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ISOPRENE FUNCTIONALIZATION
HYDROXY SULFONE TERPENE BUILDING BLOCKS BY RING OPENING OF CYCLIC ALKOXY OXOSULFONIUM INTERMEDIATES

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Abstract—Hydroxy sulfoxide 1 reacts with SO_2Cl_2 to give the (Z)-C_5 terpene building block 3b via cyclic alkoxy oxosulfonium salt 2. The conversion of 1 via the corresponding sulfone 4 leads to the (E) isomer 6b. An explanation is offered for the stereoselective course of the reactions.

The homologation of 1,4-functionalized isoprene building blocks (e.g. 3b or 6b) by alkylation of their ambident allylic anions with alkyl halides is usually complicated by the formation of both α- and γ-alkylated products, resulting in partial migration and E/Z-isomerization of the double bond.

A recent communication[1] reporting the selective α-alkylation of 6b without affection of the double bond has stimulated us to design a conversion of the hydroxy sulfoxide 1† into the chlorosulfones‡ 3a and 6a. This conversion requires an oxidation followed by an allylic transposition. We have developed a procedure to combine these two processes in a stereoselective conversion of the diastereomeric racemates 1a and 1b into the Z-chlorosulfone 3a. The method applies the elegant sulfuryl chloride induced rearrangement of β-hydroxy sulfoxides to the corresponding β-chlorosulfones, involving cyclic alkoxy oxosulfonium salts.[3] An S_Ni' ring opening of the vinyl substituted sulfonium intermediate 2 by a chloride ion leads to the Z-isomer 3a.

The E-isomer 6a is obtained by oxidation of 1 to the corresponding sulfone 4 and allylic transposition via the carbonium ion 5, following a literature procedure.[4]

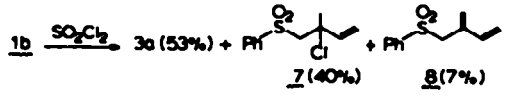
Stereochemical aspects of the sulfuryl chloride reaction

Treatment of 1a with sulfuryl chloride leads to a reaction mixture containing the Z-chlorosulfone 3a as the only primary chloride along with the corresponding tertiary isomer 7 and the diene 8 (Scheme 2). The same products are formed in a different ratio starting from the diastereomer 1b.

We assume that the three products 3a, 7 and 8 arise from cyclic intermediates of type 2 (Scheme 1), since allylic rearrangements that proceed via carbonium ions (e.g. 4 to 6a) give the E-isomers in excess.

When this assumption is correct, the different behaviour of the diastereomeric racemates can be carried back to the difference in chemical fate of their primary reaction intermediates. Scheme 3 gives the various intermediates which might explain the observed reaction pattern. The chloro oxosulfonium chlorides 9 and 13, are no doubt formed from the respective sulfoxides with retention of configuration at the sulfur atom.[5] During the rearrangement of 9 and 13 the sulfur atom will pass through a pentacoordinate state, which can undergo isomerization by a pseudo rotation process, finally leading to the cyclic sulfonium salts 12 and 16 after loss of a chloride ion from an apical position.

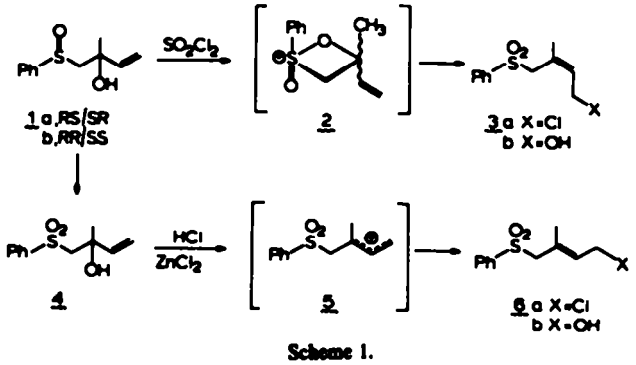
Inspection of a molecular model of 12 suggests that the C–O bond will be considerably elongated as a result of steric interaction of the vinyl substituent with both the



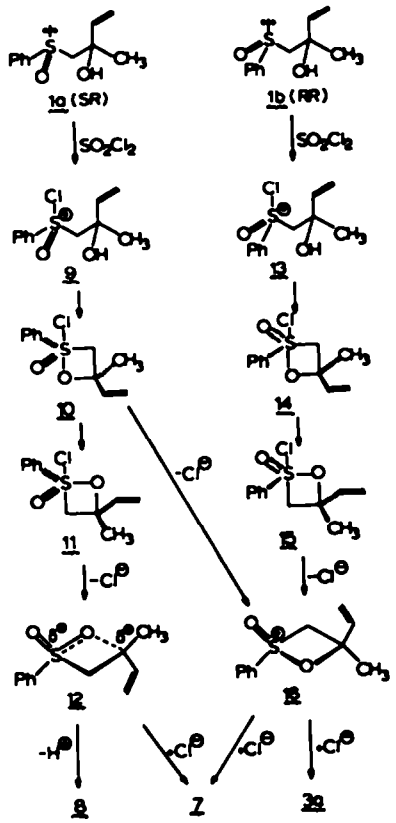
Scheme 2.

†Both diastereomeric racemates 1 have been described; see Ref. 2.

‡A procedure for the conversion of 5a into the corresponding hydroxy compound 6b is available in the literature, see Ref. 1.



Scheme 1.



Scheme 3. Only one enantiomer is shown for each racemate.

methyl group attached to the same carbon and the phenyl group at a *cis*-position across the ring. This elongation will create carbonium ion character on the tertiary carbon and make 12 more prone (compared with 16) to stabilization in a S_N1/El-fashion leading to 7 by chloride ion trapping and 8 by proton loss. The cyclic sulfonium salt 16, however, having less steric crowding, will prefer a S_N2/S_N2' mechanism, leading to a mixture of 3a and 7.

The exclusive formation of the Z-isomer 3a from the intermediate 16 presumably originates from a combination of two factors: (i) the steric interaction of the vinyl and the methyl substituent (Fig. 1, side view), which restricts the vinyl rotation (limits indicated in Fig. 1, top view), (ii) pole/dipole interaction which pilots the nucleophile in from the side that is most exposed to the positive pole of the S–O dipoles.

The penta coordinate intermediates have an increasing stability in the order 14, 10, 11 to 15 (with little difference between the structures 10 and 11) based on the following considerations: The oxygen atoms have an electron-donating nature (the "sulfoxide" oxygen because of the high coordination state of the sulfur; the ring oxygen as a result of steric hindrance leading to partial ring opening) and therefore prefer an equatorial position. The formation of 10 and 14 from 9 and 13 respectively, and pseudorotation from 10 to 11 and from 14 to 15 at one hand, combined with the loss of a chloride ion from 10 to 16 on the other hand, would explain the observed reaction pattern.

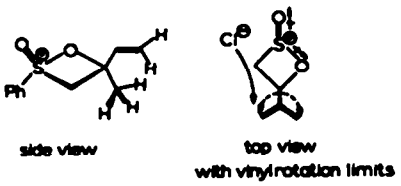


Fig. 1. Intermediate 16.

Isolation of the Z-isomer

The Z-isomer 3a may be isolated from the reaction mixture by crystallization. However the overall yield increases significantly by the addition of ether, concentrated HCl and $ZnCl_2$ in quantities just enough to create a homogeneous solution. Pure 3a begins to crystallize after some time and almost all of the isomer 7 is converted into 3a. Presumably the high initial concentration of the thermodynamically less stable isomer 3a leads to its fast and exclusive crystallization.

EXPERIMENTAL

All reactions were performed under N_2. Sulfuryl chloride was freshly distilled prior to use; NMR (TMS, $\delta = 0$) was recorded on a Varian associates model HA-100 instrument. M.ps were determined on a Leitz-Wetzlar apparatus and are not corrected.

Reaction of hydroxy sulfoxide 1 *with* SO_2Cl_2. 210 mg (1 mmole) hydroxy sulfoxide 1 was dissolved in 10 ml CH_2Cl_2. The temp. of the soln. was lowered to − 50° using an alcohol-dry ice bath. 1.2 mmole (97 μl) SO_2Cl_2 was added and the soln. was allowed to reach room temp. Water was added and the layers were separated. The CH_2Cl_2 layer was dried over $MgSO_4$, filtered and evaporated, affording a clear residue (244 mg, 100%) of the composition shown in Scheme 2.

(*z*)-1-*Phenylsulfonyl*-2-*methyl*-4-*chlorobut*-2-*ene* (3a). ^1H NMR ($CDCl_3$): 7.50–7.70 and 7.80–7.95 (m, phenyl), 5.71 (t, C_3–H), 3.83 (s, C_1–H), 3.74 (d, C_4–H), 1.80 (s, C_2–Me), m.p. 78–80°.

1-*Phenylsulfonyl*-2-*methyl*-2-*chlorobut*-3-*ene* (7). ^1H NMR ($CDCl_3$): 7.50–7.70 and 7.70–7.90 (m, phenyl), 5.95–6.25 (m, C_3–H), 5.05–5.45 (m, C_4–H), 4.70 (s, C_1–H), 1.93 (s, C_2–Me).

2-*Phenylsulfonylmethyl butadiene* (8). ^1H NMR (CCl_4): 7.40–8.00 (m, phenyl), 5.95–6.45 (m, C_3–H), 4.85–5.35 (m, C_1–H and C_4–H), 4.87 (s, methylene-H), m.p. 52–53°.

Isolation of 3a. 250 μl ether, 250 μl 30% HCl and 130 mg $ZnCl_2$ was added in succession to the crude reaction mixture (245 mg, 1 mmole). This mixture was vigorously shaken for a few minutes. After 18 hr, 2 ml water was added, the crystals were filtered off and washed with water, to give 3a (210 mg, 86%).

Oxidation of hydroxy sulfoxide 1. 10.5 g (50 mmole) hydroxy sulfoxide 1 was dissolved in 100 ml CH_2Cl_2 and cooled to − 50°. 10 g (50 mmole) 85% m-chloroperoxybenzoic acid was added slowly and the mixture was stirred overnight at −20°. The precipitate was filtered off and the mother liquor was stirred with sat. $NaHCO_3$ soln. until the CO_2-evolution ceased. The layers were separated and the organic layer was dried over $MgSO_4$. The sulfone (10.47 g, 93%) was purified by liq. chromatography (silicagel/CH_2Cl_2).

1-*Phenylsulfonyl*-2-*methyl*-2-*hydroxybut*-3-*ene* (4). ^1H NMR ($CDCl_3$): 7.50–7.70 and 7.85–8.00 (m, phenyl), 5.05–6.05 (m, C_3–H and C_4–H), 3.93 (s, OH), 3.40 (s, C_1–H), 1.56 (s, C_2–Me), m.p.: 25–28°. The conversion of 3a to 3b and 6a to 6b were carried out according to M. Julia[1] in 80% overall yield. (Z)-4-phenylsulfonyl-3-methyl-2-butenol-1 3b. ^1H NMR ($CDCl_3$): 7.50–7.70 and 7.80–8.00 (m, phenyl), 5.84 (t, C_3–H), 3.91 (s, C_4–H), 3.89 (d, C_1–H), 2.03 (S, OH), 1.80 (s, C_2–Me).

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