Conjugate Addition of Lithium Isopropyl Dithioisobutyrate to 4-Acetoxycyclopent-2-enone. Assignment of Stereochemistry in Flexible 5-Membered Rings

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Lithium isopropyl dithioisobutyrate is alkylated on the S atom by 4-bromocyclopent-2-enone but on the C atom by cyclopent-2-enone and 4-acetoxycyclopent-2-enone *via* conjugate addition; the stereochemistry of the 3,4-disubstituted cyclopentanone from the latter reaction is established by the determination of the long-range coupling constants, $^4J_{HH}$.

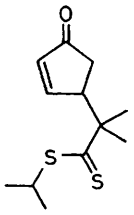
Metzner[1] recently reported that lithium methyl dithioacetate undergoes selective 1,4-*C*-addition to α-enones. In order to achieve optimum synthesis[2] of the target molecule (**1**), we have studied the addition of lithium isopropyl dithioisobutyrate (**2a**) to cyclopentenones substituted with leaving groups in the 4-position [see (**3b,c**)], the substituent serving to mask a double bond. Our investigation, underway when Metzner's communication appeared, has now been successfully completed and complements his study in several important ways. Not only is our substrate functionally more complex, our reactant is too, with methyl groups sterically shielding the α-carbon. This hindrance might be expected to favour *S*-alkylation, but it does not (*vide infra*). Since lithium dithioesters are *S*-alkylated by alkyl halides, it was of great interest to see how (**3b**), a substrate with both an activated halogen and an α-enone, would react.

The lithium thioenolate (**2a**) was prepared from isopropyl trimethylsilyl dimethylketen dithioacetal (**2b**)† in a manner analogous to the preparation of enolates from silyl enol ethers[3] (1 mol. equiv. MeLi, tetrahydrofuran,‡ 0 °C, 30 min) in order to have solutions free of di-isopropylamine [from lithium di-isopropylamide (LDA), which was used by Metzner[1] to deprotonate methyl dithioacetate]. The presence of such a base can cause the elimination of a β-keto Br or OAc substituent. The elimination of this substituent after conjugate addition would give the same overall result as its direct displacement. Compound (**2b**) was in turn prepared from chlorotrimethylsilane and (**2a**), generated from isopropyl dithioisobutyrate using LDA.[4]

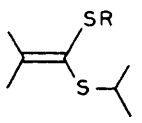
Treatment of cyclopent-2-enone (**3a**) with 1 mol. equiv. of (**2a**) at −50 °C for 30 min followed by an aqueous NH_4Cl work-up gave a quantitative yield of (**4a**) (from ^1H and ^{13}C n.m.r.), which was chromatographed on silica gel (10% ethyl acetate–hexane developer) to obtain a 70% yield of the purified product. Metzner[1] obtained a 78% isolated yield with lithium methyl dithioacetate, therefore the presence of the two α-methyl groups does not significantly modify the *C*- *vs.* *S*-reactivity of the dithioester towards (**3a**). Under the

† Satisfactory microanalytical or exact mass spectral data were obtained for these new compounds, which also exhibited consistent ^1H n.m.r., ^{13}C n.m.r., and i.r. data.

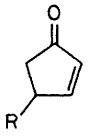
‡ The use of diethyl ether proved unsatisfactory, although it has been used with MeLi to unmask trimethylsilyl enol ethers, see ref. 3b, p. 2368.



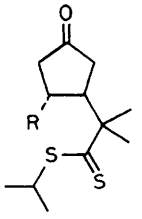
(1)



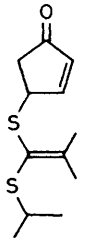
(2a) R = Li
(2b) R = SiMe$_3$



(3a) R = H
(3b) R = Br
(3c) R = OAc



(4a) R = H
(4b) R = Br
(4c) R = OAc



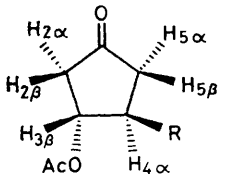
(5)

Table 1. ^{1}H N.m.r. data[a] for (**4c**).

X-H	*Y*-H	J_{xy}/Hz	δ_x/p.p.m.
2α[b]	2β	19.5	2.22
	3(β)	6.0	
	4(α)	0.5	
	5α	1.8	
	5β	0[c]	
2β	3(β)	8.0	2.79
	4(α)	0[c]	
	5α	0[c]	
	5β	1.6	
3(β)	4(α)	6.0	5.33
	5α	0[c]	
	5β	0.5	
4(α)	5α	8.5	3.22
	5β	9.5	
5α	5β	19.5	2.45
5β	—	—	2.18

[a] Obtained from spin simulations (Nicolet Technology NMCSIM Program) optimizing the fit to the observed spectrum. Couplings are absolute values, optimized to the nearest 0.2 Hz. [b] The numbering scheme is for a 3-acetoxy-4-alkylcyclopentan-1-one; α and β were assigned so that the 3-acetoxy-group has the α configuration in analogy with the usual way of picturing prostaglandins. [c] Substituting 0.1 Hz for 0 Hz perturbs the spectrum slightly, but the fit is still acceptable; 0.2 Hz gives a less acceptable fit.

same conditions, the bromoenone (**3b**)[5] gave no *C*-alkylated product, since the ^{13}C n.m.r. spectrum of the crude material contained no peaks in the region δ 220—250 p.p.m. characteristic of the thiocarbonyl group,[6] thus precluding the presence of (**4b**). The spectrum contained a number of peaks in the C=C region which was expected for *S*-alkylation products; and it was possible to isolate a small amount of (**5**),§ the product of direct displacement of the Br atom by an S atom. In contrast,



the acetate (**3c**)[5] gave only the *C*-alkylation product (**4c**)† when treated with (**2a**).

Chromatography of (**4c**) on alumina (10% ethyl acetate–hexane developer) resulted in complete elimination of acetic acid affording (**1**)† in 60% overall yield from (**3c**). Silica gel chromatography also converted (**4c**) into (**1**), but the elimination was not complete. Treatment of (**4c**) with di-isopropylamine (0.1 mol. equiv.) confirmed that this base does indeed catalyse the elimination to (**1**) ($t_{\frac{1}{2}}$ *ca.* 3.7 h at 27 °C). Compound (**4c**) also eliminates HOAc upon thermolysis at 100 °C ($t_{\frac{1}{2}}$ *ca.* 0.75 h).

The *trans*-stereochemistry of the substituents in (**4c**) was established by consideration of the four-bond coupling constants obtained from spin simulations of the 200 MHz ^{1}H n.m.r. spectrum (Table 1). The fact that $^3J_{2\alpha,3\beta} < {}^3J_{2\beta,3\beta}$ whereas $^3J_{4\alpha,5\beta} > {}^3J_{4\alpha,5\alpha}$ epitomizes the difficulty encountered when attempts are made to assign stereochemistry in flexible 5-membered rings in a manner analogous to that for 6-membered rings (*cf.* the Karplus equation).[7] Thus the value of $^3J_{3,4}$ (6.0 Hz) cannot be used to assign definitively the relative orientation of the substituents of (**4c**), since it is intermediate between the corresponding couplings in *cis*- ($^3J_{11,12}$ *ca.* 2 Hz) and *trans*- ($^3J_{11,12}$ *ca.* 9 Hz) prostaglandin E_1 derivatives.[8]

Small four-bond couplings (^4J *ca.* 2 Hz¶) have been observed in rigid or conformationally fixed systems with special geometries ('W' or 'sickle' paths),[9] and *syn*-1,3-couplings across a keto-group (*e.g.* $^4J_{2\alpha,5\alpha}$ and $^4J_{2\beta,5\beta}$) are also well-known.[7] Since a coupling constant observed in a system comprising a number of conformations is the weighted average of the coupling constants of the individual conformers, we reasoned that in flexible ring systems such as (**4c**), a small but measurable *syn*-1,3-coupling should be observed, as H atoms with this relationship are connected by an optimal path[9] in at least one conformation. The only exception to the generalization that $^4J_{syn} > {}^4J_{anti}$ in 5-membered rings** appears to be due to homoallylic coupling superseding 'W' coupling in systems where both are possible.[10] The observation that 3-H and 4-H have *syn*-1,3-couplings to H atoms adjacent to the keto-group (5β-H and 2α-H, respectively) which do not couple to each other proves that they have the opposite orientations and establishes the *trans*-stereochemistry of the substituents.

Four-bond couplings such as the ones discussed here are common in 5-membered [11] and other ring systems,[7,9] so that this method of assigning stereochemistry should be broadly applicable. It has the additional advantage that both stereoisomers are not needed for a definitive conclusion to be reached, as is usually the case when the '*syn*-upfield rule' is applied.[12] The availability of high-field n.m.r. spectrometers and spin simulation programs should make this method for determining stereochemistry in 5-membered rings as powerful as those based on the Karplus equation for 6-membered rings.

§ The crude product was unstable, turning brown upon storage in the freezer (−20 °C). Compound (**5**) was the only mobile product on t.l.c. (silica gel plates developed with 10% EtOAc–hexane). While ^{13}C n.m.r. indicated a 40% yield, only 10% could be isolated.

¶ Larger values of ^4J are observed in strained systems and in those where multiple coupling paths are present, see ref. 7.

** In six-membered rings, $^4J_{anti}$ is occasionally greater than $^4J_{syn}$ because a preferred conformation is adopted close to one of the 'non-W' maxima in the coupling function (ref. 9).

The discovery of a conjugate addition that tolerates leaving groups in the γ-position of the substrate is significant because organocuprates, the usual reagents for conjugate additions, are not compatible with such substituents.[13] Furthermore, the addition of lithium dithioesters to such substrates appears to be completely stereospecific.

Received, 4th January 1983; Com. 007

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