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# FIRST SYNTHESIS OF SIMPLE OPTICALLY ACTIVE SELENOXIDES

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Abstract: Simple optically active selenoxides (5-11 %e.e.) were prepared using a kinetic resolution procedure and were demonstrated to be configurationally unstable as a result of acid catalyzed achiral hydrate formation.

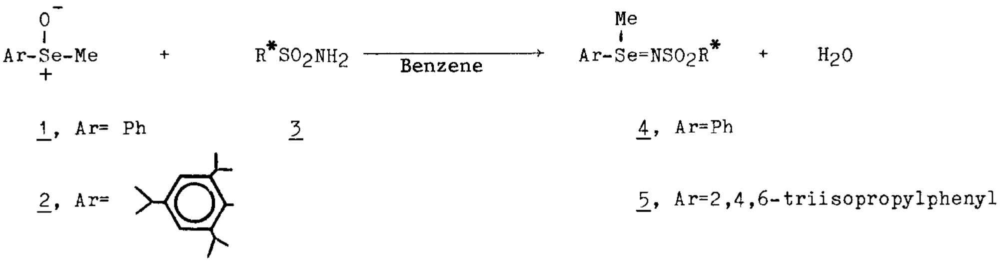
In contrast to sulfoxides, contradictions exist in reports concerning the configurational stability of the selenoxide moiety (RSe(O)R').[1] All attempts to resolve chiral selenoxides have been unsuccessful due to the facile formation of achiral hydrates ($RSe(OH)_2R'$).[2] This ability of selenoxides to form hydrates is well established and has been used to explain the general configurational lability of selenoxides.[3]

Stable diastereomeric steroidal selenoxides are, however, known.[4,5] Jones and co-workers obtained, on oxidation of steroidal selenides, two diastereomeric selenoxides which were stable at -78 °C and 25 °C, either in the presence or absence of water.[4] Similar results were reported by Back et al. on oxidation of azasteroidal selenides.[6] In this case one of the two diastereomeric selenoxides could be separated, optically pure, from an aqueous medium. Its configurational stability was attributed to intramolecular hydrogen bonding.

To date there are no examples of simple chiral selenoxides and the reasons for their instability remain unclear. We now report the first synthesis of simple, optically active selenoxides and demonstrate that their configurational instability is the result of hydrate formation.

The reaction of sulfonamides with selenoxides to afford selenium imides has previously been described by Tamagaki, Oae and Sakaki.[7] If this reaction were carried out using an optically active sulfonamide ($R^*SO_2NH_2$), under conditions of kinetic resolution, i.e. a 2:1 ratio of racemic selenoxide, 1-2, to 3, an optically active selenoxide will result (Scheme). This is provided that the two enantiomeric selenoxides react at different rates and do not racemize under the reaction conditions.

SCHEME



$$\mathrm{Ar\text{-}\underset{+}{\overset{O^-}{Se}}\text{-}Me} \quad + \quad \mathrm{R^*SO_2NH_2} \xrightarrow[\text{Benzene}]{} \mathrm{Ar\text{-}\overset{Me}{Se}{=}NSO_2R^*} \quad + \quad \mathrm{H_2O}$$

R* = (+) or (-)-10-camphor

In a 25 mL flask equipped with a Dean Stark column and argon atmosphere was placed a 2:1 mixture of the appropriate selenoxide, 1[8] or 2[9], sulfonamide, 3[1] (typically 0.32 mmoles of 3) and 0.1-0.2 g of 4A' molecular sieves in 20 mL of dry benzene. After refluxing for 2-4 h the solution was transferred, in a glove bag (argon atmosphere), to a sublimation receiver. The solvent was removed under vacuum and the selenoxide separated from the selenium imides, 4-5,[11] by sublimation at 60-80 °C/0.01 mm. Optically active selenoxides were isolated in 45-56% yields with enantiomeric excesses 5-11% percent. These results are summarized in the Table.

The enantiomeric excesses (%e.e.) and absolute configurations of selenoxides 1-2 were determined using Eu(hfc)$_3$ and Pirkle's solvent, (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[12] As evident from the results summarized in the Table the chiral sulfonamide, 3, controls the configuration of the selenoxide. Thus (+)-3 and (-)-3 afforded selenoxides 1-2 of opposite configuration (Table).

With methyl phenyl selenoxide (1), sulfonamides (+)-3 and (-)-3 react faster with the (R) and (S) selenoxide enantiomers, respectively, resulting in selenoxides having the (S) and (R) configurations, respectively.[13] The reverse is true for selenoxide 2 where (+)-3 and (-)-3 react faster with the (S) and (R) selenoxide enantiomers, respectively (Table). Dreiding and space filling CPK models suggest that in the latter case steric factors govern the chiral recognition.

We demonstrated recently that polar effects are important in the oxidative kinetic resolution of sulfoxides using chiral 2-sulfonyloxaziridines.[14] The chiral recognition in these cases was determined by a dipole-dipole interaction of the sulfinyl group with the camphor carbonyl group. The source of chiral recognition for the kinetic resolution of methyl phenyl selenoxide (1) by camphorsulfonamide 3 is suggested to involve similar polar interactions. For methyl 2,4,6-triisopropylphenyl selenoxide (2) such a dipole-dipole interaction would be sterically unfavorable as a consequence of the isopropyl groups adjacent to the selenoxide moiety.

The effect of temperature, water and acid on the configurational stability of chiral selenoxides, 1-2, was investigated by monitoring the loss of optical activity (racemization) by polarimetry. Thermally, chiral selenoxides 1-2 were stable to prolonged (1-2 days) heating (60 °C) in chloroform or benzene when care was exercised to exclude moisture.

Table: Properties of Chiral Selenoxides

| Selenoxide (%Yield)[a] | | $R^*SO_2NH_2$ | $[\alpha]_D$[b] | %E.e. | Configuration | $t_{1/2}$ racem.[c] (hours) |
|---|---|---|---|---|---|---|
| 1 | (48) | (+)3 | -2.5 | 10.0 | (S)[d] | <0.002 |
| 1 | (40) | (-)3 | +2.0 | 8.8 | (R)[d] | <0.002 |
| 2 | (50) | (+)3 | -4.0 | 8.6 | (R) | 30.0 |
| 2 | (51) | (-)3 | +2.0 | 5.6 | (S) | 30.0<br><0.002[e] |

a) Isolated yields.
b) Average of several determinations; (c 0.5-2.8, $CHCl_3$).
c) One to five equivalents of water added.
d) See reference 16.
e) p-Toluenesulfonic acid monohydrate added.

Addition of approximately one equivalent of water to (+) or (-)-methyl phenyl selenoxide (1) in chloroform resulted in complete racemization in less than 10 seconds ($t_{1/2}$ <0.002 h). This selenoxide was so sensitive to moisture that it was necessary to carry out all transfers in a dry argon environment. By contrast, (+) or (-)-methyl-2,4,6-triisopropylphenyl selenoxide (2) was stable in the presence of 5-6 equivalents of water for more than 3 days ($t_{1/2}$=30 h). Indeed, optically active 2 could be handled under ordinary atmospheric conditions without loss of optical activity. Addition of a trace of p-toluenesulfonic acid monohydrate to (+)(S)-2, however, resulted in complete racemization in less than 10 seconds ($t_{1/2}$ <0.002 h).

These results are consistent with previous suggestions[2,3] that the configurational lability of selenoxides is due to the facile formation of achiral hydrates ($RSe(OH)_2R'$) which are acid catalyzed.[15] The much greater optical stability of methyl 2,4,6-triisopropylphenyl selenoxide (2) compared to methyl phenylselenoxide (1) is undoubtedly due to steric inhibition of formation of the tetra-coordinate hydrate in the former.

In summary, kinetic resolution of selenoxides using optically active sulfonamides is a new and useful method for preparing chiral selenoxides for study. The configurational lability of optically active selenoxides is the result of acid catalyzed hydrate formation.

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