Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 49 (2008) 520–522

Synthesis of cyclic disulfides using didecyldimethylammonium bromide as phase transfer catalyst

Sachin U. Sonavane, Mandan Chidambaram, Sanaa Khalil, Joseph Almog and Yoel Sasson*

Casali Institute of Applied Chemistry, Hebrew University of Jerusalem, 91904, Israel

Received 28 September 2007; revised 5 November 2007; accepted 14 November 2007
Available online 19 November 2007

Abstract—A convenient, practical and general method for the synthesis of symmetrical and unsymmetrical cyclic disulfides based on the reaction of sulfur with sodium sulfide in the presence of didecyldimethylammonium bromide (DDAB) as a phase transfer catalyst is described.
© 2007 Published by Elsevier Ltd.

The disulfide moiety occurs in proteins and is also found in a variety of small molecule natural products and pharmacologically active compounds.[1] In addition, cyclic and acyclic disulfides are useful intermediates in the synthesis of biologically-active compounds, both in pharmaceutical and agrochemical intermediates[2] and in the preparation of self-assembled monolayers on gold nanoparticles.[3] Acyclic disulfides are typically prepared through oxidation of thiols.[4] Similarly, cyclic disulfides are typically prepared by the oxidative dimerization of α,ω-dithiol using reagents such as I_2, NEt_3,[5] Br_2,[6] $K_3Fe(CN)_6$,[7] H_2O_2/KI/AcOH,[8] lead thiolates[9] and supported silica gel.[10] More recently, reactions of α,ω-bisthiocyanates with samarium diiodide,[11] tetrathiomolybdate[12] or tetrabutylammonium fluoride[13] have been reported for the synthesis of cyclic disulfides.

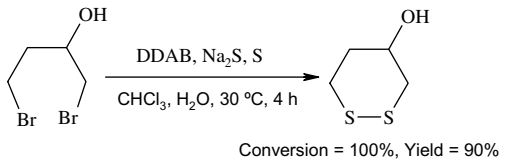
The most commonly used method for the direct conversion of aryl/acyl halides to disulfides involves the use of Na_2S/S.[14] However, the methods currently available for the preparation of disulfides often involve several steps and the transformation is usually effected at 70–90 °C over a long period of time (20–30 h)[14] giving only moderate yields of the corresponding disulfide. Aliphatic polysulfides were prepared by PTC reaction of Na_2S with dibromoalkanes.[15] Disulfide and other polysulfide anions are easily obtained by mixing aqueous solutions of S^{2-} with sulfur. Several analytical methods were recently developed to assess the polysulfide distribution in various sulfur/sulfide mixtures.[16] Hase used Li_2S_2 for the preparation of dialkyldisulfides.[17] The same reagent was later used for the synthesis of cyclic disulfides.[18]

Despite the plethora of processes available in the literature for the synthesis of cyclic disulfides, the preferred method varies with ring size. The most common procedures involve the oxidation of a dithiol by various oxidizing agents. Cyclic disulfides have also been obtained by steam distillation of an appropriate Bunte salt.[19] The reaction of 1,3-dielectrophiles with S_4^{2-} followed by desulfurization with copper is a method to produce 1,2-dithiolanes, usually in moderate yields.[20] Harpp et al. have reported the high-yield preparation of cyclic disulfides by oxidation of alkyltin thiolates using iodine or bromine without the need for high dilution.[6]

We recently showed that DDAB is quite effective as a phase transfer catalyst and in bringing about the formation of disulfides from alkyl halides.[21] It was of interest to us to find out whether cyclic disulfides could be formed efficiently from 1,*n*-dihalo compounds at higher dilution using the same methodology. For forensic chemistry applications, we were interested in making ninhydrin derivatives substituted by long aliphatic chains bearing cyclic disulfides at the end. 4-Hydroxydithiane, a potential building block (entry 2), has been prepared in the past via a relatively complicated procedure involving oxidative cyclization of 1,4-dithio-2-butanol with $FeCl_3 \cdot 6H_2O$, and the process took several

* Corresponding author. Tel./fax: +972 2 6528250; e-mail: ysasson@huji.ac.il

0040-4039/$ - see front matter © 2007 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2007.11.075



Scheme 1.

days.[22] Our pathway afforded the same compound in 91% yield, at 30 °C (Scheme 1, Table 1).

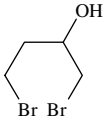
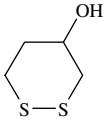
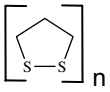
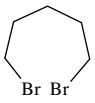
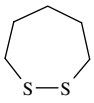
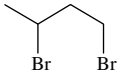
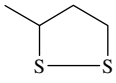
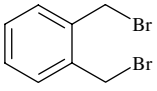
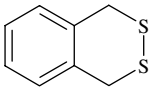
As a part of a program directed towards the synthesis of functionalized cyclic disulfides for monolayer adsorption studies, we required a simple route to disulfides from dihalides that would not affect base-sensitive functionalities (specifically esters) and which did not require specialist reagents or reaction conditions. Herein we report that DDAB catalyzes the formation of cyclic disulfides from the corresponding 1,*n*-dibromo compounds (Scheme 1) in moderate to excellent yields under mild conditions. The process affords symmetrical as well as unsymmetrical cyclic disulfides. The reaction is fast, and is carried out at room temperature.

In a generalized procedure 1,4-dibromo-2-butanol (in chloroform) was stirred with aqueous sodium sulfide and sulfur in the presence of DDAB as a phase transfer catalyst at room temperature. The yield of the corresponding cyclic disulfide was high (90%) with complete conversion of the starting dihalide.

To explore the utility of this catalytic system further, several dibromides were reacted under the optimized reaction conditions (Table 1). All were converted into the corresponding cyclic disulfides with excellent yields. Dibromides were preferred to dichlorides due to their higher reactivity as described in our earlier report.[21] 1,3-Dibromopropane reacted readily at room temperature (30 °C, 2 h). However, attempts to isolate pure 1,2-dithiolane always led to polymeric material. This is in accordance with the earlier observation that unsubstituted dithiolanes are prone to fast polymerization.[6,23]

Treatment of 1,3-dibromobutane at room temperature initially posed a few problems. A polymer was obtained instead of the desired 3-methyl-1,2-dithiolane. Possible reasons could be the higher reactivity of the primary bromide compared to the secondary bromide, as well as the electron donating nature of the methyl substituent. This problem, however, was somewhat overcome by carrying out the reaction in the dark and in a more dilute solution. In this case the 1,2-dithiolane was obtained in 35% isolated yield along with an unknown by-product, perhaps a polymer. To find out whether the present methodology could be extended effectively to the synthesis of higher cyclic dithianes, 1,4-dibromobutane and 1,5-dibromopentane were reacted in a similar manner and produced the corresponding dithianes.

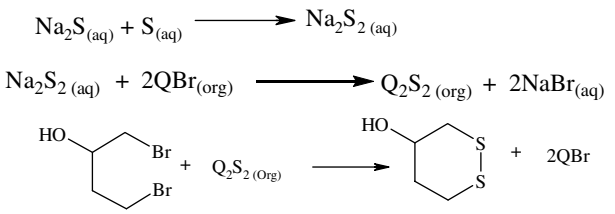
Table 1. Synthesis of cyclic disulfides using didecyldimethylammonium bromide as a phase transfer catalyst

Entry	Reactant	*T* (h)	Product	% Conversion[a]	% Yield[b] (mp/bp)
1		3		96	80 (34–37 °C)
2		4		100	91 (42–45 °C)
3		3		80	71 (oily gel)
4		5		86	62 (59–63 °C, bp)
5		4		88	35 (46–53 °C, bp)
6		4		71	63 (76–80 °C)

Reaction conditions: A mixture of sulfur powder (10 mmol), sodium sulfide (10 mmol) and water (25 ml) was stirred at 50 °C for 30 min. The solution was cooled to RT, DDAB (4 mol %) was added, followed by substrate (5 mmol) and chloroform (50 ml) and stirring continued at 30 °C.

[a] Conversion based on GC analysis with area minimization.

[b] Isolated yields.



Scheme 2.

The present methodology is more effective for the direct conversion of dihalides to cyclic disulfides (35–90%) than reported procedures (4–60%).[24] Thus, this methodology provides a simple, versatile and general route to the construction of a wide variety of medium-sized cyclic disulfides. In this study we were able to demonstrate again the utility and efficiency of DDAB as a phase transfer catalyst.

We propose a putative reaction mechanism using 1,4-dibromo-2-butanol as a model substrate. Aqueous sodium sulfide with sulfur forms Na_2S_2. The latter reacts with the phase transfer catalyst to form the ion pair Q_2S_2, which is extracted into the organic phase and reacts with the substrate to yield the cyclic disulfide and the original catalyst as shown in Scheme 2.

It is known that the size of the polysulfide anion in water (S_x^{-2} where $x = 2, 3, 4, 5$) can be determined by controlling the sulfide/sulfur ratio.[25] We therefore assume that tri, tetra and higher polysulfides could be synthesized using the method described above.

In conclusion, a simple, convenient and practical method has been developed for the synthesis of symmetrical and unsymmetrical cyclic disulfides using DDAB as a phase transfer catalyst.

General procedure: A mixture of sulfur powder (10 mmol), sodium sulfide (10 mmol) and water (25 ml) was stirred for 30 min at 50 °C. After dissolution, the reaction mixture was cooled to room temperature and DDAB (4 mol %) was added. A mixture of substrate (5 mmol) and chloroform (50 ml) was added and the reaction mixture was stirred for the appropriate period of time at 30 °C. The progress of the reaction was monitored by GC and GC–MS. After completion of the reaction, the product was extracted twice with diethyl ether. The combined organic layers were washed with water and dried over sodium sulfate. The organic layer was concentrated under reduced pressure to afford a crystalline (or liquid) dialkyl disulfide. The pure solid products were obtained by purification on a short silica gel column using petroleum ether as the eluent and recrystallization from ethanol. All the products had satisfactory ^{1}H NMR, IR and GC–MS.

Acknowledgement

M.C. is grateful to the Pikovski-Valazzy Fund for financial support.

References and notes

1. (a) Freeman, F.; Aregullin, M.; Rodriguez, E. *Rev. Heteroat. Chem.* **1993**, *9*, 1–19; (b) Kishi, Y.; Nakatsuga, S.; Fukuyama, T.; Havel, M. *J. Am. Chem. Soc.* **1973**, *95*, 6493–6495; (c) Tabashi, K.; Kawashima, Y. *Chem. Pharm. Bull.* **1993**, *41*, 1066–1073.
2. (a) Koval, L. V. *Russ. Chem. Rev.* **1994**, *63*, 735–750; (b) Billard, T.; Langlois, B. R. *Tetrahedron Lett.* **1996**, *37*, 6865–6868.
3. (a) Nuzzo, R. G.; Allara, D. L. *J. Am. Chem. Soc.* **1983**, *105*, 4481–4483; (b) Biebuyck, H. A.; Bain, C. D.; Whitesides, G. M. *Langmuir* **1994**, *10*, 1825–1831, and references cited therein.
4. Capozzi, G.; Menichetti, S.; Nativi, C. In *Syntheses of sulphones, sulphoxides and cyclic sulphides*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons, 1994; pp 529–648.
5. Field, L.; Barbee, R. B. *J. Org. Chem.* **1969**, *34*, 36–41.
6. Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1970**, *35*, 3259–3263.
7. Cleland, W. W. *Biochemistry* **1964**, *3*, 480–482.
8. Field, L.; Khim, Y. H. *J. Org. Chem.* **1972**, *37*, 2710–2714.
9. Cragg, R. H.; Weston, A. F. *Tetrahedron Lett.* **1973**, *14*, 655–656.
10. (a) Crank, G.; Makin, M. I. H. *Aust. J. Chem.* **1984**, *37*, 2331–2337; (b) Movassagh, B.; Lakourag, M. M.; Ghodreti, K. *Synth. Commun.* **1999**, *29*, 3597–3603.
11. Jia, X.; Zhang, Y.; Zhou, X. *Tetrahedron Lett.* **1994**, *35*, 8833–8834.
12. Prabhu, K. R.; Ramesha, A. R.; Chandrasekaran, S. *J. Org. Chem.* **1995**, *60*, 7142–7143.
13. Burns, C. J.; Field, L. D.; Morgan, J.; Ridley, D. D.; Vignerich, V. *Tetrahedron Lett.* **1999**, *40*, 6489–6492.
14. (a) Kutil, B.; Cuda, J.; Kempny, L. Czech Patent CS 187958, 1982; Kutil, B.; Cuda, J.; Kempny, L. *Chem. Abstr.* **1982**, *97*, 72064z; (b) Toru, T.; Kenjiro, I.; Kawanobe, T. Japan Patent JP 2001039947, 2001; Toru, T.; Kenjiro, I.; Kawanobe, T. *Chem. Abstr.* **2001**, *134*, 162815; (c) Gopalan, A. S.; Jacobs, H. K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1897–1900.
15. Ueda, M.; Oishi, Y.; Sakai, N.; Imai, Y. *Macromolecules* **1982**, *15*, 248–251.
16. Kamyshny, A.; Ekeltchlk, I.; Gun, J.; Lev, O. *Anal. Chem.* **2006**, *78*, 2631–2639.
17. Hase, T. A.; Perakyla, H. *Synth. Commun.* **1982**, *12*, 947–950.
18. Weyerstahl, P.; Oldenburg, T. *Flavour Frag. J.* **1998**, *13*, 177–184.
19. Affleck, J. G.; Dougherty, G. J. *J. Org. Chem.* **1950**, *15*, 865–868.
20. Backer, H. J.; Evenhuis, N. *Trav. Chim. Pays-Bas* **1937**, *56*, 129–136.
21. Chidambaram, M.; Sonavane, S. U.; Zerda, J.; Sasson, Y. *Tetrahedron* **2007**, *63*, 7696–7701; Sonavane, S. U.; Chidambaram, M.; Almog, J.; Sasson, Y. *Tetrahedron Lett.* **2007**, *48*, 6048–6050.
22. Luttringhaus, von A.; Kabuss, S.; Prinzbach, H.; Langen- bucher, F. *Liebigs Ann. Chem.* **1962**, *653*, 195–211.
23. Harpp, D. N.; Bodzay, S. J.; Aida, T.; Chan, T. H. *Tetrahedron Lett.* **1986**, *27*, 441–444.
24. (a) Dodson, R. M.; Nelson, V. G. *J. Org. Chem.* **1968**, *33*, 3966–3968.
25. Jaroudi, O. E.; Picquenard, E.; Gobeltz, N.; Demortier, A.; Corset, J. *Inorg. Chem.* **1999**, *38*, 2917–2923.