Tetrahedron Letters,Vol.25,No.28,pp 3029-3032,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

STEREOESPECIFIC SYNTHESES OF 2,3-DIMETHYL-1,4-OXATHIAN S-OXIDES

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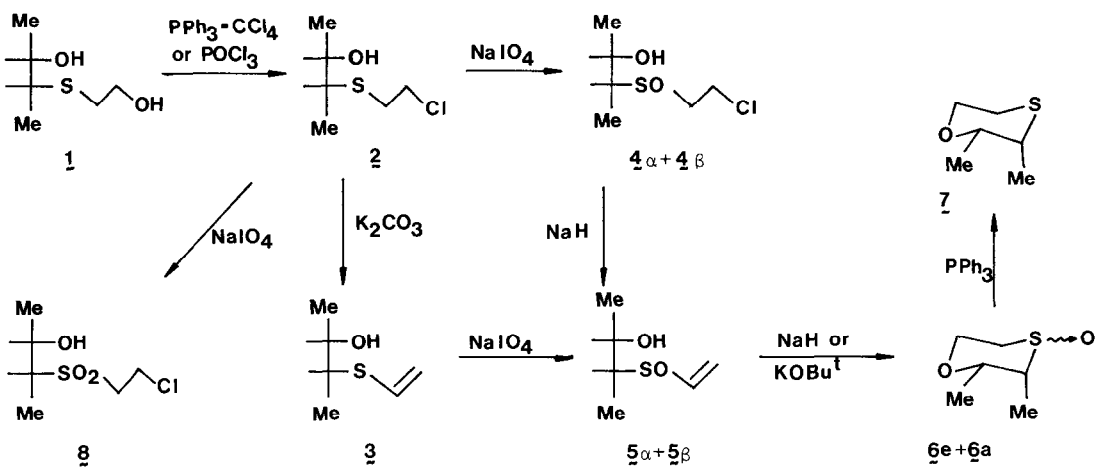
The stereoespecific syntheses of cis- and trans-2,3-dimethyl-1,4-oxathian, their diastereomeric S-oxides and their S-dioxide derivatives are reported. The key step in the synthetic pathways is the cyclization of a 2-hydroxyalkyl vinylsulphoxide, by intramolecular conjugated addition with retention of configuration in the C and S chiral centers.

1,4-Oxathians have scarcely been studied from a conformational viewpoint[1]. Several methods have been reported to prepare 1,4-oxathians[2], but they are not that satisfactory for the stereoespecific synthesis of their 2,3-dialkyl derivatives. In this paper, a new method for the obtention of diastereomerically pure S-oxides of cis- and trans-2,3-dimethyl-1,4-oxathians is reported.

The synthesis of cis-2,3-dimethyl-1,4-oxathian, 7 , was carried out according to the sequence shown in scheme 1.



Scheme 1

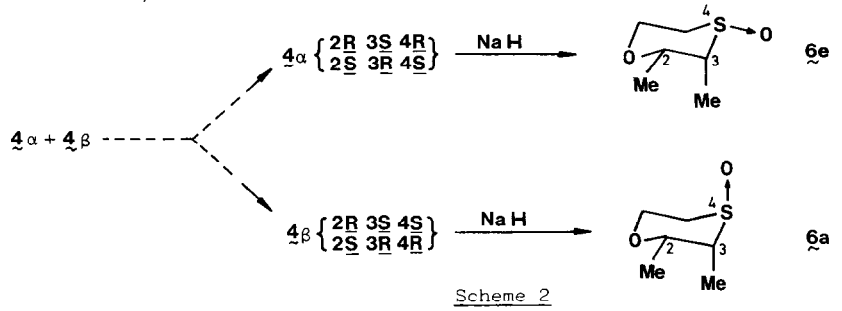
The erythro-diol 1 was obtained by the opening of the trans-1,2-dimethyloxirane with 2-mercaptoethanol following the procedure described by Evans[3]. Attempts to cyclize compound 1 with acid catalysis (BF_3 , TsOH , H_2SO_4) were unsuccesful and complex mixtures were obtained in all cases. Similar unsuccessful results have been obtained by other authors in several attempts to cyclize related diols[4]. This failure can be expalined because the anchimeric assistance of the sulphenylic sulphur gives a thiiranium salt intermediate, wich precludes the intramolecular

S_N2 attack of the second hydroxyl group to give the 1,4-oxathian.

Chlorination of the primary hydroxyl group of 1, by reflux during 20 hours with PPh_3 (1 eq.) in CCl_4[5], afforded compound 2 (yield 90%). The reaction of diol 1 with $POCl_3$ (1 eq.) at 0°C [6] yields a 85:15 mixture (by ^{1}H-nmr) of compound 2 and its regioisomer (erythro-2-chloro-3-(2-hydroxyethylthio) butane). The reaction of 2 with several bases under different conditions , did not afford the desired 1,4-oxathian, but the vinylsulphide 3 was produced in quantitative yield. Cyclization was then attempted using the sulphoxides 4α and 4β as intermediates.

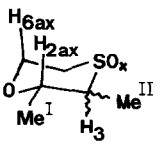
Oxidation of 2 with $NaIO_4$ (1 eq.) gave the diastereomeric mixture of sulphoxides 4α and 4β (yield 95%), which by reaction with NaH (1.5 eq.) in DMF[7] at 40°C during 18 hours, cyclized to the corresponding 1,4-oxathian S-oxides 6e+6a[8]. The latter reaction involves two steps, elimination of HCl to give 5α +5β , and nucleophilic conjugated addition[9] of alkoxide to the vinylsulphoxide group. This was demonstrated by stopping the above reaction of 4α +4β after 2 hours. At this point, the components of the initial mixture had completely disappeared and the only reaction products were the vinylsulphoxides 5α and 5β , which were isolated and characterized. These compounds were identical to those obtained by oxidation of vinylsulphide 3 with $NaIO_4$(1 eq.). When the mixture 5α +5β was left for 3 days at room temperature, in DMF containing strong bases (NaH or $KOBu^t$), a mixture of 6e+6a was isolated (yield 80%). These results indicated that the vinylsulphoxides were intermediates in the conversion of 4α +4β to 6e+6a. The cis-2,3-dimethyl-1,4-oxathian 7, was obtained by reduction of stereomeric mixture of cyclic sulphoxides with PPh_3.

From the observed $J_{2,3}$ values in both 6e and 6a (1.7-1.9 Hz), it could be deduced that the cyclization occurred without epimerization on C-3. In addition, the configuration of the sulphur also remains apparently unaltered in this process[10]. In order to confirm this assumption, which would allow us to assign the relative configuration of the chiral centers in acyclic hydroxysulphoxides 4α and 4β , these compounds were separated by column chromatography on silica gel (eluent $CHCl_3$:MeOH 25:3) and cyclized independently (scheme 2). Compound 4α (δ_{CH-O}= 4.51, δ_{CH-S}=2.81 , δ_{CH_3-CO}=1.43 and δ_{CH_3-CS}=1.25 ppm) yielded only sulphoxide 6e, whereas 4β (δ_{CH-O} =4.36, δ_{CH-S}=2.75, δ_{CH_3-CO} ~ δ_{CH_3-CS}=1.33 ppm) yielded 6a. As the axial or equatorial arrangement of the sulphinylic oxygen can easily be established from the chemical shifts of the H_{2ax} and H_{6ax} axial protons in the oxathian ring, which must be greatly deshielded in the sulphoxide 6a[11] (see table 1), the configurational assignment of acyclic sulphoxides could be established (see scheme 2).



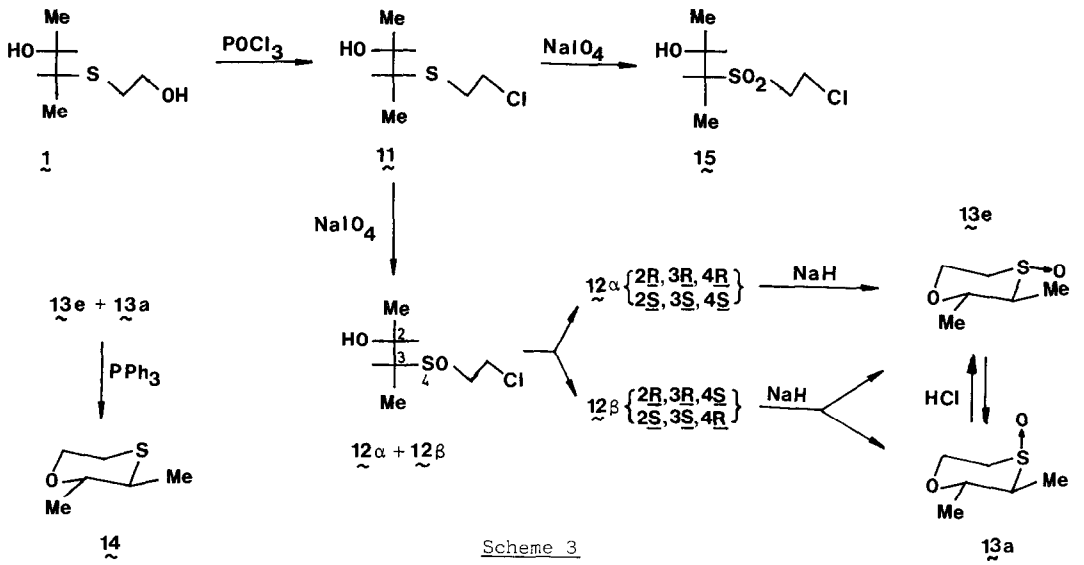
Scheme 2

Table 1. Significant ^{1}H-nmr parameters of 1,4-oxathians and derivatives



Compound	$J_{2,3}$	Chemical shifts, δ (ppm)				
		2ax	6ax	3	MeI	MeII
7	2.3	4.01	3.79	2.54	1.15	1.39
6e	1.6	3.70	3.62	3.12	1.30	1.32
6a	1.9	4.55	4.43	2.62	1.20	1.24
9	2.0	4.30	3.99	2.82	1.27	1.42
14	9.0	3.34	3.69	2.70	1.22	1.10
13e	9.7	3.40	3.69	2.53	1.31	1.41
13a	9.7	4.09	4.40	2.34	1.26	1.30
16	9.8	3.74	4.06	2.88	1.30	1.31

The synthesis of the trans-2,3-dimethyl-1,4-oxathian 14 was carried out in similar way. The threo-diol 10 was quantitatively obtained from the bromohydrin of cis-butene by reaction with 2-mercaptoethanol. The observed regioselectivity in the chlorination of 10 with $POCl_3$ was higher than 97% (the minor regioisomer was not detected by ^{1}H-nmr). The oxidation of 11 with $NaIO_4$ yielded a mixture of 12α and 12β (97%) which were separated by chromatography. The cyclization of 12α (δ_{CH-O}=4.39, δ_{CH-S}=2.80, δ_{CH_3-CO}=1.38 and δ_{CH_3-CS}=1.29 ppm) with NaH/DMF at 40°C afforded only 1,4-oxathian 13e, whereas 12β (δ_{CH-O}=4.26, δ_{CH-S}=2.80, δ_{CH_3-CO}=1.32 and δ_{CH_3-CS}=1.13 ppm), in identical conditions, yielded a mixture (1:1) of 13e and 13a. Similar results were obtained at 20°C. Epimerization of sulphoxide 13e in HCl[12] yielded a mixture of 13a and 13e (4:1),

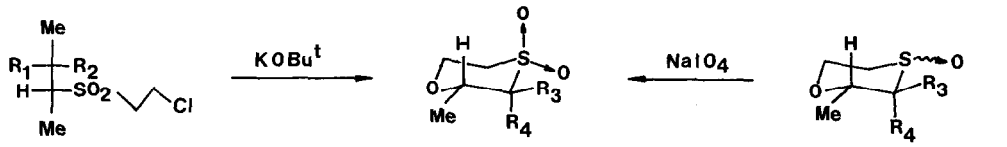


Scheme 3

suggesting that 13a was more stable than 13e. This mixture remain unaltered despite treatment with NaH/DMF at 40°C for 3 days. This result indicates that the epimerization of sulphur had

taken place on the α-sulphinyl carbanion intermediate.

Sulphones 9 and 16 were prepared by oxidation of the corresponding sulphoxides 6 and 13 with $NaIO_4$. The cyclization of sulphones 8 and 15, which in turn were obtained by oxidation of



8 : R_1 = H, R_2 = OH
15 : R_1 = OH, R_2 = H

9 : R_3 = H, R_4 = Me
16 : R_3 = Me, R_4 = H

6e + 6a : R_3 = H, R_4 = Me
13e + 13a : R_3 = Me, R_4 = H

Scheme 4

sulphides 2 and 11 with excess $NaIO_4$, required only 2 hours at room temperature. Compound 8 yielded only sulphone 9, whereas in the cyclization of 15 epimerization on C-3 took place, yielding a mixture (1:5) of 9 and 16 (scheme 4).

The scope of this method as a more general procedure for the obtention of 1,4-oxathians and derivatives is under study. We think that the careful selection of starting products (β-hydroxythiols and epoxides, bromohydrins or β-dihaloalkanes) will permit the synthesis of any C-alkyl (or aryl) substituted 1,4-oxathian. The conformational analysis of these compounds and the anomalous cyclization of sulphoxide 12β and sulphone 15 are also being studied.

REFERENCES AND NOTES

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3. Rooney R.P. and Evans S.A.; J.Org. Chem., 1980, 45, 180.
4. Black D.K.; J.Chem.Soc. (C), 1966, 1708.
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6. In similar conditions, the reaction of compound 1 with $SOCl_2$ yielded an equimolecular mixture of both regioisomers.
7. Yields are lower in other solvents such as acetonitrile or THF.
8. Subindexes e and a indicate the equatorial or axial arrangement of the sulphinylic oxygen.
9. Intermolecular conjugated additions to vinylsulphoxides, acting as nucleophile amines (Abbot D.J., Colonna S. and Stirling C.J.M.; Chem. Comm., 1971, 471), sodium methoxide (Tsuchihashi G., Mitamura S. and Ogura K.; Tetrahedron Lett., 1973, 2469) and stabilized carbanions (Tsuchihashi G., Mitamura S., Inone S. and Ogura K.; Tetrahedron Lett., 1973, 323) have been reported.
10. As estimated by ^{1}H-nmr, the ratio 4α:4β was essentially the same as the ratio 6e:6a.
11. Foster A.B., Inch T.D., Qadir M.H. and Weber J.M., Chem. Comm., 1968, 1086; Cook M.J., Kemia-Kemi, 1976, 3, 16. The use of this criterium has been possible because all sulphoxides exhibit values of $J_{5ax,6ax}$ larger than 11 Hz.
12. Mislow K.; Rec. Chem. Prog., 1967, 28, 217.

(Received in UK 8 May 1984)