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STEREOSELECTIVITY IN NUCLEOPHILIC SUBSTITUTION OF TRITHIANE DERIVATIVES

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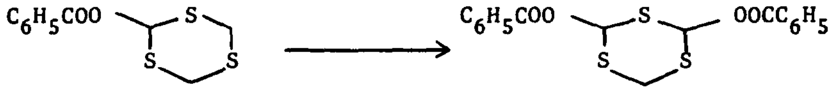
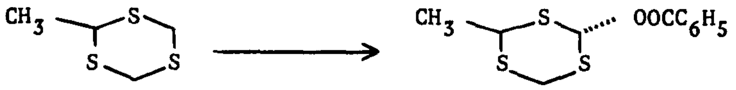
Cuprous ion-catalyzed benzoyloxylation of 2-benzoyloxy-1,3,5-trithiane (1) with t-butyl peroxybenzoate was found to afford cis-2,4-dibenzoyloxy-1,3,5-trithiane (2) almost exclusively.1) Since the final step of the reaction is known to be the attack on the carbonium ion by the benzoate anion,2) and the conformation of 2-benzoyloxy-1,3,5-trithiane is benzoyloxyl-axial form,1) it appears that the reaction proceeds by the axial attack of the benzoate anion. In order to test the generality of the stereoselectivity, further study was undertaken.



(1) (2)

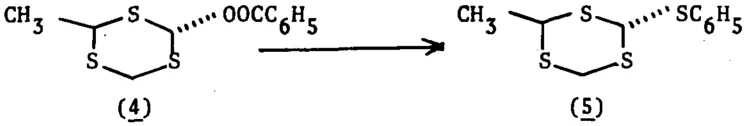
Treatment of 2-methyl-1,3,5-trithiane (3) in benzene with t-butyl peroxybenzoate in the presence of cuprous chloride yielded only trans-2-methyl-4-benzoyloxy-1,3,5-trithiane (4), mp 105-107°C, as a benzoyloxylated compound. The stereochemistry of this compound was assigned for the following reasons. PMR spectra of 4 in $CDCl_3$ at room temperature show signals at δ 7.18 for the methine proton at the foot of the benzoyloxyl group and at δ 3.86 and 4.92 for the methylene protons. The methine proton signal is broad and one of the methylene signals at higher field shows fine splittings. The chemical shift of the methine proton at the foot of the methyl group and that of the low-field signal of the methylene group show down field shift, compared with those of the corresponding signals of 2-methyl-1,3,5-trithiane. These data are consistent with the structure assignment of the axial-benzoyloxyl and equatorial-methyl conformation.



(3) (4)

The results suggest that stereochemical relations are inverted, when they are compared with those of the 2-benzoyloxytrithiane case, but the reaction is still stereoselective. Apparent reversal of the stereochemical relation is not surprising if one considers the stable conformations of the parent compounes. The benzoyloxyl-axial isomer is almost exclusive in 1, whereas the methyl-equatorial isomer is predominant in 3. If the attack by the benzoate anion takes place from the axial side of the benzoyloxyl-axial form of 4-benzoyloxy-1,3,5-trithian-2-yl ion and that of methyl-equatorial form of 4-methyl-1,3,5-trithianyl cation, it will result in the formation of the cis and the trans form, respectively. Thus the axial attack takes place preferentially in this reaction.

Since benzenethiolysis of 1 is known to proceed by S_N1 mechanism,3) the reaction of 3 will provide another example of tests on the stereoselectivity. Accordingly, compound 4 was treated with benzenethiol in benzene. The product was a 6 : 1 mixture of trans-2-methyl-4-phenylthio-1,3,5-trithiane (5), mp 126-127°C, and a cis-isomer. The stereochemistry of the products was assigned by the spectral data: the methine proton at the foot of the phenylthio group gives a broad singlet at δ 5.55 due to the equatorial-equatorial long range coupling and the methylene protons a quartet at δ 3.69 and 4.99, the former showing coupling with $J = 1.0$ Hz. On the other hand, the minor product gives a sharp singlet at δ 5.07 for the methine proton at the foot of the phenylthio group and a sharp AB quartet at δ 4.01 and 4.22 for the methylene. The reaction proceeds with retention of configuration predominantly.



The preferential formation of 5 cannot be a result of thermodynamic control The cis and the trans isomers of 5 could be equilibrated using benzoic acid as a catalyst at 80°C within 20 hours. The ratio trans/cis in $CDCl_3$ under these conditions was 1.8 as judged from the integrated intensities of PMR signals and is far less than the ratio obtained by the reaction. The preferential formation of the trans form by benzenethiolysis of 4 must be attributed to the kinetic control. Axial attack on carbonium ion is again favored.

Benzenethiolysis of 2 in C_6H_6 afforded a mixture of cis- and trans-2,4-bis(phenylthio)-1,3,5-trithianes in 1 : 3 ratio. Examination of PMR spectra at appropriate intervals reveals that the ratio is constant throughout the reaction period. Since the equilibration of cis and trans isomers takes more than 10 hours in the presence of benzoic acid, the ratio may be taken as a result of kinetic control. The inferior stereoselectivity of the reaction must at least partly be derived by the presence of the phenylthio group. 2-Phenylthio-1,3,5-trithiane is known to exist both as equatorial and axial isomers$^{4)}$ and the 4-phenylthio-1,3,5-trithian-2-yl cation sill take similar conformations. The equatorial form is expected to give the trans isomer and the axial form the cis isomer.

In order to obtain information of the origin of the remarkable stereoselectivity of the nucleophilic substitution of the trithiane system, the solvent effect on the selectivity was examined. The reaction of 4 with benzenethiol in various solvents at room temperature was examined by PMR spectra. The results are given in Table 1.

Table 1. Solvent Effects on the Stereoselectivity in the Reaction of trans-2-Benzoyloxy-4-methyl-1,3,5-trithiane with Benzenethiol

Solvent	Dielectric Constant	trans/cis
C_6H_6	2.28	6.5
C_6H_5SH	4.4	6
$CHCl_3$	4.81	7
$(CH_3)_2CO$	20.7	ca. 4
$[(CH_3)_2N]_3PO$	30	2.5

The polarity effect is not apparent with the solvents of low dielectric constant, but is clear when the dielectric constant is high. The phenomenon may be understood on the ground of the ion-pair, as was the case of 1,3-dithianide anion,[5)] although the placing of ions is still in question. If a tight ion-pair is formed in less polar solvents, the direction of the attack by the nucleophile will be limited and increasing population of a free ion in polar solvents will decrease the selectivity. However, there still remains a possibility that a free ion which is abundant in polar solvents favors the attack from the axial side for unknown reasons. Further study is needed to solve the problem.

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