Orientational Effect of the Phenylsulfonyl Group in the Thermal Spiroketalization of Dihydroxyketone Equivalents

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The thermal cyclization of a dihydroxyketone equivalent **4b** leads to the predominant formation of crystalline 4-(benzenesulfonyl)-1,6-dioxaspiro[4.5]decane (**8**). Under similar reaction conditions the tetrahydrofuranylidene derivative **6** is obtained from ketone **4c**. It does appear that the phenylsulfonyl group is a factor which influences the course of the reaction leading to the preferential formation of one of the possible stereoisomers.

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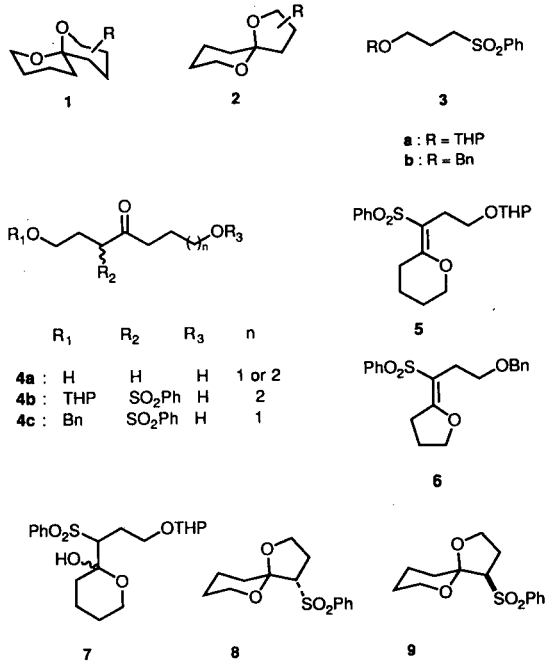
Introduction.

The study of natural and synthetic spiroketals has experienced notable advances in recent years [1,2]. As part of a program related with biologically active spirosolanes we focused our interest on spiroketals some time ago [3]. Among the methods that have been used for the synthesis of spiroketals the thermodynamically controlled acid-catalyzed cyclation of dihydroxyketones of type **4a** is well known. Thereby the formation of spiro[5.5]ketals such as **1** seems generally to proceed with maximization of the anomeric effect *i.e.* bisaxial arrangement of the C–O bonds and minimization of steric effects in the absence of other related factors [1,4]. On the contrary, information about factors related to the formation of spiro[4.5]ketals such as **2** is scarce, particularly for ring systems of simpler substitution pattern. Therefore, we decided to investigate the role of the phenylsulfonyl group in the formation of spiroketal **8** from dihydroxyketone equivalent **4b**.

Results and Discussion.

Spiroketal precursors **4b** and **4c** were prepared as described [5,6] by addition of dilithiated sulfones **3a** and **3b** to δ-valerolactone and γ-butyrolactone at −60°, respectively. Compounds **4b** and **4c** show an intense C=O infrared absorption band at 1720 cm^{-1}, thus indicating that the equilibrium between **4b** and **7** is shifted towards the former. Refluxing of **4b** in toluene for 3 hours using a water separator afforded after purification a crystalline solid for which ^1H nmr, 2D ^1H-^1H and 2D ^{13}C-^1H correlation techniques are in agreement with structure **8**. This reaction was monitored by ir spectroscopy and the following changes were observed. Firstly, the carbonyl band at 1720 cm^{-1} slowly disappeared and was replaced by a band at 1632 cm^{-1} which is assigned to vinylic ether **5**. This band eventually disappeared as **5** was converted to **8**.



Further evidence for the intermediacy of vinyl ethers during this spirocyclization reaction was obtained by the isolation of derivative **6** upon refluxing **4c** in toluene for 3 hours. The ir spectrum of **6** which was characterized by combustion analysis and ms spectroscopy, shows an absorption band at 1638 cm^{-1}. The 300 MHz ^1H nmr spectrum of exocyclic vinyl ether **6** shows, in addition to the aromatic and benzylic resonances, four well resolved triplets in the range from 4.2-2.5 ppm for the methylenic protons, thus indicating a planar ring geometry that may be favored by electron delocalization. Also, the allylic methylene protons of the tetrahydrofuran ring appear at 3.17 ppm because of the proximal relationship of the anisotrop-

ic sulfonyl group, thereby establishing an *E*-geometry for the thermodynamically more stable stereoisomer **6** [7]. Moreover, the structure of **6** was finally secured by two dimensional nmr correlation analysis.

The experimental data for the thermal cyclization of **4b** is consistent with a multistep mechanism proceeding through the intermediacy of the nonobservable hemiketal **7**, tetrahydropyran-2-ylidene derivative **5** which undergoes spirocyclization to give **8**. One important result of this work is the stereochemical outcome of the whole process which seems to be influenced by the stereoelectronic interaction between the phenylsulfonyl group and the oxygen atom located at the tetrahydropyranyl ring. We propose that the formation of *E*-exocyclic vinyl ether **6** and antispiroketal **8** from their corresponding ketone precursors isolated in yields of 91% and 70%, respectively, is attributed to this interaction. These results are analogous to those observed for the homologous spiro[5.5]ketals where a compromise between anomeric and steric effects has been proposed, although the C–O bond of the tetrahydropyran ring has only an approximate axial orientation to the five-membered ring [1]. The results presented above indicate that the phenylsulfonyl group can be used as a synthetic tool to control the stereochemical outcome of spiroketal formation from dihydroxyketone equivalents. Moreover, the possibility of removing this group under relatively mild conditions may be employed for the stereoselective synthesis of higher substituted spiro[4.5]ketals and other related natural products. Thus, so far, the phenylsulfonyl group has been used in connection with spiroketal synthesis from dihydroxyketone equivalents only as a carbanion stabilizing tool in order to connect fragments in the route to appropriate precursors [8,9]. Furthermore, the efficient and convenient method for the stereoselective preparation of functionalized exocyclic vinyl ethers has potential for the elaboration of natural products containing five member rings. Both aspects are currently under progress and will be reported on due course.

EXPERIMENTAL

Melting points were determined on an Electrothermal apparatus and are given uncorrected. Chemicals and solvents were used as received; THF was distilled from sodium metal in the presence of benzophenone under dry argon. Infrared spectra were determined on a Perkin-Elmer 1320 spectrophotometer. Routine proton magnetic resonance spectra were recorded on a Hitachi Perkin-Elmer R-24A 60 MHz spectrometer. Two dimensional nmr correlation spectra were recorded on a General Electric QE 300 MHz spectrometer in deuteriochloroform solutions. Combustion analysis and mass spectra were performed by Oneida Research Services, Whitesboro, NY 13492. Thin-layer chromatography was carried out utilizing silica gel, standard grade, Aldrich catalog No. 28,854-3 and E. Merck silica gel 60 F (230-400 mesh) was used for flash chromatography.

E-1-(Benzenesulfonyl)-3-benzyloxy-1-(tetrahydrofuran-2-ylidene)-propane (**6**).

3-(Benzenesulfonyl)-1-benzyloxy-7-hydroxy-4-heptanone (**4c**, 2.07 g, 5.50 mmoles), in toluene (100 ml) was refluxed for three hours using a water separator. After removal of the solvent under reduced pressure the oily residue was purified by flash column chromatography on silica gel eluting with acetone/pentane 1:4 to afford a liquid that solidified upon standing at 4°. Recrystallization from 2-propanol gave **6** (1.79 g, 91%). Compound **6** had mp 74-74.5°; ir (carbon tetrachloride): 3070, 3035, 2900, 2880, 1638, 1448, 1320, 1308, 1180, 1155, 1128, 1080 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform): δ 7.81 (m, 2H, ArH), 7.43 (m, 3H, ArH), 7.28 (m, 5H, ArH), 4.44 (s, 2H, OCH_2Ar), 4.17 (t, J = 6.98 Hz, 2H, OCH_2 oxolane), 3.51 (t, J = 7.7 Hz, 2H, CH_2OBn), 3.17 (t, J = 7.7 Hz, 2H, allylic oxolane CH_2), 2.63 (t, J = 7.7 Hz, 2H, allylic CH_2), 2.05 (m, 2H, $CH_2CH_2CH_2$); ^{13}C nmr (deuteriochloroform): δ 138.4, 128.0, 127.3, 127.2 (ArC), 142.5, 138.5, 132.7, 126.6 (SO_2ArC), 170.2 (=CO), 107.3 ($=CSO_2$), 72.4 (benzylic C), 71.8 (OCH_2 oxolane), 68.3 (CH_2OBn), 30.1 (allylic oxolane CH_2), 27.4 (allylic CH_2), 24.1 ($CH_2CH_2CH_2$); ms: m/z (ion, relative intensity) 359 ($M^+ + 1$, 21), 267 (12), 217 (100).

Anal. Calcd. for $C_{20}H_{22}O_4S$: C, 67.0; H, 6.1; S, 8.9. Found: C, 67.1; H, 6.2; S, 8.5.

4-(Benzenesulfonyl)-1,6-dioxaspiro[4.5]decane (**8**).

3-(Benzenesulfonyl)-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8-hydroxy-4-octanone (**4b**, 4.00 g, 10.41 mmoles), in tetrahydrofuran (150 ml) was refluxed for three hours using a water separator. The solvent was removed by evaporation *in vacuo* and the liquid residue upon treatment with pentane/diethyl ether 2:1 resulted in spontaneous crystallization. Recrystallization from pentane/diethyl ether gave colorless needles of **8** (2.06 g, 70%), mp 131-132.5°; ir (carbon tetrachloride): 3075, 2965, 2880, 1448, 1327, 1310, 1150, 1075, 1028, 899 cm^{-1}; ^1H nmr (300 MHz, deuteriochloroform) δ 7.86 (m, 2H, ArH), 7.52 (m, 3H, ArH), 4.06-3.96 (ddd, J = 12.4, 8.3, 4.0 Hz, 1H, OCH oxolane), 3.82-3.71 (m, 2H, OCH oxolane, OCH oxane), 3.63 (dd, J = 8.8, 5.7 Hz, 1H, $CHSO_2$), 3.59-3.50 (m, 1H, CH oxane), 2.27-2.05 (m, 4H, methylenic CH_2 at C3 and C10), 1.90-1.41 (m, 4H, all others); ^{13}C nmr (deuteriochloroform) δ 139.5, 133.6, 129.1, 128.2 (ArC), 105.9 (OCO), 71.1 (CSO_2), 64.4 (CO oxolane), 61.7 (CO oxane), 30.7 (C10), 27.9 (C3), 24.9 (C8), 19.4 (C9); ms: m/z (ion, relative intensity) 283 ($M^+ + 1$, 74), 141 (100).

Anal. Calcd. for $C_{14}H_{18}O_4S$: C, 59.5; H, 6.4; S, 11.3. Found: C, 59.6; H, 6.4; S, 10.8.

3-(Benzenesulfonyl)-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8-hydroxy-4-octanone (**4b**) and 3-(benzenesulfonyl)-1-benzyloxy-7-hydroxy-4-heptanone (**4c**) were prepared according to the procedure of Savoia and Umani-Ronchi [5] and were used after flash column chromatography without further purification in the thermal cyclization reactions.

Compound **4b**.

This compound had ir (carbon tetrachloride): 3640-3300, 3070, 2945, 2867, 1720, 1449, 1325, 1310, 1150, 1080, 1035 cm^{-1}; ^1H nmr (60 MHz, carbon tetrachloride/TMS): δ 7.55 (m, 5H, ArH), 4.35 (m, 2H, OCHO, $CHSO_2Ph$), 3.61 (m, 6H, CH_2O oxane, CH_2OH, CH_2O), 2.62 (m, 3H, $CH_2C=O$, OH), 2.15 (m, 2H, CH_2CSO_2), 1.58 (m, 10H, all others).

Compound **4c**.

This compound had ir (carbon tetrachloride): 3640-3360, 3090-3000, 2940, 2870, 1720, 1450, 1365, 1325, 1312, 1218, 1149, 1085 cm^{-1}; ^1H nmr (60 MHz, carbon tetrachloride/TMS): δ 7.79-7.10 (m, 10H, ArH), 4.32 (m, 3H, $CHSO_2$, CH_2Ar), 3.57-3.26 (m, 4H, CH_2OBn, CH_2OH), 2.68 (m, 3H, $CH_2C=O$, OH), 2.15 (m, 2H, CH_2CSO_2), 1.75 (m, 2H, $CH_2CH_2CH_2$).

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