Chapter 4

Thiophene *S*-Oxides

Thies Thiemann

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79080

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 SO_2 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].

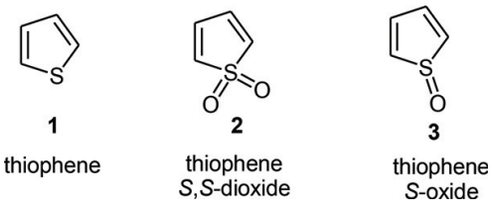
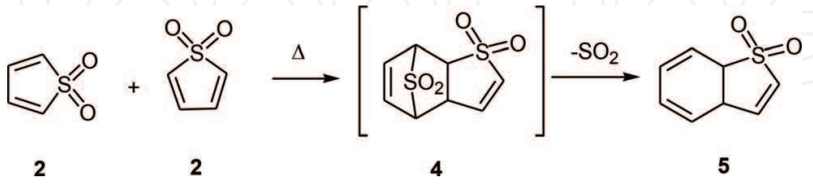


Figure 1. Structure of thiophene (**1**) and oxygenated thiophenes **2** and **3**.



Scheme 1. Dimerisation of unsubstituted thiophene *S*,*S*-dioxide (**2**).

Much of the early work on the oxidation of thiophenes to thiophene *S*,*S*-dioxides involved hydrogen peroxide (H_2O_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**)

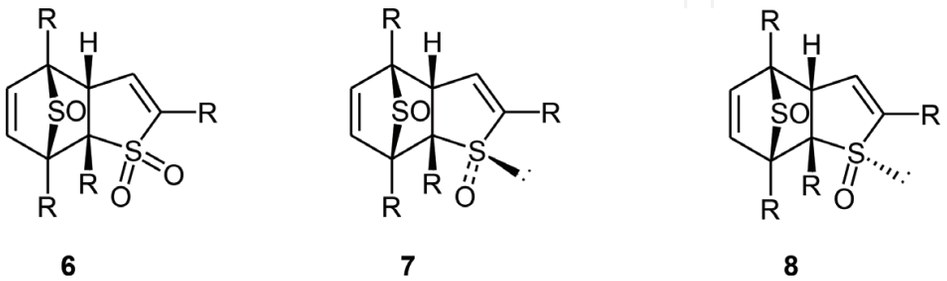
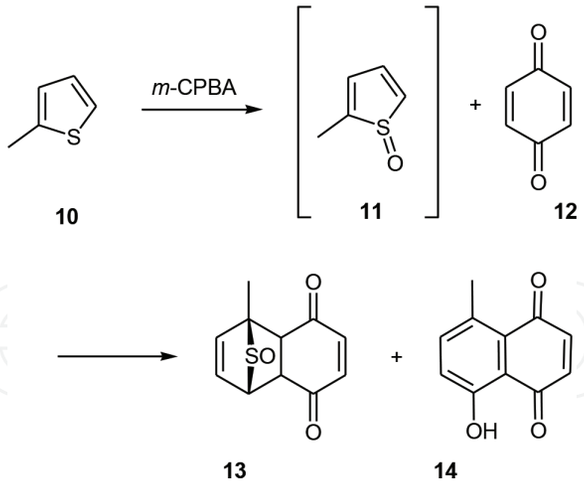
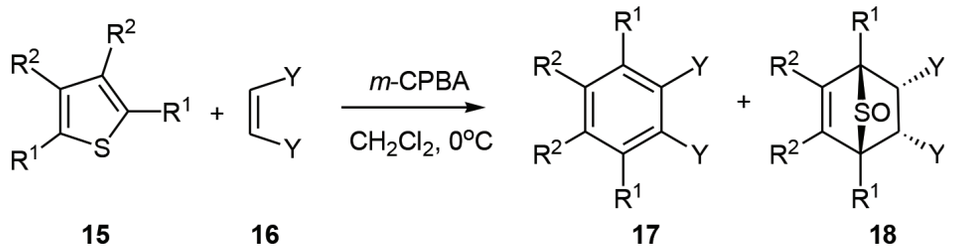


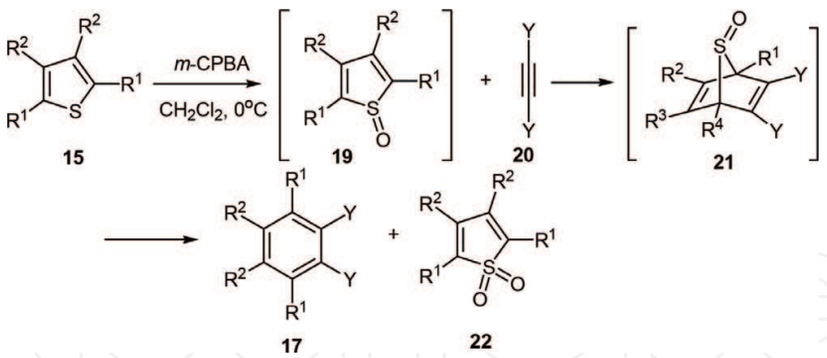
Figure 2. Sesquioxides obtained by dimerization of elusive thiophene *S*-oxide and by cycloaddition of thiophene *S*-oxide to thiophene *S*,*S*-dioxide.



Scheme 2. Thiophene *S*-oxide (**11**), created *in situ*, reacts in Diels-Alder type fashion with *p*-benzoquinone (**12**).

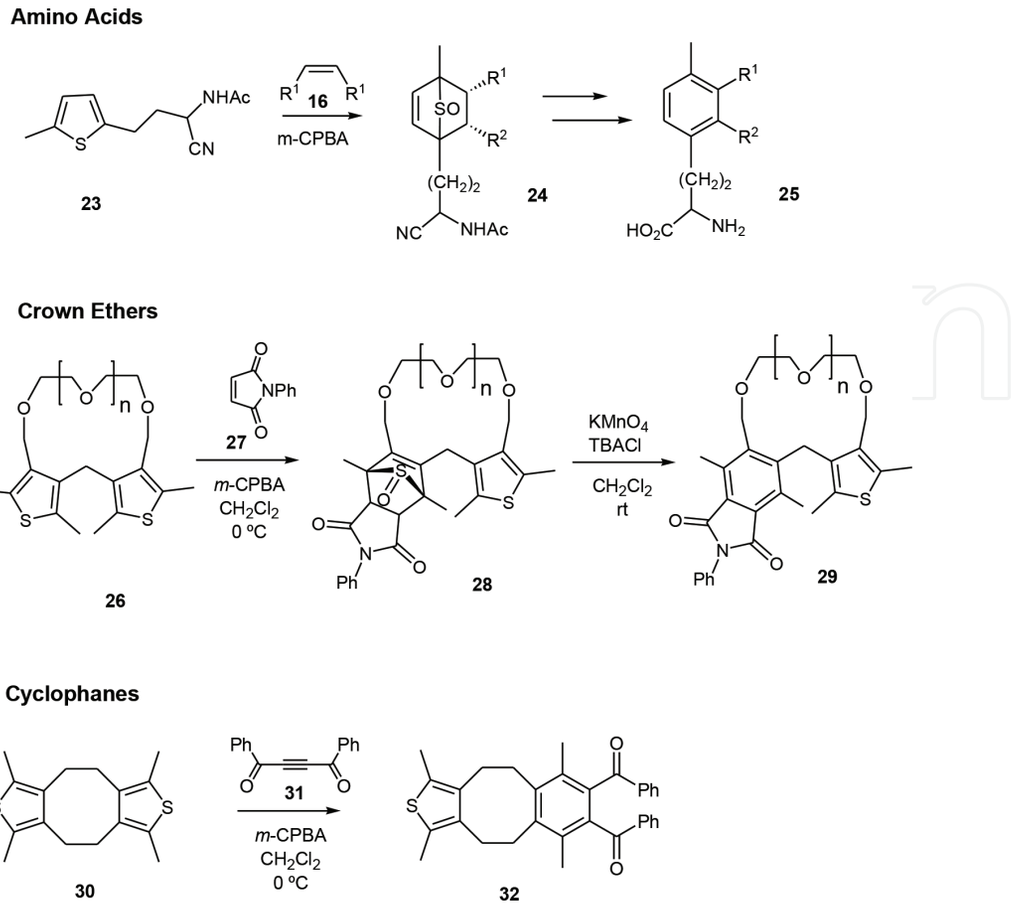


Scheme 3. Cycloaddition of thiophene *S*-oxides, prepared *in situ*, with alkenes.



Scheme 4. Cycloaddition of thiophene *S*-oxides (**19**), prepared *in situ*, with alkynes.

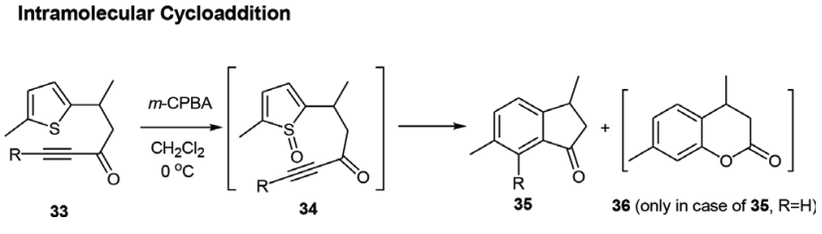
have used the cycloaddition of thiophene *S*-oxides **19**, created *in-situ*, as a key step. The formation of the 7-thiabicyclo[2.2.1]heptene *S*-oxides (such as **13**, **18**) proceeds with stereocontrol. The cycloadditions yield predominantly *endo*-cycloadducts, with the oxygen of the sulfoxy bridge directed towards the incoming dienophile, exhibiting the *syn*-π-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



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**.

substituted cyclopentadienes [20]. Thiophene *S*,*S*-dioxides **2** 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 π-electron density. Thus, thiophene *S*,*S*-dioxides **2** 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].

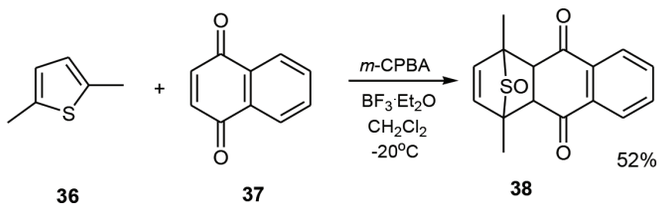
Oxidation of the thienyl-unit in **33** leads to an intramolecular cycloaddition, where indanones **34** are obtained (**Scheme 6**) [24].



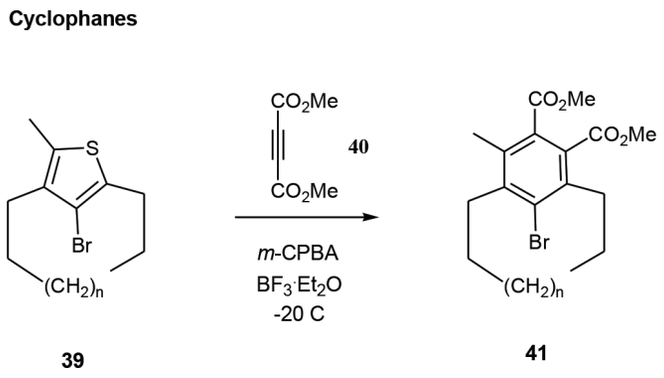
Scheme 6. Intramolecular cycloaddition of *in situ* prepared thiophene *S*-oxide **34**.

2. Cycloaddition reactions of thiophene *S*-oxide prepared in situ in the presence of Lewis acids: thiophene *S*-oxides are isolated

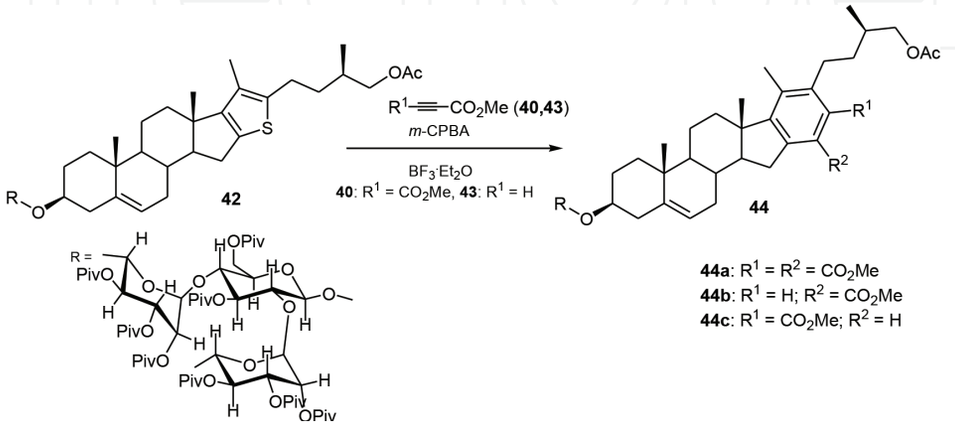
Yields of cycloadducts have been found to be much higher, when oxidative cycloaddition reactions of thiophenes are carried out with *meta*-chloroperoxybenzoic acid (*m*-CPBA) or with H_2O_2 at lower temperatures such as at −20°C in the presence of a Lewis acid catalyst such as $BF_3{\cdot}Et_2O$ [11, 12, 25, 26] (**Scheme 7**) or of trifluoroacetic acid (CF_3CO_2H) [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.



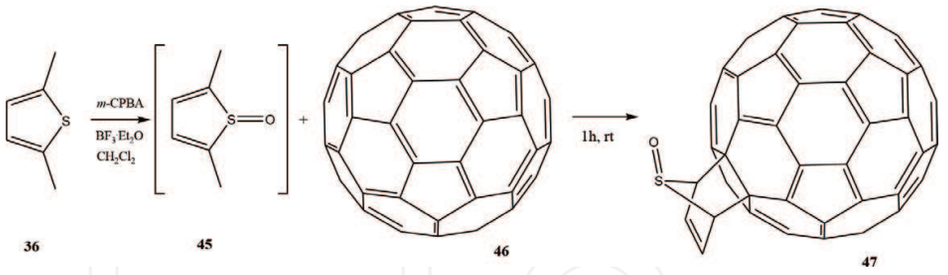
Scheme 7. Oxidative cycloaddition of thiophene **36** to naphthoquinone (**37**) in the presence of $BF_3{\cdot}Et_2O$.



Scheme 8. Preparation of multifunctionalized cyclophane **41** by oxidative cycloaddition of thiophenophane **39** in the presence of $BF_3{\cdot}Et_2O$.



Scheme 9. Preparation of aethiosides A–C (**44a–c**) by oxidative cycloaddition of thienosteroidal sapogenin **42**.



Scheme 10. Cycloaddition of 2,5-dimethylthiophene *S*-oxide (**45**), prepared *in situ*, to C60 (**46**).

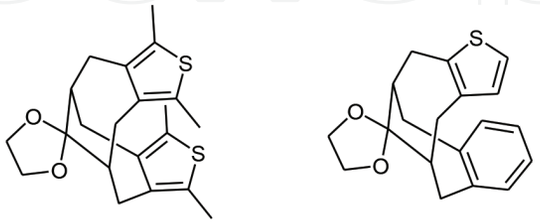


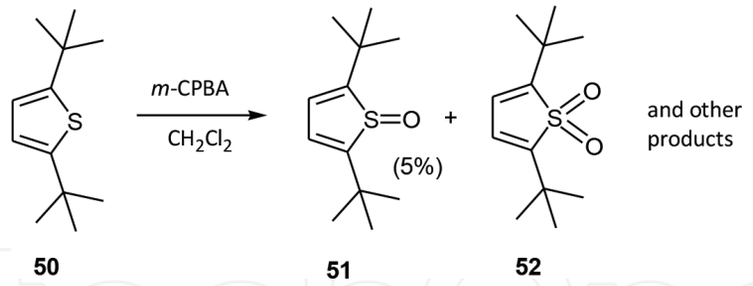
Figure 3. Orthothiophenophanes **48** and **49** do not allow for enough reaction volume and do not undergo oxidative cycloadditions with either alkynes or alkenes under the conditions (*m*-CPBA, $BF_3{\cdot}Et_2O$, CH_2Cl_2) [31].

Under the conditions *m*-CPBA/$BF_3{\cdot}Et_2O$, 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 $BF_3{\cdot}Et_2O$ [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 $BF_3{\cdot}Et_2O$ catalyzed oxidative cycloaddition of the thieno-containing steroidal saponin **42** (**Scheme 9**) [26]. Furthermore, Zeng and Eguchi [29] were able to functionalize C60 (**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 $BF_3{\cdot}Et_2O$ [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

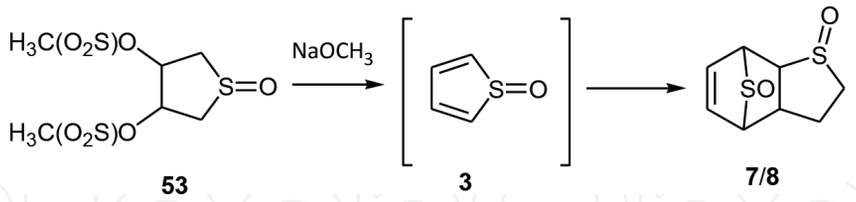


Scheme 11. Isolation of 2,5-bis-*tert*-butylthiophene *S*-oxide **51** by simple thiophene oxidation with *meta*-chloroperoxybenzoic acid (*m*-CPBA) [32].

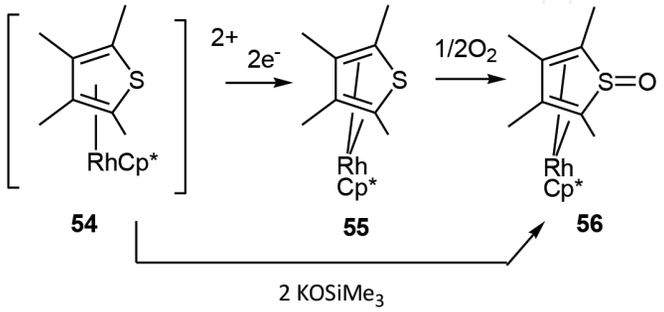
prepared by double elimination from 3,4-dimesyloxy-2,3,4,5-tetrahydrothiophene *S*-oxide (**53**) and studied in solution. While subsequently the latter part of the assertion was thrown into doubt, the isolation of sesquioxides **7/8** from the reaction indicated at least the presence of thiophene *S*-oxide under these conditions [33] (**Scheme 12**).

Interestingly, a toluene solution of η5-ethyltetramethylcyclopentadienyl-η^4-tetramethylthienyl rhodium complex [Cp*Rh(η^4-TMT)] (**54**) can be oxidized with dry oxygen to [Cp*Rh(TMTO)] (**56**), which features a η^4-coordinated thiophene *S*-oxide ligand. Complex **56** was isolated and an X-ray crystal structure was carried out. Alternatively, [Cp*Rh(η^4-TMT)] (**54**) can be oxidized electrochemically to [Cp*Rh(η^4-TMT)]$^{2+}$ (**55**), which can also be obtained by protonation of [Cp*Rh(TMTO)] (**56**). Reaction of [Cp*Rh(η^4-TMT)]$^{2+}$ (**55**) with potassium methylsilanolate ($KOSiMe_3$) leads back to [Cp*Rh(TMTO)] (**56**) [34] (**Scheme 13**).

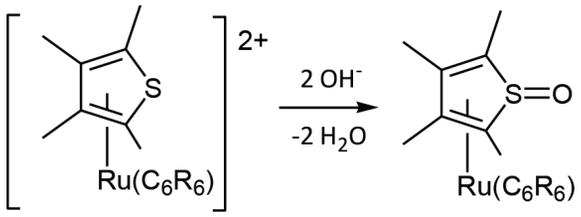
The reaction of the cationic transitory ruthenium complex $[Ru(C_6R_6)(C_4R_4S)]^+$ (**57**) with hydroxyl anion (OH^-) gives $Ru(C_6H_6)(C_4R_4SO)$ (**58**) [35] (**Scheme 14**). Here, in contrast to the complex [Cp*Rh(TMTO)] (**56**), the thiophene *S*-oxide ligand in $Ru(C_6H_6)(C_4R_4SO)$ (**58**) is not



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



Scheme 13. Oxidation of [Cp*Rh(η^4-TMT)] (**54**) to [Cp*Rh(TMTO)] (**56**) [34].

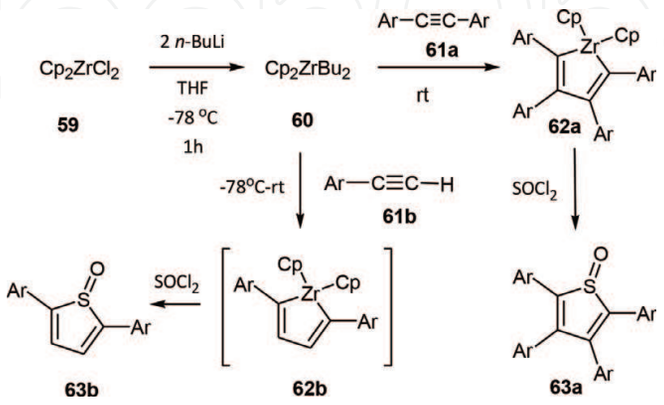


Scheme 14. Base hydrolysis of $[Ru(C_6R_6)(C_4R_4S)]^+$ (**57**) [34].

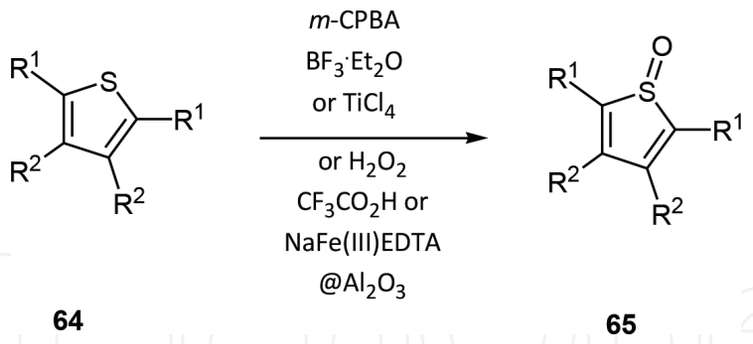
stable, but opens to an acetylpropenethiolate. Stable osmium thiophene *S*-oxide complexes of type (cymene)Os(C_4Me_4S=O) have also been prepared [36]. In neither of the cases, was it tried to decomplex the thiophene *S*-oxide ligand.

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 ($SOCl_2$), developed by Fagan et al. [37, 38] and by Meier-Brocks and Weiss [39]. Typically, tetraarylzirconacyclopentadienes **62a** can be synthesized easily by reacting $CpZrCl_2$ (**59**), *n*-BuLi and diarylethyne (**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 ($TiCl_4$) [43] or boron trifluoride etherate ($BF_3{\cdot}Et_2O$) [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 H_2O_2 in presence of NaFe(III) ethylenediaminetetraacetate/Al_2O_3 has been reported [48, 49] (**Scheme 16**) as has been the use of the reaction system $[(C_{18}H_{37})_2(CH_3)_2N]_3[SiO_4H(WO_5)_3]$ [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



Scheme 15. Synthesis of tetraarylthiophene *S*-oxides **63a/b** by reaction of tetraarylzirconacyclopentadienes **62a/b** with $SOCl_2$.



Scheme 16. Preparation of thiophene *S*-oxides **65** by oxidation of thiophenes **64** in the presence of a Lewis acid or a protonic acid.

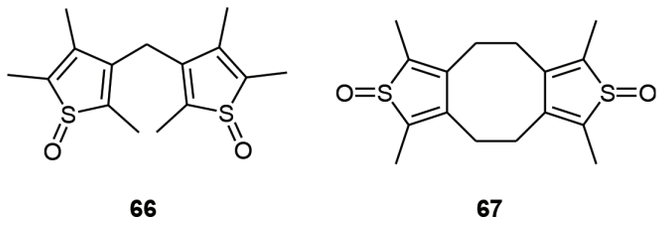


Figure 4. Known bisthienyl-*S*-oxides **66** and **67**.

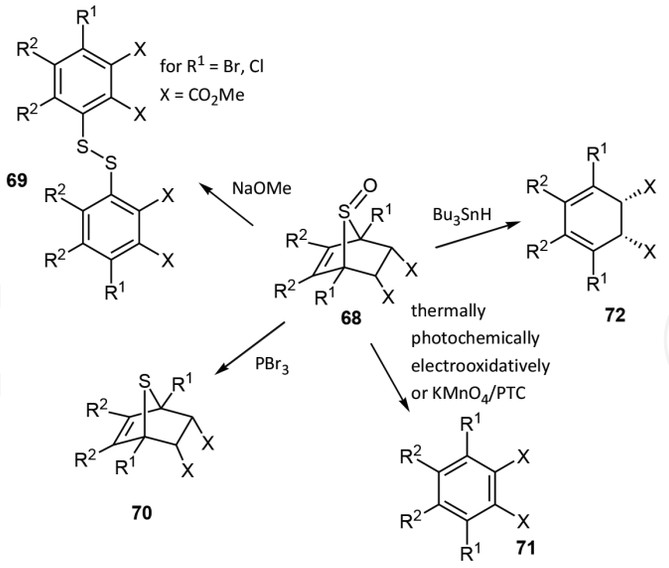
peracid, but also coordinates to the oxygen in the formed thiophene *S*-oxide, thus reducing the electron-density on the sulfur of the thiophene *S*-oxide, making it less prone to undergo a second oxidation to the thiophene *S*,*S*-dioxide.

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, $BF_3{\cdot}Et_2O$ CH_2Cl_2, −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

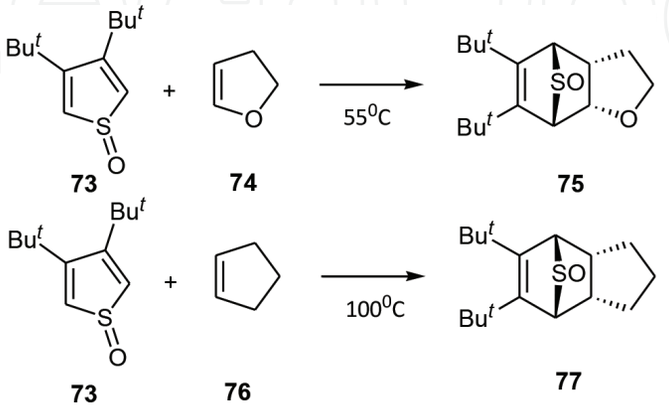
4.1. [4 + 2]-cycloaddition reactions

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-thiabi-cyclo[2.2.1]heptene *S*-oxides **68**. These in turn could be converted to substituted arenes **71** by either pyrolysis [15], photolysis [51], or PTC-catalyzed oxidative treatment with $KMnO_4$ [15] or electrochemical oxidation [18] or 7-thiabicyclo-[2.2.1]heptenes (**70**) by reaction of **68** with PBr_3 [52]. Reaction of **68** with tributyl-tin hydride gives cyclic dienes such as **72** [—X—X— = —(CO)N—Ph(CO)—]. Base catalyzed cleavage of the sulfoxy bridge of 1,4-dihalo-7-thiabicyclo[2.2.1]heptane *S*-oxides **68** (R^1 = Cl or Br) leads to the generation of diaryl disulfides such as **69** (**Scheme 17**).



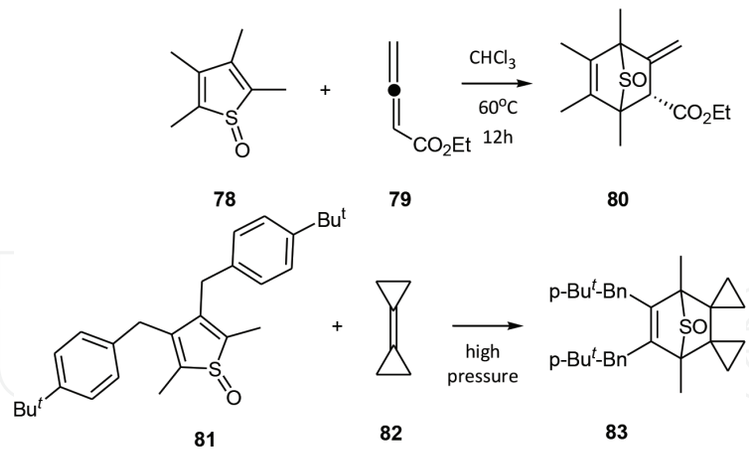
Scheme 17. 7-Thiabicyclo[2.2.1]heptene S-oxides **68** as versatile precursors to arenes.

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 benzyne (**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].

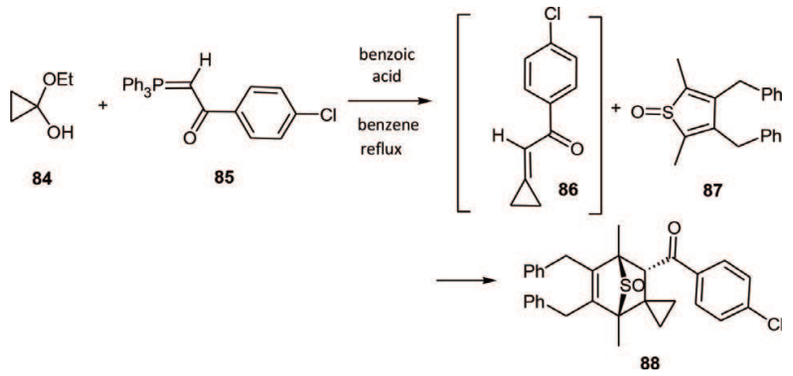


Scheme 18. 3,4-Bis-*tert*-butylthiophene *S*-oxide (**73**) cycloadding to electron-rich and electron-neutral alkenes.

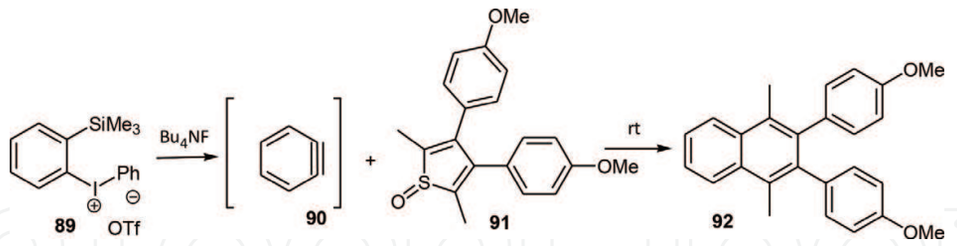
http://dx.doi.org/10.5772/intechopen.79080



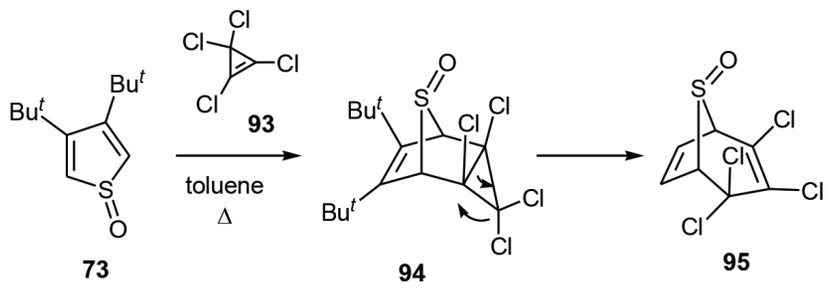
Scheme 19. Thiophene *S*-oxides cycloadd to allenes and to bicyclopropylidene (**82**) under high pressure.



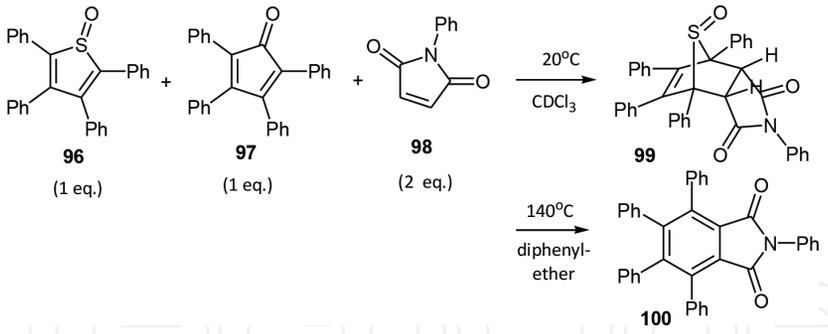
Scheme 20. One pot Wittig reaction—Diels Alder reaction with thiophene *S*-oxide **87** as diene.



Scheme 21. Cycloaddition of thiophene *S*-oxide **91** with benzyne (**90**), prepared *in situ*.



Scheme 22. Cycloaddition of thiophene *S*-oxide (**73**) with tetrachlorocyclopropene (**93**).

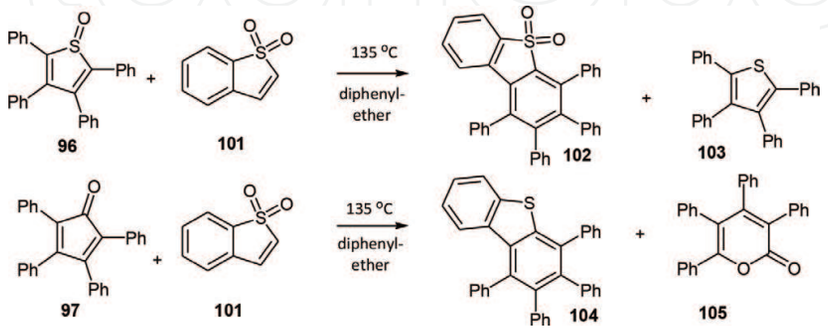


Scheme 23. Thiophene *S*-oxide **96** competes efficiently with tetracyclone **97** for *N*-phenylmaleimide (**98**).

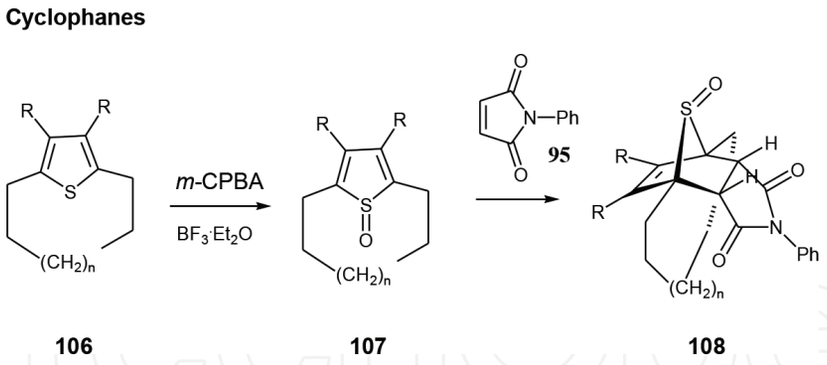
Thiophene *S*-oxides are good precursors for the preparation of heavily substituted arenes such as **100** [58] (**Scheme 23**). Often, tetraarylcyclopentadienones **97** are used to synthesize oligoaryl benzenes by cycloaddition reaction. However, tetraphenylthiophene *S*-oxide (**96**) is the more 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 $KMnO_4$/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 dibenzothiophene *S*,*S*-dioxide **102**, but with **97** gives dibenzothiophene **104** [59] (**Scheme 24**). The reason for this difference lies in the tendency of tetracyclines such as **94** to be oxidized to pyrones **102** 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].



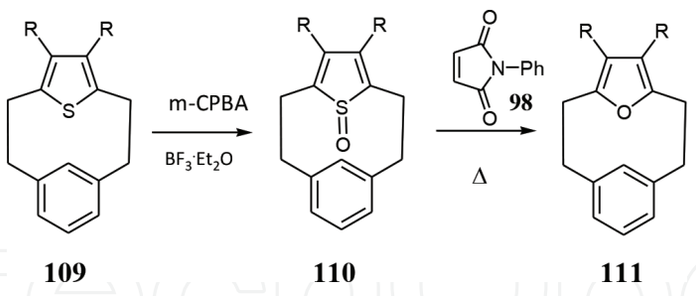
Scheme 24. Comparison of the cycloaddition of tetraphenylthiophene *S*-oxide **96** and tetracyclone **97** with benzo[*b*] thiophene *S*,*S*-dioxide (**101**). Tetracyclone **97** gives pyrone **105** as side product [59, 60].



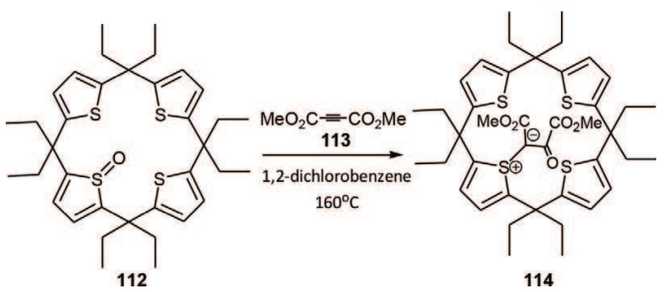
Scheme 25. Multifunctionalized cyclophanes **108** by cycloaddition of thiophenophane *S*-oxides **106**.

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].

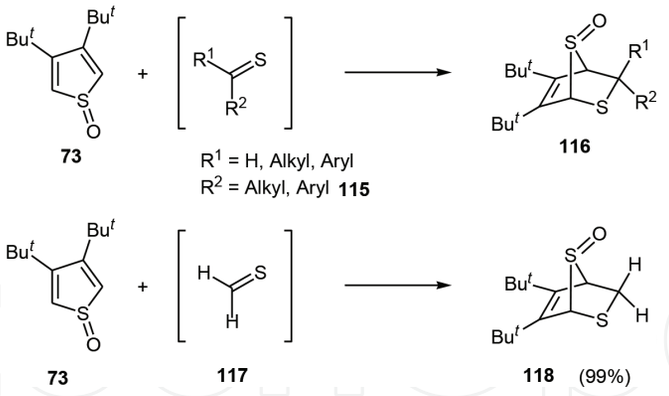
Not all thiophene *S*-oxides undergo cycloaddition reactions with alkynes or alkenes. In general, appreciable reaction volume is needed to allow for the forming sulfoxy-bridge in the primary cycloadducts and, in some cases, of the subsequent extrusion of SO. Also, when considerable strain is associated 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 26. [2.2]Metathiophenophane *S*-oxide **109** does not undergo cycloaddition but rearranges to [2.2]furanophane **111**.



Scheme 27. Thiacalixarene *S*-oxide **112** reacts with dimethyl acetylenedicarboxylate (**113**) to the thiacalixarene *S*,*C*-ylide **114**.

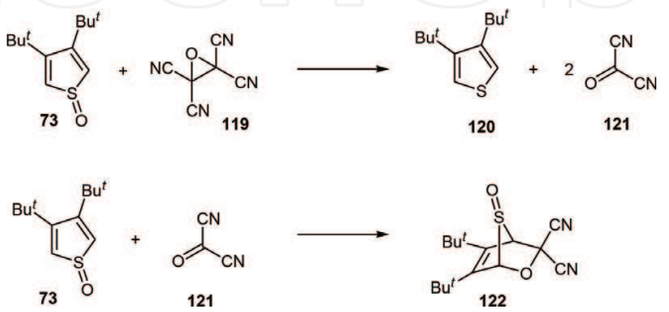


Scheme 28. Hetero-Diels-Alder reactions of 3,4-bis-*tert*-butylthiophene *S*-oxide (**73**).

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*-π-face while the lesser product from the *anti*-π-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 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 *syn*-π-facial in that the dienophile adds *syn* 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 *syn*- 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 sulfoxy-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 sulfoxy moiety [77] (**Figure 5**). This would be even more so, when the oxygen of the sulfoxy-unit is complexed by $BF_3{\cdot}Et_2O$.

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 $\sigma^*_{S=O}$ with the π-system (see also above/below) [23] (**Figure 6**).

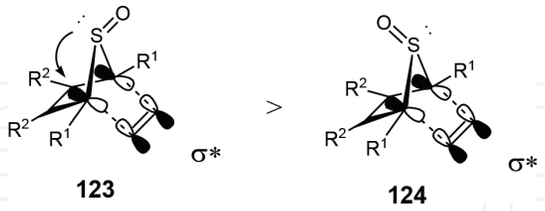


Figure 5. Transition state **123** preferred over transition state **124**.

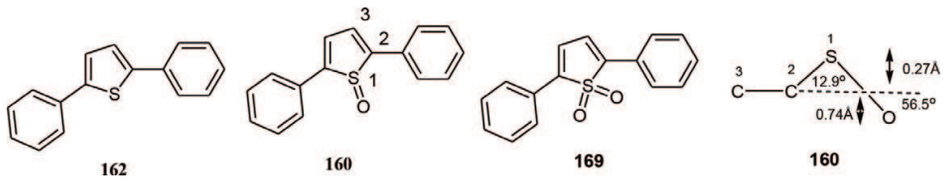
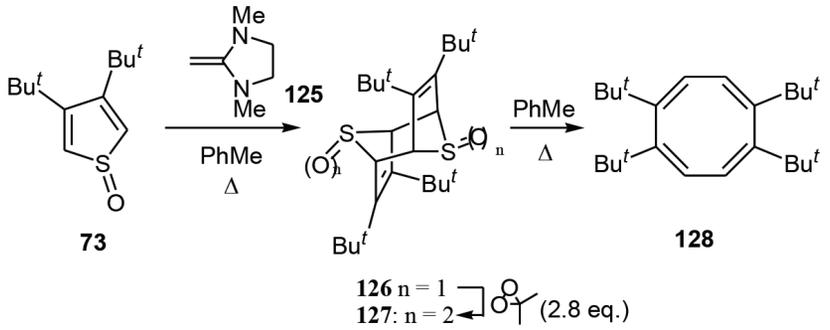


Figure 6. Structural feature of thiophene S-oxide **160.**

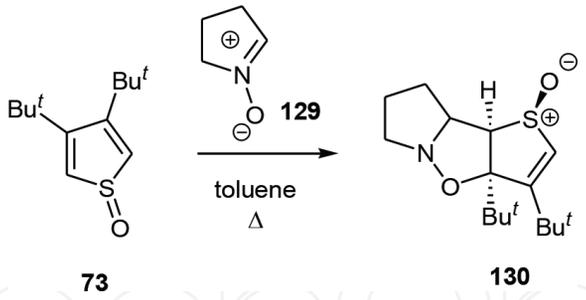
4.2. Further cycloaddition reactions

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 sulfoxy bridges to sulfone **127** with dimethyldioxirane as oxidant is followed by thermally driven extrusions of the SO_2 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].



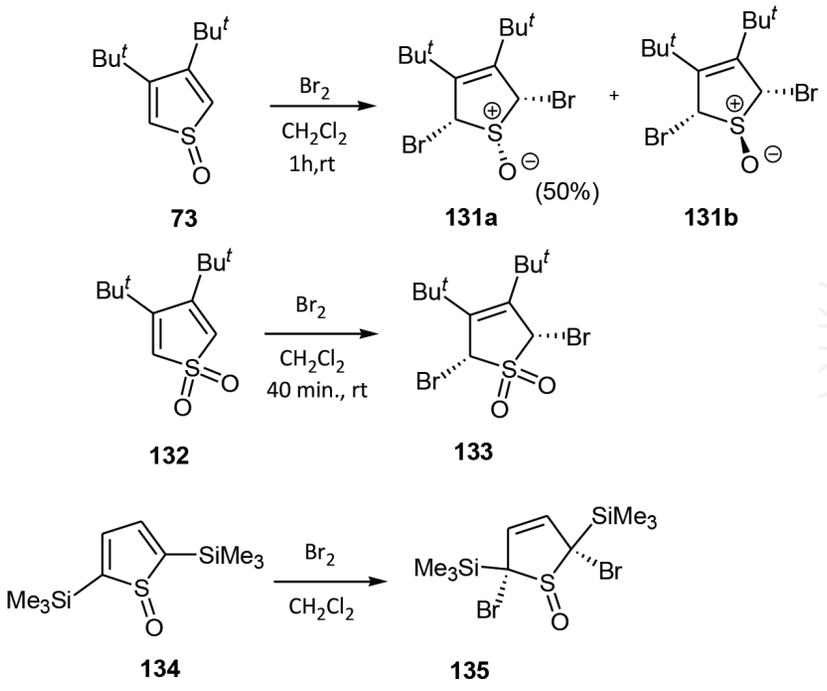
Scheme 30. [4π + 4π]-cycloaddition of thiophene *S*-oxide (**73**) to dimer **126**.



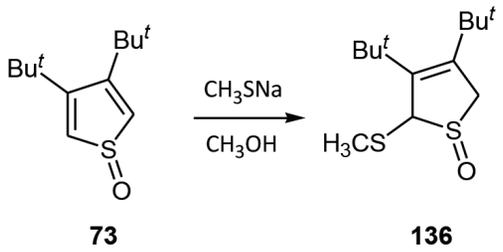
Scheme 31. [3 + 2]-cycloaddition of thiophene *S*-oxide (**73**) with pyrroline *N*-oxide (**129**) as 1,3-dipole.

4.3. Additions to thiophene *S*-oxides and other reactions

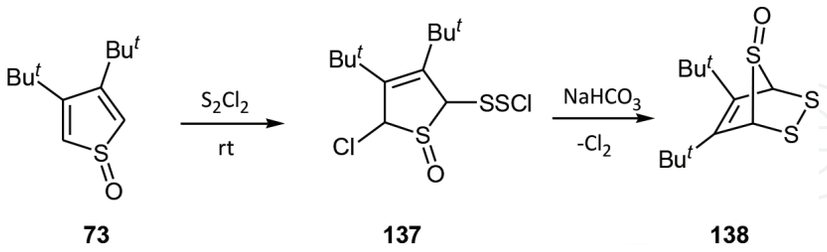
1,4-Additions are known for both 3,4-disubstituted and 2,5-disubstituted thiophene *S*-oxides [81–83]. Thus, bromine adds *cis* to both 3,4-bis-*tert*-butylthiophene *S*-oxide (**73**) [81] and 2,5-bis-trimethylsilylthiophene *S*-oxide (**134**) [82] to give the 2,5-dibromo-2,5-dihydrothiophene S-oxide 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 (S_2Cl_2) could be added to thiophene *S*-oxide **73**, leading to the rapid formation of adduct **137** (**Scheme 34**) [84]. **137**, however, is not stable



Scheme 32. Bromination of thiophene *S*-oxides **73** and **134** and thiophene *S*,*S*-dioxide **132**.



Scheme 33. Addition of methylthiolate to thiophene *S*-oxide (**73**).

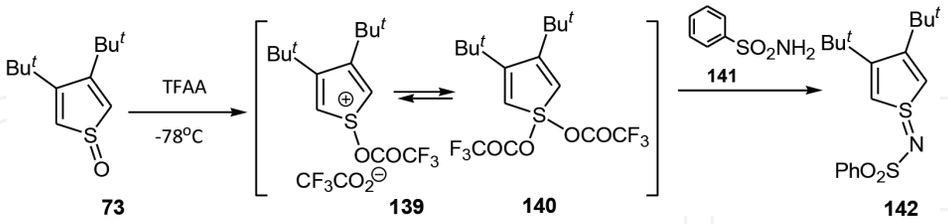


Scheme 34. Addition of disulfur dichloride (S_2Cl_2) to thiophene S-oxide **73**.

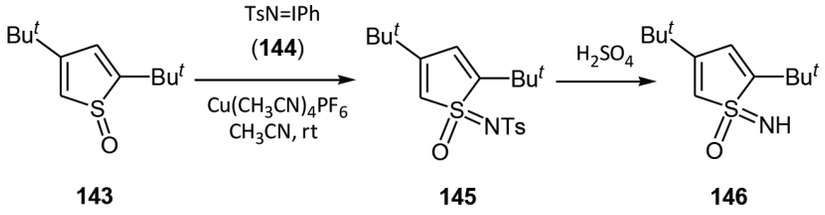
and transforms into **138**. **138** can be obtained with a 98% yield, when **137** is treated with aq. $NaHCO_3$ (**Scheme 34**) [84].

The sulfoxy 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 $Cu(CH_3CN)_4PF_6$ as catalyst. Further reaction of **145** with H_2SO_4 leads to *N*-unsubstituted sulfoximine **146** (**Scheme 36**) [86].



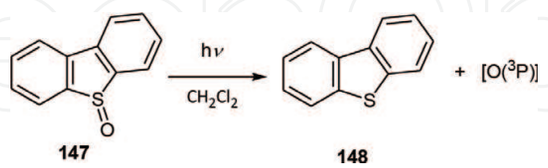
Scheme 35. Preparation of thiophene *S*-imide **142** from thiophene *S*-oxide **73**.



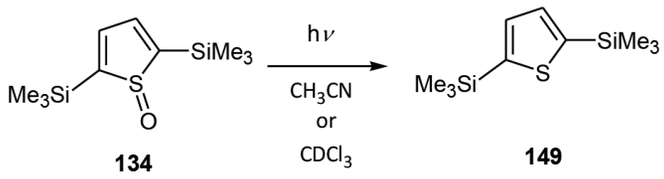
Scheme 36. Thiophene sulfoximines **145** and **146** from thiophene *S*-oxide **143**.

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 [$O(^3P)$] 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

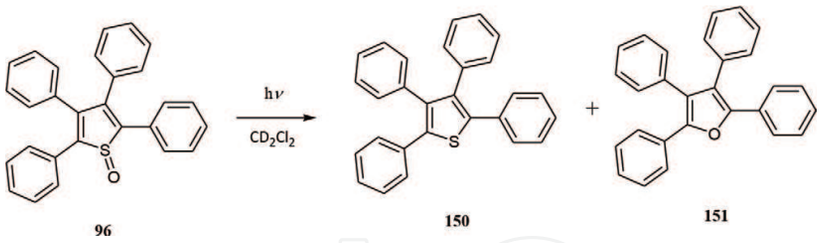


Scheme 37. Photodeoxygenation of dibenzothiophene *S*-oxide (**147**).



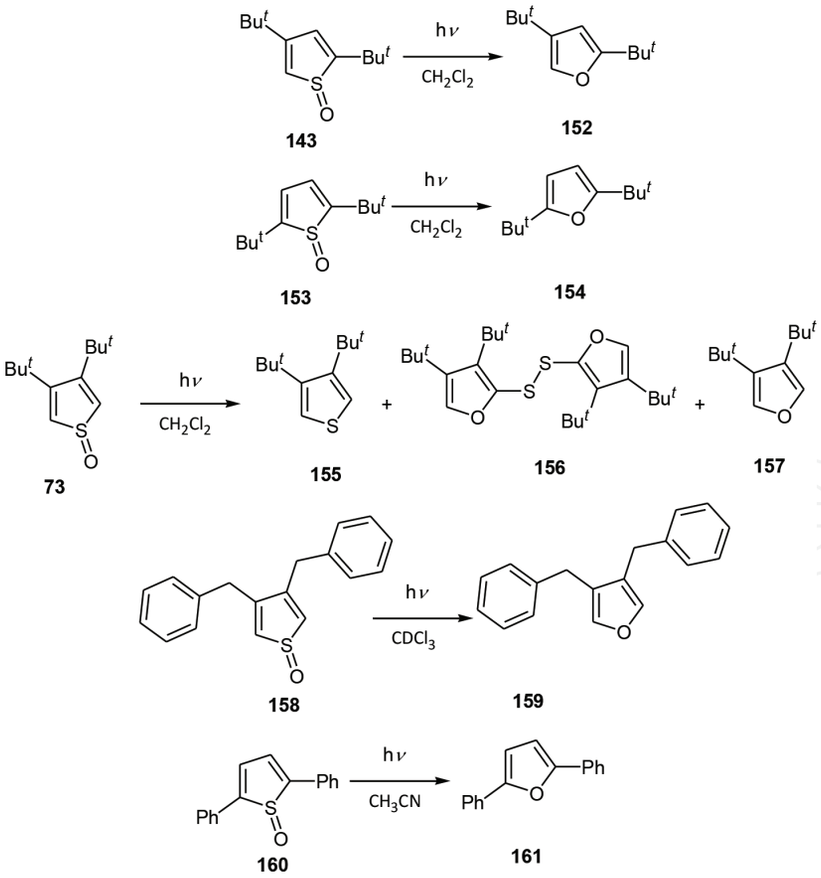
Scheme 38. Photolysis of 2,5-bis(trimethylsilyl)thiophene *S*-oxide (**134**).

http://dx.doi.org/10.5772/intechopen.79080



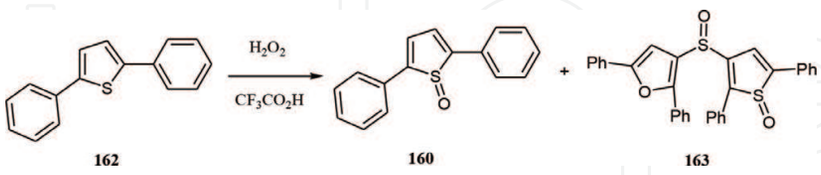
Scheme 39. Photolysis of tetraphenylthiophene *S*-oxide (**96**).

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 sulfoxy 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

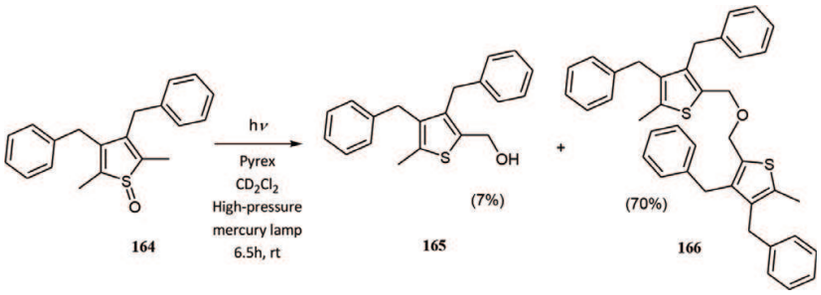


Scheme 40. Photolysis of 2,4-bis(*tert*-butyl)-, 2,5-bis(*tert*-butyl), 3,4-bis(*tert*-butyl), 3,4-dibenzyl-, and 2,5-diphenylthiophene *S*-oxide (**143**, **153**, **73**, **158**, and **160**).

Mansuy, Dansette et al. in their oxidation of 2,5-diphenylthiophene (**162**) with H_2O_2/CF_3CO_2H 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**).



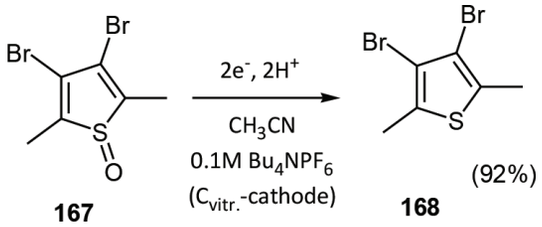
Scheme 41. Formation of furan **163** in the oxidation of 2,5-diphenylthiophene (**162**).



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_4NPF_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-liganded 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 sulfoxy 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 diphenylthiophene [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*-butylthiophene *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-2yl)-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].

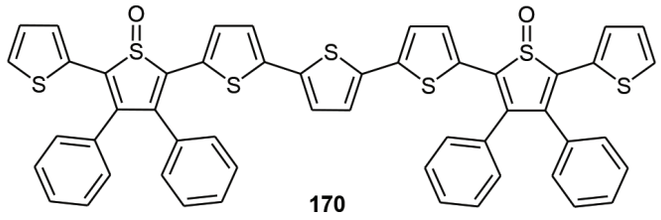


Figure 7. Oligothiophene *S*-oxide **170**.

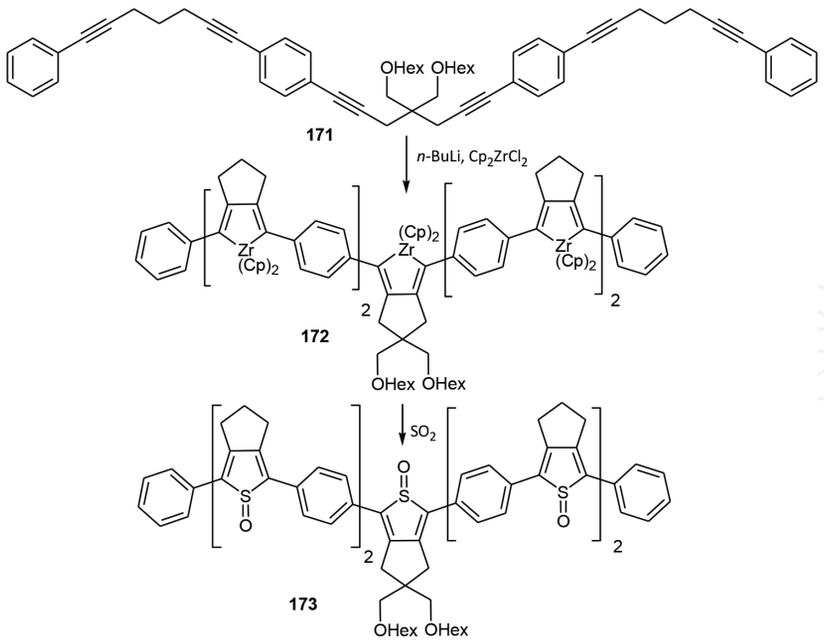
4.7. Oligomers and polymers incorporating thiophene *S*-oxide units

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].

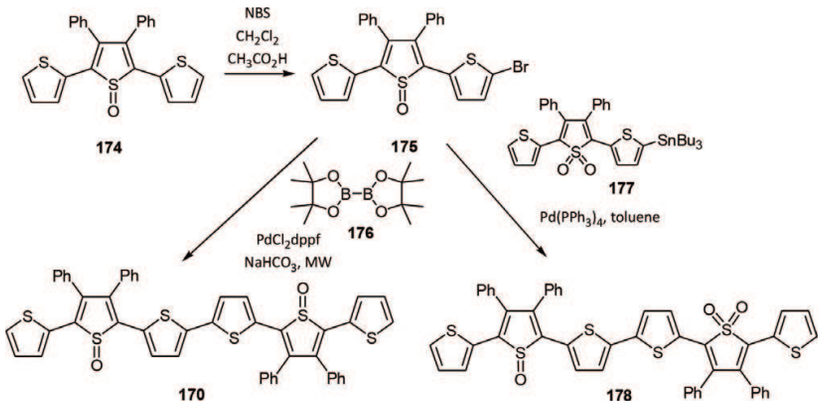
A number of synthetic approaches exist towards the preparation of oligothiophenes with thienyl *S*-oxide units. Oxidation of a pre-prepared oligo- or polythiophene is more difficult to achieve and leads to modest yield [110]. However, two strategies can be seen as promising. One is the transformation 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.

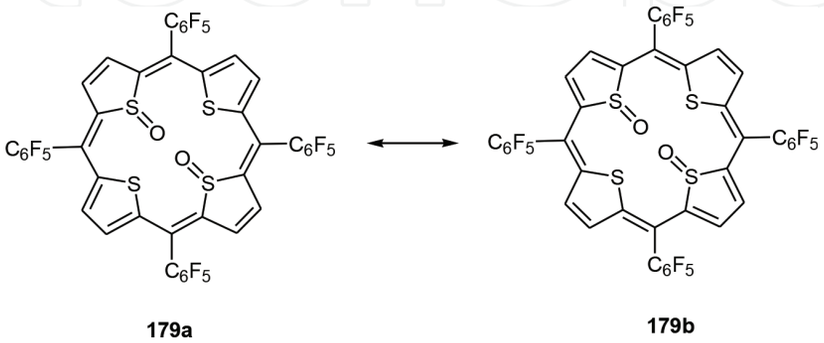


Figure 8. Tetrakis(pentafluorophenyl)tetrathiaisophlorin dioxide (**179**).

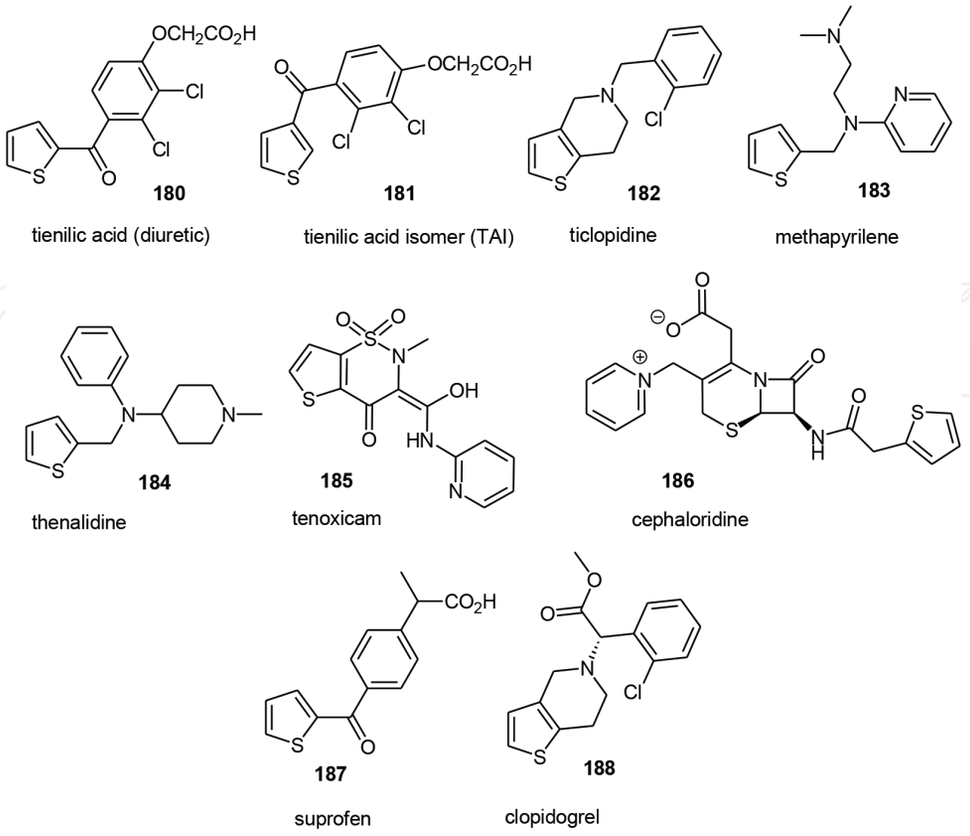
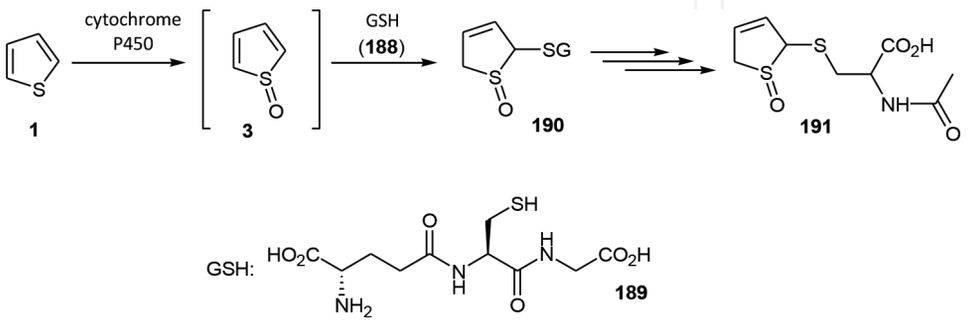
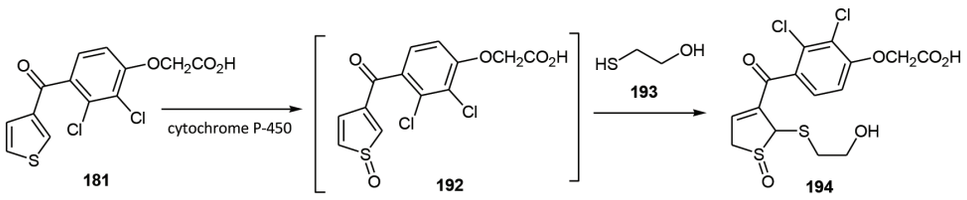


Figure 9. Thiophene-containing pharmaceuticals.

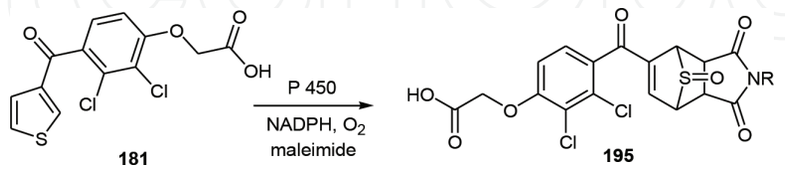
electrophilic metabolites that bind to hepatic proteins [116, 117]. Oxidative metabolism of thiophenes in rats involves thiophene *S*-oxides [118–120]. It has been found [119, 121] that rats administered with thiophene (**1**) in corn oil showed dihydrothiophene *S*-oxide **191** in their urine as a 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**,



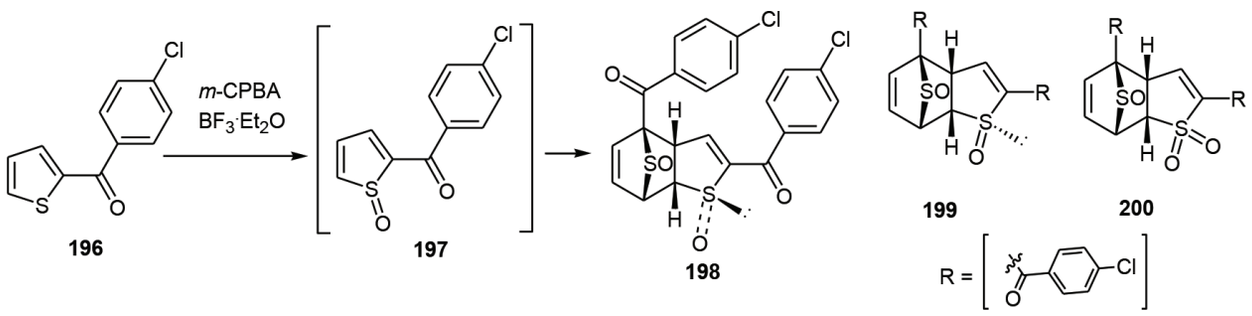
Scheme 46. Cytochrome P450 mediated transformation of thiophene **1** to adduct **191**.



Scheme 47. Transformation of tienilic acid regioisomer **181** to thiophene *S*-oxide and its addition of mercaptoethanol (**193**).



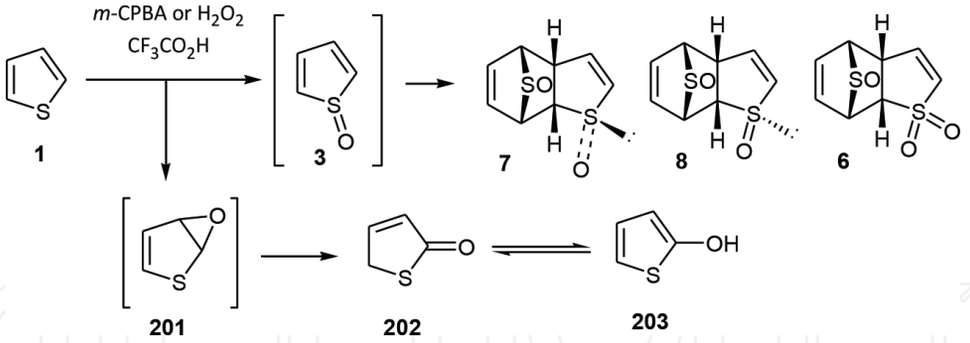
Scheme 48. Cycloaddition of the thiophene S-oxide derivative of **181** to maleimide.



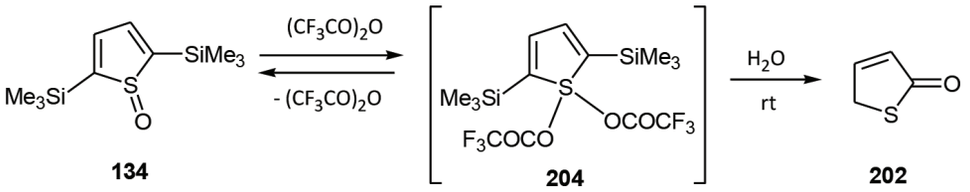
Scheme 49. Formation of sequioxides **198**–**200** by dimerization of thiophene *S*-oxide **197**.

which was then trapped as a Diels Alder product with maleimides, for example as **195** [120] (**Scheme 48**).

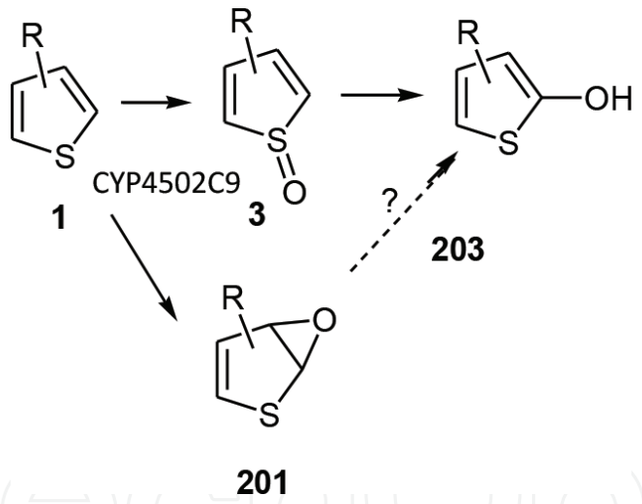
The oxidation of 2-(4-chlorobenzoyl)thiophene (**196**), a molecule in structure close to tienilic acid, by H_2O_2 in the presence of trifluoroacetic acid (TFA) and by *m*-CPBA, $BF_3{\cdot}Et_2O$, both in CH_2Cl_2, gives sesquioxides **198**–**200** that clearly indicate that a thiophene *S*-oxide structure **197** is formed as an intermediate [122] (**Scheme 49**). Nevertheless, the oxidation of thiophene (**1**) itself with H_2O_2 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 (**202**). There is one report of a Pummerer-like rearrangement reaction that leads from the purified and isolated thiophene *S*-oxide **134** to thiophen-2-one (thiolactone **202**) [123] (**Scheme 51**). Still, the current understanding is that the 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 51. Pummerer reaction of thiophene *S*-oxide **134** to thiolactone **202**.



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**.

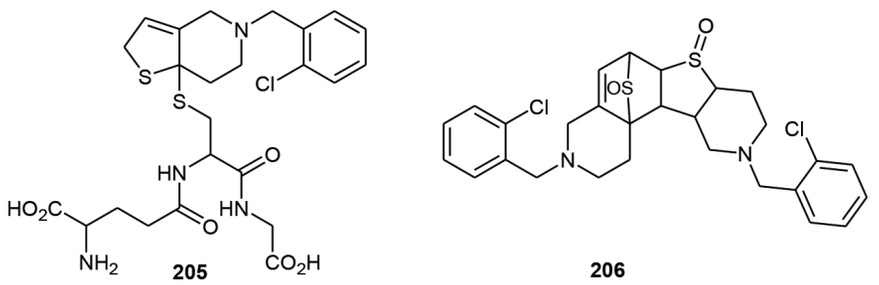
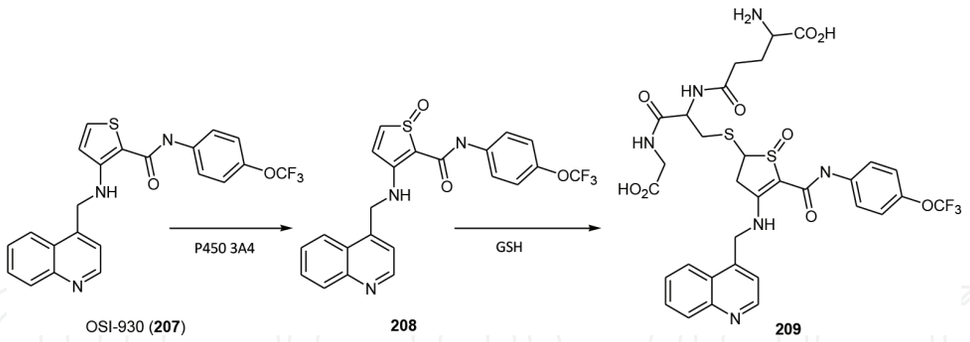


Figure 10. Metabolites of ticlopidine that derive from a ticlopidine *S*-oxide intermediate.

http://dx.doi.org/10.5772/intechopen.79080



Scheme 53. *In vivo* oxidation of anticancer drug OSI-930 (**207**) to OSI-930 sulfoxide (**208**) and addition of glutathione (GSH) to provide identified metabolite **209**.

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 P540 mediated, oxidative metabolism of thiophene-containing compounds, including a number of important thiophene containing pharmaceuticals. Addition of nucleophiles *in vivo* leads to mechanism based inhibition (MBI) and to toxic side effects of the thiophenes, including nephrotoxicity.

Author details

Thies Thiemann

Address all correspondence to: thies@uaeu.ac.ae

Department of Chemistry, College of Science, United Arab Emirates University, Al Ain, Abu Dhabi, United Arab Emirates

References

[1] Lanfry M. Sur les oxythiophènes. Comptes Rendus. 1911;**153**:73-76

[2] Lanfry M. ur les oxy-b-méthylthiophènes. Comptes Rendus. 1911;**153**:821-822

[3] Bailey WJ, Cummins EW. Cyclic dienes. III. Synthesis of thiophene 1-dioxide. Journal of the American Chemical Society. 1954;**76**:1932-1936

[4] Bailey WJ, Cummins EW. Cyclic dienes. IV. The dimerization of thiophene 1-dioxide. Journal of the American Chemical Society. 1954;**76**:1936-1940

[5] Nagasawa H, Sugihara Y, Ishii A, Nakayama J. Thiophene 1,1-dioxide: Synthesis, isolation, and properties. Bulletin of the Chemical Society of Japan. 1999;**72**:1919-1926

[6] Benders PH, Reinhoudt DN, Trompenaars WP. Thiophene and its derivatives: Part 1. In: Gronowitz S, editor. The Chemistry of Heterocyclic Compounds: A Series of Monographs. Vol. 44. New York: John Wiley & Sons; 1985. p. 713

[7] Benders PH, Reinhoudt DN, Trompenaars WP. Cycloaddition reactions of thiophenes, thiophene 1-oxides, and 1,1-dioxides. Chemistry of Heterocyclic Compounds. 2008;**44**:671-744

[8] Raasch MS. Thiophene-1,1-dioxides, sesquioxides, and 1-oxides. Chemistry of Heterocyclic Compounds. 2008;**44**:571-628

[9] Melles J, Backer HJ. Sesquioxydes obtenus par oxydation de thiophenes: (propriétés du groupe sulfonyle XXXVI). Recueil des Travaux Chimiques des Pays-Bas. 1953;**72**:491-496

[10] van Tilborg WJM. Improved method for the synthesis of dialkyl-substituted thiophene 1,1-dioxides. Synthetic Communications. 1976;**6**:583-589

[11] Li YQ, Thiemann T, Sawada T, Mataka S, Tashiro M. Lewis acid catalysis in the oxidative cycloaddition of thiophenes. The Journal of Organic Chemistry. 1997;**62**:7926-7936

[12] Li YQ, Matsuda M, Thiemann T, Sawada T, Mataka S, Tashiro M. Lewis acid catalyzed oxidative cycloaddition of thiophenes. Synlett. 1996:461-464

[13] Torssell K. Diels-Alder reactions of thiophene oxides generated *in situ*. Acta Chemica Scandinavica. 1976;**30**:353-357

[14] Naperstkow AM, Macaulay JB, Newlands MJ, Fallis AG. Pi-facial diastereoselectivity in Diels-Alder reactions of 2,5-dimethylthiophene oxide. Tetrahedron Letters. 1989;**30**:5077-5080

[15] Li YQ, Thiemann T, Sawada T, Tashiro M. Novel crown ethers by oxidative cycloaddition of thiopheno-crown ethers. Journal of the Chemical Society, Perkin Transactions. 1994;**1**: 2323-2329

[16] Thiemann T, Dongol KG, Thiemann T. A new route to non-natural aryl-containing amino acids and their precursors from thiophenes. Journal of Chemical Research. 2003:527-528; Journal of Chemical Research (S). 2003;**27**:901-942

[17] Thiemann T, Li YQ, Thiemann C, Sawada T, Ohira D, Tashiro M, Mataka S. Oxidative cycloaddition of structures with multiple core thiophenes. Heterocycles. 2000;**52**:1215-1230

[18] Thiemann T, Sa e Melo ML, Campos Neves AS, Li YQ, Mataka S, Tashiro M, Geissler U, Walton DJ. Preparation and electrooxidative SO-extrusion of halogenated 7-thiabicyclo [2.2.1]heptane 7-oxides. Journal of chemical research. Synopses. 1998;**22**:346-346

[19] Arima K, Ohira D, Mataka S, Thiemann T. Cycloaddition reactions of benzo[*b*]thiophene *S*-oxides. IOSR Journal of Applied Chemistry (IOSR-JAC). 2018;**11**(3):19-27

[20] For the parent compound, thiophene *S*,*S*-dioxide, B. Jursic calculated the HOMO energy to be −11.03 eV (by AM1 semiempirical method): B. Jursic, suitability of furan, pyrrole and thiophene s dienes for Diels-Alder reactions viewed through their stability and reaction barriers for reactions with acetylene, ethylene and cyclopropene. An AM1 semi-empirical and B3LYP hybrid density functional theory study. Journal of Molecular Structure: Theochem. 1998;**454**:105-116

[21] A notable exception is the reactivity tetrahalothiophene S,S-dioxides, which already undergoes cycloadditions at room temperature: Raasch MS. Annulations with tetrachlorothiophene 1,1-dioxides. The Journal of Organic Chemistry. 1980;**45**:856-867

[22] Certain other electron-acceptor substituted thiophene *S*,*S*-dioxides such as sulfonyl-, alkoxycarbonyl-, or cyano-thiophene *S*,*S*-dioxides react as dienophiles at room temperature:

Moiseev A, Tyurin DD, Balenkova ES, Nenajdenko VG. Reactions of acceptor substituted thiophene-1,1-dioxides with cyclopentadiene: Control of selectivity by substitution. Tetrahedron. 2006;**62**:4139-4145

[23] Levandowski BJ, Herath D, Gallup NM, Houk KN. Origin of π-selectivity in thiophene 1-oxide cycloadditions. The Journal of Organic Chemistry. 2018;**83**:2611-2616

[24] Thiemann T, Li YQ, Mataka S, Tashiro M. Intramolecular oxidative cycloaddition of thiophenes. Journal of Chemical Research. 1995;**19**:384-384; (M), 1995;**19**:2364-2379

[25] Li YQ, Thiemann T, Mimura K, Sawada T, Mataka S, Tashiro M. Oxidative cycloaddition of thiophenophanes—[n](2.5)parathiophenophane (n=8,10-12,14), [8](2,4)metathiophenophane and [2.2](2,5)parametathiophenophane. European Journal of Organic Chemistry. 1998:1841-1850

[26] Wang Z, Li M, Liu X, Yu B. Synthesis of steroidal saponins bearing an aromatic E ring. Tetrahedron Letters. 2007;**48**:7323-7326

[27] Treiber A, Dansette PM, Mansuy D. Mechanism of the aromatic hydroxylation of thiophene by acid-catalyzed peracid oxidation. The Journal of Organic Chemistry. 2002;**67**: 7261-7266

[28] Wang P, Min J, Nwachukwu JC, Cavett V, Carlson KE, Guo P, Zhu M, Zhang Y, Dong C, Katzenellenbogen JA, Nettles KW, Zhou H-B. Identification and structure—Activity relationships of a novel series of estrogen receptor ligands based on 7-thiabicyclo[2.2.1] hept-2-ene 7-oxde. Journal of Medicinal Chemistry. 2012;**55**:2324-2341

[29] Zeng HP, Eguchi S. Selective formation of mono-and tetra-cycloadducts by the Diels-Alder reaction of [60]fullerene with 2,5-dimethylthiophene S-oxides. Synlett. 1997:175-176

[30] Eguchi S, Ohno M, Kojima S, Shirakawa Y, Zeng HP. [4+2]-cycloaddition of C60 with electron-deficient dienes and application of the adducts to further functionalization in fullerenes, recent advances in the chemistry and physics of fullerenes and related materials (K. M. Kadish, R. S. Ruoff, eds.). The Electrochemical Society Proceedings. 1997; **97**(14):338-346

[31] Thiemann T, Ohira D, Li YQ, Sawada T, Taniguchi M, Tashiro M, Mataka S. Thieno[3.3] orthocyclophanes. Preparation and structures. New Journal of Chemistry. 1999;**23**:675-678

[32] Mock WL. Stable thiophene sulfoxides. Journal of the American Chemical Society. 1970; **92**:7610-7612

[33] Procházka M. Űber Thiophen-1-oxid. Collection of Czechoslovak Chemical Communications. 1965;**30**:1158-1168

[34] Skaugset AE, Rauchfuss TB, Stern CL. Oxidation of coordinated thiophene: Preparation of Cp*Rh(tetramethylthiophene-S-oxide). Journal of the American Chemical Society. 1990;**112**:2432-2433

[35] Krautscheid H, Feng Q, Rauchfuss TB. Base hydrolysis of ruthenium(II) thiophene complexes and reactions of the coordinated ligands. Organometallics. 1993;**12**:3273-3281

[36] Skaugset AE. PhD [thesis]. University of Illinois at Urbana-Champaign; 1992

[37] Fagan PJ, Nugent WA, Calabrese JC. Metallacycle transfer from zirconium to main group elements: A versatile synthesis of heterocycles. Journal of the American Chemical Society. 1994;**116**:1880-1889

[38] Fagan PJ, Nugent WA. Synthesis of main group heterocycles by metallacycle transfer from zirconium. Journal of the American Chemical Society. 1988;**110**:2310-2312

[39] Meier-Brocks F, Weiss E. Tetraphenylzirkonacyclopentadien-derivate als Synthone für Tetraphenylthiophenemonoxid und substituierte Germanole. Journal of Organometallic Chemistry. 1993;**453**:33-45

[40] Jiang B, Tilley TD. General, efficient route to thiophene 1-oxides and well-defined, mixed thiophene-thiophene-1-oxide oligomers. Journal of the American Chemical Society. 1999; **121**:9744-9745

[41] Suh MC, Jiang B, Tilley TD. An efficient, modular synthetic route to oligomers based on zirconocene coupling: Properties for phenylene-thiophene-1,1-dioxide chains. Angewandte Chemie (International Ed. in English). 2000;**39**:2870-2873

[42] Miller RW, Dodge NJ, Dyer AM, Fortner-Buczala EM, Whalley AC. A one-pot method for the preparation of 2,5-diarylthiophene-1-oxides from arylacetylenes. Tetrahedron Letters. 2016;**57**:1860-1862

[43] Nakayama J, Yu T, Sugihara Y, Ishii A. Synthesis and characterization of thiophene 1-oxides kinetically stabilized by bulky substituents at the 3- and 4-positions. Chemistry Letters. 1997;**26**:499-500

[44] Furukawa N, Zhang SZ, Sato S, Higaki M. Simple procedure for the synthesis of 2,5-bis (silylated)thiophene *S*-oxides with *m*-chloroperbenzoic acid in the presence of $BF_3{\cdot}Et_2O$. Heterocycles. 1997;**44**:61-66

[45] Furukawa N, Zhang D, Horn E, Takahashi O, Sato S. X-ray crystallographic analysis of 2,5-bis(diphenylmethylsilyl)thiophene monoxide and the Diels-Alder reaction of thiophene monoxide with dienophiles. Heterocycles. 1998;**47**:793-809

[46] Pouzet P, Erdelmeier I, Ginderow D, Mornon JP, Dansette PM, Mansuy D. Thiophene S-oxides—Convenient preparation, first complete structural characterization and unexpected dimerization of one of them, 2,5-diphenylthiophene-1-oxide. Journal of the Chemical Society, Chemical Communications. 1995;**31**:473-474

[47] Pouzet P, Erdelmeier I, Ginderow D, Mornon JP, Dansette PM, Mansuy D. Thiophene 1-oxides. 5. Comparison of the crystal structures and thiophene ring aromaticity of 2,5-diphenylthiophene, its sulfoxide and sulfone. Journal of Heterocyclic Chemistry. 1997;**34**: 1567-1574

[48] Magerramov AM, Nagieva IT, Allakhverdiev MA. Oxidation of 3,4-dibromo-2,5-dimethylthiophene by hydrogen peroxide on a biomimetic catalyst – Fe(III) ethylenediaminetetraacetate/Al_2O_3. Azerbaidzhanskii Khimicheskii Zhurnal. 2002:27-36

[49] Nagieva IT. The mechanism of the heterogeneous catalytic monooxidation of thiophene derivatives at the S position by hydrogen peroxide. Russian Journal of Physical Chemistry A. 2009;**83**:1873-1878

[50] Ma B, Zhao W, Zhang F, Zhang Y, Wu S, Ding Y. A new halide-free efficient reaction-controlled phase-transfer catalyst based on silicotungstate of $[(C_{18}H_{37})_2(CH_3)_2N]_3[SiO_4H(WO_5)_3]$ for olefin epoxidation, oxidation of sulfides and alcohols with hydrogen peroxide. RSC Advances. 2014;**4**:32054-32062

[51] Thiemann C, Thiemann T, Li YQ, Sawada T, Nagano Y, Tashiro M. SO-photoextrusion of 7-thiabicyclo[2.2.1]hept-2-ene 7-oxides. Bulletin of the Chemical Society of Japan. 1994; **67**:1886-1893

[52] Li YQ, Thiemann C, Ohira D, Mataka S, Tashiro M, Thiemann T. From thiophene S-oxides to 7-thiabicyclo[2.2.1]hept-5-enes. Journal of Chemical Research. 2009;**33**:702-704

[53] Takayama J, Sugihara Y, Takanayagi T, Nakayama J. Syn-pi-face and endo-selective, inverse electron-demand Diels-Alder reactions of 3,4-di-tert-butylthiophene 1-oxide with electron-rich dienophiles. Tetrahedron Letters. 2005;**46**:4165-4169

[54] Otani T, Takayama J, Sugihara Y, Ishii A, Nakayama J. Pi-facial selective Diels-Alder reactions of 3,4-di-tert-butylthiophene 1-oxide and 1-imide and formation of 1,2-thiazetidines. Journal of the American Chemical Society. 2003;**125**:8255-8263

[55] Thiemann T, Ohira D, Li YQ, Sawada T, Mataka S, Rauch K, Noltemeyer M, de Meijere A. [4+2]-cycloaddition of thiophene S-monoxides to activated methylenecyclopropanes. Journal of the Chemical Society, Perkin Transactions. 2000;**1**:2968-2976

[56] Thiemann T, Fujii H, Ohira D, Arima K, Li YQ, Mataka S. Cycloaddition of thiophene *S*-oxides to allenes, alkynes and to benzyne. New Journal of Chemistry. 2003;**27**:1377-1384

[57] Takayama J, Sugihara Y, Nakayama J. SO_2-extrusion of an 8-thiabicyclo[3.2.1]octa-2,6-diene 8,8-dioxide and rearrangement of the resulting cycloheptatriene. Heteroatom Chemistry. 2005;**16**:132-137

[58] Thiemann T, Iniesta J, Walton DJ. [4+2]-cycloaddition of sterically hindered thiophene S-oxides to alkenes and SO-extrusion reactions of the cycloadducts. Phosphorus, Sulfur and Silicon. 2017;**191**:876-884

[59] Iniesta J, Matsumoto T, Thiemann. Cycloaddition of benzo[*b*]thiophene-*S*,*S*-dioxide—A route to substituted dibenzothiophenes and dibenzothiophene *S*,*S*-dioxides. Journal of Chemical Research. 2008;**23**:109-114

[60] Thiemann T, Iniesta J, Walton D. Thermal oxidation of tetracyclones (2,3,4,5-tetraarylcyclopentadienones). Journal of Chemical Research. 2008;**23**:173-180

[61] Iguchi K, Sugihara Y, Nakayama J. Preparation of sterically congested compounds: 6,7-di-t-butyl-1,4-naphthoquinone, 2,3,6,7-tetra-t-butylanthraquinone, and 2,3,6,7-tetra-t-butylanthracene. Bulletin of the Chemical Society of Japan. 2008;**81**:304-306

[62] Thiemann T, Tanaka Y, Iniesta J. Brominated thiophenes as precursors in the preparation of brominated and arylated anthraquinones. Molecules. 2009;**12**:1013-1031

[63] Thiemann T, Tanaka Y, Iniesta J, Varghese HT, Panicker CY. Arylation of chloroanthraquinones by surprisingly facile Suzuki-Miyaura cross-coupling reactions. Journal of Chemical Research. 2009;**33**:732-736

[64] Joseph T, Varghese HT, Panicker CY, Thiemann T, Viswanathan K, van Alsenoy C. Infrared and Raman spectroscopic analysis and theoretical computation of the first hyperpolarizability of a monoarylated anthraquinone, 1-(4-methoxy-phenyl)-4-methylanthraquinone. Journal of Molecular Structure. 2011;**1005**:17-24

[65] Takeuchi N, Nakahodo T, Fujihara H. Remarkably stable *S*-oxides of calix[4]thiophenes and their sulfonium ylide from reaction of *S*-oxide with acetylene derivative. Chemistry Letters. 2017;**46**:389-391

[66] Takayama J, Fukuda S, Sugihara Y, Ishii A, Nakayama J. Pi-facial selective hetero Diels-Alder reactions of 3,4-di-tert-butylthiophene 1-oxide. An excellent trapping reagent for thioaldehydes and thioketones. Tetrahedron Letters. 2003;**44**:5159-5162

[67] Nakayama J, Tai A, Isawa S, Furuya T, Sugihara Y. Tetracyanoethylene oxide not only oxidizes sulfides to sulfoxides but also reduces sulfoxides to sulfides. Tetrahedron Letters. 2005;**46**:1395-1397

[68] Otani T, Miyoshi M, Shibata T, Matsuo T, Hashizume D, Tamao K. Thermally stable monosubstituted thiophene 1-oxide and 1-imides stabilized by a bulky rind group at their 3-position: Synthesis, structure, and inversion barriers on the sulfur atom. Bulletin of the Chemical Society of Japan. 2017;**90**:697-705

[69] Boyd D, Sharma DD, Haughey SA, Malone JF, McMurray BT, Sheldrake GN, Allen CC, Dalton HJ. Enantioselective dioxygenase-catalysed formation and thermal racemization of chiral thiophene sulfoxides. Journal of the Chemical Society, Chemical Communications. 1996;**32**:2363-2364

[70] Houk KN, Stozier RW. Lewis acid catalysis of Diels Alder reactions. Journal of the American Chemical Society. 1973;**95**:4094-4096

[71] Alston PV, Ottenbrite RM. Secondary orbital interactions determining regioselectivity in the Lewis acid catalyzed Diels-Alder reaction II. Journal of Organic Chemistry. 1975;**40**: 1111-1116

[72] Ishida M, Inagaki S. In: Inagaki S, editor. Orbitals in Chemistry. Vol. 289. Berlin: Springer-Verlag; 2009. pp. 183-183

[73] Cieplak AS. Stereochemistry of nucleophilic addition to cyclohexanone. The importance of two-electron stabilizing interactions. Journal of the American Chemical Society. 1981; **103**:4540-4552

[74] Cieplak AS, Tait BD, Johnson CR. Reversal of π-facial diastereoselection upon electronegative substitution of the substrate and the reagent. Journal of the American Chemical Society. 1989;**111**:8447-8462

[75] Cieplak AS. Inductive and resonance effects of substituents on π-face selection. Chemical Reviews. 1999;**99**:1265-1336

[76] Macaulay JB, Fallis AG. Heteroatom-directed pi-facial diastereoselection in Diels-Alder cycloadditions of plane-nonsymmetric cyclopentadienes. Journal of the American Chemical Society. 1990;**112**:1136-1144

[77] Li YQ. Dissertation. Fukuoka, Japan: Kyushu University; 1997

[78] Nakayama J, Takayama J, Sugihara Y, Ishii A. Reaction of 3,4-di-t-butylthiophene 1-oxide with 2-methylene-1,3-dimethylimidazolidine: Methylene transfer and [4+4]-dimerization. Chemistry Letters. 2001;**30**:758-759

[79] Takayama J, Sugihara A, Ishii A, Nakayama J. Preparation of 1,4,5,8-tetra-*tert*-butyl-1,3,5,7-cyclooctatetraene by twofold SO_2 extrusion. Tetrahedron Letters. 2003;**44**:7893-7896

[80] Nakayama J, Furuya T, Suzuki Y. Pi-face-selective 1,3-dipolar cycloadditions of 3,4-di-tert-butylthiophene 1-oxide with 1,3-dipoles. Phosphorus, Sulfur and Silicon. 2009;**184**: 1175-1183

[81] Nakayama J, Furuya T, Ishii A, Sakamoto A, Otani T, Sugihara Y. Regio- and stereoselective addition of molecular bromine to S-oxidized derivatives of 3,4-di-t-butylthiophene: Exclusive 1,4-cis additions. Bulletin of the Chemical Society of Japan. 2003;**76**:619-625

[82] Zhang S-Z, Sato S, Horn E, Furukawa N. Exclusive cis-1,4-addition in the bromination of 2,5-bis(trimethylsilyl)-thiophene monoxide. Heterocycles. 1998;**4**:227-234

[83] Otani T, Sugihara Y, Ishii A, Nakayama J. Michael additions of oxygen and sulfur nucleophiles to 3,4-di-t-butyl-1[(p-tolyl)sulfonylimino]-1,1-dihydrothiophene. A comparison study with 3,4-di-t-butylthiophene 1-oxide and 1,1-dioxide. Chemistry Letters. 2000;**29**:744-745

[84] Nakayama J, Aoki S, Takayama J, Sakamoto A, Sugihara Y, Ishii A. Reversible disulfur monoxide (S_2O)-forming retro-Diels-Alder reaction. Disproportionation of S_2O to trithiozone (S_3) and sulfur dioxide (SO_2) and reactivities of S_2O and S_3. Journal of the American Chemical Society. 2004;**126**:9085-9093

[85] Otani T, Sugihara Y, Ishii A, Nakayama J. Preparation of 3,4-di-t-butylthiophene 1-imide and its N-substituted derivatives. Tetrahedron Letters. 2000;**41**:8461-8465

[86] Nakayama J, Otani T, Sugihara Y, Sano Y, Ishii A, Sakamoto A. Syntheses and structures of sulfilimine, sulfone diamine, and sulfoximine derivatives of a monocyclic thiophene, 3,4-di-tert-butylthiophene. Heteroatom Chemistry. 2001;**12**:333-348

[87] Nakayama J, Sano Y, Sugihara Y, Ishii A. Thiophene sulfoximides: 2,4- and 3,4-di-tert-butyl-1-imino-1,1-dihydrothiophene 1-oxides. Tetrahedron Letters. 1999;**40**:3785-3788

[88] Gurria GM, Posner GH. Photochemical deoxygenation of aryl sulfoxides. The Journal of Organic Chemistry. 1973;**38**:2419-2420

[89] Wan Z, Jenks WS. Oxenoid reactivity observed on the photolysis of certain aromatic sulfoxides. Journal of the American Chemical Society. 1995;**117**:2667-2668

[90] Gregory DD, Wan Z, Jenks WS. Photodeoxygenation of dibenzothiophene sulfoxide: Evidence for a unimolecular S—O cleavage mechanism. Journal of the American Chemical Society. 1997;**119**:94-102

[91] Rockafellow EM, McCulla RD, Jenks WS. Deoxygenation of dibenzothiophene S-oxide and dibenzoselenophene S-oxide: A comparison of direct and sensitized photolysis. Journal of Photochemistry and Photobiology A. 2008;**198**:45-51

[92] Arima K, Ohira D, Watanabe M, Miura A, Mataka S, Thiemann T, Iniesta J, Walton D. The photochemistry of thiophene S-oxides. Photochemical & Photobiological Sciences. 2005;**4**:808-816

[93] Heying MJ, Nag M, Jenks WS. Photochemistry of thiophene S-oxide derivatives. Journal of Physical Organic Chemistry. 2008;**21**:915-924

[94] Stoffregen SA, Lee SY, Dickerson P, Jenks WS. Computational investigation of the photochemical deoxygenation of thiophene-S-oxide and selenophene-Se-oxide. Photochemical & Photobiological Sciences. 2014;**13**:431-438

[95] Nakayama J, Hiraiwa S, Fujihara T. Photolysis and photo-oxidation of 3,4-di-tert-butylthiophene 1-oxide. Journal of Sulfur Chemistry. 2008;**29**:243-250

[96] Thiemann T, Ohira D, Arima K, Sawada T, Mataka S, Marken F, Compton RG, Bull SD, Davies SG. Photochemical and electrochemical behavior of thiophene S-oxides. Journal of Physical Organic Chemistry. 2000;**13**:648-653

[97] Valcarel JI, Walton DJ, Fujii H, Thiemann T, Tanaka Y, Mataka S, Mason TJ, Lorimer JP. The sonoelectrooxidation of thiophene S-oxides. Ultrasonics Sonochemistry. 2004;**11**:227-232

[98] Iniesta J, Alcock H, Walton DJ, Watanabe M, Mataka S, Thiemann T. Electrochemical oxidation of tetracyclones and tetraphenylthiophene S-oxide. Electrochimica Acta. 2006; **51**:5682-5690

[99] Hashmall JA, Horak V, Khoo LE, Quicksall CO, Sun MK. Molecular structure of selected *S*-methylthiophenium tetrafluoroborates and dibenzothiophene *S*-oxide. Journal of the American Chemical Society. 1981;**103**:289-295

[100] Rozas I. Comparative study of aromaticity in five-membered rings containing S, SO, and SO_2 groups. Journal of Physical Organic Chemistry. 1992;**5**:74-82

[101] Julg A, François P. Recherches sur la géométrie de quelques hydrocarbures non-alternants: Son influence sur les énergies de transition, une nouvelle définition de l'aromaticité. Theoretica Chimica Acta. 1967;**7**:249-259

[102] Holloczki O, Nyulaszi L. Analogy between sulfuryl and phosphino groups: The aromaticity of thiophene-oxide. Structural Chemistry. 2011;**22**:1385-1392

[103] Di Maria F, Zangoli M, Palama IE, Fabiano E, Zanelli A, Monari M, Perinot A, Caironi M, Maiorano V, Maggiore A, Pugliese M, Salatelli E, Gigli G, Viola I, Barbarella G. Improving the property-function tuning range of thiophene materials via facile synthesis of oligo/polythiophene-S-oxides/oligo/polythiophene-S,S-dioxides. Advanced Functional Materials. 2016;**26**:6970-6984

[104] Lukevics E, Arsenyan P, Belyakov S, Pudova O. Molecular structure of thiophene 1,1-dioxides, thiophene S-oxides and their derivatives. Chemistry of Heterocyclic Compounds. 2002;**38**:632-645

[105] Fichou D, editor. Handbook of Oligo- and Polythiophenes. Wiley-VCH Verlag; 1999

[106] Malytskyi V, Simon JJ, Patrone L, Raimundo JM. Thiophene-based push-pull chromophores for small molecule organic solar cells (SMOCs). RSC Advances. 2015;**5**:354-397

[107] Takimiya K, Osaka I, Mori T, Nakano M. Organic semiconductors based on [1]benzothieno [3,2-b][1]benzothiophene substructure. Accounts of Chemical Research. 2014;**47**:1493-1502

[108] Tanaka K, Wang S, Yamabe T. Electronic structures of substituted derivatives of polythiophene. Design of narrow-band-gap polymers. Synthetic Metals. 1989;**30**:57-65

[109] Bongini A, Barbarella G, Zambianchi M, Arbizzani C, Mastragostino M. Thiophene S-oxides: Orbital energies and electrochemical properties. Journal of the Chemical Society, Chemical Communications. 2000:439-440

[110] Sano R, Suzuki T, Kawai T, Iyoda T. Direct sulfur oxidation of poly(3-hexylthiophene). Memoirs of the Graduate School of Engineering, Tokyo Metropolitan University. 1999;**49**: 183-193

[111] Mishra VL, Furuyama T, Kobayashi N, Goto K, Miyazaki T, Yang J-S, Shinmyozu T. Synthesis, optical properties, and electronic structures of tetrakis(pentafluorophenyl) tetrathiaisophlorin dioxide. Chemistry—A European Journal. 2016;**22**:9190-9197

[112] Thiemann T, Kumazoe K, Arima K, Mataka S. Studies towards dibenzothiophene S-oxide arrays and their photochemical activity. Rep. Inst. Adv. Mat. Kyushu Univ. 2001; **15**(1):63-71; Chemical Abstracts. 2002;**136**:19-802

[113] Kumazoe K, Arima K, Mataka S, Walton DJ, Thiemann T. Photobehaviour of substituted dibenzothiophene-S-oxides and oxygenated bis(dibenzothiophene)s. Journal of Chemical Research. 2003;**27**(S):60-61; 2003;**27**(M):248-264

[114] McMurty RJ, Mitchell JR. Renal and hepatic necrosis after metabolic activation of 2-substituted furans and thiophenes including furosemide and cephaloridine. Toxicology and Applied Pharmacology. 1977;**42**:285-300

[115] Beaune P, Dansette PM, Mansuy D, Kiffel L, Finck M, Amar C, Leroux JP, Homberg JC. Human anti-endoplasmatic reticulum autoantibodies appearing in a drug-induced hepatitis are directed against a human liver cytochrome P-450 that hydroxylates the drug. Proceedings of the National Academy of Sciences of the United States of America. 1987; **84**:551-555

[116] Dansette PM, Amar C, Smith C, Pons C, Mansuy D. Oxidative activation of the thiophene ring by hepatic enzymes. Hydroxylation and formation of electrophilic metabolites during metabolism of tienilic acid and its isomer by rat liver microsomes. Biochemical Pharmacology. 1990;**39**:911-918

[117] Dansette PM, Amar C, Valadon P, Pons C, Beaune PH, Mansuy D. Hydroxylation and formation of electrophilic metabolites of tienilic acid and its isomer by human liver microsomes. Catalysis by a cytochrome P450 IIC different from that responsible for mephenytoin hydroxylation. Biochemical Pharmacology. 1991;**40**:553-560

[118] Treiber A, Dansette PM, El Amri H, Girault J-P, Ginderow D, Mornon J-P, Mansuy D. Chemical and biological oxidation of thiophene: Preparation and complete characterization of thiophene S-oxide dimers and evidence for thiophene S-oxide as an intermediate in thiophene metabolism in vivo and in vitro. Journal of the American Chemical Society. 1997;**119**:1565-1571

[119] Dansette PM, Thang DC, El Amri H, Mansuy D. Evidence for thiophene S-oxide as a primary reactive metabolite of thiophene in vivo: Formation of a dihydrothiophene sulfoxide mercapturic acid. Biochemical and Biophysical Research Communications. 1992;**186**:1624-1630

[120] Dansette PM, Thebault S, Durand-Gasselin L, Mansuy D. Reactive metabolites of thiophenic compounds: A new trapping method for thiophene sulfoxides. Drug Metabolism Reviews. 2010;**32**(Suppl. 1):233-234 presentation at ISSX, Istanbul

[121] Mansuy D, Valadon P, Erdelmeier I, Lopez-Garcia P, Amar C, Girault JP, Dansette PM. Thiophene S-oxides as new reactive metabolites: Formation by cytochrome P450 dependent oxidation and reaction with nucleophiles. Journal of the American Chemical Society. 1991;**113**:7825-7826

[122] Ho MT, Treiber A, Dansette PM. Oxidation of 2-(4-chlorobenzoyl)thiophene into 1-oxide Diels-Alder dimers, sesquioxide and a sulfone-water adduct. Tetrahedron Letters. 1998; **39**:5049-5052

[123] Sato S, Zhang S-Z, Furukawa N. The Pummerer-like reaction of 2,5-bis(trimethylsilyl) thiophene S-oxide with trifluoroacetic anhydride: Intermediary formation of sulfurane. Heteroatom Chemistry. 2001;**15**:444-450

[124] Rademacher PM, Woods CM, Huang QB, Szklarz GD, Nelson SD. Differential oxidation of two thiophene-containing regioisomers to reactive metabolites by cytochrome P450 2C9. Chemical Research in Toxicology. 2012;**25**:895-903

[125] Dansette PM, Bertho G, Mansuy D. First evidence that cytochrome P450 may catalyze both S-oxidation and epoxidation of thiophene derivatives. Biochemical and Biophysical Research Communications. 2005;**338**:450-455

[126] Shimizu S, Atsumi R, Nakazawa T, Fujimaki Y, Sudo K, Okazaki O. Metabolism of ticlopidine in rats: Identification of the main biliary metabolite as a glutathione conjugate of ticlopidine S-oxide. Drug Metabolism and Disposition. 2009;**37**:1904-1915

[127] Ha-Duong NT, Dijols S, Macherey AC, Goldstein JA, Dansette PM, Mansuy D. Ticlopidine as a selective mechanism-based inhibitor of human cytochrome P450 2C19. Biochemistry. 2001;**40**:12112-12122

[128] Medower C, Wen L, Johnson WW. Cytochrome P450 oxidation of the thiophene-containing anticancer drug 3-[(quinolin-4-ylmethyl)-amino]-thiophene-2-carboxylic acid (4-trifluoromethoxyphenyl)amide to an electrophilic intermediate. Chemical Research in Toxicology. 2008;**21**:1570-1577

[129] Jaladanski CK, Taxak N, Varikoti RA, Bharatam PV. Toxicity originating from thiophene containing drugs: Exploring the mechanism using quantum chemical methods. Chemical Research in Toxicology. 2015;**28**:2364-2376