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A Study of the Intramolecular Cyclization Reactions of Some Derivatives of 3-Arylsulfonyl Cycloalkanols[1]

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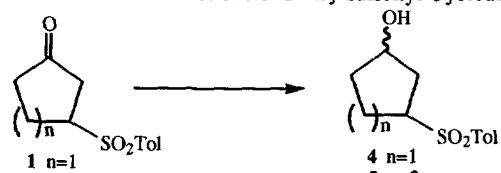
Abstract: Carbonate and acyl derivatives of 3-arylsulfonylcyclohexanols and heptanols, upon deprotonation with LHMDS in THF at -78°C, undergo an intramolecular cyclization reaction to give bicyclic lactones or the corresponding acyl transfer products in synthetically useful yields. In contrast, the corresponding cyclopentyl derivatives show different reactivity.

The intramolecular cyclization reactions of α-sulfonylcarbanions provide a valuable approach for the preparation of a variety of carbocyclic systems.[2,3] The extension of these reactions to synthesize oxacyclic and other heteroring systems is also of interest.[4] The cyclization reactions of some γ and δ acyloxy sulfones has been investigated in our laboratory and found to be a convenient route for the preparation of a number of functionalized dihydrofurans and dihydropyrans.[5] Cyclization of the corresponding carbonate derivatives of γ and δ hydroxy sulfones can be used to synthesize chiral lactones of biological interest in good yields.[6] As a part of this program, we have also developed methods for the preparation of some chiral hydroxysulfones in high optical purities[7,8]

In this communication, we would like to describe the results of our study on the intramolecular cyclization of the carbonate and acyl derivatives of 3-arylsulfonylcycloalkanols. This reaction allows us to exploit our earlier findings to generate useful methodology to prepare bicyclic systems. The hydroxysulfones needed for this study could be conveniently prepared by the reduction of the corresponding ketosulfones[9] **1-3** (Table 1). However, our attempts to develop convenient procedures for the reduction of these ketosulfones so as to access either the *cis* or the *trans* product alcohols in high diastereoselectivity were not successful.[10] The reduction of ketones **1** and **2** with sodium borohydride, borane-THF, L-Selectride® and 9-BBN gave the *cis* alcohol as the major product (with the exception of L-Selectride® in the reduction of **2**). The isomeric alcohols could be separated by careful column chromatography and readily identified by comparison of our spectral data for these compounds with those reported earlier by Rothberg.[11] It is interesting to note that the use of the more sterically hindered reducing agent 9-BBN did not significantly enhance the diastereoselectivity of this reduction relative to the results obtained from use of sodium borohydride or borane-THF. Reduction of **3** with sodium borohydride or borane-THF gave a 1:1 mixture of isomers which were not readily separable by chromatography.

Table 1. Results of the Reductions of 3-Arylsulfonyl Cycloalkanones



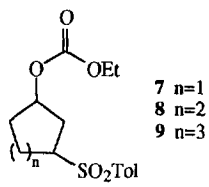
1 n=1
2 n=2
3 n=3

4 n=1
5 n=2
6 n=3

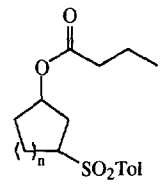
Substrate	Reagent	Product	Yield%[a]	*cis*/*trans* ratio[b]
1	$NaBH_4$	4	80	10:1
2	"	5	82	8.3:1
3		6	97[c]	1:1
1	BH_3-THF	4	91	3.3:1
2	"	5	89	5:1
3	"	6	97[c]	1:1
1	9-BBN	4	62	2:1
2	"	5	48	3.7:1
1	L-Selectride®	4	57	>95% *cis*
2	"	5	60	1:2

a) purified yield b) determined by ^1H NMR of the crude products c) crude yield

The reaction of alcohols **4-6** (*cis* or *trans* or mixtures of the two isomers) with ethyl chloroformate in pyridine at 0°C gave the carbonates **7-9** in good yields (80-89%). The corresponding butyrates **10-12** were prepared by treating the alcohols with butyryl chloride in the presence of triethylamine in THF at 0°C (74-95% yield).[12]

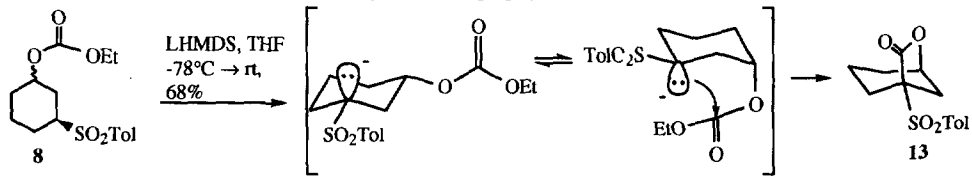


7 n=1
8 n=2
9 n=3



10 n=1
11 n=2
12 n=3

The *cis* (>95% isomeric purity) cyclohexyl carbonate **8** was treated with lithium hexamethyldisilyl amide, LHMDS, (2.2 eq.) in THF at -78°C to achieve its deprotonation according to our previously published procedure.[6,13] The resultant α-sulfonyl carbanion readily cyclized under the reaction conditions to give the lactone **13** in 68% yield after purification by chromatography (Scheme 1).

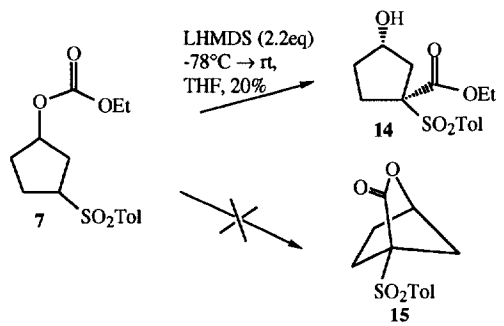


Scheme 1

Our studies show that both the *cis* and *trans* isomers of the carbonate **8** can be individually cyclized to give the lactone **13** under these reaction conditions. This observation is not surprising but does provide some mechanistic insight. For cyclization to the lactone to occur, the initially formed α-sulfonyl carbanion from *cis* **8** must equilibrate to the carbanion of the opposite configuration. Our results suggest that the energy barrier for the inversion of the initially formed sulfonyl carbanion in these systems is low, allowing their rapid equilibration

even at -78°C.[11,14] Hence, a mixture of the *cis* and *trans* carbonates of **8** can be used directly in the cyclization reaction providing synthetic simplicity.

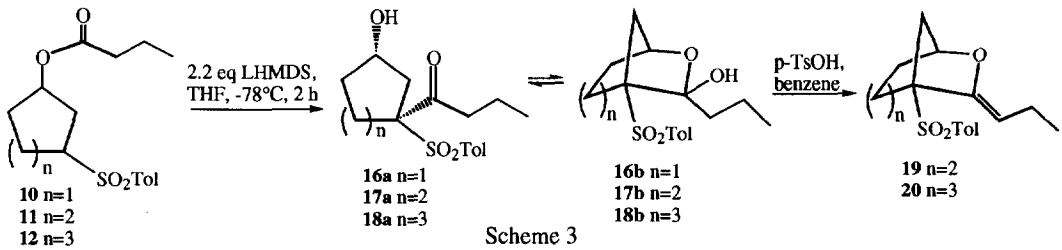
Cyclization of a 1:1 mixture of *cis* and *trans* cycloheptyl carbonate **9** under the same conditions, gave similar results and the corresponding sulfonyl lactone was obtained in 70% yield. In contrast, the cyclopentyl carbonate **7** (>95% *cis*) did not give the desired lactone **15** under similar reaction conditions (Scheme 2). When the carbonate **7** was treated with 2.2 eq of LHMDS at -78°C and the reaction mixture quenched after warming to room temperature, a mixture of products was obtained. The hydroxyester **14** was isolated in 23% yield along with minor amounts of the *cis* and *trans* carbonate **7**, and *cis* and *trans* alcohol **4**. This suggests that some of the initially formed α-sulfonyl carbanion does cyclize to give an intermediate that opens up preferentially to the product **14**. Alternatively, lactone **15** may be formed but subsequent ring opening with ethoxide gives **14**. Isolation of significant quantities of isomerized starting materials from this reaction also seems to indicate that the cyclization of the initially formed sulfonyl carbanion in the cyclopentyl carbonate system is unfavorable.



Scheme 2

The intramolecular cyclization reactions of the butyrates **10-12** have also been studied (Scheme 3). When the cyclohexyl butyrate **11** (>95% *cis*), was treated with 2.2 eq LHMDS in THF at -78°C, the acyl transfer product **17a** was isolated in 53% purified yield along with some starting material (25%). The hydroxyketone **17a** was expected to be in equilibrium with the corresponding lactol **17b**.[5] However, the ^{1}H NMR and IR spectra of the product from this reaction did not indicate the presence of the lactol **17b**. Treatment of **17a** with a catalytic amount of p-TsOH in refluxing benzene gave the exocyclic enol ether **19** as a single geometric isomer in 74% yield. The *Z* geometry of the double bond in **19** has been established by NOE studies (irradiation of the vinyl proton gave an 8% NOE enhancement of the aromatic protons).

When the cycloheptyl butyrate **12** (1:1 mixture of *cis* to *trans*), was treated with 2.2 eq of LHMDS in a similar fashion, the major product was **18a** (51%) with no **18b** observed, along with 28% of recovered starting material. Dehydration of **18a** occurred readily in the presence of a catalytic amount of p-TsOH at room temperature in benzene to give a single isomer of the exocyclic enol ether **20** in 89% yield. NOE studies suggest that the double bond geometry in **20** is also *Z* (irradiation of the vinyl protons gave a 7% NOE enhancement of the aromatic protons). In contrast, cyclization of cyclopentyl butyrate **10**, using similar conditions gave a mixture of products including *cis* and *trans* **10** and *cis* and *trans* alcohol **4**. None of the desired product **16a** or the corresponding lactol **16b**, expected from an intramolecular acyl transfer, could be isolated from this reaction.



Scheme 3

In conclusion the cyclization reactions of the carbonate and acyl derivatives of 3-arylsulfonylcyclohex- and heptanols promise to be a useful route for the preparation of some bicyclic lactones[15] and other structures of interest. In contrast the cyclization of the corresponding cyclopentyl analogs appears to be of limited synthetic value. Extensions of this methodology including the use of the synthetic intermediates generated from our study are in progress. Methods for the preparation of the scalemic *cis* or *trans* 3-sulfonylcycloalkanols[16] described in this work are also under investigation in order to extend the usefulness of this study to asymmetric synthesis.

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