Addition of Thiols to Sulfonylacetylenes: Synthetic Applications

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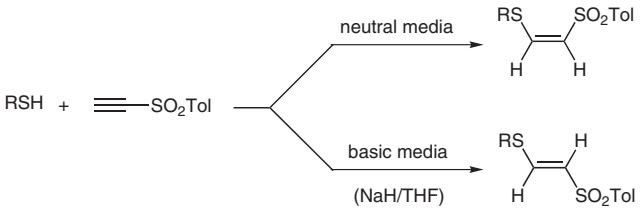
Dedicated to Professor Victor Riera on the occasion of his 70th birthday

Abstract: The addition of propane-1,3-dithiol to *p*-toluenesulfonylacetylene affords the dithioacetal **1**. This compound is a useful building block for the synthesis of new functionalized sulfanylvinylsulfonyl derivatives.

Key words: dithioacetals, base-induced, ring-opening, S-alkylation, sulfanylvinylsulfonyl derivatives

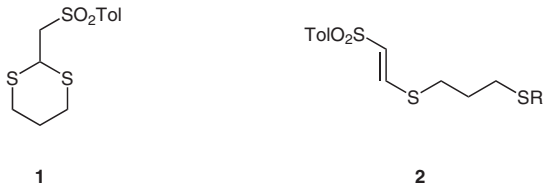
The base-catalyzed addition of thiols to acetylenic sulfones has been scarcely studied despite the fact that the first report of this reaction was published as early as in 1964.[1] Some examples concerning the regio-[2] and stereoselectivity[3] of this reaction have been reported and the process has been used for the protection of the thiol functionality.[4] Concerning the stereochemistry of this reaction we have recently reported that it may be controlled depending on the reaction conditions (Scheme 1).[5]



Scheme 1

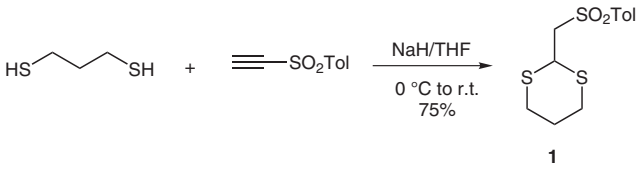
On the basis of these precedents, we have considered the synthetic uses of cyclic thioacetals such as **1**[6] in order to obtain the hitherto unknown highly functionalized *E*-sulfanylvinylsulfonyl derivatives **2** (Figure 1).

The synthesis of thioacetal **1** and oxathioacetal **3** was achieved by the reaction of propane-1,3-dithiol and 2-mercaptoethanol with *p*-toluenesulfonylacetylene in the presence of NaH (1.1 equiv) in THF as solvent (Scheme 2).[7]



1 2

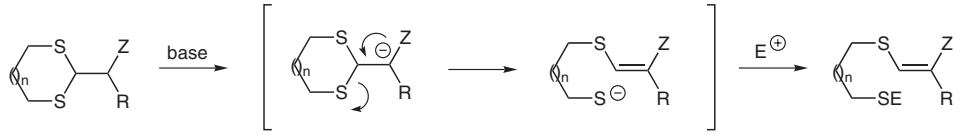
Figure 1 Compounds **1** and **2**



Scheme 2

The 1,3-dithianyl group attached to a carbon atom bearing one or two electron-withdrawing groups such as ester,[8] ketone[9] or TMS[10] undergoes dithiane ring-cleavage with concomitant substitution reaction on the anionic sulfur atom (Scheme 3).

Similar reactions have been observed in related α,β-unsaturated acetals and ketals.[11] To the best of our knowledge, this reaction has never been applied to derivatives such as **1** or **3** with an arylsulfonyl group as electron-withdrawing substituent. Thus, we decided to explore the behavior of



Scheme 3

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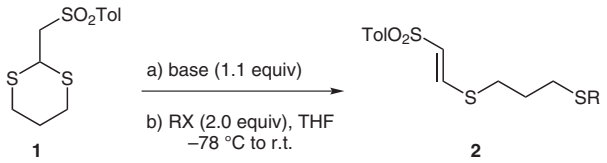
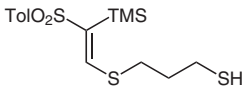
Table 1 Sequential Base-Induced Ring-Opening–S-Alkylation of Dithioacetal **1**



1 **2**

Entry	Base	Time (h)	Electrophile	Product (R)	Yield (%)[a]	Yield (%)[a] of recovered **1**
1	LDA	18	MeI	**2a** (Me)	75	–
2	LDA	18	BnOMs	**2b** (Bn)	35[b]	6
3	LDA	18		**2c** 	60	20
4	BuLi	4		**2c** 	65	10
5	LDA	18		**2d** 	64	20
6	BuLi	4		**2d** 	48	18
7	LDA	18	$MeOCH_2Br$	**2e** (CH_2OMe)	75	–
8	LDA	18	$MeOCOCH_2Br$	**2f** (CH_2CO_2Me)	36	20
9	LDA	2	$PhCOCH_2Br$	**2g** (CH_2COPh)	30	–[c]
10	LDA	18	Me_3SiCl	**4**[d]	24	–

[a] Isolated yields.
[b] The reaction with BnBr under different experimental conditions gave 25–28% of compound **2b** and 36–46% of recovered starting material.
[c] Almost 50% of starting material was recovered in different experiments.
[d] Compound **4** was the only isolated product. The stereochemistry of the double bond was confirmed by NOE experiment. For a discussion on the mechanism of this silicon migration, see ref. 10a.



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compounds **1** and **3** towards basic reagents in the presence of representative electrophiles.

The reaction of compound **3** with different basic reagents (LDA, organolithium derivatives) in the presence of different electrophilic reagents afforded complex reaction mixtures from which we were unable to isolate any identifiable product with the exception of starting material. In sharp contrast, the reaction of compound **1** with LDA or BuLi under different experimental conditions gave rise to the expected product arising from the sequence ring-opening–S-alkylation process. The results are given in Table 1.

It should be pointed out that only *E*-diastereoisomers were obtained and that these products constitute new functionalized sulfanylvinylsulfonyl derivatives, suitable building blocks for further useful transformations.[12]

In summary, a new aspect of the addition reaction of thiols to sulfonylacetylene has been considered: the sequence ring-opening–S-alkylation reactions of dithioacetals **1**, giving new functionalized sulfanylvinylsulfonyl derivatives.

Reagents obtained from commercial sources were used as received, and solvents were dried prior to use. Silica gel 60 F254 was used for TLC, and the spots were detected with UV or $KMnO_4$ solution. Flash column chromatography was carried out on silica gel 60. Melting points were determined on a Büchi 512 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 instrument at 300 (^1H) and 75 MHz (^{13}C) in $CDCl_3$ solution, with Me_4Si as internal reference; δ in ppm. Elemental analyses were performed at the Universidad Complutense de Madrid.

1,3-Dithian-2-ylmethyl 4-Methylphenyl Sulfone (1)

To a solution of propane-1,3-dithiol (0.1 mL, 1 mmol) in THF (5 mL) at 0 °C, was added NaH (60% in mineral oil, 44 mg, 1.1 mmol). After stirring for 10 min, a solution of *p*-toluenesulfonylacetylene (198 mg, 1.1 mmol) in THF (5 mL) was added and the mixture was stirred for 3 h at r.t. The reaction was quenched with phosphate buffer and extracted with CH_2Cl_2. The organic extracts were collected and dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction product was purified by column chromatography on silica gel using a mixture of hexane–EtOAc (5:1) as eluent affording 276 mg (96%) of **1** as a white solid; mp 107–108 °C.

IR (KBr): 2902.7, 1317.3, 1151.4, 732.9 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.74–1.94 (m, 1 H), 1.98–2.16 (m, 1 H), 2.45 (s, 3 H), 2.84 (dt, *J* = 9.7, 3.4 Hz, 4 H), 3.50 (d, *J* = 6.6 Hz, 2 H), 4.46 (t, *J* = 6.6 Hz, 1 H), 7.35 (d, *J* = 8.3 Hz, 2 H), 7.82 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.5, 24.6, 29.3, 38.9, 60.7, 128.0, 129.7, 136.3, 144.9.

Anal. Calcd for $C_{12}H_{16}O_2S_3$: C, 49.97; H, 5.59; O, 11.09; S, 33.35. Found: C, 50.09; H, 5.48; O, 10.99; S, 33.40.

2-{[(4-Methylphenyl)sulfonyl]methyl}-1,3-oxathiolane (3)

To a solution of 2-mercaptoethanol (0.07 mL, 1 mmol) in THF (5 mL) at 0 °C, was added NaH (60% in mineral oil, 44 mg, 1.1 mmol). After stirring 10 min, a solution of *p*-toluenesulfonylacetylene (198 mg, 1.1 mmol) in THF (5 mL) was added and the mixture was stirred for 20 min at 0 °C. The reaction was quenched with phosphate buffer and extracted with CH_2Cl_2. The organic extracts were collected and dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude reaction product was purified by column chromatography on silica gel using a mixture of hexane–EtOAc (5:1) as eluent affording 206 mg (80%) of **3**. This compound had been previously obtained in 9% isolated yield.[4a]

Base-Induced Ring-Opening–S-Alkylation of Dithioacetal 1; General Procedure

To a solution of *n*-BuLi (1.1 equiv, 1.6 M solution in hexane) cooled to –78 °C or LDA [generated by stirring a solution of diisopropylamine (1.1 equiv) and *n*-BuLi (1.1 equiv, 1.6 M solution in hexane) in THF for 30 min at –78 °C under argon] were added successively the corresponding electrophile (2 equiv, see Table 1) and **1** (1 equiv) dissolved in THF (0.1 M of **1**). The resulting solution was stirred for the time indicated in Table 1 and allowed to reach r.t. The reaction was quenched with brine and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The resulting crude was purified by silica gel chromatography eluting with hexane–EtOAc system of appropriate polarity to afford compounds **2a**–**g** and **4** (Table 1).

4-Methylphenyl (*E*)-2-{[3-Methylsulfanyl)propyl]sulfanyl}-vinyl Sulfone (2a)

Pale-yellow oil.

IR ($CHCl_3$): 2923.9, 2852.5, 1550.7, 1139.9 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.94 (q, *J* = 7.1 Hz, 2 H), 2.05 (s, 3 H), 2.43 (s, 3 H), 2.58 (t, *J* = 6.8 Hz, 2 H), 2.90 (t, *J* = 7.3 Hz, 2 H), 6.20 (d, *J* = 14.6 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.69 (d, *J* = 14.9 Hz, 1 H), 7.75 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 15.8, 22.0, 27.8, 31.2, 33.2, 122.7, 127.8, 130.3, 138.6, 144.5, 145.0.

Anal. Calcd for $C_{13}H_{18}O_2S_3$: C, 51.62; H, 6.00; O, 10.58; S, 31.80. Found: C, 51.56; H, 5.92; O, 10.70; S, 31.78.

(*E*)-2-{[3-Benzylsulfanyl)propyl]sulfanyl}vinyl 4-Methylphenyl Sulfone (2b)

Pale-yellow oil.

IR ($CHCl_3$): 2925.8, 1454.2, 1317.3, 1269.1 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.86 (q, *J* = 7.1 Hz, 2 H), 2.43 (s, 3 H), 2.49 (t, *J* = 6.9 Hz, 2 H), 2.82 (t, *J* = 7.3 Hz, 2 H), 3.68 (s, 2 H), 6.16 (d, *J* = 14.5 Hz, 1 H), 7.23–7.34 (m, 7 H), 7.67 (d, *J* = 14.5 Hz, 1 H), 7.76 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 22.0, 28.0, 30.2, 31.3, 36.6, 122.7, 127.6, 127.8, 129.0, 129.2, 130.3, 138.4, 138.6, 144.5, 145.0.

Anal. Calcd for $C_{19}H_{22}O_2S_3$: C, 60.28; H, 5.86; O, 8.45; S, 25.41. Found: C, 60.33; H, 5.91; O, 8.39; S, 25.50.

4-Methylphenyl (*E*)-2-{[3-(2-Prop-2-ynylsulfanyl)propyl]-sulfanyl}vinyl Sulfone (2c)

Pale-yellow oil.

IR ($CHCl_3$): 3286.5, 2922.0, 1595.0, 1301.9 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.96 (q, *J* = 7.1 Hz, 2 H), 2.25 (t, *J* = 2.6 Hz, 1 H), 2.41 (s, 3 H), 2.75 (t, *J* = 6.9 Hz, 2 H), 2.89 (t, *J* = 7.1 Hz, 2 H), 3.20 (d, *J* = 2.6 Hz, 2 H), 6.18 (d, *J* = 14.7 Hz), 1 H, 7.31 (d, *J* = 8.2 Hz, 2 H), 7.67 (d, *J* = 14.7 Hz, 1 H), 7.73 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.6, 22.0, 27.9, 30.6, 31.3, 71.9, 80.0, 122.7, 127.8, 130.3, 138.5, 144.5, 144.9.

Anal. Calcd for $C_{15}H_{18}O_2S_3$: C, 55.18; H, 5.56; O, 9.80; S, 29.46. Found: C, 55.12; H, 5.60; O, 9.72; S, 29.50.

(*E*)-2-{[3-Allylsulfanyl)propyl]sulfanyl}vinyl 4-Methylphenyl Sulfone (2d)

Pale-yellow oil.

IR ($CHCl_3$): 2923.9, 1635.5, 1315.4 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.88 (q, *J* = 7.0 Hz, 2 H), 2.41 (s, 3 H), 2.51 (t, *J* = 6.9 Hz, 2 H), 2.86 (t, *J* = 7.1 Hz, 2 H), 3.46 (d, *J* = 7.1 Hz, 2 H), 5.05 (d, *J* = 17.3 Hz, 1 H), 5.07 (d, *J* = 9.6 Hz, 1 H), 5.66–5.80 (m, 1 H), 6.18 (d, *J* = 14.5 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 7.67 (d, *J* = 14.7 Hz, 1 H), 7.73 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.4, 27.5, 28.9, 30.7, 34.5, 117.2, 122.1, 127.2, 129.7, 133.9, 138.1, 143.9, 144.4.

Anal. Calcd for $C_{15}H_{20}O_2S_3$: C, 54.84; H, 6.14; O, 9.74; S, 29.28. Found: C, 54.80; H, 6.21; O, 9.80; S, 29.21.

(*E*)-2-{[3-[(Methoxymethyl)sulfanyl]propyl}sulfanyl)vinyl 4-Methylphenyl Sulfone (2e)

Pale-yellow oil.

IR ($CHCl_3$): 2925.8, 2856.4, 1448.4, 1301.9 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.95 (q, *J* = 7.3 Hz, 2 H), 2.41 (s, 3 H), 2.66 (t, *J* = 7.1 Hz, 2 H), 2.88 (t, *J* = 7.1 Hz, 2 H), 3.31 (s, 3 H), 4.58 (s, 2 H), 6.18 (d, *J* = 14.9 Hz, 1 H), 7.30 (d, *J* = 8.1 Hz, 2 H), 7.68 (d, *J* = 15.3 Hz, 1 H), 7.74 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.5, 28.4, 29.7, 30.8, 55.7, 75.5, 122.3, 127.3, 129.8, 138.2, 143.9, 144.5.

Anal. Calcd for $C_{14}H_{20}O_3S_3$: C, 50.57; H, 6.06; O, 14.44; S, 28.93. Found: C, 50.62; H, 5.99; O, 14.39; S, 29.84.

Methyl ({[3-({(*E*)-2-[(4-Methylphenyl)sulfonyl]vinyl}-sulfanyl)propyl]sulfanyl}acetate(2f)
Pale-yellow oil.

IR ($CHCl_3$): 2952.8, 2925.8, 1733.9, 1301.9, 1143.7 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.96 (q, *J* = 7.0 Hz, 2 H), 2.44 (s, 3 H), 2.73 (t, *J* = 6.9 Hz, 2 H), 2.89 (t, *J* = 7.1 Hz, 2 H), 3.20 (s, 2 H), 3.74 (s, 3 H), 6.18 (d, *J* = 14.7 Hz, 1 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.68 (d, *J* = 14.7 Hz, 1 H), 7.75 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.6, 27.4, 30.7, 31.2, 33.2, 52.5, 122.4, 127.4, 129.9, 138.1, 144.1, 144.4, 170.6.

Anal. Calcd for $C_{15}H_{20}O_4S_3$: C, 49.97; H, 5.59; O, 17.75; S, 26.68. Found: C, 50.05; H, 5.61; O, 17.70; S, 26.61.

2-{[3-({(*E*)-2-[(4-Methylphenyl)sulfonyl]vinyl}sulfanyl)-propyl]sulfanyl}-1-phenylethanone (2g)
White solid; mp 60–61 °C.

IR (KBr): 2922.0, 2360.7, 1278.7, 1143.7 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 1.96 (q, *J* = 7.0 Hz, 2 H), 2.43 (s, 3 H), 2.66 (t, *J* = 6.9 Hz, 2 H), 2.89 (t, *J* = 7.1 Hz, 2 H), 3.78 (s, 2 H), 6.18 (d, *J* = 14.7 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.48 (t, *J* = 8.0 Hz, 2 H), 7.60 (t, *J* = 7.1 Hz, 1 H), 7.67 (d, *J* = 14.7 Hz, 1 H), 7.75 (d, *J* = 8.2 Hz, 2 H), 7.97 (d, *J* = 7.9 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.6, 27.3, 30.7, 30.7, 36.8, 122.3, 127.4, 128.7, 129.9, 133.6, 134.9, 138.1, 144.0, 144.4, 194.2.

Anal. Calcd for $C_{20}H_{22}O_3S_3$: C, 59.08; H, 5.45; O, 11.81; S, 23.66. Found: C, 58.98; H, 5.51; O, 11.87; S, 23.60.

3-{[(*E*)-2-[(4-Methylphenyl)sulfonyl]-2-(trimethylsilyl)-vinyl]sulfanyl}propane-1-thiol (4)
Pale-yellow oil.

IR ($CHCl_3$): 2927.7, 1251.7, 1137.9 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz): δ = 0.16 (s, 9 H), 1.40 (t, *J* = 8.1 Hz, 1 H), 2.04 (q, *J* = 7.0 Hz, 2 H), 2.43 (s, 3 H), 2.68 (s, *J* = 7.0 Hz, 2 H), 3.07 (t, *J* = 7.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.66 (d, *J* = 8.1 Hz, 2 H), 8.34 (s, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = –0.9, 21.5, 22.8, 34.0, 34.1, 127.1, 129.5, 134.8, 139.3, 143.3, 157.8.

Anal. Calcd for $C_{15}H_{24}O_2S_3Si$: C, 49.96; H, 6.71; O, 8.87; S, 26.67; Si, 7.79. Found: C, 49.89; H, 6.65; O, 8.82; S, 26.62; Si, 7.85.

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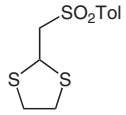

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Figure 2 Thioacetal **5**

(7) The reaction of propane-1,3-dithiol and *p*-toluenesulfonylacetylene in presence of Me_3P (THF) affords a mixture of compounds **6** and **7** (mixture of diastereomers) (Figure 3).

6 **7**

Figure 3 Compounds **6** and **7**

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