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Unambiguous Identification of Regioisomeric Tetrathiafulvalenes by Mass Spectrometry: Application to Dihalogeno Derivatives and the First Synthesis of 4,4′(5′)-Dichlorotetrathiafulvalene

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Introduction

Lithiation of tetrathiafulvalene (TTF) derivatives, followed by trapping with electrophilic reagents, constitutes a very useful approach to the synthesis of substituted tetrathiafulvalenes.[1] As first recognised by Green,[2] tetrathiafulvalenyllithium undergoes disproportionation to multilithiated species, so the formation of small quantities of disubstituted products cannot usually be avoided, even when using 1 equiv of base. In these cases and, of course, when an excess of base is used, the regiochemical outcome of the reaction seems to depend on the nature of the substituent introduced first. Thus, electron-donating groups, such as Me, direct the second lithiation to the unsubstituted ring,[2b] whereas electron-withdrawing groups, such as COOEt[2b] or CN[3] increase the acidity of the adjacent hydrogen atoms, giving rise to 4,5-disubstituted derivatives.

On the other hand, the situation is less clear-cut for chalcogen- and halogen-substituted tetrathiafulvalenes. Thus, the formation of 4,5-bis(alkylthio) and 4,5-bis(alkylseleno) derivatives has been explained[4] on the basis of the slightly increased acidity of the hydrogen atom adjacent to the chalcogen substituent, but regioisomers of general structure **2**, such as **2d**,[5] **2e**,[6] and 4,4′(5′)-bis(ethyltelluro)TTF,[7] have also been obtained in other lithiation reactions. With regard to halotetrathiafulvalenes, the sequence lithiation/halogenation is reported to give not only the 4,5-isomers **1g**[8,9] and **1h**[3b,8] but also the 4,4′(5′)-regioisomer **2f**.[10] These observations, supported by X-ray diffraction studies in some instances,[9,10] have been rationalized by a combination of the above-mentioned pK_a arguments and steric effects.[10] Nevertheless, there is one report in the literature[11] describing the formation of 4,4′(5′)-dibromotetrathiafulvalene (**2g**) and its dichloro analogue (**2h**). This structural assignment was made on the basis of NMR data only and, unfortunately, the chemical shifts of the hydrogen atoms in halotetrathiafulvalene derivatives do not differ greatly from those of TTF itself,[8] thus making such a positive assignment doubtful.

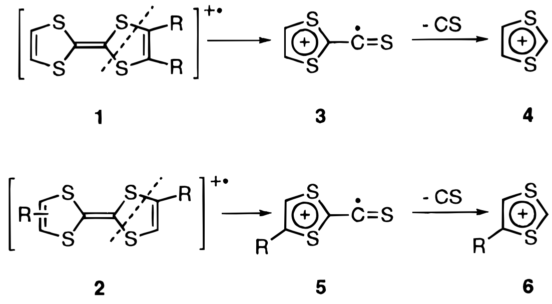
Chart 1

1a-d, g, h **2a-h**

a: R = Me **b**: R = CH_2OH **c**: R = COOMe **d**: R = SMe

e: R = TePh **f**: R = I **g**: R = Br **h**: R = Cl

Scheme 1



In this paper we report the unambiguous identification of regioisomeric disubstituted tetrathiafulvalenes (Chart 1) by means of low-resolution mass spectrometry. Using this technique we show that the previously reported 4,4′(5′)-dichlorotetrathiafulvalene (**2h**) is actually 4,5-dichlorotetrathiafulvalene (**1h**), an assignment which is further confirmed by the first unequivocal synthesis of **2h**.

Results and Discussion

Taking advantage of our experience in the mass spectrometry of tetrathiafulvalene derivatives,[12] we studied the mass spectral behavior of several pairs of regioisomers (**1a**−**d**, **2a**−**d**) bearing either electron-donating or electron-withdrawing substituents. All compounds were prepared as previously described (see Experimental Section), making use of coupling reactions of adequately substituted 1,3-dithiole derivatives to ensure their regioisomeric purity. These compounds exhibited a well-defined fragmentation pattern under electron impact ionization that resembled that of TTF itself[13] regardless of the substituents. The most abundant fragment ions were those resulting from the processes depicted in Scheme 1. For compounds **1**, cleavage of molecular ions preferentially occurred at the substituted ring in such a way that unsubstituted ions **3** (*m*/*z* 146) and **4** (*m*/*z* 102)

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Table 1. ***m/z* Values[a] and Intensities (Relative to the Base Peak) of Relevant Ions in the Mass Spectra of Compounds 1 and 2**

product	$M^{+\bullet}$	**3**	**4**	product	$M^{+\bullet}$	**5**	**6**
1a	232 (100)	146 (8)	102 (24)	**2a**	232 (100)	160 (10)	116 (42)
1b	264 (100)	146 (44)	102 (45)	**2b**	264 (100)	176 (28)	132 (32)
1c	320 (100)	146 (52)	102 (35)	**2c**	320 (100)	204 (43)	160 (15)
1d	296 (100)	146 (80)	102 (37)	**2d**	296 (100)	192 (22)	148 (18)
				2e[b]	614 (40)	352 (32)	308 (7)
				2f	456 (100)	272 (75)	228 (14)
1g	362 (76)	146 (100)	102 (28)	**2g**	362 (100)	226 (48)	182 (24)
1h	272 (100)	146 (60)	102 (65)	**2h**	272 (100)	180 (32)	136 (61)

[a] Of the most abundant isotopic ions. Ions **5** and **6** are absent in the spectra of compounds **1**. Ions **3** and **4** are absent in the spectra of compounds **2**. [b] Base peak at *m/z* 77 ($C_6H_5^+$).

were generated. On the other hand, compounds **2** gave rise to monosubstituted radical ions **5** (*m/z* = M/2 + 44) and **6** (*m/z* = M/2). Thus, the EI mass spectra of compounds **1a**–**d** clearly differ from those of their regioisomers **2a**–**d** (Table 1).

In order to further test the reliability of this methodology, we also studied the mass spectra of compounds **2e**[6] and **2f**,[10] whose structures have been determined by X-ray diffraction. As expected, they showed ions **5** and **6**, but not **3** or **4**.

The marked differences observed between the mass spectra of regioisomeric tetrathiafulvalenes, together with the aforementioned conflicting reports on dichloro- and dibromotetrathiafulvalenes, prompted us to carry out a mass spectral study of these interesting compounds.[14]

Dibromotetrathiafulvalenes were studied first. As expected, the dibromo derivative arising from the reactions of tetrathiafulvalenyllithium with either TsBr[8] or NBS was identical in all respects to that obtained using 1,2-dibromotetrachloroethane[9] and was identified as **1g**. On the other hand, the reaction of lithiated TTF with bromine[11] afforded a compound whose melting point and ^{1}H NMR data closely resembled those of **1g**, although minor differences between their ^{13}C NMR spectra were apparent. A comparison of their EI spectra (Figure 1) made it immediately clear that this product was **2g** (ions at *m/z* 226 and 182[15]), thus confirming the previous assignment.[11] This result, which has remained relatively unnoticed in the literature, reveals that the electrophile used to trap lithiated TTF plays a role in determining the regiochemistry of these reactions and casts some doubt on the currently accepted explanations based solely on the increased acidity of the adjacent hydrogen atom and/or steric effects.

We next turned our attention to dichlorotetrathiafulvalenes, for which no X-ray diffraction data are available. Although the reactions of tetrathiafulvalenyllithium with TsCl and NCS are reported to afford **1h**[8] and **2h**,[11] respectively, we found, to our surprise, that the same compound was obtained in both reactions. Its mass spectrum (showing ions at *m/z* 102 and 146) clearly pointed to structure **1h**, as reported by Bryce,[8] and not to **2h** (Figure 2).

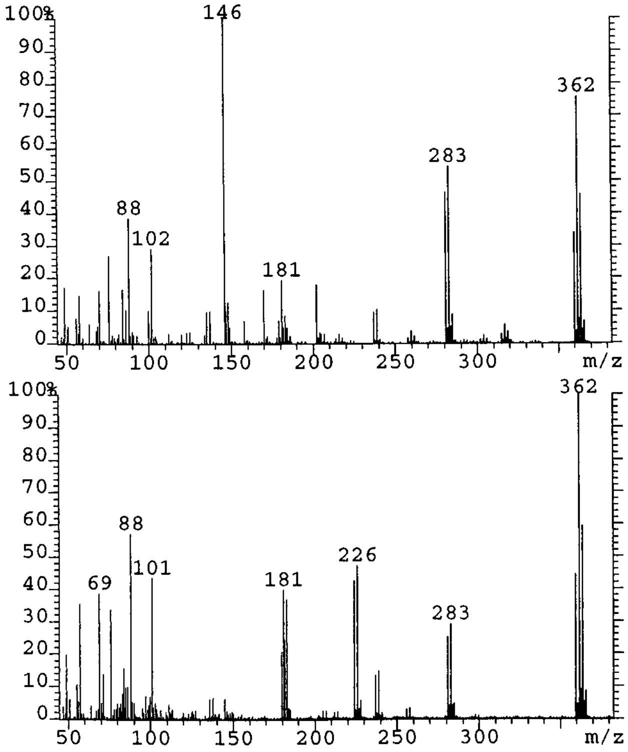

Figure 1. EI mass spectrum of **1g** (top) and **2g** (bottom).

At this point, an unambiguous (and presumably the first) synthesis of **2h** was required (Scheme 2). To that end, it was thought that compound **9** would be an adequate precursor, since the ester groups should be easily removed. We first attempted its synthesis by a similar approach to that described by Neiland *et al.*[16] for the preparation of **2f**, namely, double lithiation of **2c**, followed by treatment with *N*-chlorosuccinimide. Compound **9** was isolated, but the yields were low and an alternative, more efficient route was sought. A phosphite-mediated coupling of the previously undescribed thione **8** seemed promising, due to presence of the COOMe group, so we prepared it by sequential treatment of compound **7**[17] with LDA and TsCl, which constitutes a new, straightforward route to 4,5-disubstituted-1,3-dithiole-2-thiones. As expected, treatment of **8** with trimethyl phosphite gave (*Z/E*)-**9**, which, upon decarbomethoxylation with LiBr in HMPA afforded **2h** as a *ca.* 1:1 mixture of *Z* and *E* isomers (^{1}H NMR spectrum). Its EI mass spectrum showed the expected peaks at *m/z* 136 and 180 (Figure 2), thus demonstrating that the previous structural assignment[11] was in error and, therefore, that tetrathiafulvalene derivative **2h** had not previously been prepared. Furthermore, this result

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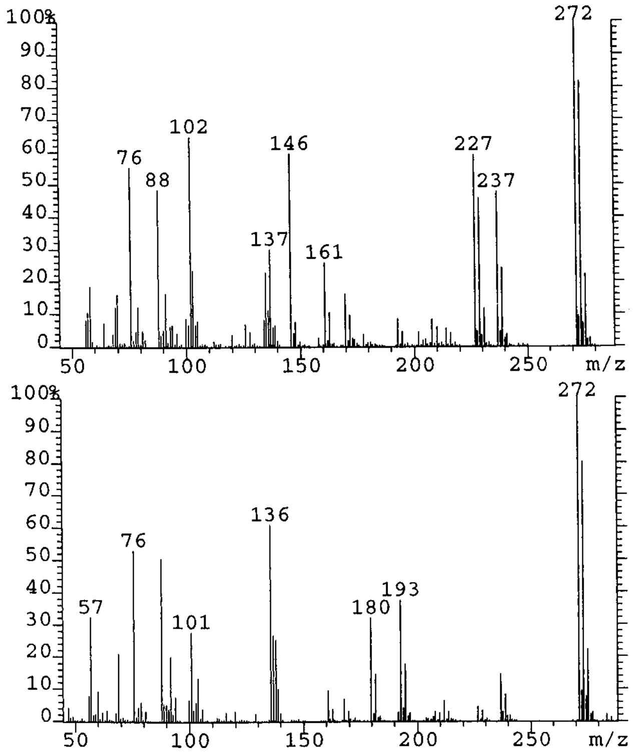
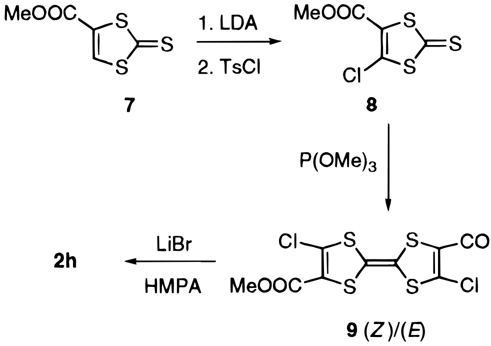


Figure 2. EI mass spectrum of **1h** (top) and **2h** (bottom).

Scheme 2



confirms the usefulness of mass spectrometry in assessing the structure of regioisomeric tetrathiafulvalenes.

In summary, low-resolution mass spectrometry allows the unambiguous structural assignment of regioisomers in the TTF series. This technique is especially advantageous when no single-crystals are available for X-ray studies and when NMR data do not allow a clear distinction between the two possible structures, as is the case for halogeno-substituted tetrathiafulvalenes. Its predictive power has been confirmed by the fragmentation pattern displayed by the hitherto undescribed 4,4′(5′)-dichlorotetrathiafulvalene (**2h**). Its synthesis has been achieved in three steps, the first of which involves the lithiation of **7**, an unprecedented reaction that paves the way to other 4,4′(5′)-disubstituted tetrathiafulvalenes.

Experimental Section

NMR spectra were recorded at 300 MHz for ^{1}H and at 75.4 MHz for ^{13}C. Mass spectra were recorded on a VG Autospec spectrometer, under the conditions previously described.[12]

Compounds **1a**,[18] **1b**,[19] **1c**,[20] **1d**,[21] **2a**,[22] **2b**,[23] **2c**,[23] and **2d**[24] have been reported in the literature. Compounds **2e** and **2f** were kindly supplied by Prof. J. Y. Becker. Compounds **1g**,[8] **1h**,[8] and **2g**[11] were prepared as previously reported and, alternatively for **1g** and **1h**, using the corresponding *N*-halosuccinimide.

Reaction of Tetrathiafulvalenyllithium with NBS. To a stirred solution of LDA (5.5 mmol), freshly prepared from diisopropylamine (0.555 g, 5.5 mmol) and *n*-BuLi (1.6 M in hexanes, 3.5 mL), in dry Et_2O (50 mL) at −78 °C under nitrogen, was added commercial TTF (1.020 g, 5 mmol). After 1 h, a solution of NBS (0.89 g, 5 mmol) in dry THF (10 mL) was added dropwise during 15 min. The reaction mixture was kept at −78 °C for 1 h and then allowed to warm to room temperature overnight. Water (40 mL) was added to the crude mixture and the ethereal layer was washed with water (3 × 100 mL) and dried (Na_2SO_4) and the solvent evaporated under vacuum. The residue was purified by column chromatography (silica gel, hexane) to afford **1g** (0.14 g, 8%) and 4-bromotetrathiafulvalene (0.23 g, 16%), whose spectroscopic and physical data were identical to those previously reported.[9]

Reaction of Tetrathiafulvalenyllithium with NCS. This reaction was carried out using the same procedure as that described above, using NCS (0.67 g, 5 mmol). After the usual workup, column chromatography (silica gel, hexane) afforded **1h** (0.20 g, 15%) and 4-chlorotetrathiafulvalene (0.08 g, 7%). Their spectroscopic and physical data were identical to those previously reported.[8]

4-Chloro-5-(methoxycarbonyl)-1,3-dithiole-2-thione (8). To a stirred solution of LDA (5.5 mmol), prepared as indicated above, was added compound **7** (0.96 g, 5 mmol). After 1 h at −78 °C under nitrogen, TsCl (1.91 g, 10 mmol) was added and the mixture was kept at this temperature for 5 h and then allowed to warm to room temperature overnight. After the usual workup, the residue was purified by column chromatography (silica gel, hexane−CH_2Cl_2 3:1) to afford **8** (0.38 g, 34%): mp 59 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (s); ^{13}C NMR ($CDCl_3$) δ 53.25, 128.58, 133.84, 157.10, 205.52; HRMS (EI$^+$) calcd for $C_5H_3ClO_2S_3$ 225.8984, found 225.8984. Anal. calcd for $C_5H_3ClO_2S_3$: C, 26.49; H, 1.33; S, 42.42. Found: C, 26.67; H, 1.18; S, 42.69.

4,4′(5′)-Dichloro-5,5′(4′)-bis(methoxycarbonyl)tetrathiafulvalene (9). A solution of **8** (0.45 g, 2.16 mmol) in freshly distilled trimethyl phosphite (12 mL) was slowly heated from 80 °C to 110 °C for 2 h under nitrogen. The mixture was allowed to cool to room temperature and the resulting red precipitate was filtered off and washed with toluene and Et_2O. Column chromatography (silica gel, hexane−CH_2Cl_2 2:1) afforded **9** as a red solid (0.23 g, 59%): mp 228−230 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s); ^{13}C NMR ($CDCl_3$) δ 52.85, 107.92, 120.35, 120.74, 130.24, 130.74, 158.54; HRMS (EI$^+$) calcd for $C_{10}H_6Cl_2O_4S_4$ 387.8526, found 387.8514. Anal. Calcd for $C_{10}H_6Cl_2O_4S_4$: C, 30.85; H, 1.55; S, 32.94. Found: C, 30.99; H, 1.34; S, 33.21.

4,4′(5′)-Dichlorotetrathiafulvalene (2h). A solution of **9** (0.15 g, 0.39 mmol) and LiBr (0.39 g, 4.49 mmol) in HMPA (13 mL) was heated at 80 °C for 2 h, during which time gas evolution (MeBr) was observed. After cooling to room temperature, water was added and the product was extracted with EtOAc. The organic layer was washed with water and dried (Na_2SO_4) and then concentrated under reduced pressure. The resulting crude product was purified by column chromatography (silica gel, hexane−CH_2Cl_2 4:1) to give **2h** (0.052 g, 49%): mp 114 °C; ^{1}H NMR ($CDCl_3$) δ 6.14 (s), 6.15 (s); ^{13}C NMR ($CDCl_3$) δ 111.06, 114.90, 117.78, 117.90; HRMS (EI$^+$) calcd for $C_6H_2Cl_2S_4$ 271.8416, found 271.8409. Anal. Calcd for $C_6H_2Cl_2S_4$: C, 26.38; H, 0.74; S, 46.94. Found: C, 26.55; H, 0.60; S, 47.22.

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