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Thia-Diels-Alder reactions of hetaryl thioketones with non-activated 1,3-dienes; evidence for a diradical mechanism

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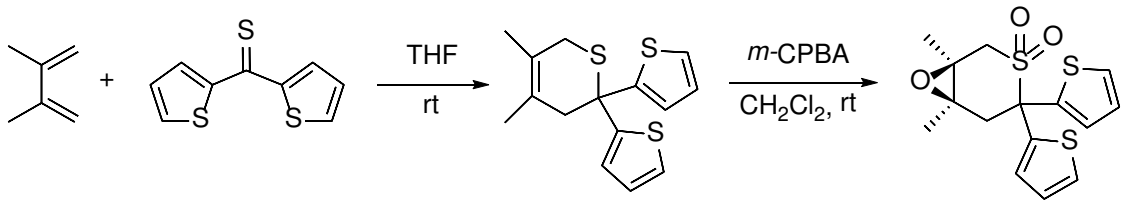


Abstract

Dihetaryl thioketones substituted with thiophen-2-yl and seleophen-2-yl rings react as superdienophilic reagents with non-activated 1,3-dienes such as 2,3-dimethylbuta-1,3-diene, cyclopentadiene and mixtures of isomeric hexa-2,4-dienes to produce the expected 2*H*-thiopyrans in good to excellent yields. In the latter case, the corresponding *cis*-3,6-dihydro-3,6-dimethyl-2,2-dihetaryl-2*H*-thiopyrans are formed as the sole products in a stereoconvergent thia-Diels-Alder reaction. A step-wise mechanism via delocalized intermediate diradicals is postulated to rationalize the observed reaction course. Treatment of 3,6-dihydro-4,5-dimethyl-2,2-di(thien-2-yl)-2*H*-thiopyran with excess *m*CPBA at room temperature leads to the oxidation of both the C=C bond and the sulfur atom in the six-membered ring.

Keywords: thia-Diels-Alder reactions, thioketones, 3,6-dihydro-2*H*-thiopyrans, reaction mechanisms, cyclic sulfones

The thia-Diels-Alder reactions constitute an important group of hetero-Diels-Alder reactions, and they can be used to synthesize six-membered sulfur-containing compounds.[1] They are of special interest for the preparation of 3,6-dihydro-2*H*-thiopyrans, which are known as relevant components of natural and biologically active products.[2] In general, thia-Diels-Alder reactions can be performed starting with thiabutadienes[3] or using thiadienophiles. In the latter case, activated thioesters,[4] dithioesters,[4,5] and thioamides[6] as well as thiourea derivatives[7] are known as prone dienophiles in reactions with non-activated 1,3-dienes. In addition, the use of some aromatic thioketones as heterodienophiles is also described,[8] but reactions with simple enolizable, aliphatic thioketones are rarely reported, as their handling is difficult.[9a] Nevertheless, the reaction of thioacetone with 2,3-dimethylbuta-1,3-diene (**1a**) was reported to afford the expected cycloadduct.[9b] On the other hand, hexafluorothioacetone reacts easily with **1a** and some other 1,3-dienes.[10a] The analogous reactions were observed with α,α,α-trifluorothioacetophenone and α,α,α-trifluorothioacetone.[10b] Various 3,6-dihydro-2*H*-thiopyrans have been prepared via the reaction of in-situ-generated thioketones bearing an electron-withdrawing group with 2,3-dimethyl-1,3-butadiene (**1a**).[11] Furthermore, several thia-Diels-Alder reactions of adamantanethione with substituted buta-1,3-dienes were reported.[12] Alkyl trimethylsilyl as well as phenyl trimethylsilyl thioketones undergo the [4+2]-cycloaddition with **1a**, and the obtained 2-silylated 3,6-dihydro-2*H*-thiopyrans were converted into 2*H*-thiopyrans by treatment with *meta*-chloroperbenzoic acid (*m*-CPBA).[13] The relatively stable diaryl thioketones react efficiently with diverse 1,3-dienes[14] and on the basis of kinetic studies were named as 'superdienophiles' by Sauer.[15] In a recent study, the volume parameters of the reaction of thiobenzophenone with isoprene were determined, and on this basis the authors concluded that a concerted reaction mechanism is followed.[16]

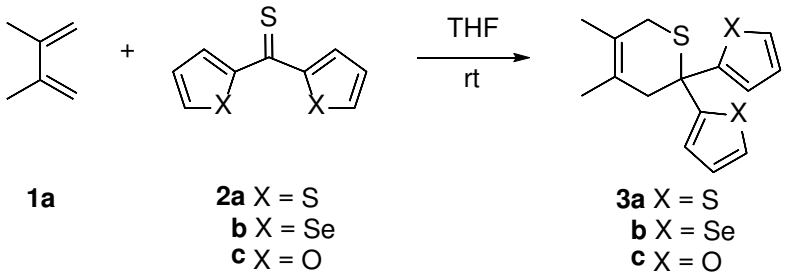
In recent reports, asymmetric thia-Diels-Alder reactions of activated dithioesters[17] as well as of aryl- and hetaryl thioketones[18] with an in-situ-generated chiral trienamine were presented. In the second case, a stepwise reaction mechanism via diradical intermediates was proposed.

The goal of the present study was to examine thia-Diels-Alder reactions of non-activated dienes with a series of dihetaryl and hetaryl phenyl thioketones **2**, which have been used as heterodienophiles only in a single study.[18]

Symmetric and non-symmetric dihetaryl thioketones **2** were obtained from the corresponding ketones by thionation with Lawesson's reagent (LR).[19] The already reported

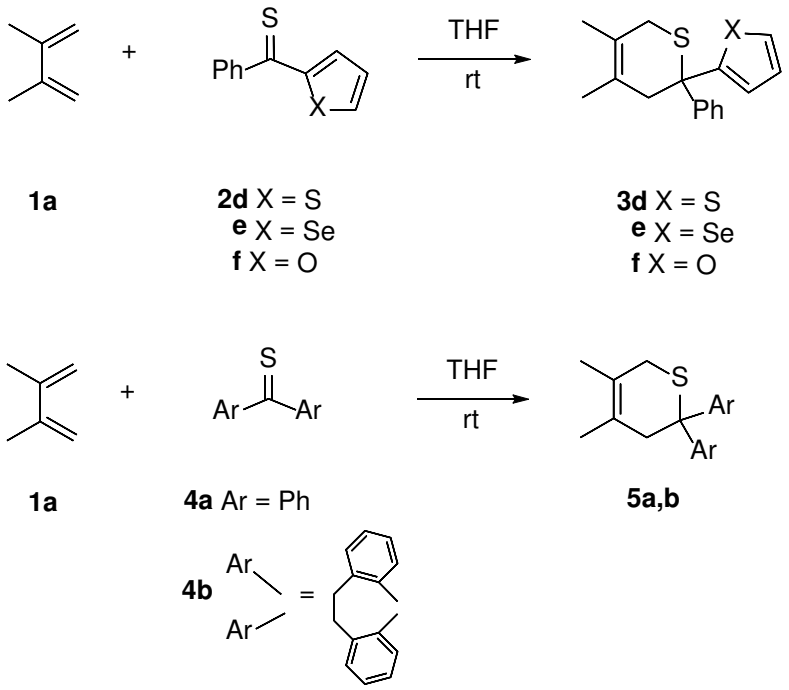
method, which relies on heating a mixture of the ketone and LR in toluene, was improved by applying microwave irradiation.[20] In that case, the reaction times were drastically reduced to two minutes, and the desired thioketones **2** were obtained in good yields. However, in the case of thiofluorenone, in contrast to the reported data,[21] instead of the desired thiofluorenone, bisfluorenylidene was obtained.

In a typical experiment, 2 mmol of 2,3-dimethylbuta-1,3-diene (**1a**) and 1 mmol of di(thiophen-2-yl) thioketone (**2a**) in THF were reacted at room temperature for 24 h. After chromatographic purification, the sole product was isolated as a solid material in 82% yield. The ^{1}H NMR spectrum confirmed the presence of the expected 3,4-dimethyl-6,6-di(thiophen-2-yl)-3,6-dihydro-2*H*-thiopyran (**3a**, Scheme 1) and this was further proven by ^{13}C-NMR and IR spectra and elemental analysis. Similarly, reactions of **1a** with di(selenophen-2-yl) and di(furan-2-yl) thioketones (**2b**,**c**) led to the desired 2*H*-thiopyrans (**3b**,**c**) (Scheme 1). However, the attempted cycloaddition of di(*N*-methylpyrrol-2-yl) thioketone and **1a** was unsuccessful, and the thioketone was recovered from the reaction mixture.



Scheme 1. Thia-Diels-Alder reactions of **1a** with dihetaryl thioketones **2a**–**c**.

In another series of experiments, hetaryl phenyl thioketones **2d**–**f** were used for the reaction with **1a** leading to a single product of type **3** in each case. In an extension of the study, thiobenzophenone (**4a**) and thiodibenzosuberone (**4b**) were converted into the corresponding 2*H*-thiopyrans **5a** and **5b**, respectively, under the same conditions (Scheme 2).

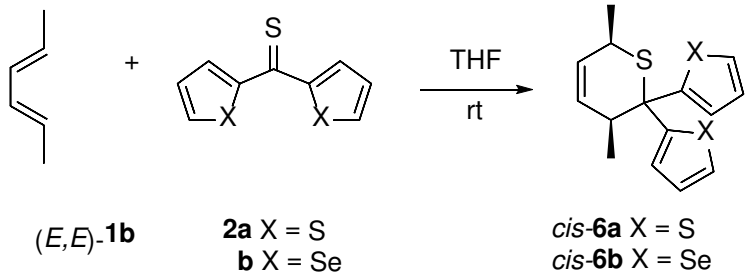


Scheme 2. Thia-Diels-Alder reactions of **1a** with hetaryl phenyl and diaryl thioketones

In order to examine the reaction mechanism of the studied thia-Diels-Alder additions of hetaryl thioketones with non-activated 1,3-dienes, additional experiments with (*E*,*E*)-hexa-2,4-diene ((*E,E*)-**1b**) were performed. The concerted [4+2]-cycloaddition predicts the stereospecific formation of a single product in each case. On the other hand, violation of the concertedness would lead to mixtures of stereoisomeric products as a result of the appearance of intermediate zwitterionic or diradical species. The reaction of (*E,E*)-**1b** with thiobenzophenone (**4a**) to give 3,6-dihydro-3,6-dimethyl-2,2-diphenyl-2*H*-thiopyran has been reported to proceed in good yields, but the configuration of the product has not been determined.[8b,14b] In a more recent study, the *cis*-configuration of the stereospecifically formed analogous products with diaryl selenoketones was established on the basis of the ^{1}H NMR data.[22] On the other hand, the analogous reactions performed with the less reactive (*E,Z*)-hexa-2,4-diene ((*E,Z*)-**1b**) and diaryl selenoketones or diaryl thioketones gave also the *cis*-configured 3,6-dihydro-2*H*-seleno- and -thiopyrans, respectively, as the major products, together with small amounts of the *trans*-isomers. These results of a stereoconvergent reaction have been explained by a concerted cycloaddition in the case of (*E,E*)-**1b** and a two-step radical pathway via reversible formation of diradical intermediates in the case of the less reactive (*E,Z*)-**1b**.[22]

In our recent publications, non-concerted [4+2]- and [3+2]-cycloadditions with hetaryl thioketones occurring via postulated intermediate diradicals were described.[18,23]

The reaction of hetaryl thioketones **2a**,**b** with excess (*E,E*)-**1b** (as a mixture with ca. 40% (*E,Z*)- and 5% (*Z,Z*)-**1b**) was performed without solvent at room temperature for 24 h and led to a single product in each case, which was isolated in quantitative yield. Based on the spectroscopic and analytical data, the structures of 3,6-dihydro-3,6-dimethyl-2,2-dihetaryl-2*H*-thiopyrans **6a** and **6b**, respectively, were assigned to the products (Scheme 3). The comparison of their ^{1}H NMR spectra with those of the corresponding 2,2-diaryl-2*H*-selenopyrans described in ref.[22] allowed the *cis*-configuration to be ascribed to the products **6**. Finally, in the case of the product formed in the reaction with **2a**, the structure of *cis*-**6a** was confirmed by X-ray crystallography (Figure 1).



Scheme 3. Stereospecific thia-Diels-Alder reaction of (*E,E*)-**1b** with dihetarylthioketones **2a,b**.

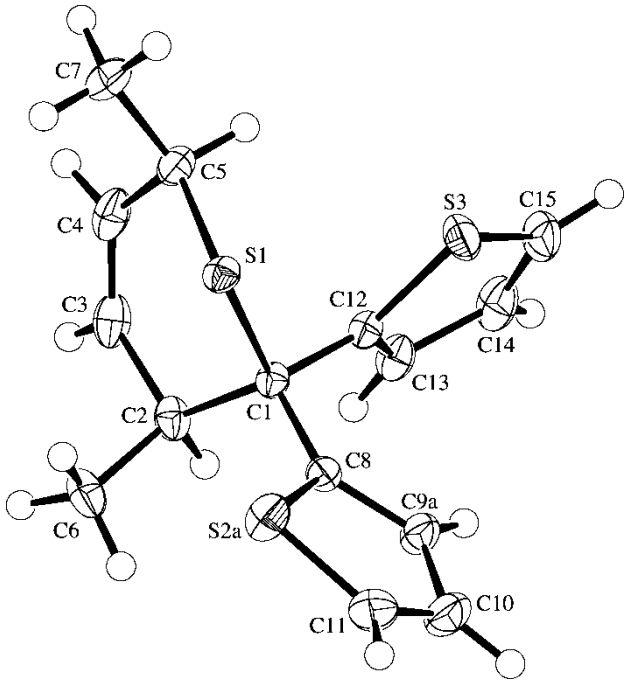


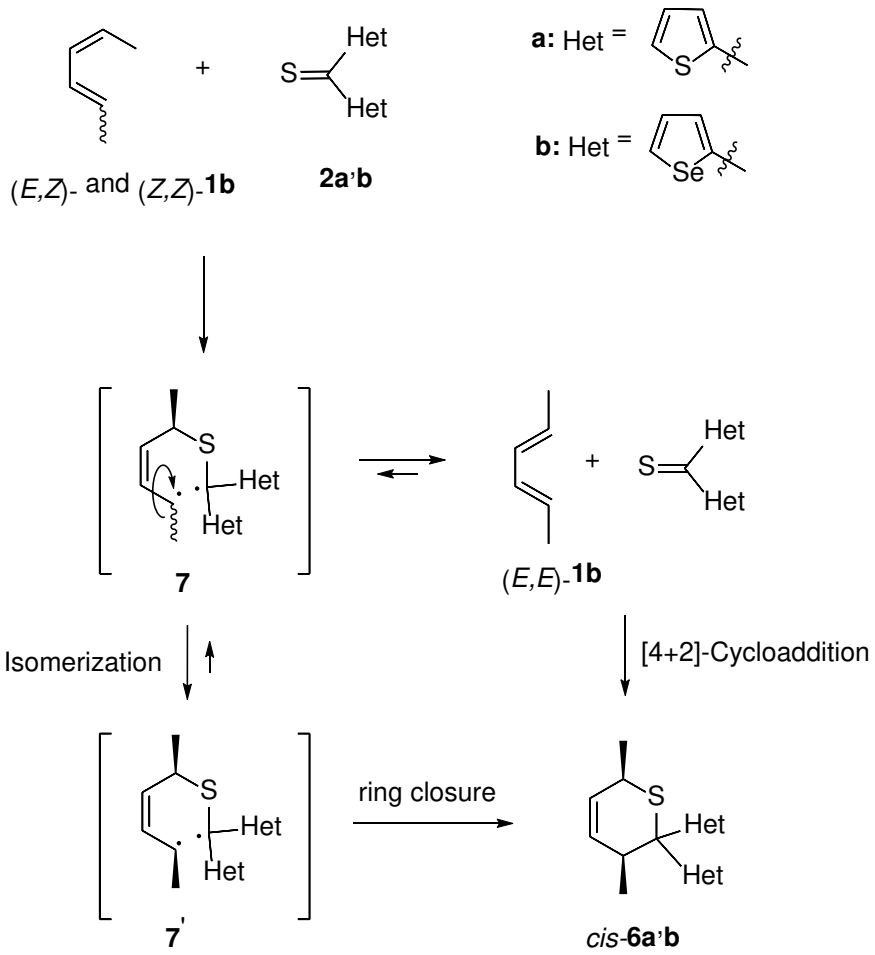
Figure 1. ORTEP plot[24] of the molecular structure of conformation A of *cis*-**6a** (with 50% probability ellipsoids; arbitrary numbering of atoms).

The ratio of the isomeric hexa-2,4-dienes **1b** used as a substrate in excess was compared with the ratio found in the sample left after the reaction with thioketones **2a**,**b**, including the amount of (*E,E*)-**1b** consumed in the quantitative formation of *cis*-**6**. Calculations performed for both reaction mixtures showed that in the course of the studied [4+2]-cycloadditions the amount of the (*E,E*)-isomer increased by ca. 12%, whereas the amounts of (*E,Z*)-, and (*Z,Z*)-isomers were reduced by ca. 12% in total. These results strongly suggest that the amounts of the obtained products *cis*-**6a** and *cis*-**6b** are higher than expected for the consumed (*E,E*)-(**1b**), based on the contents calculated for the starting mixture.

An another experiment was performed using equimolar amounts of thioketone **2a** and hexa-2,4-diene **1b** as a mixture of (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-isomers in a ratio of 22:70:8. The mixture of **2a** in **1b** was heated in a closed reaction tube at 80°C for 18 h. After this time, the green color of the starting **2a** completely disappeared, and the ^{1}H NMR analysis of the crude mixture with a weighed standard (1,1,2,2-tetrachloroethane) revealed the formation of *cis*-**6a** in 84% yield. Two characteristic doublets of this known product were accompanied by another pair of little intense two doublets located at 1.31 and 1.16 ppm, respectively, with $^2J_{H,H}$ = 6.0 Hz, which could be attributed to the isomer *trans*-**6a**. The location of these signals and the difference of the chemical shifts were similar to the data reported for the *trans*-isomer, analogous to **6a**, obtained with thiobenzophenone.[22] Based on the comparison of the intensities of these signals with the signal of the CH_2 groups of the standard used for the quantitative analysis, the yield of the postulated product *trans*-**6a** was calculated to ca. 6%. This result points out that in the course of the studied reaction substantial amount of (*E,Z*)-**1b** present in the starting mixture was consumed yielding an additional portion of the *cis*-**6a**.

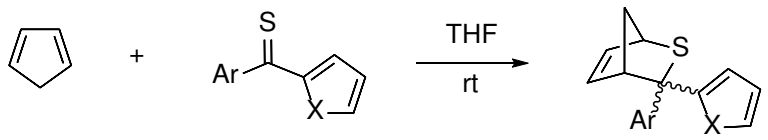
A likely explanation of the observed results is a stepwise cycloaddition of the less reactive (*E,Z*)- and (*Z,Z*)-dienes and subsequent isomerization of the intermediate diradicals **7** (Scheme 4) leading to the formation of *cis*-3,6-dimethyl-2*H*-thiopyrans *cis*-**6**. On the other hand, the postulated reversible formation of intermediate diradicals leading to the increase of the most stable (and most reactive) (*E,E*)-**1b** in the reaction mixture is also acceptable.[22] Both interpretations, however, support the proposed stepwise diradical mechanism of the formal

[4+2]-cycloadditions of non-activated electron-rich 1,3-dienes (*E,Z*)-, and (*Z,Z*)-**1b** with hetaryl thioketones (Scheme 4).



Scheme 4. Mechanistic interpretation of the step-wise reaction course of the thia-Diels-Alder reaction with (*E,Z*)- and (*Z,Z*)-hexa-2,4-diene **1b** and dihetaryl thioketones **2**.

As a third 1,3-diene, freshly prepared cyclopentadiene was used in reactions with the symmetric di(thiophen-2-yl) thioketone (**2a**) and the non-symmetric phenyl thiophen-2-yl thioketone (**2d**). In both cases, bicyclic products **8** were formed in good yields (Scheme 5). In the second case, a mixture of two stereoisomeric (*exo*, *endo*) products in a 7:3 ratio was obtained and, after chromatography, isolated as the analytically pure mixture of isomers **8b**. In analogy to the experiment with 2,3-dimethylbuta-1,3-diene, the attempted [4+2]-cycloaddition of cyclopentadiene with di(*N*-methylpyrrol-2-yl) thioketone was unsuccessful and even after 24 h in THF solution at room temperature the starting thioketone was recovered.



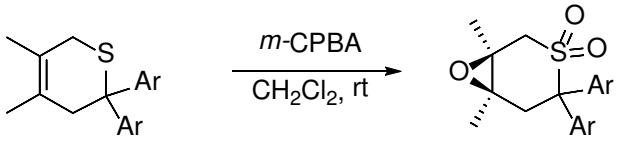
2a Ar = Thienophen-2-yl, X = S
2d Ar = Ph, X = S

8a
exo-, endo- **8b** (7:3)

Scheme 5. Thia-Diels-Alder reaction of cyclopentadiene with **2a** and **2d**.

The commercially available (*E,E*)-diphenylbuta-1,3-diene, which is known to display low reactivity towards non-activated dienophiles,[25] was also tested in the reaction with **2a** in THF solution at room temperature. In that case, however, no formation of the expected [4+2]-cycloadduct was observed even after 24 h. Instead, only gradual decomposition of the starting thioketone **2a** was observed.

Finally, the 2*H*-thiopyrans **3a** and **5a** were oxidized by treatment with excess *meta*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at room temperature for 48 h. In each case, a single product was isolated as a crystalline material in high yield. The ^{1}H-NMR spectra revealed in both cases two AB-systems attributed to two CH_2 groups. In addition, in the ^{13}C-NMR spectra, instead of three expected signals for the sp^3-C-atoms of the heterocycle, five signals were found between 40 and 70 ppm. Based on these data, the structure of the bicyclic oxiranes **9** was postulated and subsequently confirmed by elemental analysis (Scheme 6). These structures indicate that the oxidation of the S-atom of **3a** and **5a** to the sulfone group competes with the formation of the oxirane. A similar course of oxidations of 3,6-dihydro-2*H*-thiopyrans with oxone,[26] as well as of the 4,5-dimethyl-2,2-bis(trifluoromethyl) derivative with *m*-CPBA,[27] was reported (see also ref.[28]).



3a Ar = Thienophen-2-yl
5a Ar = Ph

9a Ar = Thienophen-2-yl
9b Ar = Ph

Scheme 6. Oxidation of 2*H*-thiopyrans **3a** and **5a** with *m*-CPBA

The presented study shows that, similarly to aryl thioketones, hetaryl analogues are superior heterodienophiles in thia-Diels-Alder reactions with non-activated 1,3-dienes. The [4+2]-cycloadditions can be performed under mild conditions in the absence of any catalyst. The results obtained in the reactions with (*E,E*)-hexa-2,4-diene to give *cis*-configured 3,6-dihydro-3,6-dimethyl-2*H*-thiapyrans may suggest a concerted [4+2]-cycloaddition. However, an enhanced amount of the isolated product suggests that some isomerization processes occur in the course of the reaction. The postulated diradical intermediates formed in the initial step of the reaction either isomerize to the most stable precursor of the *cis*-configured [4+2]-cycloadducts or, in a reversible process, are converted into the most reactive (*E,E*)-2,4-hexadiene, which subsequently reacts stereospecifically in a concerted manner with the starting thioketone.

In contrast to dihetaryl thioketones **2a**-**c** bearing thien-2-yl, selenophen-2-yl or furan-2-yl rings, respectively, the analogous di(*N*-methylpyrrol-2-yl) thioketone does not display reactivity of a 'superdienophilic' reagent and the expected 2*H*-thiopyran derivative was not formed in the reaction with 2,3-dimethylbuta-1,3-diene .

The treatment of 3,6-dihydro-2*H*-thiopyrans with an excess of *m*-CPBA at room temperature leads to the oxidation of the S-atom as well as the C=C bond to produce bicyclic oxiranes containing a sulfonyl group.

Experimental

Melting points were determined in a capillary using a MEL-TEMP II apparatus (*Aldrich*) and are uncorrected. IR spectra were recorded on a NEXUS FT-IR spectrophotometer in KBr pellets; absorptions (ν) in cm^{-1}. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance III instrument (600 and 150 MHz, respectively) in $CDCl_3$; chemical shifts (δ) are given in ppm, coupling constants (J) in Hz. The multiplicity of the ^{13}C signals was deduced from DEPT supported by ^{1}H-^{13}C HMQC spectra. ^{1}H NMR data are presented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant, integration. Electrospray ionization-mass spectra (ESI-MS) were recorded on a Varian500-MS IT mass spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Chemistry Faculty in Łódź. Applied reagents such as (*E,E)*-1,4-diphenylbuta-1,3-diene, 2,3-dimethylbuta-1,3-diene, hexa-2,4-diene (mixture of (*E,E)*-, *(E,Z)*-, and (*Z,Z)*-isomers in a ratio of 55:40:5), inorganic

reagents, and solvents are commercially available (Aldrich) and were used as received. The (*E,Z*)-enriched mixture of isomers of **1b** was prepared from a commercial sample based on the reported protocol.[29] The ratio of isomeric hexa-2,4-dienes was established based on the ^{1}H NMR spectrum registered in $CDCl_3$ solution. Cyclopentadiene was freshly prepared by distillation of the commercially available dimer according to the known protocol.[30] Microwave supported syntheses of thioketones **2** were performed in a microwave reactor Discover SP.

Synthesis of thioketones 2.[20] A solution of 1 mmol of the corresponding ketone and 1 mmol of Lawesson's reagent (LR) in 2 mL of dry toluene was placed in a microwave reaction tube. All reactions were performed at 150 W and reaction times were adjusted to 2 min. After cooling of the reaction mixture to room temperature, the solvent was evaporated in vacuo. The residue was purified chromatographically using a mixture of petroleum ether and chloroform (7:3) as the eluent.

Synthesis of 2*H*-thiopyrans 3. A solution of 1 mmol of the corresponding thioketone **2** and 2 mmol of 2,3-dimethylbuta-1,3-diene in 1 ml of dry THF was stirred at room temperature for 24 h. After this time, the solvent was evaporated in vacuo. The residue was purified chromatographically using CH_2Cl_2 as the eluent.

3,6-Dihydro-4,5-dimethyl-2,2-di(thiophen-2-yl)-2*H*-thiopyran (3a). Yield: 229.6 mg (82%), green solid, m.p. 80.7–81.3°C (chromatographic purification). IR spectrum, ν, cm^{-1}: 3084 (w), 2864 (m), 1425 (m), 1231 (s), 708 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.66, 1.75 (6H, 2s, 2 CH_3); 3.06, 3.10 (4H, 2s, 2 CH_2); 6.90–6.91 (2H, m); 6.98 (2H, dd, *J* = 3.6, 1.2 Hz); 7.22 (2H, dd, *J* = 5.4, 1.2 Hz). ^{13}C NMR spectrum, δ, ppm: 19.3, 20.5 (2CH_3); 33.2, 47.9, 48.4 (3C(sp^3)); 122.8, 125.8 (2C(sp^2)); 125.0, 125.4, 126.5 (6CH(arom)); 151.1 (2C(arom)). Found, %: C 61.61, H 5.45, S 32.97. $C_{15}H_{16}S_3$ (292.48). Calculated, %: C 61.59, H 5.52, S 32.88.

3,6-Dihydro-4,5-dimethyl-2,2-di(selenophen-2-yl)-2*H*-thiopyran (3b). Yield: 318.6 mg (89%), dark red solid, m.p. 68.5–69.0°C (chromatographic purification). IR spectrum, ν, cm^{-1}: 3051 (w), 2863 (m), 1445 (s), 1227 (s), 705 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67, 1.74 (6H, 2s, 2 CH_3); 3.07, 3.12 (4H, 2s, 2 CH_2); 7.12–7.14 (4H, m); 7.92 (2H, dd, *J* = 5.4, 1.8 Hz). ^{13}C NMR spectrum, δ, ppm: 19.3, 20.6 (2CH_3); 33.6, 49.7, 51.7 (3C(sp^3)); 122.8, 125.8 (2C(sp^2)); 127.4, 129.0, 130.7 (6CH(arom)); 159.2 (2C(arom)). Found, %: C 46.83, H 4.41, S 8.66. $C_{15}H_{16}Se_2S$ (386.28). Calculated, %: C 46.64, H 4.18, S 8.30.

3,6-Dihydro-4,5-dimethyl-2,2-di(furan-2-yl)-2*H*-thiopyran (3c). Yield: 210.8 mg (85%), orange solid, m.p. 53.5–54.0°C (chromatographic purification). IR spectrum, ν, cm^{-1}: 3118 (w), 2911 (m), 1498 (s), 1146 (s), 1014 (s), 737 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67, 1.74 (6H, 2s, 2 CH_3); 2.95, 2.99 (4H, 2s, 2 CH_2); 6.20–6.21 (2H, m); 6.30–6.31 (2H, m); 7.35 (2H, br *s*). ^{13}C NMR spectrum, δ, ppm: 19.4, 20.4 (2CH_3); 31.5, 41.0, 44.8 (3C(sp^3)); 122.6, 125.4 (2C(sp^2)); 107.4, 110.3, 142.1 (6CH(arom)); 154.9 (2C(arom)). Found, %: C 69.28, H 6.14, S 12.28. $C_{15}H_{16}O_2S$ (260.34). Calculated, %: C 69.20, H 6.19, S 12.32.

3,6-Dihydro-4,5-dimethyl-2-phenyl-2-(thiophen-2-yl)-2*H*-thiopyran (3d). Yield: 213.3 mg (84%), green solid, m.p. 74.7–75.2°C (chromatographic purification). IR spectrum, ν, cm^{-1}: 3053 (w), 2894 (m), 1442 (s), 1256 (m), 720 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.69, 1.80 (6H, 2s, 2 CH_3); 2.91 (1H, d, *J* = 15.6 Hz); 3.01–3.11 (3H, m); 6.92–6.94 (2H, m); 7.23–7.29 (2H, m); 7.32–7.35 (2H, m); 7.48–7.49 (2H, m). ^{13}C NMR spectrum, δ, ppm: 19.3, 20.4 (2CH_3); 32.4, 47.2, 50.8 (3C(sp^3)); 123.3, 126.2 (2C(sp^2)); 125.0, 125.7, 126.2, 127.1, 127.2, 128.2 (8CH(arom)); 145.6, 151.5 (2C(arom)). Found, %: C 71.28, H 6.29, S 22.20. $C_{17}H_{18}S_2$ (254.41). Calculated, %: C 71.33, H 6.29, S 22.38.

3,6-Dihydro-4,5-dimethyl-2-phenyl-2-(selenophen-2-yl)-2*H*-thiopyran (3e). Yield: 279.7 mg (84%), dark red solid, m.p. 74.0–74.5°C (chromatographic purification). IR spectrum, ν, cm^{-1}: 3058 (w), 2896 (m), 1490 (m), 1443 (s), 1221 (m), 700 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67, 1.77 (6H, 2s, 2 CH_3); 2.88–3.07 (4H, m); 6.99–7.00 (1H, m); 7.11–7.13 (1H, m); 7.23–7.25 (1H, m); 7.29–7.32 (2H, m); 7.49–7.51 (2H, m); 7.90–7.91 (1H, m). ^{13}C NMR spectrum, δ, ppm: 19.2, 20.4 (2CH_3); 32.5, 47.6, 52.6 (3C(sp^3)); 123.3, 126.1 (2C(sp^2)); 127.1, 127.2, 127.6, 128.1, 128.8, 130.5 (8CH(arom)); 145.7, 159.6 (2C(arom)). Found, %: C 61.07, H 5.33, S 9.90. $C_{17}H_{18}SeS$ (333.41). Calculated, %: C 61.26, H 5.40, S 9.61.

3,6-Dihydro-4,5-dimethyl-2-(furan-2-yl)-2-phenyl-2*H*-thiopyran (3f). Yield: 237.6 mg (88%), orange solid, m.p. 62.5–63.0°C (chromatographic purification). IR spectrum, ν, cm^{-1}: 3021 (w), 2888 (m), 1491 (s), 1445 (s), 1154 (s,) 1013 (s), 747 (s), 705 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.68, 1.76 (6H, 2s, 2 CH_3); 2.83 (1H, d, *J* = 16.8 Hz); 2.90–2.98 (3H, m); 6.24 (1H, d, *J* = 3.0 Hz); 6.32 (1H, dd, *J* = 3.6, 1.8 Hz); 7.22–7.25 (1H, m); 7.29–7.31 (2H, m); 7.35–7.36 (3H, m). ^{13}C NMR spectrum, δ, ppm: 19.3, 20.3 (2CH_3); 31.8, 44.1, 49.2 (3C(sp^3)); 123.0, 126.1 (2C(sp^2)); 108.0, 110.1, 127.0, 127.2, 128.3, 142.0 (8CH(arom)); 144.0, 156.5 (2C(arom)). Found, %: C 75.29, H 6.63, S 12.09. $C_{17}H_{18}OS$ (270.41). Calculated, %: C 75.55, H 6.66, S 11.85.

3,6-Dihydro-4,5-dimethyl-2,2-diphenyl-2*H*-thiopyran (5a).[14b,31] Yield: 252.0 mg (90%), white solid, m.p. 50.2–50.7°C (chromatographic purification). ^{1}H NMR spectrum (600 MHz, $CDCl_3$): δ 1.70, 1.83 (2*s*, 6H, 2 CH_3); 2.78, 2.94 (2*s*, 4H); 7.23–7.25 (*m*, 2H); 7.29–7.32 (*m*, 4H); 7.37–7.39 (*m*, 4H) ppm.

3',6',10,11-Tetrahydro-4',5'-dimethylspiro[5*H*-dibenzo[*a*,*d*]cycloheptene-2'-[2*H*]thiopyran (5b). Yield: 290.7 mg (95%), colorless crystals, m.p. 89.5–90.0°C (MeOH). IR spectrum, ν, cm^{-1}: 3056 (w), 2871 (m), 1484 (s), 1446 (s), 729 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.64, 1.96 (6H, 2s, 2 CH_3); 2.76 (2H, s); 3.01–3.08 (2H, m); 3.35 (2H, s); 4.20–4.27 (2H, m); 7.05–7.08 (2H, m); 7.10–7.14 (4H, m); 7.19 (2H, d, *J* = 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 19.0, 20.7 ($2CH_3$); 32.7, 33.1, 44.3, 50.3 (5C(sp^3)); 124.1, 126.5 (2C(sp^2)); 125.6, 126.1, 127.5, 132.0 (8CH(arom)); 140.0, 141.4 (2C(arom)). Found, %: C 82.20, H 7.12, S 10.71. $C_{21}H_{22}S$ (306.49). Calculated, %: C 82.29, H 7.25, S 10.46.

Synthesis of 2*H*-thiopyrans 6. A solution of 1 mmol of the corresponding thioketone **2** in 0.25 ml (2.2 mmol) of hexa-2,4-diene (as a 55 : 40 : 5 mixture of (*E*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-isomers) was stirred at room temperature for 24 h. Then, the diene was evaporated in vacuo and the residue was crystallized from MeOH.

***Cis*-3,6-Dihydro-3,6-dimethyl-2,2-di(thiophen-2-yl)-2*H*-thiopyran (*cis*-6a)**. Yield: 292.0 mg (100%), colorless crystals (MeOH), m.p. 76.0–76.5°C. IR spectrum, ν, cm^{-1}: 3101 (w), 2961 (w), 2857 (w), 1445 (m), 1429 (m), 1239 (s), 1223 (s), 1093 (m), 761 (m), 707 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.04 (3H, d, *J* = 6.6 Hz, CH_3); 1.31 (3H, d, *J* = 7.2 Hz, CH_3); 3.08–3.12 (1H, m); 3.29–3.34 (1H, m); 5.52 (1H, dt, *J* = 10.8, 1.8 Hz); 5.84–5.87 (1H, m); 6.88 (1H, dd, *J* = 3.6, 4.8 Hz); 6.90 (1H, dd, *J* = 3.6, 4.8 Hz); 6.97 (1H, dd, *J* = 1.2, 3.6 Hz); 7.13 (1H, dd, *J* = 1.2, 3.6 Hz); 7.19 (1H, dd, *J* = 1.2, 5.4 Hz); 7.21 (1H, dd, *J* = 1.2, 4.8 Hz). ^{13}C NMR spectrum, δ, ppm: 19.1, 19.7 ($2CH_3$); 35.5, 40.4, 54.1 (3C(sp^3)); 124.1, 124.9, 125.1, 125.3, 125.7, 126.3, 129.1, 132.6 (8CH(arom)); 150.9, 153.4 (2C(arom)). Mass spectrum (HR-ESI+): Found, *m/z*: 315.03067 $[M+Na]^+$. $C_{15}H_{16}NaS_3$. Calculated, *m/z*: 315.03063. Found, %: C 61.72, H 5.55, S 32.89. $C_{15}H_{16}S_3$ (292.48). Calculated, %: C 61.60, H 5.51, S 32.89.

***Cis*-3,6-Dihydro-3,6-dimethyl-2,2-di(selenophen-2-yl)-2*H*-thiopyran (*cis*-6b)**. Yield: 386.0 mg (100%), colorless crystals (MeOH), m.p. 97.8–98.3°C. IR spectrum, ν, cm^{-1}: 3006 (w), 2968 (w), 1445 (m), 1239 (s), 1226 (m), 1084 (w), 758 (m), 688 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.09 (3H, d, *J* = 6.6 Hz, CH_3); 1.32 (3H, d, *J* = 7.2 Hz, CH_3); 3.02–3.06 (1H, m); 3.41–3.45 (1H, m); 5.53 (1H, dt, *J* = 10.8, 1.8 Hz); 5.85–5.88 (1H, m); 7.10 (1H, dd, *J* =

3.6, 5.4 Hz); 7.13–7.16 (2H, m); 7.23–7.24 (1H, m); 7.89–7.91 (2H, m). ^{13}C NMR spectrum, δ, ppm: 19.5, 19.7 ($2CH_3$); 36.0, 40.8, 57.6 ($3C(sp^3)$); 125.7, 126.7, 128.3, 128.9, 129.1, 130.6, 130.8, 132.6 (8CH(arom)); 159.0, 162.7 (2C(arom)). Found, %: C 46.69, H 4.11, S 8.35. $C_{15}H_{16}Se_2S$ (386.28). Calculated, %: C 46.64, H 4.18, S 8.30.

Test experiment with equimolar amounts of 2a and a 70:22:8 (*E,Z*)-, (*E,E*)-, and (*Z,Z*)-mixture of isomers of 1b. A mixture of 210 mg (1.0 mmol) of thioketone **2a** in 0.10 ml (1.0 mmol) of a freshly prepared[29] 70:22:8-mixture of (*E*,*Z*)-, (*E*,*E*)-, and (*Z*,*Z*)-hexa-2,4-dienes was placed in a closed test tube. The solution was heated in an oily bath (80°C) for 18 h. After this time, the mixture was cooled to room temnperature and a weighed portion of 1,1,2,2-tetrachloroethane was added as a standard. The ^{1}H NMR spectrum of this mixture was run in $CDCl_3$ solution.

Synthesis of 2-thiabicyclo[2.2.1]heptenes (8). To a solution of 1 mmol of the corresponding thioketone **2** in dry THF at 0°C was added freshly distilled cyclopentadiene (2 mmol). The mixture was stirred at 0°C for 2 h and then for 24 h at room temperature. Then, the solvent was evaporated in vacuo and the residue was purified chromatographically.

3,3-Di(thienophen-2-yl)-2-thia[2.2.1]bicyclohept-5-ene (8a). Yield: 196.0 mg (71%), orange solid, m.p. 66.5−68.6° (decomp., green coloration), (chromatographic purification on NEt_3 treated silica gel using petroleum ether/diethyl ether (1:1) as the eluent). IR spectrum, ν, cm^{-1}: 3101 (m), 2970 (m), 2924 (s), 2854 (m), 1802 (m), 1572 (w), 1519 (w), 1434 (s), 1328 (s), 1331 (m), 1229 (s), 807 (s), 694 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.92 (1H, dt, *J* = 2.4, 9.6 Hz); 2.15–2.17 (1H, m); 3.92–3.93 (1H, m); 4.28–4.29 (1H, m); 5.80–5.81 (1H, m); 6.48–6.50 (1H, m); 6.83 (1H, dd, *J* = 3.6, 4.8 Hz); 6.85 (1H, dd, *J* = 1.8, 3.6 Hz); 6.94 (1H, dd, *J* = 3.6, 4.8 Hz); 7.08 (1H, dd, *J* = 1.2, 5.4 Hz); 7.14 (1H, dd, *J* = 1.2, 3.6 Hz); 7.18 (1H, dd, *J* = 1.2, 5.4 Hz). ^{13}C NMR spectrum, δ, ppm: 51.4, 54.8, 59.4, 64.4, 124.5, 124.67, 124.72, 126.1, 126.5, 126.6, 133.1, 138.5, 151.6, 154.1 (14C). Found, %: C 60.58, H 4.58, S 34.90. $C_{14}H_{12}S_3$ (276.44). Calculated, %: C 60.83, H 4.37, S 34.80

3-Phenyl-3-(thiophen-2-yl)-2-thia[2.2.1]bicyclohept-5-ene (8b). Yield: 240.3 mg (89%), orange solid, m.p. 79.0–80.5°C (chromatographic purification on NEt_3 treated silica gel using CH_2Cl_2 as the eluent). The compound consisted of a ca. 2:1 mixture of two stereoisomers (*endo*, *exo*). IR spectrum, ν, cm^{-1}: 3047 (w), 2939 (w), 1594 (w), 2896 (m),

1489 (m), 1442 (s), 1331 (m), 1223 (m), 717 (s), 698 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): (values for the minor isomer in italics): 1.99–2.00 (2H, m); 2.10 (1H, d, *J* = 9.0 Hz); *2.35* (1H, d, *J* = 9.0 Hz); *4.11* (1H, br s); 4.14 (1H, br s); 4.30 (2H, br s); 5.79–5.83 (2H, m); *6.41* (1H, dd, *J* = 3.0, 5.4 Hz); 6.59 (1H, dd, *J* = 2.4, 5.4 Hz); 6.79–6.80 (1H, m); 6.86–6.87 (1H, m); *6.92–6.94* (1H, m); 7.03–7.05 (1H, m); 7.12 (2H, d, *J* = 4.8 Hz); *7.18* (1H, d, *J* = 5.4 Hz); 7.21–7.37 (5H, m); 7.50 (2H, d, *J* = 7.2 Hz); 7.59 (2H, d, *J* = 7.8 Hz). ^{13}C NMR spectrum, δ, ppm: 50.7, 51.5, 53.5, 55.0, 55.5, 57.6, 67.8, 69.2, 124.48, 124.52, 126.2, 126.5, 126.60, 126.63, 126.7, 127.9, 128.3, 128.7, 133.2, 133.3, 137.8, 139.1, 145.7, 148.0, 152.8, 155.5 (32C). Found, %: C 71.06, H 5.43, S 23.56.$C_{16}H_{14}S_2$ (270.42). Calculated, %: C 71.06, H 5.23, S 23.71.

Oxidation of 2*H*-thiopyrans 3a and 5a with *m*-CPBA. A solution of 1 mmol of the corresponding 2*H*-thiopyran and 3 mmol of *m*-CPBA (70% purity) in dichloromethane was stirred at room temperature for 48 h. Then, the reaction mixture was extracted with saturated aqueous $NaHCO_3$ solution (3 x 10 ml) and distilled water (1 x 10 ml). The organic phase was dried over anhydrous Na_2SO_4 and concentrated in vacuo.

1,6-Dimethyl-4,4-di(thiophen-2-yl)-7-oxa-3-thiabicyclo[4.1.0]heptan-3,3-dioxide (9a). Yield: 291.6 mg (90%), white crystals, m.p. 171.0–171.5°C (petroleum ether). IR spectrum, ν, cm^{-1}: 3083 (w), 2925 (s), 1459 (m), 1432 (m), 1308 (s), 1120 (s), 851 (m), 700 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33, 1.53 (6H, 2s, 2 CH_3); 3.25 (1H, d, *J* = 3.0 Hz); 3.27 (1H, d, *J* = 4.2 Hz); 3.48 (1H, d, *J* = 16.2 Hz); 3.62 (1H, d, *J* = 15.6 Hz); 7.02 (1H, dd, *J* = 4.2, 5.4 Hz); 7.06 (1H, dd, *J* = 4.2, 5.4, Hz); 7.35–7.40 (3H, m); 7.41–7.42 (1H, m). ^{13}C NMR spectrum, δ, ppm: 20.8, 21.4 (2CH_3); 46.0, 53.0, 60.2, 61.1, 65.2 (5C(sp^3)); 127.17, 127.22, 127.5, 127.6, 128.9, 130.0 (6CH(arom)); 139.2, 139.5 (2C(arom)). ESI-MS: 363 (100 [M+23]$^+$, 364 (10 [M+1+23]$^+$). Found, %: C 52.96, H 4.72, S 28.35. $C_{15}H_{16}O_3S_3$ (340.49). Calculated, %: C 52.91, H 4.75, S 28.25.

1,6-Dimethyl-4,4-diphenyl-7-oxa-3-thiabicyclo[4.1.0]heptan-3,3-dioxide (9b). Yield: 296.4 mg (95%), white solid, m.p. 191.5–192.0°C (chromatographic purification). IR spectrum, ν, cm^{-1}: 3060 (w), 2926 (m), 1497 (m), 1446 (m), 1308 (s), 1124 (s), 893 (m), 697 (s). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33, 1.49 (6H, 2s, 2 CH_3); 3.13 (1H, d, *J* = 15.6 Hz); 3.25 (1H, d, *J* = 16.2 Hz); 3.50 (1H, d, *J* = 6.6 Hz); 3.53 (1H, d, *J* = 6.0 Hz); 7.30–7.37 (6H, m); 7.52–7.54 (2H, m); 7.59–7.61 (2H, m). ^{13}C NMR spectrum, δ, ppm: 21.0, 21.5 (2CH_3); 43.4, 54.5, 60.5, 60.9, 70.1 (5C(sp^3)); 128.2, 128.4, 128.5, 128.7, 129.2, 129.5 (10CH(arom)); 137.5, 137.9 (2C(arom)). ESI-MS: 246 (25), 351 (100 [M+23]$^+$, 352 (20 [M+1+23]$^+$). Found

Found, %: C 69.33, H 5.99, S 9.67. $C_{19}H_{20}O_3S$ (328.45). Calculated, %: C 69.47, H 6.15, S 9.76.

X-ray crystal-structure determination of compound *cis*-6a. Suitable single crystals of compound ***cis*-6a** ($C_{15}H_{16}S_3$) were obtained by slow evaporation of a solution of the compound in MeOH. All measurements were made on a Rigaku Oxford Diffraction SuperNova area-detector diffractometer[32] using MoKα radiation (λ = 0.71073 Å) from a micro-focus X-ray source and an Oxford Instruments Cryojet XL cooler. The data collection and refinement parameters are given below[33] and a view of the molecule is shown in Figure 1. Data reduction was performed with *CrysAlisPro*.[32] The intensities were corrected for Lorentz and polarization effects, and an empirical absorption correction using spherical harmonics[32] was applied. Equivalent reflections, other than Friedel pairs, were merged. The structure was solved by dual space methods using *SHELXT-2014*,[34] which revealed the positions of all non-hydrogen atoms. One of the thiophene rings is disordered through a rotation of approximately 180° about the ring pivot axis, thus interchanging the positions of the S-atom and a C-atom. Two positions were defined for these atoms and the site occupation factor of the major conformation refined to 0.847(3). Similarity restraints were applied to the chemically equivalent bond lengths involving the disordered atoms, while neighboring atoms from the two conformations of the disordered ring were restrained to have similar atomic displacement parameters. The non-hydrogen atoms were refined anisotropically. All of the *H*-atoms were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C-atom ($1.5U_{eq}$ for the methyl groups). The refinement of the structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2-F_c^2)^2$. A correction for secondary extinction was not applied. Refinement of the absolute structure parameter[35] yielded a value of 0.03(2), which confidently confirms that the refined model represents the true absolute structure. Neutral atom scattering factors for non-H-atoms were taken from ref.[36], and the scattering factors for H-atoms were taken from ref.[37] Anomalous dispersion effects were included in F_c;[38] the values for f' and f'' were those of ref.[39] The values of the mass attenuation coefficients are those of ref.[40] The *SHELXL-2016* program[41] was used for all calculations.

Crystal data for ***cis*-6a**: $C_{15}H_{16}S_3$, M = 292.46, crystallized from methanol, colorless, prism, crystal dimensions 0.16 × 0.18 × 0.25 mm, monoclinic, space group *Ia*, Z = 4,

reflections for unit cell determination 7331, 2θ range for unit cell determination 7 – 61°, a = 15.2401(4), b = 8.36686(16), c = 12.1476(3) Å, β = 111.886(3)°, V = 1437.33(6) Å^3, T = 160(1) K, D_X = 1.352 g·cm^{-3}, μ(Mo$K\alpha$) = 0.495 mm^{-1}, scan type ω, $2\theta_{(max)}$ = 60.8°, transmission factors (min; max) = 0.923; 1.000, total reflections measured 9233, symmetry independent reflections 3712, reflections with $I > 2\sigma(I)$ 3660, reflections used in refinement 3712, parameters refined 184, restraints 26, $R(F)$ [$I > 2\sigma(I)$ reflections] = 0.0214, $wR(F^2)$ [all data] = 0.0561 ($w = [\sigma^2(F_o^2)+(0.0340P)^2+0.2427P]^{-1}$, where $P = (F_o^2+2F_c^2)/3$), goodness of fit 1.041, final Δ_{max}/σ 0.001, $\Delta\rho$ (max; min) = 0.22; –0.25 e Å^{-3}.

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