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Stereoselections in Cyclic ß-Ketoester Alkylations

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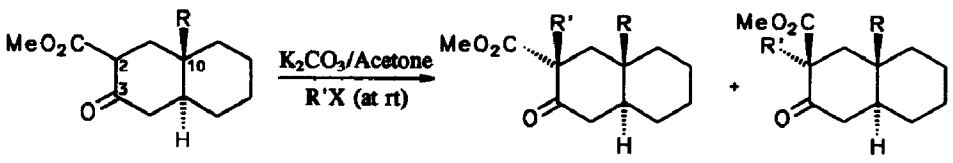
Abstract: A hyperconjugative influence may be an additional factor in *Z*-alkylation being promoted by a *syn*-axial ester in enolates formed from conformationally immobilised 6-cyclic ß-ketoesters.

The *syn*-axial ester in the extended enolate generated from a 10-ethoxycarbonyl-Δ^4-octal-3-one[1] has been shown to promote *Z*-alkylation (*syn* to C-10 ethoxycarbonyl) at C-4.[2] A polar effect was suggested[2ab] as the major influence of the ester group, but, despite attempts to strengthen its case,[2c] the suggestion appears not to have won wide acceptance for the reason that, compared with the change from *Z* to *E* (*syn* to C-10 H to *anti* to C-10 Me) seen on going from H to Me as the *syn*-axial substituent in a related instance (but under different conditions),[3] the reverse change, *E* to *Z*, on going from Me to ester appeared moderate[4] and an explanation based on the smaller steric demand of the ester group compared with a methyl[5] seemed sufficient.[6] However, though further studies have been recommended,[7] comparisons of changes in the stereochemical preferences of electrophilic reactions on enolates (e.g. alkylations) conducted under the same conditions (substrate, anion generation, nature of the counterion/alkylating agent, solvent, etc.) through a series of appropriately conformationally immobilised 6-cyclic oxo-systems, where the *syn*-axial substituent is, successively, H, CO_2R and Me, do not appear to have been reported.

For the reason that the formation of enolates, with the enolate part planar, may remain unfettered,[8] the 3-keto-2-esters,[9] **1** - **3**,[10] were chosen and two alkylating agents, methyl iodide and benzyl bromide, with a possible difference in steric demand, were employed. Potassium carbonate was the enolate-generating agent and acetone the medium. The alkylations could be presumed to be those of the free (or solubilised) enolate ions since acetone, a Class C solvent,[7] can solvate only the counterions (K^+). The major advantages of our conditions were that quantitative yields of epimeric mixtures of C-2 *Z*- and *E*-alkylated products (respectively, **4a** - **6b** and **7a** - **9b**) were realised and the formation of O-alkylated products was totally suppressed.[4] The *Z*/*E* alkylation ratios are presented as percentages in Table 1 overleaf.



1 - 3 **Z: 4a - 6b** ***E*: 7a - 9b**

1, 4 & 7: R = H; **2, 5 & 8**: R = Me; **3, 6 & 9**: R = CO_2Et
R' = Me (a-series); R' = Bz (b-series)

Table 1: Stereoselectivity in the Alkylation of Cyclic ß-Ketoesters **1** - **3**

Substrate	R	Alkylating agent	*Z*/*E* ratio(%)
1	H	CH_3I	69:31 (**4a**:**7a**)
1	H	ΦCH_2Br	21:79 (**4b**:**7b**)
2	CH_3	CH_3I	10:90 (**5a**:**8a**)
2	CH_3	ΦCH_2Br	02:98 (**5b**:**8b**)
3	CO_2Et	CH_3I	64:36 (**6a**:**9a**)
3	CO_2Et	ΦCH_2Br	17:83 (**6b**:**9b**)

Reactions continued until the ß-keto esters were entirely consumed (tlc; ~12 hr). Characterization data on the reactants **1** - **3** and their alkylated products **4a** - **9b** available from authors. *Z*/*E* ratios (±5%) based on integration of salient signals in 400 MHz ^{1}H NMR spectra of product mixtures from at least three reactions in each case.

Assignment of stereochemistry to the alkylated products is based on the following consistencies seen among ^{1}H and ^{13}C NMR spectral data (Table 2): A. the change in ^{1}H C-2 *Me* chemical shift on

Table 2: ^{1}H and ^{13}C Chemical Shifts of Stereochemical Significance in Products **4a** - **9b**[a]

	C-10 *Me*[b] (^{1}H)	C-2 *Me*[b] (^{1}H)	ΦCH_AH_B[c] (J_{AB};Δδ)	$CO_2CH_AH_BCH_3$[d] (J1,J2;Δδ)	C-2 *Me* (^{13}C)
4a	-	1.47	-	-	20.93
7a	-	1.27	-	-	21.53
4b	-	-	2.80 & 3.30 (13.6; 0.50)	-	-
7b	-	-	3.15 & 3.39 (14.2; 0.24)	-	-
5a[e]	0.85	1.35	-	-	-[f]
8a	0.93	1.27	-	-	23.15
5b[e]	0.82	-	2.84 & 3.35 (15.0; 0.51)	-	-[f]
8b	0.90	-	2.98 & 3.14 (13.2; 0.16)	-	-
6a	-	1.31	-	4.15 & 4.20 (11.0 & 7.0; 0.05)	20.95
9a	-	1.26	-	4.00 & 4.24 (11.1 & 7.3; 0.17)	23.15
6b	-	-	2.89 & 3.32 (13.2; 0.43)	3.98 & 4.16 (11.2 & 7.3; 0.09)	-
9b	-	-	2.92 & 3.10 (13.4; 0.18)	3.94 & 4.22 (12.1 & 8.0; 0.18)	-

[a] ^{1}H at 400 MHz; ^{13}C at 100 MHz; $CDCl_3$; δ ppm ex-TMS; [b] 3H, singlets; [c] 2H, AB-quartet; [d] 2H, AB-quartet of quartets; [e] Culled from spectra of mixtures, **5a** with **8a** and **5b** with **8b**; [f] ^{13}C spectra could not be recorded.

going from **4a** to **7a**, **5a** to **8a** or **6a** to **9a** is analogous to that on going from 2(ax)-methyl- to 2(eq),10-dimethyl-2-acetyldecal-3-one (δ ppm 1.40 to 1.22)[11]; B. $\Delta\delta_{AB}$ of the benzyl CH_AH_B AB-quartets in **4b**, **5b** and **6b** are larger than those in **7b**, **8b** and **9b**[12]; C. the AB-quartets of quartets due to the C-10 CO_2Et CH_AH_B in **9a** and **9b** show larger AB-anisochrony than in **6a** and **6b**[13]; D. the ^{13}C resonances of the C-2(ax) *Me*'s in **4a** and **6a** are upfield of those of the C-2(eq) *Me*'s in **7a** and **9a**[14]; E. ß-ketoester **2** and its methylated products **5a** & **8a** have been described[15] (reported[15] C-*Me* ^{1}H shifts: 0.82 & 1.37 in **5a** and 0.93 & 1.28 in **8a**).

The stereochemical preference of methylation changes from predominantly *Z* in **1** to very largely *E* in **2** and dramatically back to *Z* in **3** *to about the same extent* as with **1**. Both a reduced electrophilicity and a consequent possible enhanced steric demand due, at least in part, to decreased C-2—E^+ distance in the transition state[16] could be the reasons for the reversal of *Z/E* ratio in the benzylations. But the changes in stereochemical preference found with the methylations persist in the benzylations and factors responsible appear to operate in the same manner in the two alkylations.

Most interesting, however, is the close similarity the *Z/E* ratios in the ester-case **3** bear to those in the H-case **1**. A factor, be it polar, must be seen as operative, in addition to the lesser steric demand of CO_2Et as compared to Me, if one is to avoid being driven to the conclusion that the steric demand of CO_2Et is the same as that of H.[5] An alternative to the putative polar effect of a *syn*-axial ester group is available under the currently discussed hyperconjugative model.[17] If delocalisation from the σ-orbital of the C-1—H(ax) bond into the σ^*_E orbital of the incipient C-2—E^+ bond is better than that from the C-10—C-1 bond in accordance with the model, the *Z*-preference in the H-system **1** can be explained. While the *E*-preference in the case of the Me system **2** may result from the high steric demand of a methyl,[5] the inductive electron-release effect of that group may render the hyperconjugative ability of the C-10—C-1 bond better than that of the C-1—H(ax) bond and encourage *E*-attack. The situation could be reversed again, to one that favours *Z*-attack, when electron withdrawal by the ester function makes the C-1—H(ax) bond a better electron donor than the C-10—C-1 bond. If these propositions are supported by theory-based computations, a factor in addition to the polar effect, if any, of the ester group may be identified and the steep fall in *Z/E* ratios, attending the change H to Me, need not be due purely to the steric reason.

Our results bridge, partly atleast, the findings reported in refs. 2 and 3. The roles of solvent[18] and counterion[2c] in conditioning the stereoselectivity in ß-ketoesters **1** - **3** are currently under examination.

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