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# REGIO- AND STEREOCONTROLLED SYNTHESIS OF HYDROXYCYCLOHEXENYL SULFONES FROM OXANORBORNENES

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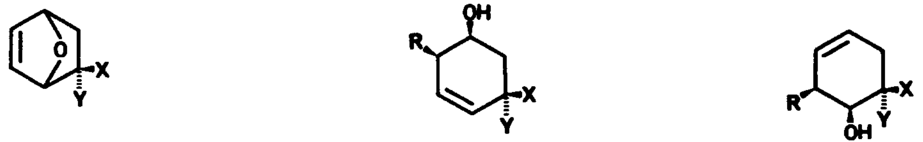
**Summary:** Organolithium reagents and lithium aluminum hydride undergo conjugate additions to oxanorbornenic vinyl sulfones **9-12** with concomitant cleavage of the oxygen bridge, to generate highly functionalized cyclohexenyl phenyl sulfones **13-16** in high yields and in a regio- and stereocontrolled fashion.

The chemistry of 7-oxabicyclo[2.2.1]heptane derivatives has attracted considerable attention in recent years[1]. Within this field, oxanorbornenic substrates **1** and **2** (Scheme I), readily available optically pure[2], have become important synthetic intermediates[3]. Many endeavors in this area proceed through a bridge opening step and this has been accomplished by base induced $\beta$-elimination in derivatives of **2**[3b] or **3**[4] (Scheme I), by treatment with strong acids in other cases[5], as well as by reductive elimination of an *endo* functionality (Cl, $SO_2Ph$)[6]. It should be noted, however, that most of these methods present certain shortcomings[5,7,8].

Recently, we reported a new regio- and stereospecific cleavage of the oxygen bridge of alcohols **4** (Scheme I) with organolithium reagents to produce cyclohexenediols **6**[9]. However, this process afforded a 2:1 mixture of the regioisomers **7** and **8** when the reaction was conducted on benzyl ether **5**. This lack of regioselectivity and our desire to develop regiocontrolled methodology towards either isomer (**7** or **8**), prompted the research described here.

**Scheme I**



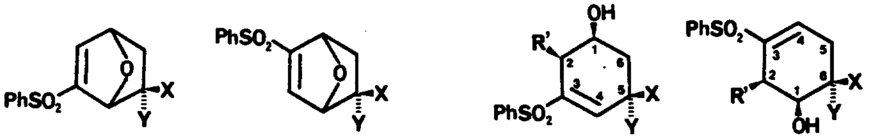
**1**, X=CN; Y=OAc,
**2**, X=Y=O
**3**, X=H, Y=$CO_2Me$, $SO_2Ph$
**4**, X=H, alkyl, vinyl; Y=OH
**5**, X=Me; Y=OBn

**6**, X=H, alkyl, vinyl
Y=OH; R=Me, *n*-Bu, Ph
**7**, X=Me, Y=OBn
R=*n*-Bu

**8**, X=Me; Y=OBn
R=*n*-Bu

An alternative strategy envisioned modification of the substrate by the introduction of a directing substituent on the double bond which could allow for the control of the regiochemistry of the process and also increase the synthetic potential of the opening products. A phenylsulfonyl functionality appeared particularly attractive, both from an accesibility of starting materials standpoint[10] and regarding its versatility in synthesis[11,12]. It was expected that conjugate addition of an organolithium reagent to model substrate 9 (Scheme II) would generate an $\alpha$-sulfonyl carbanion which would undergo $\beta$-elimination[4b,7] to give rise to adducts 13[13,14]. In this paper we describe the successful realization of this concept which has resulted in regio- and stereocontrolled methodology to achieve the cleavage of the oxygen bridge of oxanorbornenic vinyl sulfones 9-12 (Scheme II) to produce hydroxycyclohexenyl sulfones 13-16.

**Scheme II**



9 11 13 15 (X=Me; Y=OBn)
10 12 14 16 (X=Y=OCH$_2$CH$_2$O)

Our initial studies involved readily available vinyl sulfone 9[15]; when the reaction between 9 and a slight excess of MeLi (THF, -78°C) was examined, an excellent yield of cyclohexenol 13a[16] was obtained. Encouraged by this result, the reactions between 9 and other organolithium reagents were explored and these results are gathered in Table I.

**Table I. $S_N2'$ Opening Reactions of 7-Oxanorbornenic Vinyl Sulfones 9-12 with Organolithium Reagents and LiAlH$_4$.**

| Entry[b] | Substrate | R' | Product | Yield[a](%) |
|---|---|---|---|---|
| 1 | 9 | Me | 13a | 87 |
| 2[c] | 9 | *n*-Bu | 13b | 78 |
| 3[c] | 9 | Ph | 13c | 86 |
| 4[c] | 9 | -CH=CH$_2$ | 13d | 95 |
| 5 | 11 | Me | 15a | 80 |
| 6 | 10 | Me | 14a | 85 |
| 7 | 12 | Me | 16a | 75 |
| 8 | 11 | H | 15b | 65 |
| 9 | 10 | H | 14b | 62 |

[a] Yields of pure products. These yields have not been optimized. [b] In THF, -78°C. [c] In toluene, -78°C.

Thus, excellent yields of adducts 13 were realized with *n*-BuLi, PhLi and vinylLi. It should be noted that these reactions (particularly entry 2) are remarkably dependent upon the reaction conditions[17]; we found that the use of toluene as a solvent is crucial to the success of the process.

To explore the anticipated regiocontrolled bridge opening, vinyl sulfone 11 was prepared in a regiospecific fashion[10,15]. The treatment of 11 with MeLi (entry 5) afforded a good yield of adduct **15a**. Similarly, ketals 10 and 12[15] gave rise to good yields of **14a** and **16a** respectively.

The regio- and stereochemistry of **13a** and **15a** were readily established by $^1$H NMR spectroscopy[16]. For example, the splitting pattern of the vinylic protons are diagnostic (**13a**, d, $J = 1.3$ Hz; **15a**, ddd, $J = 5.4, 3.0, 2.4$ Hz). In addition, H1 exhibits one *trans* diaxial coupling (12.6 Hz) in **13a** and an equatorial axial coupling (3.7 Hz) in **15a**. The large homoallylic coupling encountered in **15a** ($J_{2,5ax} = 3.0$ Hz) is also noteworthy.

The *syn* stereochemistry observed is in good agreement with previous literature for epoxy vinyl sulfones[13d], and may be accounted for in terms of a directed addition via chelation of the organometallic reagent with the oxygen bridge. Nevertheless, the influence of steric control cannot be discarded due to the bicyclic character of our substrates.

In order to extend the scope of the methodology, the reactions between oxanorbornenic sulfones 11 and 10 and lithium aluminum hydride was studied. Thus, good yields of cyclohexenyl sulfones **15b** and **14b** were realized in what, to the best of our knowledge is the first case of an $S_N2'$ addition of a hydride reagent to a vinyl sulfone[18]. It was encountered that the reaction was very temperature dependent; nevertheless, conditions to run the cleavage effectively were developed after some experimentation[19].

In conclusion, new methodology to effect the regiocontrolled and stereospecific $S_N2'$ alkylation and reduction of readily available 7-oxanorbornenic vinyl sulfones with concurrent cleavage of the oxygen bridge has been developed. In this manner, highly functionalized cyclohexenyl sulfones, versatile synthetic intermediates[11,12,13], are produced in high yields. The use of other nucleophiles and oxabicyclic substrates are currently being pursued in our laboratories.

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(10) (a) The regioselective addition of sulfenyl halides to oxanorbornenic substrates, such as 1 and 2, controlled by substitution on C-2 is well known. See: Black, K. A.; Vogel, P. *J. Org, Chem.* 1986, *51*, 5341-5348. (b) See also: Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *Tetrahedron* 1989, *45*, 4565-4578.

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(15) For the synthesis of other oxanorbornenic vinyl sulfones, see ref. 10a. For the preparation of 10 see: Arjona, O.; Domínguez, C.; Fernández de la Pradilla, R.; Mallo, A.; Manzano, C.; Plumet, J. *J. Org. Chem.* 1989, *54*, 0000. 9, 11 and 12 were prepared in a similar fashion in 50-60% overall yield from 2. It should be pointed out that, in sharp contrast with Vogel's results (see ref. 10a), we did not encounter serious difficulties in the protection of 6-*endo*-chloro-5-*exo*-benzenesulfenyl-7-oxabicyclo[2.2.1]heptan-2-one as a ketal. Full details of these procedures will be published in due course.

(16) All new products had satisfactory spectral and analytical data, including $^1H$ NMR NOE experiments and selective decouplings.

(17) In THF, low yields of 13b were obtained along with variable amounts of desulfonylated 9 and 13b. Also, the reaction was slow even at 0°C.

(18) The transfer of hydride with allylic rearrangement in other systems is well known. See: Magid, R. M. *Tetrahedron* 1980, *36*. 1901-1930. The addition of hydride to an oxanorbornenic vinyl sulfide with opening of the bridge is mentioned in ref. 1c.

(19) The reaction was best performed at -78°C in THF using an excess of $LiAlH_4$ solution in $Et_2O$. At 0°C the product of reduction of the carbon-carbon double bond of 15b was obtained in good yield.

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