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Sulfur Monoxide Transfer from *peri*-Substituted Trisulfide-2-oxides to Dienes: Substituent Effects, Mechanistic Studies and Application in Thiophene Synthesis

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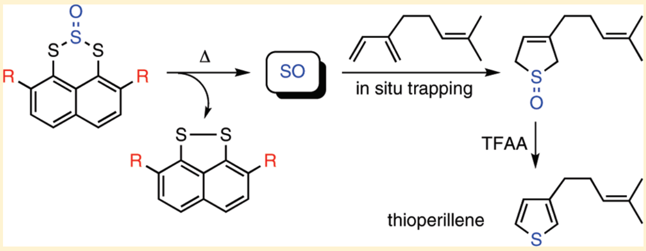
Supporting Information



ABSTRACT: Three *peri*-substituted trisulfide-2-oxides are prepared by treatment of 1,8-naphthalene dithiols with thionyl chloride and pyridine. The 1,2,3-trithiane-2-oxide ring adopts a sofa conformation in the solid state, with a pseudoaxial oxygen and evidence of ring strain (*peri*-interaction). Heating the trisulfide-2-oxides in the presence of a diene results in formal sulfur monoxide (SO) transfer to form unsaturated cyclic sulfoxides, along with a recyclable 1,8-naphthalene disulfide. The presence of *o*-methoxy or *o*-*tert*-butyl substituents on the naphthalene ring lowers the temperature and increases the rate at which SO transfer occurs. Trapping experiments and kinetic studies are consistent with the generation of triplet SO, followed by in situ trapping by diene. Transfer of SO also occurs upon irradiation at room temperature, but yields of sulfoxide are lower. Dehydration of the sulfoxides under Pummerer conditions gives thiophenes, including the naturally occurring thioperillene. Two dienes form thiophenes directly under the SO transfer conditions. The methodology is applied in a formal synthesis of the antiplatelet medication Plavix.

INTRODUCTION

The generation and trapping of small reactive molecules, such as singlet oxygen and diatomic sulfur, is of interest both theoretically and as a methodology for the synthesis of new chemical entities.[1,2] The structurally related diatomic sulfur monoxide (SO) undergoes rapid disproportionation (half-life <1 s in the gas phase), via its dimer S_2O_2, to SO_2 and S_2O.[3] Further disproportionation of S_2O gives SO_2 and S_3,[4] the latter ultimately forming the more stable sulfur allotrope S_8. Like diatomic oxygen, SO has a triplet ground state, which has been calculated to be ~20 kcal.mol^{-1} more stable than the singlet form.[5] SO has been trapped in an argon matrix and has been characterized spectroscopically.[6]

The most effective methods for the generation and in situ trapping of SO on a preparatively useful scale are based on the fragmentation of organic molecules. On the basis of the early work of Hartzell and Paige on the thermally induced fragmentation of episulfoxides,[7] Dodson and Sauer reported that episulfoxide **1** transfers SO to a 1,3-diene to give 2,5-dihydrothiophene *S*-oxides (sulfilenes) in modest yield (Scheme 1, eq 1).[8] High levels of stereochemical control were observed with 1,4-dimethylbutadienes of defined geometry, although this was still deemed consistent with a diradical-based mechanism through the initial addition of triplet SO to the diene.[9]

Although episulfoxide **1** has been the most studied source of SO to date, other episulfoxides have been used as SO transfer reagents. The heterocycle **2** is proposed to close to a *cis*-episulfoxide through a thermally allowed disrotatory 6π-electrocyclization, and the SO released is trapped with dienes in moderate yield.[10] Improved yields of sulfilenes can be obtained using the episulfoxides **3** and **4** developed by Harpp, which are also notable in that the alkene obtained upon SO extrusion can be isolated and potentially recycled.[11] Using **4**, SO transfer to four dienes was achieved in 65−80% yield in refluxing toluene over 12−36 h, which at the outset of this work represented the highest yields reported for this transformation. *trans*-2,3-Diphenylthiirane oxide **5** has been used to react SO with diazoalkanes,[12] azides[13] and ylides,[14] and was also employed by Simpkins in a $Rh_2(OAc)_4$-catalyzed transfer of SO to norbornene or norbornadiene to produce new episulfoxides, probably through formation of, and transfer from, a Rh(SO) complex.[15] Well-defined organometallic complexes of SO are relatively rare,[16] with the complex $(Ph_3P)_2Pd(SO)$, itself derived from the reaction of **1** with $(Ph_3P)_4Pd$, reported to transfer SO to dienes in low yield.[17]

The trapping of SO with 2,3-dimethylbutadiene has been used to identify reaction pathways in the oxidation of sulfines **6** and thionosulfite **7**,[18,19] and in the thermal degradation of the three-membered-ring *vic*-disulfoxide **8**.[20] More recently, Nakayama has described novel transformations of SO generated from the room temperature breakdown of the bridged bicyclic sulfoxide **9**, produced in situ from the Diels−Alder reaction of 3,4-di-*tert*-butylthiophene 1-oxide with dimethylacetylenedicarboxylate.[21] Successful in situ trapping of some strained alkenes and alkynes

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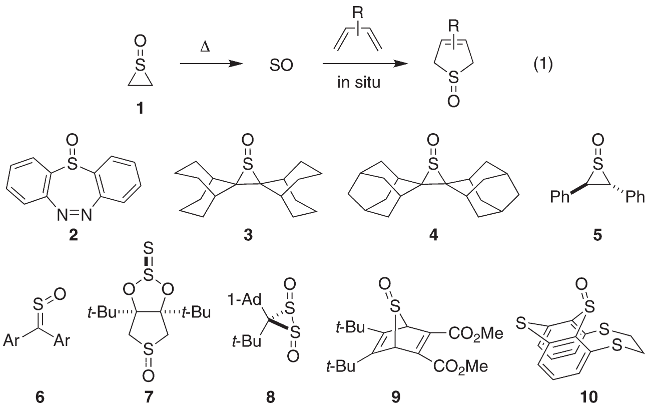
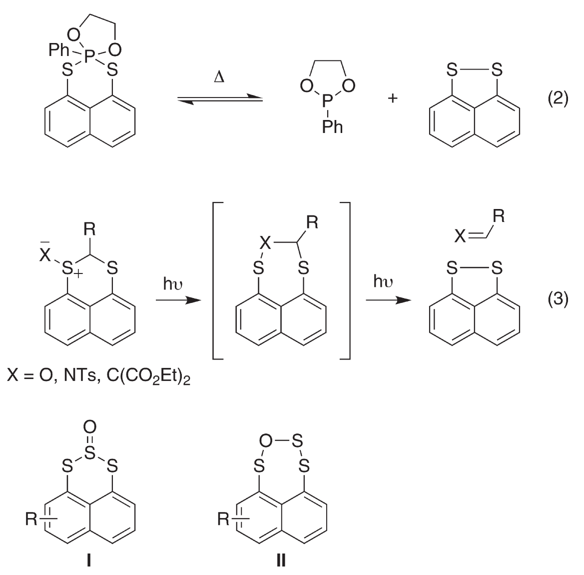
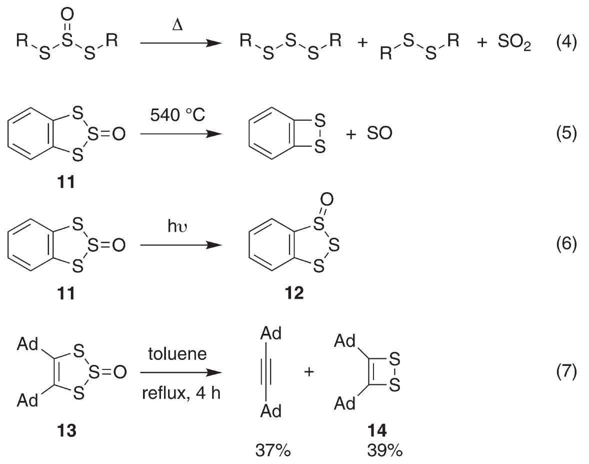
Scheme 1. Reaction of SO with Dienes, and Sources of SO Used in Trapping Reactions



Scheme 2. Extrusion Reactions of 1,8-Dithianaphthalene Derivatives with Concomitant Naphtho[1,8-*cd*][1,2]dithiole Formation, and Proposed Sources of Sulfur Monoxide



Scheme 3. Thermal and Photochemical Reactions of Trisulfide-2-oxides



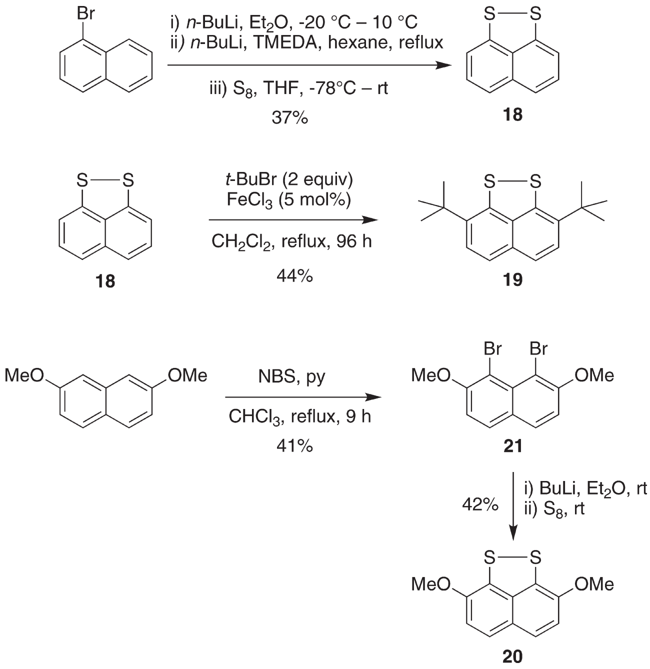
to produce three-membered-ring sulfoxides can be ascribed to generation and trapping of SO in its singlet state, which does not undergo rapid intersystem crossing under the mild reaction conditions. The photomediated ring contraction of **10** has also been shown to involve loss of SO by trapping experiments with dienes at room temperature, although in this case the triplet state is proposed to be formed.[22] Under these conditions, trapping of SO with 2,3-dimethyl 1,3-butadiene occurred in 73% yield.

Design Rationale. The driving force for SO release from **1**−**10** can be rationalized as being relief of ring strain and/or gain in conjugation. In the search for an alternative source of SO, we considered exploiting the *peri*-interaction: structural and reactivity effects arising from the close proximity of atoms or groups at the 1,8-(*peri*-)positions of a naphthalene or related ring system.[23] The sulfur atoms in 1,8-naphthalene dithiol derivatives are in closer proximity than the combined van der Waals radii of sulfur (3.7 Å). The resulting steric strain[24] can be relieved through formation of covalent sulfur−sulfur bonds under appropriate conditions.[25] Of particular interest to us was the reversible extrusion of a phosphonite from a dithiaphosphorane[26] (eq 2 in Scheme 2), and the photomediated-extrusion reactions of *peri*-fused dithiane derivatives reported by Furukawa (eq 3 in Scheme 2).[27] Although these chemistries are not limited to *peri*-substituted naphthalenes, the formation of a stable disulfide bond, as found in the product naphtho[1,8-*cd*][1,2]dithiole, would appear to be a thermodynamic driving force.

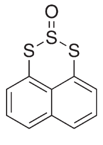
The above led us to consider *peri*-substituted trisulfide-2-oxides[28] of general structure **I**, or the isomer **II**, as potential sources of SO (Scheme 2). A survey of the literature suggested that, while the R-S-O-S-S-R sulfur−oxygen bonding motif in **II** has apparently no precedent, a number of acyclic and cyclic trisulfide-2-oxides have successfully been prepared.[29] However, the proposed loss of SO from **I** would represent an atypical reaction pathway for this functional group. The thermal degradation of acyclic trisulfide-2-oxides was investigated in detail by Field, and subsequently by Harpp.[30] A 1:1 mixture of disulfide and trisulfide are the observed products along with formation of SO$_2$, with no evidence for a decomposition pathway involving release of SO (Scheme 3, eq 4). Flash vacuum pyrolysis of 1,2,3-benzotrithiole 2-oxide **11** gives benzodithiete and SO (eq 5 in Scheme 3).[6d] However, the high temperature prohibits the use of **11** as a source of SO for trapping experiments, as the diene−SO adducts are known to degrade at temperatures as low as 135 °C through a proposed retrocycloaddition pathway.[9a,11] Irradiation of **11** results in isomerization to the 1-oxide **12** rather than release of SO (eq 6 in Scheme 3).[31] However, the formation of dithiete **14** from heating 1,2,3-trithiole-2-oxide **13** in refluxing toluene was more encouraging for the proposed use of **I** as an SO transfer reagent (eq 7 in Scheme 3).[32,33]

In this contribution we describe the synthesis of three trisulfide-2-oxides of general structure **I** and their relative reactivity in SO transfer reactions with dienes. In addition to the parent system **15**,[34] we report 2,7-disubstituted derivatives **16** and **17**, designed to probe the effect of ortho-substituents on the rate and temperature at which SO transfer occurs. The presence of appropriate ortho-substitution has been found to increase the basicity of proton sponges (1,8-bis(dimethylamino)naphthalenes), results ascribed to both buttressing effects and electronic factors.[35] The accessibility of the starting dithiol required for

Scheme 4. Synthesis of *peri*-Substituted Disulfides



trisulfide-2-oxide synthesis was a major factor in the choice of examples to be studied (vide infra).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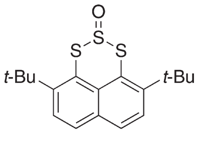

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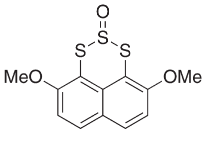


17

RESULTS AND DISCUSSION

Synthesis and Conformational Analysis of *peri*-Substituted Trisulfide-2-oxides. The known disulfide **18** represents an ideal precursor to the proposed trisulfide-2-oxide **15**. Although a number of methods have been described for the synthesis of **18**,[25a,36] the most reliable procedure in our hands was based on the known generation of 1,8-dilithionaphthalene from 1-bromonaphthalene, followed by quenching with elemental sulfur (Scheme 4).[37] Although the yield is modest, gram quantities of **18** can be prepared using this method.

The regioselective Friedel−Crafts *tert*-butylation of **18** to give **19** has been reported.[37c,38] We found this reaction to be highly capricious, whereas switching to $FeCl_3$ as catalyst gave reproducible yields of **19**.[39] The synthesis of the novel dimethoxynaphthalene disulfide **20** was based on a regioselective bromination of 2,7-dimethoxynaphthalene to give the 1,8-dibromide **21**,[40,41] followed by lithium−halogen exchange and quenching with elemental sulfur.

With disulfides **18**−**20** in hand, their conversion to the corresponding trisulfide-2-oxides **15**−**17** was addressed. Reduction of the disulfide bond in **18** to the corresponding dithiol **22** was conveniently achieved in quantitative yield using $NaBH_4$ (Scheme 5).[36b] An ethereal solution of the air-sensitive dithiol **22** and pyridine was immediately added to a solution of thionyl chloride in ether[30a,42] to give a mixture of the target trisulfide-2-oxide **15** and disulfide **18**, readily separable by column chromatography. The order of addition and the nature and stoichiometry of the base proved critical in controlling the ratio of the desired trisulfide-2-oxide **15** and the disulfide byproduct **18**.[30a] Use of two equivalents of pyridine, or changing the order of addition or the base employed, gave increased amounts of disulfide (Table 1). Attempts to effect a one-pot synthesis of **15** from **18** through disulfide reduction with $LiEt_3BH$ or $NaBH_4$ followed by direct addition of thionyl chloride to the reaction mixture gave only low yields of **15**, as did attempted trapping of the dithiolate with Bu_2SnCl_2 to make a dithiostannole prior to addition of thionyl chloride.[31,43]

Scheme 5. Synthesis of Trisulfide-2-oxides and Proposed Mechanism for Formation of Disulfide Byproducts

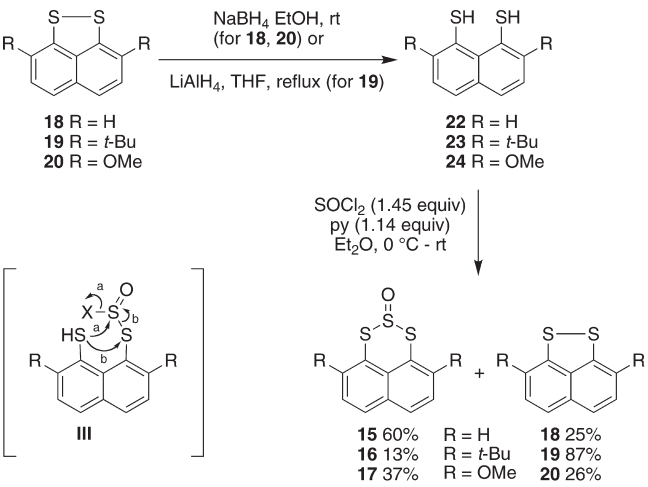


Table 1. Effect of Reagent Stoichiometry and Order of Addition on Ratio of 15:18

entry	conditions[a,b]	**15** (%)	**18** (%)
1	$SOCl_2$ (1 equiv), py (1 equiv)	29	53
2	$SOCl_2$ (1.45 equiv), py (1.14 equiv)	60	25
3	$SOCl_2$ (1 equiv)	23	58
4	$SOCl_2$ (1 equiv), py (2.0 equiv)	20	58
5	$SOCl_2$ (1.45 equiv), py (1.14 equiv)[c]	18	55

[a] Et_2O, 0 °C − rt. [b] Pyridine and **22** added to $SOCl_2$. [c] $SOCl_2$ added to pyridine and **22**.

When the same sulfinylation conditions were applied to the known di-*tert*-butyl naphthalene dithiol **23**,[37c] significantly reduced amounts of trisulfide-2-oxide **16** were obtained compared with amounts from the unsubstituted system **15**, along with increased recovery of disulfide **19**. Similarly, reduction of *o*-methoxy disulfide **20** with sodium borohydride and treatment of the resulting dithiol **24** with thionyl chloride and pyridine under our optimized conditions gave a mixture of the desired trisulfide-2-oxide **17** and recovered disulfide **20**, with the former predominating, although with lower overall recovery.[44]

Although formation of disulfides **18**−**20** in the sulfinylation reaction might arise from competing oxidation of the dithiol **22**−**24**, the ratios of disulfide:trisulfide-2-oxide do not correlate

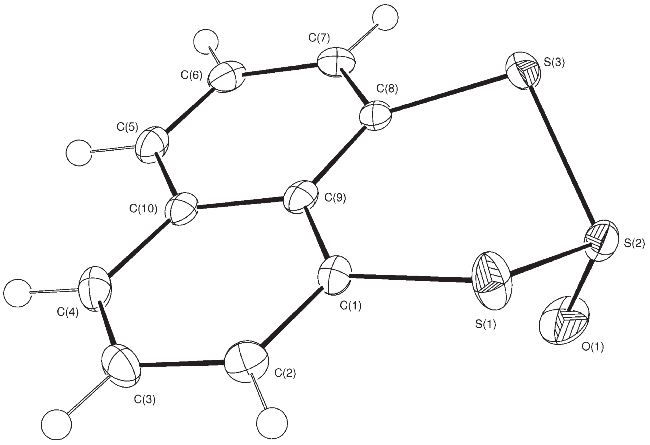


Figure 1. ORTEP view of **15** with ellipsoids drawn at the 50% probability level.

with the sensitivity of the thiols toward exposure to air. Indeed, although the colorless dithiol **22** gradually turns to the red disulfide **18** upon standing in the solid state or in solution, the *tert*-butyl dithiol **23** is much more stable, despite the expected closer proximity of the two sulfur atoms due to the buttressing effect of the *tert*-butyl groups.[45] We believe a more plausible mechanism for the formation of disulfides **18**−**20** is intramolecular addition of thiol (or thiolate) to the alternative electrophilic (nonoxidized) sulfur center in the initial adduct **III** (path b, Scheme 5). This mechanism also accounts for the different ratios of trisulfide-2-oxide:disulfide obtained with changes in ortho-substituent R and the detrimental effect of additional pyridine. The ratio of path a (leading to the desired trisulfide-2-oxides **15**−**17**) to path b (leading to disulfides **18**−**20**) will depend on a number of factors, including the nature of the nucleophile (thiol or thiolate), leaving group (X = Cl or pyridinium) and steric and electronic effects due to the ortho-substituents R.

X-ray Analyses of Trisulfide-2-oxides. The X-ray crystal structures of trisulfide-2-oxides **15**,[34] **16**, and **17** are shown in Figures 1−3 respectively, and a comparison of selected bond lengths and angles is provided in Table 2.[46]

In each case the 1,2,3-trithiane-2-oxide ring adopts a non-planar "sofa" conformation[47] with five atoms approximately coplanar and the central sulfur out of the plane. The oxygen adopts a pseudoaxial orientation. Pseudoaxial oxygen is also observed in five-membered ring trisulfide-2-oxides for which the X-ray crystal structures are known,[42,48] and can be ascribed to conformer stabilization through a combination of overlap of the nonbonding electrons on the flanking sulfur atoms with an S−O σ^* antibonding orbital, and minimization of dipole−dipole repulsions and sulfur lone pair interactions. These effects have been proposed to contribute to the preference for a sulfinyl group to occupy an axial orientation in six-membered rings containing an adjacent sulfur atom.[49]

The axial and equatorial conformations of **15**−**17** are related by either pyramidal inversion of the sulfinyl group or inversion of the trithiane ring. Pyramidal inversion of the sulfinyl group in sulfoxides does not occur at room temperature.[50] Only one set of signals is observed in the ^{1}H and ^{13}C NMR spectra of **15** at room temperature and upon cooling to −80 °C, although it is not clear to what extent the NMR of the two conformers, if present, would differ.

A number of structural features are evident from the X-ray data to suggest these trisulfide-2-oxides are somewhat strained. There is an expansion about the bond angles in the trithiane ring at

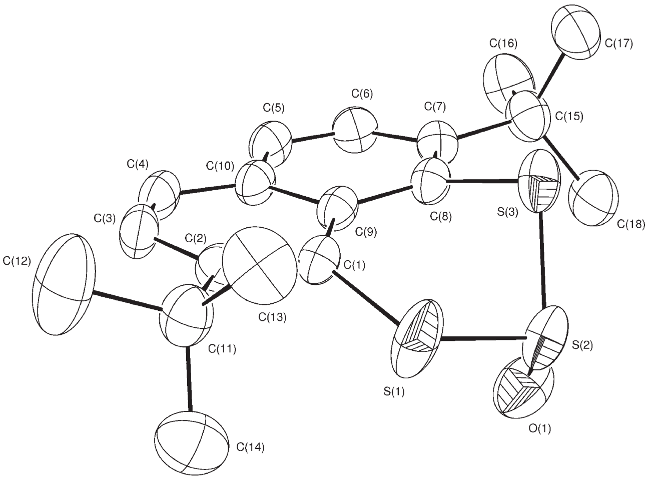


Figure 2. ORTEP view of **16** with ellipsoids drawn at the 50% probability level. Hydrogen atoms have been omitted for clarity.

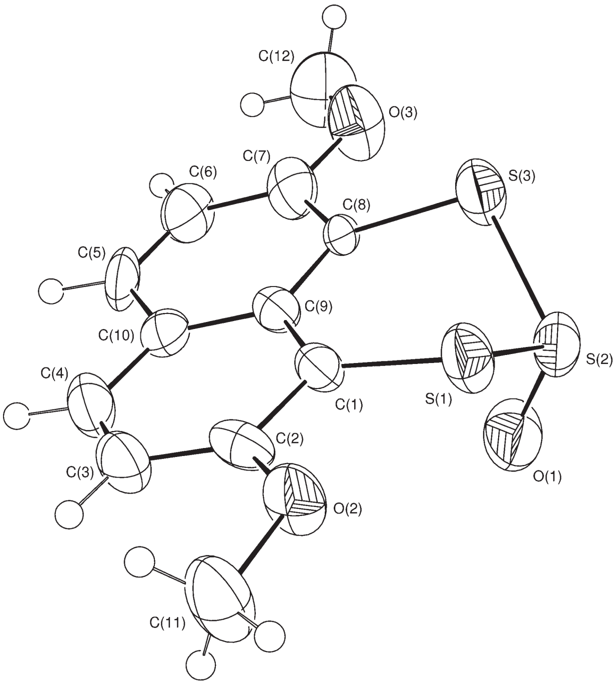


Figure 3. ORTEP view of **17** with ellipsoids drawn at the 50% probability level.

C(1), C(8), and C(9) from the ideal 120°, to accommodate the two *peri*-sulfur atoms. The unsubstituted system **15** and the dimethoxynaphthalene **17** show comparable bond lengths and angles and are close to symmetrically orientated about a plane running through O(1)−S(2)···C(9)−C(10). There is a small amount of deviation from planarity in the naphthalene ring, as can be seen from the C(1)−C(9)−C(10)−C(5) and C(8)−C(9)−C(10)−C(4) dihedral angles, with one of the *peri*-sulfur atoms slightly above the naphthalene plane (S(3)−C(8)−C(9)−C(1) dihedral angle −9.0(4) for **15** and −4(2) for **17**).

The *tert*-butyl substituted system **16** shows a far greater degree of distortion. The buttressing effect of the bulky tert-butyl

Table 2. Selected Interatomic Distances [Å] and Angles [deg] for Compounds 15−17

	15	16	17
Trisulfide-2-oxide Bond Lengths			
S(1)···S(3)	3.10	3.04	3.10
S(1)−C(1)	1.773(3)	1.782(4)	1.77(1)
S(3)−C(8)	1.773(3)	1.762(4)	1.749(9)
S(1)−S(2)	2.091(1)	2.065(2)	2.091(4)
S(2)−S(3)	2.097(1)	2.102(2)	2.091(5)
O(1)−S(2)	1.475(2)	1.470(4)	1.482(9)
C(1)−C(9)	1.428(4)	1.439(5)	1.439(5)
C(8)−C(9)	1.431(4)	1.442(5)	1.47(1)
	15	**16**	**17**
Trisulfide-2-oxide Bond Angles			
C(1)−S(1)−S(2)	103.1(1)	110.2(1)	100.5(4)
S(2)−S(3)−C(8)	100.5(1)	98.1(1)	100.9(4)
S(1)−S(2)−S(3)	95.35(4)	93.66(7)	95.7(2)
S(1)−S(2)−O(1)	109.7(1)	112.2(2)	107.6(4)
O(1)−S(2)−S(3)	108.4(1)	109.2(2)	108.6(4)
C(1)−C(9)−C(8)	126.6(2)	126.1(3)	125.7(9)
S(1)−C(1)−C(9)	125.8(2)	122.7(3)	127.4(8)
S(3)−C(8)−C(9)	124.7(2)	119.1(3)	124.6(8)
	15	**16**	**17**
Dihedral Angles			
S(1)−C(1)···C(8)−S(3)	−6.2	−31.4	−2.3
S(3)−C(8)−C(9)−C(1)	−9.0(4)	−14.5(5)	−4(2)
S(1)−C(1)−C(9)−C(8)	1.5(4)	−22.3(5)	1(2)
S(1)−S(2)−S(3)−C(8)	−64.6(1)	−69.7(1)	−65.0(4)
C(1)−S(1)−S(2)−S(3)	60.2(1)	45.0(2)	62.4(4)
C(1)−S(1)−S(2)−O(1)	−51.6(1)	−67.5(2)	−49.2(6)
O(1)−S(2)−S(3)−C(8)	48.2(1)	45.4(2)	45.6(5)
C(1)−C(9)−C(10)−C(5)	−177.3(2)	−175.2(4)	179(1)
C(8)−C(9)−C(10)−C(4)	−178.9(2)	−172.1(4)	−179(1)
S(1)−C(1)−C(2)−C(11)	–	16.3(5)	–
C(15)−C(7)−C(8)−S(3)	–	8.8(6)	–
S(1)−C(1)−C(2)−O(2)	–	–	1(1)
O(3)−C(7)−C(8)−S(3)	–	–	3(1)
O(1)−S(2)···C(9)−C(10)	0.9	6.5	0.1

substituents[45] causes a reduction in the nonbonding *peri*-S(1)···S(3) distance and their displacement above and below the mean naphthalene plane (S(1)−C(1)···C(8)−S(3) −31.4), with the naphthalene itself twisted to accommodate the structural feature (C(1)−C(9)−C(10)−C(5) −175.2(4) and C(8)−C(9)−C(10)−C(4) −172.2(4)). The trithiane ring is no longer symmetrical, notably differing in the C−S−S(O) bond angles.

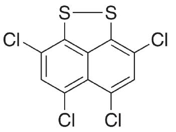
SO Transfer to Dienes. The feasibility of trisulfide-2-oxide **15** to act as an SO transfer reagent was investigated by heating in the presence of excess 2,3-dimethylbutadiene (**25a**) in solvents of increasing boiling point. The results are presented in Table 3.

For the unsubstituted trisulfide-2-oxide **15** refluxing chlorobenzene proved to be the most effective solvent to obtain sulfoxide **26a** in good yield in reasonable reaction times (Table 3, entry 3), with higher dilution providing superior yields of both **26a** and recovered disulfide **18** (compare entries 3 and 4). At lower temperatures (refluxing toluene or benzene), reaction times were longer, and yields of both sulfoxide **26a** and disulfide **18** were lower (entries 1 and 2). Use of a polar aprotic solvent (DMF) or protic solvent (pentanol) at the same temperature as refluxing chlorobenzene was not as effective in terms of yield of recovered disulfide (entries 5 and 6).

SO transfer from **15** was also successfully applied to dienes **25b**−**d** in refluxing chlorobenzene (entries 7−11). For diphenylbutadiene **25c** or myrcene **25d** a lower equivalence of diene was employed (entries 8 and 9). The reaction with myrcene was also run with an excess of trisulfide-2-oxide **15**, and good yields of sulfoxide **25d** and disulfide **18** were again obtained, although lower yields of **26d** were obtained when a 1:1 stoichiometry was employed (entries 10 and 11).

The ortho-substituted trisulfide-2-oxides **16** and **17** were also tested as SO transfer reagents with 2,3-dimethylbutadiene **25a**. With both **16** and **17**, a more rapid reaction in chlorobenzene occurred compared with **15** (entries 3, 13, and 15), with the reaction of the dimethoxytrisulfide-2-oxide **17** complete in 5.5 h. These shorter reaction times suggested that **16** and **17** might also effect SO transfer at lower temperature. Indeed, in refluxing benzene, transfer occurred with significantly improved yields and reduced reaction times compared with those with the unsubstituted **15** (entries 1, 12, and 14).

The increased rate at which both **16** and **17** transfer SO to dienes compared to **15** is notable. X-ray crystallographic analysis of **17** suggests it to be more strained than the unsubstituted **15** (vide supra), particularly in twisting of the naphthalene ring away from planarity. However, little additional strain is apparent in the X-ray structure of **17**, suggesting an electronic rather than a steric effect is in operation.[51] Unfortunately attempts to prepare *peri*-substituted trisulfide-2-oxides appended with electron-withdrawing groups on the naphthalene ring have so far met with failure. Treatment of the known tetrachlorodisulfide **27**[52] or a mixture of nitronaphthalenes **28** and **29**[53,54] under analogous conditions to those described in Scheme 5 failed to provide any of the corresponding trisulfide-2-oxides.



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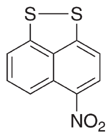

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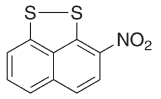

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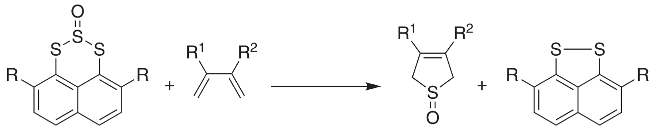
A comparison of **15** with existing SO transfer systems shows that higher yields of sulfoxides **26a**−**d** can be obtained under optimized thermal conditions, despite the slightly higher temperatures compared to conditions for Harpp's episulfoxides **3** and **4** (refluxing chlorobenzene vs refluxing toluene). Interestingly, Harpp observed that,when a pure sample of **26a** was heated for 20 h in refluxing xylene (138 °C), only 10% remained, the decomposition due to a presumed retrochelotropic process.[11] Clearly, the use of refluxing chlorobenzene (132 °C), a similarly high-boiling solvent, is not detrimental to the yield of sulfoxide over shorter reaction times (Table 3), although in practice reactions should be stopped upon consumption of **15** or diene to maximize yields of products.

It also proved possible to effect photomediated SO transfer from trisulfide-2-oxide **15** to diene **25a** at room temperature (eq 7), albeit in lower yield compared to that of the thermal case.

Table 3. Thermal SO Transfer from Trisulfide-2-oxides **15**−**17** to 1,3-Dienes[a]



15 R = H
16 R = *t*-Bu
17 R = OMe

25a-d

26a-d

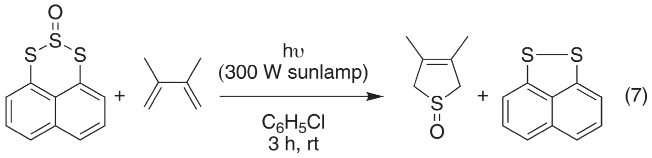
a R^1 = Me, R^2 = Me
b R^1 = H, R^2 = Me
c R^1 = Ph, R^2 = Ph
d R^1 = H, R^2 = $(CH_2)_2CH{=}CMe_2$

18 R = H
19 R = *t*-Bu
20 R = OMe

entry	trisulfide-2-oxide	diene	ratio	solvent	temp (°C)	time	sulfoxide (yield, %)[b]	disulfide (yield, %)[b]
1	**15**	**25a**	1:10	benzene	80	7 days[c]	**26a** (55)	**18** (85)
2	**15**	**25a**	1:10	toluene	110	23 h	**26a** (73)	**18** (95)
3	**15**	**25a**	1:10	C_6H_5Cl	132	10 h	**26a** (98)	**18** (99)
4[d]	**15**	**25a**	1:10	C_6H_5Cl	132	10 h	**26a** (75)	**18** (86)
5	**15**	**25a**	1:10	DMF	132	9.25 h	**26a** (95)	**18** (62)
6	**15**	**25a**	1:10	pentanol	132	10 h	**26a** (86)	**18** (37)
7	**15**	**25b**	1:10	C_6H_5Cl	132	8 h	**26b** (98)	**18** (96)
8	**15**	**25c**	1:2.5	C_6H_5Cl	132	5.75 h	**26c** (65)	**18** (92)
9	**15**	**25d**	1:2.5	C_6H_5Cl	132	6 h	**26d** (91)	**18** (90)
10	**15**	**25d**	1:1	C_6H_5Cl	132	6 h	**26d** (39)	**18** (96)
11	**15**	**25d**	2.5:1	C_6H_5Cl	132	6 h	**26d** (85)	**18** (97)
12	**16**	**25a**	1:10	benzene	80	36.5 h	**26a** (93)	**19** (94)
13	**16**	**25a**	1:10	C_6H_5Cl	132	8 h	**26a** (99)	**19** (96)
14	**17**	**25a**	1:10	benzene	80	42 h	**26a** (92)	**20** (93)
15	**17**	**25a**	1:10	C_6H_5Cl	132	5.5 h	**26a** (96)	**20** (92)

[a] All reactions run at 0.01 M in trisulfide-2-oxide except entry 4, run at 0.1 M. [b] Isolated yield after column chromatography. [c] Incomplete reaction, 8% recovered starting material **15**. [d] Reaction run at 0.1 M in trisulfide-2-oxide.

The photochemical behavior of *peri*-substituted trisulfide-2-oxides is therefore markedly different from that of the 1,2-benzo-substituted trisulfide-2-oxide **11**, which undergoes photoisomerization to the 1-oxide **12** at room temperature (Scheme 3, eq 6).[31]



(7)

15

25a
10 equiv

26a
55%

18
93%

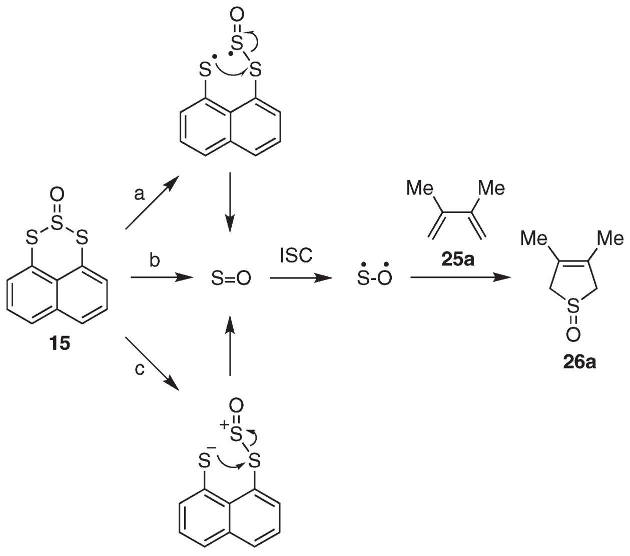
Mechanistic Studies. Although sulfoxides **26a**−**d** are known to be formed from the trapping of free SO with 1,3-dienes, we wished to establish whether an analogous mechanism was in operation in the case of **15**; i.e. does **15** first thermally degrade to SO and disulfide **18**, or does **26** form through direct SO transfer from **15** to the diene via an alternative bimolecular mechanism. The latter would raise the possibility of effecting an asymmetric SO transfer from a chiral, nonracemic trisulfide-2-oxide. A kinetic investigation into the reaction of **15** with 2,3-dimethylbutadiene **25a** was therefore undertaken (see Supporting Information for details). The reaction was found to be first order with respect to trisulfide-2-oxide **15** and zeroth order with respect to diene **25a**, with a first-order rate constant of 1.06 (±0.084) × 10^{-4} s^{-1} at 127 °C. Therefore, a mechanism based on direct SO transfer from **15** to diene **25a** can be excluded.

Additional indirect evidence for SO formation was obtained by studying the reaction in the absence of a diene. SO is known to decompose to ultimately form SO_2 and elemental sulfur, S_8, byproducts also observed in the reactions of sulfoxide **9** (a probable source of singlet SO).[21] Thermal decomposition of **15** in chlorobenzene at 140 °C in a sealed tube followed by treatment of the resulting solution with PPh_3 at room temperature for 2 h gave $Ph_3P{=}S$ in 89% yield (based on the theoretical amount of S_8 produced),[55] along with recovered disulfide **18**, indicative of efficient production of SO. The vapors from thermal decomposition of **15** under reflux were tested with wet pH paper and shown to be acidic, suggesting SO_2 formation.

Differential scanning calorimetry of a solid sample of **15** showed a sharp endotherm at 136 °C. Thermal gravitational analysis of **15** at this temperature showed a 12.2% mass loss, close to the theoretical value expected for loss of SO from **15** (13.4%).[56]

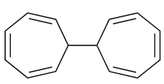
Having established that the SO transfer reaction is independent of the concentration of diene and that sulfoxide **26a** most probably arises from trapping of free SO with diene **25a**, the mechanism of the thermal breakdown of **15** was addressed. In the thermal decomposition of acyclic trisulfide-2-oxides, mechanisms based on initial heterolytic, rather than homolytic, fission of S−S(O) bonds were proposed, based on similar rates and product distributions in the presence of radical inhibitors and by investigating light/dark effects.[30] Rates of decomposition were also found to increase with increasing solvent polarity. In contrast, Nakayama proposed a mechanism based on homolytic fission of the S−S(O) bond to account for the products formed in the thermal decomposition of 1,2,3-trithiole-2-oxide **13** (Scheme 3, eq 7).[32]

Scheme 6. Proposed Mechanism of SO Transfer: (a) Homolytic Fission of S−S(O); (b) Concerted Loss of SO; (c) Heterolytic Fission of S−S(O)

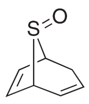


Qualitatively, SO transfer from **15** to diene **25a** was found to occur at approximately the same rate in the polar aprotic solvent DMF and the protic solvent pentanol as in chlorobenzene at the same temperature (Table 3, entries 3−5), albeit with different yields. In the absence of diene, the first order rate constants for the decomposition of **15** measured in DMF and pentanol at 127 °C were $1.11\ (\pm 0.042) \times 10^{-4}\ \mathrm{s}^{-1}$ and $1.16\ (\pm 0.035) \times 10^{-4}\ \mathrm{s}^{-1}$respectively, within experimental error of the rate constant measured in octane. Heating trisulfide-2-oxide **15** in chlorobenzene at reflux in the presence of radical traps (4-*tert*-butylcatechol, 1,4-benzoquinone, DPPH) led to the formation of disulfide **18** in a comparable yield and at a rate similar to that in the absence of radical traps.

The nature of the SO produced was also addressed. Nakayama reported that the breakdown of sulfoxide **9** at room temperature leads to formation of SO that appears to react in the singlet state, rather than the triplet ground state.[21] Diene adducts **26a**−**d** were produced, and some alkenes and alkynes were also successfully trapped. A comparison of the reaction of cycloheptatriene with the SO generated from thiirane **1** with that generated from **9** is informative. Whereas **1** gave the dimer **30** of cycloheptatriene[8b] presumed to have formed by H-abstraction by triplet SO followed by dimerization of the resulting radical, **9** gave sulfoxide **31** stereoselectively, consistent with concerted addition of singlet SO. When trisulfide-2-oxide **15** was reacted with 2.5 equiv of cycloheptatriene in refluxing chlorobenzene, we observed dimer **30** in the ^{1}H NMR of the crude reaction mixture, and no signals associated with **31**. We therefore conclude that ground state triplet SO is being formed in this process.



30



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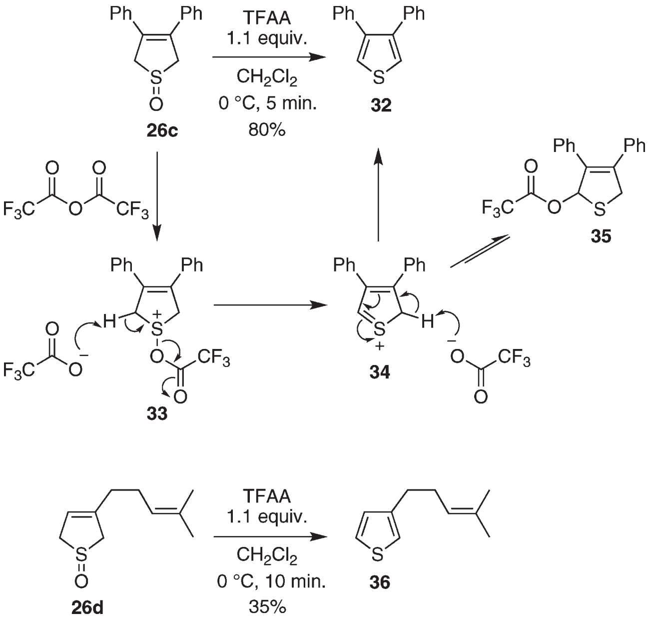
Scheme 7. Thiophene Synthesis through Dehydrative Pummerer Reaction



These studies are accommodated in the general mechanistic picture shown in Scheme 6. In a rate-determining step, trisulfide-2-oxide **15** fragments to give disulfide **18** and release SO. This breakdown may be initiated through homolytic or heterolytic fission of the S−SO bond, or through a concerted loss of SO. The available data do not allow us to unambiguously distinguish between these three pathways, although the absence of effects of solvent polarity or radical traps make the heterolytic and homolytic fission pathways less probable. The SO thus produced should be in the excited singlet state, which, after rapid intersystem crossing to the triplet ground state, undergoes trapping by diene through a diradical process to give the sulfoxide **26a**.

Application in Thiophene Synthesis. Although sulfoxides have widespread utility in organic synthesis, little work has been carried out in using the products of SO transfer to dienes in further synthetic transformations.[57] An attractive possibility is the dehydration of 2,3-dihydrothiophene 1-oxides such as **26a**−**d** to thiophenes. Isomeric 1,2-dihydrothiophene 1-oxides have been dehydrated under Pummerer conditions to give thiophenes.[58,59]

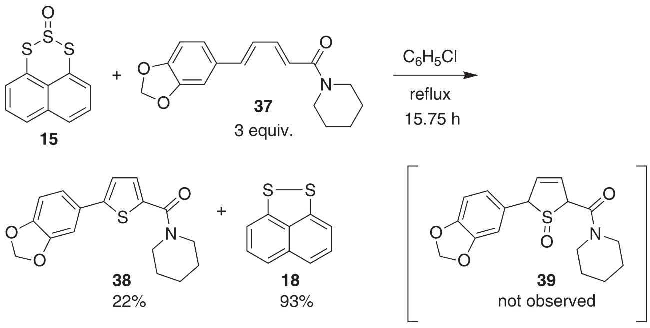
Treatment of sulfoxide **26c** with a slight excess of trifluoroacetic anhydride gave a clean and rapid transformation to 3,4-diphenylthiophene (**32**) (Scheme 7). This reaction can also be carried out in refluxing acetic anhydride (3 h, 79% yield).

A proposed mechanism for this transformation is shown in Scheme 7. After loss of trifluoroacetoxide from the sulfoxonium salt **33**, the resulting sulfonium **34** can undergo capture to form the classical Pummerer adduct **35** or deprotonation to form the thiophene **32**, with the latter pathway presumably favored by gain in aromaticity.

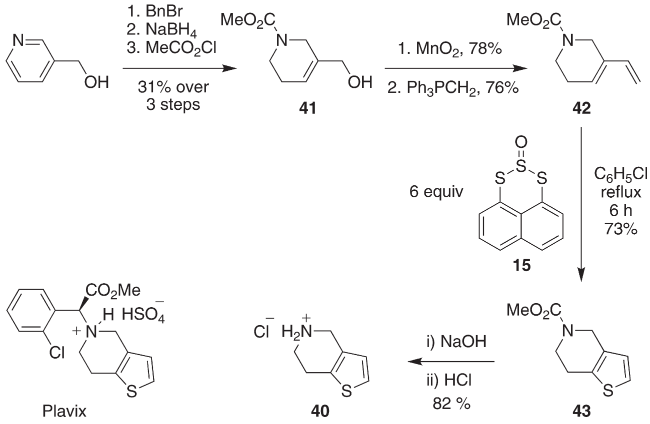
Dehydration of the myrcene adduct **26d** gave the naturally occurring thioperillene **36**, a constituent of hop oil.[60] The lower yield in this case is a consequence of the increased volatility of **36** compared to **32**, making isolation difficult.

Reaction of trisulfide-2-oxide **15** with excess piperine (**37**) in refluxing chlorobenzene gave directly the thiophene **38** (Scheme 8). The recovered diene was found to be an inseparable mixture of double bond isomers (see Supporting Information for details). Although thiophene **38** could be formed from in situ

Scheme 8. Thiophene Formation under SO Transfer Conditions



Scheme 9. Formal Synthesis of Plavix



dehydration of an intermediate sulfoxide **39** (not observed),[61] perhaps aided by the extended conjugation of the product, it might also be formed through initial reaction of **37** with other reactive sulfur species formed from the decomposition of SO.[62]

Plavix (clopidogrel bisulfate) is an antiplatelet medication used to reduce the risk of stroke. The tetrahydrothienopyridine **40** is a known intermediate in the synthesis of Plavix (Scheme 9).[63] We envisaged a novel synthesis of **40** based on trapping a suitable diene with SO followed by dehydration.[64]

Alcohol **41** was prepared from commercially available 3-(hydroxymethyl)pyridine according to a known procedure.[65] Allylic oxidation with MnO_2 followed by Wittig methylenation gave the requisite diene **42**. When diene **42** was heated with a 3-fold excess of trisulfide-2-oxide **15** in refluxing chlorobenzene, the thiophene **43** was the only observed product, obtained in 35% yield. The yield of **43** was increased to 73% through use of 6 equiv of **15**. Under these conditions, 25% of recovered diene **42**, and a 97% yield of disulfide **18** (based on **15**) were obtained. The expected intermediate sulfoxide, if formed, was again not observed. Carbamate deprotection gave **40**, and hence completed a formal synthesis of Plavix.

■ CONCLUSIONS

peri-Substituted trisulfide-2-oxides **15**−**17** have been shown to act as SO transfer reagents in trapping experiments with 2,3-dimethylbutadiene (**25a**). Using the parent system **15**, yields of sulfoxides **26a**−**d** are better than those obtained using *epi*-sulfoxides as SO sources. The disulfide byproducts **18**−**20** are easily separated and, as starting materials for the trisulfide-2-oxide syntheses, are recyclable. The presence of *o*-*tert*-butyl or *o*-methoxy groups on the naphthalene ring has been shown to increase the rate at which SO transfer occurs, suggesting both steric and electronic factors may play a role in the breakdown of the trisulfide-2-oxide. However, the longer and lower-yielding syntheses of **16** and **17** mean that **15** is for now the preferred reagent to effect this transformation, other than for the most demanding applications. The synthetic utility of the sulfilenes produced has been extended by the use of a Pummerer reaction to generate thiophenes. Certain dienes form thiophenes directly under the SO transfer conditions, a transformation which has been used in an expeditious synthesis of the core structure of the antiplatelet medication Plavix.

It should be possible to adapt the design principle described herein, namely relief of strain through formation of a stable chalcogen−chalcogen bond on a *peri*-substituted naphthalene or related ring system, to the generation of other reactive molecules.

■ ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Experimental procedures, compound characterization, kinetic data for SO transfer from **15** and cyclic voltammetry of **18** and **20**. Crystallographic information files (CIF) for compounds **16**, **17**, 1,5-dibromo-2,7-dimethoxynaphthalene (**45**), and nitronaphthalenes **28** and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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