

Cite this: *RSC Advances*, 2012, 2, 12269–12277

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PAPER

Quantitative preparation of 3,4-di(methylene)tetrahydrothiophene-1,1-dioxide by Zn-induced 1,4-debromination. A valuable 6-C reactive diene in [4+2] cycloadditions with DMAD and [60]fullerene†

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Received 12th October 2012, Accepted 12th October 2012

DOI: 10.1039/c2ra22502f

Optimum reaction conditions for the quantitative preparation of the highly reactive 3,4-di(methylene)tetrahydrothiophene-1,1-dioxide are described. The method involves the zinc-induced 1,4-debromination of 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide in acetone solvent either by using conventional heating, microwave or ultrasonic irradiation. The [4+2] cycloaddition reaction of 3,4-di(methylene)tetrahydrothiophene-1,1-dioxide with dienophiles such as DMAD and C₆₀ led to the efficient and clean formation of the corresponding Diels–Alder cycloadducts. Specifically for [60]fullerene, the short-chain C₆₀ monoadduct was formed in a short reaction time and in high overall yield (56%). In contrast, the iodine-induced 1,4-debromination using KI in toluene, in the presence of 18-crown-6 as a phase transfer catalyst, failed to give the corresponding [4+2] C₆₀ monoadduct at room temperature or in refluxing toluene and a low product yield (13%) was only obtained at a temperature of 45–50 °C.

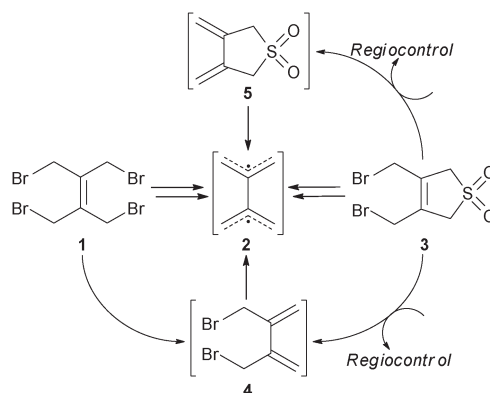
Introduction

More than a century ago, the reaction between cyclopentadiene and quinones was carried out by Albrecht in 1906.¹ The first reported Diels–Alder reaction was carried out in 1928² and the [4+2] cycloaddition is still one of the most important tools to construct cyclic molecular architectures.³ The dienophilic behaviour of [60]fullerene has been widely exploited in such reactions,⁴ as the Diels–Alder transformation is a powerful method for the covalent attachment of organic moieties on the surface of C₆₀. This approach appears to be particularly attractive and has been fruitful in preparing rigidified donor–bridge–C₆₀ electroactive systems for various applications in materials science.⁵ The advantage of the Diels–Alder strategy concerns the more rigid spatial orientation of the HOMO of the donor with respect to the LUMO of C₆₀ due to the folded-boat conformation of the cyclohexene ring, therefore favouring through-space interactions in electron transfer processes. In most cases, the key step is the preparation of versatile bis- or tetrakis(bromomethylated) derivatives which can generate the corresponding transient *o*-quinodimethane analogues *via* reductive elimination.⁶ However, in almost all of these cases an aromatic core is covalently linked to the fullerene cage through a cyclohexene ring in order to prevent the retro Diels–Alder

reaction. To date, only a limited number of short-chain fullerene derivatives have been reported in the literature, probably due to difficulties met in the synthesis and isolation of stable dienes required for the Diels–Alder reaction with C₆₀.⁷

More recently, Sambrook *et al.*⁸ reported the synthesis of a short-chain C₆₀ monoadduct and a bis-fullerene adduct by reacting the tetrabromo precursor **1** with C₆₀ in toluene solvent in an one-pot manner and by using KI in the presence of 18-crown-6 as a phase transfer catalyst. This is the only literature example reporting the utilisation of the transient intermediate 2,2'-bisallyl diradical **2** (Scheme 1) towards the synthesis of a [4+2] C₆₀ derivative.

Searching for an elegant method to access short-chain [4+2] C₆₀ monoadducts bearing functional groups for further derivatization,



Scheme 1 Precursors for the generation of the 2,2'-bisallyl diradical **2**.

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† Electronic Supplementary Information (ESI) available: Characterisation data are available. CCDC reference numbers 868567 and 868568. See DOI: 10.1039/c2ra22502f

it has been realised that despite the enormous body of literature reports dealing with the *in situ* generation and Diels–Alder reactions of mono-⁹ and bis-*o*-quinodimethanes¹⁰ and their derivatives, very few reports describe the synthesis of Diels–Alder reactions utilising the transient intermediate 2,2′-bisallyl diradical **2**. The chemistry of the diradical **2** was originally reported by Trost and Shimizu¹¹ and was subsequently extended by Hosomi *et al.*¹² Presumably, the diene-masking possibilities available for *o*-quinodimethanes^{9,10} either cannot be applied for the generation of the 2,2′-bisallyl diradical **2**¹³ or require a multi-step synthesis.^{14,15} Easily accessible and stable masked bis-diene precursors for the generation of **2** are: (a) 1,4-dibromo-2,3-bis(bromomethyl)-but-2-ene **1**,¹⁶ which can undergo sequential 1,4-debromination^{15b} and (b) 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3**,¹⁷ which can undergo 1,4-debromination^{17b,c} and SO₂ extrusion either thermally¹⁸ or chemically¹⁹ (Scheme 1).

Although the diene intermediates **4** and **5** have been known for several decades, there are very few reports describing their preparation and their subsequent Diels–Alder reactions with dienophiles.^{15,17b,c} For example, the only direct methods for the preparation of the diene-sulfone **5** were reported by Nasyrov *et al.*^{17b} and Alder *et al.*^{17c} In both cases, NaI was used as a debrominating reagent and the reactions were carried out in acetone at room temperature. Specifically, in the report of Nasyrov *et al.*,^{17b} 2 g of the starting material **3** were used at a concentration of 100 mg mL⁻¹ and the product **5** was obtained after 2 h in 60% yield, following a standard work-up procedure with Na₂S₂O₃ and recrystallization from benzene–Et₂O. The authors did not mention any instability problems of the formed diene-sulfone **5**. In the report by Alder *et al.*,^{17c} 16 g of the starting material **3** were used at a concentration of 70 mg mL⁻¹ and the product **5** was obtained after 18 h in 100% yield following a standard work-up with Na₂S₂O₃ but with no further purification. In this case, the authors reported that compound **5** polymerised rapidly upon solvent removal and it was not explained how the yield of **5** was calculated.

An indirect method for the preparation of **5** was reported by Gaoni and Sadeh.^{15b} The reaction of **1** with an excess of a Zn–Cu couple, in Et₂O and in the presence of HMPT, gave the dibromodiene **4** in 70–73% yield. Diene **4** was then reacted with sodium sulfide followed by oxidation of the resulting cyclic sulfide to afford **5** (25% overall yield from **1**). Despite the multistep, low yielding sequence, the authors clearly stated the facile polymerisation of **5** either in the absence of solvents or in solution.

It is apparent that in all procedures where **1** is utilised for either sequential^{15b} or tandem⁸ Diels–Alder reactions, chemo- or regioselective control over the diene formation is not feasible. In addition, the cycloaddition of **1** with C₆₀ results in a mixture of fullerene adducts, namely the [4+2] C₆₀ monoadduct and the bis-fullerene adduct with two fullerenes attached on the *in situ* formed bisallyl diradical **2**. These products showed very similar polarity with unreacted C₆₀ and therefore their separation could be achieved only by means of preparative HPLC.⁸ Furthermore, the disadvantage of using NaI or KI for the 1,4-debromination step lies in the fact that the presence of bromine in the reaction mixture leads to the formation of undesirable adducts, especially when C₆₀ is employed as a dienophile. This process usually requires longer reaction times^{4a} and repetitive chromatographic purification or preparative HPLC is necessary for the isolation of

the formed adducts. The alternative method of metal-induced 1,4-debromination to access the desired diene is not compatible with C₆₀ due to its pronounced electron accepting ability. It is well-established in the literature that C₆₀ is reduced by metals including zinc,^{4b} thus indicating that the pure diene intermediate (*e.g.*, **4** or **5**, Scheme 1) should be first isolated in a pure form and then subjected to the [4+2] cycloaddition reaction with C₆₀.

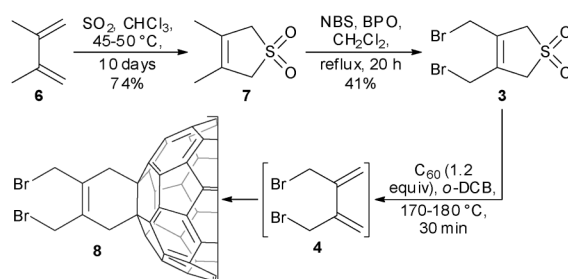
Eliminating the problem of chemoselectivity of the tetrabromo precursor **1**, a selective Diels–Alder reaction can be envisioned with the structure of **3** (Scheme 1) by taking advantage of either the chemoselective 1,4-debromination or the elimination of the sulfone moiety to form the corresponding dienes. Nevertheless, the incompatibility of C₆₀ in either iodine- or metal-induced debromination conditions results in the inefficient preparation of [4+2] C₆₀ monoadducts and is therefore a major drawback.

Probably due to instability problems, no attempts have been made in the past to optimise the conditions and therefore generalise the preparation of the highly valuable 6-C synthon **5**. Another reason might arise from the fact that simple dienophiles were used in the subsequent [4+2] cycloadditions and therefore, the scale of the reaction or the purity of **5** were not a major problem.^{15,17b,c} Finally, the one-pot reaction of **3** with simple dienophiles under the iodine-induced 1,4-debromination conditions usually results in the formation of fewer undesirable products that are easier to purify, giving higher overall yields compared with the usual low yielding reactions of C₆₀.

Our interest in the synthesis of [60]fullerene derivatives derived from the Diels–Alder reaction,²⁰ in combination with the limitations posed by the current methods which utilise synthon **2**, prompted us to investigate the optimum reaction conditions for the preparation of the diene-sulfone **5** and the subsequent efficient synthesis of a short-chain [4+2] C₆₀ monoadduct bearing a reactive site for further derivatization.

Results and discussion

The preparation of the dibromo-sulfone **3** was performed following modified literature procedures.^{17a,21} The reaction of SO₂ with 2,3-dimethyl-1,3-butadiene **6** gave the cyclic sulfone **7** in 74% yield,²¹ which was then subjected to an allylic bromination with *N*-bromosuccinimide in dry dichloromethane to furnish the dibromo-sulfone **3** in 41% yield (Scheme 2).^{17a} Product **3** showed a pronounced ability to crystallise and colourless single crystals were easily obtained by recrystallization from ethanol. The proposed structure was unambiguously confirmed by X-ray crystallography (see Supporting Information†).



Scheme 2 A chemoselective approach towards the preparation of the short-chain dibromo [4+2] C₆₀ monoadduct **8**.

Our investigation was initiated by the reaction of C_{60} with dibromo-diene **4**, generated *in situ* from **3** via thermal SO_2 extrusion (see ESI† for the DSC and TGA of **3**). The dibromo [4+2] C_{60} monoadduct **8** (Scheme 2) was obtained as a brown solid contaminated with unreacted C_{60} . Purification of **8** could not be achieved by column chromatography in all attempted eluent systems due to its similar polarity with C_{60} . This was also confirmed in the report of Sambrook *et al.*,⁸ where preparative HPLC was required for the purification of **8** synthesised starting from **1**. Nonetheless, the thermal SO_2 extrusion of **3** followed by the Diels–Alder reaction with C_{60} is advantageous compared to the literature method⁸ due to the regiocontrol over the diene formation.

Next, we examined the Diels–Alder reaction of diene **5** derived from the 1,4-debromination of dibromo-sulfone **3** with C_{60} (Table 1). This transformation was carried out under iodine-induced 1,4-debromination conditions, previously reported for the preparation of *o*-quinodimethane derivatives.^{4,8} KI was used as the de-brominating reagent in toluene in the presence of 18-crown-6 as a phase transfer catalyst. In all reported examples, the reaction between C_{60} and the *in situ* formed *o*-quinodimethanes proceeds smoothly in refluxing toluene. In the case of **3**, the one-pot cycloaddition reaction in refluxing toluene yielded only intractable baseline (TLC) material (Table 1, entry 1). At room temperature, the reaction gave no indication of product formation even after prolonged reaction periods (Table 1, entry 2) and the best result was obtained at a temperature of 45–50 °C (Table 1, entry 3). The purification of product **9** was easily achieved by column chromatography on silica gel (toluene–EtOAc = 20 : 1) followed by precipitation from $CHCl_3$ –pentane. The increased polarity of the [4+2] C_{60} monoadduct **9** compared with **8** allowed its facile separation and purification and was isolated in 13% yield.

The 1H NMR spectrum of **9** showed two broad singlets at 4.22 and 4.38 ppm which correspond to the methylenic hydrogens of the cyclohexene and the heterocyclic five-membered ring of the addend, respectively. In the ^{13}C NMR spectrum, three signals at 40.81, 59.68 and 65.32 ppm were observed corresponding to the sp^3 carbon atoms of the C_{60} core and the methylenic carbons of the organic addend. In the region between 133.11–155.14 ppm, 18 peaks were found, 17 of which are attributed to the fullerene

sp^2 carbons and one to the carbons of the double bond of the cyclohexene moiety. All the observed signals reflect nicely the C_{2v} symmetry of the molecule, which arises from the fast ring flipping of the cyclohexene unit. Finally, the MALDI-TOF mass spectra (negative mode, DCTB as the matrix) of the fullerene monoadduct **9** showed the $[M-SO_2]^-$ ion at m/z 800.0619 Da indicating that the extrusion of sulfur dioxide is facile under the mass spectrometric conditions.

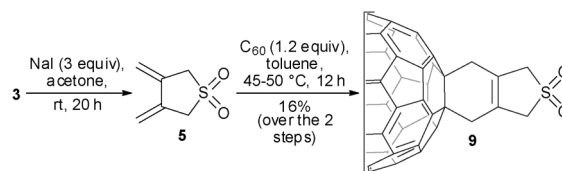
The low yield of **9** obtained following the one-pot method with KI turned our efforts to the preparation of diene **5** prior to the cycloaddition reaction with C_{60} . Following standard literature procedures,^{17b,c} we investigated the 1,4-debromination reaction of **3** using NaI in acetone (Scheme 3). Despite extensive repetition of the procedure, in our hands, the isolation of **5** or pure solutions of it was not feasible. The reaction was repeated up to a 1.65 mmol scale of **3**, as well as in dilute concentrations up to 6 mg mL^{-1} . Monitoring was performed by means of thin-layer chromatography (EtOAc–hexane = 5 : 4) and upon disappearance of the starting material a standard work-up with $Na_2S_2O_3$ was followed. Isolation of compound **5** or purification by recrystallization was never accomplished due to its rapid decomposition to a polymeric material that was not soluble in a wide range of solvents. Purification by column chromatography on silica gel (EtOAc–hexane = 5 : 4) using dry, de-acidified solvents and exchanging the solvent of the combined fractions with dry benzene was the best way to manipulate the highly reactive diene **5**. However, impurities of similar polarity were still present and further purification attempts did not prove to be effective. By subjecting a benzene solution of **5**, prepared by the aforementioned procedure, to a Diels–Alder reaction with C_{60} in toluene, at 45–50 °C for 12 h, we succeeded in isolating the adduct **9** in 16% yield. The yield and consequently the efficiency of this method are very similar to the one-pot procedure in which KI was used.

Realising the lack of an efficient and practical way for the clean preparation of **5**, we started our investigations with the reductive elimination of **3** using activated Zn-dust. Due to the electron accepting ability of C_{60} with many metals,^{4b} our initial optimisation strategy was focused on the reaction of the dibromo-sulfone **3** with activated Zn-dust in various solvents, in the absence of a dienophile in the reaction mixture (Table 2). Since diene **5** could not be isolated, TLC monitoring of the reaction reflected the stability of compound **5** in the solvents tested and at different concentrations. Of the solvents screened, acetone was the only solvent which facilitated the exclusive formation of product **5**, at refluxing temperature for 16–18 h (Table 2, entry 9). Under these conditions, no decomposition was observed and the results were optimum at a concentration of 6 mg mL^{-1} **3** in acetone, using 2.3 equiv of activated Zn-dust. In

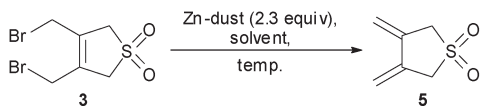
Table 1 Synthesis of **9** via the iodine-induced 1,4-debromination of **3** followed by the Diels–Alder reaction with C_{60} ^a

Entry	Temp/°C	Time	Yield of 9 (%)
1	reflux	2 h	— ^b
2	rt	5 d	— ^c
3	45–50	24 h	13 ^d

^a Conditions: **3** (0.06 mmol), C_{60} (0.07 mmol), KI (0.15 mmol), 18-crown-6 (0.45 mmol), toluene (50 mL). Results based on an average of three runs. ^b Baseline material on TLC (inseparable). ^c Starting materials on TLC. ^d Isolated yield.



Scheme 3 Synthesis of the diene-sulfone **5** by the NaI procedure and its Diels–Alder reaction with C_{60} .

Table 2 Solvent and temperature optimisation for the preparation of **5** by the Zn-induced 1,4-debromination of **3**^a


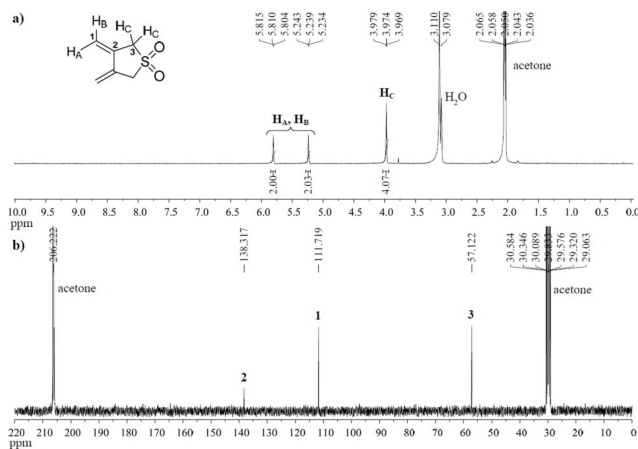
Entry	Solvent	Temp/°C ^b	Time	TLC result ^c
1	Et ₂ O	rt	3 d	starting material
2	Et ₂ O	reflux	2 d	product + decomposition
3	toluene	75–80	3 d	starting material
4	DMSO	rt	2–3h	decomposition
5	CHCl ₃	reflux	3 d	starting material
6	DMF	rt	3 d	starting material + decomposition
7	DMF	45–50	2–3 h	decomposition
8	acetone	rt	3 d	starting material
9	acetone	reflux	16–18 h	product
10	EtOAc	55–60	2 d	product + decomposition
11	THF	rt	3 d	starting material
12	THF	55–60	2–3 h	decomposition
13	acetonitrile	55–60	2 d	starting material

^a The reactions were performed up to 0.33 mmol scale of **3**. Conditions: **3** (1 equiv), concentration 6 mg mL⁻¹, activated Zn-dust (2.3 equiv). Reported results are based on an average of two runs on each scale. ^b Conventional heating. ^c TLC monitoring (EtOAc–hexane = 5 : 4).

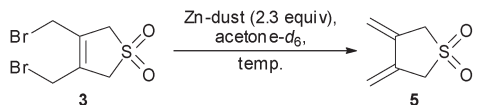
more concentrated solutions, fewer equivalents of zinc were required but decomposition material was the major result. When the reaction was carried out in refluxing Et₂O or EtOAc (Table 2, entries 2 and 10), TLC revealed the formation of product **5**, which was accompanied by decomposition material in substantial amounts. No indication of the product formation was observed when toluene, chloroform and acetonitrile (Table 2, entries 3, 5 and 13) were used as solvents, while in THF (Table 2, entries 11 and 12), the reaction failed to proceed at RT and at 55–60 °C; it afforded exclusively decomposition material.

The clean transformation of dibromo-sulfone **3** to diene **5**, under the optimum experimental conditions found (Table 2, entry 9), prompted us to attempt its NMR characterisation in an effort to confirm the results obtained by TLC analysis. For this purpose, the reaction was repeated under the conditions mentioned before but this time acetone-*d*₆ was employed as a solvent. After completion (TLC), the reaction mixture was cooled to RT, filtered and the filtrate was directly subjected to NMR analysis. The observed absorptions in the ¹H and ¹³C NMR spectra (Fig. 1) led to the unambiguous structural assignment of diene **5**, which was the sole product of the Zn-induced 1,4-debromination reaction. In both spectra, the absence of any peaks corresponding to the starting material or to other by-products provided the ultimate proof for the remarkable efficiency of the applied method.

A minor disadvantage in the synthesis of diene **5** from **3** under the optimum experimental conditions (Table 2, entry 9) is the relatively long reaction time (16–18 h). In an effort to shorten the reaction time, we used non-conventional heating methods. The Zn-induced 1,4-debromination reaction of **3** under conventional heating, microwave irradiation and sonication was carried out in acetone-*d*₆ at a concentration of 6 mg mL⁻¹ **3**. In each case, the yield of diene **5** was calculated using an equimolar amount (with respect to the starting material **3**) of 1,3,5-trimethylbenzene

**Fig. 1** (a) ¹H NMR (500 MHz, acetone-*d*₆) and (b) ¹³C NMR (125 MHz, acetone-*d*₆) of diene **5** formed by Zn-induced 1,4-debromination of **3**.

(mesitylene, bp 163–166 °C), as an internal standard. Control experiments confirmed that mesitylene is stable under the experimental conditions used in all three methods employed. The progress of the reactions was followed by TLC and upon completion the solutions were filtered and analysed by ¹H NMR spectroscopy. The diene-sulfone **5** was the sole product independent of the heating method applied and by integrating the appropriate peaks in the ¹H NMR spectra (see ESI†) the yields were calculated to be more than 97% in all cases (Table 3). Conventional heating afforded the product in 16–18 h (Table 3, entry 1), sonication in 2 h and 50 min (Table 3, entry 2) and microwave irradiation led to the quantitative formation of diene **5** in only 55 min (Table 3, entry 3). Most impressive was the fact that diene **5** remained stable under microwave irradiation and thus, this widely used method for accelerating reactions rates can be employed in the synthesis of the highly reactive diene **5**. The acetone solutions of **5** can be used directly for subsequent Diels–Alder reactions without any purification. Furthermore, when the solvent was exchanged with dry benzene and stored in the freezer at –20 °C, diene **5** was stable for several weeks as indicated by TLC.

Table 3 Calculated yields of diene **5** formed by the Zn-induced 1,4-debromination of **3** using alternative heating methods^a


Entry	Heating method	Temp/°C	Time	Yield of 5 (%) ^b
1	conventional ^c	reflux	16–18 h	99–100
2	sonication ^c	reflux	2 h 50 min	98–99
3	microwave ^{c,d}	60	55 min	97–98

^a Conditions: **3** (1 equiv), concentration 6 mg mL⁻¹, activated Zn-dust (2.3 equiv), mesitylene (1 equiv). Reported results are based on an average of two runs. ^b NMR yields using one equivalent of mesitylene (bp 163–166 °C) as an internal standard. ^c The reactions were carried out on a 0.038 mmol scale of **3**. ^d CEM Discover microwave reactor at 250 W, 21 psi.

In the next step, the Diels–Alder cycloaddition reaction of the diene-sulfone **5** with a zinc-compatible dienophile was investigated in solvents employed in our initial studies and are summarised in Table 2. The Zn-induced 1,4-debromination of **3** followed by the [4+2] cycloaddition with an excess of dimethyl acetylenedicarboxylate (DMAD) (10 equiv) was examined in a one-pot procedure for each solvent tested (Table 4). The yield of product **10** was calculated after its isolation and purification by column chromatography. Recrystallization from methanol afforded single crystals of **10** suitable for X-ray analysis, which further supported the proposed structure. It has to be mentioned here that except for acetone, which was the best solvent for the synthesis of diene **5** via the Zn-induced 1,4-debromination of **3**, we examined the cycloaddition reaction with DMAD in solvents where diene **5** was formed together with the decomposition material (Et₂O, EtOAc) and solvents where the decomposition material was the only outcome of the reaction (DMSO, DMF, THF). Our purpose was to clarify if in certain solvents the [4+2] cycloaddition reaction of **5** with DMAD is faster than its decomposition due to polymerisation and consequently to determine whether they can be employed in reactions where the dienophile is used *in situ*. The trend observed was very similar to the initial experiments (Table 4). When the reaction was carried out in acetone, product **10** was isolated in 91–92% isolated yield (Table 4, entry 5). In Et₂O, EtOAc and THF (Table 4, entries 1, 6 and 7) the isolated yields ranged from 50 to 75%, while the same reaction in either DMSO or DMF (Table 4, entries 2, 3 and 4) led only to decomposition. Finally, the one-pot Zn-induced 1,4-debromination of **3**/[4+2] cycloaddition with DMAD was repeated under microwave irradiation or sonication giving product **10** in 90–92% isolated yield, in identical reaction times with those reported in Table 3 (entries 2 and 3).

In order to complete our investigation in finding the optimum conditions for the preparation of diene **5** and its Diels–Alder reaction with dienophiles, we turned our attention to the metal reagent used for the 1,4-debromination of dibromo-sulfone **3**. Following a procedure reported by Smith and Simmons,²² the Zn–Cu couple was employed and compared with activated Zn-dust and NaI for the debromination of **3** (Table 5).

Table 4 Yields of the Diels–Alder reaction of **5** with DMAD in various solvents^a

Entry	Solvent	Temp/°C ^b	Time	Yield of 10 (%) ^c
1	Et ₂ O	reflux	3 d	72–75
2	DMSO	rt	2–3 h	decomposition
3	DMF	45–50	2–3 h	decomposition
4	DMF	rt	2 d	starting material + decomposition
5	acetone	reflux	16–18 h	91–92
6	EtOAc	55–60	2.5 d	59–62
7	THF	55–60	5 h	50–52

^a The reactions were performed up to 0.33 mmol scale of **3**. Conditions: **3** (1 equiv), concentration 6 mg mL⁻¹, activated Zn-dust (2.3 equiv), DMAD (10 equiv). Reported results are based on an average of two runs on each scale. ^b Conventional heating. ^c Isolated yields.

Table 5 Yields for the one-pot 1,4-debromination of **3**/Diels–Alder of **5** with DMAD using different reagents for the 1,4-debromination step^a

Entry	Reagent	Equivs of reagent	Temp/°C ^b	Time	Yield of 10 (%) ^c
1	Zn	2.3	reflux	16–18 h	91–92
2	Zn–Cu	16	reflux	5 d	90–93
3	NaI	3	45–50	24 h	50–54

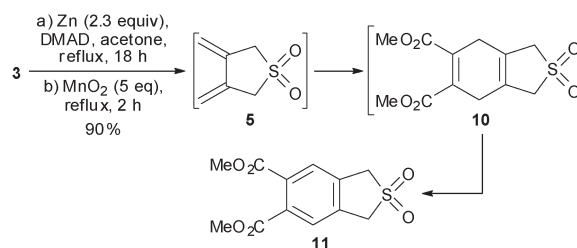
^a The reactions were carried out on a 0.076 mmol scale of **3**. Conditions: **3** (1 equiv), concentration 6 mg mL⁻¹, DMAD (10 equiv). Reported results are based on an average of two runs. ^b Conventional heating. ^c Isolated yields.

All reactions were carried out in the presence of DMAD as the dienophile. Although the procedure with Zn–Cu gave cycloadduct **10** in an excellent yield (Table 5, entry 2), an excess of the reagent was used but more importantly, the reaction required 5 d to reach completion. A wasteful stoichiometry of the Zn–Cu couple and long reaction times were also observed in the report of Gaoni and Sadeh^{15b} during the preparation of dibromo-diene **4** starting from **1** (Scheme 1). Finally, the inefficiency of NaI to promote the 1,4-debromination was confirmed by performing the reaction in the presence of DMAD (10 equiv) wherein the Diels–Alder adduct **10** was isolated in only 50–54% yield (Table 5, entry 3).

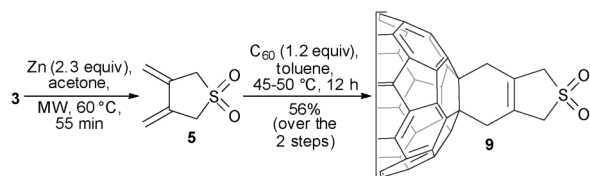
Having defined the optimum conditions for the synthesis of diene-sulfone **5** and its Diels–Alder reactions with dienophiles, we explored the versatility of the method to prepare the sulfone derivative **11**, a useful precursor for the synthesis of unusual α -amino acid derivatives. We chose this example as **11** was previously prepared in a four step sequence starting from **6**, in 27% overall yield.^{10b} Following our approach (Scheme 4), sulfone **11** was prepared in a one-pot procedure consisting of three sequential steps, namely zinc-induced 1,4-debromination of **3**, [4+2] cycloaddition of **5** with DMAD and finally oxidation of **10** with MnO₂. By this procedure, product **11** was isolated in 90% overall yield.

To reach our initial target and establish an elegant and practical method to access short-chain [4+2] C₆₀ monoadducts bearing functional groups for further derivatization, diene-sulfone **5** was subjected to a [4+2] cycloaddition reaction with C₆₀ (Scheme 5).

The diene was prepared quantitatively under our optimum conditions and used in acetone solution after the filtration of the zinc salts. The Diels–Alder reaction with C₆₀ proceeded



Scheme 4 One-pot three-step synthesis of **11**.



Scheme 5 Synthesis of the Diels–Alder [60]fullerene monoadduct **9**.

smoothly at 50 °C to successfully afford monoadduct **9**. After purification by column chromatography on silica gel (toluene–EtOAc = 20 : 1) and precipitation from CHCl₃–pentane, monoadduct **9** was isolated in 56% yield, which was a major improvement over the previous procedures involving either the preparation of **9** from **3** using KI/18-crown-6 in toluene or the preparation of **5** using the NaI procedure. By this way, a facile access to short-chain [4+2] C₆₀ monoadducts was established utilising the valuable 6-C synthon **5** and eliminating the problems arising from the use of reagents which are incompatible with C₆₀.

Conclusions

In summary, we have demonstrated a practical and efficient preparation of the reactive 3,4-di(methylene)tetrahydrothiophene-1,1-dioxide (**5**). Optimisation of the reaction parameters allowed the quantitative preparation of the diene-sulfone **5** via a zinc-induced 1,4-debromination of 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide (**3**) with no signs of polymerisation. In particular, acetone was the solvent of choice for the preparation of **5** from **3** at a concentration of 6 mg mL⁻¹. Activated Zn-dust efficiently promoted the 1,4-debromination step, while the shortest reaction time was achieved with microwave irradiation. The formed diene can be employed in Diels–Alder reactions with dienophiles either in acetone or after exchanging the solvent with dry benzene where the diene remains stable for several weeks at –20 °C. The overall yield of the one-pot procedure (formation of diene **5**/Diels–Alder reaction) when DMAD was utilised as a dienophile was more than 90%. Zinc incompatible dienophiles can be treated with acetone solutions of **5** by simple filtration of the zinc salts prior to the Diels–Alder cycloaddition.

The diene-sulfone **5** synthesised under the optimum conditions reported before was utilised for the synthesis of a [4+2] short-chain C₆₀ monoadduct bearing a masked-diene moiety capable of further derivatization. The applied method led to the successful preparation of cycloadduct **9** which was isolated in 56% yield. Dienophiles with a wide range of chemical functionalities could be employed in order to provide a novel post-synthetic modification strategy via cheletropic extrusion of SO₂ targeting novel C₆₀ derivatives for various applications in materials science. Research in this direction is currently underway in our group and the results will be presented in the near future.

Experimental section

General information

All starting materials were purchased from commercial sources and used without further purification. The solvents were dried using appropriate standard procedures. Zinc dust was activated

following a known procedure.²³ Column chromatography was carried out using Merck silica gel 60H (40–60 nm, 230–300 mesh). Thin-layer chromatography (TLC) was carried out on aluminum plates coated with Merck HF_{254/366} silica gel. Visualisation was accomplished under a 254 nm ultraviolet (UV) light source and/or by immersion in potassium permanganate (KMnO₄) or phosphomolybdic acid (PMA) solutions, followed by heating. ¹H and ¹³C NMR spectra were recorded on Bruker Avance 300 (300 MHz) and Bruker Avance III 500 Ultrashield Plus (500 MHz) spectrometers. Residual non-deuterated solvent was used as the internal standard for ¹H NMR spectra and a carbon signal of the solvent was used as the internal standard for ¹³C NMR spectra. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm) downfield from tetramethylsilane (TMS). The resonance multiplicity patterns are described as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), quintet (quin.), multiplet (m), or combinations of these. Coupling constants (*J*) are quoted in hertz (Hz). Peak assignments were aided by ¹H–¹H COSY, ¹H–¹³C HMQC, DEPT-135 and/or DEPT-90, whenever necessary. High resolution mass spectra were recorded either on a MALDI TOF Bruker Autoflex III Smartbeam instrument using DCTB as a matrix or on a LTQ Orbitrap XL spectrometer. Infrared (IR) spectra were recorded on a Shimadzu FTIR-NIR Prestige-21 spectrometer with a Pike Miracle Ge ATR accessory and bands are quoted in cm⁻¹. Differential scanning calorimetric (DSC) measurements were performed on a DSC TA Q1000 apparatus using a heating curve from 25 to 300 °C under argon atmosphere with a heating rate of 5 °C min⁻¹. The samples (0.8–1.5 mg) were measured in hermetically sealed aluminium pans. Thermogravimetric analysis (TGA) measurements were performed on a TGA TA Q500 analyser under argon atmosphere with about 10 mg of the samples at a heating rate of 10 °C min⁻¹ from 25 to 400 °C, using ceramic pans. A CEM Discover Microwave Reactor was used for microwave experiments and an Elmasonic S 30 (H) ultrasonic laboratory cleaner (220–240 V, 280 W, 50/60 Hz) was used for ultrasonic experiments. Melting points (mp) were determined on a Stuart Scientific SMP10 apparatus and were uncorrected.

3,4-Dimethyl-2,5-dihydrothiophene-1,1-dioxide (7). Prepared according to a literature procedure²¹ with the following modifications: SO₂ (g) balloons were fitted in a dry 500 mL single-neck round-bottomed flask containing a stirred solution of 2,3-dimethylbuta-1,3-diene **6** (20 mL, 14.52 g, 176.80 mmol) in dry CHCl₃ (230 mL). The reaction mixture was stirred for 10 d at 45–50 °C. The solvent was then removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc–hexane = 1 : 1). Further purification by recrystallization from methanol afforded product **7** as colourless long needles (19.13 g, 74%). *R*_f 0.36 (EtOAc–hexane = 1 : 1, PMA). mp 136–137 °C (from MeOH) (lit.,²¹ 134.5–135.5 °C). IR, ν_{max} (ATR)/cm⁻¹: 2985, 2954, 2922, 1444, 1402, 1386, 1288, 1263, 1176, 1109, 823. ¹H NMR (300 MHz, CDCl₃): δ_H 3.68 (4H, d, *J* = 1.13 Hz, 2 × CH₂), 1.74 (6H, t, *J* = 1.13 Hz, 2 × CH₃). ¹³C NMR (75 MHz, CDCl₃): δ_C 125.61 (>C=), 60.70 (CH₂), 14.60 (CH₃).

3,4-Bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide (3). Prepared according to a literature procedure^{17a} with the

following modifications: 3,4-dimethyl-2,5-dihydrothiophene-1,1-dioxide **7** (2.10 g, 14.37 mmol), *N*-bromosuccinimide (5.24 g, 29.45 mmol), benzoyl peroxide (BPO) (13.00 mg, moistened with H₂O, ~25%) and dry DCM (40 mL) were placed in a dry 100 mL single-neck round-bottomed flask fitted with a condenser and a magnetic stirrer. The resulting mixture was refluxed for 20 h under an atmosphere of dry nitrogen. The mixture was then cooled to room temperature, washed with water and dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure gave an orange oil which was purified by column chromatography on silica gel (EtOAc–hexane = 5 : 4). Recrystallization from ethanol (the ethanol solution was stored in the fridge for one day) afforded product **3** as colourless needles (1.79 g, 41%). *R*_f 0.68 (EtOAc–hexane = 5 : 4, UV or KMnO₄). mp 121–122 °C (from EtOH) (lit., ^{17a} 118–120 °C). IR, ν_{max} (ATR)/cm⁻¹: 2976, 2968, 2922, 1454, 1427, 1391, 1313, 1302, 1250, 1229, 1198, 1130, 1112, 1101, 1087, 1005, 893, 864, 818. ¹H NMR (300 MHz, CDCl₃): δ_{H} 4.07 (4H, br s, 2 × BrCH₂), 4.01 (4H, br s, 2 × CH₂-S). ¹³C NMR (75 MHz, CDCl₃): δ_{C} 131.18 (>C=), 58.43 (CH₂-S), 24.00 (Br-CH₂).

[60] Fullerene monoadduct 8. In a dry 100 mL two-neck round-bottomed flask equipped with a magnetic stirrer, condenser and a thermometer, C₆₀ (45.5 mg, 0.063 mmol) was dissolved in *o*-dichlorobenzene (40 mL) under an atmosphere of dry nitrogen. A solution of 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3** (16 mg, 0.053 mmol) in *o*-dichlorobenzene (5 mL) was added and the reaction mixture was heated at 170–180 °C for 30 min. The consumption of the starting material was monitored by TLC (toluene 100% then toluene–EtOAc = 20 : 1). The reaction mixture was allowed to reach room temperature and was subjected to column chromatography on SiO₂ (100% toluene) to remove the baseline material. Removal of the solvent under reduced pressure afforded product **8** as a brown solid which was contaminated with unreacted C₆₀. Further purification of **8** could not be accomplished due to the similar *R*_f with C₆₀ in all attempted eluent systems. The ¹H and ¹³C NMR resonances were in good agreement with the data reported in the literature.⁸

General procedures for the preparation of 3,4-di(methylene)tetrahydrothiophene-1,1-dioxide (5). **Method 1 (zinc-induced 1,4-debromination of 3).** In a dry 10 mL single-neck round-bottomed flask equipped with a magnetic stirrer and a condenser, 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3** (23 mg, 0.076 mmol) was dissolved in dry acetone (4 mL) under an atmosphere of dry nitrogen. Activated Zn-dust (11.4 mg, 0.174 mmol) was then added and the resulting mixture was refluxed for 18 h. [Alternatively, the reaction mixture can be refluxed under sonication for 2 h and 50 min.] During this time the consumption of the starting material was monitored by TLC (EtOAc–hexane = 5 : 4). [¹H NMR monitoring can also be performed using acetone-*d*₆ instead of dry acetone and mesitylene (10.52 μ L, 0.076 mmol) as an internal standard to calculate the yield of the reaction.] The reaction mixture was then filtered and the solid was washed thoroughly with dry acetone. The filtrate and washings were combined, the solvent was exchanged with dry benzene and the solution was stored in the freezer at –20 °C for subsequent reactions without further purification. Under these conditions the product was stable for several weeks giving a

single spot on the TLC (EtOAc–hexane = 5 : 4). However, complete evaporation of the solvent resulted in rapid decomposition to a polymeric material that was not soluble in any solvent tested. The yield of product **5** was calculated by ¹H NMR analysis of the reaction mixture using acetone-*d*₆ and mesitylene (10.52 μ L, 0.076 mmol) as an internal standard and was found to be quantitative (99–100% using conventional heating and 98–99% using sonication). Alternatively, the reaction can be carried out in a microwave reactor, on a 0.038 mmol scale with respect to 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3**, in a sealed tube and by heating at 60 °C (250 W, 21 PSI) for 55 min. The yield was calculated by ¹H NMR analysis of the reaction mixture using acetone-*d*₆ and mesitylene (0.038 mmol) as an internal standard and was found to be 97–98%. **Method 2 (iodine-induced 1,4-debromination of 3):** In a dry 10 mL single-neck round-bottomed flask equipped with a magnetic stirrer, 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3** (23 mg, 0.076 mmol) was dissolved in dry acetone (4 mL) under an atmosphere of dry nitrogen. NaI (34 mg, 0.227 mmol) was then added and the resulting mixture was stirred for 20 h at room temperature. The consumption of the starting material was monitored by TLC (EtOAc–hexane = 5 : 4). The reaction mixture was then filtered and the solid was washed thoroughly with acetone. The filtrate and washings were combined, the solvent was evaporated down to 2/3 volume and 5 mL DCM was added. The organic layer was washed with a 5% sodium thiosulfate solution (3 × 4 mL), water (3 × 4 mL) and dried over Na₂SO₄. Complete evaporation of the solvent resulted in rapid decomposition to a polymeric material that was not soluble in any solvent tested. Therefore, the solution was subjected to column chromatography on SiO₂ (100% DCM). The fractions containing the product were combined and the solvent was exchanged with benzene and stored in the freezer at –20 °C for subsequent reactions without further purification (impurities of similar polarity were still present). *R*_f 0.38 (100% DCM, UV or KMnO₄), *R*_f 0.60 (EtOAc–hexane = 5 : 4, UV or KMnO₄). ¹H NMR (300 MHz, acetone-*d*₆): δ_{H} 5.81 (2H, t, *J* = 1.70 Hz, 2 × =CH), 5.24 (2H, t, *J* = 1.50 Hz, 2 × =CH), 3.97 (4H, t, *J* = 1.50 Hz, 2 × CH₂). ¹³C NMR (75 MHz, acetone-*d*₆): δ_{C} 138.32 (>C=), 111.72 (=CH₂), 57.12 (–CH₂–).

[60] Fullerene monoadduct 9. Method 1 (one-pot procedure: iodine-induced 1,4-debromination of 3/[4+2] cycloaddition of 5 with C₆₀). In a dry 100 mL two-neck round-bottomed flask equipped with a magnetic stirrer, condenser and a thermometer, C₆₀ (51.9 mg, 0.072 mmol) was dissolved in dry toluene (48 mL) under an atmosphere of dry nitrogen. A solution of 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3** (18.2 mg, 0.060 mmol) in dry toluene (2 mL) was then added followed by the addition of 18-crown-6 (119 mg, 0.45 mmol) in dry toluene (2 mL) and KI (24.9 mg, 0.15 mmol). The resulting mixture was heated at 45–50 °C for 24 h and the consumption of the starting material was monitored by TLC (toluene 100% then toluene–EtOAc = 20 : 1). The reaction mixture was then allowed to cool at room temperature and the crude mixture was subjected to column chromatography on SiO₂. Unreacted C₆₀ and other impurities were eluted with toluene and the fullerene monoadduct **9** was then eluted with toluene–EtOAc = 20 : 1. Precipitation from CHCl₃–pentane afforded product **9** as a

brown solid (6.7 mg, 13%). **Method 2 (stepwise procedure: zinc-induced 1,4-debromination of 3/[4+2] cycloaddition of 5 with C₆₀):** In a dry 10 mL single-neck round-bottomed flask fitted with a magnetic stirrer and a condenser, 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3** (23 mg, 0.076 mmol) was dissolved in dry acetone (4 mL) under an atmosphere of dry nitrogen. Activated Zn-dust (11.4 mg, 0.174 mmol) was then added and the resulting mixture was refluxed for 18 h. The consumption of the starting material was monitored by TLC (EtOAc–hexane = 5 : 4). The reaction mixture was then filtered and the solid was washed thoroughly with dry acetone (10 mL). The filtrate and washings were combined and the acetone solution was added in a 250 mL two-neck round-bottomed flask fitted with a magnetic stirrer, condenser and a thermometer, containing a stirred solution of C₆₀ (65.4 mg, 0.091 mmol) in dry toluene (70 mL) under an atmosphere of dry nitrogen. The reaction mixture was heated at 45–50 °C for 12 h and the consumption of the starting material was monitored by TLC (toluene 100% then toluene–EtOAc = 20 : 1). The reaction mixture was allowed to cool at room temperature and the crude mixture was subjected to column chromatography on SiO₂. Unreacted C₆₀ and other impurities were eluted with toluene and the fullerene monoadduct **9** was then eluted with toluene–EtOAc = 20 : 1. Precipitation from CHCl₃–pentane afforded product **9** as a brown solid (36.6 mg, 56%). *R_f* 0.39 (toluene–EtOAc = 20 : 1). ¹H NMR (300 MHz, CS₂–CDCl₃, 1 : 1): δ_H 4.38 (4H, br s, 2 × CH₂), 4.22 (4H, br s, 2 × CH₂). ¹³C NMR (75 MHz, CS₂–CDCl₃, 1 : 1): δ_C 155.14, 147.60, 147.57, 146.48, 146.20, 145.60, 145.48, 145.43, 144.65, 144.52, 143.06, 142.57, 142.10, 141.95, 141.55, 140.17, 135.45, 133.11, 65.32 (sp³ C of C₆₀), 59.68 (CH₂), 40.81 (CH₂). (The 18 signals in the region 155.16–133.11 ppm correspond to sp² carbon atoms; 17 signals are attributed to sp² carbon atoms of C₆₀.) HRMS (MALDI TOF, negative mode, DCTB): calculated for C₆₆H₈ [M–SO₂][–] requires 800.0620; found: 800.0619.

Dimethyl 1,3,4,7-tetrahydrobenzo[c]thiophene-5,6-dicarboxylate-2,2-dioxide (10). (One-pot procedure: zinc-induced 1,4-debromination of 3/[4+2] cycloaddition of 5 with DMAD). In a dry 10 mL single-neck round-bottomed flask fitted with a magnetic stirrer and a condenser, 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3** (23 mg, 0.076 mmol) was dissolved in dry acetone (4 mL) under an atmosphere of dry nitrogen. Activated Zn-dust (11.4 mg, 0.174 mmol) and DMAD (107.5 mg, 93.4 μL, 0.76 mmol) were then added and the resulting mixture was refluxed for 18 h. [Alternatively, the reaction mixture can be refluxed under sonication for 2 h and 50 min.] The consumption of the starting material was monitored by TLC (EtOAc–hexane = 5 : 4). The reaction mixture was then allowed to cool at room temperature, filtered and the solid was washed thoroughly with acetone (10 mL). The filtrate and washings were combined and the solvent was evaporated under reduced pressure to give a colourless solid which was purified by column chromatography on silica gel (EtOAc–hexane = 5 : 4). Product **10** was isolated as a colourless solid (19.9 mg, 92%). Alternatively, the reaction can be carried out in a microwave reactor, in a 0.038 mmol scale with respect to 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3**, in a sealed tube and by heating at 60 °C (250 W, 21 PSI) for 55 min. *R_f* 0.39 (EtOAc–hexane = 5 : 4, UV or KMnO₄). mp

170–171 °C (from MeOH) (lit.,^{15b} 168–169 °C). IR, ν_{max} (ATR)/cm^{–1}: 2974, 2966, 1736, 1713, 1647, 1445, 1418, 1310, 1283, 1256, 1244, 1207, 1196, 1157, 1144, 1111, 1090, 1066, 1001, 941, 914, 852, 819, 783. ¹H NMR (500 MHz, CDCl₃): δ_H 3.73 (6H, br s, 2 × CO₂CH₃), 3.70 (4H, br s, 2 × CH₂), 3.03 (4H, br s, 2 × CH₂). ¹³C NMR (125 MHz, CDCl₃): δ_C 167.13 (C=O), 131.24 (>C=), 124.31 (>C=), 58.37 (CH₂), 52.43 (CO₂CH₃), 28.57 (CH₂). HRMS (APCI+): calculated for C₁₂H₁₅O₆S [M+H]⁺ requires 287.0584; found: 287.0587.

Dimethyl 1,3-dihydrobenzo[c]thiophene-5,6-dicarboxylate-2,2-dioxide (11). (One-pot procedure: zinc-induced 1,4-debromination of 3/[4+2] cycloaddition of 5 with DMAD/aromatization). In a dry 5 mL single-neck round-bottomed flask fitted with a magnetic stirrer and a condenser, 3,4-bis(bromomethyl)-2,5-dihydrothiophene-1,1-dioxide **3** (13.6 mg, 0.045 mmol) was dissolved in dry acetone (4 mL) under an atmosphere of dry nitrogen. Activated Zn-dust (6.7 mg, 0.103 mmol) and DMAD (63.6 mg, 55.0 μL, 0.45 mmol) were then added and the resulting mixture was refluxed for 18 h. The consumption of the starting material was monitored by TLC (EtOAc–hexane = 5 : 4). The reaction mixture was then allowed to cool at room temperature and MnO₂ (19.5 mg, 0.224 mmol) was added. The mixture was refluxed for another 2 h, filtered and the solid was washed thoroughly with acetone (10 mL). The filtrate and washings were combined and the solvent was evaporated under reduced pressure to give a colourless solid which was purified by column chromatography on silica gel (EtOAc–hexane = 5 : 4). Product **11** was isolated as a colourless solid (11.4 mg, 90%). The ¹H and ¹³C NMR resonances were in good agreement with the data reported in the literature.^{10b}

Acknowledgements

This work was financially supported by the Cyprus Research Promotion Foundation (Grant NEKYP/0308/02). We also thank Dr P. A. Koutentis (Department of Chemistry, University of Cyprus) for providing access to the TGA, DSC and the microwave reactor.

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