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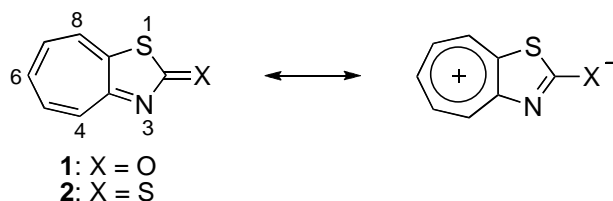
PREPARATION OF NEW HEPTAFULVENES AND THE RELATED COMPOUNDS DERIVED FROM 2*H*-CYCLOHEPTA[*d*]THIAZOL-2-ONE AND -2-THIONE

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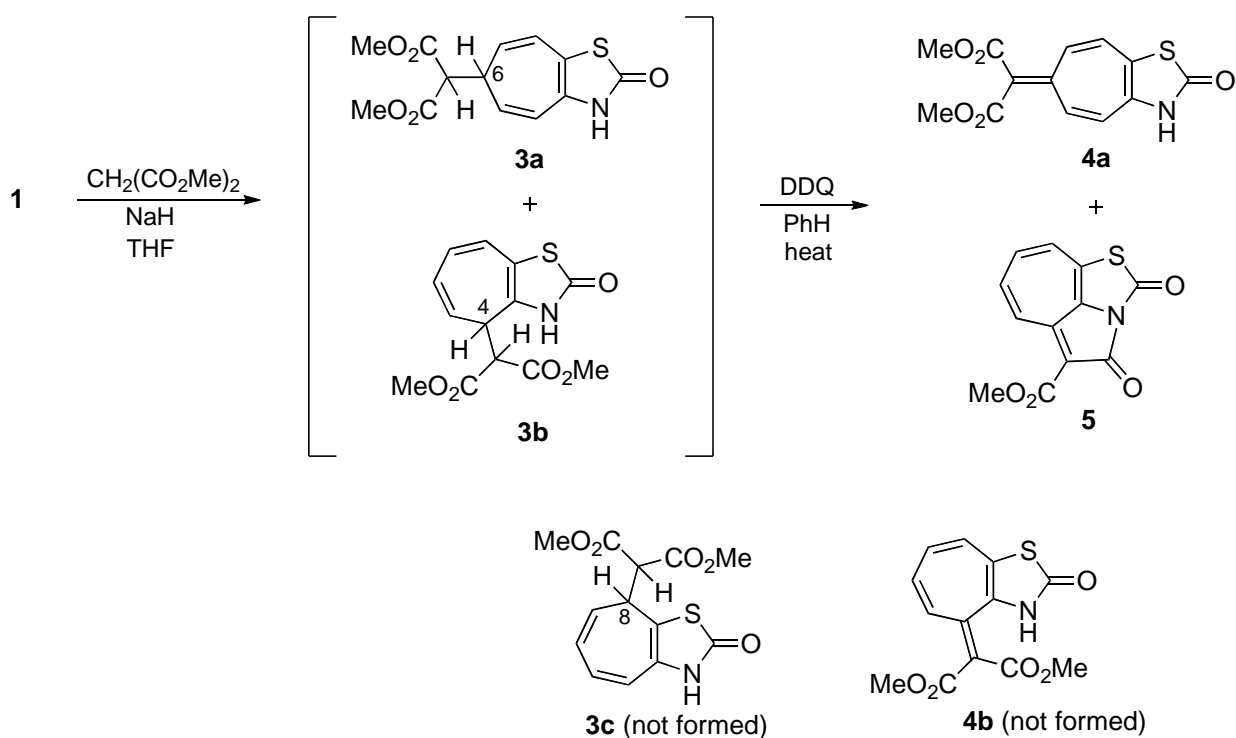
Abstract – 2*H*-Cyclohepta[*d*]thiazol-2-one reacted with dimethyl malonate in the presence of sodium hydride to generate the 6- and 4-adducts, which were oxidized by DDQ to afford a 2-thiazolone-fused heptafulvene and a tricyclic compound, respectively. The reaction of 2*H*-cyclohepta[*d*]thiazol-2-thione under the same addition conditions gave the similar 6- and 4-adducts. Oxidation of each separated adducts afforded the corresponding regioisomeric heptafulvene disulfides with thiazole rings, respectively.

2*H*-Cyclohepta[*d*]thiazol-2-one (**1**) and the sulfur analogue, -2-thione (**2**) are classified as non-benzenoid aromatics, and their chemical and physical properties are of interest because of their polarized structure similar to that of azulenes. Although some preparation methods^{1,2} and cycloaddition reactions^{3,4} of **1** were reported, no attempt for the reaction with nucleophiles is known so far as we are aware. In this manuscript, we report the reactions of **1** and **2** with dimethyl malonate in the presence of sodium hydride and the successive oxidation that furnish new thiazolone/thiazole-fused heptafulvene systems. Heptafulvenes with electron-deficient substituents are stable compounds and their highly polarized properties have attracted attention for chemists, however, their synthetic methods have not been much investigated.⁵⁻⁹



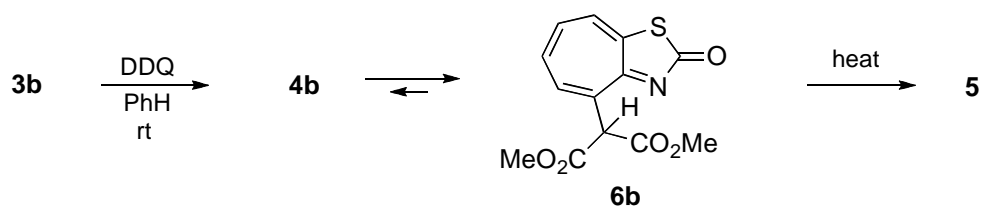
This paper is dedicated to Prof. Victor Snieckus on the occasion of the 77th birthday.

A reaction of **1** and dimethyl malonate with sodium hydride generated a mixture of **3a** and **3b**, adducts at the 6- and 4-positions, respectively. In this reaction, the 8-adduct (**3c**) was not formed. The calculated heats of formation using DFT method (B3LYP/6-31G*)¹⁰ supported these results to a certain extent (**3a**: 0 kcal/mol, **3b**: +2.6 kcal/mol, **3c**: +52.6 kcal/mol). When the mixture was oxidized by DDQ, **3a** afforded a thiazolone-fused heptafulvene, 6-[di(methoxycarbonyl)methylene]-3*H*-cyclohepta[*d*]thiazol-2-one (**4a**, 33% from **1**), whereas **3b** produced not a heptafulvene (**4b**) but a tricyclic compound, methyl 2,3-dioxo-1-thia-2a-azacyclop[*cd*]azulene-4-carboxylate (**5**, 41% from **1**).



Scheme 1

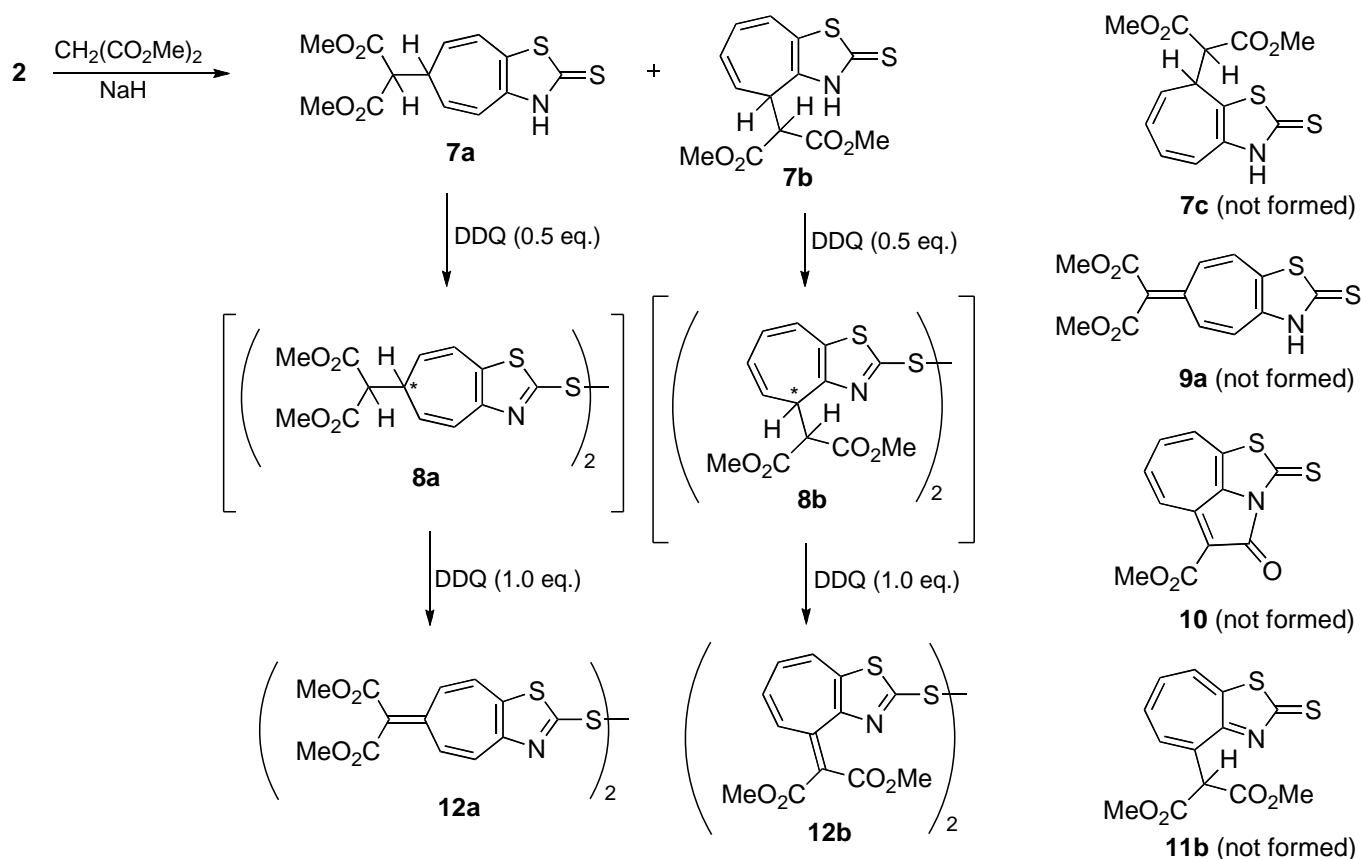
The mixture of **3a** and **3b** were able to separate by recrystallization (hexane-CH₂Cl₂). Treatment of separated **3b** with DDQ at room temperature formed 4-substituted cycloheptathiazol-2-one (**6b**, 67%), which was a tautomer of unstable **4b** (**6b**: 0 kcal/mol, **4b**: +71 kcal/mol by B3LYP/6-31G*). The intramolecular cyclization of isolated **6b** was accomplished under thermal conditions to give **5** (75%).



Scheme 2

The synthetic heptafulvene (**4a**) was an orange solid [155-156 °C (dec.)]. The ^1H NMR spectrum showed four protons at δ 6.70, 6.90, 7.08 and 7.31 as a seven-membered ring moiety and a singlet peak at δ 3.68 as CO_2Me moieties (chemically equivalent six protons). A NH proton was also observed at δ 11.23. The ^{13}C NMR spectrum showed thirteen carbons involving three kinds of carbonyl ones (δ 166.3, 166.4 and 169.7). IR and MS spectra gave N-H and C=O stretching peaks (ν 3025, 1748, 1740, 1690) and a molecular ion peak [m/z 294 (MH^+)]. The tricyclic compound (**5**) was a yellow solid [284-285 °C (dec.)]. The ^1H NMR spectrum showed four protons at δ 7.63, 7.86, 8.08 and 8.66 with appropriate coupling constants ($J = 11.2$ and/or 9.4 Hz) as a seven-membered ring moiety and a singlet peak at δ 3.79 (CO_2Me , 3H). The ^{13}C NMR spectrum showed three kinds of carbonyl carbons (δ 158.8, 162.8 and 163.7) within the twelve ones. IR and MS spectra gave three kinds of C=O stretching peaks (ν 1755, 1736 and 1705) and a molecular ion peak [m/z 262 (MH^+)]. Together with elemental analysis results of **4** and **5**, those spectral data supported their structures. Physical data of the intermediates **3a**, **3b** and **6b** were also consistent with their proposed structures, respectively.

We next focused on the chemical properties of 2*H*-cyclohepta[*d*]thiazol-2-thione (**2**), the sulfur analogue of **1**. Preparation of **2** (75%) was carried out by the thermal reaction of **1** with Lawesson's reagent.^{11,12} **2** was a reddish black solid [mp 141-142 °C (dec.)] and the structure was confirmed by the measurement of instrumental analysis data.



Scheme 3

The reaction of **2** under same addition conditions in the case of **1** afforded the 4- and 6-adducts **7a** (35%) and **7b** (48%), which were separated by recrystallization. The 8-adduct (**7c**) was not formed in a similar manner as described above. Oxidation of isolated **7a** with 0.5 mol *eq.* of DDQ at room temperature might produce not a heptafulvene monomer (**9a**) but a disulfide (**8a**) as a mixture of diastereoisomers. In the case of **7b**, the product might be a disulfide (**8b**), which was neither a tricyclic compound (**10**) nor 4-substituted cycloheptathiazol-2-thione (**11b**). The crude **8a** or **8b** was oxidized by further 1.0 mol *eq.* of DDQ to afford a heptafulvene disulfide, bis{[6-di(methoxycarbonyl)methylene]cyclohepta[*d*]thiazol-2-yl} disulfide [**12a**, a reddish orange solid; 173-174 °C (dec.), 63% from **7a**] or a 4-regioisomer (**12b**, red needles; mp 86-87 °C, 84% from **7b**), respectively. The structures of **7a**, **7b**, **12a** and **12b** were confirmed by the measurement of instrumental analysis data.

In conclusion, we have succeeded in the preparation of new thiazolone/thiazole-fused heptafulvenes derived from 2*H*-cyclohepta[*d*]thiazol-2-one (**1**) and -2-thione (**2**). Further work, aimed at the electrochemical properties arising from the contribution of their polarized structures and their chemical transformations toward the construction of functional compounds, is in progress.

EXPERIMENTAL

Mps were determined with a Laboratory Devices MEL-TEMP apparatus and are uncorrected. ¹H and ¹³C NMR spectra (SiMe₄ as the internal standard) were obtained with Bruker AV500, AM400, AV300, AC300 and/or AC200 spectrometers. IR spectra were obtained with a Perkin Elmer System 2000 FT instrument. MS spectra were obtained with a JEOL JMS700AM spectrometer. Unless otherwise stated the spectra were taken in the following solvents/media: IR, KBr; ¹H and ¹³C NMR, CDCl₃; MS spectra were taken at 70 eV by electron impact (EI) and/or fast atom bombardment (FAB) method. The progress of reactions was followed by TLC method using Merck Silica gel 60F₂₅₄.

Preparation of a heptafulvene (4a) and a tricyclic compound (5): To a solution of **1**¹ (130 mg, 8.0 x 10⁻¹ mmol) in dry THF (5.0 mL), a mixture of dimethyl malonate (1.2 mol *eq.*) and sodium hydride (1.2 mol *eq.*) in dry THF (1.0 mL) was added at 0 °C under N₂. The solution was stirred for 4 h at rt. The reaction mixture was quenched with sat. *aq.* NH₄Cl and the aqueous layer was extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give a mixture of crude **3a** and **3b**. To a solution of the mixture in benzene (6.0 mL), DDQ (1.0 mol *eq.*) was added and the reaction mixture was refluxed for 1 h. The solvent was removed and the residue was purified by SiO₂ column chromatography and/or recrystallization (hexane-CH₂Cl₂) to give **4a** (77 mg, 33%) and **5** (96 mg, 41%). The mixture of **3a** and **3b** was able to separate by recrystallization (hexane-CH₂Cl₂). A benzene (1.0 mL) solution of separated **3a** (10 mg, 3.4 x 10⁻² mmol) and DDQ (1.0 mol *eq.*) was stirred for 2 h at rt under Ar. After removal of the solvent *in vacuo*, the residue was purified

by SiO₂ column chromatography to give **4a** (6.8 mg, 68%). A benzene (2.0 mL) solution of separated **3b** (30 mg, 1.0 x 10⁻¹ mmol) and DDQ (1.0 mol *eq.*) was stirred for 2 h at rt under Ar and the solvent was removed. The resulting crude materials were recrystallized with benzene-hexane to give **6b** (20 mg, 67%). A benzene (1.0 mL) solution of **6b** (10 mg, 3.4 x 10⁻² mmol) was refluxed for 2 h under Ar and the resulting solid was purified by recrystallization (hexane-CH₂Cl₂) to give **5** (6.7 mg, 75%).

6-Adduct (3a): colorless crystals; mp 160 °C (dec.); ¹H NMR δ 2.79 (dt, *J* = 11.2, 6.0 Hz, 1H), 3.77 (s, 6H), 3.80 (d, *J* = 11.2 Hz, 1H), 5.24 (dd, *J* = 9.6, 6.0 Hz, 1H), 5.44 (dd, *J* = 9.6, 6.0 Hz, 1H), 6.34 (d, *J* = 9.6 Hz, 1H), 6.37 (d, *J* = 9.6 Hz, 1H), 9.61 (br.s, 1H); ¹³C NMR δ 38.3, 52.8 (2C), 53.2, 116.6, 119.3, 119.8, 120.6, 123.6, 132.6, 168.3 (2C), 172.2; IR (KBr) ν 3130, 1738, 1644 cm⁻¹; MS (FAB, NBA) *m/z* 296 (MH⁺). Anal. Calcd for C₁₃H₁₃NO₅S: C, 52.87; H, 4.44; N, 4.74. Found: C, 52.71; H, 4.29; N, 4.78.

4-Adduct (3b): colorless needles; mp 110 °C (dec.); ¹H NMR δ 3.49 (d, *J* = 11.2 Hz, 1H), 3.68 (s, 3H), 3.72 (s, 3H), 4.25 (dd, *J* = 11.2, 8.5 Hz, 1H), 5.54 (t like, *J* = 10.4 Hz, 1H), 6.26 (m, 1H), 6.40-6.50 (m, 2H), 9.21 (br.s, 1H); ¹³C NMR δ 37.2, 49.7, 52.9, 53.1, 113.3, 121.4, 123.1, 124.8, 127.0, 128.3, 167.3, 168.0, 174.0; IR (KBr) ν 3152, 1759, 1733, 1675 cm⁻¹; MS (FAB, NBA) *m/z* 296 (MH⁺). Anal. Calcd for C₁₃H₁₃NO₅S: C, 52.87; H, 4.44; N, 4.74. Found: C, 52.91; H, 4.26; N, 4.83.

Heptafulvene (4a): an orange solid; mp 155-156 °C (dec.); ¹H NMR (DMSO-d₆) δ 3.68 (s, 6H), 6.70 (d, *J* = 12.5 Hz, 1H), 6.90 (d, *J* = 12.5 Hz, 1H), 7.08 (dd, *J* = 12.5, 2.2 Hz, 1H), 7.31 (dd, *J* = 12.5, 2.2 Hz, 1H), 11.23 (br.s, 1H); ¹³C NMR (DMSO-d₆) δ 52.19, 52.21, 113.9, 122.9, 124.1, 126.1, 129.5, 131.9, 137.8, 148.0, 166.3, 166.4, 169.7; IR (KBr) ν 3025, 1748, 1740, 1690 cm⁻¹; MS (FAB, NBA) *m/z* 294 (MH⁺). Anal. Calcd for C₁₃H₁₁NO₅S: C, 53.24; H, 3.78; N, 4.78. Found: C, 53.06; H, 3.75; N, 4.84.

Tricyclic compound (5): a yellow solid; mp 284-285 °C (dec.); ¹H NMR (DMSO-d₆) δ 3.79 (s, 3H), 7.63 (dd, *J* = 11.2, 9.4 Hz, 1H), 7.86 (dd, *J* = 11.2, 9.4 Hz, 1H), 8.08 (d, *J* = 11.2 Hz, 1H), 8.66 (d, *J* = 11.2 Hz, 1H); ¹³C NMR (DMSO-d₆) δ 51.0, 102.0, 130.0, 131.6, 132.5, 133.9, 138.4, 139.8, 145.5, 158.8, 162.8, 163.7; IR (KBr) ν 1755, 1736, 1705 cm⁻¹; MS (FAB, Thiogly.) *m/z* 262 (MH⁺). Anal. Calcd for C₁₂H₇NO₄S: C, 55.17; H, 2.70; N, 5.36. Found: C, 55.16; H, 2.59; N, 5.43.

4-Substituted cycloheptathiazol-2-one (6b): yellow crystals; mp 135 °C (dec.); ¹H NMR δ 3.80 (s, 6H), 6.17 (s, 1H), 7.49-7.59 (m, 2H), 8.01-8.04 (m, 1H), 8.06-8.10 (m, 1H); ¹H NMR (benzene-d₆) δ 3.27 (s, 6H), 6.09 (t like, *J* = 10 Hz, 1H), 6.35 (s, 1H), 6.37 (t like, *J* = 10 Hz, 1H), 6.52 (d like, *J* = 10 Hz, 1H), 7.78 (d like, *J* = 10 Hz, 1H); ¹³C NMR δ 53.3 (2C), 56.7, 128.4, 131.5 (2C), 135.1, 137.2, 141.3, 168.1, 171.7 (2C), 177.7; IR (KBr) ν 1742, 1677 cm⁻¹; MS (FAB, NBA) *m/z* 294 (MH⁺). Anal. Calcd for C₁₃H₁₁NO₅S: C, 53.24; H, 3.78; N, 4.78. Found: C, 53.18; H, 3.62; N, 4.84.

Preparation of cycloheptathiazol-2-thione (2): A mixture of **1** (326 mg, 2.0 mmol) and Lawesson's reagent (0.5 mol *eq.*) in benzene (20 mL) was refluxed for 4 h under Ar. After removal of the solvent *in*

vacuo, the resulting crude material was purified by SiO₂ column chromatography to give **2** (270 mg, 75%). The purification should be carried out rapidly because of some lability of **2** in solution.

Cycloheptathiazol-2-thione (2): a reddish black solid; mp 141-142 °C (dec.); ¹H NMR δ 7.50-7.56 (m, 2H), 7.76-7.83 (m, 1H), 7.95-7.98 (m, 1H), 8.07 (d like, *J* = 11 Hz, 1H); ¹³C NMR δ 128.7, 132.8, 137.6, 138.2, 141.3, 165.5, 172.9, 206.3; IR (KBr) ν 1218 cm⁻¹; MS (EI) *m/z* 179 (M⁺); HRMS (EI) Calcd for C₈H₅NS₂: 178.9863. Found: 178.9860.

Preparation of heptafulvene disulfides (12a and 12b): To a solution of **2** (90 mg, 5.0 × 10⁻¹ mmol) in dry THF (3.0 mL), a mixture of dimethyl malonate (1.2 mol *eq.*) and sodium hydride (1.2 mol *eq.*) in dry THF (3.0 mL) was added at 0 °C under Ar. The solution was stirred for 4 h at rt. The reaction mixture was quenched with sat. *aq.* NH₄Cl and the aqueous layer was extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to give a mixture of crude **7a** and **7b**. The mixture was separated and purified by recrystallization (hexane-CH₂Cl₂) to give **7a** (54 mg, 35%) and **7b** (75 mg, 48%). A benzene (1.0 mL) solution of isolated **7a** (15 mg, 4.8 × 10⁻² mmol) and DDQ (0.5 mol *eq.*) was stirred for 2 h at rt under Ar and the solvent was removed. ¹H NMR spectrum of the resulting residue suggested a formation of **8a** as a mixture of diastereoisomers [δ 2.92-2.98 (m, 2H), 3.73 (d like, *J* = 11 Hz, 2H), 3.75 (s, 12H), 5.51 (m, 2H), 5.58 (m, 2H), 6.69 (d like, *J* = 10 Hz, 2H), 6.89 (d like, *J* = 10 Hz, 2H)]. DDQ (further 1.0 mol *eq.*) was added to a benzene (1.0 mL) solution of the residue and the reaction mixture was stirred for 14 h at rt under Ar. After removal of the solvent *in vacuo*, the resulting crude material was purified by SiO₂ column chromatography to give **12a** (9.3 mg, 63% from **7a**). A benzene solution (1.0 mL) of isolated **7b** (30 mg, 9.6 × 10⁻² mmol) and DDQ (total 1.5 mol *eq.*) was stirred for 14 h at rt under Ar. After removal of the solvent *in vacuo*, the residue was purified by SiO₂ column chromatography to give **12b** (25 mg, 84% from **7b**). The reaction of **7b** with DDQ (0.5 mol *eq.*) at rt for 2 h in benzene gave the similar results in the case of **7a**, which suggested a formation of **8b** as a mixture of diastereoisomers by the ¹H NMR measurement [δ 3.59 (s, 6H), 3.74 (s, 6H), 3.92 (d, *J* = 11.0 Hz, 1H), 3.94 (d, *J* = 11.0 Hz, 1H), 4.07 (dd, *J* = 11.0, 6.6 Hz, 1H), 4.11 (dd, *J* = 11.0, 6.6 Hz, 1H), 5.71 (dd like, *J* = 10, 7 Hz, 2H), 6.17-6.23 (m, 2H), 6.49-6.60 (m, 2H), 6.81 (d like, *J* = 11 Hz, 2H)].

6-Adduct (7a): brown crystals; mp 106 °C (dec.); ¹H NMR δ 2.82 (dt, *J* = 11.2, 6.3 Hz, 1H), 3.77 (s, 6H), 3.79 (d, *J* = 11.2 Hz, 1H), 5.36 (dd, *J* = 9.6, 6.3 Hz, 1H), 5.54 (dd, *J* = 9.6, 6.3 Hz, 1H), 6.40 (d like, *J* = 9.6 Hz, 2H), 10.08 (br.s, 1H); ¹³C NMR (DMSO-*d*₆) δ 38.5, 53.1 (3C), 116.8, 119.3, 121.5, 125.3, 127.4, 140.2, 168.6 (2C), 187.5; IR (KBr) ν 3050, 1737, 1058 cm⁻¹; MS (FAB, NBA) *m/z* 312 (MH⁺). Anal. Calcd for C₁₃H₁₃NO₄S₂: C, 50.14; H, 4.21; N, 4.50. Found: C, 50.32; H, 4.18; N, 4.71.

4-Adduct (7b): a brown solid; mp 94 °C (dec.); ¹H NMR δ 3.52 (d, *J* = 11.4 Hz, 1H), 3.69 (s, 3H), 3.74 (s, 3H), 4.37 (dd, *J* = 11.4, 8.5 Hz, 1H), 5.59 (t like, *J* = 10 Hz, 1H), 6.26-6.31 (m, 1H), 6.41-6.56 (m, 2H), 11.17 (br.s, 1H); ¹³C NMR δ 36.8, 49.9, 53.2, 53.4, 120.8, 123.1, 123.2, 128.2, 128.5, 131.3, 167.2, 167.7,

189.7; IR (KBr) ν 2995, 1750, 1725, 1063 cm^{-1} ; MS (FAB, NBA) m/z 312 (MH^+). Anal. Calcd for $\text{C}_{13}\text{H}_{13}\text{NO}_4\text{S}_2$: C, 50.14; H, 4.21; N, 4.50. Found: C, 49.86; H, 4.05; N, 4.43.

Heptafulvene disulfide (12a): a reddish orange solid; 173-174 °C (dec.); ^1H NMR δ 3.79 (s, 3H), 3.81 (s, 3H), 6.83 (d, $J = 12.3$ Hz, 1H), 7.08 (d, $J = 12.3$ Hz, 1H), 7.21 (dd, $J = 12.3, 2.0$ Hz, 1H), 7.29 (dd, $J = 12.3, 2.1$ Hz, 1H); ^{13}C NMR δ 52.4, 52.5, 118.7, 124.9, 128.9, 130.0, 130.7, 140.4, 147.4, 155.7, 166.0, 166.4, 166.7; IR (KBr) ν 1722, 1682 cm^{-1} ; MS (FAB, NBA) m/z 617 (MH^+). Anal. Calcd for $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_8\text{S}_4$: C, 50.64; H, 3.27; N, 4.54. Found: C, 50.49; H, 3.20; N, 4.58.

Heptafulvene disulfide (12b): red needles; mp 86-87 °C; ^1H NMR δ 3.78 (s, 3H), 3.80 (s, 3H), 6.48-6.59 (m, 2H), 6.86 (d like, $J = 10$ Hz, 1H), 8.05 (d like, $J = 10$ Hz, 1H); ^{13}C NMR δ 52.1, 52.3, 119.0, 122.9, 129.8, 130.6, 131.0, 141.1, 143.3, 149.3, 164.6, 165.9, 168.4; IR (KBr) ν 1716, 1695 cm^{-1} ; MS (FAB, NBA) m/z 617 (MH^+). Anal. Calcd for $\text{C}_{26}\text{H}_{20}\text{N}_2\text{O}_8\text{S}_4\cdot\text{CH}_2\text{Cl}_2$: C, 46.22; H, 3.16; N, 3.99. Found: C, 46.45; H, 3.04; N, 4.11.

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