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Review

Thiophene *S*-oxides as substrates in cycloaddition reactions

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ABSTRACT

Until recently, thiophene *S*-oxides have been elusive molecules. Their existence as intermediates in the peracid mediated oxidation of thiophenes to thiophene *S*,*S*-dioxides, however, made it possible to use them *in situ* as dienes in Diels Alder reactions. Over the last 15 years, their concise synthesis and handling in pure form led to their utilization in further cycloaddition reactions. The high stereoselectivity of these reactions and the chemical versatility of the cycloadducts make thiophene *S*-oxides interesting study objects for the future.

KEYWORDS: thiophene *S*-oxides, cycloaddition, π-face selective reaction, functionalized arenes, cyclohexadienes

INTRODUCTION

Five-membered heteroaromatic compounds (Figure 1) can be induced to undergo cycloaddition reactions with alkenes and alkynes, albeit often under severe reaction conditions, usually in the order of reactivity furan > pyrrole > thiophene, reflecting the increasing aromaticity furan **2** < pyrrole **3** < thiophene **1** [1]. Resonance energies have been calculated as 121 kJ/mol (thiophene), 88 kJ/mol (pyrrol), 67 kJ/mol (furan) and 250 kJ/mol (benzene) [1]. Also, within the chalcogene substituted five-membered heterocycles, thiophene exhibits the highest aromaticity: furan **2** < selenophene **4** < tellurophene **5** < thiophene **1** < benzene. Thiophene is known to undergo cycloaddition reactions at high temperatures [2], high pressure [3], with very reactive dienophiles [4], when the thiophene is part of a highly strained system [5], where the cycloaddition releases strain energy or when the thiophene is adequately donor substituted [6] (Scheme 1).

In the case of pyrroles and thiophenes, the heteroatom can be oxidized, leading to a loss of electron density needed for the aromaticity of the molecule. Thus, thiophenes **11** can be oxygenated at sulfur to lead, at least in theory, to thiophene *S*-oxides **16**, and hence to the very well-known and studied thiophene *S*, *S*-dioxides **17** (Scheme 2) [7, 8]. Thiophene *S*,*S*-dioxides **21** are classic cyclic dienes [9] and behave as such.

Compared to cyclopentadienes, thiophene *S*,*S*-dioxides possess in the sulfone group an electron-withdrawing functionality, leading both to a polarization and to a reduction of the electron density in the diene system [10]. This results in a decrease of the energy of the HOMO as compared to identically substituted cyclopentadienes [10]. Furthermore, compared to cyclopentadienes, non-substituted at C5, thiophene *S*,*S*-dioxides are sterically more exacting, 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 often necessitate higher temperatures [11, 12] in cycloaddition reactions than identically substituted cyclopentadienes.

Slightly less sure has been the status of thiophene *S*-oxides until recently. Here, calculations preceded

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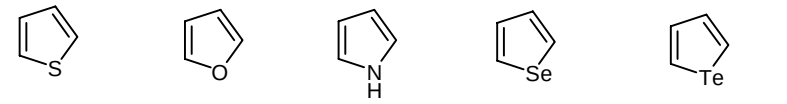


1 thiophene **2** furan **3** pyrrole **4** selenophene **5** tellurophene

Figure 1

an actual concise synthesis of this class of compounds. Initially, different calculations led to different values of aromaticity attributed to thiophene *S*-oxides, where answers varied from thiophene *S*-oxides being aromatic to thiophene *S*-oxides being pure cyclic dienes, according to possible conformations the molecule could take. Calculations also showed that certain conformations of thiophene *S*-oxides could lend the molecules an appreciable anti-aromatic character [13].

In the last 15 years, it could be shown that thiophene *S*-oxides are not only viable intermediates in oxidation reactions of thiophenes but also are isolable substances. In both cases, they have been found to be interesting and versatile substrates in cycloaddition reactions, and it is this aspect that this review will recount.

Thiophene *S*-oxides are prepared and used as diene components *in situ*

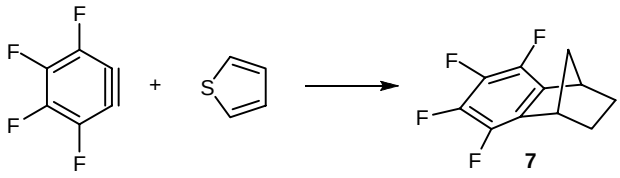
At first, the preparation of thiophene *S*-oxides was hampered [14] by the fact that simple peracid or peroxide induced oxidation of the sulfur, a general route to prepare thiophene *S*,*S*-dioxides (Scheme 2), did not lead to any appreciable amounts of thiophene *S*-oxides, as the oxidation of thiophene *S*-oxides to the corresponding *S*,*S*-dioxides was easier than the oxidation of the thiophenes to the mono-oxygenated species. That thiophene *S*-oxides are intermediates in the peracid and peroxide mediated oxidation of thiophenes to thiophene *S*,*S*-dioxides, however, was realized long ago [15], with the isolation of so-called sequioxides as by-products in the reactions [16]. Sequioxides are either self-dimerisation products, formed by cycloaddition, with the thiophene *S*-oxide intermediates playing the role of both diene and dienophile, or products stemming from the cycloaddition of the thiophene *S*-oxide to the thiophene *S*,*S*-dioxide (Figure 2).

K. Torssell [17] was the first to realize that upon oxidation, thiophenes can react in the presence of other, electron-withdrawing alkenes in a [4+2] cycloaddition, demonstrating this behavior of thiophenes by treating methyled thiophenes, eg., **24**, with *meta* chloroperoxybenzoic acid (*m*-CPBA) in the presence of quinones such as with benzoquinone **25**. Quinones make for rather poor dienophiles under the conditions, giving cycloadducts as product mixture in low yield (Scheme 3).

Nevertheless, A. M. Naperstkow, A. G. Fallis *et al.* [18] and Thiemann *et al.* [19, 20] reacted a variety of dienophiles with thiophenes under oxidative conditions, where electron-poor dienophiles such as maleimides, maleic anhydride, and acceptor-substituted alkynes gave the corresponding cycloadducts in acceptable yield (Scheme 5). In the reaction with alkenes, 7-thiabicyclo[2.2.1]heptene *S*-oxides **32** could be obtained, while the reaction with alkynes leads to substituted aromatic products, after concomitant SO extrusion from the 7-thiabicyclo[2.2.1]heptadiene *S*-oxides **29** as the primary cycloadducts, which themselves cannot be isolated under the reaction conditions (Scheme 4). The formation of the 7-thiabicyclo[2.2.1]heptene *S*-oxides **32** proceeds with complete stereocontrol. The cycloadditions yield predominantely *endo*-adducts, where the stereochemistry of the sulfoxy-moiety is controlled by the Cieplak effect [21], the oxygen of the sulfoxy group being directed towards the incoming dienophile (see below for further discussion of the stereochemistry of the cycloadducts).

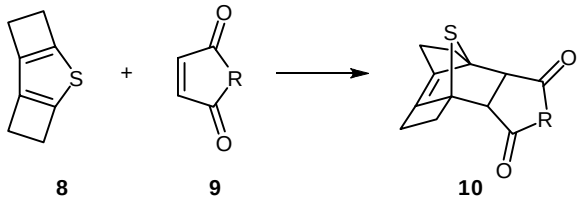
The reactions under the conditions described above (no added catalyst, slightly elevated temperatures) were used to synthesize non-natural, phenyl-substituted amino acids **35** from respective, suitably protected thienylamino acids **33** [19b] and novel areno crown ethers **37** from thieno

a) highly reactive dienophile



6 **1** D. D. Callander et al. 1966

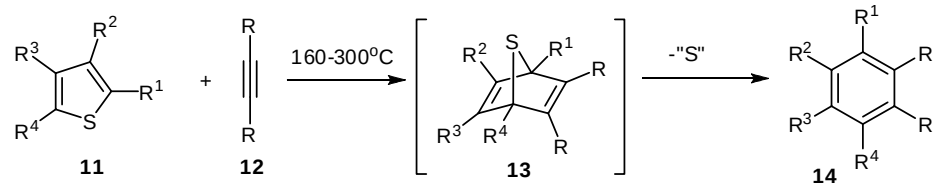
b) enhanced reactivity of the thiophene due to strain energy



8 **9** **10**

J. Nakayama et al. 1993

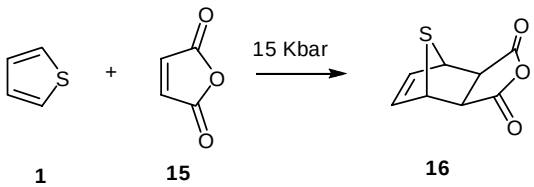
c) high temperature cycloaddition reaction



11 **12** **13** **14**

H. J. Kuhn, K. Gollnick 1972

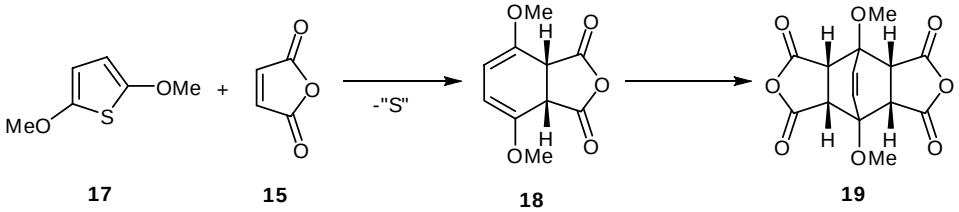
d) cycloaddition under high pressure



1 **15** **16**

H. Kotsuki et al. 1978, 1979

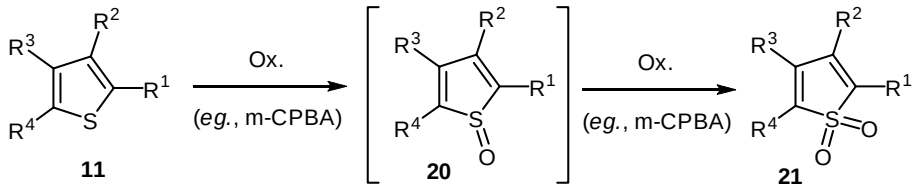
e) donor substituted thiophene



17 **15** **18** **19**

D. N. Reinhoudt et al. 1972

Scheme 1. Cycloaddition reactions of thiophenes under enhanced conditions.



Scheme 2. Oxidation of thiophenes **11** to thiophene S,S-dioxides **21** via thiophene S-oxides intermediates **20**.

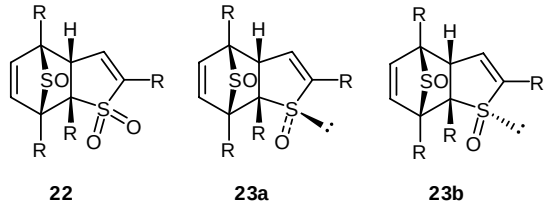


Figure 2. Typical dimerisation products formed in the oxidation of 2,5-dimethyl-thiophene.

crown ethers **35** [19a] (Scheme 6). The reactions could also be carried out intramolecularly [20], where the thienyl component and the dienophile are part of the same molecule (Scheme 6). Here the starting material was simply treated with *m*-CPBA. Thiophenes tethered to alkynes such as **39**, thiophenes tethered to alkenes do not. In the latter case only the corresponding thiophene *S*,*S*-dioxides were isolated. Also, the oxidative cycloaddition of thiophenes needs appreciable reaction volume so that such molecules as the orthothiophenophanes **43** and **44** were found not to undergo the reaction under the normal conditions used for the oxidative cycloaddition in general [22] (Figure 3, see also below).

It is beneficial to react thiophene *S*-oxides, prepared *in situ*, under Lewis acid catalysis

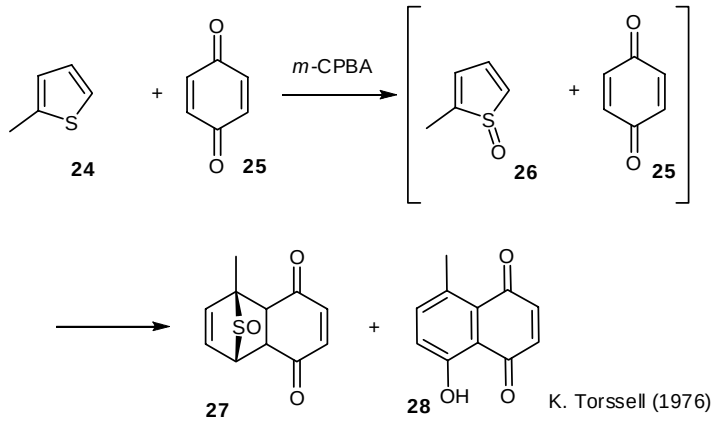
Oxidative cycloaddition reactions of thiophenes can be carried out at much lower temperatures such as at -20°C, when a Lewis acid catalyst such as $BF_3{\cdot}Et_2O$ is used [16c, d]. Again, electron-poor, deactivated dienophiles such as tetracyanoethylene, acetylene dicarboxylates, quinones, maleimides and maleic anhydride and mono-activated enes such as cyclopentenone and acrolein were used (Scheme 7). Thiophene itself has been oxidized with H_2O_2 in the presence of trifluoroacetic acid (CF_3CO_2H) and the thiophene *S*-oxide trapped *in situ* with *N*-phenylmaleimide [23].

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 [24]. Also the key step in B. Yu *et al.*'s synthesis of steroidal saponins **50**, closely related to the E-ring areno containing natural products aethiosides A-C, is a $BF_3{\cdot}Et_2O$ catalysed oxidative cycloaddition of the thieno-containing steroidal saponin **48** [25] (Scheme 8).

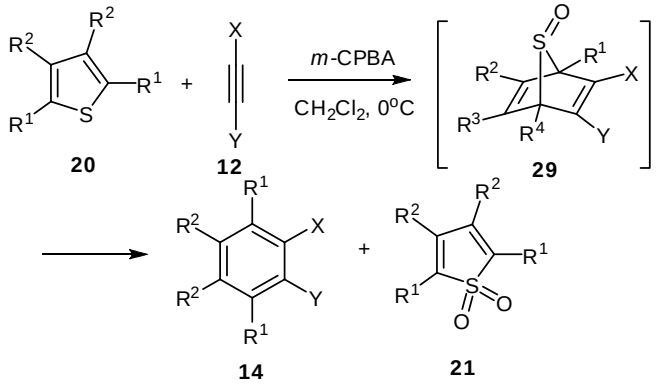
The primary cycloadducts of thiophene S-oxides with alkenes are versatile intermediates.

The 7-thiabicyclo[2.2.1]heptene *S*-oxides **51**, as primary cycloadducts from the reaction of thiophene *S*-oxides, prepared *in situ*, and alkenes, could be transformed to substituted arenes **14** by either pyrolysis [19a], photolysis [26], or PTC-catalysed oxidative treatment with $KMnO_4$ [19a] or electrochemical oxidation [27], both at rt (Scheme 9). Alternatively, the SO-bridge in **51** can be deoxygenated with PBr_3 to yield thioether-bridged **53** [28] (Scheme 9). Reaction with tributyltin hydride generates diene **54** [26] (Scheme 9). Thus, the oxidative cycloaddition of thiophenes constitutes a pathway to either substituted arenes **14** [19a, 27] or to substituted cyclohexadienes **54** [26], both under mild reaction conditions. In primary cycloadducts that exhibit a halogen substituent at each of the bridge head carbons, base catalysed cleavage of the sulfoxy bridge leads to the generation of diaryl disulfides **52** [29] (Scheme 9).

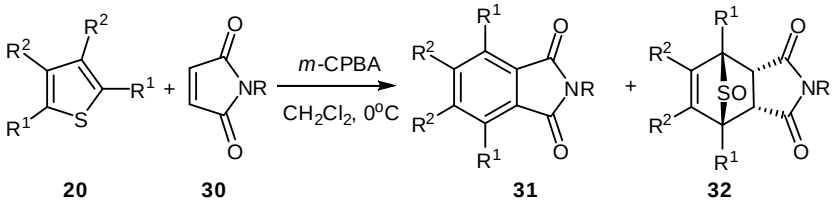
Thiophene *S*-oxides play a role in the metabolic pathway of thiophenes and their existence due to enzymatic oxidation of thiophenes can be shown by *in vitro* isolation of respective cycloadducts and *in vivo* isolation of self-dimerisation products.



Scheme 3. Cycloaddition of methylthiophene *S*-oxide (**26**), generated *in situ*, with benzoquinone (**25**).

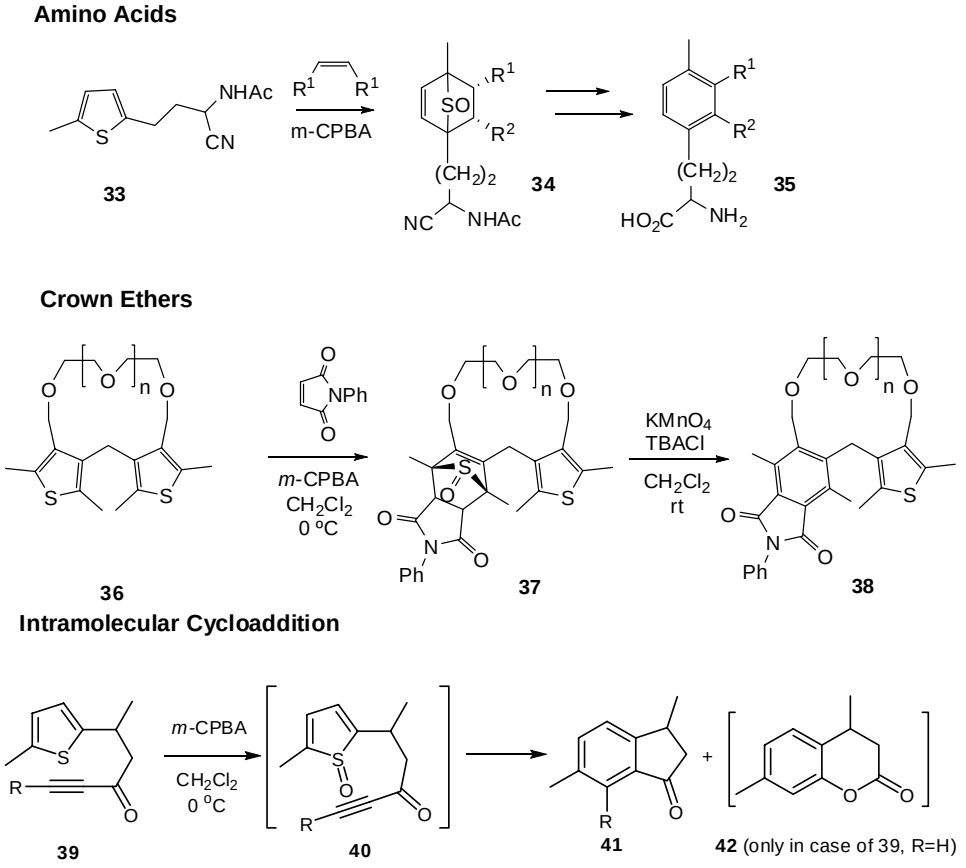


Scheme 4. Oxidative cycloaddition of thiophenes with alkynes with concomitant SO-extrusion.

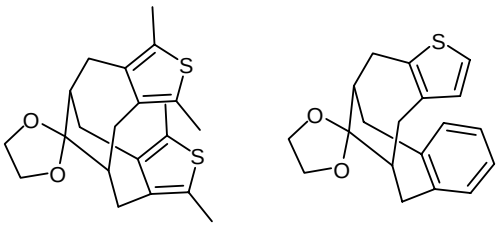


Scheme 5. Oxidative cycloaddition of thiophenes with substituted maleimides.

Interestingly, oxidative metabolism of thiophenes **1** in rats (*in vivo*) also seem to involve thiophene *S*-oxides [30], where sesquioxides **23a** and **23b** (both, R=H) were found in the urine of rats, fed with thiophene. Both **23a** and **23b** (both R-H, Figure 2) could be isolated when treating thiophene **1** itself with rat liver microsomes *in vitro*, when these were pretreated with



Scheme 6. Uses and modes of the oxidative cycloaddition of thiophenes: synthesis of aryl amino acids [19b] and areno crown ethers [19a]; the intramolecular oxidative cycloaddition [22].



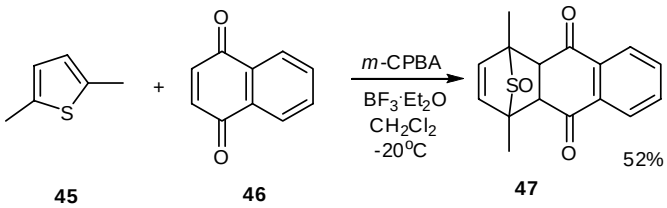
43 **44**

Thiemann et al. 1999

Figure 3. Orthothiophenophanes **43** and **44** do not allow for enough reaction volume and do not undergo oxidative cycloadditions reactions with alkenes or alkynes [28].

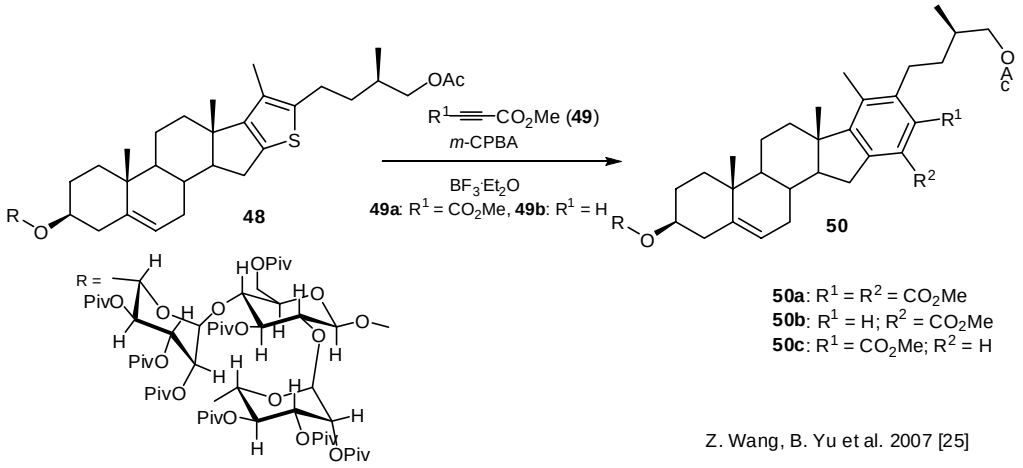
dexamethasone in the presence of NADPH and dioxygen. More recently, cycloadditions of thiophene *S*-oxides generated from thiophenes with rat liver microsomes with alkenes such as with *N*-phenylmaleimide have been carried out successfully, too (see below) [30d]. These studies had been undertaken to better understand the metabolism of the diuretic drug tienilic acid **55**, which can induce immunoallergic hepatitis (Figure 4).

Chemically, it is known that electron-donor substituted thiophenes can be oxidized easily and that electron-acceptor substituted thiophenes are much more difficult to oxidize. It has been shown, however, that with 4-chlorophenyl-(thien-2-yl)-methanone **57** [32], also aryol substituted thiophenes can be oxidized under relatively mild conditions, when either *m*-CPBA is used in the presence of $BF_3{\cdot}Et_2O$ or hydrogen peroxide in the presence of trifluoroacetic acid (TFA). The products of the chemical oxidation again were found to be dimerisation products **23a-T**, **23b-T** and **22-T** (Scheme 10).



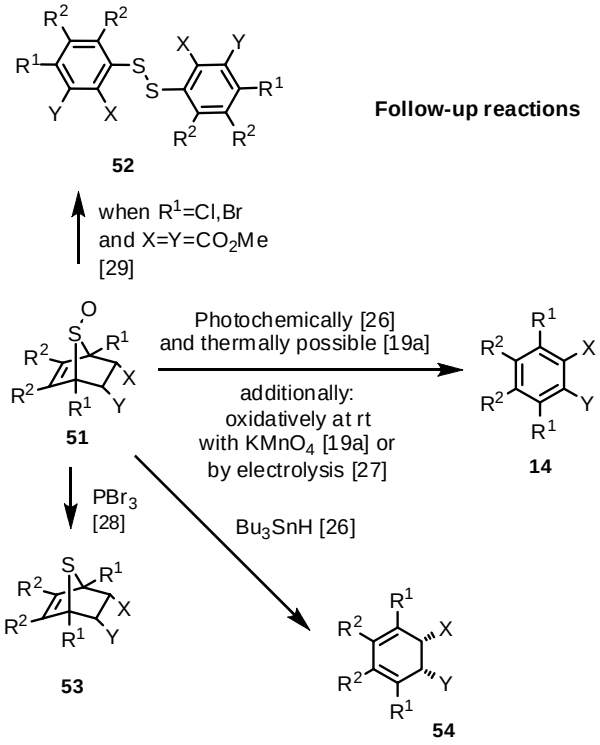
Y. Q. Li, T. Thiemann [1997]

Scheme 7. Oxidative cycloaddition of thiophenes in the presence of $BF_3{\cdot}Et_2O$ as catalyst.

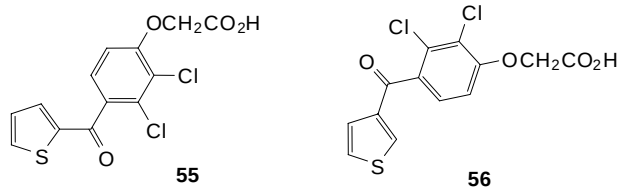


Z. Wang, B. Yu et al. 2007 [25]

Scheme 8. Steroidal synthesis with the $BF_3{\cdot}Et_2O$ catalyzed oxidative cycloaddition of a thienyl unit as a key step.



Scheme 9. 7-Thiabicyclo[2.2.1]heptene S-oxides **51** are versatile substrates for multi-functionalized arenes **14**, cyclohexadienes **54** and 7-thiabicyclo[2.2.1]heptanes **53**.



Tienilic acid

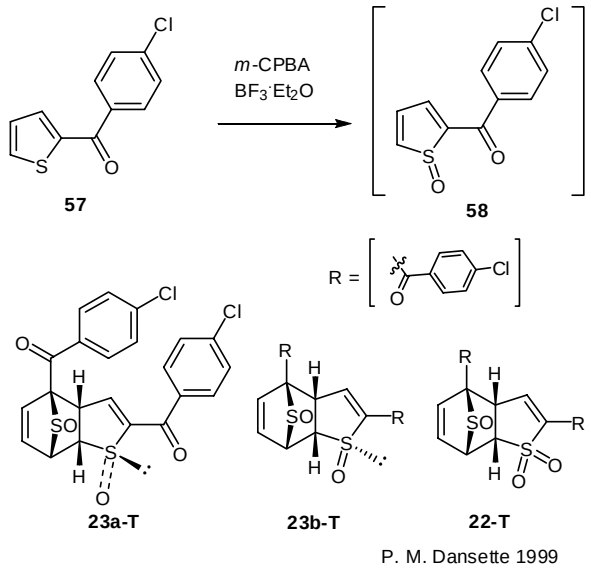
diuretic drug
(1 out of 10000 patients
develops immunoallergic
hepatitis)

Tienilic acid Isomer (TAI)

Is an oxygenated thiophene species involved as the key intermediate in the metabolism of these thienyl containing compounds?

M. P. Lopez-Garcia, P. M. Dansette, and D. Mansuy, 1994.

Figure 4. Thiophenes in medicine - the question of oxygenated thiophene metabolites with toxic characteristics [31].



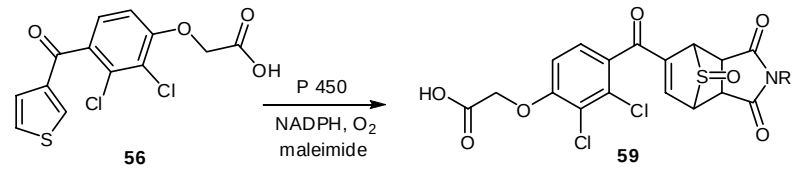
Scheme 10. Oxidative dimerisation of acceptor-substituted **57**.

The electron acceptor substituted thiophene, tienilic acid isomer (TAI) **56**, oxidized by clofibrate induced rat liver microsomes to its *S*-oxide derivative, has been trapped as a Diels Alder product with maleimides, eg. as **59** [30d] (Scheme 11). Also, Boyd *et al.* have found partially electron-acceptor substituted thiophenes such as halogenated thiophenes **60** could be oxygenated by *Pseudomonas putida* UV4 and be isolated as dimers **61** [30e]. Lastly, Thiemann *et al.* [27] could show that perhalo-substituted thiophenes could also be oxidized chemically to thiophene *S*-oxide intermediates, which then could be subjected *in situ* to [4+2]-cycloaddition reactions. Oligohalo substituted thiophene *S*-oxides could not be isolated under the conditions [27].

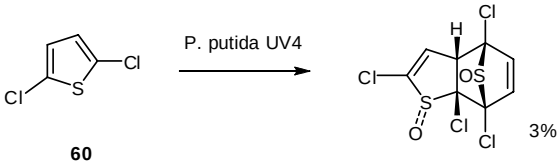
Thiophene *S*-oxides are prepared by concise synthesis and can be isolated

In more recent times, a number of groups [16c, d, 33-37] were able to come up with general synthetic approaches to isolable thiophene *S*-oxides. This involves either the peracid [16c, d, 34, 35] or hydrogen peroxide [33] mediated oxidation of thiophenes in presence of Lewis acids such as titanium tetrachloride ($TiCl_4$), boron trifluoride etherate ($BF_3{\cdot}Et_2O$) or a protonic acid such as trifluoroacetic acid (Scheme 12) or a reaction of zirconacyclopentadienes, prepared from alkynes and bis(cyclopentadienyl)zirconium dichloride [Cp_2ZrCl_2], with thionyl chloride [36, 37] (Scheme 13).

An additional route to rhodium complexed thiophene *S*-oxide [Cp*Rh(TMTO)] by oxygen oxidation of the corresponding thienyl complex [Cp*Rh(η^4-TMT)] has been forwarded [38a] (Scheme 14). Also, the reaction of the cationic transitory ruthenium complex $[Ru(C_6R_6)(C_4R_4S\text{-}OH)]^+$ with hydroxyl anion (OH^-) gives the complexed thiophene

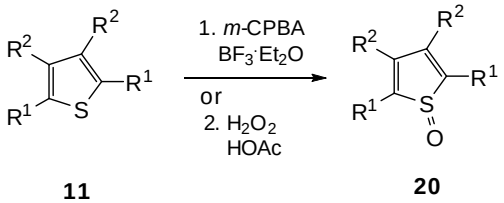


P. M. Dansette, D Mansuy et al. 2010



D. Boyd et al. 2003

Scheme 11. Enzymatic oxygenation of acceptor substituted thiophenes and trapping of the putative thiophene S-oxide intermediates as cycloadducts.



(Mansuy, Nakayama, Furukawa, Thiemann)

Scheme 12. Preparation of thiophene *S*-oxides by Lewis or proton acid catalyzed oxygenation of thiophenes.

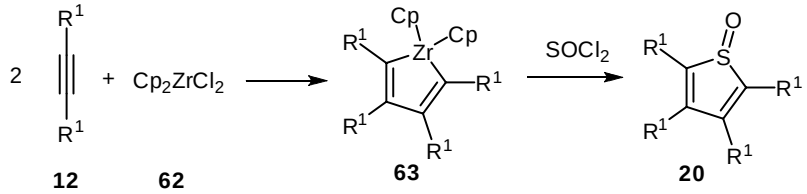
S-oxide $Ru(C_6H_6)(C_4R_4SO)$ [38b]. These complexes, however, have not yet been used as substrates in cycloaddition reactions.

In 1995, Dansette, Mansuy *et al.* [33] showed that 2, 5-diphenylthiophene *S*-oxide could be isolated when 2, 5-diphenylthiophene was reacted with H_2O_2 in the presence of trifluoroacetic acid. An X-ray crystal structural analysis was carried out subsequently [39a]. In 1996, Thiemann *et al.* [16c] published that when donor-substituted thiophenes were oxidized in the presence of $BF_3{\cdot}Et_2O$ and alkenes as dienophiles, cycloaddition reactions of *in situ* produced thiophene *S*-oxides could be run at low temperatures (see above). At the same time, thiophene *S*-oxides, remaining from the reaction, could be isolated by column chromatography and could be held in substance for a number of weeks without appreciable degradation, when in crystallized form. In 1997, both Nakayama [34] and Furukawa [35a] published a general procedure to thiophene *S*-oxides with *m*-CPBA, using either $BF_3{\cdot}Et_2O$ or $TiCl_4$ as a catalyst. Lastly, it could be shown that in a molecule exhibiting two thienyl cores, both can be oxidized to thiophene *S*-oxides, that is, under the conditions (*m*-CPBA, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -20°C) the second thiophene unit can compete successfully with a thiophene *S*-oxide for the oxidant [40] (Figure 5).

Isolated thiophene *S*-oxides can be used easily as components in cycloaddition reactions

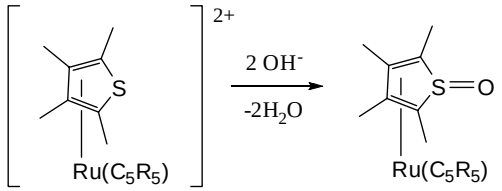
Isolated thiophene *S*-oxides were found to be excellent dienes at rt or at slightly lower or elevated temperatures [16c, 24, 35, 40, 41] (Scheme 14). In comparison to thiophene *S*, *S*-dioxides, which often need to be reacted even with electron-poor dienophiles at temperatures exceeding 100°C, thiophene *S*-oxides are much more reactive. Also, compared to the correspondingly substituted cyclopentadienone, the thiophene *S*-oxide is more reactive (Scheme 15).

At higher temperatures, tetraphenylcyclopentadienone (tetracyclone, **69**) is known to undergo oxidation to tetraphenylpyrone **72**, while tetraphenylthiophene *S*-oxide **68** is known to undergo deoxygenation to tetraphenylthiophene **74** [42]. Overall, tetraphenylthiophene *S*-oxide **68** gives a cycloadduct with benzothiophene *S*, *S*-dioxide **71** in higher

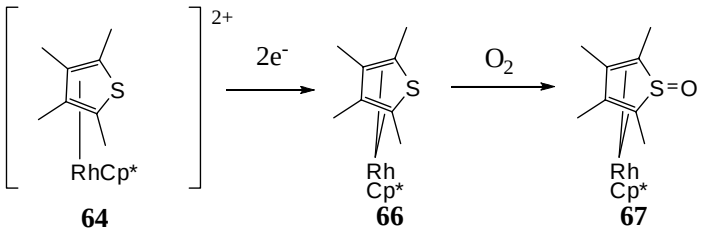


Fagan, Weiss, Tilley [36.37]

Scheme 13. Preparation of thiophene S-oxides via zirconacyclopentadienes.

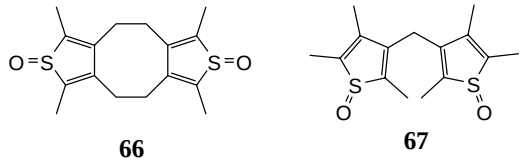


Rauchfuss 1993



Rauchfuss 1989

Scheme 14. Preparation of η^4-thienyl-*S*-oxide ruthenium and rhenium complexes [38].

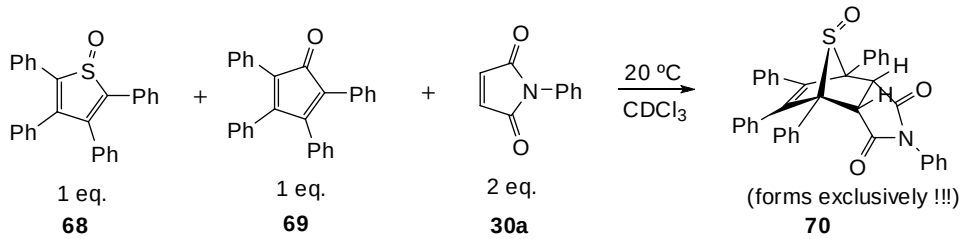


Thiemann 1997, 2000

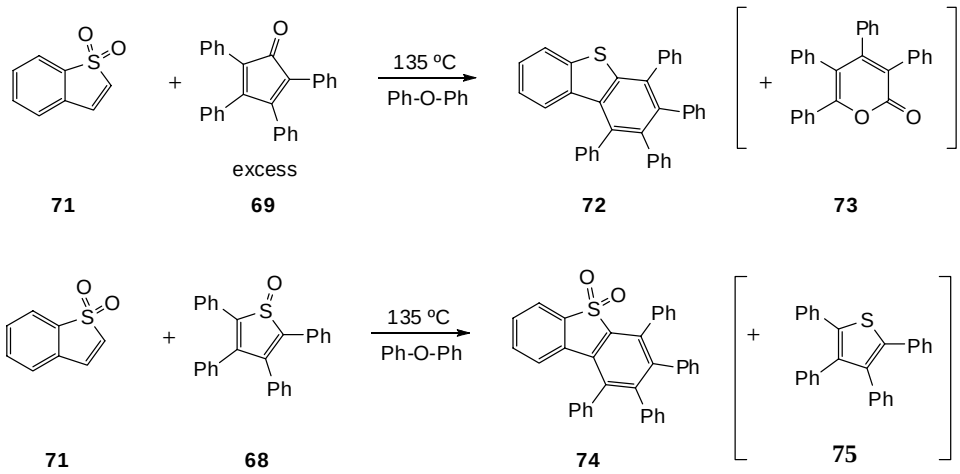
Figure 5. Compounds with two thienyl-*S*-oxide core units.

yield than tetraphenylcyclopentadienone **69** (Scheme 16). Also, the cycloadducts of the two reactions, compounds **72** and **74**, are different [43]. In the case of the reaction of tetracyclone **69** with dienophile **71**, oxygen is either transferred from the expected product **74** or from another reaction intermediate, eg., from the primary cycloadduct before its CO extrusion, to excess tetracyclone **69**, and deoxygenated **72** is formed. In the reaction between tetraphenylthiophene *S*-oxide and **71** no such oxygen transfer takes place (Scheme 16).

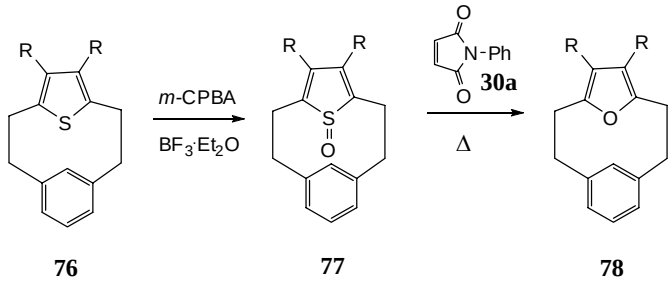
In general, appreciable reaction volume is needed to allow for the geometric prerequisites of the forming sulfoxy-bridge in the primary cycloadducts and, in some cases, of the subsequent extrusion of SO. Thus, in the attempt of cycloadding cyclophane



Scheme 15. Tetraphenylthiophene *S*-oxide **68** competes effectively with tetracyclone **69**.

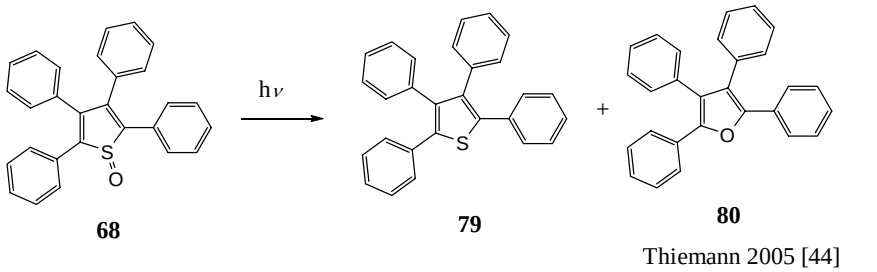


Scheme 16. Comparison of the cycloaddition of tetraphenylthiophene *S*-oxide **68** to its carbon analogon **69** shows that the molecules behave differently as tetracyclone **69** can be oxidized, easily, to pyrone **73** [43].

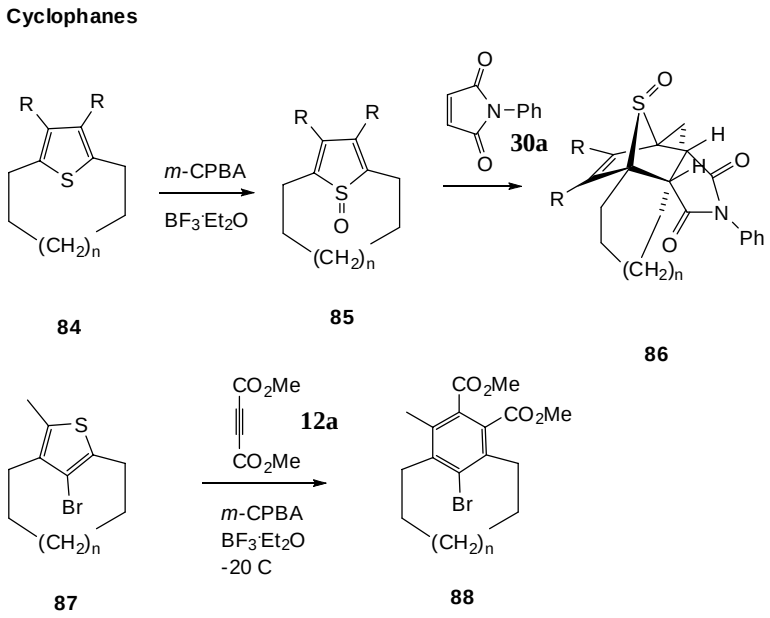


Scheme 17. Strained thiophene *S*-oxide **77** does not undergo cycloaddition reaction to **30a** but undergoes a rearrangement leading to oxygen insertion into the ring with concomitant extrusion of sulfur [24].

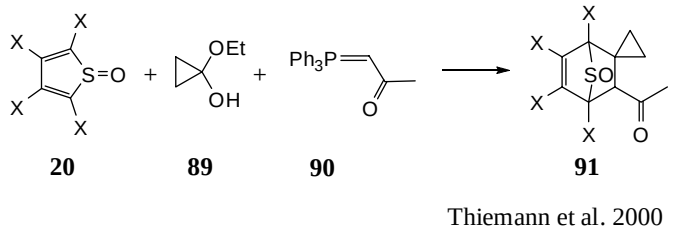
76 with alkenes, thiophenophane *S*-oxide **77** is converted to the furanophane **78** (Scheme 17) [24]. No cycloadducts can be isolated. The insertion of oxygen into a sulfur containing heteroaromatic compound with concomitant extrusion of sulfur can also be found in the photolysis of thiophene *S*-oxides such as **68** [44], in the preparation of strained thiophene *S*-oxides and of 2,5-diphenylthiophene *S*-oxide **81**, where in the late phases of the oxidation reaction the thienylfuran dimer **83** is formed (Scheme 18).



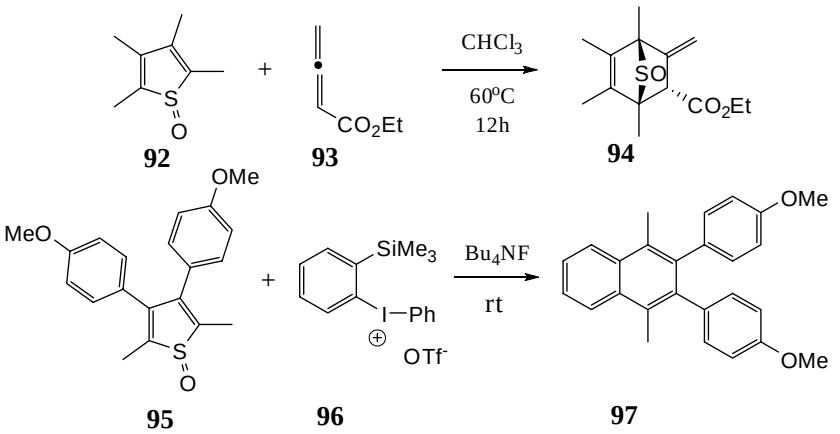
Scheme 18. The formation of furans from thiophene S-oxides under various conditions.



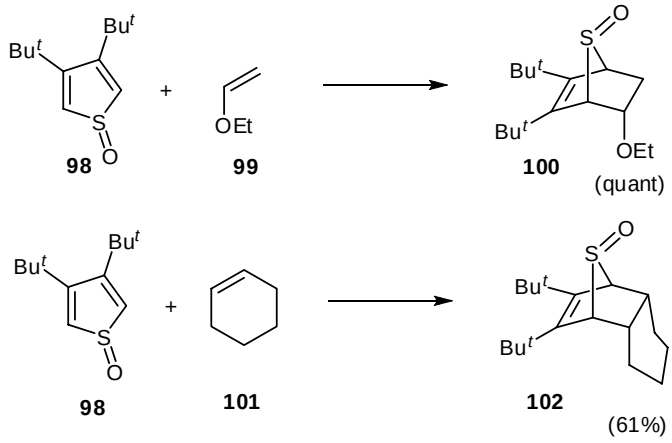
Scheme 19. Use of thiophenophane *S*-oxides to construct multifunctionalized cyclophanes [24].



Scheme 20. Thiophene *S*-oxides in multi-component reactions [47].

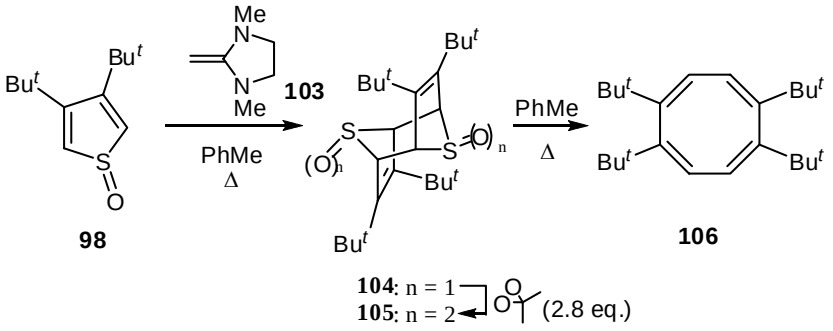


Scheme 21. Cycloaddition reactions of thiophene *S*-oxides with allene **93** and benzyne, prepared *in situ* from **96** [48].



J. Nakayama et al. 2005 [50]

Scheme 22. Inverse-demand cycloaddition of thiophene *S*-oxides.



J. Nakayama 2003 [51,52]

Scheme 23. [4 + 4] – Cycloaddition of **98** in presence of 2-methylene-1,3-dimethylimidazoline **103**.

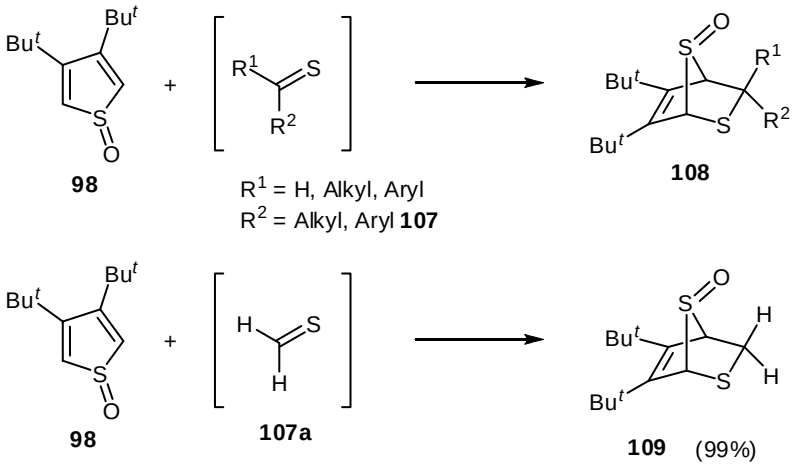
The use of isolated thiophene *S*-oxides as dienes in cycloaddition reactions have been manifold. Thus, thiophene *S*-oxides have been utilized in the synthesis of cyclophanes such as **86** and **88** [24] (Scheme 19). J. Nakayama *et al.* [45] have used thiophene *S*-oxides as reactants to prepare sterically overfreighted anthraquinones, while Thiemann *et al.* [46a] have used halogenated thiophene *S*-oxides prepared *in situ* to synthesize halogenated anthraquinones, which could easily be transformed further to arylated anthraquinones [46b, c]. Thiophene *S*-oxides can be included as substrate in a multi-component reaction as shown in Scheme 20, where a Diels-Alder reaction is performed concomitant to a Wittig olefination [47]. Initially only electron withdrawing alkenes and acetylenes, including such dienophiles as allenes [48], benzyne [48] (Scheme 21) and C_{60} [49] were used in the cycloaddition reactions with isolated thiophene *S*-oxides, however, J. Nakayama *et al.* found that at least 3,4-bis-*tert*-butylthiophene *S*-oxide could also be reacted with electron-rich dienophiles [50] in inverse electron demand Diels-Alder type cycloadditions, where enolethers could reacted at rt and cyclic alkenes necessitated elevated temperatures up to 100°C [50] (Scheme 22).

When heated with 2-methylene-1, 3-dimethylimidazoline **103**, 3,4-bis(*tert*-butyl)thiophene *S*-oxide **98** undergoes a [4π+4π]-cycloaddition, giving the head-to-head dimer **104** (Scheme 23) [51]. Oxidation of the two sulfoxy bridges to sulfone **105**, utilizing dimethyldioxirane as oxidant, with subsequent double, thermally driven SO_2-extrusion was shown to lead to 1,2,5,6-tetra(*tert*-butyl) octatetraene **106** [52] (Scheme 23).

J. Nakayama *et al.* could establish that 3,4-bis-*tert*-butylthiophene *S*-oxide **98** reacts as a diene also with thioaldehydes **107a** and thioketones **107**, generated *in situ*, in *hetero*-Diels-Alder fashion [53] (Scheme 24). Here, the cycloadducts were found by X-ray crystallography and ^{1}H NMR spectroscopy to be *endo*-products stemming from a reaction at the *syn*-π-face to the S=O bond. Even thiobenzophenone could be reacted in good yield, although here two isomeric products are produced, with the lesser product stemming from anti-π-face cycloaddition reaction. Finally, Xx reacts with carbonyl cyanide [**112**, $CO(CN)_2$], created *in situ* by oxidation of tetracyanoethylene oxide (**110**, TCNO) with thiophene *S*-oxide **98**, in *hetero*-Diels-Alder fashion to furnish **113** [54] (Scheme 25).

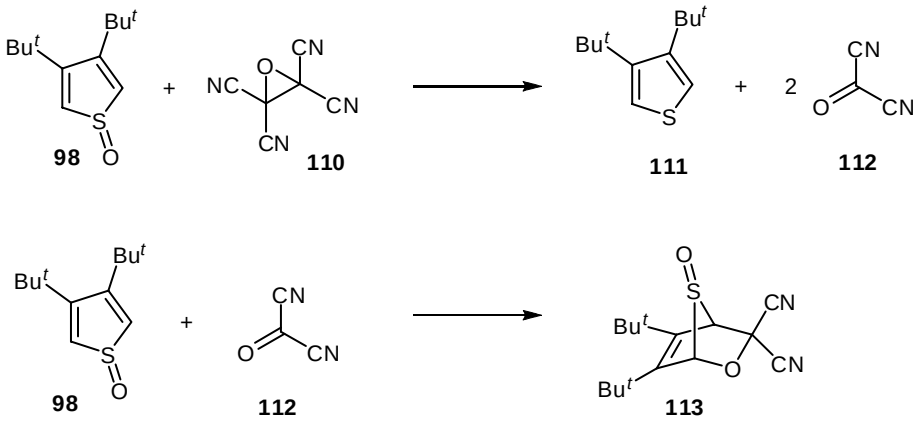
Stereochemistry of the cycloadducts

It has been found that thiophene *S*-oxides can invert through their sulfur. This inversion has also



J. Nakayama et al. 2003 [53]

Scheme 24. Hetero-Diels-Alder reaction with thioaldehyde **107a** and thioketones **107** as hetero-dienophiles.



J. Nakayama et al. 2005 [54]

Scheme 25. Hetero-Diels-Alder reaction of thiophene S-oxide **98** with carbonyl cyanide **112**, formed in situ from tetracyanoethylene oxide **110**.

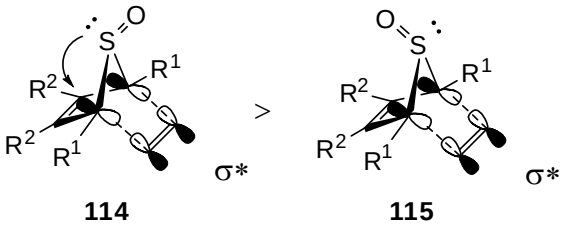


Figure 6. The lone pair on sulfur stabilizes the σ^* orbital of the incipient σ-bonds better (transition state **114**) than the electrons on the oxygen (transition state **115**).

been studied by racemisation of enantiomerically enriched thiophene *S*-oxides, prepared by enzymatic oxidation. Nevertheless, the 7-thiabicyclo[2.2.1]heptene *S*-oxide systems generated by the cycloaddition of the thiophene *S*-oxides to alkenes are formed as one diastereoisomer only, where the sulfoxy group is configurational stable. All the cycloadducts are *endo*-products. 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 [55]. The lone pair of the sulfur is directed towards the side of the newly formed double bond of the cycloadduct. The π-facial selectivity can be explained by the Cieplak effect [19c, 21]. 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 [56]. 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 [19c] (Figure 6). This would be even more so, when the oxygen of the sulfoxy-unit is complexed by $BF_3{\cdot}Et_2O$.

CONCLUSION

Thiophene *S*-oxides, whether in pure form or prepared *in situ*, make for good dienes in [4 + 2] – cycloaddition reactions. These include normal and inverse electron demand reactions as well as Hetero-Diels-Alder reactions. The versatility of the products, especially of the 7-thiabicyclo[2.2.1]heptene S-oxides as cycloadducts of thiophene *S*-oxide

with alkenes, allows for the transformation of thiophenes to functionalized arenes and to functionalized cyclohexadienes at rt. The authors expect the area of thiophene *S*-oxides to harbor more exciting chemistry in the future.

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