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PHENYLSULFENYLATIONS OF LINEARLY CONJUGATED METAL DIENOLATES OF 1(9)-OCTALIN-2-ONE DERIVATIVES[1]

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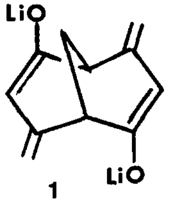
Summary —— The position of reaction of sodium and lithium dienolates of 1(9)-octalin-2-one derivatives with various phenylsulfenylating agents was found to be dependent upon the nature of the leaving group and the presence of an α methyl substituent.

The phenylsulfenylation of metal enolates of saturated ketones provides a general method of synthesis of α-phenylthio ketones.[2] However, a recent report on the reaction of the dilithium salt 1 of 4,8-dimethylbicyclo[3.3.1]nona-3,7-diene-2,6-dione with benzenesulfenyl chloride in tetrahydrofuran (THF) at low temperature appears to provide the only published example of the phenylsulfenylation of a linearly conjugated dienolate of α,β-unsaturated ketone.[3,4] It was observed that while 1 underwent O-silylation with trimethylsilyl chloride and α-alkylation with alkyl halides, γ-attack occurred exclusively when benzenesulfenyl chloride (and also benzeneselenenyl bromide and molecular bromine) was employed as the electrophilic reagent.[3] These results prompted us to report the results of phenylsulfenylations of linearly conjugated sodium or lithium dienolates 2a-c derived from 1,10-dimethyl-1(9)-octalin-2-one (3a) and 10-methyl-1(9)-octalin-2-one (3b) with various phenylsulfenylating



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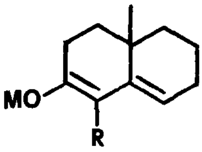
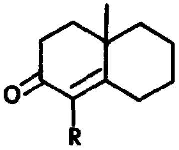
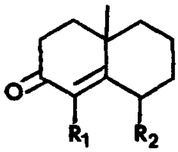


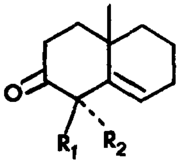
2 a. $R = CH_3$, $M = Na$
b. $R = CH_3$, $M = Li$
c. $R = H$, $M = Na$



3 a. $R = CH_3$
b. $R = H$
c. $R = SPh$



4 a. $R_1 = CH_3$, $R_2 = SPh$
b. $R_1 = SPh$, $R_2 = OH$



5 a. $R_1 = CH_3$, $R_2 = SPh$
b. $R_1 = SPh$, $R_2 = CH_3$
c. $R_1 = R_2 = SPh$

agents. It was found that the position of attack on the dienolate system is quite dependent on both the nature of the phenylsulfenylating agent and the presence of a methyl substituent at the α position.

The sodium dienolates **2a** and **2c** were prepared by reaction of the corresponding enones with sodium hydride in THF[5a] or 1,2-dimethoxyethane (DME).[5b] The lithium dienolate **2b** was prepared by cleavage of the corresponding dienol acetate[6a] (obtained from treatment of the enone **3a** with acetic anhydride and a catalytic amount of concentrated sulfuric acid) with 2 equiv of methyllithium in THF at 0°.[6b]

The results of the phenylsulfenylations of the octalone dienolates are presented in the Table. Crude reaction mixtures were subjected to column chromatography on silica gel to effect product isolation. The sodium dienolate **2c** was reacted with benzenesulfenyl chloride under the same conditions as those used in the reaction of **2a**. However, a complex mixture of products, none of which could be isolated in pure form, was produced.

TABLE. Reactions of Octalone Dienolates **2a-c** with Phenylsulfenylating Agents

Metal Dienolate	Sulfenylating Agent (1.1 equiv)	Conditions	Products (Yields)
2a	PhSSPh	DME, 25°, 1.5 h	**4a**[7,8] (68%)
	PhSSPh	THF, 25°, 2 h	**4a** (73%)
	PhSCl	THF, -78°, 30 min -78 → 25°, 30 min	**4a** (52%) + **5a**[7,9] (10%)
	$PhSSO_2Ph$	DME, reflux, 4 h	**5a** (58%) + **5b**[7,9] (5%)
2b	PhSSPh	THF, 25°, 21 h	recovered 3a only
	PhSCl	THF, -78°, 20 min -78° → 25°, 1 h	**4a** (15%) + **5a** (16%)
	$PhSSO_2Ph$	THF, 25°, 5 h	**5a** (69%) + **5b** (trace)
2c	PhSSPh	DME, 25°, 12 h	**3c** (51%)
	$PhSSO_2Ph$	DME, 25°, 1 h	**3c** (56%) + **5c**[7] (12%) + **4b**[7] (14%)

The possibility existed that the α-phenylthio-β,γ-unsaturated ketone **5a** might have been formed kinetically from reaction of **2a** with diphenyl disulfide and subsequently rearranged to the more stable γ-sulfenylation product **4a**. A light-induced 1,3-allylic rearrangement[10] or SN-2' reaction with thiophenoxide anion, which is produced in the reaction medium, seemed to provide possible pathways for such a process. However, it was found that **5a** did not rearrange to **4a** in significant yield under the conditions previously described for carrying out light-induced 1,3-shifts of allylic phenylthio groups.[10] Also, compound **5a** was found to undergo simple desulfenylation[11] rather than rearrangement to **4a** when treated with excess sodium thiophenoxide in DME for 16 h at 25°. The results indicate that the observed γ-sulfenylation of **2a** with diphenyl disulfide occurred in a kinetically controlled process.

In the reactions with diphenyl disulfide, there was a complete reversal in the position of sulfenylation in going from the unsaturated sodium dienolate **2c** to the methyl-substituted species **2a**. Thus **2c** yielded only the α-attack product **3c** while **2a** gave the γ-attack product **4a**. Diphenyl disulfide is not a highly reactive sulfenylating agent,[11] but as in the case of alkylating agents,[3,9b,c,12] it apparently attacks the α position of the dienolate system preferentially when it is unsubstituted. Possibly the presence of a methyl group significantly reduces the rate of attack at the α position as well as the overall reactivity of the dienolate. If the sulfenylation reaction is highly endothermic, the transition state may have sufficient product character that the thermodynamically more stable conjugated enone **4a**, rather than the deconjugated isomers **5a** or **5b**, is formed directly.

The involvement of a late transition state probably does not account for the fact that a significant quantity of the γ-sulfenylation product **4a** was formed when dienolates **2a** and **2b** were reacted with benzenesulfenyl chloride. This reagent is highly electrophilic[13] and should react very exothermically with dienolates of the type **2**. It seems possible that a pathway involving initial O-sulfenylation followed by attack of the sulfenylating agent on the dienol intermediate competes with direct sulfenylation at the α (or γ) position. Steroidal dienol ethers and acetates are known to undergo reaction at the γ position with highly electrophilic reagents.[14] Also the trimethylsilyl dienol ether derived from cyclocitral reacts with methyl methanesulfonate predominately at the γ position.[4c] The sodium dienolate **2a** should exist more in the form of a solvent-separated ion pair and thus be more prone to O-sulfenylation than the lithium dienolate **2b**. Perhaps this accounts for the fact that a higher γ/α-sulfenylation product ratio was observed for **2a** than **2b**. We also suggest that the γ-substitution products obtained from reaction of the dilithium salt **1** with phenylsulfenyl chloride and other reactive electrophilic reagents possibly are produced by a pathway similar to that proposed for the formation of **4a**.

Phenyl benzenethiosulfonate, which is of intermediate reactivity between diphenyl disulfide and benzenesulfenyl chloride, like reactive alkylating agents,[3,9b,c,12] gave mainly α-attack products with the three dienolates studied. Thus mixtures containing mainly **5a** (bottomside attack at C-1) and some **5b** (topside attack at C-1) were obtained from dienolates **2a** and **2b**. The dienolate **2c** gave the enone **3c** (C-1 sulfenylation followed by reconjugation of the double bond) as the major product along with the α,α-bissulfenylated ketone **5c** and the α-phenylthio-γ-hydroxyenone **4b** as minor products. Deprotonation at C-1 of the α-phenylthio-β,γ-unsaturated ketone formed initially from **2c** followed by α-sulfenylation of the dienolate intermediate readily accounts for the formation of **5c**, but the production of **4b** is more difficult to explain. Among other possibilities, we suggest that **5c** may undergo loss of thiophenoxide anion to form an allylic cation followed by attack of water at C-8 (γ to the carbonyl function) during work-up.

REFERENCES AND NOTES

1. This investigation was supported in part by Public Health Service Grant No. CA 12193 from the National Cander Institute.
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4. a. Reactions of conjugated dienolates derived from the α,β-unsaturated esters, methyl 3-methyl-2-butenoate and ethyl farnesoate (ref. 4b), and from the α,β-unsaturated aldehyde, cyclocitral (ref. 4c), with methyl methanethiosulfonate have been reported to occur at the α position; b. P. R. Ortiz de Montellano and C. K. Hsu, *Tetrahedron Lett.*, 4215 (1976); c. D. A. Engler, *Diss. Abst. B*, 38, 1205 (1977).
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7. Correct elemental analysis and/or exact mass data have been obtained for all new compounds. The ir and nmr absorptions were in agreement with the structural assignments.
8. The 8α-phenylthio enone epimer of **4a** was not isolated. However, examination of the nmr spectrum of the sulfenylation reaction mixture obtained under non-acidic work-up conditions, indicated that it was formed in significant yield but was isomerized to the more stable 8β compound (**4a**) during acidic work-up.
9. a. The stereochemistry of the methyl and phenylthio groups at C-1 in **5a** and **5b** was assigned on the basis of the finding that reaction of the conjugate sodium dienolate of the α-phenylthio-α,β-unsaturated ketone **3c** with methyl iodide in THF gave almost exclusively ketone **5b**. It has been generally observed (ref. 9b,c) that alkylating agents undergo mainly bottomside attack at the 1-position of conjugate dienolates of 10-methyl-1-(9)-octalin-2-one derivatives in aprotic solvents; b. Y. Nakadaira, J. Hayashi, H. Sato, and K. Nakanishi, *J. Chem. Soc., Chem. Commun.*, 282 (1972); c. F. H. Bottom and F. J. McQuillin, *Tetrahedron Lett.*, 1975 (1967).
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