Tetrahedron Letters 49 (2008) 6670–6673

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A powerful method to prepare sulfur-rich macrocycles

Andrzej Z. Rys [a], Imad A. Abu-Yousef [b,*], David N. Harpp [a]

[a] Department of Chemistry, McGill University, Montreal, Canada H3A 2K6
[b] Department of Chemistry, American University of Sharjah, PO Box 26666, Sharjah, United Arab Emirates

ARTICLE INFO

Article history:
Received 14 July 2008
Revised 6 September 2008
Accepted 9 September 2008
Available online 13 September 2008

Keywords:
Macrocylces
Polysulfanes
Elemental sulfur
Sulfenyl chloride
Thiosulfenyl chloride

ABSTRACT

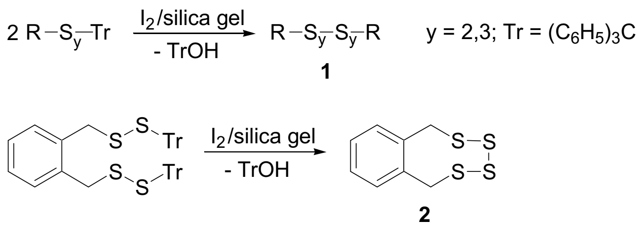
Various cyclic polysulfanes (up to a 16-membered ring) have been selectively obtained from the corresponding disubstituted trityl-protected polysulfane benzene derivatives upon treatment with elemental iodine in the presence of silica gel. Depending on the position of the sulfur-rich moieties and the presence of a methylene linker between the benzene ring and sulfur atoms, two types of products containing either one or two benzene subunits have been isolated. The scope of the reaction, its selectivity, and mechanism are discussed.

The inherent instability of the S–S bonds causes polysulfanes vulnerable toward nucleophiles (especially those with unfavorable sulfur–sulfur interactions). This nucleophilic assault cleaves the molecule, resulting in either equilibration that is, cleaving and re-forming the polysulfanes but with different number of sulfur atoms or even causing a complete disintegration of the sulfur-rich moiety. The latter process is the origin of one of the most interesting properties of both synthetic and naturally-occurring polysulfanes, that is, their cytotoxicity. In their hosts, polysulfanes can act as natural antibacterials and antifungals.[1] The mechanism of this protective activity involves a negatively charged sulfur species formed as a result of the S–S scission, inducing a release of hydroxyl radicals.[2] A reaction cascade can be induced as in calicheamicin, esperamicin, and leinamycin resulting in a selective cleavage of DNA via a generated diradical species.[3] Recently, there has been considerable interest in new, similar products[4] in living organisms.[5] Nevertheless, due to the instability of the S–S bonds in polysulfanes, numerous analogs might have escaped detection to date.[6]

To access this class, existing methodologies have certain limitations as an exclusive formation of a thermodynamic product[7] and/or drawbacks such as working with difficult-to-purify sulfur chlorides S_yC1_2 ($y > 1$). As polysulfanes do not separate easily, a non-selective, direct reaction of thiols and sulfenyl chlorides is likely unsuitable for preparative purposes,[8] thus, other methodologies involving protected thiols have been developed. An effective technique, based on ligand-transfer methodology was developed by Steudel[9] involving the coupling of sulfenyl chlorides with sulfur-rich transition metal ligands. The use of sulfenyl chlorides, however, brings some inconveniences, such as their preparation by chlorination of thiols with either sulfuryl chloride or chlorine.[9] An interesting way to prepare benzyl disulfanes was reported by Tarbell[10] involving the coupling of two molecules of trityl benzyl sulfanes, (TrSR) using iodine in methanol. This method has resulted in its common use.[11]

We recently extended the original Tarbell approach[12] to prepare linear polysulfanes involving unsymmetrical trityl-substituted polysulfane precursors. Taking an advantage of the ease with which the trityl group is removed, a series of tetra- and hexasulfanes **1** were prepared when a suitable starting material was treated with iodine in ether in the presence of silica gel (Scheme 1). The same approach was followed to prepare a cyclic eight-membered ring tetrathiocin **2**—a known and relatively stable compound (Scheme 1).[13]

Here, we report our results in the preparation of new unstable polysulfanes. A series of *o*-, *m*-, and *p*-substituted trityl polysulfanes **3**–**7**, with two and three sulfur atoms, were used as starting

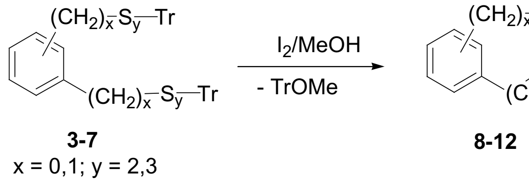


Scheme 1.

---

* Corresponding author. Tel.: +971 6 515 2410; fax: +971 6 515 2450.
E-mail address: iabuyousef@aus.edu (I. A. Abu-Yousef).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.051



Scheme 2.

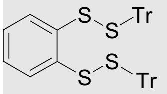
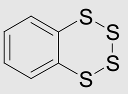
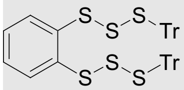
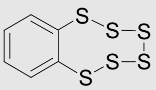
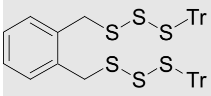
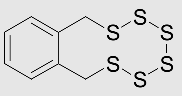
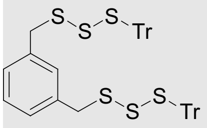
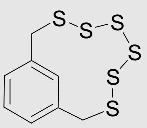
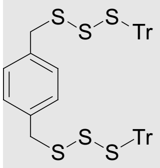
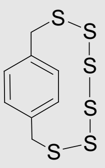
materials. They were synthesized from the corresponding dithiols and trityl sulfenyl/thiosulfenyl chlorides.[12] Compounds **3**–**7** in CH_2Cl_2 were coupled using iodine in the presence of either methanol or silica gel (source of hydroxyl groups), to give various polysulfanes (Scheme 2); the results are shown in Table 1.

The reaction is usually completed in less than 1 min, and the amount of some impurities started to increase with extended reaction times such as 10 min (a time required for the linear polysulfanes to react). Excess iodine and some remaining reactive species such as trityl iodide were destroyed with an aqueous solution of sodium thiosulfate. The aqueous layer is then separated, and the organic layer is washed with water; the product is eluted with hexanes.

It is crucial to acidify the crude polysulfane with a small amount of acetic acid before column chromatography, as it prevents equilibration of the product when loaded on the column. Acetic acid is also added to the solution before removal of the solvent to prevent polymerization.

Two *ortho*-substituted benzene derivatives **3** and **4** gave the corresponding cyclic tetra- and hexasulfanes **8** and **9**, respectively. While hexasulfane **9** is a novel structure, a 3,4-dimethyl-substituted analog of tetrathiocin **8** was reported by Feher.[14] Both compounds **8** and **9** have been isolated as yellow oils; they did not solidify even after 5 days at −25 °C. They have been characterized by ^1H and ^{13}C NMR, EI MS and exact mass EI MS. Mass spectra indicate that thermal stabilities of the products differ from each other. While a molecular ion peak *m*/*z* 204 [M^+] for tetrasulfane **8** was the most abundant, only a weak molecular ion peak of hexasulfane **9** at *m*/*z* 268 [M^+] was observed. It was accompanied by peaks corresponding to sulfur loss, starting with *m*/*z* 236 [M^+-S], *m*/*z* 204 [M^+-2S], and with *m*/*z* 172 [M^+-3S] corresponding to trithiole $C_6H_4S_3$ being the most abundant.

Table 1
Reactions of trityl polysulfanes **3**–**7** with I_2 in the presence of either methanol or silica gel

Starting material		Product		% Yield	ROH
	**3**		**8**	57	Silica gel
	**4**		**9**	58	Silica gel
	**5**		**10**	72	Silica gel MeOH
	**6**		**11**	27	Silica gel
	**7**		**12**	0	MeOH

Apparently, hexasulfane **9** isolated from the column was contaminated with its dimer **13**. The dimer is much less soluble, and because of that it was isolated from the collected fractions and characterized by a single crystal X-ray crystallography (Fig. 1).[15]

1,2-Bis-trityltrisulfanylmethylbenzene (**5**) gave the corresponding hexasulfane **10** in 72% yield. Column chromatography resulted in the isolation of a pure product that solidified when solvent was removed. The product was characterized by ^1H, ^{13}C NMR, and by single crystal X-ray crystallography (Fig. 2).[16] Only a broad 120–170 °C melting range was observed despite repeated recrystallizations. A separate experiment has demonstrated that **10** starts to decompose even below the temperature when initial melting occurs. Thus, heating a sample of **10** for 10 min at 110 °C resulted in its partial conversion (ca. 1/3 of the sample) to some unidentified (likely polymeric) species characterized by a broad ^1H NMR peak at 4.25 ppm.

The reaction has been extended to the other bis-trityltrisulfanylmethylbenzene derivatives. Treatment of 1,3-bis-trityltrisulfanylmethylbenzene (**6**) with iodine in the presence of silica gel resulted in hexasulfane **11** as a main product. Compound **11** has been characterized by ^1H and ^{13}C NMR as well as by single crystal X-ray crystallography (Fig. 3).[17]

In spite of applying the same coupling conditions to 1,4-bis-trityltrisulfanylmethylbenzene (**7**), no major product has been observed in the crude reaction mixture. Apparently, cyclic *para*-substituted derivatives are less stable than the other polysulfanes, as recovery of products from the column was poor and compounds in the isolated fractions have partly polymerized in test tubes leaving insoluble residues.

The low stability of compounds **8**, **9**, **11**, **12**, and to a lesser extent **10** is not unexpected. Polysulfanes, in general, are not thermally stable; even methyl polysulfanes that are considered relatively stable produce an equilibrated mixture after extended heating.[18] While linear polysulfanes do not differ significantly from each other, with their stability slightly affected by increasing number of sulfur atoms, in cyclic polysulfanes differences are significant. Depending on the nature of the molecule, either even or

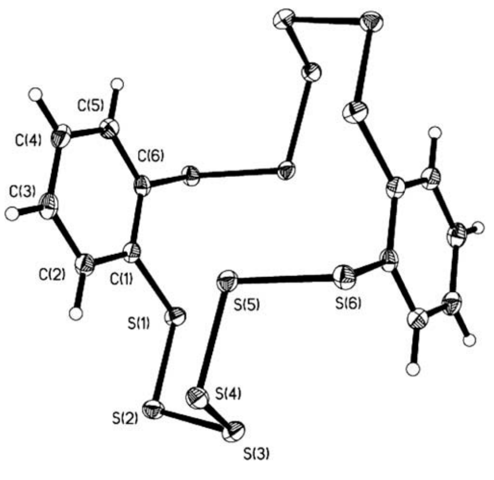


Figure 1. Crystal structure of dimer **13**. Selected bond lengths (Å) and angles (°): C(1)–S(1) 1.786(2), S(1)–S(2) 2.046(8), S(2)–S(3) 2.056(8), S(5)–S(6) 2.061(8), C1–S1–S2 105.31(8), S1–S2–S3 107.01(3), S4–S5–S6 105.98(3).

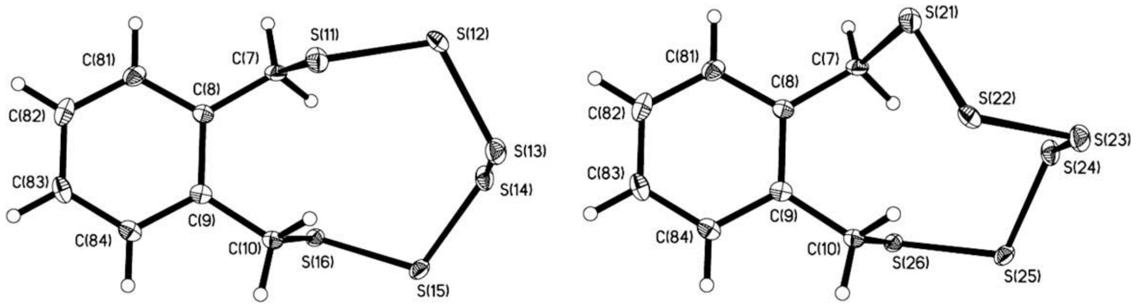


Figure 2. Crystal structure of **10**; two conformers present in the crystal. Selected bond lengths (Å) and angles (°): C(7)–S(11) 1.863(5), C(7)–S(21) 1.703(9), S(11)–S(12) 2.032(2), S(21)–S(22) 2.046(9), S(12)–S(13) 2.060(6), C7–S11–S12 103.36(19), C7–S21–S22 105.3(5), S11–S12–S13 109.07(3), S13–S14–S15 109.09(3).

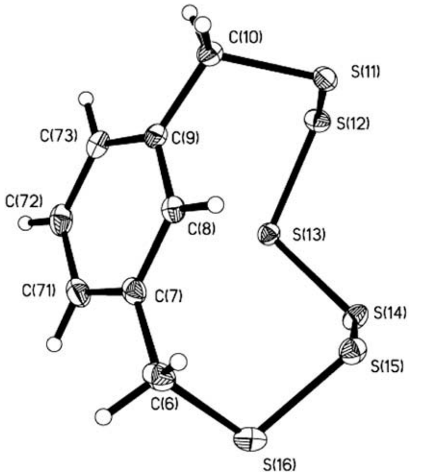


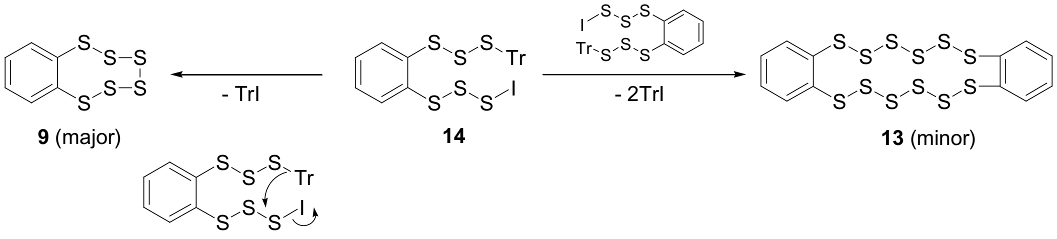
Figure 3. Crystal structure of **11**. Selected bond lengths (Å) and angles (°): C(10)–S(11) 1.831(18), S(11)–S(12) 2.034(7), S(12)–S(13) 2.074(6), C10–S11–S12 103.52(6), S11–S12–S13 108.37(3), S13–S14–S15 109.09(3).

odd numbers of sulfur atoms are preferred and for some, no stable compound can be isolated. For instance, in a homologous series of benzene polysulfanes, only two of them, tri- and pentasulfane (otherwise known as trithiolane and pentathiepin) are stable enough to be prepared in reaction with elemental sulfur under thermal conditions.[7] Other homologs require much milder methodologies.

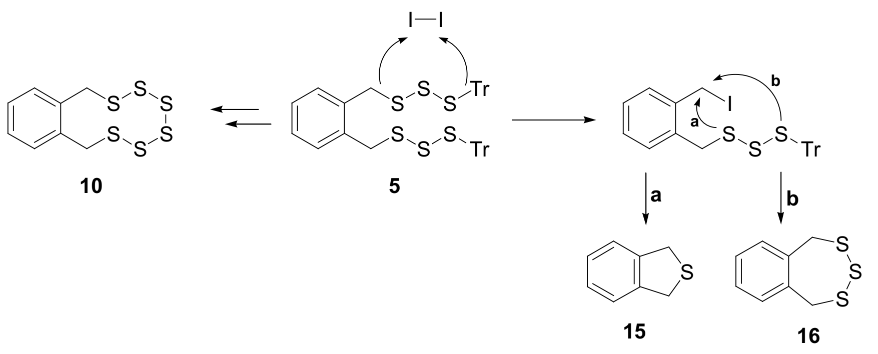
Our procedure is mild and suitable for a range of polysulfanes, and consists of two steps. Initially, the Tr–S bond is cleaved by iodine with the formation of a sulfenyl iodide. The latter is attacked by a sulfur atom from another trityl-protected polysulfide moiety. Thus, in such a reaction, trityl polysulfanes closely mimic polysulfane anions R–S_x–S^- that are easily oxidized with iodine.

Sulfenyl iodide **14** that likely form in the initial step of the reaction could be easily attacked by a sulfur atom adjacent to a trityl group giving **9** (Scheme 3). Indeed, we had previously demonstrated[19] that an analogous mechanism accounts for an insertion of two sulfur atoms into the S–S bond of various disulfanes.

The reaction outcome is very little dependent on the sequence or rate at which the reagents are added. It is a fast, instantaneous addition that proves to be more advantageous in terms of product



Scheme 3.



Scheme 4.

purity. These observations suggest that the rate of ring closure in intermediate **14** must significantly outpace its formation. A similar, parallel formation of octasulfane altogether with a minor hexadecasulfane dimer product was reported by Steudel.[20]

The cyclizations described here usually result in the formation of some side products. We have studied this process in detail in the case of 1,2-bistrityltrisulfanylmethylbenzene (**5**). According to the ^{1}H NMR data of the benzylic protons, major side-products, monosulfane **15** and trisulfane **16** formed in ca. 20% yield (Scheme 4).

The reaction conditions involved either methanol or silica gel as a trap for the trityl cation Tr^+, resulting in its isolation as TrOMe or TrOH. Contrary to the preparation of linear polysulfanes, their cyclic analogs are easily separated from tritylmethyl ether, and so we could select a trap depending on the optimal outcome. Replacing silica gel with methanol resulted in a ca. 20% improvement in the yield of hexasulfane **10**. Compounds **8** and **9** were obtained in better yield with silica gel as the trap. It is crucial to use two solvents, CH_2Cl_2 to dissolve polysulfanes and Et_2O as the solvent of choice for iodine.

In sum, an efficient one-step method to prepare cyclic polysulfanes characterized by a very simple workup has been described. Combined with our improved methodology to prepare trityl polysulfanes, it becomes a useful method of choice to convert thiols to corresponding cyclic derivatives.

Acknowledgment

We thank the Natural Sciences and Engineering Research Council (NSERC) of Canada for financial support of this work.

References and notes

1. Makarieva, T. N.; Stonik, V. A.; Dmitrenok, A. S.; Grebnev, B. B.; Iskov, V. V.; Rebachyk, N. M. *J. Nat. Prod.* **1995**, *58*, 254–258.
2. (a) Chatterji, T.; Gates, K. S. *Biorg. Chem. Med. Lett.* **1998**, *8*, 535–538; (b) Brzostowska, E. M.; Greer, A. *J. Am. Chem. Soc.* **2003**, *125*, 396–404.
3. (a) Zein, N.; Sinha, A. M.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198–1201; (b) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *PNAS* **1989**, *86*, 2–6.
4. For most recent articles and references see: (a) Liu, H.; Fujiwara, T.; Nishikawa, T.; Mishima, Y.; Nagai, H.; Shida, T.; Tachibana, K.; Kobayashi, H.; Mangindaan, R. E. P.; Namikoshi, M. *Tetrahedron* **2005**, *61*, 611–8615; (b) Nakazawa, T.; Xu, J.; Nishikawa, T.; Oda, T.; Fujita, A.; Ukai, K.; Mangindaan, R. E. P.; Rotinsulu, H.; Kobayashi, H.; Namikoshi, M. *J. Nat. Prod.* **2007**, *70*, 439–442.
5. Aebisher, D.; Brzostowska, E. M.; Mahendran, A.; Greer, A. *J. Org. Chem.* **2007**, *72*, 2951–2955.
6. Aebisher, D.; Brzostowska, E. M.; Sawwan, N.; Ovalle, R.; Greer, A. *J. Nat. Prod.* **2007**, *70*, 1492–1494.
7. Chenard, B. L.; Miller, T. J. *J. Org. Chem.* **1984**, *49*, 1221–1224.
8. (a) Feher, F.; Laue, W. *Z. Anorg. Allgem. Chem.* **1956**, *287*, 45–50; (b) Feher, F.; Langer, M.; Volkert, R. *Z. Naturforsh.* **1972**, *B27*, 1006–1007.
9. (a) Steudel, R.; Foerster, S.; Albertsen *J. Chem. Ber.* **1991**, *124*, 2357–2359; (b) Steudel, R.; Kustos, M.; Pridohl, M.; Westphal, U. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1994**, *93*, 61–72; (c) Steudel, R.; Kustos, M. *J. Org. Chem.* **1995**, *60*, 8056–8061.
10. (a) Tarbell, D. S.; Harnish, D. P. *Chem. Rev.* **1951**, *49*, 1–90; (b) Tarbell, D. S.; Harnish, D. P. *J. Am. Chem. Soc.* **1952**, *74*, 1862–1863.
11. Ma, M.; Zhang, X.; Peng, L.; Wang, J. *Tetrahedron Lett.* **2007**, *48*, 1095–1097.
12. Abu-Yousef, I. A.; Rys, A. Z.; Harpp, D. N. *J. Sulfur Chem.* **2006**, *27*, 15–24.
13. Abu-Yousef, I. A.; Rys, A. Z.; Harpp, D. N. *J. Sulfur Chem.* **2007**, *28*, 251–258.
14. Feher, F.; Langer, M.; Volkert, R. *Z. Naturforsch.* **1972**, *B27*, 1006–1007.
15. *X-ray data for* **13**: $C_{12}H_8S_{12}$, $M_r = 536.90$, Triclinic, $P1$, $a = 7.1504$ (2), $b = 9.0951$ (2), $c = 9.2690$ (2) Å, $\alpha = 116.6240$ (10)°, $\beta = 106.8760$ (10)°, $\gamma = 95.1970$ (10)°, $V = 498.22$ (2) Å^3, $Z = 1$, $D_x = 1.789$ Mg m^{-3}, Cu Kα radiation, $\lambda = 1.54178$ Å, $\theta = 5.63$–68.54°, $\mu = 12.188$ mm^{-1}, $T = 100(2)$ K, $wR(F^2) = 0.0916$, $S = 1.061$, 1767 independent reflections.
16. *X-ray data for* **10**: $C_8H_8S_6$, $M_r = 296.50$, Orthorhombic, P_{na21}, $a = 20.0135$ (17), $b = 11.8715$ (10), $c = 5.0624$ (5) Å, $V = 1202.78$ (19) Å^3, $Z = 4$, $D_x = 1.637$ Mg m^{-3}, Cu *K*α radiation, $\lambda = 1.54178$ Å, $\theta = 41.89$–66.91°, $\mu = 10.158$ mm^{-1}, $T = 100$ (2) K, $wR(F^2) = 0.1301$, $S = 1.064$, 2038 independent reflections.
17. *X-ray data for* **11**: $C_8H_8S_6$, $M_r = 296.50$, Monoclinic, $P2_{1/c}$, $a = 11.7855$ (5), $b = 7.6457$ (3), $c = 13.2922$ (5) Å, $\beta = 101.823$ (2)°, $V = 1172.33$ (8) Å^3, $Z = 4$, Cu *K*α radiation, $\mu = 10.42$ mm^{-1}, $T = 150$ (2) K, $wR(F^2) = 0.095$, $S = 1.06$, 2280 independent reflections.
18. Pickering, T. L.; Saunders, K. J.; Tobolsky, A. V. *J. Am. Chem. Soc.* **1967**, *89*, 2364–2367.
19. Rys, A. Z.; Harpp, D. N. *Tetrahedron Lett.* **2000**, *41*, 7169–7172.
20. Steudel, R.; Hassenberg, K.; Pickardt, J. *Eur. J. Org. Chem.* **2001**, 2815–2817.