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Synthesis and reactivity of dipropargylic disulfides: tandem rearrangements, cyclization, and oxidative dimerization☆

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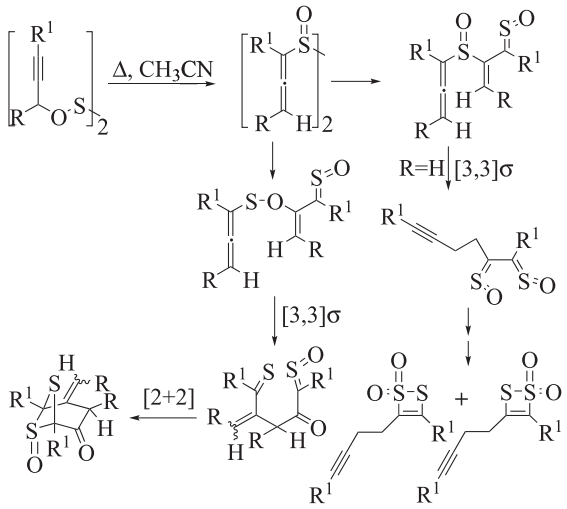
ABSTRACT

Synthesis and facile rearrangement and cyclization reaction of new dipropargylic disulfides are described. A possible mechanism for these transformations involving an initial double [2,3]-sigmatropic rearrangement to the elusive diallenyl disulfides via a thiosulfoxide intermediates is suggested.

1. Introduction

In recent years a major goal of our investigations has been the use of tandem multiple sigmatropic rearrangements and cyclizations of sulfur and selenium bridged propargylic systems, for the preparation of novel complex polycyclic heteroatom systems, which are of synthetic, mechanistic, and probable medicinal interest, in a manner exercising atom economy. Prompted by our recent discovery of an unprecedented sequence of sigmatropic rearrangements and cycloadditions transforming dipropargylic dialkoxy disulfides to novel dithiabicyclic derivatives,[2] (Scheme 1) related to naturally occurring zwiebelanes isolated from allium species,[3–5] we have prepared several dipropargylic disulfides for further oxidation and propargyl/allene isomerization to the corresponding α-disulfones. The latter have attracted little attention relative to the considerable interest in the reactivity of *vic*-disulfoxides.[6,7] This may be due in part to the greater thermodynamic stability of the former. In the event, we were surprised to discover that dipropargylic disulfides themselves undergo facile rearrangement and cyclization reactions under mild thermal conditions.



Scheme 1. Tandem sigmatropic rearrangements and cyclization of dipropargylic dialkoxy disulfides.

2. Results and discussion

While the preparation of disulfides in general is well documented,[8] only one single dipropargyl disulfide has been previously reported.[9] Furthermore, while the preparation of

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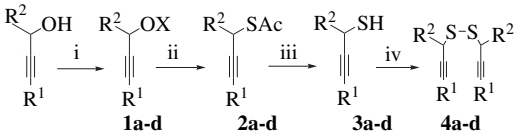
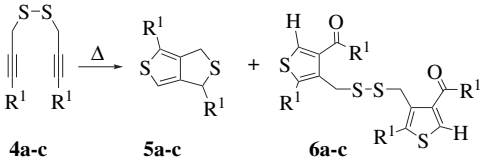
disulfides is usually straightforward, the preparation of propargylic disulfides proved quite challenging. After an extensive review of literature data, an alcohol–thioacetate–thiol route was chosen. A variety of literature methods for the transformation of thioacetate (**2**) to the corresponding thiol (**3**) investigated by us, including reduction with lithium aluminum hydride,[9] alkaline hydrolysis,[10,11] and nickel boride catalyzed methanolysis[12] proved unsuccessful. Eventually, we succeeded in preparing several dipropargyl disulfides (**4**) in reasonable yields by the method described in Scheme 2, involving the use of acidic conditions for the conversion of the propargyl thioacetates (**2**) to the corresponding thiols **3** and the one-pot oxidation of the latter by iodine at 0 °C. Though as a rule the disulfides in question exhibit high reactivity under thermal conditions (see below), the substitution pattern has a significant effect on their stability and reactivity. Thus, while γ-substituted disulfides **4b** and **4c** are stable at room temperature, unsubstituted compound **4a** slowly undergoes decomposition and should be used soon after preparation. With regard to α-substituted disulfide **4d**, we were able to prepare it by oxidation of the corresponding thiol at −78 °C and characterize it only by low-temperature ^{1}H and ^{13}C NMR spectra. Attempted isolation or raising the temperature results in complete decomposition into a mixture of unidentified products.



a: R^1= R^2 = H, X = Ms; **b**: R^1=Me, R^2 = H, X = Ms; **c**: R^1= Ph, R^2 = H, X = Ms; **d**: R^1= H, R^2 = Me, X = Ts;

Scheme 2. Preparation of propargylic disulfides. Reagents and conditions: (i) $MeSO_2Cl$, Et_3N, Et_2O, 1.5 h, 0 °C to rt (**1d**: *p*-TosCl, Et_2O rt, 5 h); (ii) AcSK, MeOH, 2 h, rt (**2d**: reflux, 5 h); (iii) concd HCl, MeOH, reflux, overnight; (iv) I_2, MeOH, 0 °C, 0.5 h (**4d**: −78 °C, 15 min).

With these compounds at hand, we studied their thermal reactivity in various organic solvents. Chromatographic separation of the reaction mixture and extensive spectroscopic determinations, which included full analysis of ^{1}H and ^{13}C NMR data with the aid of 2D techniques, as well as IR and HRMS, revealed formation of two products: thieno-thiophene derivatives **5** and thienyl disulfides **6** in a ratio depending on the reaction conditions (Scheme 3, Table 1).



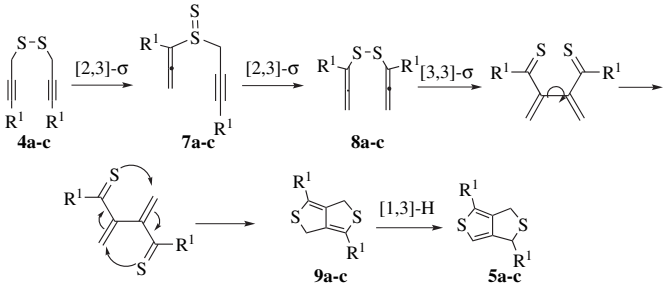
Scheme 3. Thermal reactivity of dipropargylic disulfides.

Table 1
Thermal reactivity of dipropargylic disulfides **4a–c**

Entry	Compound	R^1	Solvent	T °C	Reaction Time (h)	**5**:**6** Ratio[a]	Isolated yield[b] (%)
1	**4a**	H	$CHCl_3$	60	1.5	1:2	40
2	**4a**[c]	H	$CHCl_3$	60	2.0	10:1	80[d]
3	**4b**	Me	$CHCl_3$	60	160	5:1	65
4	**4b**	Me	CH_3CN	60	100	1:2.6	55
5	**4b**	Me	DMSO	70	24	**6b** only	45
7	**4c**	Ph	$CHCl_3$	60	24	6:1	53
8	**4c**	Ph	CH_3CN	60	16	3:1	48

[a] Determined according ^{1}H NMR spectra.
[b] Total yield of products **5** and **6** after column chromatography.
[c] The reaction was performed under Ar.
[d] The yield of product **5a**.

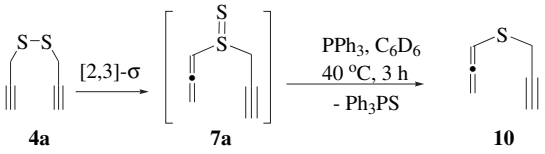
On increasing the polarity of the solvent the reaction is accelerated and the yield of the thienyl disulfides **6** rises. These results may be most reasonably explained by the mechanisms presented in Schemes 4 and 7.



Scheme 4. Thieno-thiophenes from dipropargylic disulfides.

The proposed mechanism for the formation of compounds **5**, involves an initial double [2,3]-sigmatropic rearrangement via a thiosulfoxide intermediate **7** to the elusive diallenyl disulfide **8**. As previously shown by us,[13] disulfide **8** undergoes a [3,3]-sigmatropic rearrangement followed by a double Michael type intramolecular addition to yield **9**. Finally, prototropic aromatization converts intermediate **9** to the isolated product **5** (Scheme 4). The transformation of **4** to **5** is a remarkable example of a five-step tandem process and of atom economy.

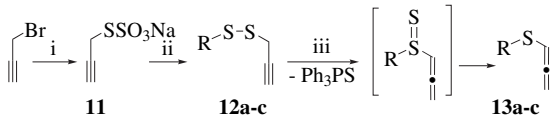
A double [2,3]-sigmatropic rearrangement of α-substituted diallyl disulfides to the thermodynamically more stable γ-substituted derivatives involving a thiosulfoxide intermediate, analogous to the rearrangement of **4** to **8**, has been previously reported by Baldwin.[14] More recently, the sigmatropic rearrangement of an allylic disulfide followed by desulfurization has been used by Crich for the preparation of peptide derived allylic sulfides.[15] To confirm the involvement of the monoallene thiosulfoxide intermediates in the sigmatropic rearrangement of dipropargylic disulfides, desulfurization of the postulated thiosulfoxide with triphenylphosphine was attempted. Indeed, on heating of dipropargyl disulfide **4a** in the presence of triphenylphosphine in deuteriobenzene (in an NMR-tube), formation of allenyl propargyl sulfide **10** was detected almost immediately (Scheme 5). Conversion of **4a** to sulfide **10** at 40 °C proceeds to completion with $t_{1/2}$ =115 min. However, since **10** proved unstable under attempted chromatographic separation from triphenylphosphine sulfide and excess triphenylphosphine, it was characterized by its ^{1}H and ^{13}C NMR spectra only.



Scheme 5. Sigmatropic rearrangement and desulfurization of dipropargyl disulfide.

Further evidence for the proposed mechanism has been obtained from triphenylphosphine induced sulfur degradation of a number of mixed propargyl disulfides **12a–c** to the allenyl sulfides **13a–c**, which were isolated by column chromatography (Scheme 5). The required mixed disulfide **12a–c** were obtained by the reaction of propargylthiosulfate **11** with the corresponding thiolate (Scheme 6).[16] (Formation of the desired unsymmetrical propargylic disulfides was usually accompanied by the formation of small quantities of symmetrical dialkyl or diaryl disulfides. While we were unable to separate these by-products from disulfides **12a–c** by chromatography, reductive desulfurization was nevertheless

carried out upon such mixtures since symmetrical dialkyl or diaryl disulfides are known to be stable to heating with triphenylphosphine for long periods.[17,18]) It should be noted that synthesis of compound **11** presented a challenge since the conventional procedure involving interaction of the appropriate bromide with sodium thiosulfate in water/methanol mixture[19] did not result in any desired product. This hurdle was overcome by carrying out the reaction under phase transfer catalysis conditions (Scheme 6).

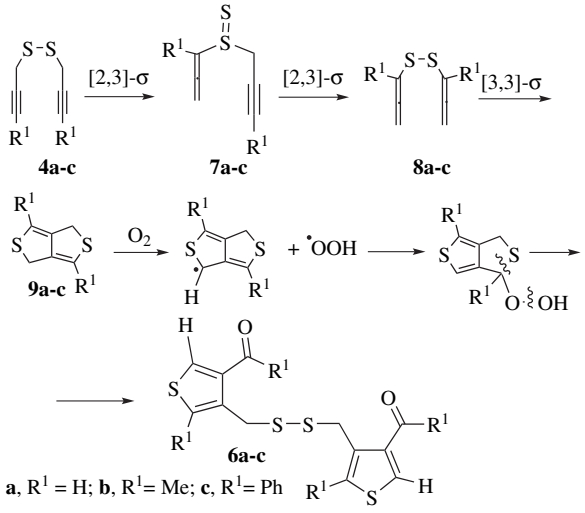


12a, 13a:R = Bn; **12b, 13b**: 4-Tol; **12c, 13c**: 4-Bu^{t}C$_6$H$_4$

Scheme 6. Synthesis, rearrangement and desulfurization of propargylic disulfides. Reagents and conditions: (i) $Na_2SSO_3 \cdot 5H_2O$, $CHCl_3/H_2O$ (4:1), 4 h, reflux, catalyst $BnEt_3NCl$, yield 78%; (ii) RSH/KOH, H_2O, 0.5 h, 0 °C; (iii) PPh_3, C_6H_6, 60 °C.

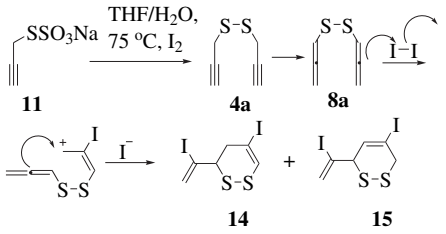
In order to provide further support of the suggested mechanism for the transformation of propargyl disulfides to allenyl sulfides, the effect of substitution on the rate of reaction was investigated. We have thus found that while both dipropargyl and benzyl propargyl disulfides **10** and **12a** react at the same rate ($t_{1/2}$ =115 min), the rate of the reaction of aryl propargyl disulfides **12b** and **12c** was considerably slower ($t_{1/2}$ =289 min).

Formation of disulfides **6** may be explained by air oxidation of the unstable intermediates **9** followed by dimerization, as shown in Scheme 7. An alternative mechanism involving hydrolytic cleavage of one ring of **9** followed by oxidative steps leading to **6** is also conceivable. To prove the involvement of air oxidation in the formation of compounds **6** we have carried out the thermal rearrangement of disulfide **4a** under an Ar atmosphere. Under these conditions the ratio of products **5a**/**6a** changed drastically from 1:2 to 10:1. Compounds of type **6** are related to the thienyl disulfides found as components of distilled oils and extracts of *Allium* species.[20]



Scheme 7. Oxidative dimerization of dipropargylic disulfides.

Supporting the proposed formation of bis-allene intermediates **8**, is the finding that in the preparation of unsubstituted dipropargyl disulfide **4a** by reaction of sodium propargylthiosulfate **11** with iodine in aqueous THF at 75 °C,[21] the two isomeric dihydrodithiins **14** and **15** were obtained in moderate yield in a 1:1 ratio (Scheme 8). Conversion of **14** to **15** may occur by a reversible [1,3]-H shift.



Scheme 8. Synthesis of iodo-dithiins.

3. Conclusions

In summary, we presented here a synthesis of new dipropargylic disulfides, which undergo facile tandem rearrangements and cyclization reaction under mild thermal conditions. The reaction involves elusive thiosulfoxide intermediates and affords novel thiophene derivatives.

4. Experimental section

4.1. General

Melting points were obtained on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet 60 SXB FTIR instrument. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AC-200, DPX-300 or DMX-600 spectrometers in either $CDCl_3$ or other deuterated solvents, using TMS as internal standard. Chemical shifts are reported in δ units, and coupling constants in Hz. COSY and NOSY experiments have been carried out in order to assign ^{1}H and ^{13}C spectra and confirmed the structures of new compounds. High-resolution mass spectra were obtained on a VG-Fison Autospec instrument. Other mass spectra were obtained on a Finningan GC/Ms 4021, with either electronic (EI) or chemical ionization (CI), or on Q ToF micro MS with electrospray (ES). Column chromatography was performed with Merck silica gel 60 (230–400 mesh), and TLC was run on precoated Merck silica gel plates 60 F_{254} (2.00 mm). All commercially available chemicals were used without further purification. Preparation of propargyl mesylates and thioacetates were described by us previously.[22]

4.2. General procedure for the preparation of disulfides 4a–c

To a solution of the respective thioacetate (3.9 mmol) in MeOH (20 mL), 5 drops of concd HCl were added at room temperature and the reaction mixture was heated to reflux overnight. After cooling to 0 °C and 12.5 mL of a 5% solution of I_2 (0.49 g, 1.95 mmol) in MeOH was added slowly. Powdered Na_2SO_3 was added to the reaction mixture to destroy excess I_2, methanol was evaporated under reduced pressure, and the residue was diluted with diethyl ether (50 mL). The ether solution was washed with water (30 mL×2), dried over anhydrous $MgSO_4$, and evaporated to give the products as yellow oils. Disulfides **4a** and **4b** were obtained sufficiently pure, and to avoid possible decomposition upon chromatography, were used as it. Disulfide **4c** was purified by flash chromatography on silica gel with EtOAc/hexanes (1:6) as eluent.

*4.2.1. 3-(Prop-2-ynyldithio)prop-1-yne (**4a**).* Colorless oil (0.18 g, 65%); ν_{max} (neat) 3304, 3277, 2118, 1648, 1400, 1219, 630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.62 (d, J=2.6 Hz, 4H), 2.37 (t, J=2.6 Hz, 2H); ^{13}C (75 MHz, $CDCl_3$): δ 79. 6 (*C*q), 72.8 (*C*H), 27.3 (*C*H$_2$); *m*/*z* (CI, CH_4) 141 (53, $[M-H]^+$); HRMS (CI, CH_4): found 140.9832. $C_6H_5S_2$ requires 140.9833.

*4.2.2. 1-(But-2-ynyldithio)but-2-yne (**4b**).* Colorless oil (0.189 g, 57%); ν_{max} (neat) 2242, 1738, 1223, 1156, 1056, 1027 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 3.57 (q, J=2.6 Hz, 4H), 1.85 (t, J=2.6 Hz 6H); ^{13}C (75 MHz, $CDCl_3$): δ 80.5 (*C*q), 74.6 (*C*q), 28.3 (*C*H_2), 3.8 (*C*H_3); m/z (CI, CH_4) 170 (71, M^+); HRMS (CI/CH_4): found 170.0235. $C_8H_{10}S_2$ requires 170.0224.

*4.2.3. {3-[(3-Phenylprop-2-ynyl)dithio]prop-1-ynyl}benzene (**4c**).* Yellow oil (0.34 g, 60%); R_f (14% EtOAc/hexanes) 0.5; ν_{max} (neat) 3055, 2306, 1593, 1262, 1094, 1024, 801, 751, 686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45–7.28 (m, 10H), 3.85 (s, 4H); ^{13}C (75 MHz, $CDCl_3$): δ 131.8 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 122.9 (C *ipso*), 85.0 (≡*C*–), 84.7 (≡*C*–), 28.9 (*C*H_2); m/z (CI/CH_4) 294 (100, M^+); HRMS (CI/CH_4): found 294.0550. $C_{18}H_{14}S_2$ requires 294.0537.

*4.2.4. But-3-yne-2-thiol (**3d**).* To a solution of *S*-(1-methylprop-2-ynyl) ethanethioate (0.2 g, 1.56 mmol) in CD_3OD (2 mL), 0.1 mL of concd HCl was added at room temperature and the reaction mixture was heated at 50 °C until completion of the reaction as indicated by NMR determination (overnight). According to its NMR spectrum thiol **3d** was obtained as a pure compound and was used without isolation. ^1H NMR (200 MHz, CD_3OD) δ 3.73 (qd, J=6.9, 2.4 Hz, 1H), 2.68 (d, J=2.4 Hz, 1H), 1.52 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 87.3 (Cq), 71.6 (*C*H), 26.9 (*C*H), 20.6 (*C*H_3).

*4.2.5. 3-[(1-Methylprop-2-ynyl)dithio]but-1-yne (**4d**).* To a stirred solution of but-3-yne-2-thiol **3d** prepared from 0.2 g of *S*-(1-methylprop-2-ynyl) ethanethioate in CD_3OD (2 mL) cooled to −78 °C, a 5% solution of I_2 (0.2 g, 0.78 mmol) in CD_3OD (2 mL) was slowly added dropwise. Powdered Na_2SO_3 was added to the reaction mixture to destroy excess I_2, following filtration. This methanolic solution of pure disulfide **4d** (obtained as a mixture of two diastereomers) could be stored at −78 °C for 24 h.

^1H NMR (200 MHz, CD_3OD): δ 3.93 and 3.92 (qd, J=7.2, 2.4 Hz, 1H each), 2.81 (d, J=2.4 Hz, 1H for both diastereomers), 1.53 and 1.52 (d, J=7.2 Hz, 3H each), ^{13}C (75 MHz, CD_3OD): δ 84.9 (≡C– for both diastereomers), 73.9 (≡*C*H for both diastereomers), 36.8 and 36.5 (–*C*H– each), 21.7 and 20.5 (–*C*H_3 each).

4.3. General procedure for the rearrangement of disulfides 4a–c

The disulfide (1 mmol) was dissolved in the appropriate dry solvent (5 mL) and heated under stirring at 60–70 °C until disappearance of the starting material as shown by TLC (for solvents and time see Table 1). After evaporation of the solvent ($CHCl_3$ or CH_3CN) the crude reaction mixture was subjected to column chromatography on silica gel. In the case of entry 4 (Table 1), the DMSO solution was diluted with dichloromethane (30 mL) and washed with water (20 mL×3). The combined organic phase was dried over $MgSO_4$ and evaporated to give the mixture of compounds **5a–c** and **6a–c**, which were separated by column chromatography on silica gel.

*4.3.1. 1H,3H-Thieno[3,4-c]thiophene (**5a**)[23].* White solid, mp 59–60 °C (0.019 g, 13.4%); R_f (25% CH_2Cl_2/hexanes) 0.24; ν_{max} (KBr): 2925, 2371, 1388, 1262, 1034, 804 cm^{-1}; UV (hexane) λ_{max} 230; ^1H NMR (300 MHz, $CDCl_3$): δ 6.83 (s, 2H), 3.92 (s, 4H); ^{13}C (75 MHz, $CDCl_3$): δ 146.3 (C), 115.1 (*C*H), 30.7 (*C*H_2); m/z (CI, CH_4) 143 (21, MH^+), 142 (23, M^+), 141 (16, $[M-H]^+$); HRMS (CI/CH_4): found 142.9991. $C_6H_7S_2$ requires 142.9989.

*4.3.2. 1,4-Dimethyl-1H,3H-thieno[3,4-c]thiophene (**5b**).* White solid, mp 49–50 °C (0.092 g, 54.2%, reaction was carried out in chloroform); R_f (14% EtOAc/hexanes) 0.84; ν_{max} (KBr) 3391, 2927, 1510, 1255, 1058, 806, 746 cm^{-1}; UV (hexane) λ_{max} 232; ^1H NMR (300 MHz, $CDCl_3$): δ 6.53 (d, J=1.2 Hz, 1H), 4.45 (qq, J=6.6 Hz, 1.2 Hz, 1H), 3.79 (q, J=1.2 Hz, 2H), 2.30 (t, J=1.2 Hz, 3H), 1.56 (d, J=6.6 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$): δ 151.6 (C), 142.96 (C), 128.1 (C), 111.1 (*C*H) 42.1 (*C*H), 29.6 (*C*H_2), 23.8 (*C*H_3), 13.5 (*C*H_3); m/z (CI/CH_4) 170 (53, M^+), 155 (100, M^+-CH_3); HRMS (CI/CH_4): found 170.0219. $C_8H_{10}S_2$ requires 170.0224.

*4.3.3. 1,4-Diphenyl-1H,3H-thieno[3,4-c]thiophene (**5c**).* Yellow needles, mp 119–120 °C (0.133 g, 45.4%, reaction was carried out in chloroform); R_f (10% EtOAc/hexanes) 0.49; ν_{max} (KBr) 3441, 2927, 1387, 1265, 1056, 759, 698 cm^{-1}; UV (hexane) λ_{max} 284; ^1H NMR (300 MHz, $CDCl_3$): δ 7.54–7.25 (m, 10H), 6.61 (s, 1H), 5.55 (s, 1H), 4.23 (s, 2H); ^{13}C (50 MHz, $CDCl_3$): δ 151.3 (C), 142.7 (C), 141.5 (C), 134.0 (C) 133.6 (C), 128.9 (*C*H), 128.7 (*C*H), 127.9 (*C*H), 127.6 (*C*H), 127.4 (*C*H), 126.8 (*C*H), 115.2 (*C*H), 50.5(*C*H), 32.0 (*C*H_2); m/z (CI/CH_4) 295 (100, MH^+), 294 (98, M^+), 261 (47, $[M-HS]^+$); HRMS (CI/CH_4): found 294.0536. $C_{18}H_{14}S_2$ requires 294.0537.

*4.3.4. 4-({[(4-Formylthien-3-yl)methyl]dithio}methyl)thiophene-3-carbaldehyde (**6a**).* Light-brown solid, mp 130–132 °C (0.084 g, 26.6%, reaction was carried out in chloroform); R_f (25% hexanes/CH_2Cl_2) 0.15; ν_{max} (KBr) 3092, 2924, 1676(C=O), 1268, 915, 753 cm^{-1}; UV (hexane) λ_{max} 232, 345; ^1H NMR (600 MHz, $CDCl_3$): δ 9.98 (d, J=1.2 Hz, 2H), 8.10 (d, J=3.6 Hz, 2H), 7.19 (dd, J=3.6, 1.2 Hz, 2H), 4.01 (s, 4H); ^{13}C (75 MHz, $CDCl_3$): δ 185.3 (*C*H=O), 140.3 (*C*H), 139.2 (C), 137.1 (C), 126.2 (*C*H), 36.3 (*C*H_2); m/z (CI, CH_4): 315 (10, MH^+), 157 (35, $M^+/2$), 125 (100); HRMS (CI, CH_4) found 314.9651. $C_{12}H_{11}O_2S_4$ requires 314.9642.

*4.3.5. 1-[4-({[(4-Acetyl-2-methylthien-3-yl)methyl]dithio}methyl)-5-methylthien-3-yl]ethanone (**6b**).* Light-brown solid, mp 160–162 °C (0.04 g, 10.8%, reaction was carried out in chloroform); R_f (14% EtOAc/hexanes) 0.18; ν_{max} (KBr) 3082, 2922, 1660(C=O), 1263, 1047, 755 cm^{-1}; UV (hexane) λ_{max} 232, 345; ^1H NMR (600 MHz, $CDCl_3$): δ 7.80 (s, 2H), 4.14 (s, 4H), 2.50 (s, 6H), 2.45 (s, 6H); ^{13}C (75 MHz, $CDCl_3$): δ 193.5(C=O), 139.7 (C), 138.3 (C), 134.2 (C), 131.7 (*C*H), 36.0 (*C*H_2), 28.4 (*C*H_3), 13.6 (*C*H_3); m/z (CI/CH_4): 370 (11, M^+), 185 (24, $M^+/2$), 153 (100, $M^+-C_8H_9S_3O$), HRMS (CI, CH_4) found 370.0152. $C_{16}H_{18}O_2S_4$ requires 370.0190.

*4.3.6. Bis(2-Phenyl-4-benzoyl-3-thienylmethylene)disulfide (**6c**).* Orange solid, mp 220–223 °C (0.047 g, 7.6%, reaction was carried out in chloroform); R_f (10% EtOAc/hexanes) 0.12; ν_{max} (KBr) 3061, 1648)C=O), 1445, 1250, 1076, 907, 697 cm^{-1}; UV (hexane) λ_{max} 284; ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 (s, 2H), 7.60–7.35 (m, 20H), 3.91 (s, 4H); ^{13}C (75 MHz, $CDCl_3$): δ 191.7 (*C*=O), 139.8 (C), 138.6 (C), 133.8 (C) 133.1 (*C*H), 132.5 (*C*H), 130.1 (*C*H), 129.9 (*C*H), 129.6 (*C*H), 128.7 (*C*H), 128.3 (*C*H), 53.4 (*C*H_2); m/z (CI/CH_4) 619 (82, MH^+), 309 (86, $M^+/2$); HRMS (CI, CH_4) found 619.0943. $C_{36}H_{27}O_2S_4$ requires 619.0894.

4.4. Preparation of sodium propargylthiosulfate 11

To a solution of propargyl bromide (0.96 mL, 9 mmol) in chloroform (8 mL), a solution of sodium thiosulfate pentahydrate (2.7 g, 9 mmol) and benzyltriethylammonium chloride (0.2 g, 0.9 mmol) in water (2 mL) was added and the reaction mixture was heated at 60 °C with vigorous stirring for 4 h. The reaction mixture was then evaporated to dryness and the residue was extracted with MeOH (2×50 mL). The combined methanol extract was evaporated and the residue was washed with CH_2Cl_2 to remove the catalyst and the remaining propargyl bromide. The resulting solid was dried in vacuum to give the title compound **11** (1.22 g, 78%) as a white-cream solid; ν_{max} (KBr) 3289, 2952, 2951, 2252, 2117, 1621, 1404, 1237, 1204, 1042, 653 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ=2.88 (t, J=2.6 Hz, 2H), 4.03 (d, J=2.6 Hz, 2H); ^{13}C NMR (75 MHz, D_2O) δ 22.9 (*C*H_2), 72.9 (C), 80.1 (C); ToF ES-MS m/z (%) 151 (100, $HC{\equiv}CCH_2SSO_3^-$), 113 (41, $HS-SO_3^-$).

4.5. General procedure for the preparation of disulfides 12a–c

The respective thiol (1.61 mmol) was added under stirring to an aqueous solution (5 mL) of KOH (0.1 g, 1.78 mmol) and the reaction mixture was heated to reflux for 1 h. After cooling to 0 °C an aqueous solution (5 mL) of sodium propargylthiosulfate **11** (0.56 g, 3.22 mmol) was added. The resulting mixture was further stirred at room temperature for 1 h, diluted with diethyl ether (50 mL), washed with 10% KOH (15 mL) and H_2O (15 mL), dried over $MgSO_4$, and evaporated to give the crude product (**12a–c**). The NMR spectra showed the presence of small amounts of the corresponding symmetrical benzyl or aryl disulfides.

*4.5.1. [(Prop-2-ynyldithio)methyl]benzene (**12a**).* Total yield 65%, benzyl disulfide content 12%. ν_{max} (neat) 3094, 3071, 3026, 2924, 2564, 2054, 1954, 1881, 1749, 1698, 1620, 1447, 1411, 1259, 1221, 1070, 1032, 916, 761, 703 cm^{-1}; ^1H NMR (200 MHz, C_6D_6): δ 7.16–7.00 (m, 5H), 3.69 (s, 2H), 2.80 (d, J=2.6 Hz, 2H), 1.88 (t, J=2.6 Hz, 1H), ^{13}C (200 MHz, C_6D_6): δ 137.5 (C *ipso*), 129.6 (*C*H), 128.6 (*C*H), 127.5 (*C*H), 80.1 (≡C–), 72.6 (≡*C*H), 43.4 (*C*H_2), 27.1 (*C*H_2); m/z (CI, CH_4) 194 (3, M^+), 91 (100, $C_7H_7^+$); HRMS (CI, CH_4) found 194.0211. $C_{10}H_{10}S_2$ requires 194.0224.

*4.5.2. 1-Methyl-4-(prop-2-ynyldithio)benzene (**12b**).* Total yield 60%, 4-tolyl disulfide content 10%; ν_{max} (neat) 3300, 3018, 2919, 2863, 2118, 1896, 1683, 1634, 1489, 1398, 1302, 1220, 1078, 957, 805, 643 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ AA'XX' system: 7.38 and 6.82 (d, J=8.2 Hz, 2H each), 3.13 (d, J=2.6 Hz, 2H), 2.04 (s, 3H), 1.95 (t, J=2.6 Hz, 1H), ^{13}C (200 MHz, C_6D_6): δ 137.8 (C *ipso*), 133.0 (C *ipso*), 129.9 (*C*H), 129.3 (*C*H), 79.0 (≡C–), 72.8 (≡CH), 27.1 (*C*H_2), 21.1 (*C*H_3); m/z (CI, CH_4) 194 (77, M^+); HRMS (CI, CH_4) found 194.0258. $C_{10}H_{10}S_2$ requires 194.0224.

*4.5.3. 1-tert-Butyl-4-(prop-2-ynyldithio)benzene (**12c**).* Total yield 56%, 4-*tert*-butylphenyl disulfide content 15%; ν_{max} (neat) 3291, 2970, 2952, 2902, 2359, 1902, 1650, 1592, 1483, 1397, 1362, 1267, 1202, 1082, 961, 823, 634 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ AA'XX' system: 7.45 and 7.16 (d, J=8.6 Hz, 2H each), 3.14 (d, J=2.4 Hz, 2H), 1.95 (t, J=2.4 Hz, 1H), 1.16 (s, 9H), ^{13}C (200 MHz, C_6D_6): δ 151.1 (C *ipso*), 133.1 (C *ipso*), 129.0 (*C*H), 126.2 (*C*H), 79.09 (≡C–), 72.9 (≡*C*H), 34.7 (*C*$(CH_3)_3$), 31.4 (*C*H_3), 27.2 (*C*H_2); m/z (CI, CH_4) 236 (5.5, M^+); HRMS (CI, CH_4) found 236.0687. $C_{13}H_{16}S_2$ requires 236.0693.

4.6. General procedure for the desulfurization of disulfides 12a–c and 4a

Triphenylphosphine (0.26 g, 1 mmol) was added to a solution of the corresponding disulfide (0.5 mmol) in benzene (10 mL) and the reaction mixture was heated at 60 °C. After completion the reaction (TLC), benzene was evaporated to give the crude reaction mixture as a viscous oil, from which the pure sulfides **13a–c** were separated by column chromatography on silica gel with hexane as eluent.

*4.6.1. 1-(Prop-2-ynylthio)allene (**10**)*[24]. ^1H NMR (700 MHz, C_6D_6): δ 5.61 (t, J=6.3 Hz, 1H), 4.70 (d, J=6.3 Hz, 2H), 2.92 (d, J=2.6 Hz, 2H), 1.87 (t, J=2.6 Hz, 1H); ^{13}C (700 MHz, C_6D_6): δ 206.12 (=*C*=), 86.58 (=*C*H), 80.44 (=*C*H_2), 79.56 (≡*C*–), 71.69 (≡*C*H), 20.47 (*C*H_2).

*4.6.2. [(Propa-1,2-dienylthio)methyl]benzene (**13a**).* Yellow oil (0.045 g, 56%); R_f (hexanes) 0.54; ν_{max} (neat) 3058, 1957 (=*C*=), 1891, 1481, 1432, 1097, 746, 698, 508 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 7.16–7.00 (m, 5H), 5.59 (t, J=6.3 Hz, 1H), 4.66 (d, J=6.3 Hz, 2H), 3.61 (s, 2H); ^{13}C (75 MHz, C_6D_6): δ 206.7 (=C=), 137.6 (C_{ipso}), 129.1 (*C*H), 128.6 (*C*H), 127.3 (*C*H), 87.1 (=*C*H), 80.4 (=*C*H_2), 37.2 (*C*H_2); m/z (CI, CH_4) 163 (22, MH^+), 162 (17, M^+), 161 (14, $[M-H]^+$), 124 (64, $[C_7H_8S]^+$); HRMS(CI, CH_4) found 163.0582. $C_{10}H_{11}S$ requires 163.0581.

*4.6.3. 1-Methyl-4-(propa-1,2-dienylthio)benzene (**13b**).* Yellow oil (0.04 g, 50%); R_f (hexanes) 0.58; ν_{max} (neat) 2922, 1943 (=*C*=), 1897, 1493, 805, 708 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ AA'XX' system: 7.25 and 6.87 (d, J=7.8 Hz, 2H each), 5.83 (t, J=6.5 Hz, 1H), 4.64 (d, J=6.5 Hz, 2H), 2.01 (s, 3H); ^{13}C (200 MHz, C_6D_6): δ 208.1 (=*C*=), 137.2 (C_{ipso}), 134.6 (C_{ipso}), 130.0 (*C*H), 129.8 (*C*H), 87.3 (=*C*H), 78.7 (=*C*H_2), 20.6 (*C*H_3); m/z (CI, CH_4) 163 (73, MH^+), 123 (63, MH^+–'$C_3H_4^{\bullet}$'), 91 (91, MH^+–'$C_3H_4S^{+\bullet}$'); HRMS (CI, CH_4) found 163.0579. $C_{10}H_{11}S$ requires 163.0580.

*4.6.4. 1-tert-Butyl-4-(propa-1,2-dienylthio)benzene (**13c**).* Yellow oil (0.058 g, 57%); R_f (hexanes) 0.62; ν_{max} (neat) 3061, 2959, 1942 (=*C*=), 1898, 1105, 822, 704 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ AA'XX' system: 7.31 and 7.17 (d, J=8.4 Hz, 2H each), 5.86 (d, J=6.4 Hz, 1H), 4.65 (d, J=6.4 Hz, 2H), 1.17 (s, 9H); ^{13}C (200 MHz, C_6D_6): δ 209.0 (=C=), 150.4 (C_{ipso}), 135.1 (C_{ipso}), 133.1 (C_{ipso}), 129.7 (*C*H), 126.2 (*C*H), 87.2 (=*C*H), 78.8 (=*C*H_2), 34.3 (*C*$(CH_3)_3$), 31.2 (*C*H_3); m/z (CI, CH_4) 204 (7, M^+), 166 (51), 151 (100); HRMS (CI, CH_4) found 204.0999. $C_{13}H_{16}S$ requires 204.0973.

Iodo-dithiins. To a solution of freshly prepared sodium propargylthiosulfate **11** (0.0435 g, 0.25 mmol) in 1:1 THF/H_2O (3 mL) I_2 (0.0635 g, 0.25 mmol) was added and the mixture was heated with stirring at 75 °C for 3 h. The reaction mixture was then diluted with dichloromethane (20 mL) and washed with water (10 mL×3). The combined organic phase was dried over $MgSO_4$ and evaporated. Pure iodo-dithiins **14** and **15** were isolated by column chromatography on silica gel, with CH_2Cl_2/hexanes (1:6) as eluent.

*4.6.5. 5-Iodo-3-(1-iodovinyl)-3,4-dihydro-1,2-dithiine (**14**).* Dark oil (0.0077 g, 15.5%); R_f (14% CH_2Cl_2/hexanes) 0.69; ν_{max} (neat) 2921, 1606, 1464, 1408, 1248, 1214, 1136, 1029, 950, 736, 715 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ=3.03 (ddd, J=18.6, 7.7, 1.8 Hz, 1H), 3.08 (ddd, J=18.6, 5.0, 1.8 Hz, 1H), 3.81 (ddd, J=7.7, 5.0, 1.0 Hz, 1H), 6.00 (d, J=2.5 Hz, 1H), 6.20 (dd, J=2.5, 1.0 Hz, 1H), 6.98 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.5 (C-4), 57.8 (C-3), 88.7 (C-5), 105.6 (*C*-vinyl), 126.0 (C-6), 128.6 (*C*H_2-vinyl); m/z (CI, CH_4) 395.8 (20, M^+), 269.9 (40, $[M-I]^+$), 143.0 (38.0); HRMS (CI, CH_4) found 395.7995. $C_6H_6I_2S_2$ requires 395.8000.

*4.6.6. 5-Iodo-3-(1-iodovinyl)-3,6-dihydro-1,2-dithiine (**15**).* Dark oil (0.007 g, 14%); R_f (14% CH_2Cl_2/hexanes) 0.57; ν_{max} (neat) 2921, 2851, 1678, 1464, 1087, 908, 812 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.47 (dd, J=17.8, 1.8 Hz, 1H), 3.60 (dt, J=17.8, 1.0 Hz, 1H), 4.84 (br, 1H), 6.04 (d, J=2.4 Hz, 1H), 6.40 (dd, J=2.4, 1.2 Hz, 1H), 6.78 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.4 (C-6), 52.3 (C-3), 77.2 (C-5), 104.8 (*C*-vinyl), 125.6 (C-4), 130.5 (*C*H_2-vinyl); m/z (CI, CH_4) 395.8 (26, M^+), 324.8 (18), 279.1 (54), 268.9 (38, $[M-I]^+$), 198.9 (100), 142.0 (59); HRMS (CI, CH_4) found 395.7998. $C_6H_6I_2S_2$ requires 395.8000.

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References and notes

1. Presented in part at the 73rd Meeting of the Israel Chemical Society, Tel-Aviv, Feb. 4–5, 2008; Taken from Meridor D., M.Sc. Thesis, Bar-Ilan University, 2008.
2. Braverman, S.; Pechenick, T.; Gottlieb, H. E.; Sprecher, M. *J. Am. Chem. Soc.* **2003**, *125*, 14290.
3. Block, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1135.
4. Block, E.; Bayer, T.; Naganathan, S.; Zhao, S.-H. *J. Am. Chem. Soc.* **1996**, *118*, 2799.
5. Block, E.; Thiruvazhi, M.; Toscano, P. J.; Bayer, T.; Grisoni, S.; Zhao, S.-H. *J. Am. Chem. Soc.* **1996**, *118*, 2790.
6. Freeman, F. *Chem. Rev.* **1984**, *84*, 117.

7. Lacombe, S. M. *Rev. Heteroatom Chem.* **1999**, *21*, 1.
8. Gundermann, K.-D.; Humke, K. In *Houben-Weyl Methoden der Organische Chemie*; Klaymann, D., Ed.; Thieme: Stuttgart, 1985; pp 129–187.
9. Minozzi, M.; Nanni, D.; Walton, J. C. *J. Org. Chem.* **2004**, *69*, 2056.
10. Naud, C.; Calas, P.; Blancou, H.; Commeyras, A. *J. Fluorine Chem.* **2000**, *104*, 173.
11. Jeong, L. S.; Kim, H. O.; Moon, H. R.; Hong, J. H.; Yoo, S. J.; Choi, W. J.; Chun, M. W.; Lee, C. K. *J. Med. Chem.* **2001**, *44*, 806.
12. Choi, J.; Yoon, N. M. *Synlett* **1995**, 1073.
13. Braverman, S.; Freund, M. *Tetrahedron* **1990**, *46*, 5759.
14. Hoefle, G.; Baldwin, J. E. *J. Am. Chem. Soc.* **1971**, *93*, 6307.
15. Crich, D.; Brebion, F.; Krishnamurthy, V. *Org. Lett.* **2006**, *8*, 3593.
16. Hiver, P.; Dicko, A.; Paquer, D. *Tetrahedron Lett.* **1994**, *35*, 9569.
17. Challenger, F.; Greenwood, D. *J. Chem. Soc.* **1950**, 26.
18. Moore, C. G.; Trego, B. T.; City, W. G. *Tetrahedron* **1962**, *18*, 205.
19. Milligan, B.; Swan, J. M. *J. Chem. Soc.* **1963**, 6008.
20. Block, E.; Thiruvazhi, M. *J. Agric. Food Chem.* **1993**, *41*, 2235.
21. Westlake, H. E., Jr.; Dougherty, G. *J. Am. Chem. Soc.* **1942**, *64*, 149.
22. Braverman, S.; Cherkinsky, M.; Birsa, M. L.; Tichman, S.; Goldberg, I. *Tetrahedron Lett.* **2001**, *42*, 7485.
23. Zwanenburg, D. J.; Wynberg, H. *J. Org. Chem.* **1969**, *34*, 333.
24. Cheng, Y. S. P.; Garratt, P. J.; Neoh, S. B.; Rumjanek, V. M. *Isr. J. Chem.* **1985**, *26*, 101.