The chemistry of thiophene $S$-oxides$^1$ and related compounds

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Abstract
The synthesis and reactivity of thiophene $S$-oxides is discussed, with special emphasis on the use of thiophene $S$-oxides as dienes in Diels-Alder type reactions, on the photochemistry and on the electrochemistry of the molecules. Where useful, the reactivity is compared to that of benzo[$b$]thiophene $S$-oxides, dibenzothiophene $S$-oxides, and tetracyclones.

Keywords: Thiophene $S$-oxides, Diels Alder reaction, photochemistry, electrochemistry

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Introduction
While thiophene $S,S$-dioxides $^1$ are well-known compounds, thiophene $S$-oxides $^2$ (Figure 1) have remained an elusive species until fairly recent times. As the methods of preparation and derivatization of thiophenes $^3$ are inherently different from those of all-carbon arenes, thiophene
$S$-oxides $2$ were viewed as interesting building blocks with the *proviso* that they could be synthesized from thiophenes directly and would prove be suitable cyclic dienes for cycloaddition reactions that would lead to multi-functionalized arenes, thus complementing existing routes to these compounds. This has been shown to be the case. Furthermore, thiophene $S$-oxides $2$ have been found to exhibit a wealth of interesting reactivity. In the following, some of the chemistry of thiophene $S$-oxides $2$ is detailed with an emphasis on reactions carried out in our laboratory.

![Figure 1](image_url)
1. Preparation and Structure

Thiophenes 3 can be oxidized to thiophene S-oxides 2, a route taken in the oxidation of thiophenes 3 with hydrogen peroxide or with peracids to yield the normally very stable thiophene S,S-dioxides 1 of cyclic diene character. In fact, a long time before their actual isolation and characterization, thiophene S-oxides 2 were considered as intermediates in the oxidation of thiophenes 3 to thiophene S,S-dioxides 1. This was due to the fact that dimeric cycloadducts, the so-called sesquioxides 7 – 9 (Figure 2), can be found as side-products in these reactions. These stem from the cycloaddition of thiophene S-oxide to thiophene S-oxide (for 7 and 8) or to thiophene S,S-dioxide (for 9). Interestingly, sesquioxides can also be found in oxidatively treated, thiophene-containing fuel.

That the oxidation of thiophenes can be stopped at the monoxide stage is a matter of adding a Lewis acid such as boron trifluoride etherate in the case of the peracid oxidants and of a proton acid such as trifluoroacetic acid in the case of hydrogen peroxide (Scheme 1). The same holds true for the oxidation of benzothiophenes 10 to benzothiophene S-oxides 4, the acid most likely having a dual function, namely to activate the peroxide/peracid and to complex to the monoxide once it is formed, hindering by the withdrawal of electron density from sulfur a further oxidation to the corresponding thiophene- or benzothiophene-S,S-dioxide.

![Scheme 1](image)

Figure 2
1. 

![Scheme 1](image)

via oxidation of thiophenes

(Mansuy, Nakayama, Furukawa, Thiemann)

2. 

![Scheme 1](image)

via zirconacyclopentadiene derivatives

(Fagan, Weiss, Tilley)

3. 

![Scheme 1](image)

(Prochazka)

4. 

![Scheme 1](image)

(to our knowledge, this has not been realized yet)

Scheme 1
The oxidation of thiophenes is not the only path to thiophene S-oxides. The second, versatile approach to aryl substituted thiophene S-oxides is via reaction of thionyl chloride with zirconacyclopentadienes 13,11 themselves prepared from diarylacetylenes 11 and dicyclopentadienylzirconium dichloride (12) (Scheme 1). Interestingly, the first preparation of a thiophene S-oxide, namely of 15, if only as a transient, detected species, utilized neither of the two routes, but rather took advantage of a bis-dehydromesylation of the tetrahydrothiophene S-oxide 14 (Scheme 1).12 In contrast, the all-carbon analogs of thiophene S-oxides, the tetra-arylcylopentadienones (tetracyclones) 6 are routinely prepared by the Weiss reaction.13 A similar preparation of thiophene S-oxides via dibenzyl sulfoxide (16) has not been reported thus far.

Thiophene S-oxides 2 and also benzo thiophene S-oxides 4 are much more sensitive than their dioxide counterparts. Depending on their substitution pattern, some of them cannot be kept in substance at room temperature. The thiophene S-oxides have been discussed as having an aromatic, anti-aromatic, and purely cycloalkadiene-like character.14 What has been found, also from X-ray crystal structures (Figure 3),7b,8,15 is that they are in fact dienes, where the lone pair of the sulfur does not interact with the cyclic diene moiety, the heterocyclic ring being puckered, this in contrast to the much better studied tetracyclones, which are planar molecules.16 Tetraaryl- substituted thiophene S-oxides are pale yellow, while tetra-arylcylopentadienones are dark purple. Thiophene S-oxides, however, do invert at the sulfur with different substituents at the C2/C5 positions leading to different barriers of inversion.2,17
2. Thiophene-\(S\)-oxides in [4 + 2]-Cycloaddition Reactions

Thiophene-\(S\)-oxides are useful dienes and add stereoselectively to a row of dienophiles (Scheme 2).\(^{18,19}\) With acetylenes 20 as the ene components, the substituted arenes 22 form directly. The sulfoxide bridge in 7-thiabicyclo[2.2.1]heptadiene \(S\)-oxides 21 is extruded spontaneously. With alkenes 18 as ene component, 7-thiabicyclo[2.2.1]heptene \(S\)-oxides 19 are formed. The stereochemistry at sulfur is controlled in the cycloaddition, stereoselectivity stemming from the ‘Cieplak’-effect (23 vs. 24, Scheme 2).\(^{20}\) Often, these cycloaddition reactions occur at room temperature. A competitive experiment at room temperature between tetracyclone 6 and tetraphenylthiophene \(S\)-oxide (2) and \(N\)-phenylmaleimide (25) leads to exclusive formation of 7-thiabicyclo[2.2.1]heptene \(S\)-oxide 26 (Scheme 3). Tetra-arylthiophene \(S\)-oxides are thermally stable for limited periods of time, so that they can be reacted with substrates under microwave irradiation, successfully. While thiophene \(S\)-oxides are useful dienes in Diels Alder reactions, it is much more difficult to react them as the ene component as either self-dimerization occurs with the less substituted thiophene-\(S\)-oxides or the molecules are too sluggish to react in case of heavily substituted thiophene-\(S\)-oxides.

Scheme 2
For normal electron demand cycloaddition reactions:
Thiophene S-oxides are more reactive towards electron-deficient dienophiles than tetracyclone

Competitive experiment:

\[
\begin{array}{c}
\text{Ph} & \text{Ph} & \text{S} & \text{O} & \text{Ph} & \text{Ph} \\
\text{Ph} & \text{Ph} & \text{O} & \text{Ph} & \text{Ph} & \text{Ph} \\
\text{Ph} & \text{Ph} & \text{N} & \text{Ph} & \text{Ph} & \text{N} \\
\end{array}
\]

1 eq. 1 eq. 2 eq. (forms exclusively !!!)

(26)

\[20^\circ C \text{CDCl}_3\]

Note: Both thiophene S-oxides and tetracyclones are stable under microwave irradiation (no difference when compared to the stability of the compounds under purely thermal conditions at the same temperature). The reaction of 2,5-dialkyl-3,4-dibenzothiophene S-oxide with p-naphthoquinone in diphenyl ether takes less than 2 min. under microwave irradiation (120 °C). The effect of the microwave-specific component vs. the purely thermal component in the microwave irradiated reaction still needs to be studied.

Scheme 3

Benzo[b]thiophene-S-oxides 10 and benzo[b]thiophene-S,S-dioxides 27 \(^{21}\) are good enes in Diels Alder reactions. Self-adducts only form at high temperatures. Benzo[b]thiophene S,S-dioxides 27 have also been reacted with both an excess of tetracyclone 6 and of tetraphenylthiophene S-oxide (2a) as diene, where the reaction has been performed in diphenyl ether at 135 °C. Here, interestingly, part of the tetracyclone 6 is oxidized to \(\alpha\)-pyrone 29, probably by the initially formed cycloadduct sulfone, giving substituted dibenzothiophenes 28 as the final products.\(^{21}\) In the case of tetraphenylthiophene S-oxide (2a), dibenzothiophene S,S-dioxides 30 are formed (Scheme 4). Both benzo[b]thiophene S-oxides such as 34\(^{18a}\) and benzo[b]thiophene S,S-dioxides such as 31 can be reacted as formal dienes with electron deficient acetylenes and alkenes as long as either the C2- or C3 position of the oxygenated benzo[b]thiophenes carry a substituent (Scheme 5).\(^{22}\)
7-Thiabicyclo[2.2.1]heptene S-oxides 19 themselves are versatile synthetic intermediates. Oxidative extrusion of the sulfoxy bridge leads to multi-functionalized arenes 22. The extrusion can be accomplished thermally,\textsuperscript{23} electrochemically,\textsuperscript{23} photochemically\textsuperscript{24} or by using KMnO\textsubscript{4} as oxidant\textsuperscript{25} under phase transfer conditions (Scheme 6). The last three reactions are run at room temperature. As the reaction of thiophenes to thiophene S-oxides also proceeds at room temperature or below, the above represents a two-step procedure of transforming substituted thiophenes to substituted arenes at room temperature. This transformation, also run as a one-pot
oxidation - cycloaddition reaction,\textsuperscript{26} has been used to prepare multi-functionalized cyclophanes such as \textbf{41} and \textbf{43} (Scheme 7),\textsuperscript{27} crown ethers such as \textbf{45} (Scheme 8)\textsuperscript{25} and phenyl-substituted amino acids \textbf{49} (Scheme 8)\textsuperscript{28} from their thiényl precursors. Furthermore, 7-thiabicyclo[2.2.1]heptene S-oxides \textbf{19} can be transformed to 7-thiabicyclo[2.2.1]heptenes \textbf{37} by action of PBr\textsubscript{3},\textsuperscript{24} to substituted cyclohexadienes \textbf{38} with Bu\textsubscript{3}SnH\textsuperscript{24} and to diphenyl disulfides \textbf{36},\textsuperscript{29} when halo substituted 7-thiabicyclo[2.2.1]heptene S-oxides are reacted with base (Scheme 6).

\textbf{Scheme 6}
Scheme 7

**Cyclophanes**

\[
\begin{align*}
R \quad \text{(CH}_2\text{n)} & \quad \text{(CH}_2\text{n)} \\
\text{(CH}_2\text{n)} & \quad m-\text{CPBA} \\
\text{(CH}_2\text{n)} & \quad \text{BF}_3 \cdot \text{Et}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{40} & \quad \text{41} \\
\text{42} & \quad \text{43} \\
\end{align*}
\]

[ref. 27]

**Crown Ethers**

\[
\begin{align*}
\text{44} & \quad \text{45} \\
\text{46} & \quad \text{47} \\
\end{align*}
\]

[ref. 28]

**Amino Acids**

\[
\begin{align*}
\text{47} & \quad \text{48} \\
\text{49} & \quad \text{50} \\
\end{align*}
\]

[ref. 28]
3. Photochemistry of Thiophene S-Oxides

When thiophene S-oxides are left in solution exposed to daylight, most revert slowly to the corresponding thiophenes, where a number of other products can be in evidence. This deoxygenation occurs in the dark, too, but much more slowly. Thiophene S-oxides exhibit a certain cytotoxicity. Typical examples are shown in Fig. 4.

![Chemical structures](image)

**Figure 4**
Studies on the interaction between 3,4-dibenzyl-2,5-dimethylthiophene S-oxide (2b) and isolated dsDNA have been carried out electroanalytically.\textsuperscript{31} As 2b shows very low solubility in polar solvents, a mixture of dsDNA and compound in pH 7.4 phosphate buffer was placed on the glassy carbon electrode surface and dried for 24h. It was found that 2b does not damage dsDNA directly. Only after an initial reductive step of 2b at -1.6V vs. SCE was damage to dsDNA observed due to the appearance of an oxidation peak corresponding to 8-oxoguanine in the differential pulse voltammogram. The preparation of water-soluble thiophene S-oxides in form of carbohydrate-substituted thiophene-S-oxides for studies in polar aqueous or alcoholic solvents has been unsuccessful thus far.\textsuperscript{32} Nevertheless, the possibility that the cytotoxicity of the molecules is also linked to their deoxygenation has been considered.\textsuperscript{33}

![Photochemical reactions of thiophene S-oxides: Pathway 1](image)

**Scheme 9**

As light accelerates the deoxygenation of the thiophene S-oxides 2, photochemical investigations of thiophene S-oxides were initiated, although the authors were aware of the fact that the mechanisms leading to deoxygenation and operating in the light- reaction and in the dark- reaction might well be different. It was found that the molecules exhibit a rich photochemistry,\textsuperscript{34} which depends on the substitution pattern of the thiophene S-oxides. Photo-irradiation of 2- or 5- alkylated thiophene-S-oxides such as 2b with a proton in a position alpha to the heterocyclic ring leads to hydroxylated thiophenes such as to 50 and 51 (Scheme 9). The presence of a reductant in the reaction mixture, such as of an amine, leads to exclusive deoxygenation to the parent thiophene compound 53 (Scheme 11). In the presence of thiophenol 54, again exclusive photodeoxygenation is found. Here, diphenyl disulfide 55 is obtained as the oxidized product (Scheme 11). It is believed that water is formed concomitantly. The nature of the initially liberated oxygen species has been a matter of discussion.
Photochemical reactions of thiophene S-oxides: Pathway 2

Insertion of the oxygen into the heterocyclic ring and extrusion of sulfur

\[ \text{B} \rightarrow \text{O} \]

Scheme 10

When dibenzothiophene S-oxides are photo-irradiated, deoxygenation also occurs.\(^3\) It is this transformation that has initiated the discussion on the nature of such a photo-extruded oxygen. A mono-molecular process has been considered.\(^3\) In such a case, the liberated oxygen species may be monoatomic oxygen \(\text{O}(^3\text{P})\). This mechanism has been supported by trapping experiments.\(^3\)\(^,\)\(^3\)\(^7\) New work by Jenks and his co-workers indicates that in the case of dibenzothiophene S-oxides the photochemical active state is the lowest singlet, not the lowest triplet.\(^3\)\(^7\) Previously, the possibility of release of singlet oxygen via an excited benzothiophene S-oxide dimer has been put forward.\(^3\)\(^8\) Attempts to substitute dibenzothiophene S-oxides in such a way that formation of an excited dimer would be sterically unfavorable, led to the observation that while 4,6-trimethylsilyldibenzothiophene S-oxide deoxygenates less effectively than non-substituted dibenzothiophene S-oxide or 4,6-dimethyl dibenzothiophene S-oxide, the equally bulky 4,6-bis-(2,5-dimethylphenyl)dibenzothiophene S-oxide deoxygenates very efficiently.\(^3\)\(^9\) This seems to indicate that steric requirements do not influence the rate of deoxygenation but rather that the nature of the substituent (substituent effect) influences the outcome of the photoreaction.
Photochemical reactions of thiophene S-oxides: Pathway 3
Exclusive deoxygenation, often found in the presence of an additive that can be oxidized

\[
\begin{align*}
\text{MeO} & \quad \text{OMe} \\
\text{MeO} & \quad \text{OMe}
\end{align*}
\]

\chem{\text{MeO} \quad \text{OMe} \quad \text{S} \quad \text{MeO} \quad \text{OMe} \quad \text{h} \nu \quad \text{CD}_2\text{Cl}_2 \quad \text{(non-dried)} \quad \text{piperidine or dibenzylamine} \quad \text{(5 eq.)}}

\chem{\text{MeO} \quad \text{OMe} \quad \text{S} \quad \text{MeO} \quad \text{OMe} \quad \text{53} \quad (44\% \text{ isolated yield})}

\chem{\text{MeO} \quad \text{OMe} \quad \text{S} \quad \text{MeO} \quad \text{OMe} \quad \text{h} \nu \quad \text{CD}_2\text{Cl}_2 \quad \text{2.5h, rt} \quad \text{S} \quad \text{MeO} \quad \text{OMe} \quad \text{53}}

\chem{\text{MeO} \quad \text{OMe} \quad \text{S} \quad \text{MeO} \quad \text{OMe} \quad \text{54} \quad + \quad \text{MeO} \quad \text{PH}_{2} \quad \text{SH} \quad \text{h} \nu \quad \text{CD}_2\text{Cl}_2 \quad \text{2.5h, rt} \quad \text{MeO} \quad \text{OMe} \quad \text{S} \quad \text{MeO} \quad \text{OMe} \quad \text{53} \quad + \quad \text{MeO} \quad \text{PH}_{2} \quad \text{S-S} \quad \text{OMe} \quad \text{55}}

[ref. 34]

Scheme 11

In thiophene-S-oxides that do not possess a substituent at C2 or C5 with a proton alpha to the heterocyclic ring system the photo-irradiation leads to a different reaction outcome. Thus, both 2,5-diphenylthiophene S-oxide and 2,5-bis-(t-butyl)thiophene S-oxide (2e) (Scheme 10) give significant amounts of furans. Small quantities of difuryl disulfides can be isolated as side products. The authors have postulated oxathiin (Scheme 10) as a possible intermediate. Important, though, is that this transformation represents a photo-induced extrusion of sulfur from thiophene derivatives.

4. Electrochemistry of Thiophene S-Oxides

Thiophene S-oxides exhibit interesting electrochemistry, which differs from that of the corresponding C-analogs, the tetracyclones. In the reductive electrochemistry, the main reaction is a reduction of thiophene S-oxide 2 to the thiophene 3;\textsuperscript{40} in the case of the tetracyclone 6 it is the formation of its stable radical anion followed by further reduction.\textsuperscript{41}
Electrochemistry of Tetraphenylthiophene S-oxide (constitutes part of an electrochemical oxidative desulphurisation of thiophenes)

\[
\begin{align*}
2a & \xrightarrow{1.6 \text{ V vs SCE}} & 56 \\
& \text{Pt-electrode} & \text{MeCN/Bu4NPF6} & + \\
\end{align*}
\]

(stereochemistry of the dibenzoylestilbene was verified by 'wet'-chemical synthesis)

(favoured at higher potential)

Scheme 12

The oxidative electrochemistry of the classes of molecules also differs – under forced electro-oxidative conditions thiophene S-oxides 2 form diphenacylstilbenes under extrusion of sulfur,\(^4\) while the tetracyclones 6 form \(\alpha\)-pyrones 58. Ultrasonication of the substrates at 40 and 850 kHz during the electro-oxidation enhanced the current for both tetraphenylthiophene S-oxide and tetracyclone,\(^4\) but did not mitigate\(^3\) the fouling processes that are often associated with the oxidative processes.

Indications that 2-substituted benzothiophene-S-oxides ring-open oxidatively have been obtained.\(^4\) The electro-oxidative extrusion of sulfur may find some future application in an electro-oxidative desulfurization of benzo- and dibenzothiophene containing fuels.

\[
\begin{align*}
6 & \xrightarrow{1.45-1.50 \text{ V vs. SCE}} & 58 \\
& \text{Pt-electrode} & \text{MeCN/Bu4NPF6} & + \\
\end{align*}
\]

Scheme 13
Acknowledgements

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References and Notes

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44. Iniesta, J.; Thiemann, T., unpublished results.