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A SIMPLE, EFFICIENT SYNTHESIS OF LENTHIONINE AND 1,2,4,6-TETRATHIEPANE FROM DIMETHYL DISULFIDE

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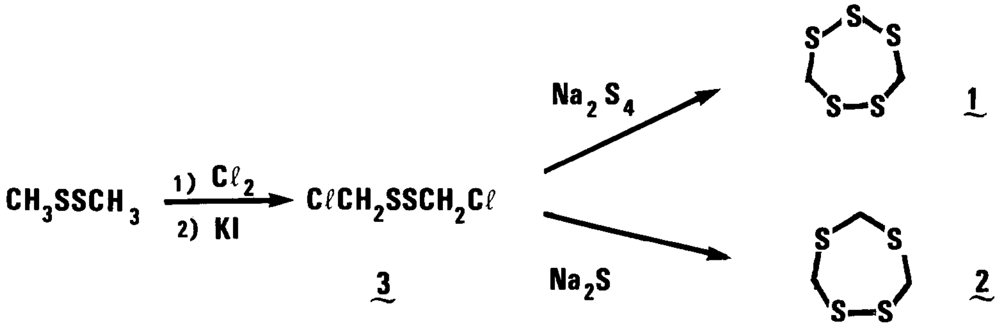
Summary: A synthetic route to the important cyclic polysulfide, lenthionine, and a related natural product is outlined.

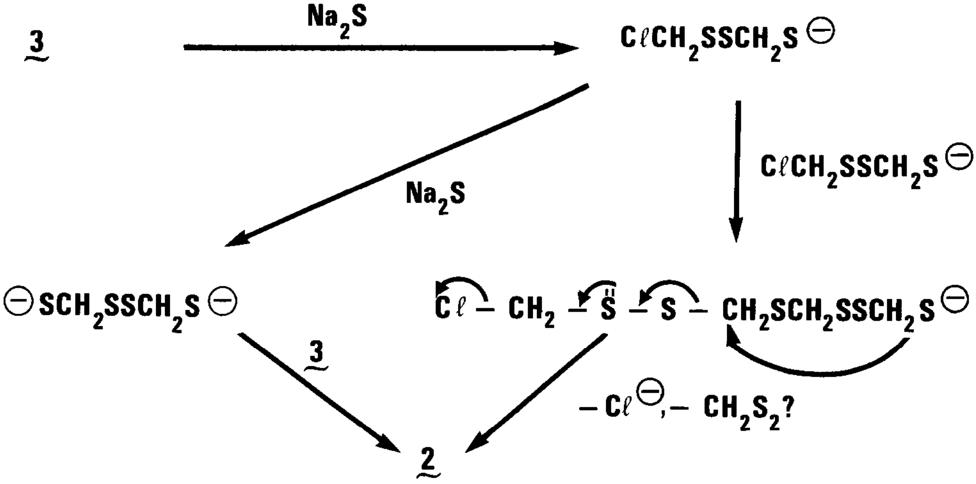
The novel natural products lenthionine (1,2,3,5,6-pentathiepane) 1 and 1,2,4,6-tetrathiepane 2 have been isolated from the edible Shiitake mushroom (*Lentinus edodes*)[1] and the red alga *Chondria californica*.[2,3] Previously reported synthesis of these polythiepanes,[1,4] which have shown promise as potential antibiotics, have been characterized by low yields. We describe here a straightforward syntheses of lenthionine and 1,2,4,6-tetrathiepane, starting from dimethyl disulfide and proceeding *via* bischloromethyl disulfide 3 as the common intermediate (Scheme 1).



Scheme 1

Adaptation of the general procedure of Tjan *et al.*[5] for the synthesis of bis-α-chloroalkyl disulfides yielded bischloromethyl disulfide 3 in 79% yield.[6,7,8] Reaction of sodium tetrasulfide (Na_2S_4)[9] with 3 yielded lenthionine in 43% yield. This material was identical in all respects with authentic material prepared by the procedure of Morita and Kobayashi.[1] The use of sodium tetrasulfide to synthesize cyclic trisulfides[10] has been reported previously.

The closely related 1,2,4,6-tetrathiepane 2 was also prepared from 3 in 52% yield, by reaction with sodium sulfide. There was no indication of the competing formation of 1,2,4-trithiolane, as reported by previous workers.[5] The unexpected formation of tetrathiepane 2 from this reaction can be explained by two possible pathways (Scheme 2) in which bischloromethyl disulfide appears to function as a methylene-transfer reagent. Further investigations of the synthetic utility of 3 are continuing.



Scheme 2

Experimental

Lenthionine, 1. Sodium sulfide nonahydrate (1.20 g,5.0 mmol) and sulfur (0.48 g,15.0 mmol) in 100 ml water were refluxed for 1½ h. After cooling to room temperature, 1 drop of Adogen® 464[13] and bischloromethyl disulfide 3 (0.81 g,5.0 mmol) in 100 mL benzene were added over a period of 2 h. After stirring for a further 1 h, extraction with benzene, drying (Na_2SO_4) and evaporation yielded a yellow oil. Thick layer chromatography (SiO_2,$CC\ell_4$) yielded lenthionine (0.24 g, 43%) and recovered 3 (0.31 g,38%). Recrystallization (dioxane) yielded 1, m.p.56-58°C, lit.[1] m.p.60-61°C; ^{1}H-NMR: δ($CDC\ell_3$) 4.30 (s,4H), lit.[2] δ($CDC\ell_3$) 4.33 (s,4H) ppm; m/e=188(M^+).

1,2,4,6-Tetrathiepane, 2. The disulfide 3 (0.81 g,5.0 mmol) in 100 mL benzene was added to sodium sulfide nonahydrate (1.20 g,5.00 mmol) in 100 mL water. Work up as in synthesis of 1, yielded pure 2 after chromatography (0.22 g,52%), m.p.76-78°C (lit.[1] mp.79°C); ^{1}H-NMR: δ($CDC\ell_3$) 4.21 (s,4H), 4.25 (s,2H), lit.[1] δ($CDC\ell_3$) 4.24 (s,4H), 4.28 (s,2H) ppm; m/e=170(M^+).

References and Notes

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