Reaction of Thiocarbonyl *S*-Methylides with Acetylenic Dipolarophiles and an Unexpected Rearrangement of the Cycloadducts[1])

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Dedicated to Professor *Hans-Jürgen Hansen* on the occasion of his 65th birthday

The 1,3-dipolar cycloaddition of 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-methylide (**2a**), generated *in situ* by thermal extrusion of N_2 from the corresponding 2,5-dihydro-1,3,4-thiadiazole **1a**, with electron-deficient acetylenic compounds yields spirocyclic 2,5-dihydrothiophene derivatives of type **4** (*Scheme 2*). Mixtures of diastereoisomers are obtained in the case of propiolates. The strained cyclooctyne also undergoes smooth cycloadditions with thioketone *S*-methylides (*Scheme 3*). Under acidic conditions, the spirocyclic products of type **4** and **6a** isomerize, *via* opening of the cyclobutanone ring and aromatization of the five-membered ring, to thiophene derivatives of type **7** (*Scheme 4*).

Introduction. – Reactions of thiocarbonyl ylides with electron-poor olefinic dipolarophiles offer a convenient and versatile access to tetrahydrothiophene derivatives (*cf.* [1–4]). This methodology was successfully applied for the synthesis of some naturally occurring products such as biotin [5][6], for stereocontrolled preparation of precursors of natural products [7][8], as well as for polycyclic tetrahydrothiophenes, which result from both inter- and intramolecular 1,3-dipolar cycloadditions [9–11]. Recently, the parent thiocarbonyl ylide was reported to react with [60]fullerene to yield a thiophene derivative [12].

In contrast, reactions of thiocarbonyl ylides with acetylenic dipolarophiles are less common and mostly limited to acetylene dicarboxylates. There are successful reactions reported with the parent species [13] as well as with alkyl and aryl substituted ones [14–16]. Kinetic studies by *Huisgen* and co-workers showed that, in general, the reactivity of dimethyl acetylenedicarboxylate (DMAD) is comparable with that of dimethyl fumarate but much lower than that of 'superdipolarophilic' thioketones [17]. However, acetylenedicarboxylates are sufficiently reactive to intercept thiocarbonyl ylides before they undergo 1,3-electrocyclization to give thiiranes or dimerization to yield 1,4-dithianes. The reactivity scale given in [17] begins with methyl propiolate as the least reactive dipolarophile towards thiobenzophenone *S*-methylide.

A convenient method for the generation of thiocarbonyl ylides is the thermal extrusion of N_2 from 2,5-dihydro-1,3,4-thiadiazoles of type **1a** [3][4]. Due to the easy

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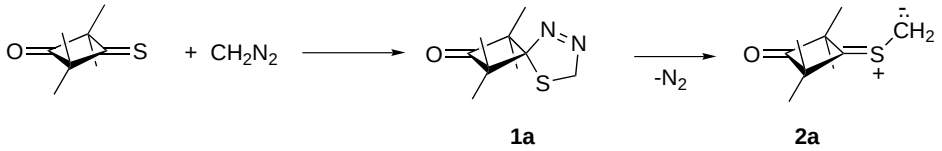
[2]) Postdoctoral stay at the University of Zurich, August 1999 – July 2000.

availability of starting materials, one of the most frequently used representatives of thiocarbonyl ylides prepared by this method is 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-methylide (**2a**) [18] (*Scheme 1*). A similar protocol is followed for the generation of adamantane-2-thione *S*-methylide (**2b**) [19].

Scheme 1

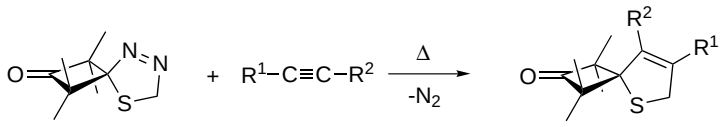


1a **2a**

The aim of the present work was the comparison of the reactivity of DMAD with other acetylenic dipolarophiles, including cyclooctyne, in the 1,3-dipolar cycloaddition with **2a**.

Results. – The precursor **1a** was dissolved in excess DMAD and heated until the evolution of N_2 ceased. After removing excess DMAD, the mixture was analyzed by ^{1}H-NMR spectroscopy, and the 2,5-dihydrothiophene **4a** was detected as the only product (*Table 1* and *Scheme 2*). After typical workup, **4a** was isolated as a colorless solid in 65% yield. The structure of the product was confirmed by the spectroscopic data. Two *singlets* at 1.46 and 1.24 ppm, and two *quadruplets* at 26.9 and 20.3 ppm for the 4 Me groups of the cyclobutanone ring in the ^{1}H- and ^{13}C-NMR spectrum, respectively, show the C_s symmetry of the molecule.

Scheme 2



1a **3** **4**

Table 1. *Reaction of* **1a** *with Acetylene Derivatives*

3	R^1	R^2	**4**	R^1	R^2	Yield [%]
a	MeOCO	MeOCO	**a**	MeOCO	MeOCO	65
b	CN	CN	**b**	CN	CN	41
c	PhCO	PhCO	**c**	PhCO	PhCO	63
d	H_2NCO	H_2NCO	no reaction			
e	MeOCO	H	**d**	MeOCO	H	55
			e	H	MeOCO	25
f	*t*-BuOCO	H	**f**	*t*-BuOCO	H	75
			g	H	*t*-BuOCO	*ca.* 8
g	EtOCO	Me	no reaction			
h	EtOCO	Ph	no reaction			
i	Ph	H	no reaction			

Reactions with symmetrically substituted acetylenes **3b** and **3c** were carried out in CH_2Cl_2 solutions with equimolar amounts of **1a** and **3**. Due to the low solubility of **3d**, 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) was used as the solvent for this experiment. In the cases of **3b** and **3c**, the expected cycloadducts **4b** and **4c**, respectively, were isolated in satisfactory yields (*Table 1*), whereas the diamide **3d** did not react. The molecular structure of **4c** has been established by X-ray crystallography (*Fig. 1*).

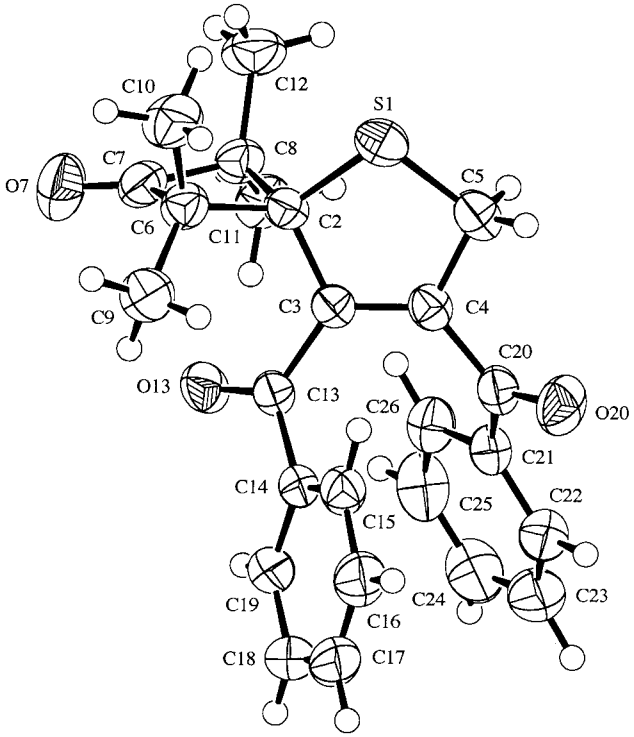
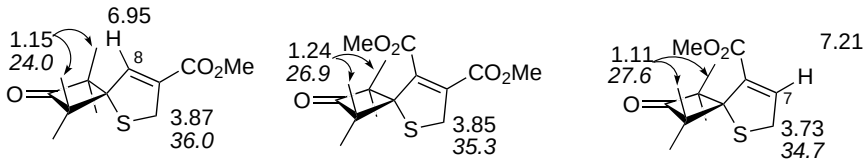


Fig. 1. *ORTEP Plot* [20] *of the molecular structure of* **4c** (with 50% probability ellipsoids)

Methyl and *tert*-butyl propiolate (**3e** and **3f**, resp.) were used as solvents for the reaction with **1a**. In both cases, mixtures of regioisomers **4d**/**4e** and **4f**/**4g** were formed in the ratio of 2:1 and 9:1, respectively (^{1}H-NMR analysis), and the isomers were separated by means of fractionated crystallization and chromatography. All attempts to isolate the minor product **4g** in pure form were unsuccessful; therefore, NMR data were taken from the mixture of isomers after separation of the main portion of **4f** by crystallization from MeOH. The determination of the structure of the regioisomers **4d** (main product, more polar) and **4e** (minor product, less polar) was based on the comparison of selected chemical shifts with those of diester **4a** shown below.

In addition, H–C(8) of **4d** shows a typical allylic coupling with CH_2(5) (^4J = 2.0 Hz) whereas the ^3J coupling of H–C(7) with CH_2(5) of **4e** is 2.9 Hz. This



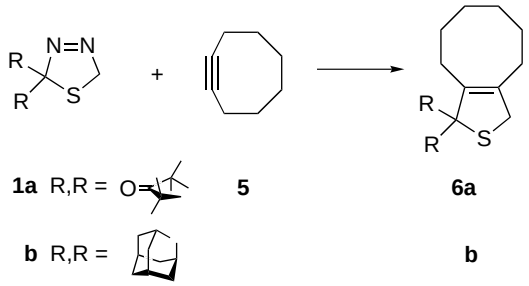
4d **4a** **4e**

assignment of the structures is strongly supported by NOE experiments: the NOESY spectrum of **4d** shows an intensive cross-peak between H–C(8) (6.95 ppm) and the Me signal at 1.15 ppm, as well as a weak one with CH_2(6) at 3.87 ppm. On the other hand, no NOE could be observed between the Me signals (1.43 and 1.11 ppm) and H–C(7) (7.21 ppm) of isomer **4e**.

As expected, the non-symmetrically substituted acetylenes **3g**–**i** did not react with **1a** on heating in CH_2Cl_2 solution. In addition to unchanged acetylene derivatives, only the thiirane corresponding to **2a** [21] was identified.

In contrast to alkyl- and aryl-substituted acetylenes, which are useless as dipolarophiles, strained cyclooctyne easily undergoes 1,3-dipolar cycloadditions with various dipoles such as azomethine ylides [22][23], diazo compounds [24][25], nitrile oxides [25], and thiosulfines (thiocarbonyl *S*-sulfides) [26]. Moreover, it was shown to react with 9*H*-fluorene-9-thione *S*-oxide, which belongs to the sulfines (thiocarbonyl *S*-oxides) known as less reactive 1,3-dipoles [27]. Therefore, we decided to test its reactivity towards thiocarbonyl ylides **2a** and **2b**. The reaction was carried out in the typical manner with CH_2Cl_2 as a solvent. In each case, the expected cycloadduct **6a** and **6b**, respectively, was formed and isolated albeit in rather low yield (*Scheme 3*). Unlike the products obtained from the reaction with sulfines [27], **6a** and **6b** were rather stable compounds, which were fully characterized by spectroscopic methods.

Scheme 3



Attempted purification of **6a** by chromatography (SiO_2) led to an isomeric compound, isolated as a crystalline material. Along with a *singlet* at 1.56 ppm for two Me groups, the characteristic pattern of an i-Pr group (*sept.* at 2.79 and *d* at 0.89 ppm, $J = 6.7$ Hz) was observed in the ^{1}H-NMR spectrum. In the IR spectrum (KBr), the C=O absorption appeared at 1702 cm^{-1}, indicating that the strained cyclobutanone ring of **6a** (C=O at 1769 cm^{-1}) was no longer present. Based on these observations, we

postulated the structure **7f**, a fused thiophene derivative, for the product (*Scheme 4*). This structure was unambiguously confirmed by an X-ray crystal structure determination (*Fig. 2*).

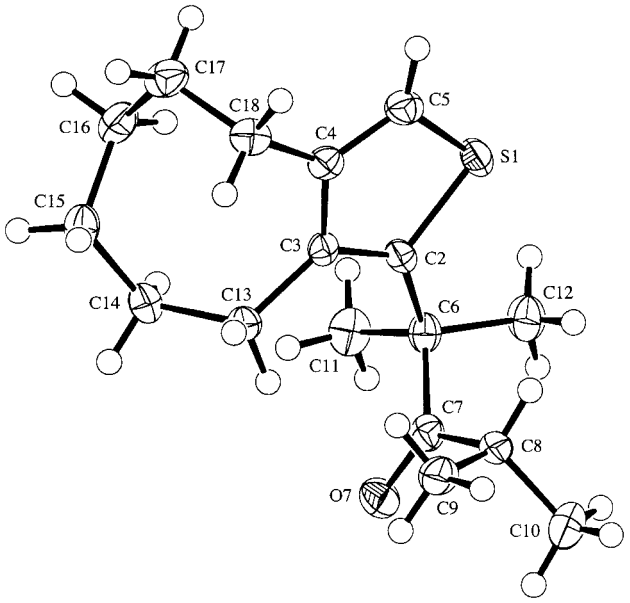


Fig. 2. *ORTEP Plot* [20] *of the molecular structure of* **7f** (with 50% probability ellipsoids)

To gain more insight into this novel isomerization, solutions of **6a** were treated with acids as well as with bases. Whereas no reaction was observed in the presence of different bases (pyridine, DBU, KF, NaOH), a fast conversion of **6a** → **7f** took place with CF_3COOH. Based on this observation, spirocyclic cyclobutanone derivatives **4a**–**g** were treated with CF_3COOH under similar conditions (*Scheme 4* and *Table 2*).

Scheme 4

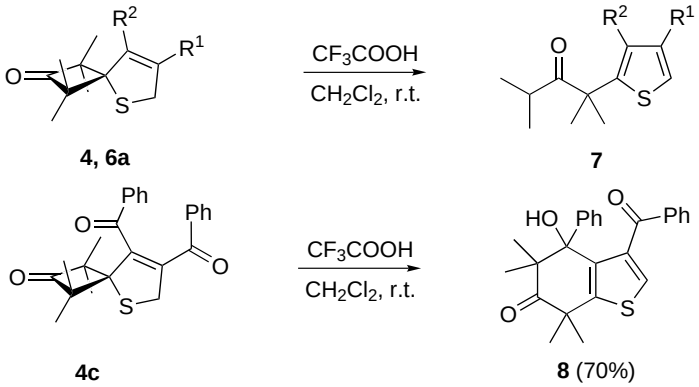


Table 2. *Acid-Catalyzed Isomerization of Spirocyclic Compounds* **4** *and* **6a** *to Thiophenes* **7**

4	R^1	R^2	Reaction Time at r.t. [h]	**7**	Yield [%]
a	MeOCO	MeOCO	48	**a**	97
b	CN	CN	48	**b**	79
d	MeOCO	H	20	**c**	93
e	H	MeOCO	120	no reaction	
f	*t*-BuOCO	H	20	**d**[a])	90
g	H	*t*-BuOCO	20	**e**[a])	53
6a	$-(CH_2)_6-$		5 min	**f**	60

[a]) The corresponding carboxylic acids were obtained.

The reactions were slower than in the case of **6a**, but, after 20–48 h at room temperature, the corresponding thiophene derivatives **7a–c** were isolated in high yields. Unexpectedly, the sterically more shielded methyl ester **4e** did not undergo the isomerization, and, even after 120 h, no corresponding isomer of type **7** could be detected. In the case of the regioisomeric *tert*-butyl esters **4f** and **4g**, the thiophene carboxylic acids **7d** and **7e**, respectively, were obtained.

It turned out that the dibenzoyl derivative **4c** in the presence of CF_3COOH does not yield the expected 3,4-dibenzoylthiophene of type **7** but a different isomeric product. In the ^{1}H-NMR spectrum, the expected signals of an i-Pr group are absent. The ^{13}C-NMR spectrum shows only two CO absorptions at 214.3 and 192.7 ppm, instead of the three signals expected for the corresponding thiophene of type **7**. The IR data confirm the conversion of the cyclobutanone ring to a less strained unit. Finally, the structure has been established by X-ray crystallography to be **8** (*Scheme 4* and *Fig. 3*), obviously formed by a secondary aldol-type cyclization.

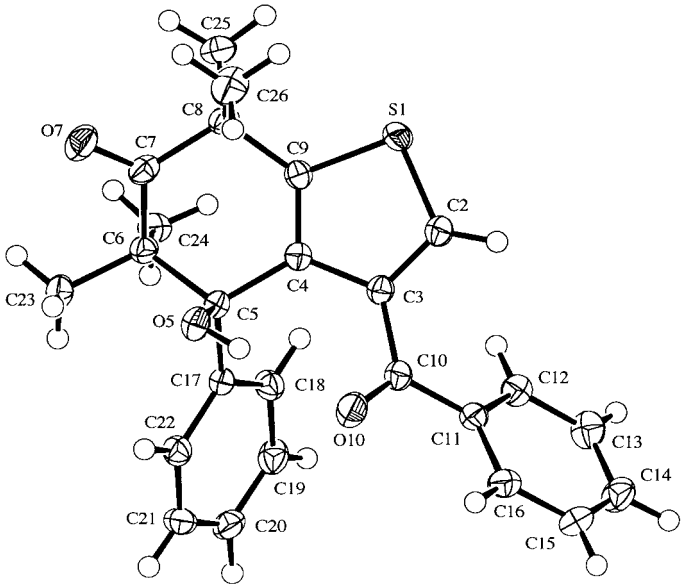
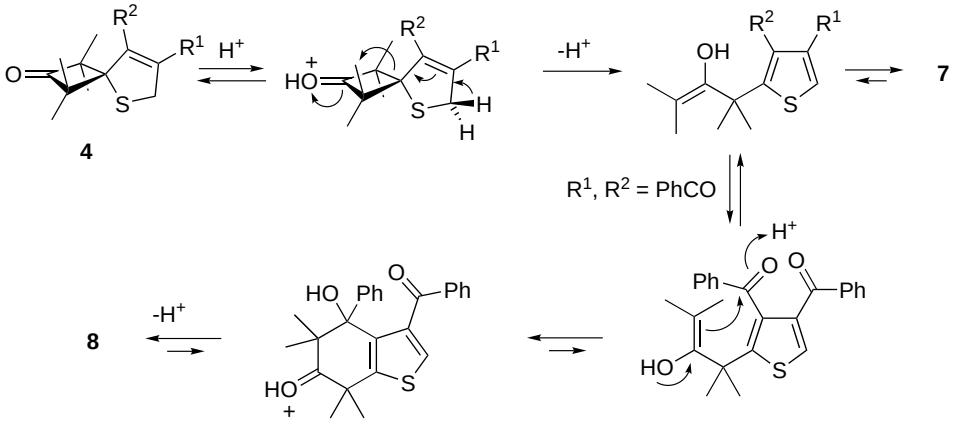


Fig. 3. *ORTEP Plot* [20] *of the molecular structure of* **8** (with 50% probability ellipsoids)

Discussion. – The results presented show that 1,3-dipolar cycloadditions of thiocarbonyl ylide **2a** with electron-poor acetylenes and the strained cyclooctyne proceed smoothly to give spirocyclic 2,5-dihydrothiophene derivatives **4** and **6a**, respectively. Apparently, the presence of alkyl, aryl, as well as amide groups as acetylene substituents reduce the dipolarophilic activity of these derivatives (*cf.* [28]), and they are not able to compete with the 1,3-dipolar electrocyclization of **2a** leading to the corresponding thiirane.

The acid-catalyzed isomerization of the primary cycloadducts **4** and **6a** to give thiophene derivatives **7** involves the ring opening of the cyclobutanone, and the driving force of this reaction is, beside the removal of transannular strain, the aromatization of the dihydrothiophene ring. A plausible mechanistic explanation of this rearrangement *via* protonation of the cyclobutanone is shown in *Scheme 5*.

Scheme 5

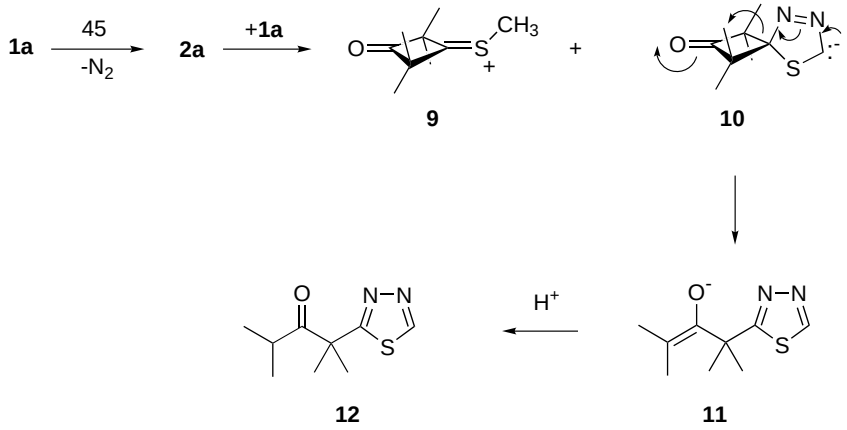


A similar aromatization/ring opening process was observed during thermal decomposition (45°) of **1a** in MeOH solution [29] (*Scheme 6*). However, in this reaction, similar to other comparable cases reported [30][31], the rearrangement occurs in an anionic system.

Many ring opening reactions of 2,2,4,4-tetramethylcyclobutane-1,3-dione induced by nucleophilic reagents such as *Grignard* reagents [32], primary amines [33], alcohols [34], as well as sulfoxonium ylides [35] are known. A similar ring opening for this dione was observed in two-phase systems ($CHCl_3$/aq. NaOH/TEBA (= benzyltriethylammonium chloride)) leading to 3-oxopentanoic acid derivatives [36]. The study presented shows that the ring opening/aromatization process can also take place under acidic conditions, even in the presence of SiO_2.

An interesting reaction is the formation of the fused thiophene derivative **8** (*Schemes 4* and *5*). We propose that, in analogy to other examples, the corresponding 3,4-dibenzoylthiophene of type **7** is formed as an intermediate. The enol form is assumed to undergo an acid-catalyzed intramolecular aldol addition to form a six-membered carbocyclic ring.

Scheme 6



We thank the analytical units of our institutes for spectra and analyses and Mr. *J. Toedtli* for his help with the X-ray crystal-structure determinations. Financial support by the *Polish State Committee for Scientific research* (Grant No. 3 TO9A 007 16), the *Swiss National Science Foundation*, and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged. *T. G.* thanks the *Dr. Helmut Legerlotz-Stiftung* for a scholarship.

Experimental Part

1. *General*. See [37]. M.p.: in capillary on a *Büchi-SMP-125* instrument; uncorrected. IR Spectra: *Perkin-Elmer FT-IR-1600*, in KBr, unless otherwise stated. NMR Spectra: *Bruker ARX 300* (^{1}H: 300 MHz, ^{13}C: 75.5 MHz) in $CDCl_3$, unless otherwise stated; ^{13}C-NMR spectra are C,H-decoupled, multiplicities deduced from DEPT measurements. EI-MS at 70 eV, CI-MS with NH_3.

2. *Starting Materials*. The 2,5-dihydro-1,3,4-thiadiazoles **1a** and **1b** were prepared according to [38][39] from 2,2,4,4-tetramethyl-3-thioxocyclobutanone and adamantane-2-thione (=tricyclo[3.3.1.1^{3,7}]decane-2-thione), resp., and CH_2N_2. *Cyclooctyne* (**5**) and *dibenzoylacetylene* (=*1,4-diphenylbut-2-yne-1,4-dione*; **3c**) were synthesized from (*Z*)-cyclooctene and 1,4-diphenylbut-2-ene-1,4-dione ('dibenzoylethene'), resp., by addition of Br_2 and twofold elimination of HBr according to the protocols in [40][41]. *Acetylenedicarboxamide* (**3d**) was prepared from dimethyl acetylenedicarboxylate (DMAD; **3a**) by treatment with conc. NH_3 [42]. Reaction of **3d** with P_2O_5 in sulfolane yielded *acetylenedicarbonitrile* (**3b**) [43]. All other acetylene derivatives, **3a**, **e**–**i**, were purchased by *Fluka* or *Aldrich*.

3. *Reaction of 2,5-Dihydro-1,3,4-thiadiazoles* **1a**,**b** *with Acetylene Derivatives* **3a**–**i** *and* **5**. 3.1. *General Procedures. Method A*. A soln. of **1** (2.0 mmol), and **3b**, **c**, or **5** (2.0 mmol) in CH_2Cl_2 (3 ml) was stirred at 42–44° for *ca*. 5 h. For the reaction of **1a** with **3d**, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (DMPU) was used as the solvent. In all cases, 1 equiv. of N_2 (*ca*. 44 ml) was evolved (gas burette). After evaporation of the solvent i.v., the residue was analyzed by ^{1}H-NMR spectroscopy; only one product was formed in each case. Usual workup gave pure products **4** and **6**, respectively.

Method B. An aliquot (2 mmol) of **1a** was dissolved in 2 ml of the acetylene derivative, **3a**, **e**–**i**, and stirred at 42–44° for *ca*. 5 h. After evaporation of excess acetylene, the crude mixture was analyzed by ^{1}H-NMR spectroscopy. Workup by distillation, crystallization, and chromatography yielded pure products.

3.2. *Dimethyl 1,1,3,3-Tetramethyl-2-oxo-5-thiaspiro[3.4]oct-7-ene-7,8-dicarboxylate* (**4a**). *Method B*; crystallization from MeOH: 410 mg (65%). M.p. 77–78.5° ([18]: 76–78°). IR: 1782*vs* (C=O), 1727 v*s* (C=O), 1435*s*, 1277*s*, 1231*s*, 1096*s*. ^{1}H-NMR: 3.85 (*s*, CH_2); 3.80, 3.74 (2*s*, 2 MeO); 1.46, 1.24 (2*s*, 4 Me). ^{13}C-NMR: 217.3 (*s*, C=O (ketone)); 165.7, 164.5 (2*s*, 2 C=O (ester)); 143.2, 141.6 (2*s*, C(7), C(8)); 73.6 (*s*, C(4)); 65.6 (*s*, C(1), C(3)); 52.5, 52.4 (2*q*, 2 MeO); 35.3 (*t*, CH_2); 26.9, 20.3 (2*q*, 4 Me). ESI-MS: 335 (100, $[M+Na]^+$), 265 (24, $[M-MeS]^+$). Anal. calc. for $C_{15}H_{20}SO_5$ (312.38): C 57.67, H 6.45, S 10.26; found: C 57.35, H 6.31, S 10.10.

3.3. *1,1,3,3-Tetramethyl-2-oxo-5-thiaspiro[3.4]oct-7-ene-7,8-dicarbonitrile* (**4b**). *Method A*; prep. TLC (SiO_2, CH_2Cl_2) and crystallization from CH_2Cl_2/hexane: 200 mg (41%). M.p. 134–136°. IR: 2230*w* (C≡N), 1790v*s* (C=O), 1260v*s*, 1095v*s*, 1015v*s*. ^{1}H-NMR: 3.96 (*s*, CH_2); 1.44, 1.41 (2*s*, 4 Me). ^{13}C-NMR: 215.2 (*s*, C=O); 131.3, 129.7 (2*s*, C(7), C(8)); 114.0, 111.9 (2*s*, 2 CN); 72.7 (*s*, C(4)); 66.9 (*s*, C(1), C(3)); 37.0 (*t*, CH_2); 25.5, 19.5 (2*q*, 4 Me). EI-MS: 247 (5, $[M+1]^+$), 246 (11, $M^{+\cdot}$), 203 (31), 175 (100), 161 (53), 147 (8), 71 (9), 70 (16). Anal. calc. for $C_{13}H_{14}N_2SO$ (246.33): C 63.39, H 5.73, S 13.03; found: C 62.90, H 5.71, S 12.30.

3.4. *7,8-Dibenzoyl-1,1,3,3-tetramethyl-5-thiaspiro[3.4]oct-7-en-2-one* (**4c**). *Method A*; crystallization from CH_2Cl_2/hexane: 510 mg (63%). M.p. 175–177° (decomp.). IR: 1780v*s* (C=O), 1654v*s* (C=O), 1597*s*, 1318*s*, 1296*s*, 1276v*s*, 760*s*, 700v*s*. ^{1}H-NMR: 7.46–7.11 (*m*, 10 arom. H); 4.14 (*s*, CH_2); 1.59, 1.36 (*s*, 4 Me). ^{13}C-NMR: 216.7 (*s*, C=O), 195.8, 192.6 (2*s*, 2 C=O); 150.4, 146.4 (2*s*, C(7), C(8)); 139.2, 137.4 (2*s*, 2 arom. C); 133.4, 132.9, 129.1, 128.3, 128.2, 128.1 (6*d*, 10 arom. CH); 77.7 (*s*, C(4)); 65.6 (*s*, C(1), C(3)); 37.3 (*t*, CH_2); 27.6, 22.2 (2*q*, 4 Me). CI-MS: 423 (18), 422 (73, $[M+NH_4]^+$), 405 (100, $[M+1]^+$), 387 (67, $[M-OH]^+$), 373 (13), 307 (28), 283 (6). Anal. calc. for $C_{25}H_{24}SO_3$ (404.54): C 74.23, H 5.98, S 7.93; found: C 73.85, H 5.78, S 7.66.

Suitable crystals for the X-ray crystal-structure determination were obtained from CH_2Cl_2/hexane.

3.5. *Methyl 1,1,3,3-Tetramethyl-2-oxo-5-thiaspiro[3.4]oct-7-ene-7-carboxylate* (**4d**) *and -8-carboxylate* (**4e**). *Method B*; 2:1 mixture of regioisomers. Fractionated crystallization from CH_2Cl_2/hexane gave 280 mg (55%) of pure **4d**. M.p. 102–103°. IR: 1771v*s* (C=O), 1709 v*s* (C=O), 1638*m*, 1446*m*, 1343*s*, 1255*s*, 1233*m*, 1084*s*. ^{1}H-NMR: 6.95 (*t*, *J* = 2.0, CH); 3.87 (*d*, *J* = 2.0, CH_2); 3.79 (*s*, MeO); 1.32, 1.15 (2*s*, 4 Me). ^{13}C-NMR: 219.7 (*s*, C=O (ketone)); 163.9 (*s*, C=O (ester)); 143.7 (*d*, CH); 134.1 (*s*, C(7)); 72.2 (*s*, C(4)); 65.4 (*s*, C(1), C(3)); 51.9 (*q*, MeO); 36.0 (*t*, CH_2); 24.0, 20.1 (2*q*, 4 Me). ESI-MS: 277 (100, $[M+Na]^+$), 207 (44), 173 (37), 157 (6). Anal. calc. for $C_{13}H_{18}SO_3$ (254.35): C 61.39, H 7.13, S 12.61; found: C 61.40, H 7.11, S 12.41.

Prep. TLC of the mother liquor (Al_2O_3, hexane/AcOEt 12:1), followed by crystallization from hexane, yielded 130 mg (25%) of pure **4e**. M.p. 75–77°. IR: 1778v*s* (C=O), 1715v*s* (C=O), 1439*s*, 1326*s*, 1343*s*, 1258*s*, 1230*s*, 1194*s*, 1104*s*, 1006*m*, 970*m*, 729*m*. ^{1}H-NMR: 7.21 (*t*, *J* = 2.9, CH); 3.74 (*s*, MeO); 3.73 (*d*, *J* = 2.9, CH_2); 1.43, 1.11 (2*s*, 4 Me). ^{13}C-NMR: 218.0 (*s*, C=O (ketone)); 165.1 (*s*, C=O (ester)); 145.3 (*d*, CH); 137.4 (*s*, C(8)); 72.4 (*s*, C(4)); 64.7 (*s*, C(1), C(3)); 51.8 (*q*, MeO); 34.7 (*t*, CH_2); 27.6, 20.3 (2*q*, 4 Me). ESI-MS: 277 (100, $[M+Na]^+$), 207 (12). Anal. calc. for $C_{13}H_{18}SO_3$ (254.35): C 61.39, H 7.13, S 12.61; found: C 61.19, H 7.08, S 12.67.

3.6. tert-*Butyl 1,1,3,3-Tetramethyl-2-oxo-5-thiaspiro[3.4]oct-7-ene-7-carboxylate* (**4f**) *and -8-carboxylate* (**4g**). *Method B*; 9:1 mixture of regioisomers. Fractionated crystallization from hexane gave 440 mg (75%) of pure **4f**. M.p. 130–132°. IR ($CHCl_3$): 1765v*s* (C=O), 1705v*s* (C=O), 1370*s*, 1280*s*, 1160v*s*, 1090*s*. ^{1}H-NMR: 6.83 (*t*, *J* = 2.1, CH); 3.82 (*d*, *J* = 2.1, CH_2); 1.50 (*s*, *t*-Bu); 1.31, 1.15 (2*s*, 4 Me). ^{13}C-NMR: 220.1 (*s*, C=O (ketone)); 162.8 (*s*, C=O (ester)); 142.4 (*d*, CH); 136.1 (*s*, C(7)); 81.4 (*s*, Me_3C); 72.0 (*s*, C(4)); 65.3 (*s*, C(1), C(3)); 36.1 (*t*, CH_2); 28.0 (*q*, Me_3C); 24.0, 20.1 (2*q*, 4 Me). CI-MS: 315 (7), 314 (41, $[M+NH_4]^+$), 297 (3, $[M+1]^+$), 260 (6), 259 (13), 258 (100), 141 (6). Anal. calc. for $C_{16}H_{24}SO_3$ (296.26): C 64.87, H 8.11, S 10.82; found: C 64.62, H 8.01, S 10.52.

The minor isomer **4g** could not be obtained in pure form by prep. TLC. The following data were taken from the spectra of the mixture **4f**/**4g**: ^{1}H-NMR: 7.10 (*t*, *J* = 2.9, CH); 3.68 (*d*, *J* = 2.9, CH_2); 1.48 (*s*, *t*-Bu); 1.45, 1.23 (2*s*, 4 Me). ^{13}C-NMR: 213.5 (*s*, C=O (ketone)); 164.0 (*s*, C=O (ester)); 151.6 (*d*, CH); 144.4 (*s*, C(7)); 83.9 (*s*, Me_3C); 75.9 (*s*, C(4)); 64.5 (*s*, C(1), C(3)); 34.4 (*t*, CH_2); 27.8 (*q*, Me_3C); 25.2, 21.0 (2*s*, 4 Me).

3.7. *1′,3′,4′,5′,6′,7′,8′,9′-Octahydro-2,2,4,4-tetramethylspiro[cyclobutane-1,1′-cycloocta[*c*]thiophene]-3-one* (**6a**). *Method A*; distillation (bulb-to-bulb, 120°/10^{-2} Torr), followed by crystallization from pentane: 210 mg (38%). M.p. 52–54°. IR: 2936*s*, 1769v*s* (C=O), 1468*m*, 1440*m*. ^{1}H-NMR: 3.44 (*s*, CH_2S); 2.21–2.27, 1.68–1.50, 1.31–1.26, 0.90–0.88 (4*m*, 6 CH_2); 1.44, 1.12 (2*s*, 4 Me). ^{13}C-NMR: 221.6 (*s*, C=O), 138.8, 138.3 (2*s*, C(3′a), C(9′a)); 75.7 (*s*, C(1)); 64.5 (*s*, C(2), C(4)); 37.1 (*t*, CH_2S); 31.9, 30.5, 27.4, 26.5, 26.1 (5*t*, 6 CH_2); 27.1, 20.5 (2*q*, 4 Me). CI-MS: 296 (14, $[M+NH_4]^+$), 281 (6), 280 (19), 279 (100, $M^{+\cdot}$). Anal. calc. for $C_{17}H_{26}SO$ (278.45): C 73.33, H 9.41, S 11.51; found: C 73.05, H 9.26, S 11.28.

3.8. *1,3,4,5,6,7,8,9-Octahydrospiro[cycloocta[*c*]thiophene-1,2′-tricyclo[3.3.1.1^{3,7}]decane]* (**6b**). *Method A*; distillation (bulb-to-bulb, 110°/10^{-2} Torr): 180 mg (30%). Colorless oil. IR ($CHCl_3$): 2920v*s*, 2847*s*, 1448*m*. ^{1}H-NMR: 3.31 (*s*, CH_2S); 2.60–2.64, 2.30–2.35, 1.37–2.10 (3*m*, 4 CH, 11 CH_2). ^{13}C-NMR: 140.9, 137.1 (2*s*, C=C); 74.0 (*s*, C(1)); 39.3, 39.0, 26.4, 26.0 (4*d*, 4 CH); 38.8 (*t*, CH_2S); 37.8, 37.4, 36.4, 34.5, 32.6, 29.6, 29.1, 27.5, 27.4, 26.6, 24.7 (11*t*, 11 CH_2). EI-MS: 288 (42, $M^{+\cdot}$), 253 (10), 243 (14), 181 (11), 180 (69), 168 (12), 167 (100), 161 (10), 147 (20), 137 (18), 135 (21), 133 (11), 131 (11), 122 (21), 121 (11), 115 (13), 111 (12), 107 (11), 105 (34), 97 (38), 93 (27).

3.9. *Reactions of* **1a** *with* **3d**, **g**–**i**. According to *Method A*, a soln. of **1a** and **3d** in 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (DMPU) was stirred at *ca.* 43° for 5 h. The only new product was *4,4,6,6-*

tetramethyl-1-thiaspiro[2.3]hexan-5-one (thiirane); **3d** was recovered in quant. yield. The same thiirane was formed as the sole product, when soln. of **1a** in **3g**, **3h** or **3i** were stirred at 42–45° (*Method B*).

4. *Acid-Catalyzed Rearrangement of 2,5-Dihydrothiophenes* **4** *and* **6a**. *General Procedure*. To a soln. of **4** or **6a** (1.0 mmol) in CH_2Cl_2 (3 ml) was added CF_3COOH (0.3 ml). The mixture was stirred at r.t. for 20–48 h in the case of **4** and 5 min in the case of **6a** (see *Table 2*). After evaporation of the solvent, the residue was analyzed by ^{1}H-NMR spectroscopy, and the product was purified by crystallization, distillation, or chromatography.

4.1. *Dimethyl 2-(1,1,3-Trimethyl-2-oxobutyl)thiophen-3,4-dicarboxylate* (**7a**). From **4a**, 48 h, crystallization from hexane: 300 mg (97%). M.p. 104–106°. IR: 1728v*s* (C=O), 1467*s*, 1278*s*, 1237*s*. ^{1}H-NMR: 7.91 (*s*, CH); 3.84, 3.83 (2*s*, 2 MeO); 2.97 (*sept.*, $J = 6.7$, Me_2CH); 1.57 (*s*, Me_2C); 1.00 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 213.7 (*s*, C=O (ketone)); 165.9, 162.2 (2*s*, 2 C=O (ester)); 149.2, 132.9 (2*s*, C(3), C(4)); 131.0 (*s*, C(2)); 130.2 (*d*, C(5)); 52.3, 52.0 (2*q*, 2 MeO); 51.3 (*s*, Me_2C); 35.4 (*d*, Me_2CH); 26.0, 20.6 (2*q*, 4 Me). CI-MS: 331 (17), 330 (100, $[M+NH_4]^+$), 313 (21, $[M+1]^+$), 299 (10), 298 (72). Anal. calc. for $C_{15}H_{20}SO_5$ (312.38): C 57.67, H 6.45, S 10.26; found: C 57.67, H 6.53, S 10.19.

4.2. *2-(1,1,3-Trimethyl-2-oxobutyl)thiophen-3,4-dicarbonitrile* (**7b**). From **4b**, 48 h: 190 mg (79%) crude **7b**. The product could not be purified as it decomposes easily. *Data of Crude* **7b**: ^{1}H-NMR ($(CD_3)_2CO$): 8.37 (*s*, CH); 2.97 (*sept.*, $J = 6.7$, Me_2CH); 1.68 (*s*, Me_2C); 0.96 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR ($(CD_3)_2CO$): 212.2 (*s*, C=O); 162.1, 159.7 (2*s*, C(3), C(4)); 136.5 (*d*, C(5)); 130.1 (*s*, C(2)); 118.0, 114.2 (2*s*, 2 CN); 52.7 (*s*, Me_2C); 35.9 (*d*, Me_2CH); 25.5, 19.4 (2*q*, 4 Me).

4.3. *Methyl 5-(1,1,3-Trimethyl-2-oxobutyl)thiophen-3-carboxylate* (**7c**). From **4d**, 20 h, distillation (bulb-to-bulb, 110°/$1.7 \cdot 10^{-2}$ Torr): 240 mg (93%). Colorless oil. IR (neat): 2975*s*, 1714v*s* (C=O), 1451*s*, 1242v*s*, 1092*s*. ^{1}H-NMR: 8.01 (*d*, $J = 1.3$, H–C(4)); 7.37 (*d*, $J = 1.3$, H–C(2)); 3.87 (*s*, MeO); 2.99 (*sept.*, $J = 6.7$, Me_2CH); 1.59 (*s*, Me_2C); 0.93 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 215.4 (*s*, C=O (ketone)); 163.3 (*s*, C=O (ester)); 149.5 (*s*, C(3)); 133.0 (*s*, C(5)); 132.0 (*d*, C(4)); 124.9 (*d*, C(2)); 51.8 (*q*, MeO); 50.8 (*s*, Me_2C); 34.6 (*d*, Me_2CH); 25.7, 20.6 (2*q*, 4 Me). CI-MS: 274 (10), 273 (25), 272 (100, $[M+NH_4]^+$), 183 (22, $[M-(i\text{-}Pr)]^+$). Anal. calc. for $C_{13}H_{18}SO_3$ (254.35): C 61.39, H 7.13, S 12.61; found: C 61.20, H 7.18, S 12.20.

4.4. *5-(1,1,3-Trimethyl-2-oxobutyl)thiophen-3-carboxylic Acid* (**7d**). From **4f**, 20 h, crystallization from hexane: 220 mg (90%). M.p. 108–109°. IR ($CHCl_3$): 2935*s*, 1705v*s* (C=O), 1690v*s* (C=O), 1465*s*, 1260v*s*, 1015*s*, 995*s*. ^{1}H-NMR: 11.8 (br. *s*, OH); 8.14, 7.40 (2*d*, $J = 1.3$, H–C(5), H–C(2)); 3.00 (*sept.*, $J = 6.7$, Me_2CH); 1.60 (*s*, Me_2C); 0.94 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 214.9 (*s*, C=O (ketone)); 167.8 (*s*, COOH); 150.0 (*s*, C(3)); 133.8 (*d*, C(4)); 132.4 (*s*, C(5)); 124.9 (*d*, C(2)); 50.9 (*s*, Me_2C); 35.7 (*d*, Me_2CH); 25.8, 20.6 (2*q*, 4 Me). CI-MS: 259 (7), 258 (100, $[M+NH_4]^+$), 169 (24), 153 (11), 152 (24). Anal. calc. for $C_{12}H_{16}SO_3$ (240.21): C 59.97, H 6.71, S 13.34; found: C 59.84, H 6.52, S 13.39.

4.5. *2-(1,1,3-Trimethyl-2-oxobutyl)thiophene-3-carboxylic Acid* (**7e**). Mixture of **4f**/**4g**, 20 h, prep. TLC (SiO_2, CH_2Cl_2/MeOH 9:1) and crystallization from hexane/Et_2O: 220 mg (53%). M.p. 61–64°. The substance contained small amounts of its isomer **7d**. ^{1}H-NMR: 7.56, 7.15 (2*d*, $J = 5.7$, H–C(4), H–C(5)); 2.93 (*sept.*, $J = 6.7$, Me_2CH); 1.66 (*s*, Me_2C); 1.04 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 214.3 (*s*, C=O (ketone)); 166.8 (*s*, COOH); 160.7 (*s*, C(2)); 131.4 (*d*, C(4)); 127.2 (*s*, C(3)); 121.6 (*d*, C(5)); 52.0 (*s*, Me_2C); 36.0 (*d*, Me_2CH); 27.1, 20.5 (2*q*, 4 Me). CI-MS: 258 (8, $[M+NH_4]^+$), 249 (26), 241 (5, $[M+1]^+$), 233 (11), 232 (100), 190 (6), 172 (28).

4.6. *2-(3,4,5,6,7,8-Hexahydrocycloocta[*c*]thiophen-1-yl)-2,4-dimethylpentan-3-one* (**7f**). From **6a**, 5 min, prep. TLC (SiO_2, hexane/AcOEt 10:1) and crystallization from pentane: 170 mg (60%)[3]. IR: 2928*s*, 1702v*s* (C=O), 1467*s*, 1039*m*, 736*m*. ^{1}H-NMR: 6.81 (*s*, CH); 2.79 (*sept.*, $J = 6.7$, Me_2CH); 2.61 (*t*, $J = 6.3$, CH_2); 2.42 (*t*, $J = 6.1$, CH_2); 1.61 (*m*, 2 CH_2); 1.56 (*s*, Me_2C); 1.54 (*m*, CH_2); 1.42 (*m*, CH_2); 0.89 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 216.5 (*s*, C=O); 144.9 (*s*, C(3′a)); 140.4 (*s*, C(1′)); 139.1 (*s*, C(9′a)); 117.5 (*d*, CH); 50.8 (*s*, Me_2C); 35.1 (*d*, Me_2CH); 31.8, 31.7, 27.6, 26.2, 26.0, 25.8 (6*t*, 6 CH_2); 26.1, 21.0 (2*q*, 4 Me). EI-MS: 278 (3, $M^{+\cdot}$), 209 (5), 208 (14), 207 (100, $[M-(C_3H_7C=O)]^+$), 164 (6), 136 (8), 122 (6), 111 (6), 91 (6). Anal. calc. for $C_{17}H_{26}SO$ (278.45): C 73.33, H 9.41, S 11.51; found: C 73.27, H 9.45, S 11.60.

Crystals suitable for an X-ray crystal-structure determination were grown from pentane/CH_2Cl_2/acetone.

4.7. *3-Benzoyl-4-hydroxy-5,5,7,7-tetramethyl-4-phenylbenzo[*b*]thiophen-6-one* (**8**). From **4c**, 48 h, crystallization from MeOH: 283 mg (70%). M.p. 166–168°. IR: 1715v*s* (C=O), 1634v*s* (C=O), 1453v*s*, 1237v*s*, 990*s*, 740*s*. ^{1}H-NMR: 7.65 (*s*, H–C(2)); 7.00–7.64 (*m*, 10 arom. H); 5.84 (*s*, OH); 1.70, 1.65, 1.34, 0.95 (4*s*, 4 Me). ^{13}C-NMR: 214.3 (*s*, C=O); 192.7 (*s*, C=O (benzoyl)); 148.9, 143.5, 139.9, 139.6, 138.0 (5*s*, 5 C); 135.8, 132.6, 129.6, 128.1, 127.2, 126.9, 126.6 (7*d*, 11 CH); 79.0 (*s*, C(4)); 53.4, 45.7 (2*s*, C(5), C(7)); 32.4, 30.8, 22.2, 21.8 (4*q*,

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[3]) In this case, the reaction took also place in the presence of SiO_2 instead of CF_3COOH. On the other hand, no reaction was observed in the presence of pyridine, DBU, KF, or NaOH.

4 Me). CI-MS: 404 (<1, $M^{+\cdot}$), 389 (8), 388 (26), 387 (100, $[M-OH]^+$), 355 (4), 255 (5). Anal. calc. for $C_{25}H_{24}SO_3$ (404.54): C 74.23, H 5.98, S 7.93; found: C 74.03, H 5.95, S 7.81.

Crystals suitable for an X-ray crystal-structure determination were obtained from CH_2Cl_2/hexane.

4.8. *Attempted Isomerization of* **4e**. According to the *General Procedure*, a CH_2Cl_2 soln. of **4e** and CF_3COOH was stirred at r.t. for 20 and 48 h. As no product could be detected by TLC, the reaction time was prolonged up to 120 h, but no product was formed. The starting material **4e** was recovered in almost quant. yield.

5. *Crystal-Structure Determination of* **4c**, **7f**, *and* **8** (see *Table 3* and *Figs. 1–3*)[4]). All measurements were performed on a *Rigaku AFC5R* diffractometer with graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12-kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects but not for absorption. Data collection and refinement parameters are given in *Table 3*, views of the molecules are shown in *Figs. 1–3*. The structure was solved by direct methods using SIR92 [44] in the cases of **4c** and **8**, and SHELXS97 [45] in the case of **7f**, which revealed the position of all non-H-atoms. The non-H-atoms were

Table 3. *Crystallographic Data of Compounds* **4c**, **7f**, *and* **8**

	4c	**7f**	**8**
Crystallized from	CH_2Cl_2/hexane	pentane/CH_2Cl_2/acetone	MeOH
Empirical formula	$C_{25}H_{24}O_3S$	$C_{17}H_{26}OS$	$C_{25}H_{24}O_3S$
Formula weight [g mol^{-1}]	404.52	278.45	404.52
Crystal color, habit	pale-yellow, prism	colorless, tablet	colorless, tablet
Crystal dimensions [mm]	$0.40\times0.42\times0.45$	$0.12\times0.30\times0.46$	$0.18\times0.45\times0.50$
Temp. [K]	273(1)	173(1)	173(1)
Crystal system	triclinic	orthorhombic	monoclinic
Space group	$P\bar{1}$	*Pbcn*	$P2_1/c$
Z	2	8	4
Reflections for cell determination	25	25	25
2θ Range for cell determination [°]	37–40	30–39	36–40
Unit cell parameters a [Å]	11.625(3)	18.237(3)	16.121(2)
b [Å]	13.012(2)	15.310(2)	8.387(2)
c [Å]	8.0200(9)	11.266(1)	15.281(2)
α [°]	93.08(1)	90	90
β [°]	107.86(1)	90	91.597(9)
γ [°]	109.62(1)	90	90
V [Å^3]	1070.9(4)	3145.4(7)	2065.3(5)
D_x [g cm^{-3}]	1.254	1.176	1.301
μ(MoK_α) [mm^{-1}]	0.174	0.197	0.180
Scan type	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
$2\theta_{(max)}$ [°]	55	55	55
Total reflections measured	5168	4700	5249
Symmetry independent reflections	4926	3615	4738
Reflections used [$I>2\sigma(I)$]	3536	2237	3563
Parameters refined	359	173	267
Final R	0.0434	0.0463	0.0421
wR ($w=[\sigma^2(F_o)+(0.005F_o)^2]^{-1}$)	0.0399	0.0387	0.0404
Goodness of fit	1.987	1.569	1.705
Secondary extinction coefficient	$3.4(2)\times10^{-6}$	$3.9(3)\times10^{-7}$	$5.0(4)\times10^{-7}$
Final Δ_{max}/σ	0.0002	0.0003	0.0002
$\Delta\rho$ (max; min) [e Å^{-3}]	0.22; −0.21	0.30; −0.24	0.33; −0.23

[4]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-167147–167149 for **7f**, **8**, and **4c**, resp. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44-(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

refined anisotropically. All of the H-atoms in **4c** were located in a difference-electron-density map, and their positions were allowed to refine together with individual isotropic displacement parameters. In the case of **7f**, all of the H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom. In the case of **8**, the OH H-atom was placed in the position indicated by a difference-electron-density map, and its position was allowed to refine together with an isotropic displacement parameter. All of the remaining H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom. Refinement of the structures was carried out on F by full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was applied in each case. Neutral-atom-scattering factors for non-H-atoms were taken from [46a] and the scattering factors for H-atoms from [47]. Anomalous dispersion effects were included in F_c [48]; the values for f' and f'' were those of [46b], and the values of the mass attenuation coefficients were those of [46c]. All calculations were performed using the teXsan crystallographic software package [49].

In **4c**, the five-membered ring has an envelope conformation with S(1)[5]) as the envelope flap; the deviation from the least-squares plane defined by C(2) to C(5) (mean deviation 0.023 Å) is 0.487(1) Å. The two C=O C-atoms C(13) and C(20) are in the same plane as C(2) to C(5), but the benzoyl moieties at C(3) and C(4) are twisted out of this plane considerably (torsion angles C(4)–C(3)–C(13)–C(14) 44.7(2)°, C(3)–C(13)–C(14)–C(15) 28.3(3)° and C(3)–C(4)–C(20)–C(21) 51.9(3)°, C(4)–C(20)–C(21)–C(26) 9.7(3)°), and the two C=O groups are oriented almost antiparallel.

The structure of **7f** consists of fused five- and eight-membered rings, whereby the thiophene ring is planar (mean deviation 0.002 Å), and the cyclooctane ring is puckered.

The OH group of **8** forms an intramolecular H-bond with the O(10)-atom of the benzoyl group at C(3) of the thiophene ring. This interaction forms a seven-membered ring with a graph set motif of S(10) [50]. The five-membered ring is essentially planar (mean deviation from plane 0.012 Å), while the fused six-membered ring has an envelope conformation with C(6) as the envelope flap (mean deviation of the plane defined by C(4), C(5), C(7) to C(9): 0.030 Å; deviation of C(6) –0.665(2) Å).

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