

The Macrocyclization Reaction of Terminal Dibromoalkanes with Sulfide on Alumina. The Use of a Solid Support as an Alternative to the High Dilution Technique.

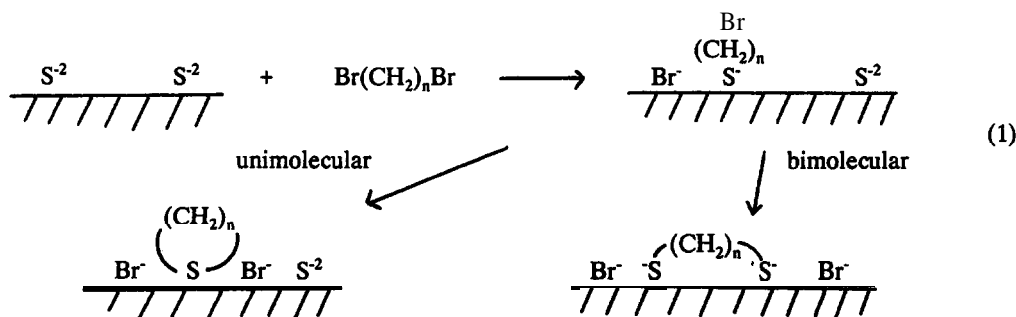
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Abstract: The reaction of a series of terminal dibromoalkanes with S⁻² on Al₂O₃ has been examined. The use of a solid support for the macrocyclization represents a viable alternate procedure to the more traditional high dilution technique in solution. The cyclizations also occur with thioacetamide on unactivated alumina.

The synthesis of large rings from acyclic precursors (macrocyclization) has always been difficult to achieve. The reason for this is that the desired unimolecular cyclization reaction competes with an analogous bimolecular reaction. To inhibit the bimolecular reaction, the chemistry is normally performed under high dilution, either by using a large volume of solvent or by very slowly adding the reagents to a small volume of solvent.* A machine has even been invented to facilitate the slow addition of reagents.³

Because the high dilution technique does not always work well, alternate procedures are desirable. The surface of a solid would appear to be a viable medium in which to run the macrocyclization reactions. The reaction of a series of terminal dibromoalkanes with S⁻² on Al₂O₃ in two steps (eq. 1) represents a test of this concept. In the first step, S⁻² reacts with Br(CH₂)_nBr to form a surface-bound, immobile thiolate. If the distance between the sulfur of the thiolate and the closest S⁻² is greater than the length of the thiolate, it follows that the bimolecular reaction of thiolate with S⁻² cannot occur and only cyclization is possible. One can control the average distance between S⁻²s by controlling the quantity of S⁻² adsorbed on the surface. Thus, the yield of cyclized product should increase as the concentration of sulfide on the surface is decreased.⁴



Another factor may also favor the macrocyclization reaction on solids. There is experimental⁶ and theoretical⁶ evidence that the rate at which two ends of a chain find each other is considerably greater when one end of the chain is immobile than when both ends of the chain are free to move. This will favor the unimolecular reaction, at the expense of the bimolecular reaction, on the solid as compared to solution counterpart.

Regen and co-workers were the first to prepare S^2/Al_2O_3 and use it to prepare dialkyl sulfides in close to quantitative yield.⁷ Gleiter⁸ and Nicolaou⁹ have subsequently used the reagent in the syntheses of a few cyclic sulfides containing two triple bonds. Our reagent is prepared by adsorption of Na_2S from aqueous solution onto **unactivated** Brockmann Activity 1 neutral alumina and then activating the resulting solid at a given temperature under vacuum. S^2/Al_2O_3 has interesting, although unexplained, chemical and physical properties. Unlike Na_2S , Al_2O_3 , and H_2O , the reagent is colored and the color depends on the concentration of S^2 . The reagent must either be used immediately or stored under argon because, when exposed to air, the free-flowing powder becomes gummy and gives poor yields of desired product. Activation temperature is also critical: the yield of product decreases as the activation temperature of the solid increases beyond 95°. A solid activated at 95° gives the best results.

The reactions were performed by **slurrying** a solution of $Br(CH_2)_nBr$ in 10 ml of toluene with S^2/Al_2O_3 at 95° for 20 hours; longer reaction times did not improve yields. Solvent and alumina are important because reactions run in the absence of solvent or alumina produced very low yields of products. The ratio of $Br(CH_2)_nBr$ to S^2 was kept at approximately 1:2 in all cases. The results of reactions run on freshly prepared S^2/Al_2O_3 are summarized in Table 1.

Table 1. Cyclic Sulfide Yields in the Reaction of $Br(CH_2)_nBr$ with S^2/Al_2O_3

Ring size	Concentration of S^2 on Al_2O_3 (mmol/g)		
	6.32×10^{-4} ^a	1.69×10^{-3} ^a	7.80×10^{-3} ^b
3 ^c			1.5 (1.8) ^d
4 ^c			9.3
5			44.7
6	55.1	79.2	
7	59.7	62.4	
8	38.4	47.1	
9	37.7	26.2	
10	15.7	12.6	
11	12.4	9.0	
13	20.4	15.6	
17	28.6	19.1	

a) Al_2O_3 activated at 95°. b) Al_2O_3 activated at 110°. c) Reaction run in a sealed tube at 140°. d) Yield of 1,4-dithiane.

The first thing to note is that all the cyclization reactions attempted were successful, even with $Br(CH_2)_2Br$ and $Br(CH_2)_3Br$, but the product yields varied greatly. A plot of yield versus ring size (not

shown) follows the usual pattern observed for cyclization reactions? the yields are low for small rings, increase steadily for **4-** through 7-membered rings, gradually decrease for the larger **8-** through **11-** membered rings, and then gradually increase for still larger rings. Our **results** compare favorably to the high dilution reactions run in **refluxing ethanol** or **HMPA-MeOH at 55°**,¹² as well as the heterogeneous reactions run with solid **Na₂S·9H₂O** in ethanol at room temperature.” Our yields are considerably higher than those obtained in refluxing ethanol and similar in several cases to those obtained in the other two media. Even in those cases where our yields are not as good as those obtained in **HMPA-CH₃OH** and **Na₂S·9H₂O-ethanol**, the surface chemistry may still be superior because of the ease which the reactions are run. Although the data are not yet extensive, the prediction that the yield of product goes up as the concentration of **S²⁻** on **Al₂O₃** goes down is born out for reactions which form rings with 7 or more methylene groups.

A few reactions were also run in solution, but not with the high dilution technique. **1,5-Dibromopentane** and 0.833 M **Na₂S·9H₂O** in a **1:2** ratio in **refluxing ethanol** and in **HMPA** at 95° afforded only trace amounts of pentamethylene sulfide after 20 hours, and **1,12-dibromododecane** in **HMPA** gave no cyclic sulfide. Because the average distance between sulfide anions in these solutions (12.6 Å) is considerably greater than it is for 6.32 x 10⁻⁴ mol **S²⁻**/g of alumina (6.36Å), the least concentrated surface used in this study, the difference in product yields between the two methods is particularly noteworthy.

There is an alternate way in which to generate **S²⁻** in situ on **Al₂O₃**. Hydrolysis of thioacetamide affords **H₂S** which has been used classically to precipitate metal cations and, more recently, in the synthesis of large rings.^{2b} **Unactivated Al₂O₃** has a surface layer of OH groups (and physisorbed **H₂O**)¹⁴ which could react with thioacetamide to form **H₂S**. Indeed, when **Br(CH₂)_nBr** (1.00 mmol) is treated with thioacetamide (2.00 mmol) and **unactivated Al₂O₃** (1.0 g) in refluxing toluene for 10 hours under argon, the corresponding cyclic sulfide and disulfide are formed in respectable yields (eq. 2). Other combinations of thioacetamide and **Al₂O₃** afforded lower yields of products. The results of these experiments are shown in Table 2.

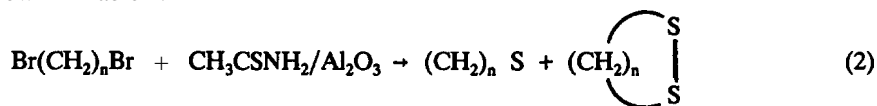
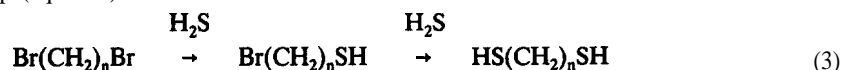


Table 2. Yields of Cyclic Sulfides and Disulfides in the Reaction of **Br(CH₂)_nBr** with **Thioacetamide/Al₂O₃**

Precursor Br(CH₂)_nBr	Cyclic Sulfide	Cyclic Disulfide
n=5	28.3	31.2
6	17.9	26.3
9	8.9	16.4
12	15.2	28.4
n=5 (Silica Gel)	25.3	26.4

These reactions are interesting because significant amounts of cyclic disulfides are generated in addition to the expected sulfides. At least with **1,5-dibromopentane**, unactivated silica, which also contains surface OH groups and physisorbed **H₂O**, gave comparable yields of the two products as unactivated **Al₂O₃** did. That the presence and nature of the **Al₂O₃** used in the **cyclizations** is important is born out by the fact that no reaction occurred in the absence of unactivated **Al₂O₃** or the presence of **Al₂O₃** activated at **400°**, which removes its physisorbed **H₂O** and approximately 50% of the surface OH groups?⁴

Why do these reactions afford disulfides when the ones on **S²⁻/Al₂O₃** do not? In the latter case the chemistry involves anions such as **S²⁻** and thiolates which remain attached to the surface. It is not possible to liberate dithiols, which are the precursors to the disulfides, from the surface by extraction of the solid with toluene or diethyl ether. With thioacetamide, however, the chemistry involves neutral species such as **H₂S** and thiols, which are free to leave the surface at one place and return, and perhaps react, at another. Here it is possible to generate dithiols in solution which form disulfides on oxidation with **O₂** during workup (eqs. 3-4).



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