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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Contents

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.

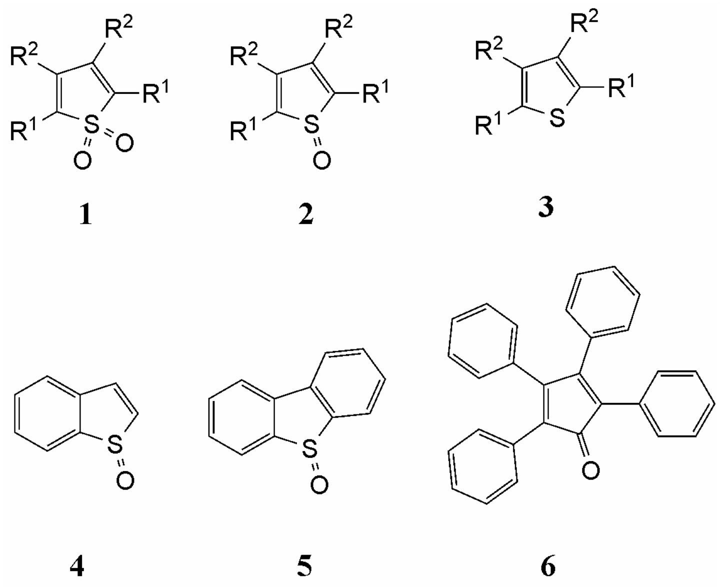


Figure 1

1. Preparation and Structure

Thiophenes **3** can be oxidized to thiophene *S*-oxides **2**,[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**[3] 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),[4,5] 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.[6]

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[5,7] and of a proton acid such as trifluoroacetic acid in the case of hydrogen peroxide (Scheme 1).[8] The same holds true for the oxidation of benzothiophenes **10** to benzothiophene *S*-oxides **4**,[9,10] 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.

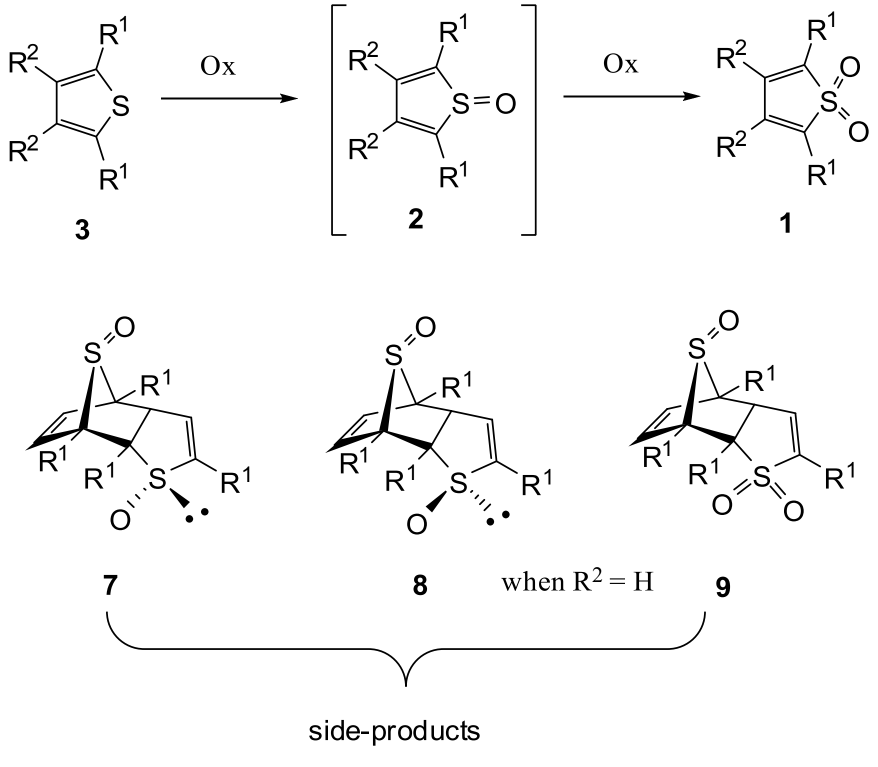
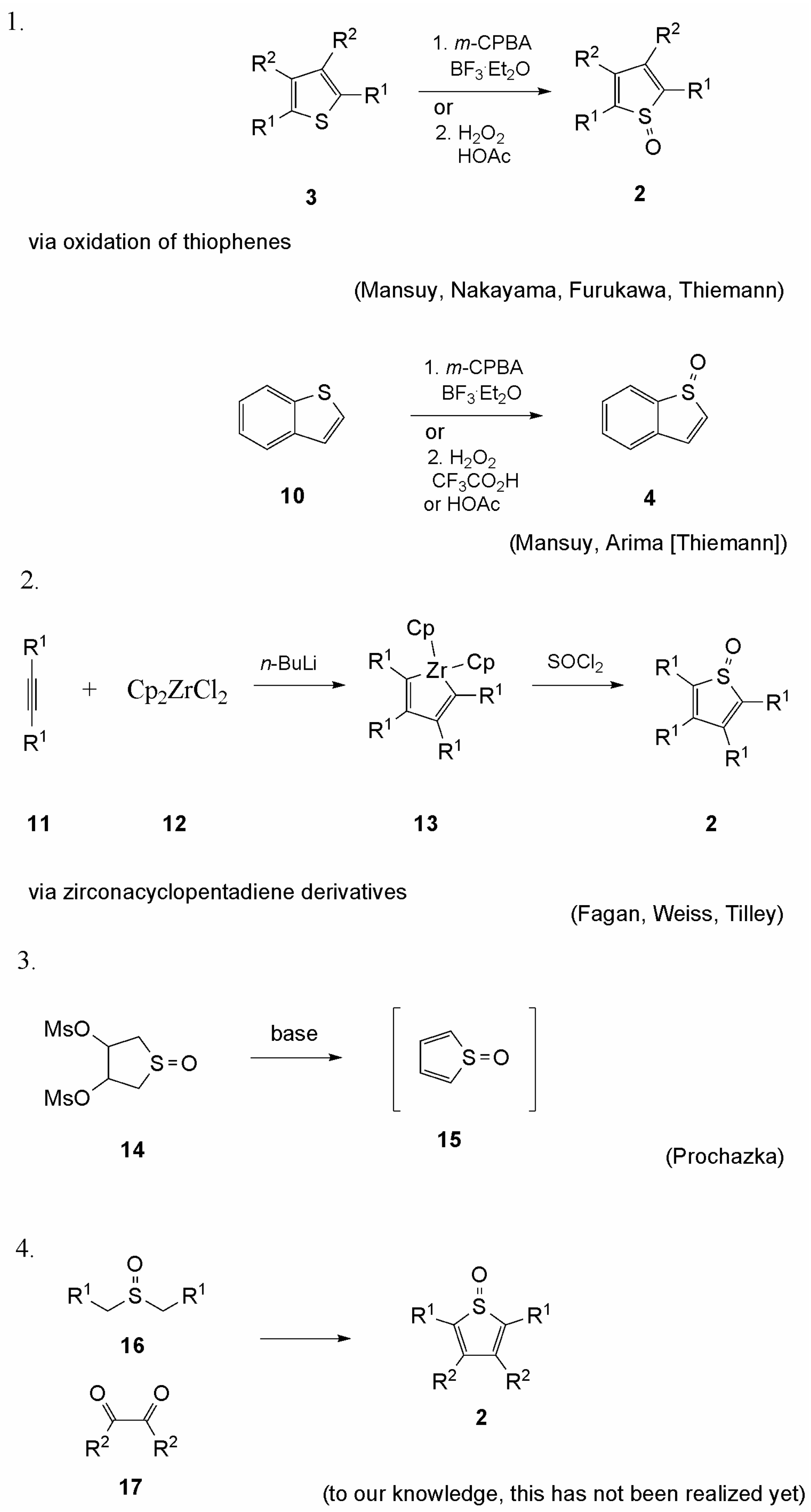
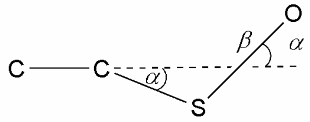


Figure 2


1.
1. m-CPBA
BF3·Et2O
or
2. H2O2
HOAc
3
2
via oxidation of thiophenes
(Mansuy, Nakayama, Furukawa, Thiemann)
1. m-CPBA
BF3·Et2O
or
2. H2O2
CF3CO2H
or HOAc
10
4
(Mansuy, Arima [Thiemann])
2.
Cp2ZrCl2
n-BuLi
SOCl2
11
12
13
2
via zirconacyclopentadiene derivatives
(Fagan, Weiss, Tilley)
3.
base
14
15
(Prochazka)
4.
16
17
2
(to our knowledge, this has not been realized yet)

Scheme 1



α = 9.3° for 3,4-bis(*tert*-butyl)thiophene *S*-oxide[7d]
12.9° for 2,5-diphenylthiophene *S*-oxide[8,15a]
13.6° for 2,5-bis(diphenylmethylsilyl)thiophene *S*-oxide[15b]

β = 47.5° for 3,4-bis(*tert*-butyl)thiophene *S*-oxide[7d]
56.5° for 2,5-diphenylthiophene *S*-oxide[8,15a]

S - O = 1.484(3) A for 2,5-diphenylthiophene *S*-oxide[8,15a]
1.471(2) A for 2,5-bis(diphenylmethylsilyl)thiophene *S*-oxide[15b]
1.494(1) A for 3,4-bis(*tert*-butyl)thiophene *S*-oxide[7d]

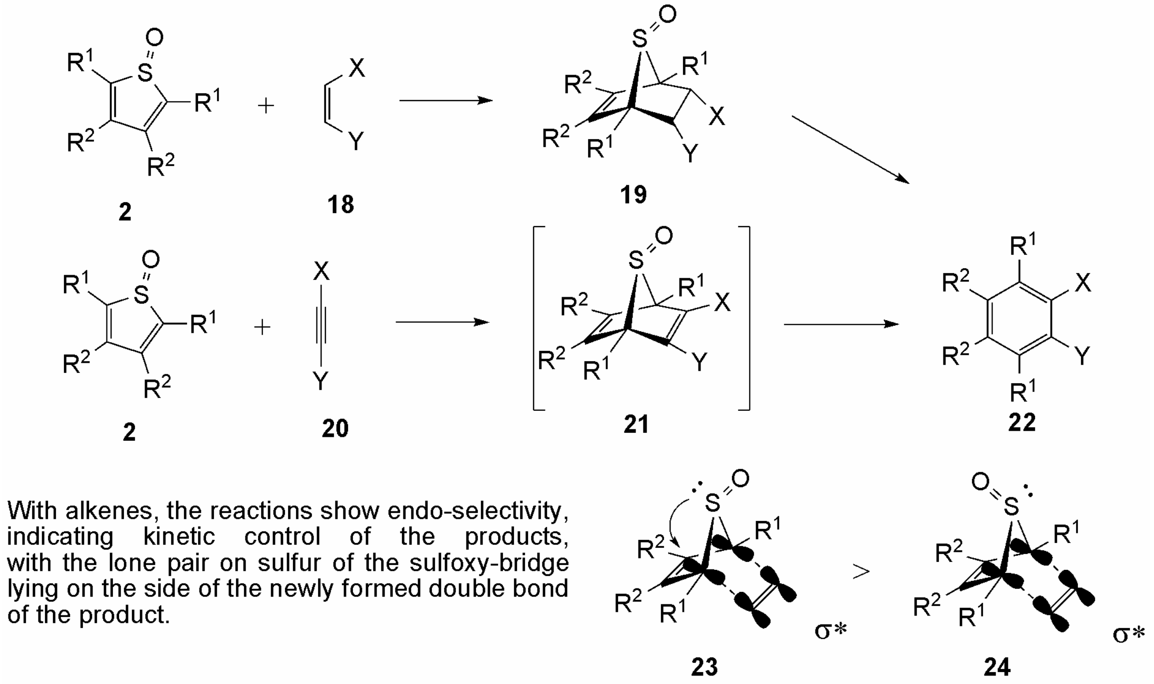
Structural parameters from X-ray structural analyses of thiophene *S*-oxides

Figure 3

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-arylcyclopentadienones (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 benzothiophene *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] Tetra-aryl- substituted thiophene *S*-oxides are pale yellow, while tetra-arylcyclopentadienones 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



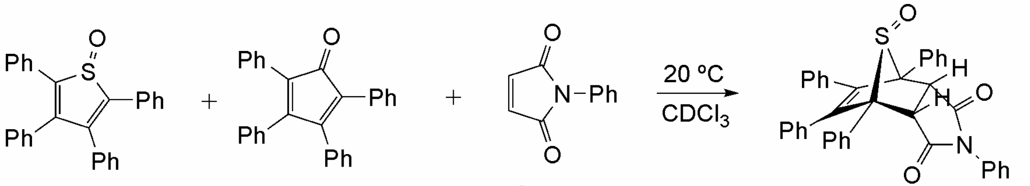
With alkenes, the reactions show endo-selectivity, indicating kinetic control of the products, with the lone pair on sulfur of the sulfoxy-bridge lying on the side of the newly formed double bond of the product.

Scheme 2

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.

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

Competitive experiment:



1 eq. **2** 1 eq. **6** 2 eq. **25**

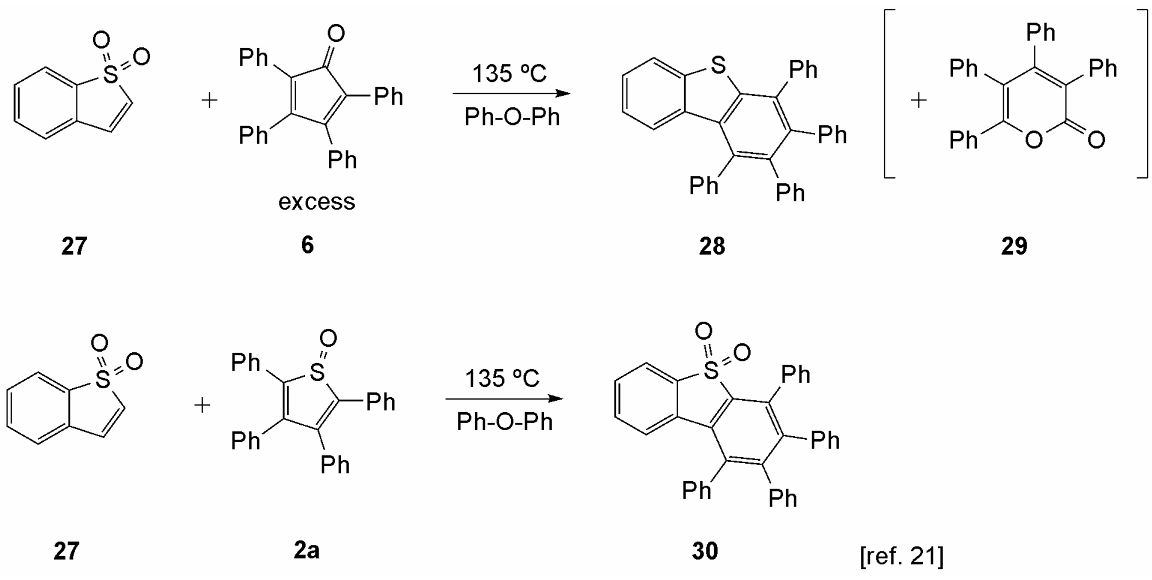
(forms exclusively !!!) **26**

(the reaction completes at 45 °C in 90 min.)

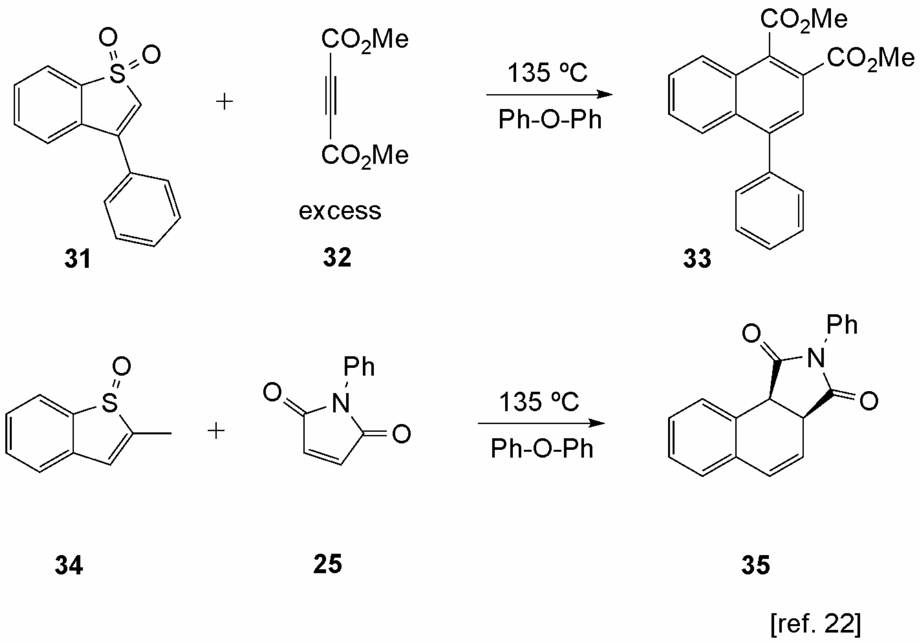
Note: Both thiophene *S*-oxides and tetracyclones are stable under microwave irradiation (no difference when compared to the stability of the compounds under purely thermal conditions at the same temperature). The reaction of 2,5-dialkyl-3,4-dibenzylthiophene S-oxide with p-naphthoquinone in diphenyl 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 α-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]

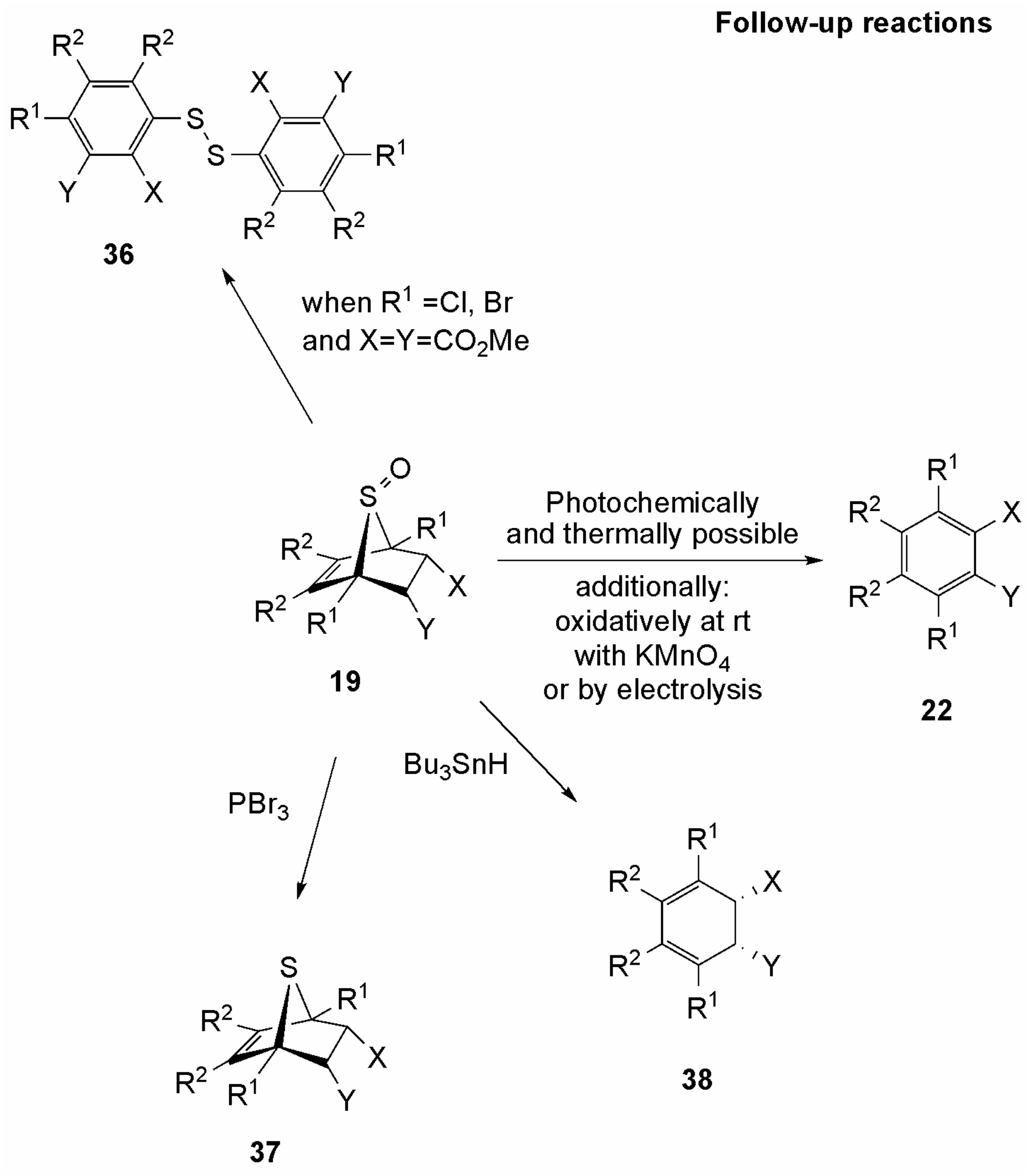


Scheme 4

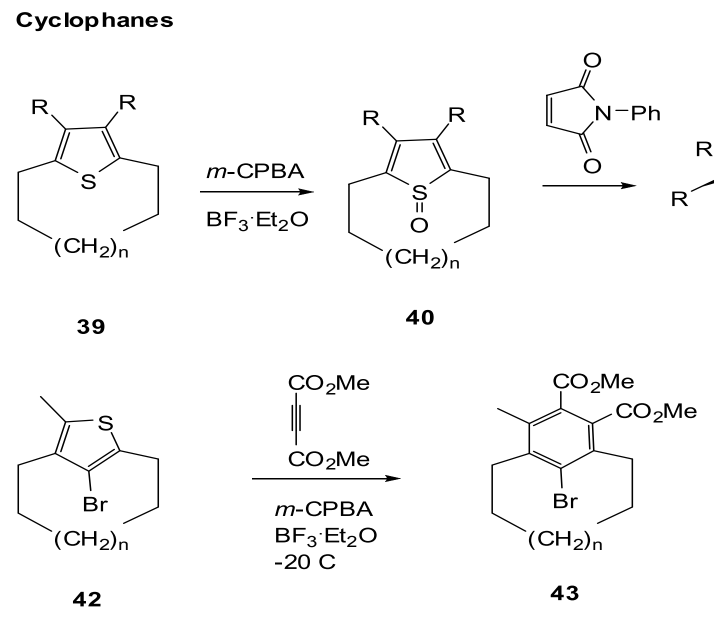


Scheme 5

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,[23] electrochemically,[23] photochemically[24] or by using $KMnO_4$ as oxidant[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,[26] has been used to prepare multi-functionalized cyclophanes such as **41** and **43** (Scheme 7),[27] crown ethers such as **45** (Scheme 8)[25] and phenyl-substituted amino acids **49** (Scheme 8)[28] from their thienyl precursors. Furthermore, 7-thiabicyclo[2.2.1]heptene *S*-oxides **19** can be transformed to 7-thiabicyclo[2.2.1]heptenes **37** by action of PBr_3,[24] to substituted cyclohexadienes **38** with Bu_3SnH[24] and to diphenyl disulfides **36**,[29] when halo substituted 7-thiabicyclo[2.2.1]heptene *S*-oxides are reacted with base (Scheme 6).

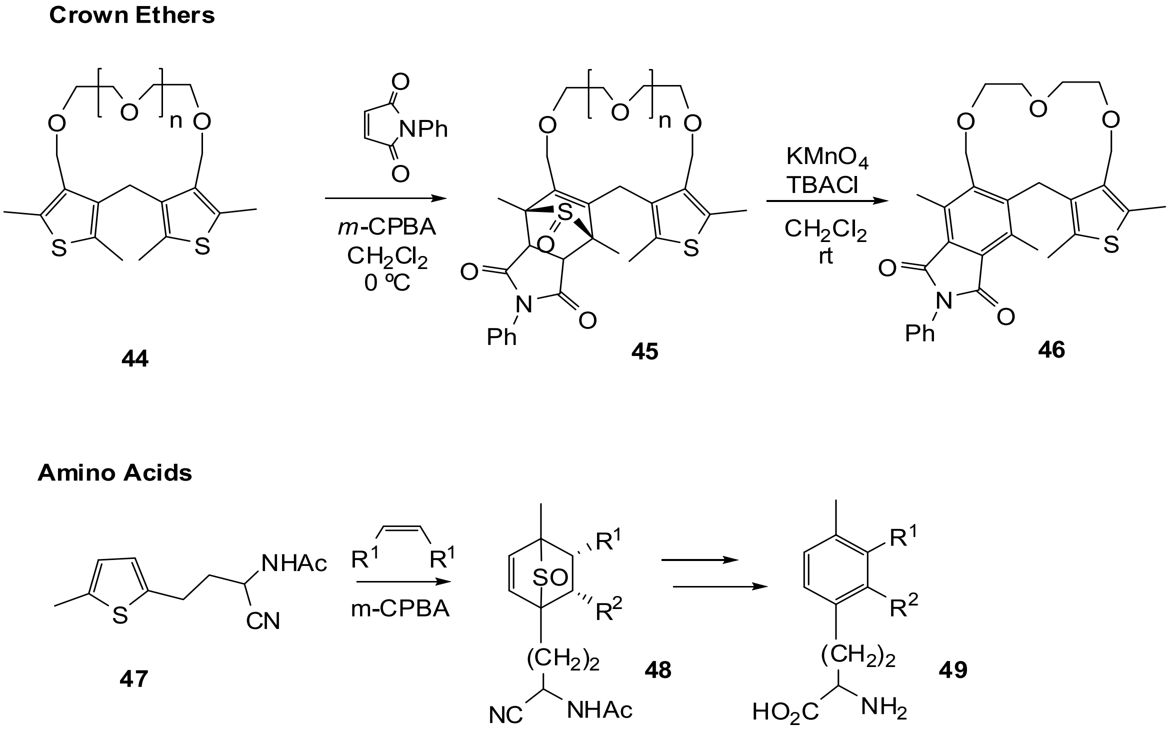


Scheme 6



[ref. 27]

Scheme 7



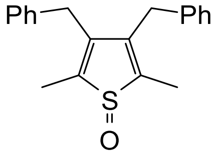
[ref. 28]

Scheme 8

3. Photochemistry of Thiophene *S*-Oxides

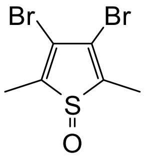
When thiophene *S*-oxides are left in solution exposed to daylight, most revert slowly to the corresponding thiophenes, where a number of other products can be in evidence. This deoxygenation occurs in the dark, too, but much more slowly. Thiophene *S*-oxides exhibit a certain cytotoxicity.[30] Typical examples are shown in Fig. 4.

Cytostatic activity of some thiophene S-oxides *vs*. NCI cancer cell lines



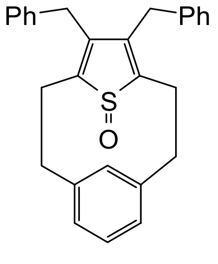
2b

CNS SF-268 Growth Percentage: -83



2c

NCI-H460 (Lung) Growth Percentage: -80



2d

CNS SF-268 Growth Percentage: -82

NCI-H460 (Lung) Growth Percentage: -87

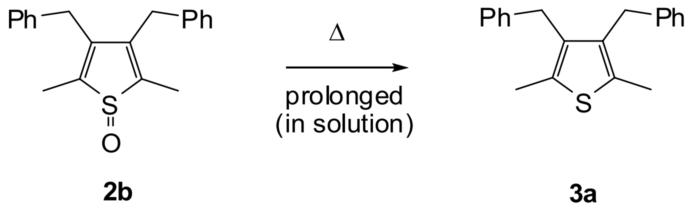
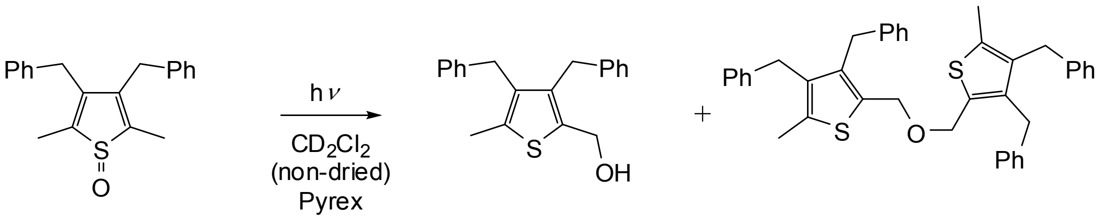


Figure 4

Studies on the interaction between 3,4-dibenzyl-2,5-dimethylthiophene *S*-oxide (**2b**) and isolated dsDNA have been carried out electroanalytically.[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.[32] Nevertheless, the possibility that the cytotoxicity of the molecules is also linked to their deoxygenation has been considered.[33]

Photochemical reactions of thiophene S-oxides: Pathway 1

Loss of oxygen and concomitant oxygen insertion into C-H bond of an alkyl substituent



2b **50** **51**

Irradiation with a mercury high pressure lamp (100 Watt); for *c* = 0.16 M in **2b**: **50** (7%); **51** (70%)
for *c* = 0.016 M in **2b**: **50** (35%); **51** (35%)

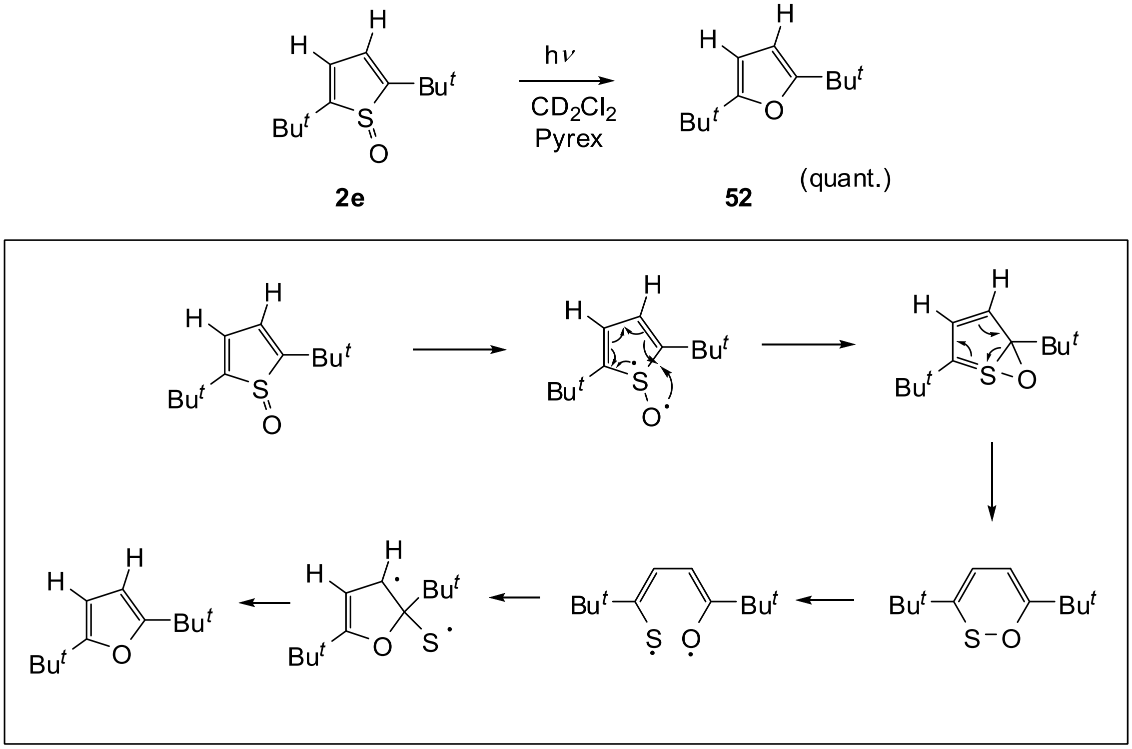
[ref. 34]

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,[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

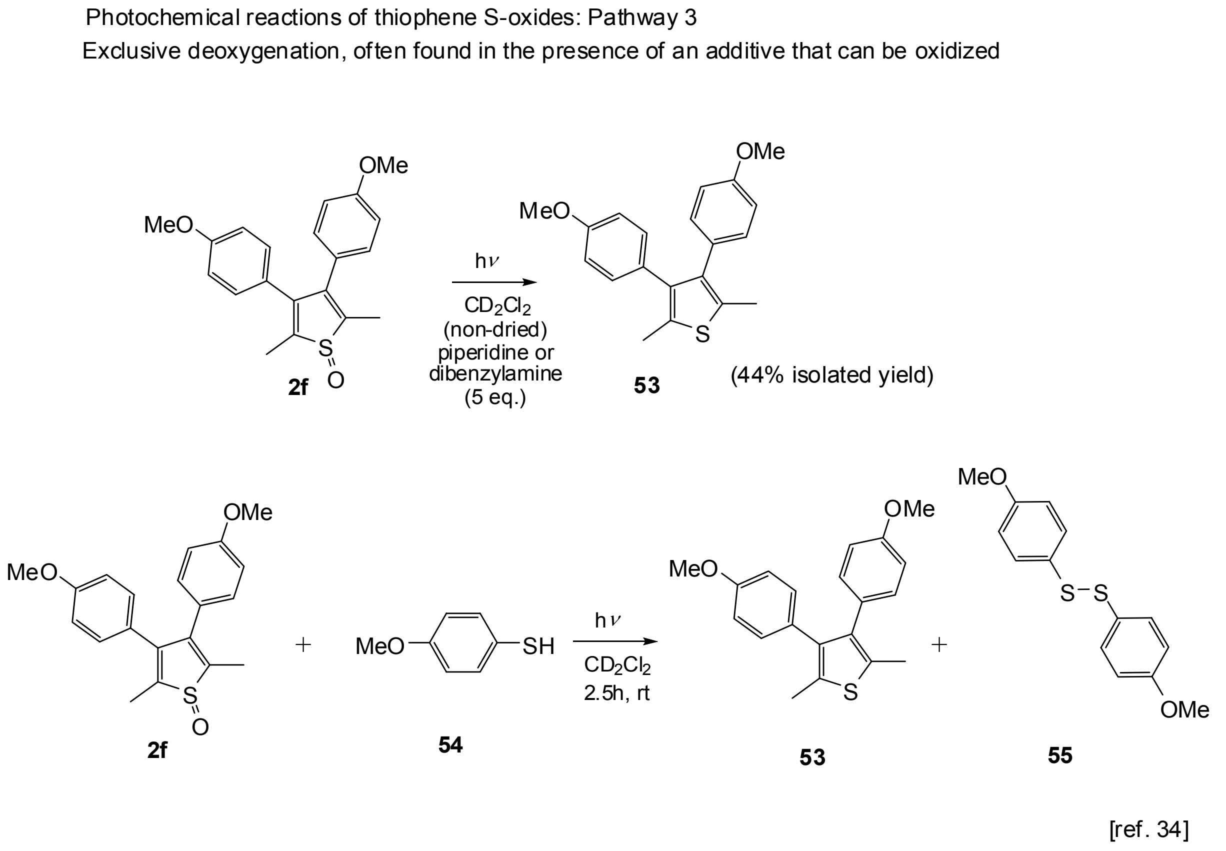
Insertion of the oxygen into the heterocyclic ring and extrusion of sulfur



[ref. 34]

Scheme 10

When dibenzothiophene *S*-oxides are photo-irradiated, deoxygenation also occurs.[35] 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.[36] In such a case, the liberated oxygen species may be monoatomic oxygen O(^{3}P). This mechanism has been supported by trapping experiments.[36,37] 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.[37] Previously, the possibility of release of singlet oxygen via an excited benzothiophene *S*-oxide dimer has been put forward.[38] 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-dimethyldibenzothiophene *S*-oxide, the equally bulky 4,6-bis-(2,5-dimethylphenyl)dibenzothiophene *S*-oxide deoxygenates very efficiently.[39] 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.



[ref. 34]

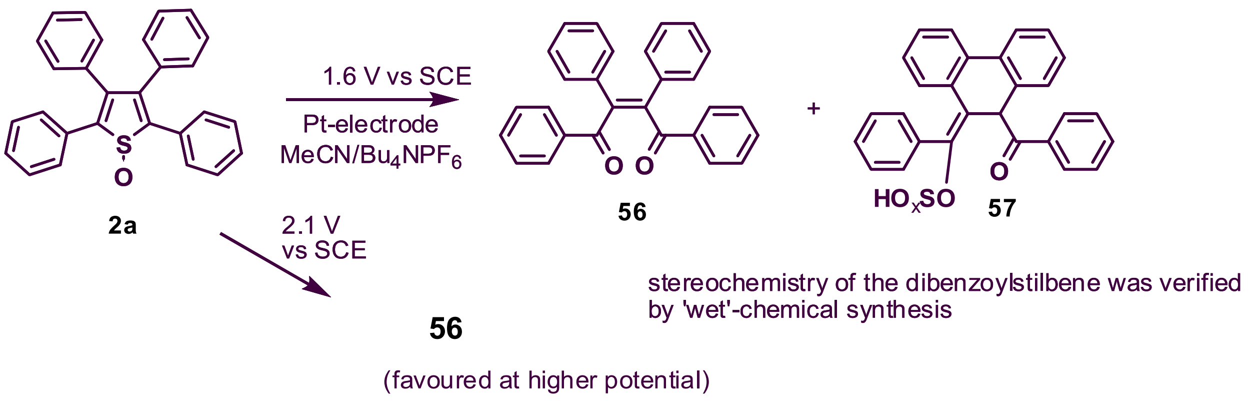
Scheme 11

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**,[40] in the case of the tetracyclone **6** it is the formation of its stable radical anion followed by further reduction.[41]

Electrochemistry of Tetraphenylthiophene *S*-oxide
(constitutes part of an electrochemical oxidative desulfurisation of thiophenes)



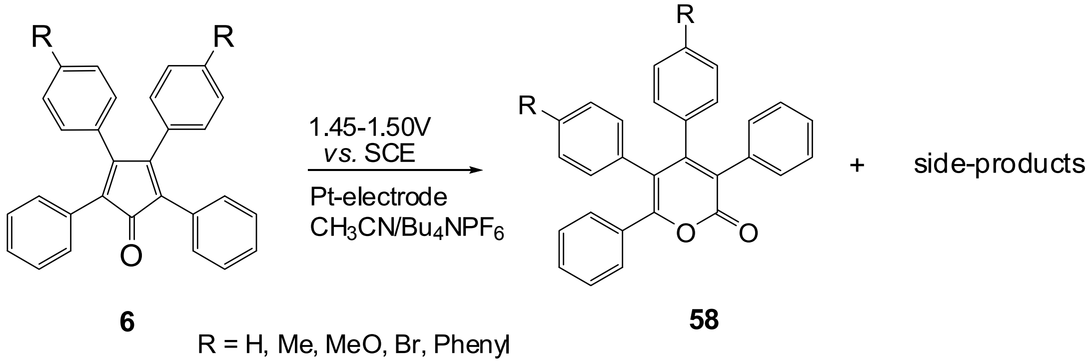
stereochemistry of the dibenzoylstilbene was verified by 'wet'-chemical synthesis

[ref. 42]

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,[42] while the tetracyclones **6** form *α*-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,[43] but did not mitigate[23] the fouling processes that are often associated with the oxidative processes.

Indications that 2-substituted benzothiophene-*S*-oxides ring-open oxidatively have been obtained.[44] The electro-oxidative extrusion of sulfur may find some future application in an electro-oxidative desulfurization of benzo- and dibenzothiophene containing fuels.



[ref. 42]

Scheme 13

Acknowledgements

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