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STEREOSELECTIVE CONVERSION OF LITHIATED BENZYLIC OR ALLYLIC 3-METHYL-1(Z),3-BUTADIENYL SULFIDES INTO CIS-DISUBSTITUTED CYCLOPROPANE COMPOUNDS

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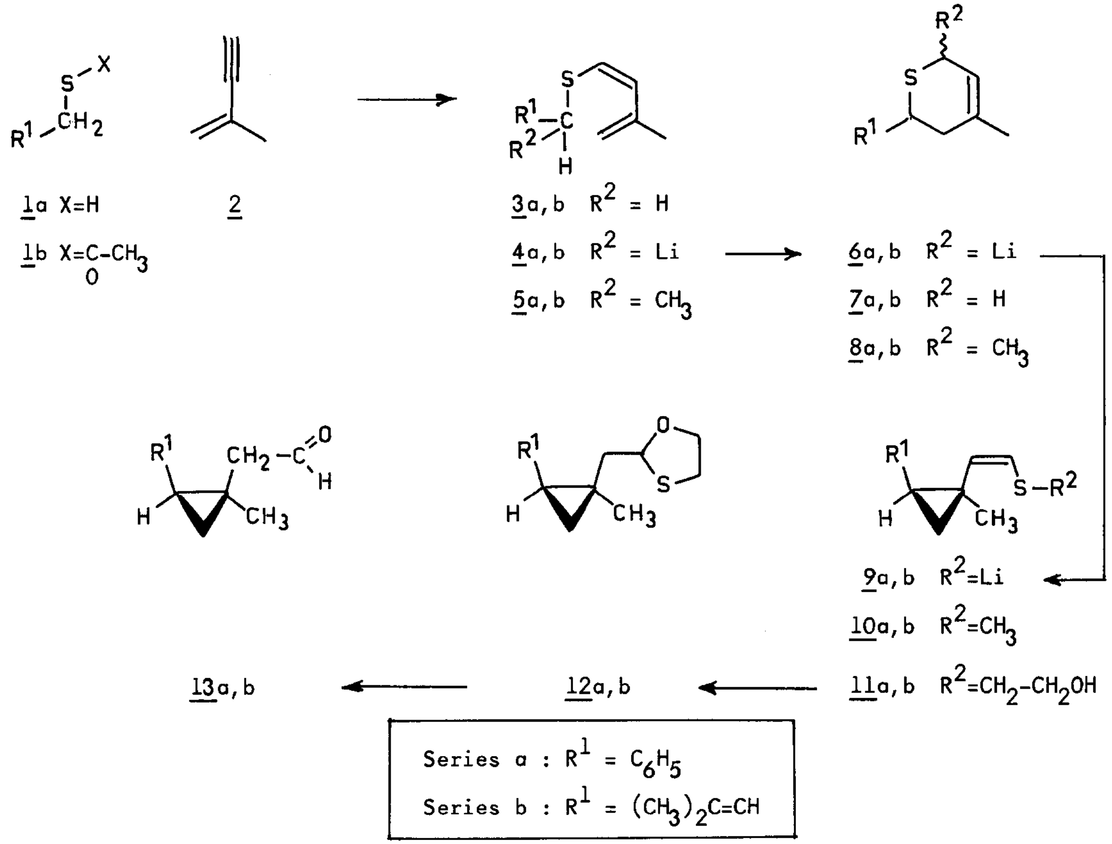
Summary

The lithio-thiacyclohexenes 6 are intermediates in the title conversion 4 → 9.

In the course of our study of the nucleophilic trans-addition of thiols to 1-alkyn-3-ols [1], we have shown that various 3-methyl-1(Z),3-butadienyl sulfides 3 are available through addition of thiols to 2-methyl-1-buten-3-yne in basic medium [2]. Thus the sulfide 3a was obtained after reaction in dimethyl sulfoxide solution in the presence of 0.2 equiv. of potassium hydroxide powder at room temperature, in 75 % yield. Similarly, the thioacetate 1b affords the (Z)-sulfide 3b (62%) in the presence of 1.2 equiv. of sodium hydroxide.

Formation of a C-C bond between the methylene carbon adjacent to sulfur and the terminal carbon of the isoprenoid chain looked attractive due to the (Z) structure of compounds 3, the synthetic goal being the di-substituted thiacyclohexene 8 with R^1,R^2 = regular terpenoid chains. Thus we first examined the properties of the lithio derivatives 4, expecting that these derivatives would give an intramolecular 1,4-addition to afford the cyclic carbanion 6 [3].

Addition of 1.1 equiv. of n-butyllithium (for 3a) or sec-butyllithium (for 3b) to a cooled solution (-78°) of the 1.3-dienes 3 in tetrahydrofuran resulted in rapid metalation (30 min) [4]. Subsequent reaction at - 78° with methyl iodide afforded the compounds (5a,b). Quenching of the lithio derivatives (4a,b) with diverse electrophiles was carried out under various conditions and the results are summarized in the table. At - 47°, the compound 4b is stable, but 4a is smoothly converted into the cyclic lithio derivative 6a. After stirring at - 30°, the lithio species did not give unique products when quenched with methyl iodide. The addition of one equiv. of hexamethylphosphoramide (HMPA) to the solutions of lithio derivatives (4a,b) gave more rewarding results. Treatment with methyl iodide smoothly yielded the cyclopropane compounds (10a,b) charac-



terized by the (Z) structure of the vinyl thioether group [5] and by the cis position of the two unsaturated side chains [6].

Mild conditions for converting the lithium ene-thiolates 9 into the corresponding aldehydes 13 without destroying the fragile divinyl cyclopropane system were now sought. Quenching of the ene-thiolates 9 with ethylene oxide afforded the β-hydroxyethyl vinyl sulfides (11a,b) which were treated in chloroform with 0.1 equiv. of methanesulfonic acid at 0° during 10 min; the oxathiolannes (12a,b) were obtained with overall yields of 45 % and 42 % from (3a,b) [8]. Final hydrolysis with methyl iodide in wet acetonitrile or with chloramine T in wet methanol [9] gave the aldehydes 13a (75 %) and 13b (51 %) [10].

Three features of this study are particularly noteworthy: (i) the conversion 4a → 6a is a new case of the rare electrocyclisation reaction which was previously observed for lithiated C_{10} isoprenoid sulfones [11]; (ii) the overall transformation 3 → 12 represents a new synthesis of cyclopropane compounds; (iii) the rearrangement of the intermediate lithio thiacyclohexenes 6 → 9 is highly stereoselective. The present state of our work does not allow us to propose a mechanism for this rearrangement. However it is possible that the favoured conformation of the carbanions 6 has the side chain R^1 oriented quasi equatorially for steric reasons, as it was already discussed for the rearrangement of lithiated nerol oxide [10] and this would account for the stereoselectivity observed.

Table

Substrate	Conditions [i]	Yield % [ii]	Products				
			5	7	8 (trans:cis)	10	11
3a	Quenching at -78° with CH_3I	88	100	-	-	-	-
3b	idem	80	100	-	-	-	-
3a	Warming to -47° then 2 h at -47°; quenching with CH_3I	75	-	-	100 (72/28)	-	-
3b	idem	(93)	100	-	-	-	-
	Warming to -30° then 2 h at -30°; quenching with						
3a	H_2O	50[iii]	-	100	-	-	-
3a	CH_3I	(92)	-	-	41 (71/29)	59	-
3b	CH_3I	(95)	25	-	5	70	-
	1 equiv HMPA added, warming to -30° then 2 h at -30° and quenching with						
3a	CH_3I	70	-	-	-	100	-
3b	CH_3I	72	-	-	-	100 [iv]	-
3a	ethylene oxide	(85)	-	-	-	-	100
3b	ethylene oxide	(71)	-	-	-	-	100

i In all cases, 1.1 equiv. of n.BuLi (for 3a) or of sec.BuLi (for 3b) was added to a cooled (-78°) solution of the 1,3-diene 3 in THF and the mixture stirred at that temperature for 30 min.

ii The numbers in brackets are the yields of crude products.

iii The lithium thiolate 9a is eliminated by washing the organic phase with water during the work up.

iv ca 4 % of the trans isomer can be detected in the ^{1}H-N.M.R. spectrum.

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3. It was already reported that the 1,4-addition of simple R-Li to 1,3-butadienyl sulfides is possible: R.H. Everhardus, R. Grüfing, L. Brandsma, Recl. Trav. Chim. Pays Bas, 97, 69 (1978).
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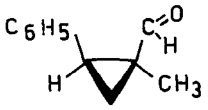
5. Lithio carbanions derived from 5,5-disubstituted 4-thiacyclohexenes have been shown to rearrange into cyclopropane compounds: J.F. Biellmann, J.B. Ducep, J.J. Vicens, Tetrahedron, 32, 1801 (1976).
6. The cis structure of the compound 10a was proved by the ^{1}H-N.M.R. spectrum and by ozonolysis to yield the corresponding cis-aldehyde 14, which was found identical (^{1}H-N.M.R. and 2,4-dinitrophenylhydrazone) with an authentic sample. The latter was obtained by the following route: the reduction of benzaldehyde by zinc in presence of boron trifluoride [7] and 1-acetoxy-2-methyl-2-propene furnished a mixture of the two cis and trans acetates 15. Hydrolysis and oxidation with PCC provided the aldehydes which were separated into cis and trans compounds.



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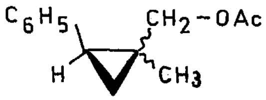

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