Preparation of a Novel Tricyclic Trisufide Using an Intramolecular Thiocarbonyl Trapping Reaction

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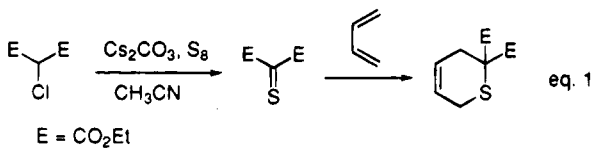
Introduction

The chemistry of thiocarbonyls received much attention in the last few years.[2] Many examples using thiocarbonyls as a source of carbon–carbon bond forming reactions are known.[3] Recently, a novel and efficient use of thiocarbonyls in Diels–Alder reactions appeared.[4] The approach entailed reacting diethyl chloromalonate with elemental sulfur in the presence of a mild base. The C_2 acidic carbon provided a latent leaving group and a nucleophilic center to generate the intermediate thiocarbonyl. These were then trapped *in situ* with various dienes to give the Diels–Alder products in high yield (eq 1).

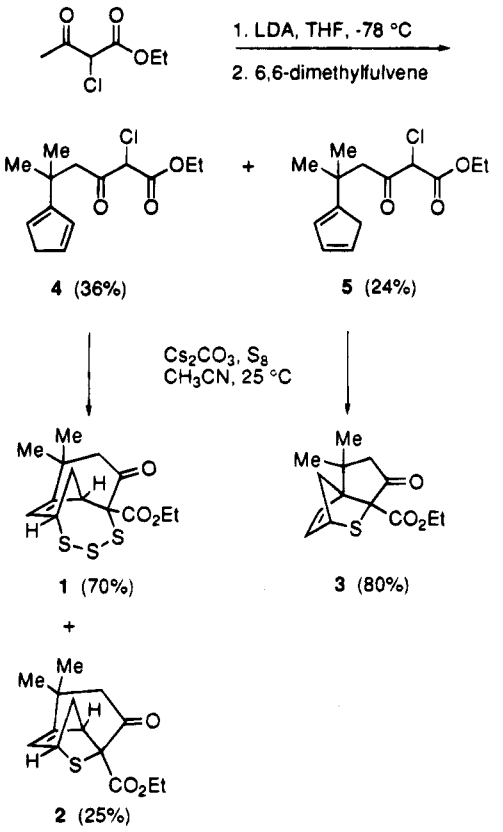


We decided to expand this concept using an intramolecular version of this reaction as shown in Scheme 1. By tethering a diene moiety off the thiocarbonyl precursor, we would generate a system capable of undergoing the desired intramolecular reaction. Along with the expected intramolecular products **2** and **3**, we also obtained a novel tricyclic trisulfide **1**. This compound has a unique structural motif with the trisulfide moiety as part of a [4.2.1] bicyclic system. The bicyclic system is also fused to a cyclohexanone system forming an interesting array of three fused rings.

Results and Discussion

The chemistry used to prepare compound **1** is outlined in Scheme 1. The dianion of 2-chloroacetoacetate[5] was generated at −78 °C using lithium diisopropylamide (LDA) followed by treatment with dimethylfulvene. This reaction provided a 3:2 mixture of the desired precursors **4** and **5** for the intramolecular thiocarbonyl trapping reaction. The two compounds were separated[6] and each

Scheme 1



was subjected to the thiocarbonyl-generating reaction conditions. The chloro esters were added to a stirred suspension of sulfur (2 equiv) and cesium carbonate (1.2 equiv) in acetonitrile at 25 °C over 60 min. In addition to the desired thiocarbonyl Diels–Alder adducts **2** and **3**, we obtained the novel tricyclictrithiapin **1** in good yield.[7] The trisulfide **1** is obtained only from the one precursor **4**. Subjecting compound **4** to identical reaction conditions at −30 °C does not produce the trisulfide **1** and only the adduct **2** is obtained.

Both compounds **1** and **3** were crystallized from 50% ether in hexane and gave crystals suitable for X-ray crystallography. The ORTEP drawing of **1** is shown in Figure 1. Analyzing the crystallographic parameters for **1** shows minor evidence of strain in the molecule. The bond lengths and angles for the trisulfide moiety are typical based on a survey of the Cambridge crystallographic database. No other major distortions of bond distances or angles for other atoms exist. Examining the bond lengths and angles for compound **3** also shows no major evidence of strain.

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(2) (a) Kirby, G. W.; McGregor, W. M. *J. Chem .Soc. Perkin. Trans. 1* **1990**, 3175. (b) Larsen, S. D. *J. Am. Chem. Soc.* **1988**, *110*, 5932. (c) Vedejs, E.; Stults, J. S.; Wilde, R. G. *ibid* **1988**, *110*, 5452. (d) Usov, V. A.; Timokhina, L. V.; Voronkov, M. G. *Russ. Chem. Rev.* **1990**, *59*, 378. (e) McGregor, W. M.; Sherrington, D. C. *Chem. Soc. Rev.* **1993**, 199.

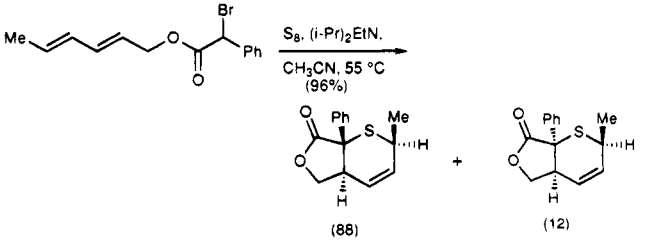
(3) Metzner, P. *Synthesis* **1992**, *12*, 1185 and references cited therein.

(4) Abelman, M. M. *Tetrahedron Lett.* **1991**, *32*, 7389.

(5) Rigby, J. H.; Senanayake, C. H.; Rege, S *J. Org. Chem.* **1988**, *53*, 4596.

(6) This separation is very tedious, and identical results were obtained subjecting a mixture of **5** and **6** to the thiocarbonyl-forming reaction.

(7) An additional example of this reaction has been demonstrated in the following system:



0022-3263/95/1960-3554$09.00/0

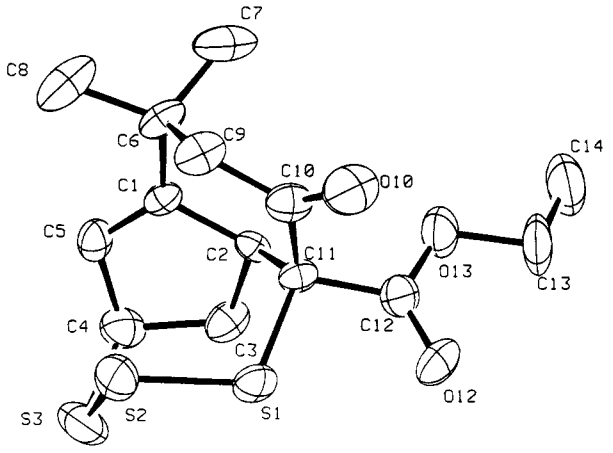
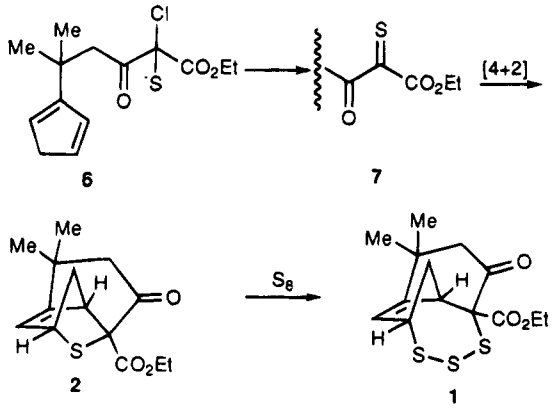


Figure 1. ORTEP drawing of trisulfide **1**.

Scheme 2



The initial mechanism proposed for the thiocarbonyl formation[4] is also at work in these reactions. This mechanism is shown in Scheme 2. Compound **4**, in the presence of base, reacts with elemental sulfur to give the anion **6**. This anion undergoes an intramolecular displacement of chloride ion to give the thiocarbonyl intermediate **7**. This intermediate undergoes the facile [4 + 2] to give compound **2**. The inherent strain in this tricyclic sulfide renders the C–S bond susceptible to attack by the excess sulfur present in the reaction. Further addition of two sulfur atoms gives compound **1**. This would produce the bicyclic [4.2.1] system relieving the strain in compound **2**. Sulfur is known to add to strained double bonds giving cyclic trisulfide species.[8] In addition, the low temperature results are consistent with this mechanism. At the lower temperature, sulfur is unable to insert into the carbon–sulfur bond of compound **2**, allowing for the isolation of this compound as the only product.

The results obtained with compound **3** further support this explanation. The lack of inherent strain in compound **3** renders it resistant to attack by elemental sulfur. As a result, it is the only product isolated from the reaction sequence in Scheme 1.

Conclusions

We have further demonstrated the utility of generating thiocarbonyls in high yield from α-chloro-β-keto esters. The thiocarbonyl intermediates react with adjacent dienes in an intramolecular [4 + 2] cycloaddition to give the desired products **2** and **3** along with an unexpected byproduct. The trisulfide **1** is a novel structure and the first trithiapin with X-ray crystallographic information. This approach shows promise in generating complex tricyclic systems efficiently. These tricyclic systems are interesting heterocycles and may be used as precursors to highly functionalized carbocyclic intermediates.

Experimental Section

All reactions were carried out with continuous stirring under an atmosphere of dry nitrogen. Commercial reagents were used as received without additional purification. THF was distilled from sodium benzophenone ketyl. Ethyl 2-chloroacetoacetate, 6,6-dimethylfulvene, and LDA were purchased from Aldrich Chemical Co. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using tetramethylsilane as an internal standard. Melting points are uncorrected. TLC was performed on E. Merck 15719 silica gel plates. Flash chromatography was carried out using EM Science silica gel 60 (230–400 mesh). X-ray data collected on a Enraf-Nonius CAD4 diffractometer using Mo Kα radiation @ 0.87 cm^{-1}. Structure solved by direct methods (MULTAN). Tabular results of coordinates, bond distances, angles and isothermal parameters were submitted to the Cambridge Crystallographic Database; they are available on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge, CB2 1EZ, UK.

Ethyl 2-Chloro-5-(1,4-cyclopentadienyl)-5-methyl-3-oxohexanoate (4) and Ethyl 2-Chloro-5-(1,3-cyclopentadienyl)-5-methyl-3-oxohexanoate (5). A solution of ethyl 2-chloroacetoacetate (0.58 g, 5.5 mmol) in THF (5 mL) at −78 °C was treated with LDA (6.0 mL, 12.0 mmol, 2.0 M in THF) dropwise via syringe. After 1 h, 6,6-dimethylfulvene (0.90 g, 5.5 mmol) was added neat at −78 °C via syringe. The cooling bath was removed and the reaction was allowed to reach rt. The reaction was quenched with saturated NH_4Cl solution, diluted with ether (60 mL), and washed with saturated NH_4Cl solution (20 mL). The organic layer was separated and dried ($MgSO_4$), and the solvent was removed at reduced pressure. Chromatography (silica gel, benzene:cyclohexane 1:1) gave the desired adducts **4** and **5** in a 3:2 ratio (0.89 g; 60%). **4**: oil; TLC R_f = 0.45 (silica gel, 50% benzene/cyclohexane); ^{1}H NMR ($CDCl_3$) δ 6.6 (m, 1 H), 6.45 (m, 1 H), 6.15 (bs, 1 H), 4.6 (s, 1 H), 4.25 (m, 2 H), 2.95 (m, 2 H), 2.8 (m, 2 H), 1.35 (t, J = 9 Hz, 3 H), 1.3 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 174.0, 155.6, 133.5, 131.0, 125.1, 123.8, 62.9, 61.8, 51.0, 45.0, 41.0, 28.5, 14.0; CIMS (NH_3) m/z 271 (M + H$^+$, 48%); HRMS calcd for $C_{14}H_{20}O_3Cl$ (M + H$^+$) 271.1101; found 271.1108; **5**: oil; TLC R_f = 0.40 (silica gel, 50% benzene/cyclohexane); ^{1}H NMR ($CDCl_3$) δ 6.25 (m, 1 H), 6.2 (m, 1 H), 6.10 (bs, 1 H), 4.6 (s, 1 H), 4.2 (m, 2 H), 2.95 (m, 2 H), 2.8 (m, 2 H), 1.35 (t, J = 9 Hz, 3 H), 1.3 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 164.8, 153.2, 134.6, 131.7, 125.7, 124.8, 62.8, 61.4, 50.1, 43.6, 40.2, 27.3, 13.8; CIMS (NH_3) m/z 271 (M + H$^+$, 38%); HRMS calcd for $C_{14}H_{20}O_3Cl$ (M + H$^+$) 271.1101; found 271.1108.

Trisulfide 1 and Sulfide 2. To a stirred suspension of sulfur (20 mg, 0.63 g atom) and Cs_2CO_3 (145 mg, 0.44 mmol) in CH_3CN (2 mL) was added a solution of **4** (100 mg, 0.37 mmol) in CH_3CN (4 mL) dropwise over 1 h. After addition was complete, the reaction mixture was filtered (Celite) and the solvent was evaporated. Chromatography (silica gel, 10–30% ether/hexane) gave trisulfide **1** (50 mg, 70%) as a solid and sulfide **2** as an oil (22 mg, 25%). **1**: colorless trapezoidal blocks from ether:hexane (1:1); mp 75 °C; TLC R_f = 0.45 (silica gel, 20% ether in hexane); ^{1}H NMR ($CDCl_3$) δ 5.2 (t, J = 3 Hz, 1 H), 4.45 (dd, J = 8, 2 Hz, 1 H), 4.3 (q, J = 9 Hz, 2 H), 4.15 (dd, J = 8, 2 Hz,1 H), 3.1 (d, J = 13 Hz, 1 H), 2.7 (m, 1 H) , 2.55 (d, J = 10 Hz, 1 H), 2.4 (d, J = 13 Hz, 1 H), 1.4 (s, 3 H), 1.25 (t, J = 9 Hz, 3 H), 1.2 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.3, 167.9, 152.8, 120.9, 73.9, 62.9, 59.4, 55.8, 50.9, 37.9, 37.0, 27.9, 26.9, 14.0; CIMS (NH_3) m/z 348 (M + NH_4^+, 100%), 331 (M + H$^+$, 26%); Anal. Calcd for $C_{14}H_{18}O_3S_3$: C, 50.88; H, 5.49. Found: C, 50.48; H, 5.37. **2**: oil, TLC R_f = 0.35 (silica gel, 20% ether/hexane); ^{1}H NMR ($CDCl_3$) δ 6.2 (s, 1 H), 4.3 (m, 3 H), 4.1 (s, 1 H), 2.6 (q, J = 9 Hz, 2 H), 1.9 (s, 2 H), 1.3 (s, 3 H), 1.25 (t, J = 9 Hz, 3 H), 1.2 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.2, 167.8, 134.8, 129.3, 73.8, 62.8,

(8) Bartlett, P. D.; Ghosh, T. *J. Org. Chem.* **1987**, *52*, 4937; Shields, T. C.; Kurtz, A. N. *J. Am. Chem. Soc.* **1969**, *91*, 5415.

59.3, 55.6, 50.8, 37.8, 36.9, 27.8, 26.8, 13.9; CIMS (NH_3) *m/z* 284 ($M + NH_4^+$, 100%); HRMS calcd for $C_{14}H_{19}O_3S$ ($M + H^+$) 267.1055; found 267.1056.

Sulfide 3. Prepared using a similar procedure as for **1** and **2**. **3**: colorless solid, mp 79 °C; TLC $R_f = 0.25$ (silica gel, 20% ether/hexane); ^1H NMR ($CDCl_3$) δ 6.5 (m, 1 H), 6.35 (m, 1 H), 4.15 (m, 3 H), 2.75 (d, $J = 14$ Hz, 1 H), 2.45 (d, $J = 14$ Hz, 1 H), 1.75 (d, $J = 8$ Hz, 1 H), 1.55 (t, $J = 8$ Hz, 1 H), 1.4 (s, 3H), 1.25 (t, $J = 9$ Hz, 3 H), 1.2 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.3, 170.6, 137.6, 133.3, 74.7, 62.2, 54.9, 54.8, 52.2, 35.1, 28.9, 27.7, 13.8; CIMS (NH_3) *m/z* 284 ($M + NH_4^+$, 100%). Anal. Calcd for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81. Found: C, 62.68; H, 6.72.

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