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RETROALDOL REACTIONS OF β-HYDROXY-α-PHENYLSULFENYL CYCLOHEXANONE DERIVATIVES[1]

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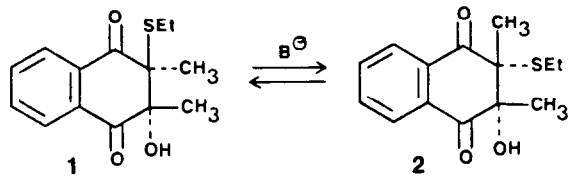
Abstract: Upon treatment with strong bases β-hydroxy-α-phenylsulfenyl cyclohexanone derivatives undergo retroaldol reactions to give open-chain keto (or aldehydo) enolates which can be trapped with electrophilic or nucleophilic reagents.

It is known that α-sulfenyl substituents have a stablizing effect upon enolates of carbonyl compounds.[3] Therefore, it is not surprising that α-hydroxy-β-phenyl(or alkyl)sulfenyl carbonyl compounds undergo relatively facile retroaldol reactions.[4,5] For example, Silverman[4] has found that the trans dihydronaphthaquinone derivative 1 undergoes base-promoted (ethyl thiolate or methoxide ion) rearrangement to the cis isomer 2 via a retroaldol cleavage - recyclization mechanism; and Hoye and Kurth[5] have found that treatment of the threo β-hydroxy-α-phenylsulfenyl ester 3 with lithium diisopropylamide in tetrahydrofuran (THF) at -78°, warming to 0°, and quenching with aqueous acid led to the formation of benzaldehyde and methyl α-phenylsulfenyl propanoate in nearly quantitative yield.



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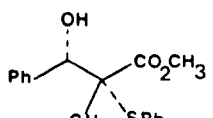

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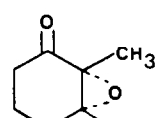

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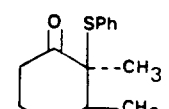

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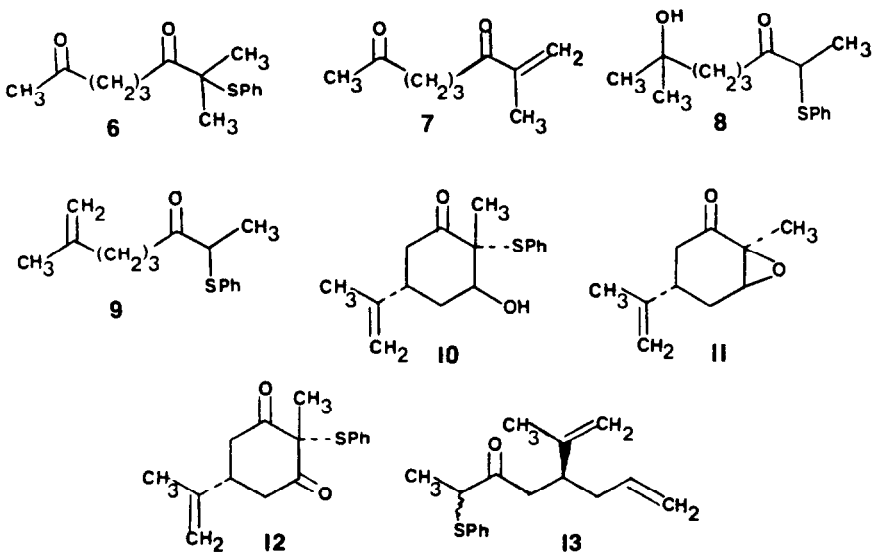
We became intrigued by the possibility that the reaction of cyclic β-hydroxy-α-sulfenyl ketones with strong bases might lead to open-chain keto (or aldehydo) metal enolates which could be trapped at the enolate moiety with electrophilic reagents and/or at the carbonyl moiety with nucleophilic reagents. Since α-sulfenylated ketones are highly versatile synthetic intermediates,[3d] it appeared that these reactions would be potentially useful for the synthesis of a variety of functionalized acyclic compounds. We have carried out reactions of this type on two cyclohexanone derivatives and wish to report our results.

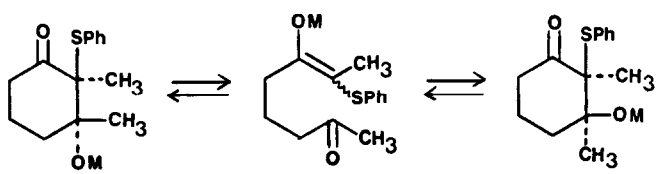
When the epoxide of 2,3-dimethylcyclohexanone 4[6] was treated with thiophenol and triethyl amine[4,7] in diethyl ether, the β-hydroxy-α-phenylsulfenyl ketone 5[8,9] was obtained in 78% yield. Dropwise addition of compound 5 to a stirred mixture of 1 equiv sodium hydride and methyl iodide in THF at 0°, stirring for 1 h at 0° and then at room temperature for 1 h led to the isolation of the 1,5-diketone 6[8] in 65% yield. Oxidation of the sulfide to the sulfoxide (1 equiv m-chloroperbenzoic acid, CH_2Cl_2, -78°) and thermal elimination (CCl_4, solid $CaCO_3$, reflux, 8 h) of phenylsulfenic acid[10] gave enedione 7[8] in 88% yield from 6. Slow, dropwise addition of a solution of 2 equiv of methyllithium in ether to a rapidly stirred solution of 5 in THF at -70° followed by quenching of the reaction mixture with aqueous ammonium chloride allowed the isolation of the δ-hydroxy ketone 8[8] in 72% yield. In another experiment ketol 5 was added to a solution of 2 equiv of methylene triphenylphosphorane in dimethyl sulfoxide (DMSO)[11] and the mixture was stirred for 8 h at 25° and then 1.5 h at 60°. After quenching of the reaction mixture with water, the usual workup and chromatography of the crude product on silica gel gave enone 9[8] in 60% yield.



The β-hydroxy-α-phenylsulfenyl ketone 10 was prepared in 68% yield after chromatography on silica gel by treatment of carvone epoxide 11[12] with thiophenol and triethylamine in acetonitrile at room temperature. The spectral properties of 10 supported its structural assignment, but further verification was obtained by oxidation of the hydroxyl group with chromic acid to produce the 1,3-diketo sulfide 12.[8]

Ketol 10 exhibited considerably different behavior from that of ketol 5 when treated with sodium hydride and methyl iodide or with methyllithium because in neither case was the desired product derived from trapping of the open-chain intermediate isolated. The products of these reactions were not fully characterized but the NMR spectrum of the mixture derived from the sodium hydride-methyl iodide reaction indicated that 10, its C-3 epimer,[13] and the corresponding O-methylated compounds were present. Also, NMR analysis indicated that reaction of 10 with methyllithium gave a mixture of 1,3-diols resulting from axial and equatorial addition to the carbonyl groups in 10 and its C-3 epimer. However, we were pleased to find that the ketol 10 reacted with methylene triphenylphosphorane in DMSO under the conditions described for 5 to give the acyclic enone 13[8] as a mixture of diastereomers in 51% yield after chromatography on silica gel.

Apparently, in the case of ketone 5 deprotonation of the hydroxyl group via the basic reagent produces the alkoxide 5A which undergoes a facile retroaldol reaction to produce the lithium or sodium keto enolate 5B which is in equilibrium with the starting alkoxide 5A and also its cis isomer 5C. The position of the equilibrium would be expected to be influenced by the metal cation and the solvent; but, under the various reaction conditions employed above, either the concentration of 5B is relatively high or it is much more reactive toward the electrophile reagent, methyl iodide, and the two nucleophilic reagents, methyllithium and methylene triphenylphosphorane, than are the cyclic species 5A and 5C.



5A 5B 5C

It appears that the steric and electronic effects of the β-methyl group in 5 provide significant stabilization of the open-chain species. The behavior of 10, where hydrogen is present at β-posiiton, suggests the concentration of the open-chain aldehydo enolate in equilibrium with the cyclic alkoxides is extremely low. Thus, only the Wittig reagent, which would be expected to be much more reactive with the aldehyde group of the open-chain species than with the carbonyl group of the cyclic alkoxides, produced an acyclic product.

Further studies on retroaldol reactions of ketols 5 and 10 followed by trapping of the open-chain intermediates under various conditions are in progress. Also, related systems with more powerful electron withdrawing groups than phenylsulfenyl groups at the α-position are being investigated.

References and Notes

1. This investigation was supported by Grant No. CA28355 awarded by the National Cancer Institute, DHHS.

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8. All new compounds gave mass spectral data consistent with the assigned structures. The ir and nmr data obtained were as follows: 5, ir(CCl_4) 3640 (free OH) and 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.18 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 1.66-2.66 (m, 6H), 3.38 (br s, 1H, OH), 7.18 (s, 5H, phenyl). 6, ir(CCl_4) 1720 (C=O) and 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.40 (s, 6H, gem dimethyl), 1.70-2.97 (br absorption, 6H), 2.10 (s, 3H, $COCH_3$), 7.22 (s, 5H, phenyl). 7, ir (CCl_4) 3080 (=CH_2) 1715 (unconjugated C=O), 1675 (conjugated C=O), 1645 cm^{-1} (conjugated C=C); nmr ($CDCl_3$) δ 1.87 (s, 3H, vinyl CH_3), 2.13 (s, 3H, $COCH_3$), 2.33-2.96 (m, 6H), 5.70 (br s, 1H), 5.90 (br s, 1H). 8, ir 3610 (free OH) and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.15 (s, 6H gem dimethyl), 1.37 (d, J=7 Hz, 3H, $CHCH_3$), 1.37-2.80 (m, 7H), 3.68 (q, J=7 Hz, 1H, $CHCH_3$), 7.15 (s, 5H, phenyl). 9, ir (CCl_4) 3070 (=CH_2), 1710 (C=O) and 1645 (C=C); nmr ($CDCl_3$) δ 1.38 (d, J=7 Hz, 3H, $CHCH_3$), 1.67 (s, 3H vinyl, CH_3), 1.66-2.17 (m, 4H), 2.57 (t, J=7 Hz, 2H), 3.72 (q, J=7 Hz, 1H, $CHCH_3$), 4.62 (br s, 2H, =CH_2), 7.22 (s, 5H, phenyl). 10, ir (CCl_4) 3625 (free OH, 3060 (=CH_2), 1710 (C=O), 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.18 (s, 3H, CH_3), 1.77 (s, 3H, vinyl CH_3), 1.83-3.50 (m, 6H), 4.10 (t, J=3 Hz, CHOH), 4.72 (s, 2H, =CH_2), 7.17 (s, 5H, phenyl). 12, ir (CCl_4) 1720 and 1690 (C=O); nmr ($CDCl_3$) δ 1.27 (s, 3H, CH_3), 1.77 (s, 3H vinyl CH_3), 2.03-3.53 (m, 5H), 4.77 (br s, 2H, =CH_2), 7.23 (s, 5H, phenyl). 13, ir (CCl_4) 1710 (C=O) and 1645 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.35 (two d's, J=7 Hz ea, 3H total, $CHCH_3$), 1.67 (s, 3H, vinyl CH_3), 1.80-3.00 (m, 5H), 3.67 (m, 1H), 4.68 (br s, 2H), 4.78 (br s, 1H), 5.03-5.97 (m, 1H), 7.27 (s, 5H, phenyl).

9. The trans stereochemistry of 6 was not rigorously established, but was assigned by analogy with the results of cleavages of other α,β-epoxy ketones with thiols in the presence of base, see ref. 4 and 7c.

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