Successive Cycloadditions between 4-Fluoro-5-trifluoromethyl-1,2-dithiole-3-thione and Dimethyl Acetylenedicarboxylate: New Fluorinated Thiaheterocycles through New Reaction Mechanisms

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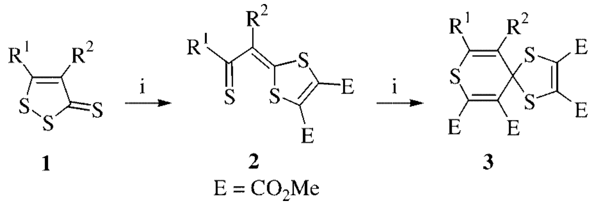
The cycloaddition reaction between dimethyl 2-(1-fluoro-2-trifluoromethyl-2-thioxoethylidene)-1,3-dithiole-4,5-dicarboxylate and dimethyl acetylenedicarboxylate proceeds efficiently under irradiation conditions in air. A study of the reaction conditions resulted in the proposal of a chain mechanism initiated by a photochemically induced single-electron transfer to oxygen. On the other hand, the cycloadduct can be transformed into a rearranged hydroxylated product by filtration through silica gel. Either the cycloadduct or its rearranged product can be obtained selectively in a one-pot process from the parent 1,2-dithiole-3-thione.

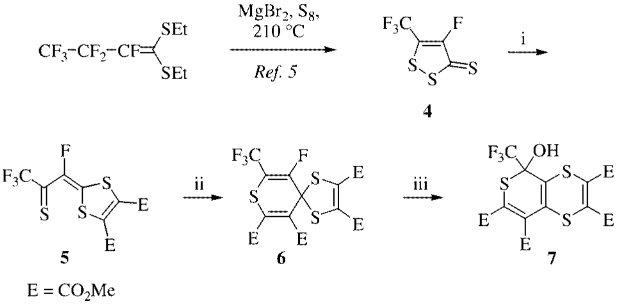
Introduction

1,2-Dithiole-3-thiones **1** are known to undergo 1,3-dipolar cycloaddition reactions with dimethyl acetylenedicarboxylate (DMAD). The resulting 1:1 adducts **2** further react with DMAD in a [4+2] cycloaddition to yield the corresponding 1:2 adducts **3** (Scheme 1).[1,2] Generally, conversion of **2** into **3**, or direct conversion of **1** into **3**, was accomplished by heating of the reactants at reflux in solvent.[3,4] The reported experimental procedures did not mention any particular precautions necessary for performing these reactions, except for one report mentioning the low stability of compound **2** in light and under oxygen, achieving the cycloaddition in the dark and under nitrogen.[3c]



Scheme 1. i: DMAD

We have recently described the synthesis of a new 4-fluoro-5-trifluoromethyl-1,2-dithiole-3-thione **4**, which reacted as a 1,3-dipole with DMAD to give the thioketone derivative **5** (Scheme 2).[5] Because of the presence of electron-withdrawing substituents, compound **5** readily reacted with 2,3-dimethylbutadiene as a heterodienophile.[5] Compound **5** can also be regarded as a heterodiene and should react with dienophiles, as mentioned above for nonfluorinated analogues. On the other hand, compound **5** proved to be unstable when exposed to daylight. These observations prompted us to consider its chemical and photochemical behaviour more carefully. Here we report our detailed study of the reaction between **5** and DMAD, with emphasis on the influence of experimental conditions, especially on the roles of light, oxygen and moisture. This study allowed us to achieve a selective one-pot synthesis of the 1:2 adduct and also of a new type of organofluorosulfur compound resulting from its reaction with water. The various parameters considered brought us to propose an unprecedented



Scheme 2. i: DMAD. ii: hν (air), DMAD. iii: H_2O (−HF) (see text).

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Table 1. Influence of the experimental conditions

Entry	Conditions[a]			Conv. (%)	Products (%)
	Dark or hν	Atmosphere	Time (h)		
1	Dark	Air	24	0	0
2	Daylight	Air	16	100	**6** +**7** (95)(1:1)[b]
3	Tungsten lamp	Air	0.5	100	**6** (93)[c]
4	Tungsten lamp	Argon	0.5	0	0
5	Dark	Argon +5% mol DCNQ	16	90	**6** (55)[c]

[a] Equimolar amounts of **5** and DMAD in CH_2Cl_2 (0.02 M) at room temp. [b] NMR yield and product ratio. [c] Isolated yields.

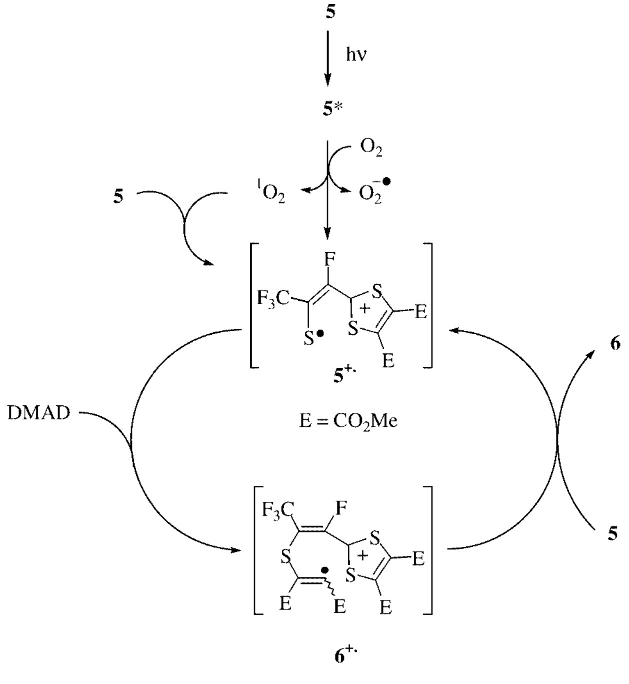
single-electron transfer-induced mechanism consistent with the observed roles of light and oxygen, although this paper is mainly devoted to optimisation and preparative aspects.

Results and Discussion

When compound **5** was treated without any precautions (in daylight and in air) with DMAD in dichloromethane, a quantitative conversion into a (1:1) mixture of the spiro cycloadduct **6** and the hydroxy compound **7** occurred (Scheme 2; Table 1: Entry 2). The poor reproducibility of the results prompted us to examine the influence of the reaction conditions carefully. Several experiments were carried out, with variation of light exposure and the nature of the reaction atmosphere. The results are summarized in Table 1.

These experiments clearly show that cycloaddition between **5** and DMAD is not a simple thermal process, as was generally considered in the literature for nonfluorinated analogues **2**,[1−4] and even demonstrated in one report.[3c] At least for our fluorinated substrate, both light and oxygen play crucial roles (Entries 1−4). Compound **7**, which is observed only after long reaction times in daylight and in nondried air (Entries 2) results from the reaction between **6** and water (vide infra). The last experiment (Entry 5) confirms (i) that under a dry atmosphere no trace of **7** could be observed, and (ii) that a stronger oxidant such as dichlorodicyanoquinone (DCNQ) can replace oxygen and light to initiate the conversion of **5** into **6**. Moreover, as this experiment was carried out in the presence of a catalytic amount of DCNQ (5 mol %), the occurrence of a chain process has to be considered.

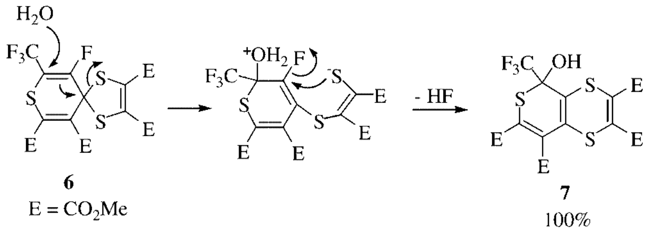
A proposed mechanism to account for the high efficiency of the reaction under light and oxygen according to these experimental data is depicted in Scheme 3. The oxidative initiation step most probably consists of a single-electron transfer from the excited substrate **5*** to molecular oxygen, to give the corresponding radical cation $\mathbf{5}^{+\cdot}$.[6] Radical addition of $\mathbf{5}^{+\cdot}$ to DMAD affords the radical cation adduct $\mathbf{6}^{+\cdot}$, which in turn acts as an oxidant towards the substrate **5**, the corresponding single-electron transfer constituting the chain transfer step, with concomitant formation of the adduct **6**. Possible initiation by electron transfer from **5** to singlet oxygen cannot be ruled out. Singlet oxygen can act as an electron acceptor,[7] and photosensitization of oxygen by a nonfluorinated conjugated dithiole of the type **5** structure has already been claimed.[8] This point, as well as the occurrence of the intermediate radical cation, is under current investigation and will be clarified further. Such a radical cation [4+2] cycloaddition is unprecedented for enethione-type dienes, but is a well known way to enhance the rates of various Diels−Alder reactions.[9]



Scheme 3

The adduct **6** is an intermediate towards the hydroxy derivative **7**. This was confirmed, as well as the role of water, by a total conversion of **6** into **7** by simple silica gel filtration. The reaction pathway proposed in Scheme 4 accounts for this transformation, which could be the result of two addition-elimination steps. Owing to the high efficiency of the reaction over silica gel, in this case we cannot exclude an acid-catalysed dithiole ring-opening prior to water addition.

The structure of compound **7** was confirmed by single-crystal X-ray diffraction. The perspective view of molecule **7** and selected geometrical parameters are given in Figure 1. The S(1)S(2)S(3)C(1−7) central bicyclic system is essentially nonplanar: in the S(1)C(1−5) heterocycle the deviations from the least-squares plane exceed 0.21 Å, and the S(2)S(3)C(2)C(3)C(6)C(7) heterocycle is folded over the



Scheme 4

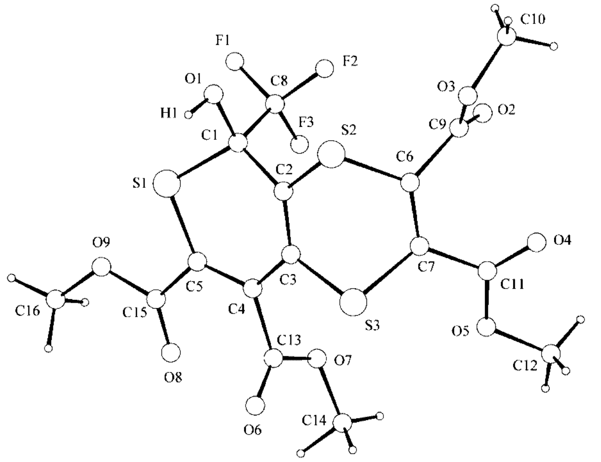
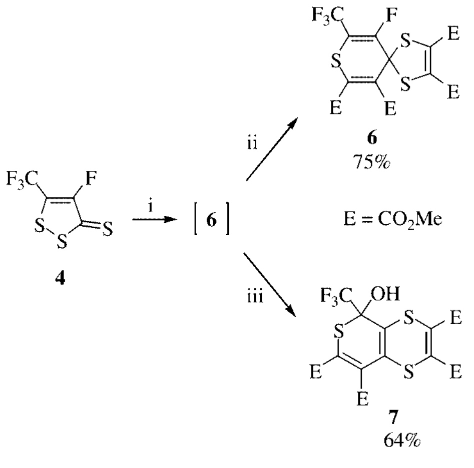


Figure 1. Perspective view and labelling scheme for the molecule **7**; selected bond lengths [Å] and angles [°]: S(1)−C(1) 1.833(3), S(1)−C(5) 1.744(3), S(2)−C(2) 1.779(3), S(2)−C(6) 1.766(3), S(3)−C(3) 1.788(3), S(3)−C(7) 1.762(3), C(1)−C(2) 1.515(4), C(2)−C(3) 1.330(4), C(3)−C(4) 1.461(4), C(4)−C(5) 1.354(4), C(6)−C(7) 1.344(5), C(1)S(1)C(5) 103.44(14), C(2)S(2)C(6) 98.66(14), C(3)S(3)C(7) 100.27(15)

S(2)−S(3) line by 55.51°. The bond lengths and angles in molecule **7** are unexceptional.[10]

We then took advantage of our better knowledge and of control over the reaction conditions to achieve one-pot preparations of either **6** or **7** directly from the parent 1,2-dithiole-3-thione **4**. The two compounds **6** or **7** were prepared in overall isolated yields of 75% and 64%, respectively, by direct mixing of **4** and 2 molar equivalents of DMAD in CH_2Cl_2 (Scheme 5). Two successive "dark" and "light" cycloadditions, followed by a suitable workup (crystallisation or silica gel filtration, respectively), provided the desired pure compounds **6** or **7** (see Exp. Sect.).



Scheme 5. i: 1) DMAD (2 equiv.), CH_2Cl_2, dark, 0.5 h; 2) hν, O_2, 0.5 h. ii: evaporation, then crystallisation. iii: evaporation, followed by filtration through silica gel

Conclusion

The second step of the successive cycloaddition reactions between DMAD and 1,2-dithiole-3-thione, previously known as a thermal process, was shown to proceed, in the case of 4-fluoro-5-trifluoromethyl-1,2-dithiole-3-thione (**4**), by a chain reaction initiated by a photoinduced electron transfer to oxygen. The final 1:2 adduct **6** was prepared selectively, but it was easily converted into a new product **7**, the formation of which is the result of a rearrangement−hydrolysis sequence. Thanks to better knowledge of the influence of the experimental reaction parameters, and hence of the mechanisms, we achieved the direct and selective preparation of **6** or **7** from the parent 1,2-dithiole-3-thione **4** in one-pot reactions.

Experimental Section

General Remarks: Melting points are uncorrected. FT-IR spectra were recorded with a MIDAC Corporation Spectrafile IR™ apparatus. ^1H, ^{13}C and ^{19}F spectra were recorded with a Bruker AC 250 in $CDCl_3$ as solvent. Tetramethylsilane ($\delta = 0.00$ ppm) or $CHCl_3$ ($\delta = 7.27$ ppm) were used as internal standards for ^1H and ^{13}C NMR spectra and $CFCl_3$ for ^{19}F NMR spectra. MS data were obtained with a Trace MS Thermoquest apparatus (GCMS) at 70 eV in the electron impact mode. Elemental analyses were performed with a Perkin−Elmer CHN 2400 apparatus. All reactions were monitored by GCMS. Silica gel (Merck 9385, 40−63μm) was used for flash chromatography. DMAD and CH_2Cl_2 were obtained from commercial sources and were used without further purification.

Tetramethyl 10-Fluoro-9-trifluoromethyl-1,4,8-trithiaspiro[4.5]deca-2,6,9-triene-2,3,6,7-tetracarboxylate (6): A solution of 1,2-dithiole-3-thione (**4**, 0.24 g, 1.09 mmol) and DMAD (0.31 g, 2.18 mmol) in CH_2Cl_2 (10 mL) was kept in the dark at room temperature. After 0.5 h, the dark red solution was irradiated with a 500-W tungsten lamp for 0.5 h in the open flask. Solvent was then removed by evaporation. The residue was treated with diethyl ether (5 mL) and the resulting solution was quickly transferred into another flask. After the mixture had been left standing in a refrigerator at −20 °C for 4 h, crystals were removed by filtration and washed with cool ether (1 mL) to give the spiro compound **6** as yellow crystals (0.41 g, 75%). M.p. 123−125 °C. ^1H NMR: $\delta = 3.80$ (s, 6 H, 2 × CH_3), 3.87 (s, 3 H, CH_3), 3.93 (s, 3 H, CH_3) ppm. ^{19}F NMR: $\delta = -59.89$ (d, 3 F, $^4J_{F,F} = 15.5$ Hz, CF_3), −99.09 (q, 1 F, $^4J_{F,F} = 15.5$ Hz, CF) ppm. ^{13}C NMR: $\delta = 53.5$ (s, 2 × CH_3), 53.6 (s, CH_3), 54.4 (s, CH_3), 66.8 (d, $^2J_{C,F} = 27.5$ Hz, C-5), 104.7 (dq, $^2J_{C,F} = 36.0$, $^2J_{C,F} = 20.7$ Hz, C−CF_3), 120.4 (q, $^1J_{C,F} = 276.1$ Hz, CF_3), 127.1 (s, C−C=O), 127.4 (s, 2 × C−C=O), 128.8 (d, $^3J_{C,F} = 6.7$ Hz, C−C=O), 149.8 (dq, $^1J_{C,F} = 270.6$, $^3J_{C,F} = 3.0$ Hz, CF), 160.0 (s, 2 × C=O), 160.8 (s, C=O), 163.9 (s, C=O) ppm. IR (KBr): $\tilde{\nu} = 3013$, 2959, 2843, 1750 (C=O), 1724 (C=O), 1656, 1582, 1434, 1318, 1254, 1189 cm^{-1}; MS: m/z (%) = 504 (1) [M^+], 445 (100) [M^+ − $COOCH_3$]. $C_{16}H_{12}F_4O_8S_3$ (504.44): calcd. C 38.10, H 2.40; found C 38.10, H 2.20.

Tetramethyl 5-Hydroxy-5-trifluoromethyl-5*H*-1,4,6-trithianaphthalene-2,3,7,8-tetracarboxylate (7): The crude reaction mixture, obtained in a procedure analogous to that described above, was purified by silica gel column chromatography, eluting with petroleum ether/diethyl ether (4:6), to give the heterocycle **7** as yellow crystals (0.32 g, 1.0 mmol, 64%). $R_f = 0.35$ (petroleum ether/ether, 4:6). M.p. 143−145 °C. ^{1}H NMR: $\delta = 3.84$ (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 5.57 (broad s, 1 H, OH) ppm. ^{19}F NMR: $\delta = -82.49$ (s, CF_3) ppm. ^{13}C NMR: $\delta = 53.67$ (s, CH_3), 53.77 (s, $2 \times CH_3$), 53.93 (s, CH_3), 82.6 (q, $^2J_{C,F} = 34.5$ Hz, $C-CF_3$), 123.2 (q, $^1J_{C,F} = 286.6$ Hz, CF_3), 127.7 (s, C_q), 128.4 (s, C_q), 130.7 (s, C_q), 135.2 (s, C_q), 136.3 (s, C_q), 139.0 (s, C_q), 161.6 (s, C=O), 162.4 (s, C=O), 162.9 (s, C=O), 166.1 (s, C=O) ppm. IR (KBr): $\tilde{\nu} = 3197$ (broad, OH), 2958, 1745 (C=O), 1727 (C=O), 1703 (C=O), 1596, 1573, 1523, 1439, 1312, 1257, 1195, 1174, 1137 cm^{-1}. MS: *m/z* (%) = 502 (4) [M$^+$], 369 (100). $C_{16}H_{13}F_3O_9S_3$ (502.45): calcd. C 38.25, H 2.61; found C 38.35, H 2.36.

X-ray Structure Determination of 7: Crystal data: $C_{16}H_{13}F_3O_9S_3$, M = 502.45, triclinic, $a = 8.801(2)$, $b = 10.250(2)$, $c = 13.472(4)$ Å, $\alpha = 86.06(2)$, $\beta = 71.61(2)$, $\gamma = 68.38(2)°$, $V = 1070.5(5)$ Å^3, $Z = 2$, $d = 1.557$ g·cm^{-1}, space group $P\bar{1}$ (No. 2), $\mu = 4.00$ cm^{-1}, $F(000) = 512.9$, crystal size ca. $0.28 \times 0.28 \times 0.28$ mm. All crystallographic measurements were performed at 20 °C on a CAD-4-Enraf−Nonius diffractometer operating in the ω-2θ scan mode (the ratio of the scanning rates $\omega/2\theta = 1.2$). The intensity data were collected within the range $1 < \theta < 27°$ ($0 < h < 11$, $-13 < k < 13$, $-17 < l < 17$) with the use of graphite monochromated Mo-K_α radiation ($\lambda = 0.71069$ Å). Intensities of 4980 reflections (4663 unique reflection, $R = 0.016$) were measured. Data were corrected for Lorentz and polarisation effects and an empirical absorption correction based on azimuthal scan data[11] were applied. The structure was solved by direct methods and refined by the full-matrix, least-squares technique in the anisotropic approximation by use of the CRYSTALS program package.[12] In the refinement, 3033 reflections with $I > 3\sigma(I)$ were used. All hydrogen atoms were located in the different Fourier maps and included in the final refinement with fixed positional and thermal parameters (only atom H(1) was refined isotropically). Convergence was obtained at $R = 0.052$ and $R_w = 0.058$, GOF = 1.104 (284 refined parameters; obsd./variabl. 10.7; the largest and minimal peaks in the final difference map, 0.31 and −0.54 e/Å^3). The Chebushev weighting scheme[13] with parameters 0.66, −0.08, 0.18, and −0.31 was used.

CCDC-194403 (**7**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

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[6] As has been pointed out by a referee, our fluorinated substrate could be more difficult to oxidise than non-fluorinated analogues, which would explain the necessity for light excitation. While a CF_3 group should undoubtedly make a substrate more difficult to oxidise, this effect could be reduced by the π-donor character of the vinylic fluorine atom: R. D. Chambers, J. F. S. Vaughan, *Top. Curr. Chem.* **1997**, *192*, 1−38 and references cited therein. Although we are currently trying to obtain electrochemical characterisation of our fluorinated substrate, any comparison with non-fluorinated analogues will be difficult as no electrochemical data are available in the literature.

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