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New intramolecular alkylation and Michael addition reactions of hydroxysulfone derivatives—stereoselective preparation of functionalized cyclic ethers

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Abstract

A number of bromoacetal derivatives of γ and δ hydroxysulfones have been prepared and shown to undergo intramolecular alkylation reactions in good yields to give highly functionalized oxacyclic ring systems. Tetrahydrofuranyl and tetrahydropyranyl ring systems have also been prepared using the Michael addition reactions of the acrylate derivatives of hydroxysulfones.

The intramolecular cyclization reactions of α-sulfonylcarbanions involving a variety of electrophiles have been a valuable approach for the preparation of carbocyclic and heterocyclic ring systems.[1,2] Some time ago we disclosed that the intramolecular cyclization reactions of γ and δ acyloxysulfones of the type **1a** provided a convenient route for the preparation of a number of functionalized chiral non-racemic dihydrofurans and dihydropyrans.[3] Similarly, cyclization reactions of the corresponding carbonate derivatives **1b** were shown to be a useful tool for the preparation of a variety of lactones and bicyclic lactones in good yields.[4] Another reaction of recent interest has been the intramolecular conjugate addition of nucleophiles to functionalized vinylsulfones. These reactions have been used to synthesize a number of oxacyclic and other heteroring systems.[5]

In this communication, we would like to report on the intramolecular alkylation and Michael addition reactions of derivatives of hydroxysulfones of the types **2** and **3**, respectively. These reactions provide a new and convenient stereoselective route to a variety of functionalized five-, six- or seven-membered oxacyclic ring systems, further enhancing the synthetic utility of hydroxysulfones.

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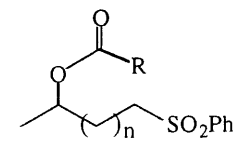
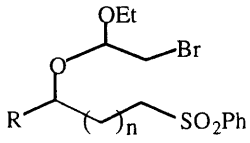


1a R=alkyl **1b** R=OR



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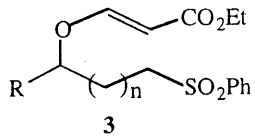
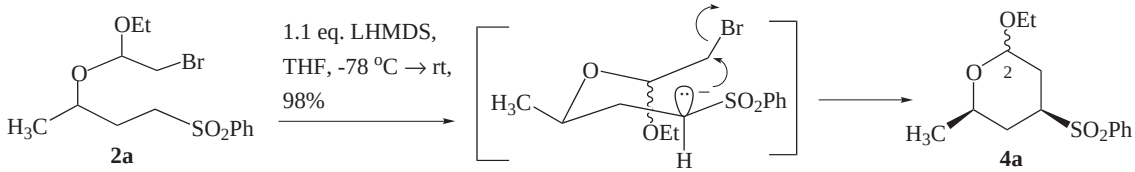


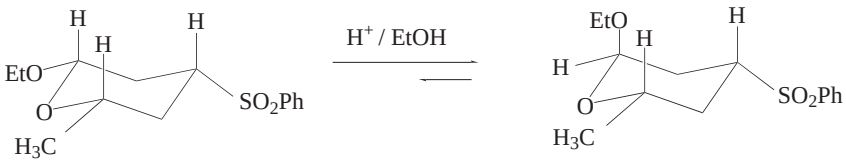
3

The bromoacetals required for this study were conveniently prepared by reaction of the corresponding hydroxysulfones with *N*-bromosuccinimide and ethyl vinyl ether in good yields (61–70%).[6,7] Treatment of the bromoacetal **2a** with lithium hexamethyldisilazane (LHMDS, 1.1 equiv.) in THF at −78°C gave the corresponding α-sulfonyl carbanion, which underwent ready intramolecular alkylation upon warming to room temperature (Scheme 1). Surprisingly, only two diastereomers of the cyclization product **4a** (1:1) were obtained in high yield after careful silica gel chromatography of the product mixture.[8] The relative stereochemistry of each of these diastereomers was determined by analysis of their ^{1}H NMR spectra and the two products were found to be epimers differing in the configuration at C-2. Since **2a** is a 1:1 diastereomeric mixture of acetals, we propose that the alkylation of the sulfonyl carbanion occurs with a high degree of stereoselectivity through a chair-like transition state in which both the alkyl and phenylsulfonyl groups prefer to be pseudoequatorial.



Scheme 1.

The stereochemistry of the products **4a** could be readily confirmed by their acid-catalyzed exchange reactions. When a 1:1 diastereomeric mixture of **4a** was treated with *p*-TsOH in ethanol for 4 days, the major isomer that was isolated was the anomer with the ethoxy group in the axial position (approximately 4:1 ratio of the two anomers, Eq. (1)). It is possible that this thermodynamic preference is due to the anomeric effect of the ethoxy group in oxacyclic systems. The equilibration studies have also been repeated with pure samples of each of the two diastereomers of **4a** with both ethanol and methanol giving similar results.

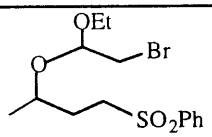
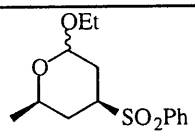
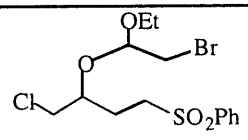
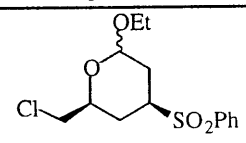
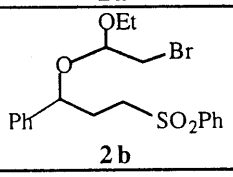
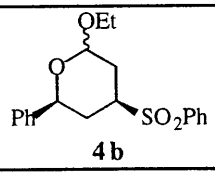
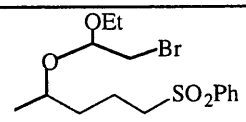
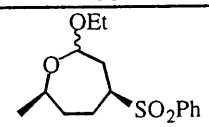


(1)

The results of the intramolecular cyclization reactions of the bromoacetals investigated so far are shown in Table 1. As can be seen from the table, the chloromethyl derivative **2c** undergoes cyclization in excellent yield to give **4c**. The cyclization can also be readily extended to prepare seven-membered oxacyclic ring systems such as **4d**.[9]

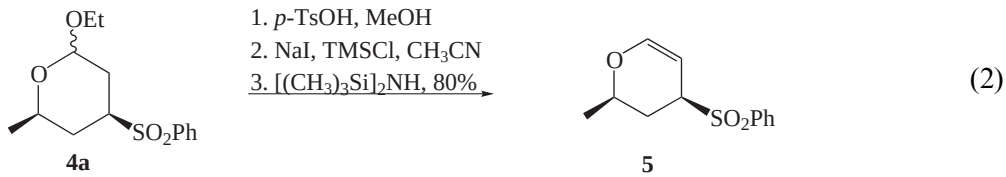
The lactol ethers, **4a**–**d**, are useful intermediates in organic synthesis. For example, the diastereomeric mixture of ethyl lactol ethers **4a** was readily converted to the corresponding

Table 1
Intramolecular cyclization reactions of bromoacetals

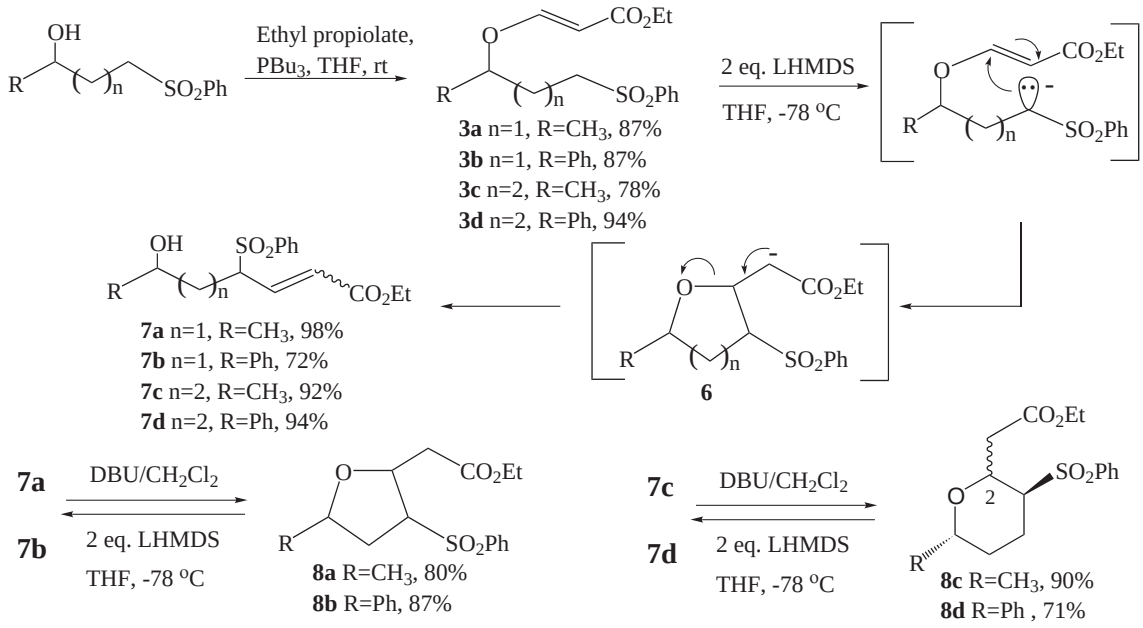
substrate	product	yield[a]	substrate	product	yield[a]
 **2a**	 **4a**	98%	 **2c**	 **4c**	94%
 **2b**	 **4b**	75%	 **2d**	 **4d**	64%

[a] 1:1 mixture of two diastereomers

glycal derivative **5** in high yields by a three-step procedure (Eq. (2)).[10] The synthetic utility of such glycal derivatives has recently received much interest, particularly in the area of polysaccharide synthesis.[11,12]



(2)



Scheme 2.

Highly functionalized oxacyclic ring systems are also accessible by the intramolecular cyclization reactions of the acrylate derivatives of hydroxysulfones using a conjugate addition strategy. The acrylate adducts **3a–d** were easily prepared by the reaction of the corresponding hydroxysulfones with ethyl propiolate.[13] When sulfone **3a** was treated with 2.0 equiv. of LHMDS at −78°C and the reaction quenched after 1 h, the desired cyclic product **8a** (Scheme 2) was not isolated. Instead the product that was obtained after chromatography as an inseparable mixture of diastereomers was the predominantly *trans*-hydroxy α,β-unsaturated ester **7a** in 98% yield. However, the isomeric mixture of esters **7a** could be cyclized by treatment with DBU at room temperature to give a separable diastereomeric mixture (2:1) of tetrahydrofuran **8a** in 80% yield.

It is interesting to note that treatment of **8a** with 2 equiv. of LHMDS at −78°C leads to rapid ring opening to give back **7a**. In view of these results, we propose that the initially formed sulfonyl carbanion from the acrylate derivative **3a** undergoes a Michael addition to give intermediate **6**. However, **6** is not stable under the reaction conditions and undergoes rapid ring opening.

Similar treatment of acrylate derivatives **3b–d** with LHMDS led to the isolation of products **7b–d**, which could be recyclized with DBU to get **8b–d** (in each case a mixture of two diastereomers). The two diastereomers of **8c** (2:1) obtained from the cyclization could be separated by column chromatography and the products were found to differ only at the stereochemistry at C-2 by ^{1}H NMR analysis.[14] The relative stereochemistry of the two diastereomers of **8d** could also be assigned by spectral analysis, while that of the diastereomers of **8a** and **8b** are under investigation.

In conclusion, the intramolecular alkylation of bromoacetal derivatives of hydroxysulfones can be achieved in synthetically useful yields to give a variety of functionalized six- and seven-membered oxacyclic ring systems with stereochemical control. The acrylate derivatives of hydroxysulfones also show useful reactivity and can be used to access substituted tetrahydrofuranyl or pyranyl ring systems. Given the current interest in the synthesis of cyclic ether containing natural products[15] and the availability of the starting hydroxysulfones in high optical purities,[16,4a] these intramolecular cyclization strategies should provide valuable intermediates for synthetic applications.

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7. Spectroscopic and elemental analysis of all compounds are in agreement with the assigned structures.
8. **4a diastereomer 1**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95–7.50 (m, 5H), 4.94 (d, $J=2.5$ Hz, 1H), 3.83 (ddq, $J=12.4$, 2.1, 6.2 Hz, 1H), 3.72–3.33 (m, 3H), 2.05–1.69 (m, 3H), 1.54–1.35 (m, 1H), 1.30–1.05 (m, 6H); anal. calcd for $C_{14}H_{20}SO_4$: C, 59.13%; H, 7.09%. Found: C, 58.77%; H, 6.95%. **4a diastereomer 2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95–7.50 (m, 5H), 4.38 (dd, $J=9.4$, 1.8 Hz, 1H), 4.00–3.82 (m, 1H), 3.60–3.43 (m, 2H), 3.23 (dddd, $J=12.7$, 12.7, 3.8, 3.8 Hz, 1H), 2.14–1.94 (m, 2H) 1.58–1.36 (m, 2H), 1.30–1.05 (m, 6H); anal. calcd for $C_{14}H_{20}SO_4$: C, 59.13%; H, 7.09%. Found: C, 59.06%; H, 7.17%.
9. The relative stereochemistry of **4d** has been assigned based on the precedence observed for the six-membered ring system. Acid-catalyzed exchange studies on the two diastereomers of **4d** show that they differ in the stereochemistry at the anomeric carbon. Assignment of the stereochemistry is currently under investigation.
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14. **8c major diastereomer**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00–7.50 (m, 5H), 4.79 (ddd, $J=10.7$, 4.6, 4.5 Hz, 1H), 4.26–4.06 (m, 2H), 3.88 (ddq, $J=11.9$, 2.1, 6.0 Hz, 1H), 3.41 (ddd, $J=12.3$, 4.5, 4.4 Hz 1H), 3.20–2.90 (m, 2H), 2.15–1.70 (m, 3H), 1.35–1.15 (m, 1H), 1.26 (t, $J=7.1$ Hz, 3H), 1.07 (d, $J=6.0$ Hz, 3H); anal. calcd for $C_{16}H_{22}SO_5$: C, 58.88%; H, 6.79%. Found: C, 58.68%; H, 6.65%.
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