**Straightforward Access to New Cage-Functionalized Sulfur Heterocycles**

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Received 6 August 2003

**Abstract:** Reaction of pentacyclo[5.4.0.0²,6.0³,10.0⁵,8]undecane-8-thione (7) with diazomethane (9a) and 2-diazopropane (9b) afforded the 1,3,4-thiadiazolines 12a and 12c, which subsequently were used as precursors of reactive thiocarbonyl ylides 13a, b, respectively. Diphenyldiazomethane reacted rapidly with 7 to yield thirane 14c as the final product. When decomposition of 12a or 12c was carried out in the presence of dipolarophiles, such as TCNE, DMAD or N-methylmaleimide, new cage-functionalized heterocycles were obtained.

**Key words:** cage thiolkenes, diazo compounds, cycloaddition, spiro-heterocycles, thiocarbonyl ylides

Cage compounds (polycyclic hydrocarbons) are of considerable interest not only as highly symmetrical ‘non-natural products’, but also as biologically active materials. Pentacyclo[5.4.0.0²,6.0³,10.0⁵,8]undecane-8,11-dione (1) is a relatively easily prepared compound in this class and was described for the first time by Cookson and co-workers in 1958. The chemistry of this unusual cage di-one has been studied by several teams worldwide. In particular, numerous 4-oxa- and 4-aza-annulated derivatives were reported. Other reactions of cage compounds, especially of diketone 1, with bases, Lewis acids, etc., and their various applications in synthesis of new complexation agents have been studied widely.

Recently, we described the reaction of 1 with gaseous H₂S/HCl mixture in methanol solution and found that the product formation depended on reaction conditions. Two new cage thiones 2 and 3 were isolated and after additional saturation with H₂S/HCl mixture, 4-thiahexacyclo[5.4.1.0²,6.0³,10.0⁵,9.0⁸,11]dodecane 4 and 5 were found as the final products (Scheme 1).

On the other hand, the chemistry of structurally comparable adamantane thione (8) is well established and has received considerable attention in the synthesis of sulfur heterocycles. In particular, it reacts easily with diazomethane to give a mixture of regioisomeric 1,3,4- and 1,2,3-thiadiazolines 10a and 10b (Scheme 3).

Thermal [3+2] cycloreversion of 10a led to the evolution of nitrogen, and adamantane S-methylide 11 (thiocarbonyl ylide) was presumably generated as the reactive intermediate. 1,3-Dipoles of this type were broadly ex-
plored for the preparation of sulfur-containing heterocyclic systems. The aim of this work is to study the reactions of cage thione 7 with selected diazo compounds and to examine the reactivity of subsequently generated cage-functionalized thiocarbonyl ylides.

Addition of the petroleum ether solution of diazomethane (9a) to the red-colored cage thione 7 dissolved in the same solvent at 0 °C led to discoloration of the mixture. The solvent was removed and examination of the oily residue using 1 H NMR analysis showed that a mixture of two regioisomeric products 12a and 12b was obtained (Scheme 4). Based on the literature data describing the formation of analogous products 10a and 10b from 8 and 9a, we ascribe the low-field shifted signal of CH₂ group to 1,3,4-thiadiazoline 12a (s, 5.82 ppm). For 1,2,3-thiadiazoline 12b, the CH₂ group gave a high-field shifted AB system at δ = 4.33 and 4.89 with J_{AB} = 18 Hz. Comparison of the intensity of both signals revealed the ratio of 12a to 12b to be ca. 3:1. When the reaction was performed at –10 °C this ratio changed to 2:1. Attempted separation of 12a and 12b, either by crystallization or by chromatography, was in vain and further decomposition was observed. However, heating a mixture of 12a and 12b at 45 °C led to evolution of nitrogen from 12a exclusively, giving a mixture of exo- and endo-thiiranes 14a and 14b, along with unchanged 12b. According to a well-established mechanism for the formation of thiiranes from 1,3,4-thiadiazolines, an elusive thiocarbonyl ylide 13a is a key intermediate in these reactions (Scheme 5).

Reaction of 7 with 2-diazopropane (9b) was carried out in petroleum ether at 0 °C. 1 H NMR analysis of the crude reaction mixture showed that only one product was formed giving a signal of two methyl groups at δ = 1.72. Pure product 12c was obtained as a relatively stable colorless solid. Heating 12c in benzene solution at 45 °C led to evolution of nitrogen to yield 14b. Tentatively, we describe this product as an endo-isomer. This result shows that 7 reacts with 9b regio- and stereoselectively (Scheme 5).

As a third diazo compound, diphenyldiazomethane (9c) was tested in the reaction with 7. In this case however, even at –20 °C immediate evolution of nitrogen and precipitation of a colorless solid, identified as thiirane 14c was observed (Scheme 6). At –60 °C, the discoloration of reaction mixture was very slow but no evolution of N₂ was observed. Lower stability of aromatic substituted 1,3,4-thiadiazolines is well known. 14

Thiocarbonyl ylides are electron-rich 1,3-dipoles and react easily with electron-deficient dipolarophiles to yield mainly 5-membered sulfur heterocycles as product of [3+2] cycloaddition. In some instances, extremely electron-deficient dipolarophiles, such as tetracyanoethylene (TCNE) or dimethyl 1,2-dicyanofumarate, were shown to intercept sterically crowded thiocarbonyl ylides to give 7-membered products via nonconcerted (stepwise) mechanism. 15

1,3,4-Thiadiazoline 12a can be regarded as a precursor of thiocarbonyl ylide 13a, useful for the preparation of new cage-functionalized sulfur in a ‘one-pot’ procedure, without preliminary separation of 12b. Heating a mixture of 12a and 12b in the presence of C,C-dipolarophiles, such as TCNE, N-methylmaleimide or dimethyl acetylenedicarboxylate (DMAD) led to formation of expected [3+2] cycloadducts 15a–c (Scheme 7).

Analysis of the 1 H NMR spectra recorded for crude products showed evidences for the formation of one stereoisomer (only one 2-CH₂ signal was observed). Separation of crude mixtures afforded only one stereoisomeric product in each case. Spectroscopic data do not allow an orientation of the sulfur atom (exo or endo) in the new heterocyclic ring. In order to answer this elusive problem, the X-ray single crystal diffraction analysis of 15a was...
performed. The result showed that the sulfur atom occupies an endo-position.\textsuperscript{16} Tentatively, the same orientation of S-atom was assigned for products 15b and 15c.

Pure crystalline 2,2-dimethyl-1,3,4-thiadiazoline 12c was heated up to 45 °C in the presence of the above listed dipolarophiles to yield product 16a–c (Figure 1). By using the same procedure with products 15a–c obtained from 12a, the endo-product was assigned for each of these reactions. The \textsuperscript{1}H NMR spectra revealed two signals for the methyl groups in the heterocyclic ring.

Figure 1 Structures of adducts 16a–c

Thioketones are known as superior interceptors of the thiocarbonyl ylides and according to Huisgen, thiobenzophenone (super dipolarophile) is more reactive than TCNE toward thiobenzophenone S-methylide.\textsuperscript{17} For this reason thiobenzophenone was tested in the reaction with 12a, but in this case the analysis of the crude mixture showed that at least three 1,3-dithiolanes were formed. Chromatographic work-up led to the separation of one product in pure form, but its rigorous structure determination can be established unambiguously only by X-ray analysis.\textsuperscript{18} Based on chemical shift of 2-CH\textsubscript{2} group in 1,3-dithiolane ring in the \textsuperscript{13}C NMR spectrum at $\delta = 34.3$, we suggest that from two possible isomers 17a or 17b, only 17a can be postulated as the structure of isolated product (Scheme 8). This conclusion results from the comparison with series of other 1,3-dithiolanes prepared from aromatic thioketones and adamantane-thione S-methylide 11.\textsuperscript{11}
In conclusion, the reactions of cage thione 7 with diazo compounds 9a,b gave 1,3,4-thiadiazolines 12a and 12c which can be used as precursors of thiocarbonyl ylides 13a,b, respectively. Both intermediates are trapped with electron-poor C,C-dipolarophiles to afford thiophene derivatives 15a–c and 16a–c. Reactions of 12a with thiobenzophenone and thione 18 yielded 1,3-dithiolanes 17a and 17b. These results show that in spite of remarkable steric hindrance, cage thione 7 and its S-methylides 13a,b can be used as building blocks for preparation of cage-functionalized sulfur heterocycles via 1,3-dipolar cycloaddition.

Melting points were determined in capillary by using a Meltemp 2 apparatus and are uncorrected. IR spectra were obtained by using NEXUS FT-IR spectrometer. Elemental analyses data were obtained at Polish Academy of Science and Justus-Liebig University in Giessen. Mass spectral data herein were obtained by using a Varian MAT-112S, which was operated in the EI mode. 1H and 13C NMR spectra were recorded with Tesla BS687 and Bruker 400 Hz spectra were recorded in CDCl3 by using TMS as an internal standard.

Diazomethane (9a)19 and 2-diazoargentane (9b)19 were freshly prepared directly before an experiment as solutions in petroleum ether. Diphenyldiazomethane (9c)20 was obtained as a violet crystalline solid. 1,3,4-Thiadiazoline 12b was prepared from 18 and 9a according to literature protocol.21 Petroleum ether used had bp 40–60°C.

Reaction of Cage Thione 7 with Diazo Compounds 9a–c: General Procedure

Thione 7 (176 mg, 1 mmol) was dissolved in petroleum ether (2 mL) and cooled down in an ice-bath (0°C). Next, freshly prepared solution of diazo compound in petroleum ether was added in small portions (2 mL), till the red-colored solution turned colorless. Then a small excess of diazo compound was added and the whole mixture was stirred additionally for 5 min. The resulting solution was concentrated under reduced pressure.

1,3,4-Thiadiazoline 12a and 1,2,3-Thiazolidine 12b

Reaction of 7 with 9a gave an oily residue, which was a mixture of 1,3,4-thiadiazoline 12a and 1,2,3-thiazolidine 12b as an oil in a ratio of 3:1; yield: 195 mg (90%); used as such in subsequent reactions.

IR (film): 2960 (s), 2860 (s), 2720 (w), 1450 (s), 1365 (s), 1305 (m), 1275 (m), 1260 (m), 1155 (w), 1085 (s), 1055 (m), 1030 (m), 1010 (m), 990 (m), 745 (s) cm–1.

1H NMR (CDCl3): δ = 0.70–3.12 (m, 12 H), 1.38 (s, 3 H), 1.47 (s, 3 H).

13C NMR (CDCl3): δ = 29.9 (t), 30.5 (q), 30.6 (q), 34.7 (t), 35.8 (d), 42.1 (d), 43.0 (d), 45.9 (d), 46.4 (d), 47.4 (d), 54.8 (d), 105.5 (s), 114.9 (s).

Thirane 14c

The crude solid residue obtained from the reaction of 7 with 9c was recrystallized from MeOH–hexane; colorless crystalline solid; yield: 160 mg (49%); mp 198–199 °C.

IR (KBr): 2970 (s), 2960 (m), 2875 (s), 1330 (m), 1275 (m), 1260 (m), 1155 (w), 1085 (s), 1055 (s), 1030 (m), 1010 (m), 990 (m), 745 (s) cm–1.

1H NMR (CDCl3): δ = 1.19–1.99 (m, 4 H), 2.28–3.39 (m, 8 H), 3.61 (AB, JAB = 30 Hz, 1 H), 3.73 (AB, JAB = 30 Hz, 1 H).

Decomposition of 1,3,4-Thiadiazolines: General Procedure

The corresponding 1,3,4-thiadiazoline (1 mmol) was dissolved in benzene (2 mL) and heated in an oil bath up to 50 °C. The volume of N2 evolved was measured with a gas burette. When the evolution of N2 was complete (ca. 25 mL in 0.5 h), the solvent was removed under reduced pressure. For crude reaction mixture, 1H NMR and IR were measured.

Exo-14a and Endo-14a

A mixture of endo-14a and exo-14a was obtained as an oil from the decomposition of 1,3,4-thiadiazoline 12a; yield: 78% (150 mg).

IR (film): 2955 (s), 2860 (m), 1740 (w), 1580 (w), 1450 (w), 1310 (w), 1275 (w) cm–1.

1H NMR (CDCl3): δ = 0.62–3.71 (m, 26 H), 2.01 (s, 2 H), 2.15 (s, 2 H).

14b

Compound 14b was obtained as an oil by the decomposition of 2,2-dimethyl-1,3,4-thiadiazoline 12c; yield: 20% (45 mg).

IR (film): 2955 (s), 2860 (s), 2720 (w), 1450 (s), 1365 (s), 1275 (m), 1260 (m), 1155 (w), 1085 (s), 1055 (m), 1030 (m), 1010 (m), 990 (m), 745 (s) cm–1.

1H NMR (CDCl3): δ = 0.70–3.12 (m, 12 H), 1.38 (s, 3 H), 1.47 (s, 3 H).

Reactions of 12 with Dipolarophiles: General Procedure

To corresponding 1,3,4-thiadiazoline 12a or 12c (1 mmol) dissolved in benzene (2 mL) was added a dipolarophile (1 mmol) and the resulting mixture was stirred and heated up to 45 °C. The volume of N2 evolved was measured with a gas burette. When the evolution of N2 was complete (ca. 25 mL in 2 h), the solvent was removed under reduced pressure and the crude reaction mixture was worked up after 1H NMR control.

15a

The residue from the reaction of 12a with TCNE was separated by preparative layer chromatography (silica gel, ElOAc) and the resulting main fraction was recrystallized from MeOH–CH2Cl2 to give 15a as a colorless crystalline solid; yield: 40 mg (13%); mp 194–198 °C (dec.).

IR (KBr): 2980 (s), 2970 (s), 2940 (s), 2890 (m), 2875 (m), 2250 (w), C=N), 1470 (m), 1445 (m), 1315 (m), 1295 (m), 1275 (m), 1250 (m), 1235 (w) cm–1.

1H NMR (CDCl3): δ = 1.19–1.99 (m, 4 H), 2.28–3.39 (m, 8 H), 3.61 (AB, JAB = 30 Hz, 1 H), 3.73 (AB, JAB = 30 Hz, 1 H).

16a

The residue obtained from the reaction of 12c with TCNE was separated by preparative layer chromatography (silica gel, hexane–CH₂Cl₂, 1:1) and the isolated main fraction was recrystallized from hexane–CH₂Cl₂ to give 16a as a colorless crystalline solid; yield: 97 mg (56%); mp 216–218 °C.

IR (KBr): 3095 (w), 2960 (m), 2935 (m), 2860 (w), 1770 (w), 1705 (s), 1498 (s), 1465 (s), 1440 (s), 1410 (m), 1330 (m), 1265 (m), 1245 (w), 1215 (w), 1185 (m) cm⁻¹.

1H NMR (CDCl₃): δ = 0.95–1.70 (m, 6 H), 1.77 (s, 3 H), 1.95 (s, 3 H), 2.13–2.96 (m, 6 H).

13C NMR (CDCl₃): δ = 28.9 (q), 30.6 (q), 34.9 (t), 36.2 (d), 40.6 (d), 43.4 (d), 43.8 (d), 45.1 (d), 46.5 (d), 47.0 (d), 47.6 (s), 55.9 (d), 57.1 (s), 67.9 (s), 109.8 (s), 110.6 (s), 110.9 (s).

MS (EI): m/z (%) = 318 (M⁺, 20), 240 (90), 79 (85), 46 (100), 40 (30).


16b

The residue obtained from the reaction of 12a with N-methylmaleimide was separated by preparative layer chromatography (silica gel, hexane–CH₂Cl₂, 3:7) and the isolated main fraction was recrystallized from MeOH to give 16b as a colorless crystalline solid; yield: 90 mg (60%); mp 200–202 °C.

IR (KBr): 2970 (m), 2960 (m), 2865 (m), 1770 (s), C=O, 1685 (s), 1435 (m), 1385 (m), 1275 (m), 1240 (w), 1070 (w), 985 (w) cm⁻¹.

1H NMR (CDCl₃): δ = 1.00–1.08 (m, 1 H), 1.25–1.32 (m, 1 H), 1.55 (s, 2 H), 1.80–1.87 (m, 1 H), 2.22–2.28 (m, 8 H), 2.97 (s, 3 H), 3.05–3.34 (m, 3 H).

13C NMR (CDCl₃): δ = 27.3 (t), 33.9 (t), 34.0 (s), 35.4 (d), 41.5 (d), 41.7 (d), 42.27 (d), 42.31 (d), 45.9 (d), 46.1 (d), 47.8 (s), 48.3 (d), 55.1 (d), 65.0 (s), 77.2 (s), 175.7 (s), 178.3 (s).

MS (EI): m/z (%) = 318 (M⁺, 20), 240 (90), 79 (85), 66 (100), 40 (30).


16c

The residue obtained from the reaction of 12c with DMAD was separated by preparative layer chromatography (silica gel, hexane–CH₂Cl₂, 2:3) and the isolated main fraction was recrystallized from MeOH to give 16c as a colorless crystalline solid; yield: 75 mg (41%); mp 128–128 °C.

IR (KBr): 2970 (s), 2945 (m), 2875 (m), 1725 (s), C=O, 1685 (w), 1635 (m), 1460 (m), 1435 (m), 1380 (w), 1365 (w), 1300 (m), 1270 (s), 1220 (m), 1055 (m), 1010 (m) cm⁻¹.

1H NMR (CDCl₃): δ = 1.58 (s, 3 H), 1.57–1.66 (m, 2 H), 1.78 (s, 3 H), 2.00–2.06 (m, 1 H), 2.18–2.56 (m, 4 H), 2.73–2.81 (m, 1 H), 2.98–3.05 (m, 1 H), 3.73 (s, 3 H).

13C NMR (CDCl₃): δ = 32.4 (q), 30.0 (t), 32.7 (q), 34.6 (t), 36.6 (d), 41.4 (d), 43.6 (d), 43.7 (d), 44.0 (d), 46.2 (d), 47.0 (d), 52.0 (d), 52.4 (d), 55.2 (q), 56.8 (q) 68.3 (s), 142.0 (s), 147.5 (s), 164.8 (s), 167.1 (s).

MS (EI): m/z (%) = 318 (M⁺, 20), 240 (90), 79 (85), 66 (100), 40 (30).

Compound 19a from the Reaction of 12a and 12b with Thiobenzophenone

A mixture of 1,3,4-thiadiazoline 12a and 12b (220 mg, 1 mmol) was dissolved in THF (2 mL) and thiobenzophenone (198 mg, 1 mmol) was added. The blue solution was stirred and heated in an oil bath at 45 °C. The volume of N₂ evolved was measured with a gas burette. When the evolution of N₂ was complete (ca. 25 mL in 15 min), the solvent was removed under reduced pressure. The residue was separated by preparative layer chromatography (silica gel, hexane–CH₂Cl₂, 1:1) and the main fraction was recrystallized from MeOH to give 19a as a colorless crystalline solid; yield: 60 mg (18%); mp 204–206 °C.

IR (KBr): 3045 (m), 3000 (m), 2975 (s), 2955 (s), 2940 (s), 1950 (w), 1490 (s), 1465 (m), 1440 (s), 1035 (m), 785 (m), 750 (s), 735 (s), 705 (s) cm⁻¹.

1H NMR (CDCl₃): δ = 0.82–0.91 (m, 1 H), 1.17–1.68 (m, 4 H), 2.05–2.12 (m, 1 H), 2.28–2.49 (m, 2 H), 2.85–2.94 (m, 1 H), 3.18–3.46 (m, 4 H), 7.18–7.29 (m, 6 H), 7.68–7.73 (m, 4 H).

13C NMR (CDCl₃): δ = 23.7 (q), 24.4 (q), 28.0 (q), 28.6 (d), 34.0 (t), 36.2 (q), 41.9 (d), 42.2 (d), 43.1 (d), 44.77 (d), 44.83 (d), 46.9 (d), 49.8 (s), 54.4 (d), 56.5 (d), 60.3 (s), 62.6 (s), 175.6 (s), 175.7 (s).
Compound 19a from the Reaction of 12a and 12b with 18
A mixture of 1,3,4-thiadiazoline 12a and 12b (220 mg, 1 mmol) was dissolved in THF (2 mL) and the monothione 18 (160 mg, 1 mmol) was added. This mixture was stirred and heated at 45 °C. The volume of N₂ evolved was measured with a gas burette. When the evolution of N₂ was complete (ca. 25 mL in 15 min), the solvent was removed under reduced pressure. The residue was separated by preparative layer chromatography (silica gel, hexane–CH₂Cl₂, 2:3) and the main fraction was recrystallized from hexane to give 19a as a colorless crystalline solid; yield: 150 mg (43%); mp 106–108 °C.

IR (KBr): 2965 (s), 2930 (m), 2870 (m), 1775 (s), 1730 (w), 1635 (w), solid; yield: 120 mg (35%); mp 112–114 °C.

Compound 19b from the Reaction of 12d with 7
A mixture of 1,3,4-thiadiazoline 12d (200 mg, 1 mmol) was dissolved in THF (2 mL) and the cage thione 7 (180 mg, 1 mmol) was added. This mixture was stirred and heated in an oil bath at 45 °C. The volume of N₂ evolved was measured with a gas burette. When the evolution of N₂ was complete (ca. 25 mL in 2 h), the solvent was removed under reduced pressure. The residue was separated by preparative layer chromatography (silica gel, hexane–CH₂Cl₂, 2:3) and the main fraction was recrystallized from hexane to give 19b as a colorless crystalline solid; yield: 120 mg (43%); mp 114–116 °C.

IR (KBr): 2965 (s), 2930 (m), 2870 (m), 1775 (s), 1730 (w), 1635 (w), solid; yield: 120 mg (35%); mp 112–114 °C.

1H NMR (CDCl₃): δ = 1.08–1.23 (m, 3 H), 1.30 (s, 3 H), 1.35 (s, 3 H), 1.58–1.72 (m, 3 H), 2.04–2.73 (m, 8 H), 2.66 (s, 2 H).

13C NMR (CDCl₃): δ = 22.2 (q), 22.4 (q), 24.0 (q), 24.8 (q), 29.7 (t), 34.4 (t), 36.0 (d), 41.2 (d), 42.2 (d), 43.1 (d), 44.4 (d), 45.2 (d), 46.8 (d), 48.8 (t), 53.4 (d), 65.0 (s), 66.9 (s), 69.1 (s), 220.3 (s).

MS (EI): m/z (%) = 318 (M⁺, 20), 240 (90), 79 (85), 66 (100), 40 (30).

Acknowledgment
We thank the Polish State Committee for Scientific Research (KBN Grant T09A 046 25) for financial support.

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