JOC Article

C,O-Dialkylation of Meldrum's Acid: Synthesis and Reactivity of 1,3,7,7-Tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one

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Reaction of Meldrum's acid with 3,4-bis(chloromethyl)-2,5-dimethylthiophene (**1**) or 3,4-bis(bromomethyl)-2,5-dimethylthiophene (**2**) produces the kinetically favored C,O-dialkylation product, 1,3,7,7-tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one (**4**). Recrystallization of **4** from refluxing methanol results in the methanolysis product 5-(4-methoxymethyl-2,5-dimethylthiophen-3-ylmethyl)-2,2-dimethyl[1,3]dioxane-4,6-dione (**5**). Attempts to isomerize **4** to the thermodynamically favored C,C-dialkylation product, 1,3-dimethyl-5,6-dihydro-4*H*-cyclopenta[*c*]thiophene(2-spiro-5)2,2-dimethyl-4,6-dione (**8**), result in the formation of 1,3-dimethyl-7,8-dihydro-4*H*-thieno[3,4-*c*]oxepin-6-one (**6**). The transformation occurs via a retro-Diels−Alder elimination of acetone followed by hydrolysis and decarboxylation of the resulting ketene. The ketene is trapped by *tert*-butyl alcohol, furnishing 1,3-dimethyl-6-oxo-7,8-dihydro-4*H*,6*H*-thieno[3,4-*c*]oxepine-7-carboxylic acid *tert*-butyl ester (**7**). All compounds are characterized spectroscopically as well as by X-ray crystallography of products **4**−**7**.

Introduction

Meldrum's acid (**3**, isopropylidene malonate, 2,2-dimethyl-1,3-dioxane-4,6-dione) was first reported by Meldrum in 1908.[1] It offers advantages over acyclic malonate esters in organic synthesis.[2,3] The cyclic structure of Meldrum's acid leads to high acidity ($pK_a = 4.97$) of the malonate hydrogens,[4] yet its low steric profile makes its anions very effective nucleophiles for C-alkylation and C,C-dialkylation.[2,5] Monoalkylated malonic acids and esters have found applications in pharmaceutical development.[4] Dialkylated Meldrum's acids are versatile synthetic intermediates with numerous applications.[6−9] Many reaction conditions have been developed for the alkylation of **3**, including the use of K_2CO_3 in DMF,[10] K_2CO_3 plus a phase-transfer catalyst in $CHCl_3$,[11−13] or triethylamine in DMSO.[5] We report here an unusual C,O-dialkylation of Meldrum's acid.

Results and Discussion

C,O-Dialkylation of 3,4-Bis(chloromethyl)-2,5-dimethylthiophene (1) and 3,4-Bis(bromomethyl)-2,5-dimethylthiophene (2). As part of the development of a general synthesis of cyclopenta[3,4-c]thiophenes, we attempted to dialkylate Meldrum's acid with 3,4-bis(halomethyl)-2,5-dimethylthiophenes (**1** and **2**) to give the spiro compound **8**. Preparations of indanes via reactions of 1,2-bis(haloalkyl)arenes with malonate anions are well-known.[14−18] In particular, a spiroindane was obtained by reacting α,α′-dibromo-*o*-xylene with Meldrum's acid.[5]

Treatment of 3,4-bis(bromomethyl)-2,5-dimethylthiophene **2** with Meldrum's acid and triethylamine in DMSO gives a dialkylation product in 93% yield, with 3,4-bis(chloromethyl)-2,5-dimethylthiophene **1**[19] giving the same product in 74% yield (Scheme 1). The nonequivalence of the thiophene methyl groups in the product's ^{1}H NMR spectrum indicates that the alkylation did not proceed as anticipated. Although a twisted geometry of the expected spirocycle **8** could, in principle, break the equivalence of the two isopropylidene methyl groups and possibly the four methylene hydrogens, it is hard to imagine a stable conformation that would render the thiophene methyl groups nonequivalent. The preferred ring conformation of many 2-, 2,5-di-, 2,2-di-, and 2,2,5-trisubstituted 4,6-dioxo-1,3-dioxanes is the boat form, but ring inversion is usually facile.[20] X-ray crystallography (Figure 1, Tables 1 and 2) reveals the structure

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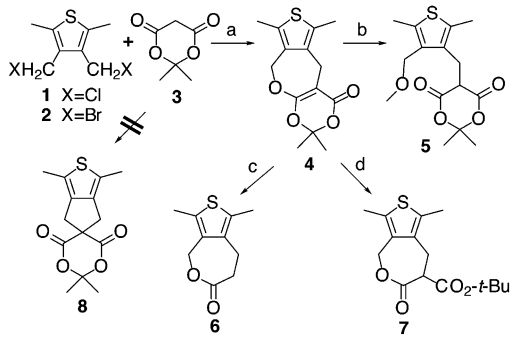
SCHEME 1 [a]



[a] Key: (a) NEt_3, DMSO, 35 °C, 8 h; (b) MeOH, reflux, 5 min; (c) KI, MeCN, 100 °C, 24 h; (d) *t*-BuOH, toluene, 50 °C, 4 h.

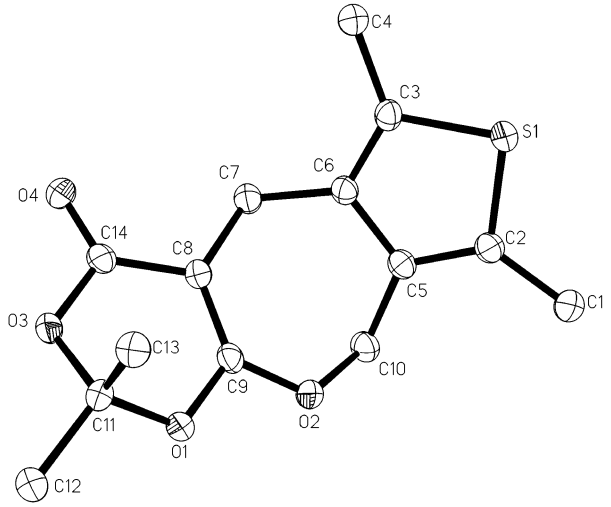


FIGURE 1. Molecular structure of 1,3,7,7-tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one (**4**). Hydrogen atoms are omitted for clarity.

TABLE 1. Crystallographic Data for Compounds 4−7

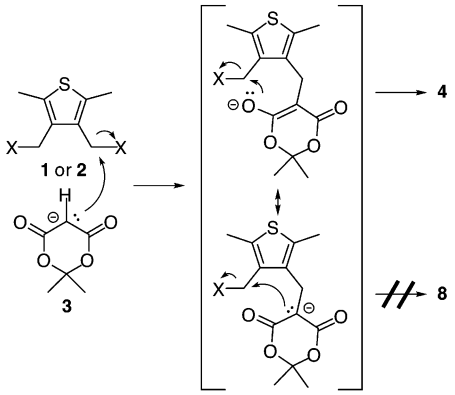
	4	5	6	7
formula	$C_{14}H_{16}O_4S$	$C_{15}H_{20}O_5S$	$C_{10}H_{12}O_2S$	$C_{15}H_{20}O_4S$
formula wt	280.33	312.37	196.26	296.37
T, K	90.0(2)	90.0(2)	90.0(2)	90.0(2)
cryst syst	triclinic	monoclinic	monoclinic	monoclinic
space grp	*P*-1	$P2_1/c$	$P2_1/c$	$P2_1/n$
Z	2	4	4	4
a, Å	7.8120(6)	11.5470(5)	6.0917(12)	23.1010(5)
b, Å	8.7760(6)	9.8590(5)	15.484(3)	5.8010(2)
c, Å	10.5470(8)	14.0290(6)	9.968(2)	11.3580(10)
α,(deg)	106.086(4)	90	90	90
β, (deg)	94.886(4)	105.410(3)	99.72(3)	99.350(2)
γ, (deg)	108.224(4)	90	90	90
V, Å^3	648.12(8)	1539.67(12)	926.7(3)	1501.85(15)
d_{calc}, g/cm^3	1.436	1.348	1.407	1.311

of the unique C,O-dialkylated product 1,3,7,7-tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one (**4**), containing a fused system of five-, six-, and seven-membered rings (Scheme 1). The molecular structure of **4** has an unusual 5−7−6 fused ring arrangement. The five atoms in the thiophene ring are coplanar to within 0.03(1) Å. The seven-membered ring is folded at atoms C7 and C10, with a dihedral angle of 54.96(8)° between the least-squares planes [C7−C6−C5−C10] and [C7−C8−C9−O2−C10]. Five atoms of the Meldrum's enolate ring, O3, C14, C8, C9, and O1, are coplanar to within 0.042(1) Å, with the isopropylidene atom C11 situated 0.623(2) Å above the plane. The dihedral angle between the [C7−C8−C9−O2−C10] and [O3−C14−C8−C9−O1] planes is 11.1(1)°. The 5−7−6 ring system of **4** resembles the oxygen-containing fused ring system in brevetoxin A, a powerful ichthyotoxin isolated from the "red tide" dinoflagellate *Gymnodinium breve*.[21]

TABLE 2. Selected Bond Distances (Å) and Angles (deg) for 4−7

	4	5	6	7
S1−C2	1.7337(19)	1.7289(19)	1.725(3)	1.731(3)
C9−O1	1.346(2)	1.353(2)	1.204(3)	1.199(4)
C9−O2	1.337(2)	1.201(2)	1.350(3)	1.345(4)
C7−C8	1.519(3)	1.533(2)	1.524(4)	1.535(4)
C8−C9	1.353(3)	1.513(2)	1.511(4)	1.528(4)
C8−C14	1.454(3)	1.513(2)		1.523(4)
C10−O2	1.465(2)		1.459(3)	1.453(3)
C10−O5	1.491(3)	1.436(2)		
S1−C2−C5	109.65(14)	110.18(13)	110.55(19)	110.1(2)
C8−C9−O1	122.96(16)	116.35(14)	124.2(3)	123.0(3)
C8−C9−O2	130.88(17)	124.87(16)	118.2(2)	118.0(3)

SCHEME 2



It is surprising that the very similar reaction of Meldrum's acid with α,α′-dibromo-*o*-xylene gives a spiroindane by normal C,C-dialkylation.[5] Apparently, the different reaction pathways result from the slightly greater distance between two halomethyl groups on the 3,4-positions of a thiophene compared to two halomethyl groups on the ortho positions of a benzene ring. Scheme 2 illustrates that intramolecular O-alkylation of the monoalkylated enolate intermediate to form the oxaazulene ring system of **4** (top) is likely to be kinetically favored over alkylation of the more distant carbon atom to form the strained pentalene ring system of **8** (bottom).

Synthesis of 4-Methoxy-3-methyl(2,2-dimethyl-1,3-dioxane-4,6-dione)-2,5-dimethylthiophene (5). Recrystallization of compound **4** from methanol yields **5** in 95% yield. X-ray crystallography (Figure 2, Tables 1 and 2) shows that **5** is a methyl ether that results from methanolysis of the oxepine ring of **4**. In the structure of **5**, the Meldrum's acid ring is in a boat configuration, with atoms C8 and C11 situated on the same side of the [O1−C9−C14−O3] plane by 0.432(2) and 0.489(2) Å. The opening of the seven-membered ring is surprisingly facile. Ordinarily such a ring-opening is promoted by the relief

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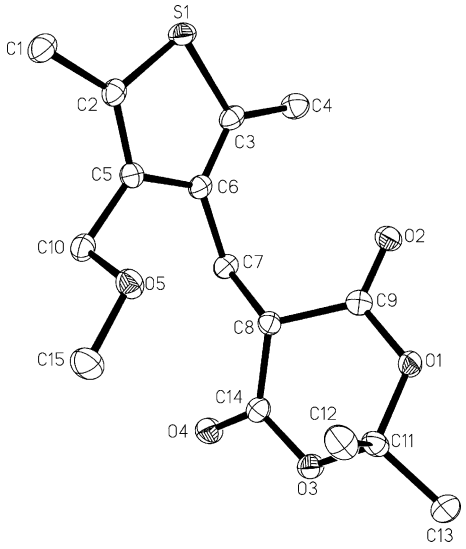
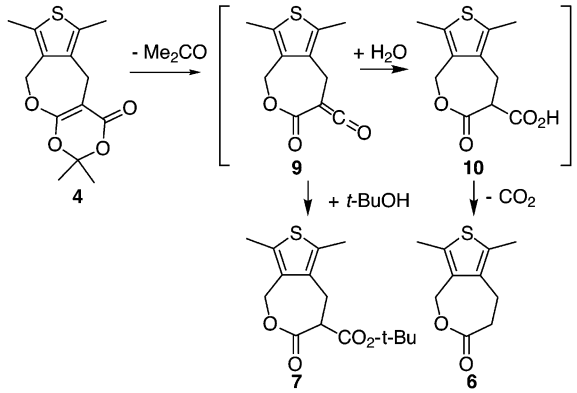


FIGURE 2. Molecular structure of 5-(4-methoxymethyl-2,5-dimethylthiophen-3-ylmethyl)-2,2-dimethyl[1,3]dioxane-4,6-dione (**5**). Hydrogen atoms are omitted for clarity.

SCHEME 3



of ring strain, e.g., homoconjugate additions of nucleophiles to spiroactivated cyclopropane derivatives of Meldrum's acid.[22,23] In these ring-opening reactions, the emerging negative charge is optimally stabilized by delocalization into the planar diester system of Meldrum's acid.

Thermolysis of 4: Syntheses of 1,3-Dimethyl-7,8-dihydro-4*H*-thieno[3,4-*c*]oxepin-6-one (6) and 1,3-Dimethyl-6-oxo-7,8-dihydro-4*H*,6*H*-thieno[3,4-*c*]-oxepine-7-carboxylic Acid *tert*-Butyl Ester (7). Spartan calculations indicate that C,C-spiroalkylated **8** (ΔH_f = −151.3 kcal/mol) is thermodynamically favored over its C,O-dialkylated isomer **4** (ΔH_f = −137.1 kcal/mol). However, an attempt to convert the kinetic product **4** into **8** by heating **4** at 100 °C in acetonitrile with a catalytic amount of KI results in the formation of the cyclic lactone, 1,3-dimethyl-7,8-dihydro-4*H*-thieno[3,4-*c*]oxepin-6-one (**6**), in 95% yield (Scheme 1). Apparently, **4** undergoes a retro-Diels−Alder elimination of acetone, producing a ketene intermediate (**9**, Scheme 3). Hydrolysis of the ketene and decarboxylation of the intermediate carboxylic acid **10** account for the formation of **6**. The ^{1}H

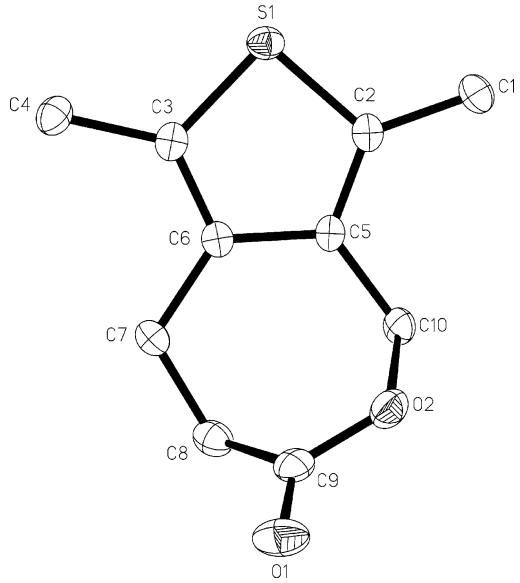
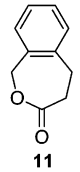


FIGURE 3. Molecular structure of 1,3-dimethyl-7,8-dihydro-4*H*-thieno[3,4-*c*]oxepin-6-one (**6**). Hydrogen atoms are omitted for clarity.

NMR spectrum of **6** closely resembles that of lactone **11**.[24,25] The structure of **6** is confirmed by an X-ray crystal



structure (Figure 3, Tables 1 and 2). The conformation of the lactone ring of **6** consists of a flat portion, with all five atoms of [C7−C6−C5−C10−C8] coplanar within 0.028(2) Å, forming a dihedral angle of 1.0(2)° with the thiophene ring. The remaining atoms, C9 and O2, are 1.164(4)° and 1.130(3)° above the [C7−C6−C5−C10−C8] plane.

When the thermolysis of **4** is carried out at 50 °C in toluene containing excess *t*-BuOH, ketene **9** is efficiently trapped to yield 1,3-dimethyl-6-oxo-7,8-dihydro-4*H*,6*H*-thieno[3,4-*c*]oxepine-7-carboxylic acid *tert*-butyl ester (**7**). Conditions for trapping the ketene intermediate are similar to those used by Sato et al.[25] The structure of **7** is confirmed spectroscopically and by using X-ray crystallography (Figure 4, Tables 1 and 2). The seven-membered lactone ring of **7** is more buckled than that of **6**. The four-atom plane [C7−C6−C5−C10] is nearly coplanar with the fused thiophene ring (dihedral angle 0.8(2)°), but the remaining atoms, C8, C9, and O2, are, respectively, 0.216(6) Å below and 0.945(7) and 1.058(5) Å above the [C7−C6−C5−C10] plane. The substituent at C8 causes this atom to move further from the [C7−C6−C5−C10] plane compared to structure **6**. In contrast to the formation of **5** by the methanolysis of **4**, opening of the oxepine ring by the bulkier nucleophile *tert*-butyl alcohol does not occur.

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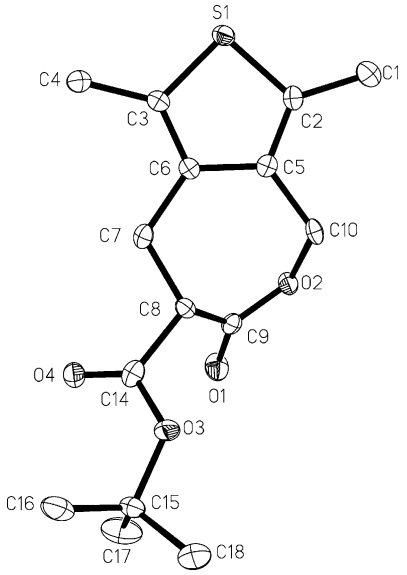

FIGURE 4. Molecular structure of 1,3-dimethyl-6-oxo-7,8-dihydro-4*H*,6*H*-thieno[3,4-*c*]oxepine-7-carboxylic acid *tert*-butyl ester (**7**). Hydrogen atoms are omitted for clarity.

Conclusions

We have described the first C,O-dialkylation of Meldrum's acid. The C,O-dialkylated product 1,3,7,7-tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one (**4**) is obtained in good yield from reactions of 3,4-bis(halomethyl)-2,5-dimethylthiophenes (**1** and **2**) with Meldrum's acid (**3**) and triethylamine. The kinetic product **4** is formed rather than the thermodynamically favored C,C-dialkylation product **8**. The oxepine ring of **4** is opened by reaction with methanol to give the methyl ether **5**. Retro-Diels−Alder elimination of acetone from **4** generates a ketene intermediate (**9**), which is trapped either by hydrolysis and decarboxylation to produce the lactone **6** or by *tert*-butyl alcohol to give the diester **7**.

Experimental Section

Synthesis of 3,4-Bis(bromomethyl)-2,5-dimethylthiophene (2). To a solution of 48% HBr (100 mL) and 36.8% aqueous formaldehyde solution (27.4 mL, 364 mmol) was added 2,5-dimethylthiophene[19,26] (5.00 g, 44.6 mmol). The solution was stirred at 25 °C for 24 h, turning green with a white solid precipitating. The crude mixture was extracted with dichloromethane (4 × 25 mL) and dried ($MgSO_4$). The combined organic extracts were reduced by rotary evaporation, yielding 3,4-bis(bromomethyl)-2,5-dimethylthiophene (13.3 g, 446 mmol) in 74.4% yield. Mp: 70−71 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.35 (s, 3H), 4.89 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.8, 24.5, 131.9, 136.0. IR (KBr, cm^{-1}): 2915 (CH), 1196 (CH_2Br). MS: *m*/*z* 298 (M^+), 219 ($M^+ - Br$). Anal. Calcd for $C_8H_{10}Br_2S$: C, 32.24; H, 3.38. Found: C, 32.60; H 3.28.

Synthesis of 1,3,7,7-Tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one (4). To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (**3**, 2.89 g, 20.0 mmol) in DMSO (30 mL) was added triethylamine (5.72 mL, 41.0 mmol), and the mixture was stirred for 30 min at 25 °C. 3,4-Bis(bromomethyl)-2,5-dimethylthiophene (**2**, 4.18 g, 20.0 mmol) was added, and the mixture was stirred for 24 h at 22 °C. The reaction mixture was filtered, and the DMSO solution was extracted with ethyl ether (6 × 50 mL). The filtrate and combined organic layers were dried ($MgSO_4$), and the volatiles were removed by rotary evaporation. The mixture was recrystallized from ethyl ether/hexane to yield large, colorless crystals of **4** (1.25 g, 93.0%). Mp: 138−139 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.63 (s, 6H), 2.31 (s, 3H), 2.37 (s, 3H), 3.57 (s, 2H), 5.09 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.4, 21.2, 24.9, 64.9, 81.2, 104.7, 129.9, 130.5, 134.5, 134.8, 164.8, 165.3. IR (KBr, cm^{-1}): 1716 (C=O), 1614 (C=C). MS: *m*/*z* 281 ($M^+ + H$), 222 ($M^+ - Me_2CO$). Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 59.89; H, 5.50.

Synthesis of 4-Methoxy-3-methyl(2,2-dimethyl-1,3-dioxane-4,6-dione)-2,5-dimethylthiophene (5). 1,3,7,7-Tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one (**4**, 40 mg, 0.14 mmol) was refluxed in methanol (5 mL) and then recrystallized by slow evaporation over 48 h, yielding large, colorless crystals of 4-methoxy-3-methyl(2,2-dimethyl-1,3-dioxane-4,6-dione)-2,5-dimethylthiophene in 95% yield (43 mg, 0.14 mmol). Mp: 118−119 °C dec. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (s, 3H), 1.75 (s, 3H), 2.37 (s, 3H), 2.45 (s, 3H), 3.26 (d, ^3J = 5 Hz, 2H), 3.30 (s, 3H), 4.25 (s, 2H), 4.60 (t, ^3J = 5 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.0, 13.1, 22.4, 25.4, 28.7, 48.3, 58.0, 66.2, 104.6, 132.5, 133.0, 133.9, 135.1, 165.6. IR ($CHCl_3$, cm^{-1}): 1745 (C=O), 1603, 1252 (CH_2OMe). HRMS: (M^+) calcd 312.1031, obsd 312.1026. MS: *m*/*z* 280 (M^+ − MeOH), 222 ($M^+ - Me_2COCH_2O$). Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.72; H, 6.85.

Synthesis of 1,3-Dimethyl-7,8-dihydro-4*H*-thieno[3,4-*c*]oxepin-6-one (6). 1,3,7,7-Tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]azulen-5-one (**4**, 120 mg, 0.429 mmol) was added to acetonitrile (10 mL) with one crystal of KI. The reaction mixture was refluxed for 24 h, and the solvent was removed in vacuo. The yellow residue was flushed through a silica plug (50:50 dichloromethane/ethyl acetate) to yield white, solid **6** (0.080 g, 0.408 mmol) in 95% yield. Mp: 102−103 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.32 (s, 3H), 2.89 (*AA*′BB′, $^3J_{AB}$ = 6 Hz, 2H), 2.99 (AA′*BB*′, $^3J_{AB}$ = 6 Hz, 2H), 5.09 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$, ppm): δ 12.6, 12.7, 23.7, 30.4, 63.6, 130.5, 130.6, 132.1, 132.2, 151.0. IR ($CHCl_3$, cm^{-1}): 1794, 1704 (C=O), 1614. HRMS: (M^+) calcd 196.0558, obsd 196.0565. MS: *m*/*z* 151 ($M^+ - CO_2H$). Numerous attempts to obtain a correct microanalysis were unsuccessful.

Synthesis of 1,3-Dimethyl-6-oxo-7,8-dihydro-4*H*,6*H*-thieno[3,4-*c*]oxepine-7-carboxylic Acid *tert*-Butyl Ester (7). 1,3,7,7-Tetramethyl-4*H*,10*H*-6,8,9-trioxa-2-thiabenz[*f*]-azulen-5-one (**4**, 0.50 g, 2.4 mmol) was dissolved in toluene (12 mL). To this mixture was added *tert*-butyl alcohol (0.19 g, 2.6 mL) under nitrogen. The solution was heated to 50 °C and stirred for 4 h. The solvent was removed in vacuo, and the resulting solid was flushed through a silica plug (50:50 dichloromethane/ethyl acetate). The solvents were removed by rotary evaporation yielding **7** (0.67 g, 2.3 mmol) in 94% yield. The compound was recrystallized from ethyl acetate/toluene to yield large, colorless plates. Mp: 131−132 °C. ^{1}H NMR (200 MHz, DMSO): δ 1.49 (s, 9H), 2.21 (s, 3H), 2.31 (s, 3H), 2.81 (dd, $^2J_{AB}$ = 17 Hz, $^3J_{AC}$ = 12 Hz), 3.02 (dd, $^2J_{AB}$ = 17 Hz, $^3J_{BC}$ = 6 Hz), 4.66 (dd, $^3J_{AC}$ = 12 Hz, $^3J_{BC}$ = 6 Hz, 1H), 5.05 (d, ^2J = 14 Hz, 1H), 5.45 (d, ^2J = 14 Hz, 1H). ^{13}C NMR (50 MHz, DMSO): δ 12.2, 12.4, 25.9, 27.5, 45.8, 63.1, 81.2, 130.4, 130.5, 130.8, 131.6, 167.7, 171.7. IR (KBr, cm^{-1}): 1744 (CO), 1157 (CO). HRMS: (M^+) calcd 296.1082, obsd 296.1084. MS: *m*/*z* 223 (M^+ − *t*-BuOH). Anal. Calcd: C, 60.79; H, 6.80. Found: C, 60.43; H, 7.09.

X-ray Crystal Structures of 4−7. X-ray-quality single crystals of **4**−**7** were obtained as noted above. These transparent prisms were mounted on glass fibers with Paratone N oil. Data were collected at 90 K on a Nonius KappaCCD diffractometer. The main programs used were DENZO-SMN to obtain cell parameters and for data reduction, SCALEPACK for absorption correction,[27] SHELXS-86 for structure solution, and SHELXL-93 for refinement. Data collection and crystal parameters are listed in Table 1. Hydrogen atoms were placed

(26) Wallace, C. E. Ph.D. Dissertation, Department of Chemistry, University of Kentucky, 1998, p 196.

in geometrically calculated positions. Routine structure solution and refinement led to the structural parameters listed in Table 2.

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Supporting Information Available: General experimental conditions; tables of crystallographic details, atomic coordinates and displacement parameters, complete bond distances and angles, and crystallographic information files (CIF) for the structures of **4**−**7**; ^{1}H NMR spectrum of 1,3-dimethyl-7,8-dihydro-4*H*-thieno[3,4-*c*]oxepin-6-one (**6**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307−326.