

ISOMERIC EXOCYCLIC AND ENDOCYCLIC DIENOLATES:

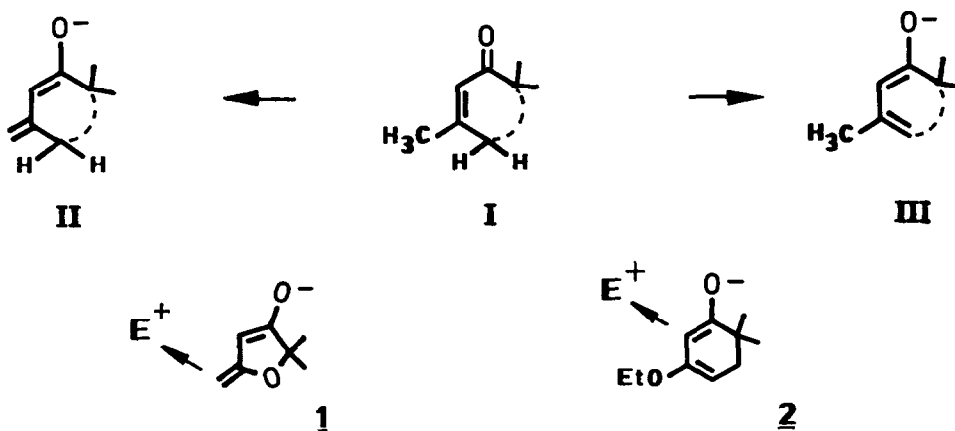
BEHAVIOR TOWARDS ELECTROPHILES

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Summary : Isomeric exocyclic and endocyclic dienolates 5 and 6 were generated and while 6 reacted with electrophiles exclusively at the  $\alpha$ -position the regioselectivity of 5 was found to be dependent on the type of electrophile employed.

Cyclic ketone dienolates have attracted much interest due to their potential in organic synthesis,<sup>1</sup> but although it is known that lithium base deprotonates the cycloalkenone system 1 to give the exocyclic dienolate II faster than the endocyclic counterpart III<sup>2</sup> still the factors governing the  $\alpha$ - vs  $\gamma$ - reaction selectivity of the resulting dienolate remain unclear. Recently a very interesting observation has revealed that the exocyclic dienolate (eg. 1) reacts with alkyl halides preferentially at the  $\gamma$ -position while the endocyclic dienolate (eg. 2) does so exclusively at the  $\alpha$ -position.<sup>3</sup> Nevertheless the authors cautioned that further studies would be required before the subtle nature of the  $\alpha$ - vs  $\gamma$ - selectivity in the alkylation of cyclic  $\beta$ -alkoxy- $\alpha$ ,  $\beta$ -unsaturated enones could be fully appreciated.



We ourselves have come across some unusual alkylation selectivity in the cyclopentenone system during our synthesis of cyclopentenoid antibiotics,<sup>4</sup> which led us to study the reactions of exocyclic

Cyclic enone ↓ Dienophile	Entry	Reaction Conditions <sup>a</sup>		Electrophile (E)	Product <sup>b</sup>				
		Additive	Temp °C		7	8	9	10	
	1	HMPA or ZnCl <sub>2</sub>	-78, -30, 0, 30	CiCOOMe	only	-	-	-	-
	2	" " "	" " "	CiCOOEt	only	-	-	-	-
	3	" " "	" " "	CiCOMe	only	-	-	-	-
	4	HMPA	0	MeI	see text	-	-	-	-
	5	"	30	H <sub>3</sub> O <sup>+</sup>	-	only	-	-	-
	6	ZnCl <sub>2</sub>	-78, -30, 0, 30	PhCHO	-	only	-	-	-
	7	"	" " "	4-OMe-C <sub>6</sub> H <sub>4</sub> CHO	-	only	-	-	-
	8	"	0	MeCHO	-	only	-	-	-
	9	HMPA or ZnCl <sub>2</sub>	-78, -30, 0, 30	CiCOOMe	-	-	-	only	-
	10	" " "	" " "	CiCOOEt	-	-	-	only	-
	11	" " "	" " "	CiCOMe	-	-	-	only	-
	12	HMPA	0	MeI	-	-	-	only	-
	13	"	30	H <sub>3</sub> O <sup>+</sup>	-	-	-	only	only <sup>c</sup>
	14	ZnCl <sub>2</sub>	-78, -30, 0, 30	PhCHO	-	-	-	only <sup>c</sup>	only <sup>c</sup>
	15	"	" " "	4-OMe-C <sub>6</sub> H <sub>4</sub> CHO	-	-	-	only <sup>c</sup>	only <sup>d</sup>
	16	"	0	MeCHO	-	-	-	only	only

<sup>a</sup> All reactions were performed in THF

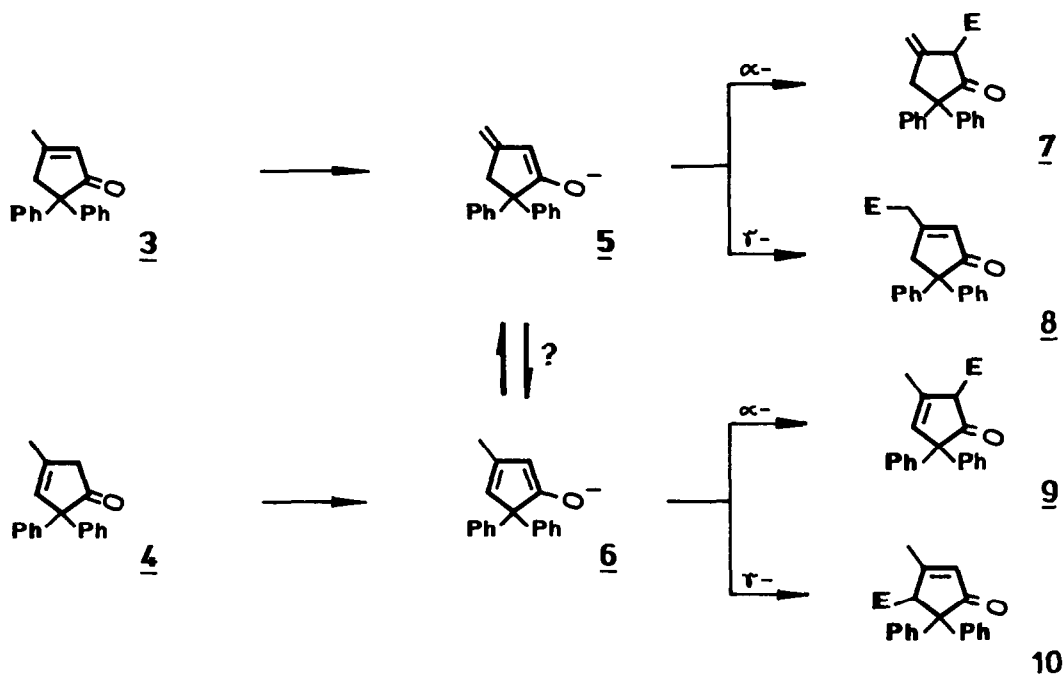
<sup>b</sup> NMR spectrum of the crude reaction material in every case (except entry 4) showed the absence of other regioisomer.

<sup>c</sup> NMR spectrum of the crude product indicated the presence of only one stereoisomer.

<sup>d</sup> Two stereoisomers (ratio 2 : 1) were present in the NMR spectrum. Separation can be performed using PLC.

and endocyclic cyclopentenoid dienolates in some detail, and we now wish to report our findings.

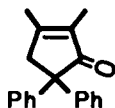
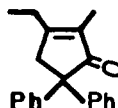
Isomeric cyclopentenones 3 and 4<sup>5</sup> were chosen as model compounds for the two-fold advantage they offer : firstly, treatment of 3 and 4 with lithium base under kinetically controlled conditions should lead specifically to the respective exocyclic and endocyclic dienolates 5 and 6 and thus allow us to directly determine their individual regioselectivity towards electrophiles, and, secondly, it should also be possible to measure the extent of isomerisation, if any, of the emerging dienolates 5 and 6 at various temperatures.



Treatment of cyclic enone 3 and 4 with lithium diisopropylamide (LDA, 1.2 eq.) in THF solution in the presence of hexamethylphosphoric triamide (HMPA) or  $\text{ZnCl}_2$  and stirring the resulting anion for 2 hr. at various intended temperatures ( $0^\circ$  and/or  $-78^\circ$ ,  $-30^\circ$ ,  $30^\circ$ ) followed by quenching with an electrophile yielded the product(s) shown in TABLE. Although identical results were obtained with either  $\text{ZnCl}_2$  or HMPA in the acylation reactions, the use of the latter is, in general, more convenient. However, in the cases of aldehydes the presence of HMPA resulted in complex mixtures and therefore only  $\text{ZnCl}_2$  could be employed to cleanly give the adducts (entries 6-8 and 14-16). In the protonation of dienolates (entries 5 and 13) the reactions were conducted only at room temperature ( $30^\circ$ ), the intention here being to investigate possible double bond isomerisation under these reaction conditions. The yield of the products shown in TABLE are all nearly quantitative as evident from direct analysis of the NMR spectra of the crude reaction mixtures after usual  $\text{NH}_4\text{Cl}$  work-up. Subsequent chromatographic purifications were performed for the complete characterisation of products. Comparison of the NMR spectrum of each purified product with that of the corresponding crude reaction mixture confirmed the absence of other regioisomers in all but one case, that of entry 4 which will be later discussed.

As can be seen from TABLE the results obtained from the present study are evidently quite

interesting. LDA indeed specifically deprotonated the conjugated cyclopentenone 3 and its non-conjugated isomer 4 to give the respective exocyclic and endocyclic dienolates 5 and 6, and, as expected, alkylation of the endocyclic dienolate 6 with various electrophiles took place essentially at the  $\alpha$ -position, a behavior not unlike that reported for the anion derived from  $\beta$ -alkoxy- $\alpha, \beta$ -unsaturated enones (eg. 2) with alkyl halides. In the case of the exocyclic dienolate 5, however, specific  $\gamma$ -alkylation was observed only in the reactions with aromatic and aliphatic aldehydes (entries 6-8) while with reactive electrophiles reaction occurred at the  $\alpha$ -position (entries 1-3). Furthermore, the reaction of 5 with alkyl halide was slow (compared to reactions with the more reactive electrophiles employed in this study) and no regioselectivity could be observed, the product ratio being dependent on reaction conditions. Thus quenching a solution of 5 in THF/HMPA with methyl iodide and leaving it to stir at 0° for 2 hr. gave, after purification of the crude reaction mixture by PLC (silica gel, 5% EtOAc in hexane), not only 8 (E = Me,  $\gamma$ -alkylation, 47%) and 11 ( $\alpha$ -alkylation, 18%) but also the dialkylation product 12 (13%) together with the starting material 3 (12%). Finally, it should be emphasized that no isomerisation of the exocyclic or endocyclic dienolate 5 and 6 could be observed at all even at 30° C.

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The observations discussed above certainly throw more light on the behavior of the cyclic dienolates. Thus, while it is again confirmed that the endocyclic dienolate reacts with electrophiles only at the  $\alpha$ -position it has also been shown that regioselectivity in the alkylation of the exocyclic dienolate is dependent on the type of electrophile employed. Moreover it has been demonstrated that the generation of specific endocyclic and exocyclic dienolates from the corresponding enones is quite feasible, and that once formed they can be used in the alkylation reaction WITHOUT ISOMERISATION.

These findings should find useful application in organic synthesis.

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