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CYCLOBUTYL PHENYL SULFOXIDE AND (*SR*)-CYCLOBUTYL p-TOLYL SULFOXIDE: NEW REAGENTS FOR THE SPIROANNELATION OF CYCLOPENTANONE

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Abstract: Cyclobutyl phenyl sulfide **2**, cyclobutyl phenyl sulfoxide **3** and (*SR*)-cyclobutyl p-tolyl sulfoxide (*SR*)-**8** have been synthesized and used for the spiroannelation of cyclopentanone. In the most effective sequence, lithiated **3** is added to ketones with formation of ß-hydroxy sulfoxides **4a-g**, which are ring enlarged and hydrolyzed to cyclopentanones **6a-e** and sulfanylcyclopentene **6f**, respectively, after reduction to ß-hydroxy sulfides **5a-f**. In an asymmetric version using (*SR*)-**8**, partial racemization during ring enlargement was observed.

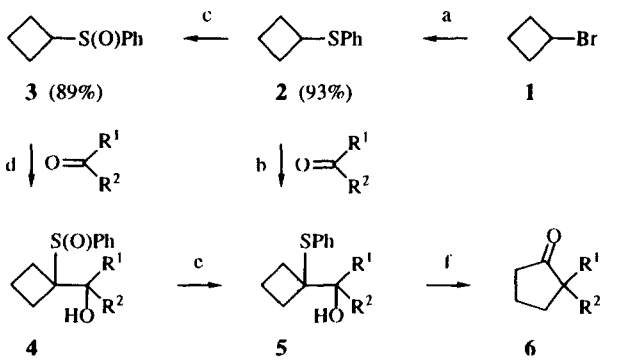
Cyclopropyl phenyl sulfide, 1973 introduced by Trost,[1] and (*SR*)-cyclopropyl p-tolyl sulfoxide,[2] 1987 introduced by Hiroi,[3] are powerful reagents for the synthesis of racemic and optically active cyclobutanones, respectively. However, nothing is known about the usefulness of cyclobutane analogs for the synthesis of cyclopentanones. A single report of Szeimies[4] on the preparation of cyclobutyl phenyl sulfide **2** exists, but cyclobutyl phenyl sulfoxide **3** and (*SR*)-cyclobutyl p-tolyl sulfoxide (*SR*)-**8** are unknown. We herein report on their synthesis and use for the spiroannelation of cyclopentanone.

Cyclobutyl phenyl sulfide **2**[4] was easily prepared by reaction of bromocyclobutane **1**[5] with sodium thiophenolate and selectively oxidized to cyclobutyl phenyl sulfoxide **3**[6] by successive treatment with titanium(III) chloride in aqueous-methanolic hydrochloric acid and hydrogen peroxide.[7] Selective deprotonotion of **2** in the cyclobutane ring proved difficult,[8] but could be achieved in 2h at -60°C using a combination of potassium tert-butoxide und n-butyllithium in tetrahydrofuran.[9] The selective deprotonation of **3** using lithium diisopropylamide in tetrahydrofuran was complete within 1 h at -78°C. Due to an extensive enolization, the reaction of kaliated **2** with cyclohexanone gave only 36% ß-hydroxy sulfide **5c**.[6] An attempt to suppress the enolization by adding lithium bromide[10] failed. The total yield remained unchanged (35%), but concurrent addition of **2** via the α-position of the phenyl ring dropped the yield of **5c** to 19%.

On the contrary, the addition of lithiated **3** to ketones proved highly efficient. With the exception of **4d**[6] (51%), high yields (76-91%) of the desired ß-hydroxy sulfoxides **4a-g**[6] were obtained. All ß-hydroxysulfoxides were solids and after a single crystallization pure. Characteristic chemical shifts were observed for the peripheral carbon atoms of the cyclobutane ring (δ = 14.08 - 15.00) and the carbon atoms bearing the phenylsulfinyl (δ = 66.51 - 70.77) and the hydroxyl group (δ = 74.76 - 86.12), respectively. An attempted ring enlargement of **4c** to

the corresponding phenylsulfinylcyclopentene by treatment with p-toluenesulfonic acid chloride in pyridine[3b] failed.

With the exception of **4g**, the reduction of all ß-hydroxy sulfoxides could readily be achieved by treatment with titanium(IV) chloride and zinc powder in tetrahydrofuran[11] and yielded the ß-hydroxy sulfides **5a-f**[6] in excellent yields (83-95%). Most characteristic were the chemical shifts for the peripheral carbon atom of the cyclobutane ring (δ = 13.46 - 15.28) and the carbon atoms bearing the phenylsulfanyl (δ = 62.05 - 65.12) and the hydroxyl group (δ = 74.43 - 86.62), respectively.



(a) PhSNa/DMF/1.5h/rflx (b) t-C_4H_9OK/n-C_4H_9Li/2h/-60°C
(c) (1) 2 $TiCl_3$/HCl/CH_3OH/H_2O, (2) 6 H_2O_2/CH_3OH/H_2O (d) 1.1 LDA/THF/1h/-78°C
(e) 3 $TiCl_4$/6 Zn/THF/0.5-1.5h/0-10°C (f) $SnCl_4$/CH_2Cl_2/20 min/0-20°C

Table 1. β-Hydroxy Sulfoxides **4**, β-Hydroxy Sulfides **5** and Cyclopentanones **6** Prepared.

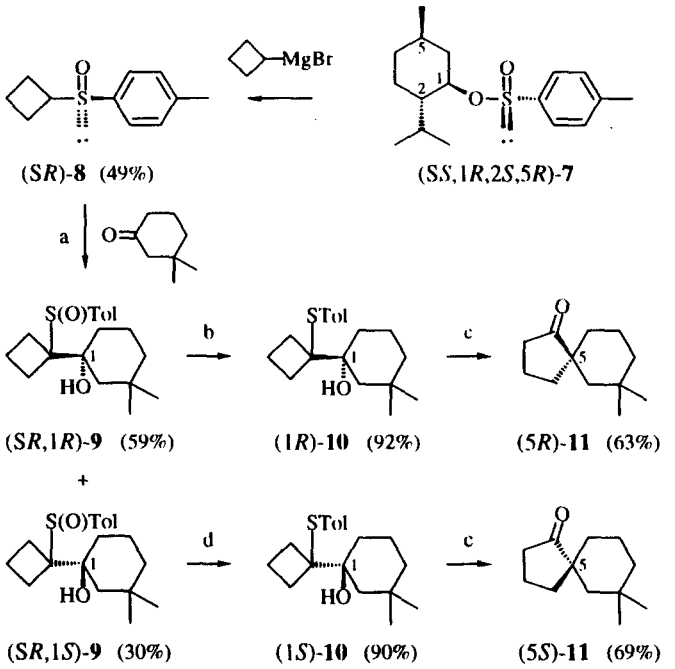
4, 5, 6	R^1 R^2	4	5	6
		Yields [%]		
a	$-(CH_2)_3-$	85	92	10
b	$-(CH_2)_4-$	81	95	7
c	$-(CH_2)_5-$	91	92, 36[a]	65
d	$-(CH_2)_2-CH(t-C_4H_9)-(CH_2)_2-$	51[b]	83	79
e	$-(CH_2)_6-$	74	93	67
f	i-C_3H_7 i-C_3H_7	76	92	84[d]
g	$-CH=CH-(CH_2)_3-$	77[c]	-	-

[a]from **2**, [b]single diastereoisomer, [c]two diastereoisomers (4.5:1), [d]sulfanylcyclopentene

To study the rearrangement and *in situ* hydrolysis of the ß-hydroxy sulfides **5a-f**, **5c** was used as a model. Treatment with 50% tetrafluoroboric acid in ether[1c] or p-toluenesulfonic acid in benzene[1c] resulted in an elimination of water with formation of the corresponding cyclohexene. However, treatment with tin(IV) chloride in dichloromethane[1c] for 15 min at 0°C and 5 min at room temperature and subsequent aqueous work-up yielded the desired cyclopentanone **6c**[12] in 65% yield. Using the same procedure, 79% **6d**[6] and 67% **6e**[13], but only 10% **6a**[13] and 7% **6b**[12] were formed. Obviously, good yields are only obtained, if the initial C_4-C_5 ring enlargement necessary for the formation of a cyclopentanone, cannot be followed by another thermodynamically favoured C_4-

C_5 or C_5-C_6 ring enlargement. In this respect, cyclohexanones, cycloheptanones, cyclooctanones and acyclic ketones are well suited for the spiroannelation described here, but cyclobutanones and cyclopentanones are not.

Having established the usefulness of cyclobutyl phenyl sulfoxide **3** as reagent for spiroannelations of cyclopentanone, we investigated an asymmetric version. Towards this end, (*SS*,1*R*,2*S*,5*R*)-menthyl p-toluenesulfinate (*SS*,1*R*,2*S*,5*R*)-**7**[14] ($[\alpha]_D$ -200°, c = 1, acetone) was reacted with cyclobutylmagnesium bromide in ether,[15] the resulting (*SR*)-cyclobutyl p-tolyl sulfoxide (*SR*)-**8**[6] ($[\alpha]^{20}_D$ +320°, c = 0.50, $CHCl_3$) lithiated as described for **3** and added to 3,3-dimethyl-cyclohexanone. Two diastereoisomers were formed, recognized as (*SR*,1*R*)-**9**[6] (59%, $[\alpha]^{20}_D$ +49°, c = 0.94, $CHCl_3$) and (*SR*,1*S*)-**9**[6] (30%, $[\alpha]^{20}_D$ +75°, c = 1.01, $CHCl_3$) by X-ray analysis[16] of the minor isomer. Reduction of the ß-hydroxy sulfoxides yielded the enantiomeric ß-hydroxy sulfides (1*R*)-**10**[6] (92%, $[\alpha]^{20}_D$ -5°, c = 0.80, $CHCl_3$) and (1*S*)-**10**[6] (90%, $[\alpha]^{20}_D$ +5°, c = 0.78, $CHCl_3$), respectively, but rearrangement and *in situ* hydrolysis gave partially racemized[17] cyclopentanones, tentatively assigned[18] as (5*R*)-**11**[6] (63%, 41% ee, $[\alpha]^{20}_D$ +31°, c = 1.01, $CHCl_3$) and (5*S*)-**11**[6] (60%, 57% ee, $[\alpha]^{20}_D$ -42°, c = 1.07, $CHCl_3$).



(a) 1.1 LDA/THF/1h/-78°C (b) 3 $TiCl_4$/6 Zn/THF/3h/5-10°C
(c) $SnCl_4/CH_2Cl_2$/20min/0-20°C (d) 3 $TiCl_4$/6 Zn/THF/0.5h/0-5°C

In summary, we have established the feasibility of cyclopentanone spiroannelations using cyclobutyl phenyl sulfoxide **3** and approached an asymmetric version using (*SR*)-cyclobutyl p-tolyl sulfoxide (*SR*)-**8**. Investigations to improve the stereoselectivity during the final ring enlargement step and to determine the absolute configuration of the ketones formed are in progress.

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6. All new compounds [**3**, **4a-g**, **5a-f**, **6d**, **6f**, (*SR*)-**8**, (*SR*,1*R*)-**9**, (*SR*,1*S*)-**9**, (1*R*)-**10**, (1*S*)-**10**, (5*S*)-**11**, (5*R*)-**11**] gave correct elemental analyses and/or high resolution mass spectroscopic data. The IR, ^{1}H-NMR, ^{13}C-NMR and mass spectra are consistent with the structures given.
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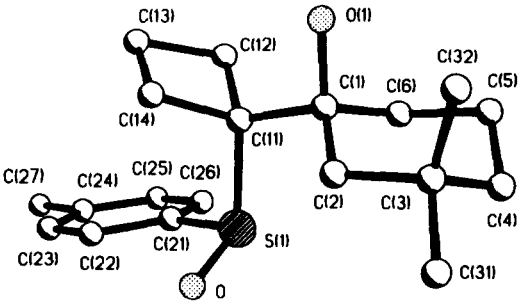
16. (*SR*,1*S*)-**9** ($C_{19}H_{28}O_2S$, M = 320.5, mp 127-128°C) formed colourless crystals from hexane, space group $P4_32_12$, $a = b = 1255.70(10)$, $c = 2314.4(3)$ pm, $\alpha = \beta = \gamma = 90°$, $V = 3.6493(6)$ nm^3, $Z = 8$, $D_{calc} = 1.167$ gcm^{-3}. 3569 reflections with $3.50 < \Theta < 22.47°$ were measured on a Stoe four-circle diffractometer using graphite-monochromated radiation Mo K_α. Of these, 2371 independant reflections were used for the structure determination and refinement. The structure was solved by direct methods. The anisotropic refinement with geometrically positioned H atoms (riding model: C-H = 96 pm, ∠HCH = 109.5°) converged at R1 = 0.0368 (wR2 = 0.0954). All calculations were performed with the program SHELXL-93. All relevant crystallographic data have been deposited with the Fachinfirmationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen (CSD-401790).



Molecular structure of (*SR*,1*S*)-**9**

17. The enantiomeric purity was determined by capillary gas chromatography using heptakis(2,6-di-*O*-methyl-3-*O*-pentyl)-ß-cyclodextrin as chiral phase.
18. ß-Hydroxy sulfides derived from 1-lithio-cyclopropyl phenyl sulfide rearrange with predominant retention of configuration at the migration terminus.[1c]

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