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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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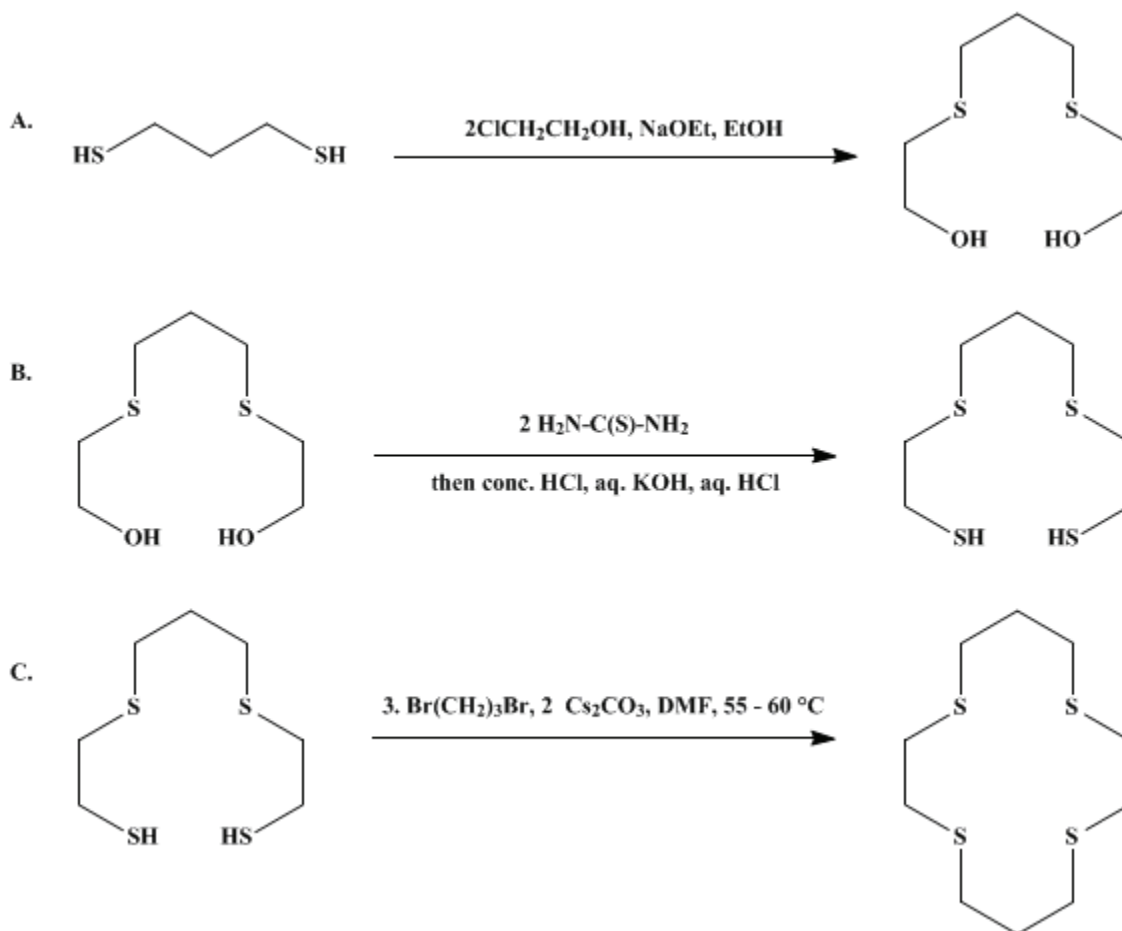
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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SYNTHESIS OF MACROCYCLIC SULFIDES USING CESIUM THIOLATES: 1,4,8,11-TETRATHIACYCLOTRIDECADECANE



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1. Procedure

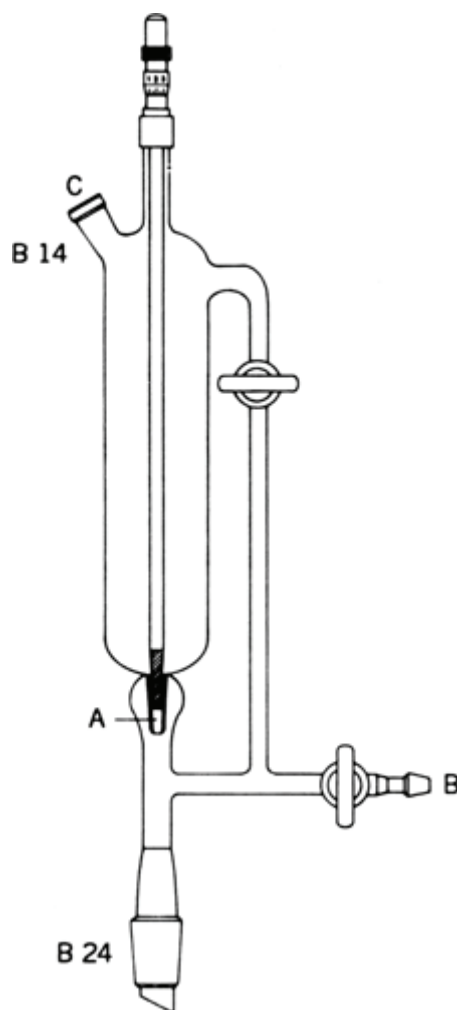
A. *3,7-Dithianonane-1,9-diol.*² A 500-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, a reflux condenser attached to a nitrogen inlet, and a pressure-equalizing dropping funnel. The flask is flushed with nitrogen and charged with 250 mL of absolute ethanol. The ethanol is stirred and 5.75 g (0.25 mol) of sodium metal is cautiously added. After the sodium dissolves, the solution is warmed to 45–50°C and 13.5 g (0.125 mol) of 1,3-propanedithiol (Note 1) is added dropwise over a period of 15 min. To the resulting solution is added dropwise 20.1 g (0.25 mol) of 2-chloroethanol (Note 1) and the mixture is refluxed for 3–4 hr. The mixture is then allowed to cool to room temperature and is filtered. The filtrate is concentrated on a rotary evaporator to a viscous liquid, which is distilled to give 17.3–20.0 g (71–82%) of 3,7-dithianonane-1,9-diol, bp 200°C (1.5 mm) (Note 2).

B. *3,7-Dithianonane-1,9-dithiol.*² In a 1-L, round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar are placed 35.0 g (0.178 mol) of 3,7-dithianonane-1,9-diol, 30.0 g (0.394 mol) of thiourea (Note 3), and 94 mL of concentrated hydrochloric acid. The mixture is stirred and refluxed for 12 hr. The resulting solution is cooled in an ice bath and 67 g (1.2 mol) of potassium hydroxide dissolved in 400 mL of water is added cautiously. The mixture is then refluxed for 3 hr. The

resulting two-phase system is cooled to room temperature and the upper aqueous phase is decanted from the oily organic layer. The aqueous phase is acidified with dilute [hydrochloric acid](#) and extracted with 300 mL of [ether](#). The ethereal extract is combined with the organic layer from the reaction mixture, and this solution is dried over anhydrous [magnesium sulfate](#). The drying agent is removed by filtration and the filtrate is concentrated on a rotary evaporator. The residual liquid is distilled to give 21.4 g (53%) of [3,7-dithianonane-1,9-dithiol](#), bp 159–162°C (1.2 mm) ([Note 4](#)).

C. *1,4,8,11-Tetrathiacyclotetradecane*. A dry, 3-L, three-necked, round-bottomed flask is equipped with a double-necked adapter for a thermometer and the 250-mL addition funnel shown in [Figure 1](#) ([Note 5](#)), a reflux condenser, and a mechanical stirrer with a 7-cm blade of Teflon. The entire system is kept under positive [nitrogen](#) pressure. The flask is charged with 2.2 L of [N,N-dimethylformamide](#) and 13.04 g (40 mmol) of [cesium carbonate](#) ([Note 6](#)). The mixture is stirred and heated to 55–60°C.

Figure 1. Addition funnel.



A solution of 9.12 g (40 mmol) of [3,7-dithianonane-1,9-dithiol](#) and 8.08 g (40 mmol) of [1,3-dibromopropane](#) ([Note 6](#)) in 300 mL of [N,N-dimethylformamide](#) is prepared. Half of this solution is placed in the addition funnel and added to the well-stirred suspension of [cesium carbonate](#) in [N,N-dimethylformamide](#) over a period of 6–9 hr. The reaction mixture is then charged with another 13.04 g (40 mmol) of [cesium carbonate](#) and the second half of the solution of [3,7-dithianonane-1,9-dithiol](#) and [1,3-dibromopropane](#) is added over a period of 6–9 hr ([Note 7](#)). After the addition is complete, the reaction mixture is allowed to cool to room temperature. The [N,N-dimethylformamide](#) is distilled off as completely as possible under reduced pressure ([Note 8](#)). The residue is taken up in 300 mL of [dichloromethane](#) and washed once with 200 mL of a saturated solution of [sodium chloride](#). The organic layer is dried over anhydrous [magnesium sulfate](#). The drying agent is removed by filtration and the

filtrate is concentrated on a rotary evaporator to a light-yellow crystalline mass. This is taken up in 200 mL of boiling 95% ethanol and the hot liquid is decanted. The remaining sediment is boiled with 125 mL of 95% ethanol and again decanted. The two ethanol solutions are combined and stored at 10°C overnight. The white crystalline product that separates is isolated by filtration and dried. The final product obtained is 6.20–6.60 g (58–62%) of 1,4,8,11-tetrathiacyclotetradecane, mp 118–119°C (lit.² mp 119–120°C) (Note 9).

2. Notes

- 1,3-Propanedithiol and 2-chloroethanol were obtained from the Aldrich Chemical Company, Inc.
- The submitters report obtaining 19.6–24.5 g (80–100%) of product, bp 179–181°C (0.5 mm). The product obtained by the checkers is pure by NMR and shows the following spectrum: ¹H NMR (CDCl₃) δ: 1.86 (quintet, 2 H, *J* = 7, CCH₂), 2.17 (br s, 2 H, OH), 2.65 (t, 4 H, *J* = 7, SCH₂), 2.73 (t, 4 H, *J* = 6, SCH₂), 3.73 (t, 4 H, *J* = 6, OCH₂).
- The checkers purchased thiourea from the Aldrich Chemical Company, Inc.
- The submitters report bp 159–161°C (0.5 mm) for the product and yields of 50–70% for reactions run with 0.1 mol of 3,7-dithianonane-1,9-diol and 0.2 mol of thiourea. The product obtained by the checkers is pure by NMR and shows the following spectrum: ¹H NMR (CDCl₃) δ: 1.63–2.07 (m, 4 H, CCH₂, SH), 2.50–2.83 (m, 12 H, SCH₂).
- The device illustrated in Figure 1 allows ready adjustment of addition rates without significant clogging. Component A is a conical ground-glass receiver for the ground-glass tapered end of a 7-mm-diameter glass rod. The rod is turned in the tapered receiver to attain the desired rate of addition. A ratchet device attached to the top of the addition funnel holds the rod in place and measures its rotation. Outlet B is connected to a mercury bubbler and nitrogen is introduced via C.
- The checkers obtained *N,N*-dimethylformamide, cesium carbonate, and 1,3-dibromopropane from the Aldrich Chemical Company, Inc. The *N,N*-dimethylformamide was distilled and stored over molecular sieves (Linde 4A) prior to use.
- The addition rate is sufficiently slow that virtually no starting material remains. The procedure avoids the need for excessively large volumes of solvent that are normally required in high dilution reactions.
- A Büchi rotary evaporator attached to a vacuum pump is used. A pressure of 1–2 mm is maintained and the flask is heated in a water bath to a maximum temperature of 60°C.
- The submitters report obtaining 6.97–8.00 g (65–70%) of product, mp 118–119.5°C. The product shows the following spectral properties: IR (KBr) cm⁻¹: 2930, 1430, 1338, 1270, 1205, 1138, 692; ¹H NMR (CDCl₃) δ: 1.90 (quintet, 4 H, *J* = 7, CCH₂), 2.65 (t, 8 H, *J* = 7, SCH₂CH₂), 2.77 (s, 8 H, SCH₂).

3. Discussion

The cyclic sulfide 1,4,8,11-tetrathiacyclotetradecane has been prepared in 7.5% yield by reaction of the bis-Na⁺ salt of 3,7-dithianonane-1,9-dithiol in boiling ethanol with 1,3-dibromopropane.² A marked improvement in yield by the use of cesium salts in *N,N*-dimethylformamide has been documented for other macrocyclic sulfides,³ as well as macrocyclic lactones^{4,5} and amines.⁶ Moreover, the nucleophilic properties of cesium salts have been used to advantage in substitution reactions.⁷

Macrocyclic sulfides, including 1,4,8,11-tetrathiacyclotetradecane, are of interest, especially as ligands for transition-metal ions in a variety of different applications.^{8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30} The methodology described here provides an efficient entry to many such macrocycles, including chiral ones that act as ligands in transition metal-catalyzed coupling reactions.²⁹

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

bis-Na⁺ salt of 3,7-dithianonane-1,9-dithiol

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium chloride (7647-14-5)

1,3-dibromopropane (109-64-8)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

2-chloroethanol (107-07-3)

dichloromethane (75-09-2)

thiourea (62-56-6)

magnesium sulfate (7487-88-9)

N,N-dimethylformamide (68-12-2)

1,3-propanedithiol (109-80-8)

CESIUM (7440-46-2)

1,4,8,11-Tetrathiacyclotetradecane (24194-61-4)

3,7-Dithianonane-1,9-diol (16260-48-3)

3,7-Dithianonane-1,9-dithiol (25676-62-4)

cesium carbonate (29703-01-3)