REVIEW

J. Chem. Research (S), 2002, 303–308
J. Chem. Research (M), 2002, 0701–0719

Thiophene *S*-oxides

Thies Thiemann* and Krishna Gopal Dongol

Institute of Advanced Material Study, Kyushu University, 6-1, Kasuga-koh-en, Kasuga-shi, Fukuoka 816-8580, Japan

Methods for the preparation of thiophene *S*-oxides, their roles in thiophene metabolism, and the structures and chemical reactivity of these compounds, are discussed.

Keywords: thiophenes, *S*-oxidation, cycloadditions, photochemistry

I Introduction

Thiophene is a heteroaromatic molecule, the resonance energy of which has been calculated to be about 121 kJ/mol (29 kcal/mol), based on experimentally determined heats of formation.[1] Nevertheless, due to the easy oxidisability of sulfur, thiophenes can be transformed to derivatives with sulfur in a higher oxidation state. Figure 1 shows a number of compounds accessible from the corresponding thiophenes either by direct oxidation or by oxidative addition.[2-6] In all of these compounds the stabilisation due to resonance energy has been much reduced. In fact, most of the compounds listed react as dienes, as in Diels–Alder reactions.[2,4] Of the compounds listed, the thiophene *S*,*S*-dioxides are the most common and best studied, and also a large number of thiophenium derivatives have been published.[6] Whereas ten years ago thiophene *S*-oxides may have been counted as among the more exotic molecules, today much of their chemistry has become known and they have gained importance in such disparate issues as the study of the *in vivo* toxicology of thiophenes and the development of new optical materials with narrow electronic band gaps.

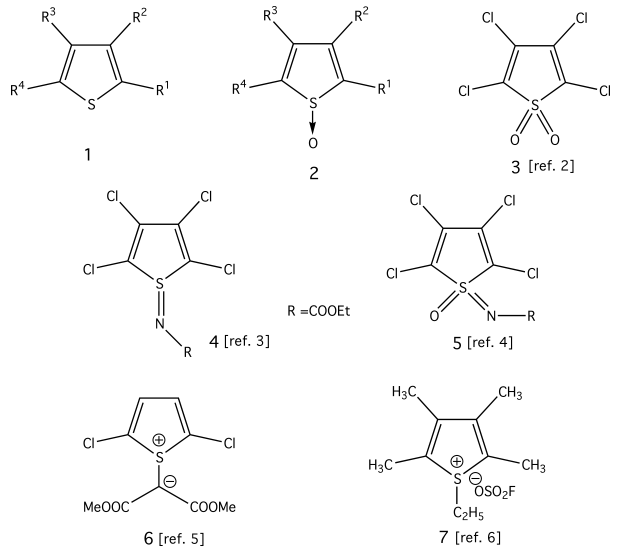
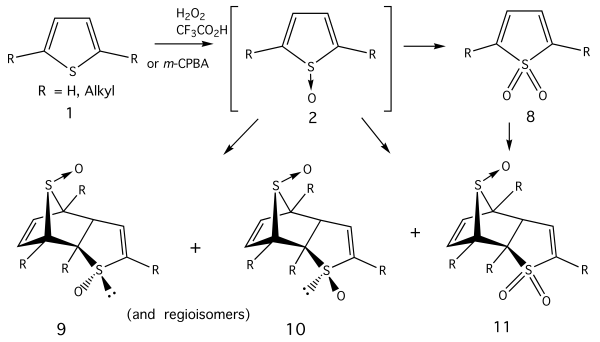


Fig. 1 Thiophene-derived heterocycles by oxidation or oxidative addition to sulfur.

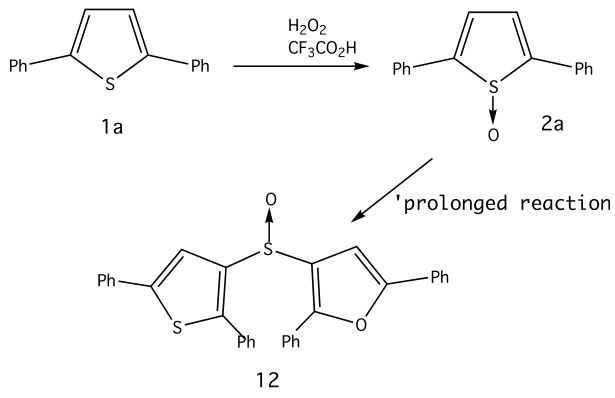
II Synthesis

For some time, thiophene *S*-oxides **2** have been thought of as intermediates[7] in the peracid oxidation of thiophenes **1** to thiophene *S*,*S*-dioxides **8**, as in these reactions dimers are seen as by-products, such as **9, 10** and **11**, which are formal [4+2]-adducts of either two thiophene S-oxides or of a thiophene *S*-oxide with a thiophene *S*,*S*-dioxide (Scheme 1).[8] These dimers can also be isolated as metabolites of thiophene *in vivo* in rats and point towards the involvement of thiophene *S*-oxides as transient species in the metabolism of thiophenes.[9]



Scheme 1
Formation of monoxide dimers and sesquioxides in the peracid oxidation of thiophenes[8h,9,12].

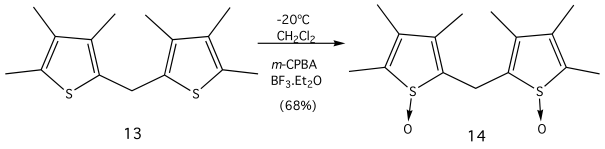
At the beginning, this ready dimerisation process complicated a direct synthesis of thiophene *S*-oxides by oxidation of thiophenes. In 1970, Mock[10] reported on the preparation of the sterically congested 2,5-di-*t*-butyl- and 2,5-di-*t*-octyl-thiophene *S*-oxides by peracid oxidation of the corresponding thiophenes. Although the steric effect of the substituents hindered dimerisation of the species, the yield of the thiophene *S*-oxides at 5% was still low. Partly, this is due to a second oxidation step of the thiophene *S*-oxides to the *S*,*S*-dioxides.



Scheme 2
Oxidation of 2,5-diphenylthiophene with CF_3CO_3H/H_2O_2. Prolonged reaction leads to the furan **12** as side product.[11]

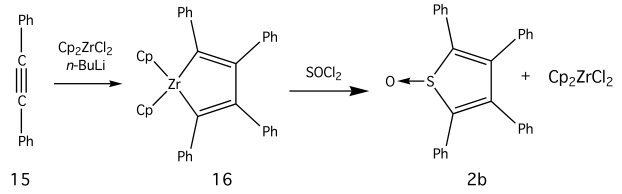
* To receive any correspondence. E-mail: thies@cm.kyushu-u.ac.jp

It took another 25 years to develop a more general route to thiophene *S*-oxides via oxidation of thiophenes. In the mid-1990s four groups[11-14] almost simultaneously reported on the preparation and isolation of thiophene *S*-oxides by the oxidation of thiophenes with either organic peracids or with H_2O_2 (Scheme 2) in the presence of either a Lewis acid (Scheme 3) or a proton acid. Here, the proton acid as well as the Lewis acid may have dual functions – the activation of the peracid and by complexation, protection of the thiophene *S*-oxide formed against further oxidation. The latter effect is quite evident in the fact that compounds carrying two or more thienyl units, such as in **8** (Scheme 3), can be oxidised selectively to *S,S′*-dioxides, so that the thiophene unit competes with success for the oxidant in the presence of a thiophene *S*-oxide moiety.[8h,15]

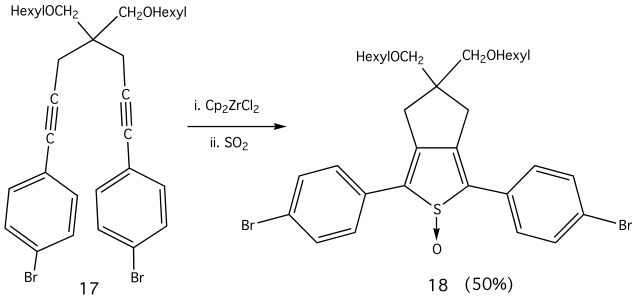


Scheme 3
Use of a lewis acid in thiophene *S*-oxidation.
The *S*-oxide is protected against further oxidation, so that a second thienyl unit in the molecule competes successfully with the monoxide.[8h]

A second way of preparation uses tetraaryl/alkylzirconacyclopentadiene derivatives as synthons for thiophene *S*-oxides (Scheme 4).[16,17] This method, which at the beginning was limited to the preparation of tetraphenylthiophene *S*-oxide **2b**,[16] has been generalised more recently to include the synthesis of tetraalkylthiophene *S*-oxides[17a] and thiophene *S*-oxides, such as **18**, as monomeric units in phenylene-thiophene *S*-oxide chains (Scheme 5).[17b]



Scheme 4
Tetraphenylzirconacyclopentadiene derivatives as synthons for tetraphenylthiophene *S*-oxide.[16a-c, 17]



Scheme 5
Route via zirconacyclopentadiene to aryl/heteroaryl thiophene *S*-oxide Oligomers.[17a]

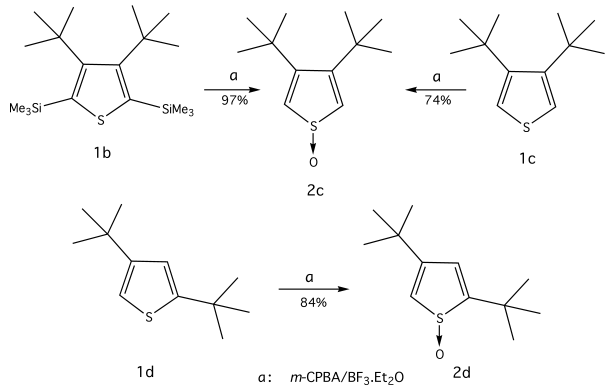
The approach makes use of the ease with which zirconium metallacycles react with main group elements to form main group heterocycles. Thus, *in situ* reaction of tetraphenylzirconacyclopentadiene, prepared from zirconocene dichloride and diphenylacetylene in the presence of n-BuLi, with thionyl chloride gives tetraphenylthiophene *S*-oxide.[16c] The yields of this reaction with zirconacyclopentadienes having mixed alkyl and aryl substituents or solely with alkyl substituents are much lower; in these cases Jiang and Tilley have found that *in situ* reaction of the zirconacyclopentadiene with sulfur dioxide gives much better results.[17]

A very interesting approach towards enantiomerically enriched thiophene *S*-oxides was undertaken by Boyd, Dalton *et al.*,[18] who subjected thiophenes and benzothiophenes to dioxygenase-catalysed sulfoxidation using intact cells of *Pseudomonas putida*. As the thiophenes were mono-substituted, *viz*., 2-methylthiophene or 3-methylthiophene, the obtained thiophene S-oxides underwent rapid dimerisation to sesquioxides or cycloadded to unreacted thiophene (*vide supra*). The cycloadduct of unsubstituted thiophene *S*-oxide with unsubstituted thiophene was formed in up to 77% ee, but the dimer of the thiophene *S*-oxide was found to be racemic, as were also the dimers of the monosubstituted thiophene *S*-oxides. This may mean that the enantiomeric excess of the thiophene - thiophene *S*-oxide cycloadducts is due to enantioselective cycloaddition rather than to enantioselective sulfoxidation. On the other hand, the benzothiophene *S*-oxides[19] themselves could be isolated and were found to be enantiomerically enriched (up to 98% ee).

The stability of the thiophene *S*-oxides depends on the ring substitution. Tetra- or tri-donor substituted thiophene *S*-oxides are usually more stable than the disubstituted compounds, the 2,5-disubstituted are more stable than the 2,4- or the 3,4-substituted isomers. 2,3-Disubstituted thiophene *S*-oxides are even more difficult to handle, due to their tendency to undergo self-dimerisation. Even sterically undemanding substituents, such as a methyl group, can provide sufficient steric protection for the molecule. Thus, 2,5-dimethylthiophene *S*-oxide is stable in solution, and can be purified after synthesis for further reactions, if kept in solution.[12] Thiophene *S*-oxides unsubstituted at C-2 and/or C-5 need bulky substituents at C-3 and C-4/(C-5), such as *t*-butyl or adamantyl groups, for additional stabilisation. While silyl groups can also act as steric stabilisers and may potentially be cleaved or used as a reactive group at a later stage, silyl-containing thiophene S-oxides are not easily synthesised due to the facile cleavage of the silyl group, both F^--catalysed (when using *m*-CPBA/BF_3) and by protolysis (H_2O_2/CF_3COOH). This fact has been used by Nakayama *et al.*[20] effectively in their synthesis of 3,4-di-t-butylthiophene *S*-oxide from 3,4-di-t-butyl-2,5-bis(trimethylsilyl)thiophene (**1b**) by oxidation with *m*-CPBA/$BF_3.Et_2O$, where the trimethylsilyl moiety as a steric protective group is slowly cleaved during the course of the reaction (Scheme 6). Careful optimisation of reaction conditions, however, allows for the preparation of 2,5-silyl substituted thiophene *S*-oxides also.[21]

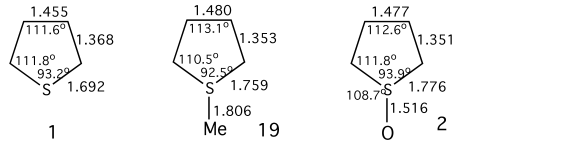
III Structure and properties

Thiophene *S*-oxides are non-planar compounds,[22] in which the lone pair of the sulfur does not interact strongly with the π-systems of the two olefinic moieties. X-ray structural analysis of 2,5-diphenylthiophene *S*-oxide has shown that the pyramidalised sulfur is positioned outside the plane defined by the four carbon atoms of the heterocyclic structure (see also Fig. 2). The oxygen of the sulfoxy-unit is positioned on the other side of that plane. The degree of the displacement of the sulfur from the plane spanned by the four ring carbons is slightly dependent on the nature of the substituents at positions C2 and C5. The sulfur of thiophene *S*-monoxide can invert,[23] possibly *via* a planar transition state. The inversion barrier has been calculated and measured experimentally[23] and has been found to

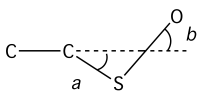


Scheme 6
Synthesis of thiophene *S*-oxides stabilised by bulky substituents.[13]

be dependent on the nature of the substituents α to the sulfoxy-moiety. Thiophene *S*-oxides show significant bond alternation when compared to the corresponding thiophenes, but slightly less than the corresponding thiophene *S*,*S*-dioxides.[24] This is especially reflected in the A indices according to Julg and François (0.99 for 2,5-diphenylthiophene, 0.79 for 2,5-diphenylthiophene *S*-oxide, but 0.18 for 2,5-diphenylthiophene *S*,*S*-dioxide, where in all cases only the five-membered heterocycles are compared).[22a,24]



Molecular structure of thiophene, *S*-methylthiophenium cation and thiophene *S*-oxide as calculated by semiempirical MNDO.[22a]



a 9.3° 3,4-di-t-butylthiophene *S*-oxide [ref. 13]
12.9° 2,5-diphenylthiophene *S*-oxide [ref. 11,24]
13.6° 2,5-bis(diphenylmethylsilyl)thiophene *S*-oxide [ref. 32a]

b 47.5° 3,4-bis(*tert*-butyl)thiophene *S*-oxide [ref. 13]
56.5° 2,5-diphenylthiophene *S*-oxide [ref. 11,24]

S-O = 1.494(1)Å 3,4-bis(*tert*-butyl)thiophene *S*-oxide [ref. 13]
1.484(3) Å 2,5-diphenylthiophene *S*-oxide [ref. 11,24]
1.471(2) Å 2,5-bis(diphenylmethylsilyl)thiophene *S*-oxide [ref. 32a]

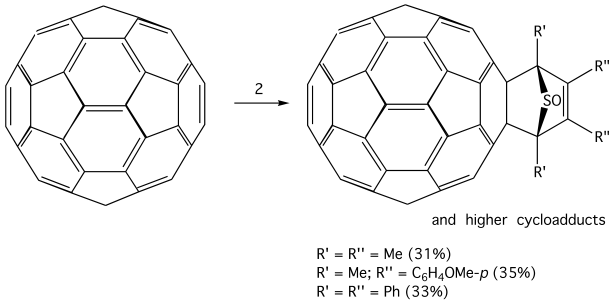
Structural parameters from X-ray structural analyses of thiophene *S*-oxides

Fig. 2 Structural features of thiophene *S*-oxides.

The electrochemical reactions of thiophene *S*-oxides have been studied.[25,26] Thiophene *S*-oxides show well defined, irreversible reduction waves. Although the processes underlying the reduction are not clearly understood, two different mechanisms seem to be at work depending on the presence or absence of a proton donor.[25] The presence of a proton donor shift the reduction potentials to more positive values. Here, the corresponding thiophenes can be isolated in almost quantitative yield.[25] In contrast to thiophenes (easily oxidised) and thiophene *S*,*S*-dioxides (easily reduced), thiophene *S*-oxides can both be oxidised and reduced at fairly moderate potentials. The nature of the substituents have a significant effect on the reduction potential of the molecules.[25,26]

IV Reactivity

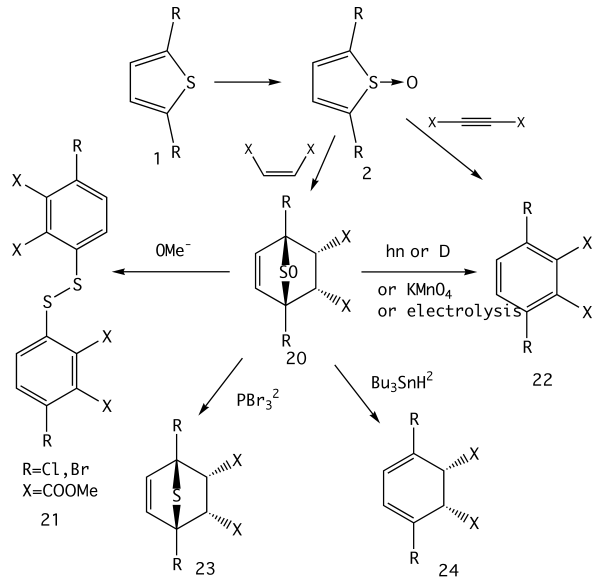
Thiophene *S*-oxides have been found to be reactive dienes in [4 + 2] cycloaddition reactions[27] with a number of alkynes and alkenes, which range from bicyclopropylidene[28] and C_{60}[29] (Scheme 7) to benzyne.[30] Already the generation of thiophene *S*-oxides by oxidation with peroxide and without isolation in the presence of dienophiles had shown their reactivity towards electron poor alkenes and alkynes (alkenes and alkynes with one or more electron withdrawing groups).[31] In many cases the dienophiles themselves are prone to oxidation; then it is necessary to isolate the thiophene *S*-oxides before subjecting them to the cycloaddition reaction.[28]



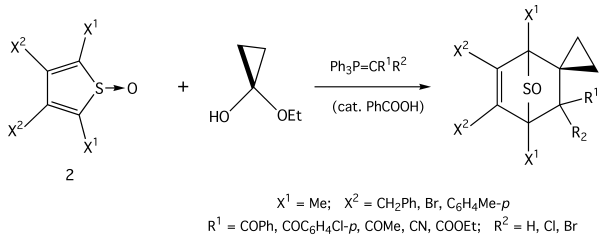
Scheme 7
Cycloaddition of thiophene oxides to buckminsterfullerene (C_{60}).[29]

While the formal cycloadducts of thiophene *S*-oxides with alkynes, the 7-thiabicyclo[2.2.1]heptadiene *S*-oxides, extrude the sulfoxy bridge spontaneously and aromatise (**22**), the reaction of thiophene *S*-oxides with alkenes leads to 7-thiabicyclo[2.2.1]heptene *S*-oxides (**20**). (Scheme 8) In the formation of these cycloadducts five new stereocenters are formed and all of them are controlled. The cycloaddition shows high to exclusive *endo*-selectivity, the lone pair of the sulfur of the sulfoxy-bridge coming to lie on the side of the newly formed double bond of the bicyclic product (**20**).[32] This stereochemical outcome has been observed for all of the cycloaddition reactions performed by the authors and has been ascertained by a number of X-ray crystal structural analyses by ourselves[8h,15,31e,32b] and by other groups.[31b,32a] The *syn*-π-facial selectivity of this reaction can best be explained by the Cieplak effect.[31b,33] The activation barriers of both *syn*- and *anti*-addition have been calculated by semi-empirical methods[34,35] as well as at the RHF/6-31G* level.[32a] The 7-thiabicyclo[2.2.1]heptene *S*-oxides (20) have been found to be viable starting materials for diaryl disulfides (**21**), arenes (**22**),[31c,e,f] and cyclohexadienes (**24**).[31e] These approaches have been used to prepare multi-functionalised crown ethers[31c] and cyclophanes[15,32b] from their corresponding thiophene precursors. The comparative stability of the tetrasubstituted thiophene *S*-oxides to a wider variety of reagents and to temperatures up to 70°C makes it possible to combine the cycloaddition with further transformations in a one-pot strategy to more complex structures, such as is shown in a combination of Wittig-olefination and cycloaddition reactions (Scheme 9).[28]

The thiophene *S*-oxide **2c** can be reacted with *N*-[(*p*-toluenesulfonyl)imino]phenyliodinane (TsN=IPh) with $[Cu(MeCN)_4PF_6]$ as catalyst to form the thiophene sulfoximide **26** (Scheme 10).[36] This can be converted into the corresponding thiophene sulfoximinium tetrafluoroborate, which can be hydrolyzed to give back the thiophene *S*-oxide. The 3,4-di-t-butylthiophene *S*-oxide (**2c**) and the 3,4-di-t-butyl-1-tolylsulfonylimino-1,1-dihydrothiophene (**25**) which can be



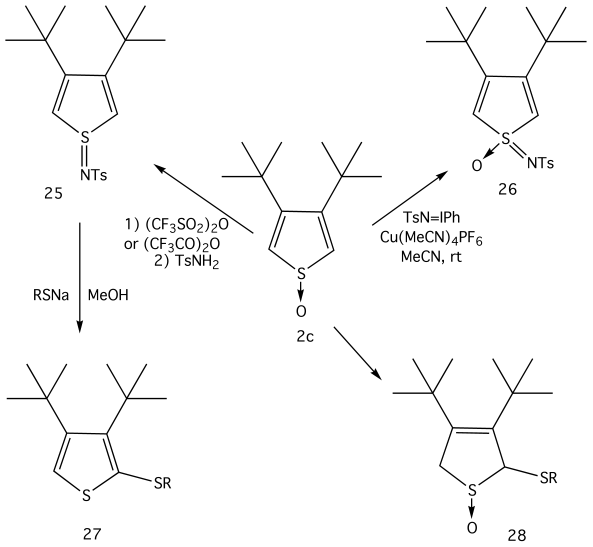
Scheme 8
Thiophene oxides as expedient intermediates. Transformations of thiophenes to functionalised arenes and cyclohexadienes.[31c,e,f]



Scheme 9
Thiophene *S*-oxides in one-pot syntheses incorporating Wittig reactions.[28]

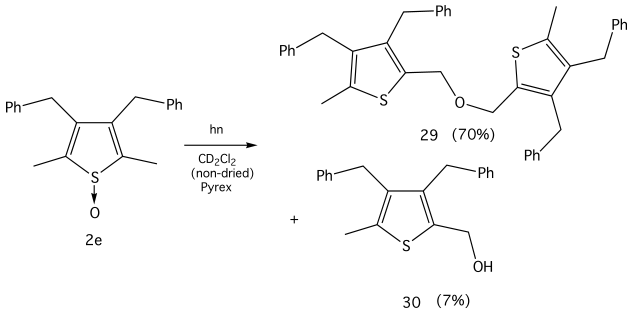
prepared from the corresponding thiophene with TsN=IPh under Cu(I) or Cu(II) catalysis, both react with mercaptides. In the case of the thiophene *S*-oxide, a 1,6-Michael addition occurs, forming **28**, while **25** gives a 2-alkylthio-substituted thiophene (**27**) (Scheme 10). Ethoxides react with the imines, but not with the thiophene *S*-oxides. *N*-substituted 1-imino derivatives of 3,4-di-*t*-butylthiophene have also been prepared by treating the corresponding thiophene *S*-oxide (**2c**) with trifluoroacetic anhydride at –78°C and subsequently reacting it with an amine, a urethane or a sulfonamide.[37]

Thiophene *S*-oxides have been found to be cancer-active compounds.[38] This biological behaviour may be related to a slow generation of oxygen due to a slow deoxygenation process of the thiophene *S*-oxides. While many of the tetrasubstituted thiophene *S*-oxides are stable in substance for an extended period of time, others slowly degrade to form a number of products, the main product often being the corresponding thiophene. Warming thiophene *S*-oxides in solution in the presence of dienophiles, often allows, apart from the cycloadducts formed, retrieval of unreacted thiophene *S*-oxides. While in most instances also a small amount of thiophene is obtained, the use of certain dienophiles, such as the strained bicyclopropylidene,[28] leads to the formation of a significant amount of thiophene as the by-product. However, no product of sufficient purity could be isolated to show a potential oxygen transfer from the thiophene *S*-oxide to the dienophile.[39]

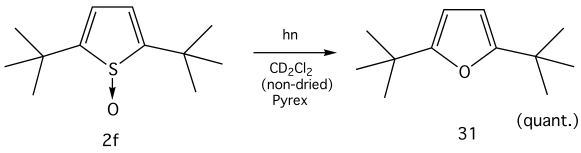


Scheme 10
Reactivity of thiophene *S*-oxides and imine analogues towards nucleophiles.[20,36,37]

When thiophene *S*-oxides are photoirradiated, a conversion takes place much more readily.[49,41] The course of the reaction depends greatly on the substituents of the thiophene *S*-oxide. Thus, when photoirradiated in dichloromethane with a high pressure mercury lamp (pyrex filter), 3,4-dibenzyl-2,5-dimethylthiophene *S*-oxide (**2e**) forms a mixture of bis-2-(3,4-dibenzyl-5-methyl-2-methylenethienyl)ether (**29**) and 3,4-dibenzyl-2-hydroxymethylene-5-methylthiophene (**30**) (Scheme 11).[25,41] On the other hand, tetraphenylthiophene *S*-oxide gives a mixture of tetraphenylthiophene as the main product and tetraphenylfuran.[40a] 2,5-Di-*t*-butylthiophene *S*-oxide (**2f**) and 2,4-di-*t*-butylthiophene *S*-oxide form the corresponding furans, *e.g.* **31**, as the major products under the conditions (Scheme 12).[40] While the exact mechanism of this transformation is not ascertained, it is assumed that the 1,2-oxathiin may be an intermediate.[42]



Scheme 11
Photochemistry of thiophene *S*-oxides. Irradiation with a mercury high pressure lamp (100 W); c = 0.16 M.[25]

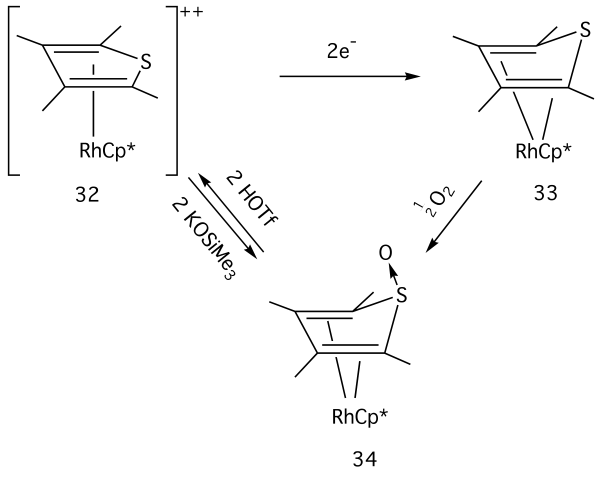


see ref. 40c

Scheme 12
Photochemistry of 2,5-di-t-butylthiophene *S*-oxide.[40c]

V Complexes with thiophene *S*-oxide as ligand

Rauchfuss and co-workers[43] have shown that Cp*Rh(η^4-tetramethylthiophene) (**33**) oxidises in a dry oxygen atmosphere to Cp*Rh(η^4-tetrathiophene *S*-oxide) (**34**). The reaction of a suspension of Cp*Rh(η^4-tetramethylthiophene) dication **32** – which features a Rh(III) species – with potassium trimethylsiloxate ($KOSiMe_3$) also gives **34**. (Scheme 13) In the first case, it seems to be established that the oxygen is activated by the Rh(I) centre of **33**.[43] An X-ray of the substance was carried out. It showed that the ligated thiophene *S*-oxide in **34** is non-planar, with the sulfur being located above the plane, away from the metal centre.[43] In contrast to the thiophene *S*-oxides themselves, however, the oxygen of the sulfoxy moiety is located on the same side of the plane as the sulfur.

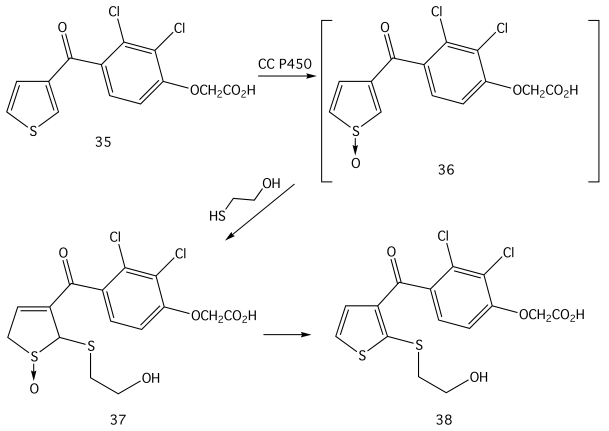


Scheme 13
Oxidation of coordinated thiophene preparation of Cp*Rh(Me_4C_4OS).[43]

VI Applications

The great interest in polythiophenes in the last two decades in connection with the desire to obtain narrow-band-gap polymers has led to preliminary investigations on using thiophene *S*-oxide units in phenylene or in heteroareno containing oligomers and polymers. First semiempirical calculations (SCF-CO method) by K. Tanaka *et al*.[44] indicated that the oxidation of thiophene moities in oligo- or poly-thiophenes would lead to a considerable change in band-gap value. Furthermore, thiophene *S*-oxides are more electron deficient than their thiophene counterparts and thus should have higher electron affinities. Both of these features have also been noted for thiophene *S,S*-dioxides by G. Barbarella *et al*.[45] It must be noted, however, that oligomers or polymers containing thienyl *S*-oxide units are photochemically not stable, but deoxygenate and thus revert to the corresponding thiophenes.[46] The conversion of thienyl *S*-oxides to furan units by photoirradiation has not been found to be a major pathway in the oligomeric structures studied thus far, when photoirradiated with a high-pressure mercury lamp using a Pyrex filter ($\lambda > 320$ nm). The rate of deoxygenation of oxidised dimeric thiophenes is in the order thienylthiophene *S*-oxide (dimer of thiophene and thiophene *S*-oxide > bis(thiophene *S*-oxide) > thienyl *S*-oxide-thiophene *S,S*-dioxide (dimer of thiophene *S*-oxide and thiophene *S,S*-dioxide).[46] Bis(thiophene *S,S*-dioxide) does not react photochemically under these conditions.[46]

Thiophene *S*-oxides and benzo[*b*]thiophene *S*-oxides have been invoked as intermediates in the *in vivo* metabolism of thiophenes and benzo[*b*]thiophenes, respectively.[9,47-50] It had been found that hepatic cytochrome P450 dependent oxidation of the diuretic drug thienilic acid (**35**) in the presence of NADPH leads to the formation of electrophilic metabolites which bind to hepatic proteins.[48] When mercaptoethanol was added during the incubation, the number of hepatic proteins bound to the reactive metabolite of thiophene decreased and the labile 3-aroyl-2-hydroxyethylthio-2,5-dihydrothiophene *S*-oxide **37**, which are in turn readily transformed into the 3-aroyl-2-hydroxyethylthio-thiophene **38**, could be isolated.[49] The occurrence of **37** can readily be explained by the intermediate formation of thiophene *S*-oxide **36** as a direct oxidation product of thiophene **35** (Scheme 14). Interestingly, the hepatic cytochrome P450 oxidation of benzo[*b*]thiophene in the presence of mercaptoethanol leads to 3-hydroxyethylthio-2,3-dihydrobenzo[*b*]thiophene *S*-oxide, which again can be explained by a Michael type addition of mercaptoethanol to a transient benzo[*b*]thiophene *S*-oxide.[47] Thus, the toxicity of thienilic acid and its ability to deactivate cytochrome P450 2C9 may be due to the occurrence of the highly electrophilic thiophene *S*-oxide. Further evidence of the oxidation of thiophene to thiophene *S*-oxide under these conditions comes from the isolation of two sesquioxides[9] from *in vitro* metabolism of labelled thiophene, which accounted for 90% of the introduced radioactivity.



Scheme 14
Thiophene S-oxide as a metabolite of thiophene. Cytochrome P450 dependent oxidation of thienilic acid and reaction with nucleophiles.[49]

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