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THE ALKYLATION OF 1,3,5-TRITHIANES

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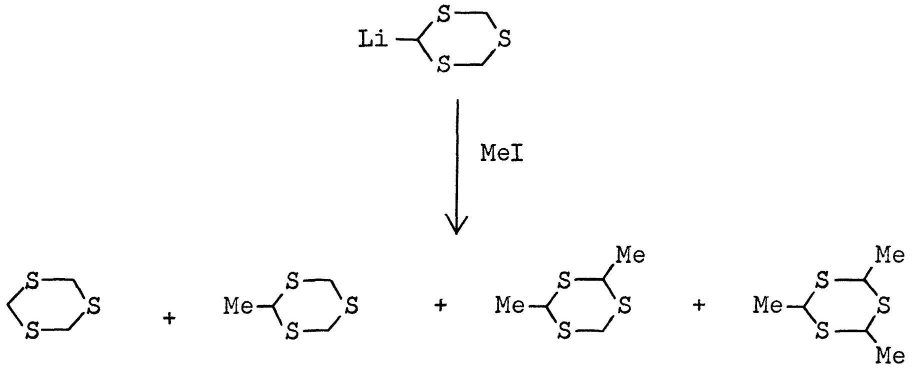
A method of synthesis of 1,3,5-trithiane derivatives which carry the desired number of methyl groups is described. Anions derived from 1,3,5-trithianes are found to undergo fast proton exchange with 1,3,5-trithianes if the latters carry a methylene group placed between two sulfur atoms.

During the course of study on the H-D exchange rates of 1,3,5-trithianes1), it has become necessary to synthesize the compounds which carry various numbers of methyl groups. The synthesis of unsymmetrical derivatives were not easy by the classical method which utilized carbonyl compounds and hydrogen sulfide. We wish to report a neat synthetic method of trithiane derivatives which involves the alkylation of lithio derivatives of 1,3,5-trithianes.

The formation of 2-lithio-1,3,5-trithiane was reported by Crouse and Seebach2) during the course of our study. We had been trying to methylate the anion to obtain 2-methyl-1,3,5-trithiane. And the anion was prepared in the following way: equimolar amount of butyllithium in ether was added to a suspension of 1,3,5-trithiane in tetrahydrofuran at -20°C and the mixture was stirred until a homogeneous and colorless solution resulted.

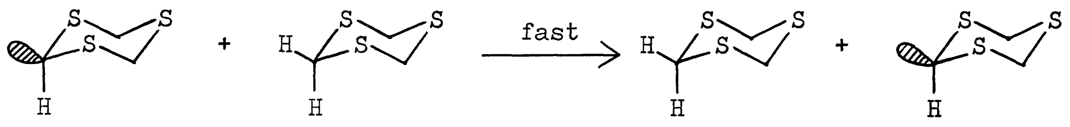
The addition of slightly excess of methyl iodide to the solution of the 2-lithio-1,3,5-trithiane from 0.05 mole of 1,3,5-trithiane gave a solid product which contained 15% of the recovered starting material which was isolated because of the poor solubility in petroleum ether. The NMR spectrum of the crude product which was extracted by petroleum ether revealed that the product contained 36% 2-methyl-1,3,5-trithiane, 25% cis-2,4-dimethyl-1,3,5-trithiane, and 10% cis,cis-2,4,6-trimethyl-1,3,5-trithiane.

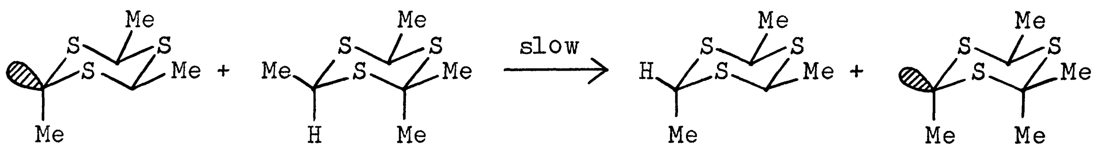


However, the reverse addition, namely the addition of a cooled ethereal solution of lithio-1,3,5-trithiane to the excess of methyl iodide in ether at -10°C afforded 2-methyl-1,3,5-trithiane only. The product was spectroscopically pure and melted at 77-82°C. The pure compound was obtained by recrystallization from hexane in 78% yield, mp. 84-85.5°C[3]. Similarly the lithiation of 2-methyl-1,3,5-trithiane with butyllithium followed by the addition of the resulting lithio derivative to methyl iodide gave cis-2,4-dimethyl-1,3,5-trithiane in a good yield, mp. 111-112.5°C. The formation of cis,cis-2,4,6-tributyl-1,3,5-trithiane on addition of butyl bromide to lithium metal and 1,3,5-trithiane in tetrahydrofuran may be the analogous phenomenon[4].

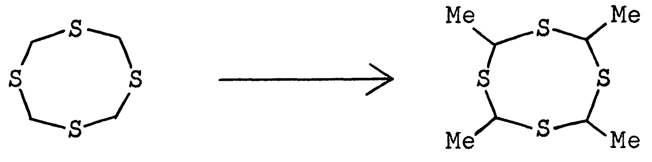
The exclusive formation of the cis forms of di- and tri-alkyl derivatives may be taken as another example of the stereoselective reaction of 1,3,5-trithianyl anion[5] which affords the equatorial substituent. This is because the methyl - equatorial conformation is prefered over the methyl-axial and the attack from the equatorial side of the anion in this conformation should give the cis isomer.

The remarkable change in the reaction paths as mentioned above does not apply to 2,4,6-trimethyl-1,3,5-trithiane. Thus adding methyl iodide to a solution of lithiated cis,cis-2,4,6-trimethyl-1,3,5-trithiane gave cis-2,2,4,6-tetramethyl-1,3,5-trithiane, mp. 75-76°C, in a good yield. Similarly cis-2,2,4,6-tetramethyl-1,3,5-trithiane afforded 2,2,4,4,6-pentamethyl-1,3,5-trithiane, mp. 73-74.5°C. Since the only difference of these starting compounds from the trithianes which gave the mixed polymethylated compounds is the fact that the former have methine groups only whereas the latter the methylene, it must be assumed that the exchange of protons between the 1,3,5-trithianes is fast only when the group involved in the reaction is the methylene. The slow exchange of the methine proton may also be attributed to the slow abstraction of the axial hydrogen[6].





In the light of the above results, we should like to cite a fact from the literature. The formation of a tetraanion was postulated during the methylation of 1,3,5,7-tetrathiocane[7] : the lithiation of 1,3,5,7-tetrathiocane followed by the treatment with methyl iodide gave an isomeric mixture of 2,4,6,8-tetramethyl-1,3,5,7-tetrathiocanes. We prefer the stepwise methylation of monoanions rather than the tetraanion, although the system is a little different from ours.



1) M. Fukunaga and M. Ōki, 3rd. International Congress of Heterocyclic Chemistry (Sendai, 1971), Abstract Papers p. 605.

2) D. N. Crouse and D. Seebach, Chem. Ber., 101, 3133 (1968)

3) Although not reported, the elemental analyses of all the new compounds checked nicely with the expected values.

4) The carbonation of the resulting reaction mixture did not give any carboxylic acid, the only isolated product besides the unreacted starting material being cis,cis-2,4,6-tributyl-1,3,5-trithiane, mp. 55-56.5°C.

5) M. Fukunaga, K. Arai, H. Iwamura and M. Ōki, Bull. Chem. Soc. Japan, in press.

6) The treatment of cis,cis-2,4,6-trimethyl-1,3,5-trithiane with butyllithium followed by the protonation or the carbonation gave exclusively the equatorial product4). The protonation of the lithio derivative of cis-2,2,4,6-tetramethyl-1,3,5-trithiane also afforded the trans isomer as a sole product. The figure of the equatorial carbanion of the two species was drawn on this account. The H-D exchange rate of the equatorial protons of 2-methyl- or cis-2,4-dimethyl-1,3,5-trithiane in t-butyl alcohol-d in the presence of the conjugate base was found to be 6×10^5 times faster than the ring-proton of cis-2,2,4,6-tetramethyl-1,3,5-trithiane1).

7) R. T. Wragg, Tetrahedron Lett., 4959 (1969).

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