S-oxide undergoes cycloaddition to give 99 (Scheme 23) [58]. 99 can be converted to the heavily substituted phthalimide 100 [58], either by extruding the SO group thermally in diphenyl ether (Scheme 23) or by reaction with KMnO₄/PTC.

Sometimes, tetraphenylthiophene S-oxide (96) and tetraphenylcyclopentadienone (97) give different products in cycloaddition reactions. A typical example is their cycloaddition to benzo[b]thiophene S,S-dioxide (101), where the reaction with 96 leads to the formation of dibenzoanthiophene S,S-dioxide 102, but with 97 gives dibenzoanthiophene 104 [59] (Scheme 24). The reason for this difference lies in the tendency of tetracyclines such as 94 to be oxidized to pyrones 105 at higher reaction temperatures, with the S,S-dioxides playing the oxidizing agent [59] (Scheme 24).

Again, cycloaddition reactions of purified thiophene S-oxides can be used to prepare multifunctionalized arenes such as cyclophanes (Scheme 25) [25]. Nakayama et al. [61] have used thiophene S-oxides to prepare sterically over freighted anthraquinones. Thiemann et al. [62] used halogenated thiophene S-oxides, albeit prepared in-situ to synthesize halogenated anthraquinones, which can easily be transformed further to arylated anthraquinones [63, 64].
The cycloaddition reactions of purified thiophene S-oxides can be combined with other transformations in one pot, such as with Wittig olefination reactions (Scheme 20) [55].

Not all thiophene S-oxides undergo cycloaddition reactions with alkynes or alkenes. In general, appreciable reaction volume is needed to allow for the forming sulfoxy-bridge in the primary cycloadducts and, in some cases, of the subsequent extrusion of SO. Also, when considerable strain is associated with the thiophene S-oxides and/or the cycloadducts, reactions other than cycloadditions can occur. Thus, strained thiophenophane S-oxide 110 does not undergo a cycloaddition with 98, but undergoes a rearrangement leading to oxygen insertion into the ring with concomitant extrusion of sulfur, leading to furanophane 111 (Scheme 26) [25]. Fujihara et al. were able to prepare the thiacalixarene S-oxide 112; again, the thiacalixarene S-oxide did not undergo a cycloaddition reaction with alkyne 113, but rather formed the thiophene-S,C-sulfonium ylide 114 (Scheme 27) [65].

Scheme 25. Multifunctionalized cyclophanes 108 by cycloaddition of thiophenophane S-oxides 106.


Scheme 27. Thiacalixarene S-oxide 112 reacts with dimethyl acetylenedicarboxylate (113) to the thiacalixarene S,C-ylide 114.
Thiophene S-oxides as cyclic dienes undergo hetero-Diels-Alder reactions, also (Scheme 28). Thus, Nakayama et al. could establish that 3,4-bis-tert-butylthiophene S-oxide 73 reacts with thioaldehydes 115/117 and thioketones 115, generated in-situ to give 2,7-dithiabicyclo[2.2.1]hept-5-ene 7-oxides 116 and 118 [66] (Scheme 28). The cycloadducts are endo-products as ascertained by X-ray crystallography and \(^1\)H NMR spectroscopy. Thiobenzophenone could be reacted with good yield; however, here two isomeric products are produced, the major product originating from the syn-\(\pi\)-face while the lesser product from the anti-\(\pi\)-face cycloaddition.

Finally, 73 reacts with carbonyl cyanide [121, CO(CN)\(_2\)], created in-situ by oxidation of tetracyanoethylene oxide (119, TCNO) with thiophene S-oxide 73, in hetero-Diels-Alder fashion to give 122 [67] (Scheme 29).

Nakayama et al. have calculated that the cycloadditions of the thiophene S-oxides are inverse electron demand reactions [53]. All of the above cycloaddition reactions are highly stereoselective, regardless whether the thiophene S-oxide is prepared and used in-situ or an isolated thiophene S-oxide is used. It is known that the thiophene S-oxides invert at the sulfur and inversion barriers have been calculated and measured experimentally for a number of these compounds [32, 68, 69]. Nevertheless, the sulfoxy group in the 7-thiabicyclo[2.2.1]heptene S-oxide systems is configurational stable. All the cycloadducts are endo-products.

**Scheme 28.** Hetero-Diels-Alder reactions of 3,4-bis-tert-butylthiophene S-oxide (73).

**Scheme 29.** Reaction of 3,4-tert-butylthiophene S-oxide (73) with tetracyanoethylene oxide (119, TCNO) and hetero-Diels Alder reaction to carbonyl cyanide (121).
In the cases where Lewis acids are used at low temperatures, this in itself is not surprising as it is known that low temperatures kinetically controlled cycloadducts are favored. Moreover, it has been stated that Lewis acid catalysis increases the extent of *endo*-addition in Diels-Alder reactions [70, 71]. The cycloadditions are seen to have *endo*-π-facial in that the dienophile adds *endo* to the oxygen. This means that the lone pair of the sulfur is directed towards the side of the newly formed double bond of the cycloadduct. A number of explanations have been given for the π-facial selectivity. Thus, Nakayama et al. rationalized that in the transition state less geometric change of the SO function would be required to reach the *endo-* rather than the *anti-* transition state geometry [53]. Also, a destabilizing interaction between the HOMO of the dienophile and the sulfur lone pair was noted in the *anti*-transition state [72]. The π-facial selectivity has also been explained by the Cieplak effect [73–75]. This effect was first proposed to account for the directing effect of remote substituents in addition reactions to substituted cyclohexanones. A large number of experimental observations in Diels-Alder reactions of dienophiles with 5-substituted cyclopentadienes have shown that the dienophiles will approach *anti* to the antiperiplanar σ-bond that is the better donor at the 5-position of the cyclopentadiene [76]. This σ-bond will best stabilize the σ-bonds formed in the transition state. Cycloadditions to thiophene S-monoxides have been predicted to occur *anti* to the lone electron-pair on sulfur, which is the better hyper-conjugative donor when compared to the oxygen of the sulfoxide moiety. The lone pair electron orbital at the sulfur will stabilize the vacant σ*-orbitals of the developing incipient σ-bonds better than any orbital associated with the oxygen of the sulfoxide moiety [77] (Figure 5). This would be even more so, when the oxygen of the sulfoxide-unit is complexed by BF$_3$/Et$_2$O.

Based on DFT computational studies, Houk et al. [23] showed that the ground state geometry of a thiophene S-oxide already resembles the molecule in its *syn* transition state. This distortion from planarity of the molecule minimizes its potential antiaromaticity which would result from a hyperconjugative effect by an overlap of σ*$_{S\equiv O}$ with the π-system (see also above/below) [23] (Figure 6).

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**Figure 5.** Transition state 123 preferred over transition state 124.

**Figure 6.** Structural feature of thiophene S-oxide 160.
4.2. Further cycloaddition reactions

When heated with 2-methylene-1,3-dimethylimidazoline (125), 3,4-bis(tert-butyl)thiophene S-oxide 73 undergoes a [4π + 4π]-cycloaddition to the head-to-head dimer 126 (Scheme 30) [78]. Oxidation of the two sulfoxyl bridges to sulfone 127 with dimethyldioxirane as oxidant is followed by thermally driven extrusions of the SO₂ bridges in 127 and gives 1,2,5,6-tetra(tert-butyl)octatetraene 128 [79] (Scheme 30).

Thiophene S-oxides react as enes in 1,3-dipolar cycloaddition reactions. Thus, 3,4-bis-tert-butylthiophene S-oxide (73) reacts with pyrroline N-oxide (129) to give cycloadduct 130 (Scheme 31) [80]. Nakayama et al. could show that 73 reacts with nitrile oxides, diazomethane, nitrile imides, nitrones, and azomethine ylides in syn-π-facial fashion [80].

![Scheme 30](image)

Scheme 30. [4π + 4π]-cycloaddition of thiophene S-oxide (73) to dimer 126.

![Scheme 31](image)

Scheme 31. [3 + 2]-cycloaddition of thiophene S-oxide (73) with pyrroline N-oxide (129) as 1,3-dipole.

4.3. Additions to thiophene S-oxides and other reactions

1,4-Additions are known for both 3,4-disubstituted and 2,5-disubstituted thiophene S-oxides [81–83]. Thus, bromine adds cis to both 3,4-bis-tert-butylthiophene S-oxide (73) [81] and 2,5-bis-trimethylsilylthiophene S-oxide (134) [82] to give the 2,5-dibromo-2,5-dihydrothiophene S-oxide derivatives 131 and 135 (Scheme 32). 3,4-Bis-tert-butylthiophene S,S-dioxide (132) undergoes cis-1,4-bromination, too [81] (Scheme 32). Also, alcohols and mercaptans have been submitted successfully to 1,4-additions with 3,4-bis-tert-butyl thiophene S-oxide (73) (Scheme 33) [83]. Interestingly, disulfur dichloride (S₂Cl₂) could be added to thiophene S-oxide 73, leading to the rapid formation of adduct 137 (Scheme 34) [84]. 137, however, is not stable.
and transforms into 138. 138 can be obtained with a 98% yield, when 137 is treated with aq. NaHCO₃ (Scheme 34) [84].

The sulfoxyl group in thiophene S-oxide can be transformed into a sulfilimine or a sulfoximine moiety [85–87]. When thiophene S-oxide 73 is reacted with trifluoroacetic acid anhydride or triflic anhydride at −78°C, a mixture of sulfonium salt 139 and sulfurane 140 forms, which can be reacted with p-toluenesulfonamide (141) to provide, as the reaction mixture warms to room
temperature, sulfilimine 142 (Scheme 35) [85, 86]. Sulfoximine 145 could be prepared by action of N-[(p-tolylsulfonyl)imino]phenyliodinane (TsN≡IPh, 144) on 2,4-bis-tert-butylthiophene S-oxide (143) in the presence of Cu(CH$_3$CN)$_4$PF$_6$ as catalyst. Further reaction of 145 with H$_2$SO$_4$ leads to N-unsubstituted sulfoximine 146 (Scheme 36) [86].

4.4. Photochemistry of thiophene S-oxides

The photochemical deoxygenation of dibenzothiophene S-oxides has been studied for quite some time [88–91] and has been found to proceed via the release of ground state atomic oxygen [O($^3$P)] upon photoirradiation (Scheme 37). Thiophene S-oxides deoxygenate photochemically as well. Nevertheless, the photochemistry of thiophene S-oxides is intrinsically more complex than that of dibenzothiophene S-oxides, often providing a mixture of products, depending on the substitution pattern of the photoirradiated thiophene S-oxide. The photolysis of 2,5-bis(trimethylsilyl)thiophene S-oxide (134) leads exclusively to deoxygenation to

Scheme 35. Preparation of thiophene S-imide 142 from thiophene S-oxide 73.

Scheme 36. Thiophene sulfoximines 145 and 146 from thiophene S-oxide 143.

Scheme 37. Photodeoxygenation of dibenzothiophene S-oxide (147).

Scheme 38. Photolysis of 2,5-bis(trimethylsilyl)thiophene S-oxide (134).
produce 2,5-trimethylsilylthiophene (149) (Scheme 38). Otherwise, in those cases, where the thiophene S-oxide does not exhibit a CH$_3$ substituent on the ring system, furans are often the main products along with (deoxygenated) thiophenes (Scheme 39). This has been noted with phenyl-substituted (96, 160) and tert-butyl substituted thiophene S-oxides (73, 143, 153) as well as with 3,4-dibenzylthiophene S-oxide (158) (Scheme 40) [92–95]. Different mechanisms have been forwarded for this photochemical formation of furans. A viable mechanism involves a cyclic oxathiin, where the first step within the photochemical reaction is initiated by the homolytic ring cleavage α to the sulfoxo group [92–94]. A rearrangement of thiophene S-oxides to produce furans can also proceed thermally as found by Thiemann et al. [18] in the transformation of thiophenophane S-oxide 110 to furanophane 111 (Scheme 26) and by
Mansuy, Dansette et al. in their oxidation of 2,5-diphenylthiophene (162) with H$_2$O$_2$/CF$_3$CO$_2$H to 2,5-diphenylthiophene S-oxide (163), where an appreciable amount of furan 164 was formed as side-product [46] (Scheme 41). In the case of methyl substituted thiophene S-oxides, hydroxyl-alkylthiophenes such as 166 and follow-up products such as ether 167 have been isolated as photoproducts [96] (Scheme 42).

**Scheme 41.** Formation of furan 163 in the oxidation of 2,5-diphenylthiophene (162).

**Scheme 42.** Photolysis of 3,4-dibenzyl-2,5-dimethylthiophene S-oxide (165).

### 4.5. Electrochemistry of thiophene S-oxides

Thiophene S-oxides such as 164 and 167 show well-defined, chemically irreversible CV reduction waves, where two reduction processes seem to compete. In the presence of a proton donor, the reduction waves experience a significant shift to more positive potentials, although the reduction potential is still dependent on the substitution pattern of the thiophene S-oxides [96]. In the presence of a proton donor such as benzoic acid at higher concentrations, the reduction of a thiophene S-oxide such as of 167 becomes a straightforward two proton—two electron reduction process to the corresponding thiophene [96]. Bulk electrolysis of thiophene S-oxides in presence of 10-fold excess of benzoic acid has been carried out and have led to the corresponding thiophenes in up to 90% isolated yield (Scheme 43) [96]. Also, thiophene

**Scheme 43.** Electrochemical reduction of 3,4-dibromo-2,5-dimethylthiophene S-oxide (167) in the presence of 10 eq. benzoic acid.
S-oxides show oxidative electrochemistry at platinum in MeCN/Bu$_4$NPF$_6$ [97]. The electrochemical oxidation of tetraphenylthiophene S-oxide under the above conditions leads mainly to the formation of diphenylacylstilbene [98]. Here, more effort needs to be invested to identify the electro-oxidative transformations of other thiophene S-oxides.

4.6. Structural studies on thiophene S-oxides

In 1990, Rauchfuss et al. published an X-ray crystal structure of the tetramethylthiophene S-oxide rhodium complex 56 [34]. The first X-ray single crystal structure determination of a non-ligated thiophene S-oxide was carried out by Meier-Brocks and Weiss on tetraphenylthiophene S-oxide. The crystal, however, showed some disorder, and only limited information could be gleaned from it [39]. In 1995, Mansuy et al. carried out an X-ray crystal structural analysis of 2,5-diphenylthiophene S-oxide (160) [46, 47], where the structure of 160 was compared to 2,5-diphenylthiophene (162) and 2,5-diphenylthiophene S,S-dioxide (169). The S▬O bond in the thiophene S-oxide was found with 1.484(3) Å to be appreciably longer than those of the thiophene S,S-dioxide with 1.418(5) Å and 1.427(5) Å, respectively [47]. The ring system of the thiophene S,S-dioxide 169 was found to be absolutely planar, while thiophene S-oxide 160 was found to be puckered, with the sulfur lying outside the plane constructed by the four ring carbons by 0.278 Å, and the sulfoxyl oxygen lying outside of the plane on the side opposite to sulfur, located by 0.746 Å away from the plane. Previously, this non-planarity of thiophene S-oxides had been predicted by MNDO [99] and ab-initio calculations [100] of the parent thiophene S-oxide itself and dibenzothiophene S-oxide. A more pronounced alteration between double and single C▬C bond was found in thiophene S-oxide 160 in comparison to diphenyldithiophene [47]. In probing the aromaticity of thiophene S-oxide 160, it can be seen that apart from its non-planarity, it exhibits relatively large bond order alternations [C(2)▬C(3) 2.11; C(3)▬C(4) 1.23, C(2)/C(5)▬S 1.11; for comparison, the bond orders in 162: C(2)▬C(3) 1.94; C(3)▬C(4) 1.46; C(2)/C(5) 1.53]. The corresponding 2,5-diphenylthiophene S,S-dioxide, though features even larger bond alternations than 160 [47]. An approach for an assessment of aromaticity is the A index as defined by Julg and François [101], which evaluates aromaticity in respect to bond alternation and bond delocalization in ring systems. Here, benzene as the aromatic system par excellence, has an A index of 1, the thiophene system in 2,5-diphenylthiophene has an A index of 0.99, the 5-membered ring system in 2,5-diphenylthiophene S-oxide’s A index is calculated at 0.79, and the parent thiophene S-oxide A index lies at 0.69 ([47], see also [102]).

Subsequently, further X-ray crystal structure analyses were carried out on thiophene S-oxide, such as on 2,5-bis(diphenylmethylsilyl)thiophene S-oxide [45], 3,4-bis-tert-butyldithiophene S-oxide (73) [43], (1,1,7,7-tetraethyl-3,3,5,5-tetramethyl-s-hydrindacen-4-yl)thiophene S-oxide [68], 1,3-bis(thien-2-yl)-4,5,6,7-tetrahydrobenzo[c]thiophene S-oxide [40], and the sexithiophene (170) (Figure 7), where two of the thienyl units were oxidized to sulfoxides [103]. As the thiophene S-oxides are not planar, they invert at the sulfur with different substituents at the C2/C5 positions leading to different barriers of inversion, which have in part been determined experimentally [32, 68, 69]. Structural features of thiophene S-oxides and thiophene S,S-dioxides have been reviewed before [104].
4.7. Oligomers and polymers incorporating thiophene S-oxide units

Oligothiophenes and polythiophenes are being studied as advanced materials with interesting electronic and nonlinear optical properties [105] with applications in photovoltaic cells [106] and field effect transistors (FETs) [107], among others. It has been noted that oxidation of thienyl-units in oligothiophenes and polythiophenes leads to a lowering of energy gaps, to greater electron affinities, and to greater ionization energies [103, 108, 109]. The introduction of thienyl-S,S-dioxides into oligothiophenes often leads to solubility problems of the materials and often leads to a noticeable increase of oxidation potentials. Therefore, there has been a recent interest in incorporating thienyl S-oxide units in oligo- and polythiophenes with the aim of greater solubility and smaller oxidation potentials and narrower energy gaps with electron-affinities similar to thienyl S,S-dioxides [103].

A number of synthetic approaches exist towards the preparation of oligothiophenes with thienyl S-oxide units. Oxidation of a pre-prepared oligo- or polythiophene is more difficult to achieve and leads to modest yield [110]. However, two strategies can be seen as promising. One is the transformation of polyarylene-alkynes 171 via oligozirconacyclopentadienes 172 to polythiophene S-oxides 173, where the zirconacyclopentadienes are reacted with SO$_2$ [41] (Scheme 44). The other takes advantage of the fact that certain thiophene S-oxides such as 2-bromo-3,4-diphenyl-thiophene S-oxide (175) are stable enough to be subjected to C–C cross-coupling reactions and subsequent halogenation reactions with N-bromosuccinimide (NBS), leading to sequences as shown in Scheme 45 [103]. Already, an FET has been synthesized with a thienyl-thienyl S-oxide polymer [103]. Also, larger π-conjugated ring systems with a thienyl S-oxide unit such as 179 have attracted some attention because of their electronic and optical properties (Figure 8) [111]. As a drawback, it may be noted that thienyl S-oxides in oligomers and polymers would not be stable towards UV radiation as opposed to thienyl S,S-dioxides [112, 113].

4.8. Thiophene S-oxides as metabolites in the enzymatic oxidation of thiophenes

Thiophenes have been known to have toxic effects [114, 115]. The understanding of the mechanism leading to the toxicity of thiophenes is of importance, as a number of drugs such as tienilic acid (180), ticlopidine (182), methapyrilene (183), thenalidine (184), tenoxicam (185), cephaloridine (186), suprofen (187), and clopidogrel (188) carry thienyl units, where some of the drugs have been taken off the market (Figure 9). Already in 1990, it was shown that hepatic cytochrome P450 mediated oxidation of the thienyl-containing tienilic acid (180) led to
Scheme 44. Preparation with oligomer 173 via zirconacyclopentadiene 172.

Scheme 45. Preparation of thienyl S-oxide containing oligomers 170 and 178 by Pd(0) Suzuki and Stille cross-coupling reactions.

Figure 8. Tetrakis(pentafluorophenyl)tetrathiaisophlorin dioxide (179).
electrophilic metabolites that bind to hepatic proteins [116, 117]. Oxidative metabolism of thiophenes in rats involves thiophene S-oxides [118–120]. It has been found [119, 121] that rats administered with thiophene (1) in corn oil showed dihydrothiophene S-oxide 191 in their urine as a major metabolite [119] (Scheme 46). This metabolite was assumed to stem from the addition of glutathione (189) to a reactive intermediate thiophene S-oxide 3 (Scheme 46). Previously, it had been shown that rat liver microsomal cytochrome P450 oxidizes 3-aroylthiophene 181, a regioisomer of tienilic acid (180), to aroylthiophene S-oxide 192, which in the presence of mercaptoethanol (193) transformed into dihydrothiophene S-oxide 194 [121] (Scheme 47). Also, 181 was oxidized by clofibrate induced rat liver microsomes to S-oxide 191.

Figure 9. Thiophene-containing pharmaceuticals.

Scheme 46. Cytochrome P450 mediated transformation of thiophene 1 to adduct 191.
which was then trapped as a Diels Alder product with maleimides, for example as 195 [120] (Scheme 48).

The oxidation of 2-(4-chlorobenzoyl)thiophene (196), a molecule in structure close to tienilic acid, by H₂O₂ in the presence of trifluoroacetic acid (TFA) and by m-CPBA, BF₃·Et₂O, both in CH₂Cl₂, gives sesquioxides 198–200 that clearly indicate that a thiophene S-oxide structure 197 is formed as an intermediate [122] (Scheme 49). Nevertheless, the oxidation of thiophene (1) itself with H₂O₂ in the presence of TFA produces apart from sesquioxides 6–8 thiophen-2-one (thiolactone 202). Thiophen-2-one (202) most likely is produced through thiophene-epoxide (201) [23] (Scheme 50). Thiophen-2-one (202) is in equilibrium with 2-hydroxythiophene (203). There is one report of a Pummerer-like rearrangement reaction that leads from the purified and isolated thiophene S-oxide intermediates formed in vivo do not lead to a 2-hydroxythiophene (203) [124] (Scheme 52), so that two separate mechanisms may exist for the cytochrome P450 2C9 (CYP2C9) mediated oxidation of thiophenes. In this regard, Dansette et al. [119] showed that CYP450s may catalyze both the reaction of thiophenes to thiophene S-oxide and to thiophene epoxides [125].
Scheme 50. Reaction of thiophene (1) leads via thiophene S-oxide (3) to sesquioxides 7–9 and in a separate pathway via thiophene epoxide 201 to thiolactone 202 and thus to 2-hydroxythiophene (203).


Scheme 52. Cytochrome P450 mediated oxidation of thiophene may lead to two pathways, one through thiophene S-oxide 3, the other through thiophene epoxide 201.

Figure 10. Metabolites of ticlopidine that derive from a ticlopidine S-oxide intermediate.
Also, the investigation of the metabolism of other thienyl-containing pharmaceuticals show that potentially both mechanisms, epoxidation of the thiophene-unit and oxidation of the thiophene-unit to thiophene S-oxide, operate concurrently. As to the thiophene S-oxide pathway, Shimizu et al. in their investigation of metabolites ticlopidine (182) in rats found both the glutathione conjugate of ticlopidine S-oxide (205) and the dimeric ticlopidine S-oxide cycloadduct (206) (Figure 10) [126, 127]. The structures could be identified by mass spectrometry, and $^1$H and $^{13}$C NMR spectrometry. Medower et al. have noted that cytochrome P450 mediated oxidation of cancer drug OSI-930 (207) leads to GSH conjugate (209), derived from OSI-930 S-oxide (208), as recognized by mass spectrometry (Scheme 53) [128].

Lastly, both possible metabolic pathways of thiophenes, via thiophene S-oxides and via thiophene epoxides, have been examined as to their energy profiles using density functional theory [129]. It was found that the formation of the thiophene epoxide (−23.24 kcal/mol) is more exothermic than the formation of the thiophene S-oxide (−8.08 kcal/mol) [129]. Also, the formation of thiophene epoxide seems kinetically favored [129]. Both possible metabolites, thiophene S-oxide and thiophene epoxide, are highly electrophilic, leading to bond formation with nucleophiles such as with amino acids, leading to a mechanism-based inactivation (MBI) of cytochrome P450.

5. Conclusion

Since the first unverified isolation of a thiophene S-oxide a little more than 50 years ago, research on thiophene S-oxides has reached a milestone. Due to mainly two synthetic routes, the controlled oxidation of thiophenes in presence of a Lewis- or proton acid and the reaction of zirconacyclopentadienes with thionyl chloride, a number of thiophene S-oxides have now become readily accessible. Thiophene S-oxides are noted to be reactive dienes in Diels-Alder type cycloadditions, where they react equally well with electron-poor and electron-rich dienophiles. Thiophene S-oxides can be stabilized by sterically exacting substituents. Then, they exhibit sufficient stability to be submitted to Pd(0)-catalyzed cross-coupling reactions without deoxygenation.
This leads to the possibility of preparing aryl-oligomers with thiophene-S-oxide subunits. By comparing oligothiophenes and oligomers with thiophene S,S-dioxide subunits, oligomers with thiophene S-oxide subunits exhibit smaller oxidation potentials and narrower energy gaps with electron-affinities greater than oligothiophenes and similar to thiophene S,S-dioxides. Nevertheless, thiophene S-oxides are not stable photochemically, but deoxygenate to the corresponding thiophenes or transform to furans by photochemical rearrangement.

Thiophene S-oxides have been found to act as intermediates in the cytochrome P450 mediated, oxidative metabolism of thiophene-containing compounds, including a number of important thiophene containing pharmaceuticals. Addition of nucleophiles \textit{in vivo} leads to mechanism based inhibition (MBI) and to toxic side effects of the thiophenes, including nephrotoxicity.

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