The Lithium Diisopropylamide-induced Fragmentation of 1,3-Dithiolane Derivatives of Several Ketones Having α-Hydrogen

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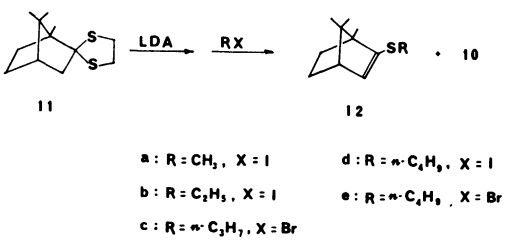
Synopsis. The reaction of 1,3-dithiolane derivatives of ketones having α-hydrogen with lithium diisopropylamide results in fragmentation to the corresponding thioketone followed by further conversion in a few steps to the other intermediate species which, on trapping with alkyl halide, leads to a vinylic sulfide and/or a sulfide bearing a secondary alkyl group.

It has been known for a long time that 1,3-dithiolane derivatives of aldehydes are easily deprotonated at the 2-positions of the rings by strong base and the generated anions undergo facile elimination to form ethylene.[1,2] Recently, Wilson and his co-workers[3] described that the treatment of 1,3-dithiolane derivatives of saturated ketones with an excess of butyllithium in ether leads to fragmentation to the corresponding thioketones, which afforded methyl sulfides by quenching the reaction mixture with methyl iodide or underwent a subsequent reduction with butyllithium to secondary thiols. They also comment that the reaction proceeds by a mechanism involving deprotonation at the 4-position of the ring as the first step. This report prompted us to publish the results of our independent studies in which the products obtained are somewhat different from those described by the above-quoted authors. Thus, we have found that the metalation of 1,3-dithiolane derivatives of several ketones having α-hydrogen with the less nucleophilic lithium diisopropylamide (LDA) in tetrahydrofuran results in fragmentation to the corresponding thiocarbonyl compounds followed by further conversion in a few steps to the other intermediate species. These, on trapping with alkyl halide, lead to vinylic sulfides and/or sulfides bearing a secondary alky group depending on choice of the starting 1,3-dithiolane derivatives. For example, when 2-methyl-2-phenyl-1,3-dithiolane (**1a**) was treated with an excess of LDA in tetrahydrofuran solution, followed by addition of an alkyl halide, we obtained the corresponding α-(alkylthio)styrene (**6a**) in excellent yield together with alkyl vinyl sulfide (**10**). The formation of the intermediate thioacetophenone (**3a**) and ethylenethiolate anion (**4**) is certain from the analogy to the reaction mode proposed by Wilson and his co-workers.[3] Presumably, **3a** is further converted to α-styrenethiolate anion (**5a**) *via* α-proton abstraction by a second LDA molecule. On quenching with alkyl halide, this leads to **6a**.

When 2-ethyl-2-phenyl-1,3-dithiolane (**1b**) was submitted to a similar fragmentation-alkylation sequence, two products, α-alkylthio-β-methylstyrene (**6b**) and 1-alkylthio-1-phenylpropane (**9b**), were isolated. Supposedly, the mechanism of the conversion of **3b** into **9b** involves three steps. The first step is a one-electron transfer between **3b** and LDA to afford a radical anion species (**7b**). The second step is the charge neutralization by alkyl halide to generate the radical species (**8b**); the last stage is the abstraction of a hydrogen radical, in which tetrahydrofuran may be serving as a donor, eventually providing **9b**. There is no direct evidence for the intermediary presence of **7b** and **8b**. However, the feasibility of the one-electron transfer is supported by analogy to the mode of reaction of thioketones, such as thiobenzophenone and di-*t*-butyl thioketone, with organometallics proposed by Ohno and his co-workers.[4] When 2-phenyl-2-propyl-1,3-dithiolane (**1c**) was cleaved under the same conditions and further quenched with methyl iodide, two products, α-methylthio-β-ethylstyrene (**6c**) and 1-methylthio-1-phenylbutane (**9c**) were also isolated, suggesting that the intermediate propyl phenyl thioketone (**3c**) behaves similarly to **3b**. The use of 2-isopropyl-2-phenyl- (**1d**) or 2-benzyl-2-phenyl-1,3-dithiolanes (**1e**) as the starting substrate and methyl iodide as the trapping agent in this reaction resulted in the exclusive formation of **9d** and **9e**, respectively. This means that in the initially formed isopropyl phenyl thioketone (**3d**) and benzyl phenyl thioketone (**3e**) a steric hindrance at their α-position may be preventing formation of the substituted ethylenethiolate anions (**5d** and **5e**). Thus, an obvious difference in behavior among the 1,3-dithiolane derivatives (**1**) submitted to this fragmentation-alkylation sequence has been noted. These experiments are summarized in Table 1, along with the ^{1}H-NMR spectroscopic data of the products.

Several 2-alkylthio-2-bornenes (**12**) have also been made in 97—99% yields from 1,3-dithiolane derivative



a: R = CH$_3$, X = I
b: R = C$_2$H$_5$, X = I
c: R = n-C$_3$H$_7$, X = Br
d: R = n-C$_4$H$_9$, X = I
e: R = n-C$_4$H$_9$, X = Br

TABLE 1. THE CONVERSION OF 2-ALKYL-2-PHENYL-1, 3-DITHIOLANES (1) INTO THE COMPOUNDS 6 AND/OR THE COMPOUNDS 9

Starting substrate	RX	Product[a]	Yield/%[b]	^{1}H-NMR (δ, in CCl_4)
1a	CH_3I	6a (R″=CH_3)	96	2.20 (s, 3H), 4.87 (s, 1H), 5.32 (s, 1H), 7.02—7.52 (m, 5H)
1a	C_2H_5I	6a (R″=C_2H_5)	97	1.21 (t, 3H, J=7 Hz), 2.62 (q, 2H, J=7 Hz), 5.09 (s, 1H), 5.37 (s, 1H), 7.03—7.60 (m, 5H)
1a	n-C_4H_9I	6a (R″=n-C_4H_9)	99	0.67—1.12 (m, 3H), 1.12—1.82 (m, 4H), 2.61 (t, 2H, J=7 Hz), 5.09 (s, 1H), 5.35 (s, 1H), 7.03—7.57 (m, 5H)
1a	n-C_4H_9Br	6a (R″=n-C_4H_9)	97	
1a	$C_6H_5CH_2Br$	6a (R″=$C_6H_5CH_2$)	98	3.74 (s, 2H), 5.12 (s, 1H), 5.34 (s, 1H), 6.68—7.60 (m, 10H)
1b	CH_3I	6b (R″=CH_3)[c]	36	1.89 (s, 3H), 1.92 (d, 3H, J=7 Hz), 5.81 (q, 1H, J=7 Hz), 7.00—7.47 (m, 5H)
		9b (R″=CH_3)	39	0.88 (t, 3H, J=7 Hz), 1.72 (s, 3H), 1.83 (m, 2H), 3.43 (t, 1H, J=7 Hz), 6.99—7.30 (m, 5H)
1b	C_2H_5I	6b (R″=C_2H_5)[c]	42	1.03 (t, 3H, J=7 Hz), 1.81 (d, 3H, J=7 Hz), 2.20 (q, 2H, J=7 Hz), 5.83 (q, 1H, J=7 Hz), 6.93—7.40 (m, 5H)
		9b (R″=C_2H_5)	44	0.87 (t, 3H, J=7 Hz), 1.08 (t, 3H, J=7 Hz), 1.40—2.15 (m, 2H), 2.16 (q, 2H, J=7 Hz), 3.57 (t, 1H, J=7 Hz), 7.00—7.40 (m, 5H)
1c	CH_3I	6c (R″=CH_3)[c]	33	1.07 (t, 3H, J=7 Hz), 1.90 (s, 3H), 2.14—2.75 (m, 2H), 5.81 (t, 1H, J=7 Hz), 7.07—7.50 (m, 5H)
		9c (R″=CH_3)	50	0.95 (t, 3H, J=7 Hz), 1.13—2.08 (m, 4H), 1.80 (s, 3H), 3.61 (t, 1H, J=7 Hz), 7.07—7.40 (m, 5H)
1d	CH_3I	9d (R″=CH_3)	58	0.89 (d, 3H, J=7 Hz), 1.05 (d, 3H, J=7 Hz), 1.09 (s, 3H), 1.65—2.50 (m, 1H), 3.29 (d, 1H, J=7 Hz), 6.93—7.25 (m, 5H)
1d	$C_6H_5CH_2Br$	9d (R″=$C_6H_5CH_2$)	55	0.72 (d, 3H, J=6 Hz), 0.98 (d, 3H, J=6 Hz), 1.65—2.28 (m, 1H), 3.21 (d, 2H, J=6 Hz), 3.23 (d, 1H, J=6 Hz), 6.82—7.48 (m, 10H)
1e	CH_3I	9e (R″=CH_3)	77	1.75 (s, 3H), 2.95 (d, 1H, J=2 Hz), 3.07 (s, 1H), 3.75 (t, 1H, J=6 Hz), 6.68—7.50 (m, 10H)

a) The formation of alkyl vinyl sulfide **10** was observed in all the work-up procedures, but the isolation of **10** was not followed up, because it has minor importance. All products were characterized by IR, mass spectrum, elemental analysis in addition to ^{1}H-NMR and further comparison of the properties to literature data where possible. b) Yield of isolated product is based on **1**. c) The products **6b** and **6c** seem to be *E*-isomers.

TABLE 2. THE CONVERSION OF 1, 3-DITHIOALNE DERIVATIVE (11) OF (+)-CAMPHOR INTO 2-ALKYLTHIO-2-BORNENES (12)

RX	Product[a]	Yield/%[b]	^{1}H-NMR (δ, in CCl_4)
CH_3I	12a	99	0.61—2.40 (m, 14H), 2.10 (s, 3H), 5.30 (d, 1H, J=4 Hz)
C_2H_5I	12b	97	0.65—2.39 (m, 14H), 1.26 (t, 3H, J=7 Hz), 2.60 (q, 2H, J=7 Hz), 5.39 (d, 1H, J=4 Hz)
n-C_3H_7Br	12c	98	0.70—2.40 (m, 19H), 2.59 (t, 2H, J=7 Hz), 5.39 (d, 1H, J=4 Hz)
n-C_4H_9I	12d	99	0.65—2.40 (m, 21H), 2.61 (t, 2H, J=7 Hz), 5.37 (d, 1H, J=4 Hz)
n-C_4H_9Br	12e[c]	98	

a) All products were characterized in the same manner as described in Table 1. b) Yield of isolated product based on **11**. c) The product **12e** is identical to **12d**.

(**11**) of (+)-camphor by the present procedure. Presumably, the intermediate (+)-thiocamphor[5] in the reaction could be easily deprotonated by LDA at the 3-position. The yields as well as the ^{1}H-NMR spectroscopic data of the produced **12** are shown in Table 2.

Experimental

Reaction Summarized in Tables 1 and 2. General Procedure: A solution of diisopropylamine (0.35 g, 3.5 mmol) in tetrahydrofuran (7 ml) was cooled to −78 °C under nitrogen, treated with 1.56 molar solution (2.12 ml, 3.3 mmol) of butyllithium in hexane, and then stirred at the same temperature for 30 min and further at −15 °C for 10 min. The solution of LDA thus prepared was cooled to −78 °C and a solution of either the 2-alkyl-2-phenyl-1,3-dithiolanes (**1**) or the 1,3-dithiolane derivative (**11**) of (+)-camphor (1.3 mmol) in tetrahydrofuran (4 ml) was added. After an additional 1 h at −15 °C, the solution was cooled again to −78 °C, and an alkyl halide (3.3 mmol) was added with stirring. The stirring was continued for 1 h at −5—−10 °C and for a further 24 h at room temperature. The mixture was then quenched with 100 ml of water and 20 ml of saturated aqueous solution of NH_4Cl, and extracted with ether (3×60 ml). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow residue, which was subjected to column chromatography.

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