Regio- and Stereoselective Formation of Tri- and Tetrasubstituted Tetrahydrofuranylidenes from Hydroxy Ketosulfones [1]

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Four tri- and tetrasubstituted *E*-1-(benzenesulfonyl)-1-tetrahydrofuranylidenes **7-10** were synthesized from their corresponding α'-benzenesulfonyl-γ-hydroxyketones **1** in good yields. The examination of the regio- and steroselectivity of these thermally induced reactions shows preference for both, the exocyclic nature of the double bond and the *E*-geometry in all tetrahydrofuranylidenes described. Structural assignments are based on infrared, ^{1}H nmr, ^{13}C nmr, 2D ^{1}H-^{1}H and ^{13}C-^{1}H correlation spectra. In contrast to tetrahydrofuranylidenes **7-10**, hemiketal **6** shows no tendency towards dehydration under the thermal reaction conditions used. This paper discusses the extent and limitations of this method as a tool of synthetic utility for the regio- and stereoselective preparation of the target compounds.

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Introduction.

Tetrahydrofuranylidene and substituted derivatives of it are synthetic intermediates of considerable interest in the route to potential antimetabolites of natural carbohydrates [2], potential antiulcer agents [3], prostacyclin (PGI_2) models [4], substituted furans [5], spiroketals [6,7] and to a variety of other cyclic and acyclic compounds [8,9]. Several methods have been developed for the stereocontrolled synthesis of various substituted tetrahydrofuranylidenes, which include reduction-isomerization of their endocyclic isomers with Pd-C/hydrogen at subambient temperatures [3], alkylidenation of ester carbonyl groups with $RCHBr_2/Zn/TiCl_4$ in the presence of *N,N,N',N'*-tetramethylethylendiamine [10], mercury(II)-induced cyclization of acetylenic alcohols [4] or reactions with the Schrock-type metal carbene complexes [11] and the Tebbe complex [12]. However, the general use of many of these reactions is limited because special techniques are required or the degree of stereocontrol observed appears to be very variable.

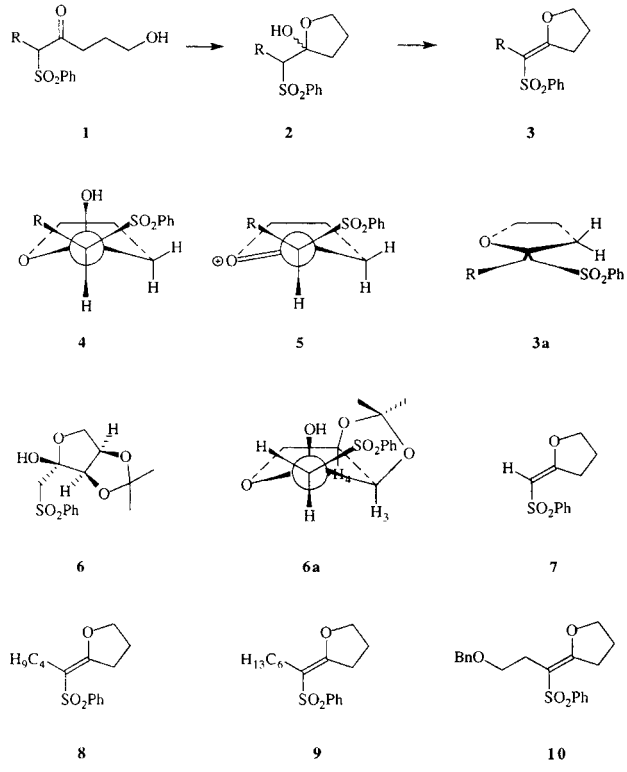
In this paper we report a direct and convenient regio- and stereoselective approach to tri- and tetrasubstituted tetrahydrofuranylidenes of type **3**.

Results and Discussion.

The thermal cyclization of 3-(benzenesulfonyl)-1-[(tetrahydro-2*H*-pyran-2-yl)oxy]-8-hydroxy-4-octanone is a very useful method for the preparation of 4-(benzenesulfonyl)-1,6-dioxaspiro[4,5]decane *via* a multistep mechanism proceeding through the intermediacy of a nonisolable hemiketal and a tetrahydropyran-2-ylidene derivative. The observed stereoselective course of this reaction was attributed to stereoelectronic interaction between the vinylic benzenesulfonyl group and the oxygen atom at the tetrahydropyranyl ring [6].

As a logical extension of previous work from our laboratory on cyclization reactions of benzenesulfonyl substituted dihydroxyketones, we initiated a similar investigation on the corresponding monohydroxyketones of type **1** in order to estimate the extent of the above indicated stereoelectronic interaction as a tool of synthetic utility for the regio- and stereoselective preparation of tri- and tetrasubstituted tetrahydrofuranylidenes **7-10**.

Hydroxyketone derivatives **1** (R = H, *n*-butyl, *n*-hexyl, $BnOC_2H_4$) were prepared by addition of γ-butyrolactone to the corresponding dilithiated sulfones in THF at −60° [6]. In contrast to these results by which the desired



hydroxyketones were readily formed, the success of the addition of 2,3-*O*-isopropylidene-D-erythronolactone [13] to dilithiomethylphenyl sulfone under the same reaction conditions proved to be a less practical route to the target hydroxyketone derivative. Thus, this addition leads almost quantitatively to hemiketal **6**, instead [14]. Presumably, the inflexible geometry of D-erythronolactone induced by its 2,3-*O*-isopropylidene functionality shifts the equilibrium between **1** and **2** toward the hemiketal. The structure of crystalline **6** obtained after column chromatography and recrystallization from isopropyl alcohol was assigned primarily on the basis of its strong infrared absorption band at 3472 cm^{-1} and the ^1H nmr, ^{13}C nmr, 2D ^1H-^1H and ^{13}C-^1H correlation spectra.

All thermal cyclization-dehydration reactions were performed by refluxing hydroxyketones **1** at 130° in toluene using a water separator and monitored at the infrared absorption bands of the newly formed C=C bonds in the corresponding tetrahydrofuranylidenes **7-10**, between 1636 and 1639 cm^{-1} (Table I). The formation of tetrahydrofuranylidenes from hydroxyketone equivalents under these conditions is operationally straightforward. In this fashion, colorless needles of *E*-2-(benzenesulfonylmethylidene)tetrahydrofuran **7** were obtained in 62% yield after column chromatography on silica gel (acetone/pentane mixtures), and recrystallization from isopropyl alcohol. The structural assignment for **7** is based upon its spectral data. The ir spectrum of tetrahydrofuranylidene **7** showed characteristic absorptions at 1636 cm^{-1}, and in the 1300 cm^{-1} range for the C=C bond and the sulfonyl group,

Table I

Preparation of *E*-Tetrahydrofuranylidenes **7-10**

Compound	**7**	**8**	**9**	**10**
Reaction Time	40 min	2.5 hr	2.0 hr	3.0 hr
Temperature [°C]	130	130	130	130
Yield [%] [a]	62	86	60	91
mp [°C] [b]	98.5-100	–	–	74-74.5
IR ν [cm^{-1}]	1636	1639	1639	1638
δ allylic H oxolane [ppm]	3.12	3.17	3.16	3.17
δ allylic C oxolane [ppm]	29.3	30.1	30.1	30.1

[a] Isolated yield. [b] Uncorrected melting points.

respectively. The postulated *E*-geometry of **7** is supported by its 300 MHz ^1H nmr spectrum that showed besides the aromatic proton signals at 7.79 and 7.42 ppm, three well resolved multiplets at 2.10 ppm (central oxolane methylene group), 3.12 ppm (allylic oxolane CH_2) and 4.23 ppm (oxolane OCH_2) and a broad singlet at 5.75 ppm arising from the vinylic proton. The ^1H nmr signal at 3.12 ppm exhibits the expected deshielding for allylic oxolane methylenic protons caused by the proximal relationship of the anisotropic sulfonyl group, **3a**, consistent with an *E*-geometry for the thermodynamically more stable stereoisomer **7** [9].

The tetrasubstituted members of this series of *E*-tetrahydrofuranylidenes showed a similar spectroscopic pattern with C=C infrared absorption bands between 1638 and 1639 cm^{-1} and the characteristic downfield shift for the allylic oxolane nmr proton signals at 3.16-3.17 ppm (Table I). Structures **8, 9** and **10** were further established by ^{13}C nmr, 2D ^1H-^1H and ^{13}C-^1H correlation spectra.

The observed preference for a resulting *E*-geometry in the isolated products by the proposed two step cyclization-dehydration mechanism seems to be determined by the stereoelectronic interaction between the vinylic sulfonyl group and the oxygen atom at the five membered ring. The extent of this tool of stereocontrol is neither decreased nor reversed significantly when the vinylic hydrogen in **7** is replaced by larger groups such as benzyloxyethyl- **10**, *n*-hexyl- **9**, or *n*-pentyl substituents **8**, according to the observed yields and reaction conditions (Table I). Also, the exocyclic nature of the C=C bond in all four tetrahydropyranylidenes may be favored by the presence of the electron-withdrawing benzenesulfonyl group over the alternative endocyclic regioisomers.

However, hemiketal **6** was remarkably stable, and all dehydration attempts toward its corresponding tetrahydrofuranylidene were unsuccessful. When **6** was refluxed in xylene at 145° for 3.5 hours, infrared monitoring showed no appreciable amounts of any product with absorption bands in the 1600-1800 cm^{-1} range. The contrasting nature of hemiketal **6** compared to the corresponding hemiketals leading to **7, 8, 9**, and **10** correlates well with the proposed reaction mechanism and reveals the limits of the applicability of the methodology to 2,3-disubstituted lactones such as 2,3-*O*-isopropylidene-D-erythronolactone.

Thus, rapid cyclization of the starting hydroxyketone equivalents occurred in nearly quantitative yields at 130° to nonisolable hemiketals of type **4** (R = benzyloxyethyl-, *n*-hexyl-, or *n*-pentyl) with exception of the stable hemiketal **6** that is already formed at room temperature. The extent of both the stereo- and regioselectivity of the overall process suggests that tetrahydrofuranylidenes **7-10** retain memory of their precursor's configuration such as **4** or the ionic intermediate **5** and their corresponding diastereomers, as a result of the stereoelectronic interaction discussed above. On the other hand, the same stereoelectronic effect may prevent dehydration of **6** to any of its stereoisomeric teterahydrofuranylidenes, in which the benzenesulfonyl group, in contrast to **7-10** would have to assume energetically unfavorable geometries with respect to both, the ring-oxygen atom or the 2,3-isopropylidene functionality in the resulting *Z*- and *E*-isomers, respectively, **6a**.

The thermal cyclization-dehydration reactions of hydroxyketone equivalents discussed above constitute a good example for the use of the benzenesulfonyl devise as

a regio- and stereoselective controlling tool in the route toward tri- and tetrasubstituted tetrahydrofuranylidenes. The applicability of this methodology to the synthesis of similar six- and four membered heterocycles was observed to be more complex, particularly in the case of the former ones where the regio-selectivity appears to be less pronounced [15]. Work is in progress to circumvent these difficulties.

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 1620 FT-IR spectrophotometer in carbon tetrachloride solutions. The ^{1}H- (300 MHz), ^{13}C- (75 MHz), and two dimensional magnetic resonance spectra were recorded on a General Electric QE-300 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.

General Procedure for the Thermal Condensation of Hydroxy Keto Sulfones to Give Tetrahydrofuranylidenes **7-10**.

The appropriate (benzenesulfonyl)hydroxy ketone of type **1** [6] in toluene (60 ml for 10 mmoles of **1**) was refluxed using a water separator. After removal of the solvent under reduced pressure the residue was purified by flash column chromatography on silica gel eluting with acetone/pentane mixtures to afford the pure tetrahydrofuranylidenes **7-10**.

E-2-(Benzenesulfonylmethylidene)tetrahydrofuran (**7**).

Reaction conditions were: 130°, 40 minutes; acetone/pentane 1:3; 1.38 g, 62% yield. This compound was obtained as colorless needles (isopropyl alcohol), mp 98.5-100°; ir: ν 3069, 2988, 2899, 1636, 1446, 1373, 1326, 1314, 1285, 1171, 1140, 1085 cm^{-1}; ^{1}H nmr: δ 7.79 (m, 2H, ArH), 7.42 (m, 3H, ArH), 5.75 (br s, 1H, vinylic), 4.23 (t, J = 6.8 Hz, 2H, OCH_2 oxolane), 3.12 (br t, J = 7.6 Hz, 2H, CH_2 allylic oxolane), 2.10 (m, 2H, $CH_2CH_2CH_2$); ^{13}C nmr: δ 173.7 (=C-O), 144.0, 132.3, 128.9, 126.3 (ArC), 99.9 (=CSO_2), 72.3 (OCH_2 oxolane), 29.3 (allylic oxolane CH_2), 23.7 ($CH_2CH_2CH_2$); ms: m/z (ion, relative intensity) 225 (M^++1, 100).

Anal. Calcd. for $C_{11}H_{12}O_3S$: C, 58.9; H, 5.3; S, 14.2. Found: C, 58.9; H, 5.4; S, 14.9.

E-1-(Benzenesulfonyl)-1-(tetrahydrofuran-2-ylidene)pentane (**8**).

Reaction conditions were: 130°, 2.5 hours; acetone/pentane 1:5; 2.4 g, 86% yield. This compound was obtained as a colorless oil; ir: ν 3067, 2958, 1639, 1446, 1368, 1314, 1236, 1157, 1087 cm^{-1}; ^{1}H nmr: δ 7.81 (m, 2H, ArH), 7.49 (m, 3H, ArH), 4.20 (t, J = 6.9 Hz, 2H, OCH_2 oxolane), 3.17 (t, J = 7.7 Hz, 2H, allylic oxolane CH_2), 2.22 (t, J = 7.2 Hz, 2H, allylic CH_2), 2.08 (m, 2H, $CH_2CH_2CH_2$ oxolane), 1.39-1.16 (m, 4H), 0.81 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C nmr: δ 168.5 (=C-O), 143.1, 132.2, 128.7, 126.8, (ArC), 111.2 (=CSO_2), 71.6 (OCH_2 oxolane), 30.9 ($CH_3CH_2CH_2CH_2$), 30.1 (allylic oxolane CH_2), 27.0 (allylic CH_2), 24.4 ($CH_2CH_2CH_2$ oxolane), 22.5 (CH_3CH_2), 13.6 (CH_3); ms: m/z (ion, relative intensity) 281 (M^++1, 100).

Anal. Calcd. for $C_{15}H_{20}O_3S$: C, 64.2; H, 7.1; S, 11.4. Found: C, 63.8; H, 7.2; S, 11.5.

E-1-(Benzenesulfonyl)-1-(tetrahydrofuran-2-ylidene)heptane (**9**).

Reaction conditions were: 130°, 2.0 hours; acetone/pentane 1:10; 1.8 g, 60% yield. This compound was obtained as a colorless oil; ir: ν 3067, 2927, 1639, 1445, 1368, 1313, 1235, 1154, 1089 cm^{-1}; ^{1}H nmr: δ 7.83 (m, 2H, ArH), 7.50 (m, 3H, ArH), 4.18 (t, J = 6.9 Hz, 2H, OCH_2 oxolane), 3.16 (t, J = 7.7 Hz, 2H, allylic oxolane CH_2), 2.21 (t, J = 7.5 Hz, 2H, allylic CH_2), 2.07 (m, 2H, $CH_2CH_2CH_2$ oxolane), 1.40-1.12 (m, 8H, alkyl), 0.82 (t, J = 6.9 Hz, 3H, CH_3); ^{13}C nmr: δ 168.5 (=CO), 143.1, 132.2, 128.7, 126.7 (ArC), 111.2 (=CSO_2), 71.6 (OCH_2 oxolane), 30.1 (allylic oxolane CH_2), 24.4 ($CH_2CH_2CH_2$ oxolane), 27.2 (allylic CH_2), 31.3, 29.0, 28.6, 22.4 (alkyl C), 13.9 (CH_3); ms: m/z (ion, relative intensity) 309 (M^++1, 100).

Anal. Calcd. for $C_{17}H_{24}O_3S$: C, 66.2; H, 7.8; S, 10.3. Found: C, 65.7; H, 7.7; S, 10.1.

E-1-(Benzenesulfonyl)-3-benzyloxy-1-(tetrahydrofuran-2-ylidene)propane (**10**).

Reaction conditions were: 130°, 3 hours; acetone/pentane 1:4; 3.2 g, 91% yield. This compound was obtained as colorless crystals (isopropyl alcohol), mp 74-74.5°; ir: ν 3070, 3035, 2900, 2880, 1638, 1448, 1320, 1308, 1180, 1155, 1128, 1080 cm^{-1}; ^{1}H nmr: 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: δ 170.2 (=C-O), 138.4, 128.0, 127.3, 127.2, (ArC), 142.5, 138.5, 132.7, 126.6 (SO_2ArC), 107.3 (=CSO_2), 72.4 (benzylic C), 71.8 (OCH_2 oxolane), 68.3 (CH_2OBn), 30.1 (allylic CH_2 oxolane), 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.

1-(Benzenesulfonyl)-1-deoxy-3,4-isopropylidene-α-D-erythropent-2,5-furanosulose (**6**).

To a magnetically stirred solution of methyl phenyl sulfone (2.0 g, 12.8 mmoles) in dry THF (50 ml) was added *n*-butyllithium (10.7 ml of a 2.5 *M* solution in hexanes) at −60°, warmed up to 0°, stirred for 0.5 hour and cooled again to −60°. At this temperature a solution of 2,3-*O*-isopropylidene-D-erythronolactone (2.0 g, 12.8 mmoles) was added, and after four hours the reaction mixture was quenched by the addition of ammonium chloride (20 ml, saturated aqueous solution) and brine (20 ml). After extraction with ethyl acetate, the organic layer was dried with magnesium sulfate and concentrated under reduced pressure. Purification of the crude product on silica gel (acetone/pentane 1:3) and recrystallization from isopropyl alcohol afforded 3.6 g (92%) of pure **6** as colorless crystals, mp 80-82.5°; ir: ν 3472, 3071, 2991, 2942, 1448, 1411, 1382, 1373, 1322, 1273, 1256, 1226, 1209, 1182, 1141, 1098, 1082, 1018 cm^{-1}; ^{1}H nmr: δ 7.93 (m, 2H, ArH), 7.62 (m, 1H, ArH), 7.52 (m, 2H, ArH), 4.79 (q, J = 5.8 Hz, J = 3.7 Hz, 1H, H-4), 4.72 (s, 1H, OH), 4.37 (d, J = 5.8 Hz, 1H, H-3), 4.10 (q, J = 10.4 Hz, J = 3.7 Hz, 1H, H_a-5), 3.86 (d, J = 10.4 Hz, 1H, H_b-5), 3.73 (d, J = 14.8 Hz, 1H, CH_aSO_2), 3.59 (d, J = 14.8 Hz, 1H,

CH_bSO_2), 1.22 (s, 3H), 1.31 (s, 3H); ^{13}C nmr: δ 140.6 (CAr), 133.7, 128.8, 128.0 (CHAr), 112.8 (C-2), 103.6 (OCO), 85.6 (C-3), 80.0 (C-4), 71.7 (C-5), 59.2 (CH_2SO_2), 26.0 (CH_3), 24.7 (CH_3); ms: m/z (ion, relative intensity) 317 (36), 158 (M^+-155), 100).

Anal. Calcd. for $C_{14}H_{18}O_6S$: C, 53.4; H, 5.7; S, 10.1. Found: C, 52.99; H, 6.2.

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REFERENCES AND NOTES

[1] Presented in part at the NIH MARC/MBRS Symposium, San Juan, Puerto Rico, October 22-24, 1992.

[2] L. Lay, F. Nicotra, L. Panza, G. Russo and E. Caneva, *J. Org. Chem.*, **57**, 1304 (1992); B. I. Glanzer and R. Csuk, *Tetrahedron*, **47**, 1655 (1991).

[3] A. Takahashi, Y. Kirio, M. Sodeoka, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, **111**, 643 (1989).

[4] M. Riediker and J. Schwartz, *J. Am. Chem. Soc.*, **104**, 5842 (1982).

[5] A. Padwa, M. Ishida, C. L. Muller and S. S. Murphree, *J. Org. Chem.*, **57**, 1170 (1992).

[6] A. Alzérreca, M. Avilés, L. Collazo and José A. Prieto, *J. Heterocyclic Chem.*, **27**, 1729 (1990).

[7] F. Perron and K. F. Albizati, *Chem. Rev.*, **89**, 1617 (1989).

[8] A. R. Katritzky, ed, *Adv. Heterocyclic Chem.*, **30**, 167 (1982).

[9] B. M. Trost and T. A. Runge, *J. Am. Chem. Soc.*, **103**, 7550 (1981).

[10] O. Takashi, K. Takai, K. Oshima and K. Utimoto, *J. Org. Chem.*, **52**, 4412 (1987).

[11] A. Aguero, J. Kress and J. A. Osborn, *J. Chem. Soc., Chem. Commun.*, 531 (1986); F. W. Hartner and J. Schwartz, *J. Am. Chem. Soc.*, **105**, 640 (1983); R. R. Schrock, *J. Am. Chem. Soc.*, **98**, 5399 (1976).

[12] S. H. Pine, R. Zahler, D. A. Evans and R. H. Grubs, *J. Am. Chem. Soc.*, **102**, 3270 (1980); S. H. Pine, R. J. Pettit, G. D. Geib, S. G. Cruz, C. H. Gallego, T. Tejerina and R. D. Pine, *J. Org. Chem.*, **50**, 1212 (1985).

[13] N. Cohen, B. L. Banner, A. Laurenzano and L. Carozza, *Org. Synth.*, **63**, 127 (1985).

[14] A. Alzérreca and D. Arbelo, unpublished results.

[15] A. Alzérreca, L. Velázquez and J. Martínez, Presented in part at the NIH MARC/MBRS Symposium, San Juan, Puerto Rico, October 22-24, 1992.