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Sulfide ion transfer from a vicinal dithiolate. A new route for the synthesis of mesocyclic trithiaethers

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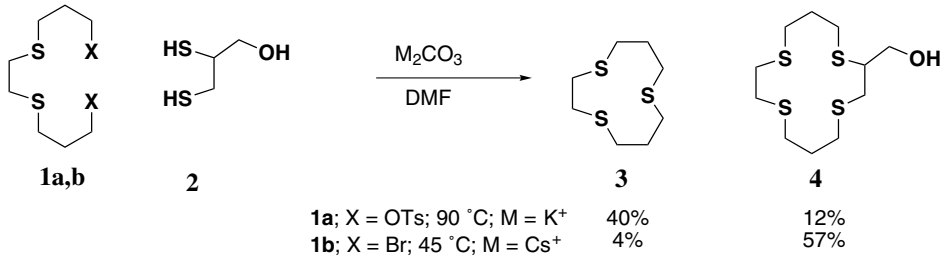
Abstract—Four mesocyclic and one macrocyclic trithiaethers have been synthesized using a sulfide ion transfer from a vicinal dithiolate. The mechanism of the sulfide ion transfer is discussed. An improved method for synthesizing 2-hydroxymethyl-1,4,8,11-tetrathiacyclotetradecane is also reported.

The preparation of mesocyclic and macrocyclic polythiaethers has been the subject of more than two decades of research.[1] Polythiaethers have found applications in coordination chemistry,[2] kinetic studies of electron transfer in Cu (I/II) systems,[3] the delivery of radioisotopes,[4] and metal ion recognition and absorption.[5] The most popular method for the preparation of polythiaethers is the reaction of dithiols employing the cesium dithiolate methodology developed by Kellog.[6]

In a project aimed at the syntheses of bipyridyl-linked polythiaethers, the preparation of 2-hydroxymethyl-1,4,8,11-tetrathiacyclotetradecane (**4**) was required. The preparation of **4** had previously been reported and had utilized the aforementioned cesium dithiolate conditions (reported yield 29%).[6d] For economic reasons, the first attempt at the cyclization of **1** and **2** was mediated by K_2CO_3.[7] Surprisingly, the main product of this reaction was 1,4,8-trithiacycloundecane (**3**), not the expected cyclotetradecane **4**. Changing the reaction temperature from 90 to 150 °C or the base from K_2CO_3 to Cs_2CO_3 resulted in no improvement in the yield of **4** (Scheme 1). It was found that conversion of the leaving group from tosylate to bromide and lowering the reaction temperature significantly improved the yield from 6% to 57% (Table 1).[8]

A plausible explanation for the formation of **3** is illustrated in Scheme 2. Following initial thiolate formation, intermolecular reaction results in the formation of the intermediate acyclic trithiaether **5**. Rather than undergoing the expected intramolecular alkylation to form the tetrathiacyclotetradecane, the newly formed sulfide undergoes an intramolecular reaction to produce the



Scheme 1.

Keywords: Mesocyclic trithiaethers; Macrocyclic trithiaethers; Cyclization reaction; Sulfide ion transfer.
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Table 1. Yield of **3** and **4** under different cyclization conditions

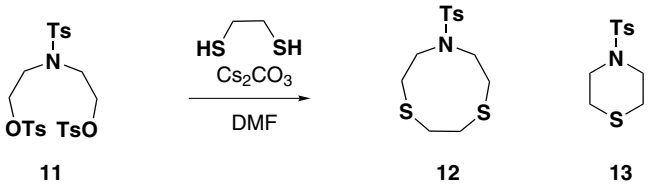
Entry	Leaving group	Base	Temp. (°C)	Yield **3** (%)	Yield **4** (%)
1	Tosylate	K_2CO_3	150	34	3
2	Tosylate	K_2CO_3	120	37	12
3	Tosylate	K_2CO_3	90	40	12
4	Tosylate	Cs_2CO_3	90	35	6
5	Bromide	Cs_2CO_3	55	17	50
6	Bromide	Cs_2CO_3	45	4	57

11-membered ring sulfonium ion **6**. Final intramolecular reaction of the remaining thiolate with the exocyclic carbon of the sulfonium ion results in the formation of 1,4,8-trithiacycloundecane **3** and (hydroxymethyl)thiirane (**7**).

An apparent sulfide ion transfer involving a vicinal dithiolate had been reported by Bradshaw during the synthesis of 2-hydroxymethyl-1,4-dithia-7,10,13,16-tetraoxacyclooctadecane (**9**). Along with 40% of the hydroxymethyl cyclooctadecane product **9**, 25% of 1-thia-4,7,10,13-tetraoxacyclopentadecane (**10**) was also isolated. However, no discussion concerning the formation of the cyclopentadecane was presented (Scheme 3).[9]

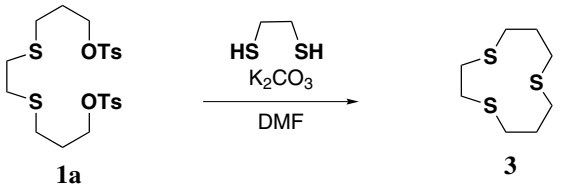
The reaction of 1,2-ethanedithiol and tritosyldiethanolamine can be used in the preparation of *N*-tosyl-7-aza-1,4-dithiacyclononane (**12**).[10] However, lower yields are obtained than via an alternative strategy. Sulfide ion transfer from 1,2-ethanedithiol to produce *N*-tosylthiamorpholine (**13**)[10a] is partially responsible for the lower yield in the attempted reaction with tritosylate **11** (Scheme 4).[11]

Recently, an analogous acid catalyzed single sulfur transfer from 1,2-ethanedithiol has been reported during the course of preparing tin templates for the synthesis of macrocyclic polythiaether ligands.[1g]



11 12 13

Scheme 4.



1a 3

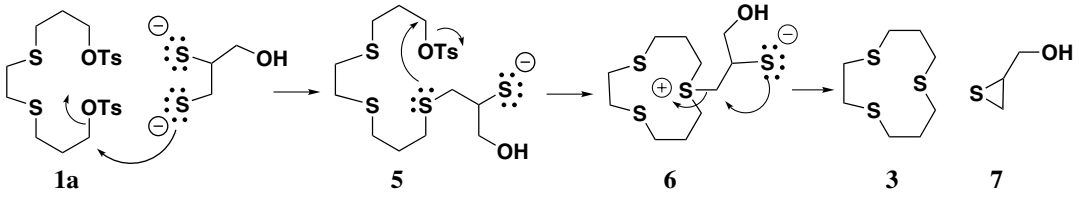
Scheme 5.

Table 2. Effect of temperature on the yield of **3**

Entry	Reaction temp. (°C)	Yield of **3** (%)
1	90	12
2	100	30
3	120	45
4	150	47

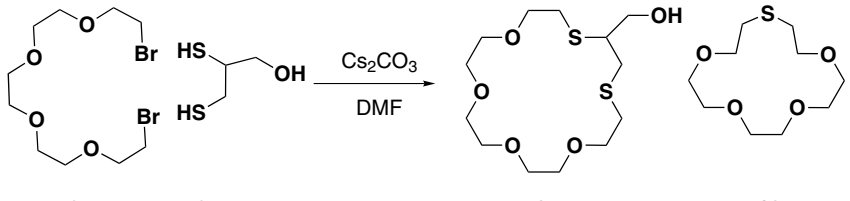
To see if the sulfide ion transfer from a vicinal dithiolate was unique to 2,3-dimercapto-1-propanol (**2**) because of the possible participation of the adjacent hydroxyl group, the reaction of **1a** was performed with 1,2-ethanedithiol (Scheme 5). The results of this study are summarized in Table 2. In accord with previous observations, the amount of sulfide ion transfer product increased with increasing temperature.

Encouraged by the results, 1,2-ethanedithiol and the appropriate ditosylate or dichloride[12] (see Scheme 6



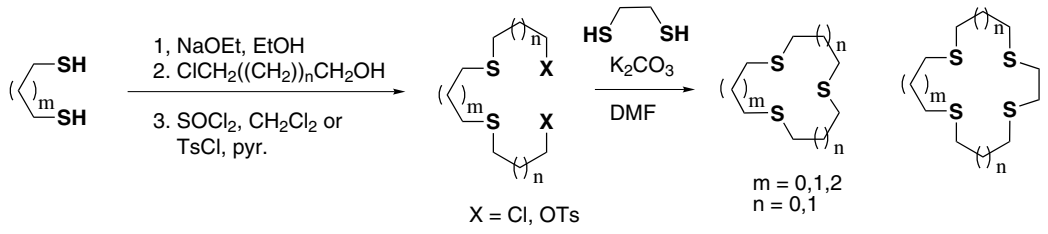
1a 5 6 3 7

Scheme 2.



8 2 9 10

Scheme 3.



Scheme 6.

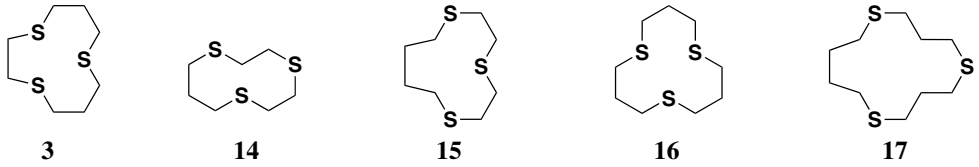


Figure 1.

Table 3. Results of synthesizing cyclic trithiaethers

Entry	X	Compound	Temp. (°C)	Ring size	Yield (%)	Yield of larger ring (ring size) (%)
1		**14**	120	10	14 (18)[a]	9 (13), $m = 1$, $n = 0$
2		**15**	150	11	28 (13)[a]	5 (14), $m = 2$, $n = 0$
3		**3**	150	11	47 (30)[a]	2 (14), $m = 0$, $n = 1$
4		**16**	150	12	47 (33)[a](32)[b]	7 (15), $m = 1$, $n = 1$
5		**17**	120	13	13	11 (16), $m = 2$, $n = 1$
6		**17**	150	13	24	5 (16), $m = 2$, $n = 1$

[a] Yield reported in Ref. 6b.
[b] Yield reported in Ref. 1f.

for their preparation)[13] were employed in the syntheses of a series of 10–13-membered ring trithiaethers (Fig. 1).[14] The data in Table 3 show that a variety of cyclic thiaethers can be synthesized in moderate to good yields. Entries 5 and 6 results give further proof that higher temperatures promote the sulfide ion transfer. Table 3 also lists, when possible, yields for the cyclic polythiaethers prepared by the traditional dithiolate procedures. The sulfide ion transfer process for the preparation of these cyclic polythiaethers provides an alternative strategy that is comparable or in most cases better than the traditional dithiolate method.

In conclusion, an interesting sulfide ion transfer has been proposed and used in the preparation of a series of mesocyclic trithioethers. The use of 2,3-dimercapto-1-propanol (**2**) over 1,2-ethanedithiol has the advantage in the ease of separation of the sulfide ion transfer product from the larger ring cyclization product but has the disadvantage of higher cost. The sulfide ion transfer is currently being looked at for the preparation of other heterocyclic ring systems and the results of these studies will be reported in due course.

Acknowledgements

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References and notes

1. (a) Kellogg, R. M. *Crown Compounds: Toward Future Applications*; VCH: New York, 1992; pp 261–284; (b) Gerbeleu, N. V.; Arion, V. B.; Burgess, J. *Template Synthesis of Macrocyclic Compounds*; WILEY-VCH: New York, 1999; pp 419–430; (c) Comba, P.; Fath, A.; Nuber, B.; Peters, A. *J. Org. Chem.* **1997**, *62*, 8459–8462; (d) Smith, R. J.; Admans, G. D.; Richardson, A. P.; Kuppers, H.; Blower, P. J. *J. Chem. Soc., Chem. Commun.* **1991**, 475–476; (e) Smith, R. J.; Salek, S. N.; Went, M. J.; Blower, P. J.; Barnard, N. J. *J. Chem. Soc., Dalton Trans.* **1994**, 3165–3170; (f) Adams, R. D.; Fallon, S. B. *J. Am. Chem. Soc.* **1994**, *116*, 10540–10547; (g) Vujasinovic, I.; Veljkovic, J.; Mlinaric-Majerski, K. *J. Org. Chem.* **2004**, *69*, 8550–8553.
2. (a) Levason, W.; Reid, G. In *Comprehensive Coordination Chemistry II*; Elsevier: San Diego, 2004; Vol. I, pp 399–409; (b) Levason, W.; Patel, B.; Reid, G. *Inorg. Chim. Acta* **2004**, *357*, 2115–2130; (c) Helm, M. L.; Vanderveer, D. G.; Grant, G. J. *J. Chem. Crystallogr.* **2003**, *33*, 625–630; (d) Grant, G. J.; Shoup, S. S.; Baucom, C. L.; Setzer, W. N. *Inorg. Chim. Acta* **2001**, *317*, 91–102; (e) Grant, G. J.; Rogers, K. E.; Setzer, W. N.; VanDereer, D. G. *Inorg. Chim. Acta* **1995**, 35–45; (f) Setzer, W. N.; Cacioppo, E. L.; Guo, Q.; Grant, G. J.; Kim, D. D.; Hubbard, J. L.; VanDerveer, D. G. *Inorg. Chem.* **1990**, *29*, 2672–2681; (g) Grant, G. J.; Carpenter, J. P.; Setzer, W. N.; VanDerveer, D. G. *Inorg. Chem.* **1989**, *28*, 4128–4131.
3. Rorabacher, D. B. *Chem. Rev.* **2004**, *104*, 651–697.
4. Cooper, S. R. *Crown Compounds: Toward Future Applications*; VCH: New York, 1992; pp 285–302.

5. (a) Fainerman-Melnikova, M.; Lindoy, L. F.; Liou, S.; McMurtrie, J. C.; Green, N. P.; Nezhadali, A.; Rounaghi, G.; Setzer, W. N. *Aust. J. Chem.* **2004**, *57*, 161–166; (b) Wroblewski, W.; Brzozka, Z. *Sensors Actuators B* **1995**, *24–25*, 183–187; (c) Gaboury, J. A.; Chen, F. U.S. Patent 6,147,225, 2000; (d) Yamashita, K.; Kurita, K.; Ohara, K.; Tamura, K.; Nango, M.; Tsuda, K. *React. Funct. Polym.* **1996**, *31*, 47–55; (e) Saito, K.; Taninaka, I.; Murakami, S.; Muromatsu, A. *Anal. Chim. Acta* **1994**, *299*, 137–144; (f) Brzozka, Z.; Cobben, P. L. H. M.; Reinhoudt, D. N. *Anal. Chim. Acta* **1993**, *273*, 139–144.
6. (a) Buter, P. J.; Kellogg, R. M. *Org. Synth.* **1987**, *65*, 150–158; (b) Setzer, W. N.; Afshar, S.; Burns, N. L.; Ferrante, L. A.; Hester, A. M.; Meehan, E. J. *Heteroatom Chem.* **1990**, *1*, 375–387; (c) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M.; Bruening, R. L.; Tarbet, B. J. *J. Heterocyclic Chem.* **1990**, *27*, 347–349; (d) Baumann, T. F.; Reynolds, J. G.; Fox, G. A. *React. Funct. Polym.* **2000**, *44*, 111–120; (e) Rawle, S. C.; Admans, G. A.; Cooper, S. R. *J. Chem. Soc., Dalton Trans.* **1988**, 93–96; (f) Blower, P. J.; Cooper, S. P. *Inorg. Chem.* **1987**, *26*, 2009–2010.
7. Pett, V. B.; Leggett, G. H.; Cooper, T. H.; Reed, P. R.; Situmeang, D.; Ochrymowycz, L. A.; Rorabacher, D. B. *Inorg. Chem.* **1988**, *27*, 2165–2169.
8. Howden, M. E. H.; Maercker, A.; Maercker, A.; Burdon, J.; Roberts, J. D. *J. Am. Chem. Soc.* **1966**, *88*, 1732–1742.
9. Bradshaw, J. S.; Campbell, M. L.; Hassell, L. A.; Baxter, J. K. *J. Heterocyclic Chem.* **1979**, *27*, 721–723.
10. (a) McAuley, A.; Subramanian, S. *Inorg. Chem.* **1990**, *29*, 2830–2837; (b) Blake, A. J.; Danks, J. P.; Fallis, I. A.; Harrison, A.; Li, W.-S.; Parsons, S.; Ross, S. A.; Whittaker, G.; Schroder, M. *J. Chem. Soc., Dalton Trans.* **1998**, 3969–3976.
11. Taschner, M. J.; Bhide, S., unpublished results.
12. **CAUTION**: β-*chloro sulfides are potent vesicants*.
13. (a) Lange, S. J.; Sibert, J. W.; Stern, C. L.; Barrett, A. G. M.; Hoffman, B. M. *Tetrahedron* **1995**, *51*, 8175–8188; (b) Guyon, V.; Guy, A.; Foos, J.; Lemaire, M.; Draye, M. *Tetrahedron* **1995**, *51*, 4065–4074; (c) Dawson, T. P. *J. Am. Chem. Soc.* **1947**, *69*, 1176; (d) Desper, J. M.; Gellman, S. H.; Wolf, R. E.; Cooper, S. R. *J. Am. Chem. Soc.* **1991**, *113*, 8663–8671; (e) Wolf, R. E.; Hartman, J. A.; Ochrymowycz, L. A.; Cooper, S. R. *Inorg. Synth.* **1988**, *25*, 122–126; (f) Edema, J. J. H.; Buter, J.; Schoonbeek, F. S.; Meetsma, A.; Bolhuis, F. V.; Kellogg, R. M. *J. Org. Chem.* **1993**, *58*, 5624–5627.
14. A 250 mL three-neck flask equipped with an internal thermometer, condenser, and pressure-equalizing addition funnel was flame dried under nitrogen and then charged with 1.17 g (8.5 mmol) of finely ground, anhydrous K_2CO_3 and 100 mL of dry DMF. After thorough degassing with N_2, the reaction mixture was stirred and heated to 150 °C. A solution of 0.38 g (4.0 mmol) of 1,2-ethanedithiol and 2.20 g (4.0 mmol) of 4,9-dithiadodecane-1,12-di-*p*-toluenesulfonate in 50 mL of dry DMF was added dropwise slowly over 8 h. The reaction mixture was then stirred at 150 °C for an additional 12 h. The mixture was cooled to room temperature, filtered, and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 5% ethyl acetate in hexanes to give 0.23 g compound **17** as a white crystalline solid mp 62.0–62.5 °C (uncorrected); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.78–1.82 (m, 4H), 1.95 (quintet, $J = 6.96$ Hz, 4H), 2.62–2.72 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 27.91, 29.93, 30.11, 31.65, 32.24; *m/z* (positive ion electrospray): 343.0, 345.0 $(M+Ag)^+$.