# Kinetic and Thermodynamic Control in the Cyclization *via* Thiiranium Ions. Stereoselective Synthesis of a 2,3,5-Trisubstituted Tetrahydropyran Ring.



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The stereoselective rearrangement of tetrahydrofuran or tetrahydropyran rings having a phenylsulfanyl group in an *exo* position, *via* the intermediate thiiranium ions, is reported. The 5- or 6-*exo*-tet cyclization of hydroxy sulfides gave the kinetic products while the 6-*endo*-tet or 5-*endo*-tet gave the thermodynamic products. The rearrangement of the 5-*exo* product to the 6-*endo*- one is an interesting way for the stereoselective synthesis of substituted tetrahydropyrans.

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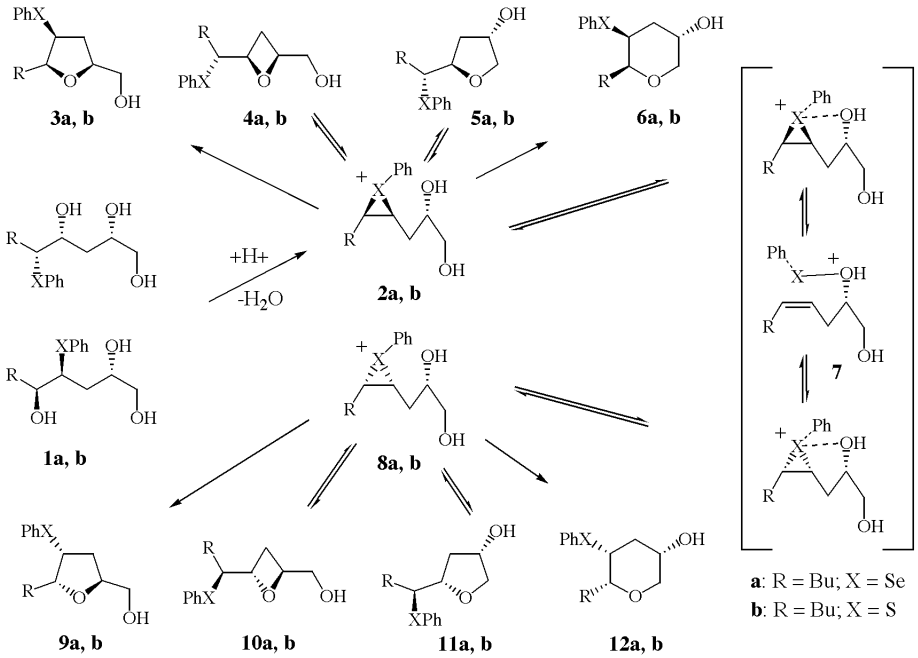
In planning an approach for the stereoselective synthesis of oxygenated heterocyclic rings such as tetrahydrofurans and tetrahydropyrans we started a study of the behavior in acid media of a mixture of hydroxy selenides and hydroxy sulfides [1]. This acid treatment furnishes a seleniranium or thiiranium ion that, by intramolecular hydroxyl capture, leads to the heterocyclic rings.

Scheme 1

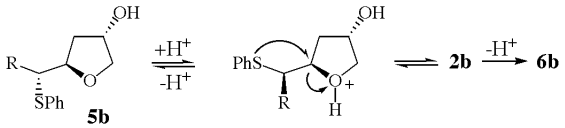



Treatment of the mixture of hydroxy selenides **1a** with a catalytic amount of perchloric acid causes a stereoconvergent elimination of water to give an intermediate seleniranium ion **2a**. Since seleniranium ion **2a** is in equilibrium with the ion **8a**, the heterocyclic rings **3a-6a** and **9a-12a** can be obtained. Acid treatment of **1a** gave first a mixture of **5a** and **11a**, then they disappeared to give a *ca*. 70/30 mixture of **6a** and **12a** [1f]. In a previous paper we have also reported the stereoselective synthesis of the 2,4-disubstituted tetrahydrofuran **5b** by acid-catalyzed cyclization of the hydroxy sulfides **1b** [1d]. No rearrangement to **6b** or to the diasteromeric structures **11b** and **12b** was observed at that acid concentration.

Here we provide new insight on the regiochemistry of the cyclization of thiiranium ions **2b** and **13**. Our results together with the extensive studies performed by Warren's group [2] give a wider view of the behaviour of hydroxy sulfides in acid media. Four modes of cyclization of the thiiranium ion **2b** are possible: i) cyclization in the 5-*endo* [3] mode to give **3b**; ii) cyclization in the 4-*exo* mode to give **4b**; iii) cyclization in the

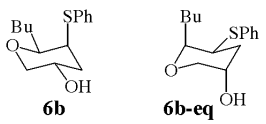
5-*exo* mode to give **5b**; iv) cyclization in the 6-*endo* [4] mode to give **6b**. Treatment of **5b** with a more concentrated perchloric acid dichloromethane solution than **1a** gave a very clean rearrangement to **6b**. The reaction was quenched after 30 minutes giving starting tetrahydrofuran **5b** (8%) and compound **6b** (92%). The rearrangement was then highly stereoselective. The rearrangement of compound **5b** to compound **6b** can be ascribed to the exocyclic position of the phenylsulfanyl group. The higher acid concentration required for the rearrangement of **5b** as compared with **5a** may be easily related to the reduced nucleophilicity of the S atom with respect to the Se atom [5].

Scheme 2




The oxetane **4b**, that was never observed, could be, if formed in the first step of the reaction, involved in a fast equilibrium, due to the exocyclic position of the PhS group, with the intermediate thiiranium ion **2b** which then cyclized following routes i, iii or iv. The observation that similar oxetane rings were readily converted into tetrahydrofuran rings was already made by Warren during the investigation of the behavior of similar hydroxy sulfides in acid media [2d]. In that case the pure 4-*exo* cyclization was responsible for 20% of the kinetic product when compared with the 5-*endo* cyclization. However, in our case the presence of an additional OH group provided different modes of cyclization. MM2 calculations performed on compounds **3b-6b**, showed **6b** as the most stable with differences of about 1.7 kcal/mol in comparison with **3c**, 2.8 kcal/mol in comparison with **5b** and more than 10 kcal/mol in comparison with **4b**. Being that compound **3b** is comparable in energy with **6b**, its lack in observation could be ascribed to a higher activation energy for the cyclization of **2b** to **3b**. The lack in observation of the oxetane ring could be attributed to both kinetic, being that the *4-exo* closure is unfavorable in comparison with *5-endo* [2d], and thermodynamic reasons because the product is less stable. The tetrahydrofuran **5b** was then the kinetic product whereas the tetrahydropyran **6b** was the thermodynamic one. Indeed, compound **6b** shows the lowest energy. Moreover the formation of **6b** is not reversible because of the *endo* position of the PhS group. The NMR spectrum of compound **6b** shows that the PhS group is in an axial position, while the reactive conformer should be **6b-eq**, being the rearrangement ineffectual to a $S_N2$ reaction.

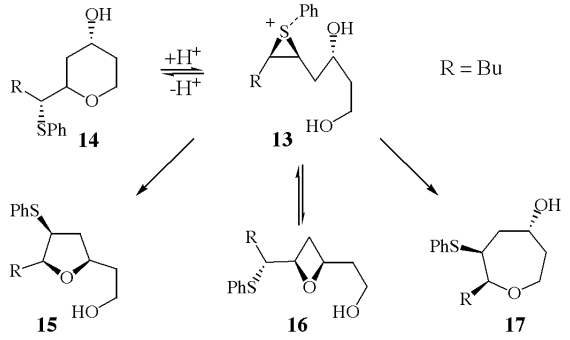
Scheme 3




The intramolecular hydrogen bond in **6b-eq** is not sufficient to compensate for the strain introduced by the presence of the butyl group lying in an axial position. MM2 calculations confirmed this idea suggesting a difference of about 1.5 kcal/mol.

Also the exocyclic position of the PhS group in compound **14**, prepared as described by us [1e], could allow this rearrangement, but differently from the corresponding selenium derivative, no equilibration occurred with a catalitic amount of perchloric acid. However, with a more concentrated acid solution compound **14** rearranged *via* **13**. Four different ring closure could be obtained from **13**: i) cyclization in the 5-*endo* mode to give **15**; ii) cyclization in the 4-*exo* mode to give **16**; iii) cyclization in the 6-*exo* mode to give **14**; iv) cyclization in the 7-*endo* mode to give **17**.

Scheme 4




The reaction was quenched after 5 days to give starting material (67%) and tetrahydrofuran **15** (23%). Compounds **16** or **17** were not found. The reaction, followed by GC-MS, showed only the slow formation of compound **15** and unidentified products. This result confirmed what we have seen for the cyclization of **1b**: the 5-*endo-tet* cyclization is disfavoured, however, being the 7-*endo* cyclization strongly disfavoured, and the 5-*endo-tet* cyclization takes place as thermodynamic product, but with low yield. MM2 calculations performed on compounds **14-17**, showed that the tetrahydropyran **14** and the tetrahydrofuran **15** are the most stable with similar energy (difference *ca.* 0.5 kcal/mol) then the oxepane **17** and the oxetane **16** are less stable with differences of about 11 and 12 kcal/mol. Even if MM2 calculations suggest very similar energies for compounds **14** and **15**, the latter was the thermodynamic product because of the *endo* position of the PhS group. MM2 calculations indicates a dihedral angle (S-C3-C2-O) of about 147°, far from the required 180°. Again the lack in observation of the oxetane ring can be then attributed to both kinetic and thermodynamic reasons. As a first comparison between hydroxy selenides **1a** and hydroxy sulfides **1b** we can say that the former are more reactive than the latter. Indeed, compound

**1a** reacted in 1 minute [1f] whereas compound **1b** gave, after 15 minutes, compound **5b** (68%) and starting material (14%) [1d]. Then if we consider that the $PhS^+$ group is a better leaving group than the $PhSe^+$, we can argue that the rate determining step is the formation of the ions **2a,b**. The stereospecific rearrangements **5b** **6b** and **14** **15** showed the non-occurence of intermediate species, as **7**, for the sulfur compounds.

In conclusion, as for the cyclization of hydroxy selenides **1a**, the cyclization of hydroxy sulfides **1b** can be regarded as an interesting way for the stereoselective synthesis of tetrahydrofurans and tetrahydropyrans and, as for **1a**, they are governed by both kinetic and thermodynamic factors: a) the order of cyclization of **2b** is 5-*exo-tet* < 6-*endo-tet* < 5-*endo-tet* <4-*exo-tet*; b) the order of cyclization of **13** is 6-*exo-tet* < 5-*endo-tet* << 7-*endo* and 4-*exo-tet*; c) the oxetanes **4** and **16** derived from the 4-*exo* cyclizations were never observed probably for both kinetic and thermodynamic reasons; d) compounds coming from the pure 5-*exo*- or *6-exo-tet* cyclizations are the kinetic products; e) compounds derived from the 6-*endo-tet* or 5-*endo-tet* cyclizations, disfavoured by Baldwin's rules [6], are the thermodynamic products of the acid catalyzed cyclization. Further investigations are under progress in order to broaden the use of this chemistry for the stereoselective synthesis of substituted tetrahydropyrans.

## EXPERIMENTAL

Dichloromethane was distilled under nitrogen from calcium hydride and used immediately. $^1$H nmr and $^{13}$C nmr spectra were recorded on a Bruker AC-E series 250 MHz spectrometer. Flash chromatography was carried out using Macherey-Nagel silica gel (0.04 - 0.063 mm). Light petroleum refers to the fraction boiling in the range 40-60 °C. Melting point was determined with a Kofler hot stage and is uncorrected. MM2 calculations were performed with the program available from the CS Chem3D Pro™ package version 5.0 distribuited by Cambridge Soft Corporation.

(±)(2*SR*,3*SR*,5*SR*)-2-Butyl-3-phenylsulfanyl-tetrahydropyran-5-ol (**6b**).

A solution of **5b** (180 mg, 0.67 mmol) in dichloromethane (20 mL) containing 15 µL of perchloric acid (70%) was vigorously stirred for 30 minutes at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with water. The organic phase was washed with brine, dried ($Na_2SO_4$) and the solvent evaporated *in vacuo*. Purification of the crude product by flash chromatography (light petroleum-ethyl acetate 7/1) gave the tetrahydropyran 166 mg of **6b** (92%) as white crystals, mp 74-5 °C, and 14 mg of starting material (8%); ir (nujol) 3350 cm$^{-1}$; $^1$H nmr ($CDCl_3$): δ 0.89 (t, 3H, J = 6.8 Hz), 1.22-1.43 (m, 4H), 1.58-1.83 (m, 3H), 2.28-2.42 (m, 1H, overlaped with 1H, OH), 3.19 (dd, 1H, J = 10.6 and 9.6 Hz), 3.46-3.60 (m, 2H), 4.03 (ddd, 1H, J = 10.6, 4.6 and 1.4 Hz), 4.13-4.25 (m, 1H), 7.18-7.33 (m, 3H), 7.40-7.44 (m, 2H); $^{13}$C nmr ($CDCl_3$): δ 13.9, 22.5, 27.9, 31.9, 38.1, 49.0, 63.0, 72.4, 79.5, 126.7, 129.0, 131.4, 135.5.

*Anal*. Calcd. for $C_{15}H_{22}O_2S$: C, 67.63; H, 8.32. Found: C, 67.50; H, 8.30.

(±)(2*SR*,3*SR*,5*RS*)-2-Butyl-5-hydroxyethyl-3-phenylsulfanyl-tetrahydrofuran (**15**).

A solution of **14** (180 mg, 0.64 mmol) in dichloromethane (20 mL) containing 25 µL of perchloric acid (70%) was vigorously stirred for 5 days at room temperature. The reaction mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with water. The organic phase was washed with brine, dried ($Na_2SO_4$) and the solvent evaporated *in vacuo*. Purification of the crude product by flash chromatography (light petroleum-ethyl acetate 5/1) gave 42 mg of the tetrahydropyran **15** (23%) as oil and 120 mg of starting material (67%); ir (liquid film) 3400 cm$^{-1}$; $^1$H nmr ($CDCl_3$): δ 0.89 (t, 3H, J = 6.9 Hz), 1.20-1.95 (m, 9H), 2.45-2.57 (m, 1H), 2.71 (br s, 1H), 3.77-3.88 (m, 3H), 3.98-4.13 (m, 2H), 7.17-7.39 (m, 5H); $^1$H nmr (DMSO-$d_6$): δ 0.90 (t, 3H, J = 7.0 Hz), 1.20-1.74 (m, 9H), 2.42-2.54 (m, 1H), 3.37-3.45 (m, 2H), 3.80-3.97 (m, 3H), 4.35 (t, 1H, J = 5.1 Hz, OH), 7.12-7.33 (m, 5H); $^{13}$C nmr ($CDCl_3$): δ 13.9, 22.6, 28.7, 31.5, 37.9, 39.8, 49.1, 61.2, 77.7, 81.8, 126.2, 128.9, 130.1, 136.1.

*Anal*. Calcd. for $C_{16}H_{24}O_2S$: C, 68.53; H, 8.63. Found: C, 68.50; H, 8.60.

Acknowledgements.

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## REFERENCES AND NOTES

[1a] L. Arista, M. Gruttadauria and E. J. Thomas, *Synlett*, 627 (1977); [b] M. Gruttadauria, R. Noto and S. Riela, *J. Heterocyclic Chem.*, **35**, 865 (1988); [c] L. Arista, M. Gruttadauria and R. Noto, *Heterocycles*, **48**, 1325 (1998); [d] M. Gruttadauria, P. Lo Meo and R. Noto, *Tetrahedron*, **55**, 4769 (1999); [e] M. Gruttadauria, P. Lo Meo and R. Noto, *Tetrahedron*, **55**, 14097 (1999); [f] M. Gruttadauria and R. Noto, *Tetrahedron Lett.*, **40**, 8477 (1999).

[2a] D. House, F. Kerr and S. Warren, *J. Chem. Soc., Chem. Commun.*, 1779 (2000); [b] V. K. Aggarwal, J. Eames, M-J. Villa, S. McIntyre, F. H. Sansbury and S. Warren, *J. Chem. Soc., Perkin Trans.1*, 533 (2000); [c] J. Eames, M. A. de las Heras, R. V. H. Jones and S. Warren, *Tetrahedron Lett.*, **37**, 4581 (1996); [d] J. Eames and S. Warren, *Tetrahedron Lett.*, **37**, 3525 (1996); [e] P. Bird, J. Eames, A. G. Fallis, R. V. H. Jones, M. Roddis, C. F. Sturino, S. O'Sullivan, S. Warren, M. S. Westwell and J. Worrall, *Tetrahedron Lett.*, **36**, 1909 (1995); [f] L. Djakovitch, J. Eames, R. V. H. Jones, S. McIntyre and S. Warren, *Tetrahedron Lett.*, **36**, 1723 (1995); [g] F. H. Sansbury and S. Warren, *Tetrahedron Lett.*, **33**, 539 (1992); [h] S. McIntyre, F. H. Sansbury and S. Warren, *Tetrahedron Lett.*, **32**, 5409 (1991); [i] F. H. Sansbury and S. Warren, *Tetrahedron Lett.*, **32**, 3425 (1991); [j] S. McIntyre and S. Warren, *Tetrahedron Lett.*, **31**, 3457 (1990).

[3] Following the Warren's nomenclature [2j] this should be a 6-*endo*/5-*exo* cyclization.

[4] Following the Warren's nomenclature [2h] this should be a 7-*endo*/6-*exo* cyclization.

[5a] T. H. Lowry and K. S. Richardson, Mechanism and Theory in Organic Chemistry, Harper & Row, New York; Third Ed., 1987, p 370; [b] R. G. Pearson, H. Sobel and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968).

[6] J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976). It should be noted that these empirical rules can be well adapted to anion-driven nucleophilic cyclization reactions while different behavior are often observed in the cationic cyclizations [1,2].