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A Cyclization Approach toward Five-Membered Heteroaromatic *o*-Quinodimethanes *via* Fused-3-Sulfolenes

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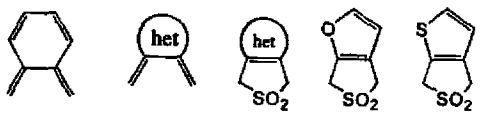
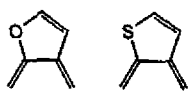
A general strategy involving the zincation of 4-bromo-3-chloro-2-sulfolene, *in situ* condensation with an α-heterosubstituted acetaldehyde, and subsequent cyclization reaction as the key steps toward the synthesis of furano- and thieno-3-sulfolenes is described. These fused-3-sulfolenes are demonstrated to be good precursors for the corresponding *o*-quinodimethanes.

It has been forty years since the first literature report[1] on the chemistry of *o*-quinodimethane **1**. Since then, a tremendous amount of effort by organic chemists has been put in this area.[2] On the other hand, the chemistry of heteroaromatic *o*-quinodimethanes **2** (HAQD's)[3] began to receive intensive attention only about a decade ago.[4] There are several general strategies toward the generation of the highly reactive HAQD's. The methodology involving the use of fused-3-sulfolenes **3** as precursors has several advantages. For example, thermolytic removal of SO_2 from 3-sulfolenes can be achieved under neutral conditions,[5] and the temperatures for thermolysis are usually not too high. In addition, derivatives are easily prepared from the parent compound *via* simple manipulation.[6] We have developed divergent strategies for the preparation of a family of heteroaromatic-fused 3-sulfolenes by properly functionalizing a sulfur-containing five-membered heterocycle.[3] In this paper, we wish to describe the details and the experimental procedures of our work on the cyclizative approach toward the preparation of furano-[7] and thiophene-fused[8] 3-sulfolenes **4** and **5** and their use as precursors for HAQD's **6** and **7**.



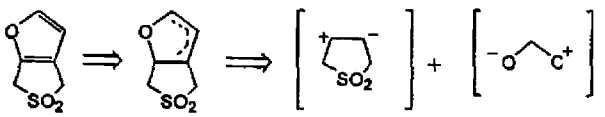
1 **2** **3** **4** **5**



6 **7**

The synthetic plan for furano-3-sulfolene **4** involved the reaction of a three-atom unit **10** with a latent form of the five-membered heterocycle **9**. It was hoped the C-C bond and C-O bond formation between the two components and, if required, the subsequent oxidative aromatization of the intermediate **8** would produce the desired target molecule **4** (Scheme I).

Scheme I



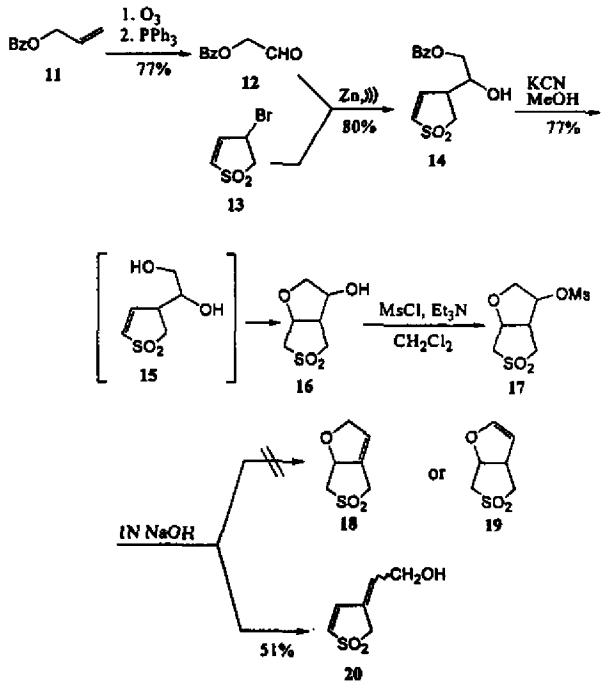
4 **8** **9** **10**

Hence, 4-bromo-2-sulfolene **13**[9] was first tested as the synthetic equivalent of **9** and α-benzoyloxyacetaldehyde **12**, prepared from the ozonolysis of allyl benzoate **11** by a standard procedure, was tested as the equivalent of **10** (Scheme II). The C-C bond formation reaction between the two molecules was performed under ultrasound-promoted zincation conditions[10] where **14** was produced as a mixture of diastereomers in good yield. Attempted reaction of the benzoate in compound **14** with $LiAlH_4$ or MeLi gave no desired alcohol **15** nor cyclized product **16**. It was found that the benzoate could be hydrolyzed easily upon treatment with KCN in MeOH. The intermediate alkoxide of compound **15** spontaneously underwent an intramolecular conjugate addition[11] to give the cyclized product **16** as a 9:5 mixture of diastereomers of which the stereochemistry was not specified.

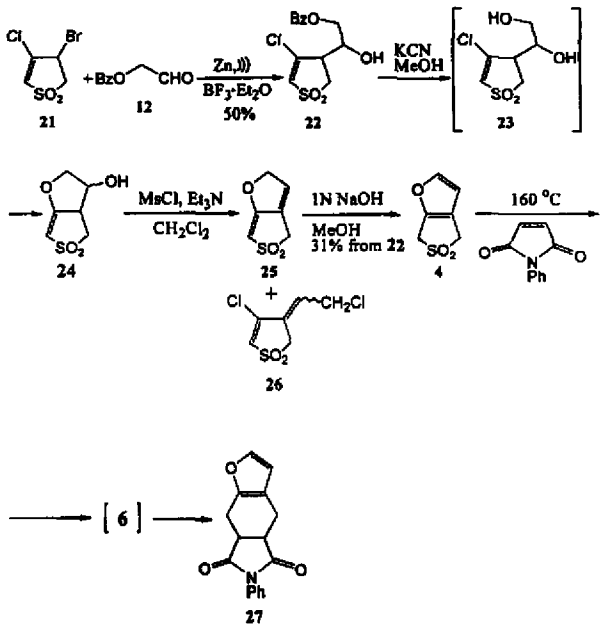
It was anticipated that dehydration of **16** and subsequent oxidation would give us the furano-3-sulfolene **4**. However, attempts toward this end were not successful. Treatment of **16** with $MsCl/Et_3N$ produced the mesylate **17**, which did not undergo spontaneous elimination reaction. A

Dedicated to Professor Yu-Shia Cheng on the occasion of her 65th birthday.

Scheme II



Scheme III



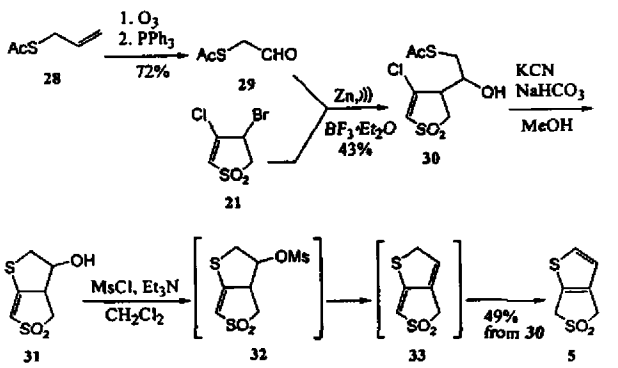
more forcing condition (1*N* NaOH) failed to cause the formation of either **18** or **19**. Instead, compound **20** was produced in 51% yield. The undesired ring-opening of the tetrahydrofuran ring of **17** may have been due to the higher acidity of the protons adjacent to the sulfonyl group. Attempts of cyclization of compound **20** were not successful after several trials.

In order to avoid the problem of ring-opening of the tetrahydrofuran ring as shown in Scheme II, compound **21**[12] was used as the starting material (Scheme III). Thus, a mixture of **21** and **12** was subjected to ultrasound-promoted zincation treatment.[10] In the presence of BF_3·Et_2O, the alcohol **22** was obtained in 50% yield, whereas the yield of **22** dropped to 38% if the reaction was performed without BF_3·Et_2O. Hydrolysis of **22** with KCN in MeOH yielded the cyclized product **24** directly. Compound **24**, which could not be purified due to its low solubility in organic solvents, was treated in its crude form with MsCl and Et_3N (10 mL) to give the diene **25**. When only 2 equiv of Et_3N was used in this reaction, another product **26**, in addition to **25**, could be obtained in 34% yield. The formation of **26** implies the incompleteness of the cyclization of the intermediate **23** to **24**. Attempts to force the cyclization to completion by adding $AgBF_4$ at the KCN-induced hydrolysis stage were in vain. The transformation of **24** to **25** under mesylation conditions indicates elimination to be easier for **24** than **16**. The double bond in compound **24** is essential because it not only prevents the ring-opening of the tetrahydrofuran ring but also facilitates the elimination of the mesylate intermediate. Compound **25**, with the correct oxidation state, was isomerized to **4** upon treatment with 1*N* NaOH.

Compound **4** proved to be a good precursor for the furano-*o*-quinodimethane **6** by thermolysis and subsequent trapping reaction. Heating a mixture of **4** and *N*-phenylmaleimide at 160 °C for 3 h yielded the cycloadduct **27**. The transient intermediate **6** was not detected.

Thieno-3-sulfolene **5** was successfully prepared by the same strategy.[8] The α-substituted aldehyde **29**, prepared from **28** by ozonolysis (Scheme IV), was used as the 3-atom unit. Direct ultrasound-promoted zincation of **21** and *in situ* condensation reaction with **29** under standard conditions gave **30** only in 24% yield. The yield could be improved to 43% when BF_3·Et_2O was present and when compound **29** was used in excess (3 equiv).

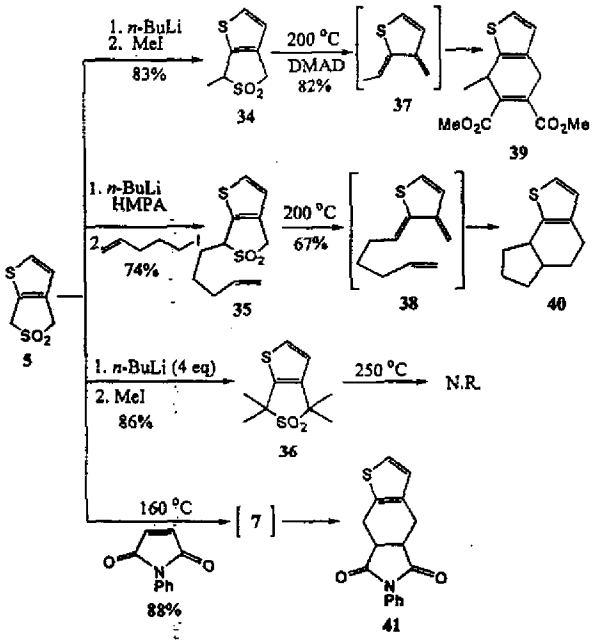
Scheme IV



Treatment of **30** with KCN and $NaHCO_3$ in MeOH directly produced the bicyclic alcohol **31**. As was the case in Scheme III, both hydrolysis of the thioester and the subsequent conjugate addition took place in one pot. Without purification, compound **31** was treated with MsCl, and a large excess of Et_3N (10 equiv) where the final target **5** was obtained in 49% yield. The possible intermediates **32** and **33** were not detected. The ease of double bond migration to convert **33** to **5** in the presence of Et_3N versus the NaOH-induced isomerization from **25** to **4** is consistent with the greater aromaticity of thiophene than furan.[13]

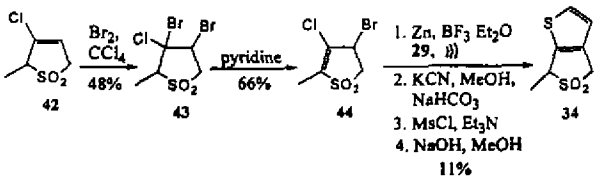
When compound **5** was treated with *n*-BuLi followed by MeI at -105 °C, the deprotonation/alkylation sequence proceeded regioselectively to produce only one monomethylated product **34**. Under similar conditions, the pentenyl-substituted product **35** was prepared regioselectively. Tetramethylated thieno-3-sulfolene **36** was obtained when **5** was treated with 4 equiv of *n*-BuLi and MeI in one pot (Scheme V).

Scheme V

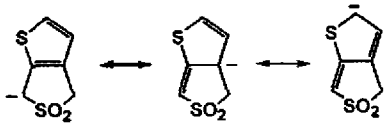


The regiochemistry of compound **34** was unambiguously proved by chemical method. Treatment of 4-bromo-3-chloro-2-methyl-2-sulfolene (**44**), prepared from the readily available compound **42**[14] *via* bromine addition and subsequent partial dehydrobromination, through the same reaction sequence for the preparation of **5**, afforded the methyl-substituted compound **34** (Scheme VI), which is identical to the product obtained from the deprotonation-methylation of compound **5**.

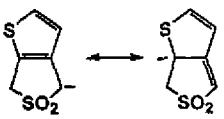
Scheme VI



The high regioselectivity for the formation of **34** and **35** from **5** can be understood by comparing the relative stability of the two possible intermediate carbanions **A** and **B**. The more stable carbanion **A**, with it's better delocalized negative charge, should form more rapidly when **5** is treated with a strong base. Kinetic factors also favor the deprotonation leading to **A** because the sulfur atom of the thiophene moiety should bring BuLi close to it through complexing with the lithium cation.



A



B

Thermolysis of the fused 3-sulfolenes **5** or **34** at 200 °C in the presence of a large excess of a dienophile caused rapid extrusion of SO_2, and the transient intermediates **7** and **37** could be trapped as Diels-Alder cycloadducts **41** and **39**, respectively (Scheme V). An intramolecular Diels-Alder reaction of the intermediate *o*-quinodimethane **38** took place efficiently when compound **35** was thermolyzed at 200 °C in benzene in a sealed tube. Compound **40** was obtained as a 3:1 mixture of stereoisomers of which the stereochemistry was not specified. On the other hand, the tetramethylated compound **36** remained intact upon heating at 250 °C for several hours. Steric hindrance of the four methyl groups may have been responsible for the difficult cheletropic extrusion of SO_2.

The strategy described in Scheme III has also been applied to the synthesis of pyrrole-fused 3-sulfolenes, the precursors of pyrrolo-*o*-quinodimethanes. This part of the work has already been published.[15] In summary, we have described herein a general and efficient route toward the synthesis of five-membered heteroaromatic-fused 3-sulfolenes from a readily available starting material **21**. This strat-

egy allows an easy entry to the generation and utilization the corresponding highly reactive heteroaromatic *o*-quinodimethanes.

EXPERIMENTAL SECTION

General Methods

^{1}H NMR spectra were determined on a Bruker ACF-200 NMR spectrometer as solutions in $CDCl_3$ or acetone-d_6. IR spectra were determined on a Perkin-Elmer 290 IR spectrophotometer. Mass spectra were determined on a VG 70-250S mass spectrometer. Elemental analyses were performed on a Perkin-Elmer 240C analyzer.

Benzoyloxyacetaldehyde (12)

A solution of allyl benzoate (2.00 g, 12.3 mmol) in CH_2Cl_2 (70 mL) was cooled at -78 °C. Ozone was passed through this solution until a blue color was sustained, upon which time triphenylphosphine (3.88 g, 14.8 mmol) was added. The mixture was gradually warmed to room temperature. The excess of solvent was removed under reduced pressure, and the crude oil was distilled to give 1.55 g (77%) of compound **12** as a colorless oil: bp 95 °C/0.4 mmHg; IR (neat) 1723, 1710, 1273, 1119 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.90 (s, 2H), 7.43-7.62 (m, 3H), 8.08-8.13 (m, 2H), 9.73 (s, 1H); MS *m/z* 164 (M^+), 136, 122, 105 (100%). HRMS $C_9H_8O_3$ requires: 164.0473; found: 164.0486.

4-(1-Hydroxy-2-benzoyloxy)ethyl-2-sulfolene (14)

A mixture of 4-bromo-2-sulfolene **13** (0.64 g, 3.26 mmol), compound **12** (0.64 g, 3.91 mmol) and Zn powder[16] (0.26 g, 3.91 mmol) in THF (10 mL) was irradiated with ultrasound in a cleaning bath at ambient temperature for 7 hr. The mixture was filtered, concentrated under reduced pressure, and purified with flash column chromatography (silica gel, hexane/EtOAc, 1:1) to give 0.74 g (80%) of compound **14** as a 6:4 mixture of diastereomers as a white solid. The two isomers could not be separated. However, the ^{1}H NMR spectrum clearly revealed it to be a mixture. IR (KBr) 3498, 1697, 1284, 1136, 1107 cm^{-1}; ^{1}H NMR (acetone-d_6, major isomer) δ 3.28-3.57 (m, 2H), 3.61-3.78 (m, H), 4.16-4.30 (m, 1H), 4.50-4.68 (m, 2H), 5.04-5.12 (m, 1H), 6.98-7.00 (m, 1H), 7.18-7.23 (m, 1H), 7.58-7.80 (m, 3H), 8.16-8.21 (m, 2H); ^{1}H NMR (acetone-d_6, minor isomer) δ 3.60-3.80 (m, 3H), 4.38-4.68 (m, 4H), 6.98-7.08 (m, 2H), 7.58-7.80 (m, 3H), 8.16-8.21 (m, 2H); MS *m/z* 282 (M^+), 160, 105 (100%), 77. HRMS $C_{13}H_{14}O_5S$ requires: 282.0562; found: 282.0542.

4-Hydroxy-2-oxa-7-thiabicyclo[3.3.0]octane 7,7-Dioxide (16)

A mixture of compound **14** (0.20 g, 0.71 mmol) and KCN (0.046 g, 0.71 mmol) in MeOH (20 mL) was stirred at room temperature for 10 h under an NaOH-containing tube to neutralize the toxic HCN formed during the reaction. The resulting mixture was concentrated under reduced pressure and filtered through a silica gel column. The crude material was purified by HPLC (LiChrosorb column, EtOAc) to give 0.076 g (60%) of two isomers of compound **16** in a 9:5 ratio. The major isomer: white solid, mp 67-68 °C; IR (KBr) 3467, 1399, 1297, 1217, 1132, 1113 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 2.95 (br s, 1H), 3.02-3.25 (m, 3H), 3.32-3.52 (m, 2H), 3.75-3.90 (m, 2H), 4.40-4.51 (m, 1H), 4.55-4.68 (m, 1H); MS *m/z* 160 (M^+ - 18, 100%), 149, 118, 81. HRMS $C_6H_{10}O_4S$ requires: 178.0300; found: 178.0316. The minor isomer: a white solid, mp 86-87 °C; IR (KBr) 3459, 1387, 1294, 1116, 1062 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 2.80-3.00 (m, 2H), 3.08-3.42 (m, 3H), 3.65 (dd, J = 2.7, 9.7 Hz, 1H), 4.19 (dd, J = 4.6, 9.7 Hz, 1H), 4.38-4.45 (m, 1H), 4.51 (d, J = 4.1 Hz, 1H), 4.82-4.92 (m, 1H); MS *m/z* 178 (M^+), 160, 119, 70 (100). HRMS $C_6H_{10}O_4S$ requires: 178.0300; found: 178.0316.

3-(2-Hydroxyethylidenyl)-2,3-dihydrothiophene 1,1-Dioxide (20)

To a solution of compound **16** (0.17 g, 0.95 mmol) in CH_2Cl_2 (10 mL) cooled at 0 °C was added sequentially methanesulfonyl chloride (0.15 mL, 1.90 mmol) and triethyl amine (0.4 mL, 2.98 mmol). The mixture was then stirred at room temperature for 20 min, after which time CH_2Cl_2 (10 mL) and 5% HCl (10 mL) were added. The layers were separated and the organic layer was concentrated under reduced pressure. To this crude oil was added MeOH (5 mL) followed by 1N NaOH (3 mL), and the mixture was stirred at room temperature for 10 min. After removal of MeOH under reduced pressure, the aqueous layer was extracted with CH_2Cl_2 (5 mL × 4). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:5) to give 77.2 mg (51%) of **20** as two stereoisomers in 1:1 ratio. Isomer A: colorless oil; IR (neat) 3507, 1675, 1629, 1291, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (br s, 1H), 3.97 (d, J = 1.4 Hz, 2H), 4.34 (d, J = 5.8 Hz, 2H), 6.00-6.08 (m, 1H), 6.68 (d, J = 6.6 Hz, 1H), 6.96 (d, J = 6.6 Hz, 1H); MS *m/z* 160 (M^+), 143, 131 (100), 95. HRMS $C_6H_8O_3S$ requires: 160.0194; found: 160.0186. Isomer B: white solid, mp 76-77 °C; IR (KBr) 3434, 1537, 1277, 1217, 1116 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (br s, 1H), 3.91 (d, J = 1.3 Hz,

2H), 4.41-4.47 (m, 2H), 5.89-6.00 (m, 2H), 6.74 (dd, J = 1.2, 6.7 Hz, 1H), 7.42 (dd, J = 0.5, 6.7 Hz, 1H); MS *m/z* 160 (M^+), 143, 131 (100), 95. HRMS $C_6H_8O_3S$ requires: 160.0194; found: 160.0206.

3-(2-Benzoyloxy-1-hydroxyethyl)-4-chloro-2,3-dihydrothiophene 1,1-Dioxide (22)

A mixture of compound **21** (0.31 g, 1.34 mmol), Zn power[16] (0.35 g, 5.36 mmol), compound **12** (0.44 g, 2.68 mmol) and BF_3-Et_2O (0.33 mL, 2.68 mmol) in THF (12 mL) was irradiated with ultrasound in a cleaning bath at ambient temperature for 4.5 hr. The mixture was filtered and concentrated under reduced pressure and purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) to give 0.21 g (50%) of compound **22** as a white solid: mp 114-115 °C; IR (KBr) 3468, 3082, 1696, 1597, 1345, 1274, 1248, 1114 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.88 (br s, 1H), 3.40-3.55 (m, 2H), 3.67-3.80 (m, 1H), 4.39 (d, J = 5.8 Hz, 2H), 4.63-4.73 (m, 1H), 6.83 (d, J = 1.5 Hz, 1H), 7.44-7.66 (m, 3H); MS *m/z* 318 (M^+ + 2), 316 (M^+), 165, 105 (100). HRMS $C_{13}H_{13}ClO_5S$ requires: 316.0172; found: 316.0169.

4,6-Dihydrothieno[3,4-*b*]furan 5,5-Dioxide (4) and 4-Chloro-3-(2-chloroethylidenyl)-2,3-dihydrothiophene 1,1-Dioxide (26)

A solution of compound **22** (0.29 g, 0.90 mmol) and KCN (0.059 g, 0.90 mmol) in MeOH (30 mL) was stirred at room temperature for 6 hr under an NaOH-containing tube to neutralize the toxic HCN formed during the reaction. After filtration through a silica gel column and concentration under reduced pressure, the crude oil was dissolved in CH_2Cl_2 (10 mL) and cooled at 0 °C. To this solution was added MsCl (0.14 mL, 1.81 mmol), and the mixture was stirred for 5 min, after which time Et_3N (1.26 mL, 9.03 mmol) was added. The resulting mixture was stirred at room temperature for 10 h, and CH_2Cl_2 (10 mL) and 5% HCl (10 mL) were added. The layers were separated and the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure and purified with flash column chromatography (silica gel, hexane/EtOAc, 1:3) to give a white solid. To the solid was then added MeOH (5 mL) followed by 1N NaOH (3 mL), and the mixture was stirred at room temperature for 1 h. After removal of MeOH under reduced pressure, the aqueous layer was extracted with CH_2Cl_2 (5 mL × 4). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:5) to give 44.1 mg (31%) of compound **4** as a white solid: mp 84-85 °C; IR (KBr) 1312, 1203, 1130, 1117, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.24 (d, J = 1.0 Hz, 2H), 4.27 (s, 2H), 6.44 (d, J = 2.0 Hz, 1H), 7.52-7.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 53.64, 56.17, 107.98, 114.17, 143.03, 145.73; MS *m/z* 158 (M^+), 94 (100). HRMS $C_6H_6O_3S$ requires: 158.0037; found: 158.0065. When the same reaction described above was performed by using only two equiv of Et_3N, compound **26** was obtained in 34% yield along with compound **4** in 22% yield. Compound **26** is a white solid: mp 93-94 °C; IR (KBr) 1551, 1300, 1134, 955 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (d, J = 5.2 Hz, 2H), 4.12 (d, J = 1.4 Hz, 2H), 6.49 (tt, J = 1.4, 5.2 Hz, 1H), 6.88 (s, 1H); MS (FAB) *m/z* 215 (M^+ + 3), 213 (M^+ + 1, 100%), 197, 181, 147, 91, 73. Anal. Calcd for $C_6H_6Cl_2O_2S$: C, 33.82; H, 2.84. Found: C, 33.94; H, 2.69.

7a,8-Dihydro-6-phenyl-*cis*-4*H*-furo[2,3-*f*]isoindole-5,7(4a*H*, 6*H*)-dione (27)

A solution of compound **4** (11.0 mg, 0.070 mmol) and *N*-phenylmaleimide (1.81 mg, 0.104 mmol) in toluene (2 mL) was heated in a sealed tube at 150-160 °C for 3 h. After the solvent was removed under reduced pressure, the crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1 :2) to give 6.9 mg (37%) of compound **27** as a pale yellow solid: mp 77-78 °C; IR (KBr) 1769, 1699, 1487, 1375, 1179 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.85-3.60 (m, 6H), 6.26 (d, J = 1.9 Hz, 1H), 7.15-7.30 (m, 3H), 7.35-7.50 (m, 3H); MS *m/z* 267 (M^+), 207, 134, 119, 62 (100). HRMS $C_{16}H_{13}NO_3$ requires: 267.0895; found: 267.0903.

Acetylmercaptoethanal (29)

A solution of potassium thioacetate (5.27 g, 46.0 mmol) and allyl bromide (4.0 mL, 50 mmol) was heated at reflux under N_2 for 3 h. After concentration under reduced pressure, the crude oil was distilled (60-65 °C/25 mmHg) to give 3.82 g of the allyl thioacetate **28**. A solution of compound **28** (0.91 g, 7.85 mmol) in CH_2Cl_2 (60 mL) was cooled at -78 °C. Ozone was passed through this solution until a blue color was sustained, upon which time triphenylphosphine (2.47 g, 9.42 mmol) was added. The mixture was gradually warmed to room temperature. The excess of solvent was removed under reduced pressure, and the crude oil was distilled to give 0.663 g (72%) of compound **29** as a pale yellow liquid: IR (neat) 1726, 1689, 1136, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.69 (d, J = 2.1 Hz, 2H), 9.50 (t, J = 2.1 Hz, 1H); MS *m/z* 118 (M^+), 90 (100), 76, 61. HRMS $C_4H_6O_2S$ requires: 118.0089; found: 118.0091.

3-(2-Acetylmercapto-1-hydroxyethyl)-4-chloro-2,3-dihydrothiophene 1,1-Dioxide (30)

A mixture of compound **21** (2.00 g, 8.6 mmol), Zn

power[16] (2.25 g, 34.5 mmol), compound **29** (1.53 g, 12.95 mmol) and BF_3·Et_2O (1.06 mL, 8.6 mmol) in THF (15 mL) was irradiated with ultrasound in a cleaning bath at 25-30 °C for 1 h. Another portion of compound **29** (1.02 g, 8.6 mmol) was added, and the irradiation was continued for 1 h. A third portion of compound **29** (0.51 g, 4.3 mmol) was added, and the mixture was irradiated again for 2 h, after which time pyridine (0.70 mL, 8.6 mmol) was added. The crude mixture was filtered through a flash column of silica gel and purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) to give 0.99 g (43%) of compound **30** as a colorless oil: IR (neat) 3484, 1679, 1604, 1315, 1241, 1139, 1037 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.62 (br s, 1H), 2.97 (dd, J = 7.6, 13.2 Hz, 1H), 3.07 (dd, J = 6.4, 13.2 Hz, 1H), 3.34-3.55 (m, 2H), 3.68 (dd, J = 3.2, 12.1 Hz, 1H), 4.29-4.41 (m, 1H), 6.97 (d, J = 1.6 Hz, 1H); MS *m/z* 252 (M^+ - 18), 174 (100), 145, 139. HRMS $C_8H_9ClO_3S_2$ requires: 251.9682; found: 251.9686.

4,6-Dihydrothieno[3,4-*b*]thiophene 5,5-Dioxide (5)

A solution of compound **30** (0.41 g, 1.52 mmol), $NaHCO_3$ (0.14 g, 1.67 mmol) and KCN (0.099 g, 1.52 mmol) in MeOH (70 mL) was stirred at room temperature for 6 h under an NaOH-containing tube to neutralize the toxic HCN formed during the reaction. After filtration and removal of MeOH under reduced pressure, the crude mixture was passed through a silica gel column using acetone as the eluent. After concentration under reduced pressure, CH_2Cl_2 (10 mL) was added, and the solution was cooled at 0 °C. Methanesulfonyl chloride (0.24 mL, 3.04 mmol) was added, and the mixture was stirred for 5 min, after which time Et_3N (2.10 mL, 15.2 mmol) was added. The resulting mixture was stirred at room temperature for 10 h, and CH_2Cl_2 (30 mL) and 5% HCl (10 mL) were added. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) of the crude oil gave 0.13 g (49%) of compound **5** as a white solid: mp 146-147 °C; IR (KBr) 3126, 1299, 1174, 1122, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.31 (br s, 2H), 4.40 (br s, 2H), 6.98 (d, J = 5.1 Hz, 1H), 7.24 (ddd, J = 0.8, 1.0, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 55.88, 56.41, 123.47, 128.08, 128.86, 131.84; MS *m/z* 174 (M^+), 110 (100), 84. HRMS $C_6H_6O_2S_2$ requires: 173.9757; found: 173.9728.

6-Methyl-4,6-dihydrothieno[3,4-*b*]thiophene 5,5-Dioxide (34) *via* Methylation Reaction

A solution of compound **5** (79.7 mg, 0.46 mmol) in THF (15 mL) cooled at -105 °C was added dropwise *n*-BuLi (2.54 M, 0.18 mL, 0.46 mmol), and then the temperature was raised to -85 °C gradually. Methyl iodide (0.11 mL, 1.83 mmol) was added at once, and the resulting mixture was stirred at -78 °C 2 h. Ethyl acetate (5 mL) was added, and the mixture was warmed to room temperature. After concentration under reduced pressure, the crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) to give 71.5 mg (83%) of compound **34** as a white solid: mp 70-71 °C; IR (KBr) 3112, 1287, 1232, 1152, 1113, 1093, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66 (d, J = 7.0 Hz, 3H), 4.28 (br s, 2H), 4.41 (br q, J = 7.0 Hz, 1H), 6.96 (d, J = 5.1 Hz, 1H), 7.40 (dd, J = 0.9, 5.1 Hz, 1H); MS *m/z* 188 (M^+), 124, 123 (100). Anal. Calcd for $C_7H_8O_2S_2$: C, 44.66; H, 4.28. Found: C, 44.73; H, 4.18.

3-Chloro-3,4-dibromo-2-methyltetrahydrothiophene 1,1-Dioxide (43)

A solution of 3-chloro-2-methyl-3-sulfolene **42** (0.492 g, 2.96 mmol) and Br_2 (0.18 mL, 3.55 mmol) in CCl_4 (25 mL) was heated at reflux for 8 h. The mixture was cooled to room temperature, and saturated $Na_2S_2O_3$ (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (25 mL × 2), and the combined organic layers were dried (Na_2SO_4), filtered, and concentration under reduced pressure. The crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 2:1) to give 0.46 g (48%) of compound **43** as two stereoisomers in 2:1 ratio. ^1H NMR of the major isomer ($CDCl_3$) δ 1.65 (d, J = 6.7 Hz, 3H), 3.78 (dd, J = 1.8, 14.5 Hz, 1H), 3.90 (q, J = 6.7 Hz, 1H), 4.15 (dd, J = 5.9, 14.5 Hz, 1H), 5.23 (dd, J = 1.8, 5.9 Hz, 1H). The minor isomer was a white solid: mp 148-149 °C; IR (neat) 1318, 1130, 825, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (d, J = 6.6 Hz, 3H), 3.53-3.78 (m, 2H), 3.82 (q, J = 6.6 Hz, 1H), 4.97 (dd, J = 7.6, 12.3 Hz, 1H); MS *m/z* 185, 183, 181, 101,65 (100). Anal. Calcd for $C_5H_7Br_2ClO_2S$: C, 18.40; H, 2.16. Found: C, 18.58; H, 2.15.

4-Bromo-3-chloro-2-methyl-4,5-dihydrothiophene 1,1-Dioxide (44)

A solution of compound **43** (0.404 g, 1.24 mmol) and pyridine (0.20 mL, 2.48 mmol) in anhydrous acetone (5 mL) was stirred at room temperature for 10 h, after which time 2% HCl (10 mL) was added. Acetone was removed under reduced pressure, and the aqueous layer was extracted with EtOAc (25 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered, and concentration under reduced pressure. The crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 2:1) to give, in addition to 20% of

43, 0.202 g (66%) of compound **44** as a white solid: mp 74-74.5 °C; IR (KBr) 3020, 1646, 1304, 1287, 1174, 1127 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.11 (d, J = 1.6 Hz, 3H), 3.82 (dd, J = 2.7, 14.6 Hz, 1H), 3.99 (dd, J = 7.6, 14.6 Hz, 1H), 4.98-5.08 (m, 1H); MS *m/z* 246 (M^+), 165, 115, 65 (100). Anal. Calcd for $C_5H_6BrClO_2S$: C, 24.46; H, 2.46. Found: C, 24.36; H, 2.46.

Synthesis of Compound 34 from 44

A mixture of compound **44** (112.6 mg, 0.46 mmol), Zn power[16] (119.9 mg, 1.83 mmol), compound **29** (81.2 mg, 0.69 mmol) and BF_3·Et_2O (0.056 mL, 0.46 mmol) in THF (5 mL) was irradiated with ultrasound in a cleaning bath at 20-35 °C for 1 h whereupon another portion of compound **29** (54.1 mg, 0.46 mmol) was added. The irradiation was continued for another 1 h, after which time a third portion of compound **29** (27.1 mg, 0.23 mmol) was added and the mixture was irradiated for 2 h. Pyridine (0.037 mL, 0.46 mmol) was added, and the resulting mixture was passed through a flash column of silica gel (hexane/EtOAc, 1:1). The crude yellow-colored oil was added to a solution of MeOH (10 mL) containing $NaHCO_3$ (19.3 mg, 0.23 mmol) and KCN (14.9 mg, 0.23 mmol), and the mixture was stirred at room temperature for 6 h under an NaOH-containing tube to neutralize the toxic HCN formed during the reaction. After filtration and removal of MeOH under reduced pressure, the crude mixture was passed through a silica gel column using acetone as the eluent. After concentration under reduced pressure, CH_2Cl_2 (5 mL) was added and the solution was cooled to 0 °C. Methanesulfonyl chloride (0.036 mL, 0.46 mmol) was added, and the mixture was stirred for 5 min, after which time Et_3N (0.32 mL, 2.3 mmol) was added. The resulting mixture was stirred at room temperature for 2 h, and CH_2Cl_2 (20 mL) and 5% HCl (5 mL) were added. The layers were separated and the organic layer was washed with $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. To this crude oil was then added MeOH (2 mL) followed by the addition of 1N NaOH (1 mL), and the mixture was stirred at room temperature for 30 min. After removal of MeOH under reduced pressure, the aqueous layer was extracted with CH_2Cl_2 (3 mL × 3). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude material was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) to give 9.8 mg (11%) of compound **34**.

4,4,6,6-Tetramethyl-4,6-dihydrothieno[3,4-*b*]thiophene 5,5-Dioxide (36)

To a solution of compound 5 (47.4 mg, 0.27 mmol) in THF (10 mL) cooled at -105 °C was added dropwise *n*-BuLi (2.54 M, 0.42 mL, 1.09 mmol), and the stirring was continued for 10 min. Methyl iodide (0.27 mL, 4.36 mmol) was added at once and the mixture was allowed to gradually warm up to -78 °C, whereupon the stirring was continued for another 20 min. Ethyl acetate (5 mL) was added and the mixture was warmed to room temperature. After concentration under reduced pressure, the crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) to give 53.7 mg (86%) of compound **36** as a white solid: mp 135-136 °C; IR (KBr) 3102, 1459, 1288, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (s, 6H), 1.69 (s, 6H), 6.90 (d, J = 5.1 Hz, 1H), 7.35 (d, J = 5.1 Hz, 1H); MS *m/z* 230 (M^+), 166, 151 (100). Anal. Calcd for $C_{10}H_{14}O_2S_2$: C, 52.14; H, 6.13. Found: C, 52.00; H, 6.28.

6-(4-Pentenyl)-4,6-dihydrothieno[3,4-*b*]thiophene 5,5-Dioxide (35)

To a solution of compound **5** (54.0 mg, 0.31 mmol) and hexamethyl phosphoramide (0.22 mL, 1.24 mmol) in THF (10 mL) cooled at -105 °C was added dropwise *n*-BuLi (2.54 M, 0.12 mL, 0.31 mmol), and the temperature was raised to -85 °C gradually. 5-Iodo-1-pentene (243.3 mg, 1.24 mmol) was added at once, and the resulting mixture was stirred at -78 °C for 2.5 h. Ethyl acetate (5 mL) was added and the mixture was warmed to room temperature. After concentration under reduced pressure, the crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) to give, in addition to 13% of compound **5**, 55.4 mg (74%) of compound **35** as a colorless oil: IR (neat) 1638, 1436, 1319, 1308, 1171, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60-1.95 (m, 3H), 2.08-2.29 (m, 3H), 4.26 (s, 2H), 4.25-4.35 (m, 1H), 4.98-5.13 (m, 2H), 5.71-5.92 (m, 1H), 6.96 (d, J = 5.2 Hz, 1H), 7.39 (dd, J = 0.7, 5.2 Hz, 1H); MS *m/z* 178 (M^+ - 64, 100%), 150, 135. HRMS $C_{11}H_{14}O_2S_2$ requires: 242.0435; found: 242.0434.

5,6-Dimethoxycarbonyl-7-methyl-4,7-dihydrobenzo[*b*]-thiophene (39)

A solution of compound **34** (71.5 mg, 0.38 mmol) and dimethyl acetylenedicarboxylate (0.23 mL, 1.90 mmol) in benzene (5 mL) was heated in a sealed tube at 200 °C for 4 h. After the solvent was removed under reduced pressure, the crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 2:1) to give 82.8 mg (82%) of compound **39** as a white solid: mp 44.5-45.5 °C; IR (KBr) 1708, 1645, 1426, 1337, 1246, 1201, 1043, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (d, J = 7.0 Hz, 3H), 3.45-3.80 (m, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 4.00-4.18 (m, 1H), 6.80 (d, J = 5.1 Hz, 1H), 7.20 (d, J = 5.1 Hz, 1H); MS *m/z* 266 (M^+), 234 (100), 219, 148. Anal. Calcd for $C_{13}H_{14}O_4S$: C, 58.63; H, 5.30. Found:

C, 58.80; H, 5.28.

Hexahydroindeno[4,5-*b*]thiophene (40)

A solution of compound **35** (54.8 mg, 0.226 mmol) in benzene (5 mL) was heated in a sealed tube at 200 °C for 2 h. After the solvent was removed under reduced pressure, the crude oil was purified by HPLC (LiChrosorb column, hexane) to give 26.8 mg (67%) of compound **40** as an unseparable mixture of stereoisomers in 3:1 ratio as a colorless oil: IR (neat) 3098, 3058, 2948, 2863, 1445, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30-1.95 (m, 7H), 2.00-2.18 (m, 1H), 2.26-2.50 (m, 1H), 2.50-2.85 (m, 2H), 3.05-3.20 (m, 1H), 6.78 (d, J = 5.1 Hz, 0.75H), 6.80 (d, J = 5.0 Hz, 0.25H), 7.05 (dd, J = 0.6, 5.0 Hz, 0.25H), 7.06 (dd, J = 0.6, 5.1 Hz, 0.75H); MS *m/z* 178 (M^+, 100), 150, 149, 135. HRMS $C_{11}H_{14}S$ requires: 178.0816; found: 178.0804.

7a,8-Dihydro-6-phenyl-*cis*-4*H*-thieno[2,3-*f*]isoindole-5,7(4a*H*,6*H*)-dione (41)

A solution of compound **5** (27.2 mg, 0.16 mmol) and *N*-phenylmaleimide (54.1 mg, 0.31 mmol) in benzene (3 mL) was heated in a sealed tube at 200 °C for 4 h. After the solvent was removed under reduced pressure, the crude oil was purified by HPLC (LiChrosorb column, hexane/EtOAc, 1:1) to give 38.9 mg (88%) of compound **41** as a white solid: mp 158-159 °C; IR (KBr) 1772, 1687, 1390, 1311, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78-2.93 (m, 1H), 2.96-3.10 (m, 1H), 3.36-3.59 (m, 4H), 6.88 (d, J = 5.0 Hz, 1H), 6.91-7.05 (m, 2H), 7.10 (dd, J = 0.5, 5.0 Hz, 1H), 7.35-7.43 (m, 3H); MS *m/z* 283 (M^+), 136, 135 (100), 110, 91. Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.63; N, 4.94. Found: C, 67.37; H, 4.40; N, 4.90.

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Fused-3-sulfolenes; Heteroaromatic *o*-quinodimethanes; Ultrasound promoted zincation.

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