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ON THE MECHANISM OF THE ADDITION OF DITHIANYLIDENE ANIONS TO CYCLIC α,β-UNSATURATED KETONES

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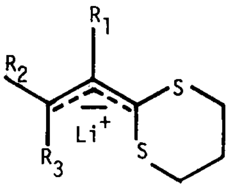
Abstract: The high diastereoselectivity in the 1,4-addition of dithianylidene anions to α,β-unsaturated ketones is demonstrated to proceed through an alkoxy-Cope rearrangement.

We have previously reported that dithianylidene anions undergo 1,4-addition to cyclic α,β-unsaturated ketones in aprotic media.[1a] In the particular case of lithium anion 1a (in THF), when treated with 2-methylcyclopentenone, the principal stereoisomer was shown to be the 1,4-γ adduct 2a.[1b] We have examined this reaction in detail using the dithianylidene anion 1b and cyclopentenone to ascertain the factors controlling the high diastereoselection in the 1,4-γ addition process.

Crotonaldehyde (>95% E-isomer) was converted into its dithiane ($HS(CH_2)_3SH$, $BF_3 \cdot Et_2O$, $HOAc/CHCl_3$, -30° to 25°C, 4h, 85%), providing an 88/12 (E/Z) mixture of isomers. Metalation (0.88 equiv. n-BuLi-hexane, THF, 0°C, 2h) of the mixture, in an attempt to selectively deprotonate the E-isomer, provided a 94/6 (E/Z) mixture of anions as determined by α-deuteration (D_2O) of the anions and nmr integration of the residual dithiane methine protons vs. the vinylic protons.

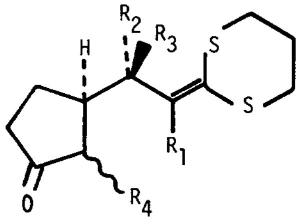
Addition of 1 equiv. (based upon anion) of cyclopentenone at -78°C to the anions afforded three characterizable addition products [1,2-α(3),1,4-γ(2b,c),1,4-α(4)][2] and protonated dithianes (Table). The ratio of 1,2-α:1,4-γ:1,4-α products was shown (VPC) in an independent experiment conducted at -78°C, to be invariant with time (15 sec., 1h, 2h, 3h), demonstrating the kinetic nature of the mixture. When the reaction mixture was allowed to warm from -78°C to 25°C, the ratio of protonated dithianes (from deprotonation



1a, $R_1=R_2=CH_3$; $R_3=H$

1b, $R_1=R_3=H$; $R_2=CH_3$

1c, $R_1=R_2=H$; $R_3=CH_3$

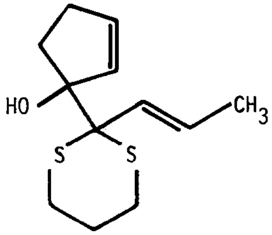


2a, $R_1=R_3=R_4=CH_3$; $R_2=H$

2b, $R_1=R_2=R_4=H$; $R_3=CH_3$

2c, $R_1=R_3=R_4=H$; $R_2=CH_3$

2d, $R_1=H$; $R_2,R_3=H,CH_3$; $R_4=CH_3$



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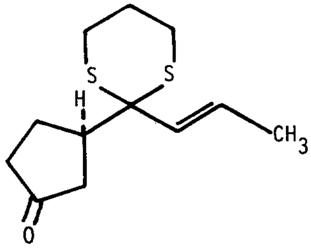

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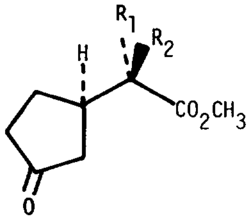

5a, $R_1=H$; $R_2=CH_3$

5b, $R_1=CH_3$; $R_2=H$

Table:

Entry	Temp	Time	Standard[c]	Dithiane		1,2-α	1,4-γ	1,4-α
				E	Z			
1	-78°C	1h[a]	100	65	17	80	21[d]	5
2	0°C	1h	100	58	15	71	27	4
3	0°C	2h[b]	100	47	12	63	37[e]	4
4	25°C	12h	100	60	17	0	89[f]	4

a) then -78°C to 0°C over 0.5h, b) elapsed time at 0°C, c) Ph_2S, d) 2b/2c (70/30), e) 2b/2c, (80/20), f) 2b/2c (90/10).

of cyclopentenone) to adducts remained essentially constant as did the ratio of dithianes and adducts to the internal standard (Ph_2S). The warming process transformed the 1,2-adduct into the 1,4-γ isomer. A dissociation-recombination mechanism for the interconversion would require a repartitioning of the dithiane anion and cyclopentenone between deprotonation and addition products, thereby increasing the amount of the dithianes at the expense of the adducts. When one equiv. of HMPA was added to the anion 1b,c in THF prior to the addition of cyclopentenone at -78°C, the 1,4-α adduct was the principal product of kinetic addition.[1] Treatment of the reaction mixture of entry 1 (i.e., the resultant anions) with 1 equivalent of HMPA, failed to generate additional 1,4-α adduct upon warming. If dissociation had occurred in the presence of HMPA, an increase in the amount of 1,4-α adducts would have been anticipated. Only the 1,2-α to 1,4-γ isomerization occurred. In another experiment, addition of the 2-methylcyclopentenone to the reaction mixture prior to the warming process failed to generate any crossover 1,4-γ adduct 2d. These three experiments support an intramolecular alkoxy-Cope rearrangement as the operative mechanism.[3] Since there is a strong preference for a chairlike transition state for such rearrangements,[4] the warming process should increase the amount of the 1,4-γ adduct 2b derived from the chairlike transition state beyond the amount present in the kinetic mixture. A sample of the kinetic (entry 1) 1,4-γ isomers was collected (VPC) and was shown to be a 70/30 mixture of 2b/2c (270 MHz nmr, integration of the vinylic hydrogen). Based upon the intercedence of a chairlike rearrangement, the ratio of 2b/2c at 0°C (entry 3) was 80/20 (calculated 83/17); at 25°C, 90/10 (calculated 94/6).[5]

The structure of 2b was confirmed in the following way. Ozonolysis (O_3, CH_2Cl_2/CH_3OH, -78°C) of a 90/10 mixture of 2b/2c followed by treatment of the intermediate methoxy hydroperoxide with Ac_2O/Et_3N gave rise to a 90/10 mixture of ketoesters 5. The major component was identical (270 MHz nmr) with the methyl ester 5a formed by the addition of 1-diethylamino-1-propyne[6] to cyclopentenone followed by acid hydrolysis and subsequent diazomethane esterification.[7]

Haynes has noted that the lithium anions of allyl alkyl (and aryl) sulfides give principally 1,2-α and 1,2-γ addition products with cyclopentenone at -78°C in THF.[8] It is not unreasonable to assume that these adducts would undergo rearrangement to 1,4-adducts at ambient temperature in light of the present results and the observations of Evans concerning the alkoxy-Cope rearrangement of substrates bearing thiophenyl substituents.[9]

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1. a) F.E. Ziegler ad C.C. Tam, Tetrahedron Letters, 4717 (1979); b) F.E. Ziegler and J.-M. Fang, J. Org. Chem., 46, 825 (1981). For a full account of this work, see F.E. Ziegler, J.-M. Fang, and C.C. Tam, J. Am. Chem. Soc., in press.
2. 2b: nmr (500 MHz) δ 1.02 (3H, d, J = 6.6 Hz, CH_3), 5.76 (1H, d, J = 9.9 Hz, vinyl H); ms (70eV, m/e (rel. intensity)) 242 (M^+, 10), 159 ($C_7H_{11}S_2^+$, 100), 2c: nmr (500 MHz) δ 1.03 (3H, d, J = 6.6 Hz, CH_3), 5.74 (1H, d, 9.9 Hz, vinyl H); ms (70eV, m/e (rel. intensity)) 242 (M^+, 36), 159 ($C_7H_{11}S_2^+$, 100), 3: nmr (500 MHz) δ 1.86 (2H, d, J = 6.6, 1.5 Hz, CH_3), 5.58 (1H, d, J = 15.0 Hz, E-olefin vinyl H), 5.85 (2H, m, Z-olefin vinyl H), 6.07 (1H, dq, J = 15.0, 7.0 Hz, E-olefin vinyl H), and 6.02 (2H, m, Z-olefin vinyl H); ms (70eV, m/e (rel. intensity)) 225 (M^+-17, 13), 224 (M^+-18, 100). 4: nmr (270 MHz) δ 1.82 (3H, dd, J = 6.7, 1.4 Hz, CH_3), 5.45 (1H, dq, J = 15.1, 1.6 Hz, vinyl H), and 5.96 (1H, dq, J = 15.1, 6.5 Hz, vinyl H); ms (70eV, m/e (rel. intensity)) 242 (M^+, 36), 159 ($C_7H_{11}S_2^+$, 100).
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4. D.A. Evans and J.V. Nelson, J. Am. Chem. Soc., 102, 774 (1980).
5. At 0°C, 2b/2c = 21(0.7)+(80-63)/21(0.3) = 5.03; at 25°C, 2b/2c = 21(0.7)+80/21(0.3) = 15.03.
6. We thank Professor Stork (Columbia) for a sample of the ynamine.
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