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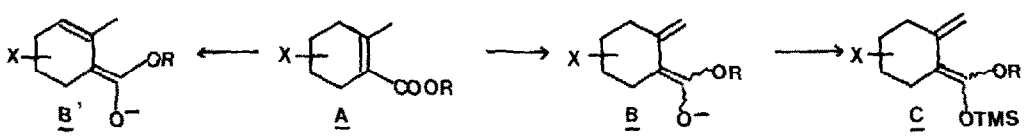
REGIOSELECTIVE DIENOLATE FORMATION AND ALKYLATION OF ALKYL 2-METHYL CYCLOHEXENE-1 CARBOXYLATES

Jean-Pierre GESSON*, Jean-Claude JACQUESY and Martine MONDON

Laboratoire de Chimie XII, E.R.A. N° 556, 40, Avenue du Recteur Pineau - 86022 Poitiers - France.

Summary - *Exocyclic deprotonation and α alkylation with methyliodide of title compounds have been observed. A clarification of Hagemann ester ethylene ketal reactivity toward strong bases is given.*

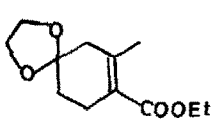
Dienolate anions derived from α,β unsaturated esters have been frequently used in synthesis in the past years[1]. We have investigated the formation and reactivity of such anions starting from substituted alkyl 2-methyl cyclohexene-1 carboxylates as part of a general route to anthracycline antibiotics.



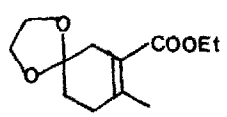
Compounds such as A, where X may be a functional group (such as a protected carbonyle) suitable for further elaboration of various anthracyclines, are susceptible of two alternative deprotonations : either on the exocyclic methyl group or on the endocyclic methylene group to give respectively B or B'.

Trapping of the former anion by TMSCl will then give conjugated silyl acetal C whose reaction with various naphtoquinones may be an expeditive and general route to anthracycline aglycones.

Considering known anthracycline chemistry[2] compounds 1 and 2[3] were chosen as possible precursors.



1



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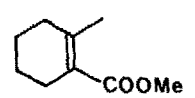
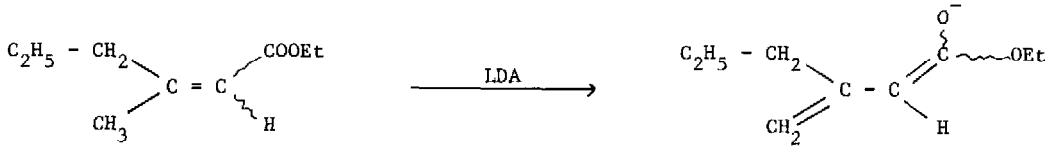


3

Unfortunately White[4] has reported that treatment of 1 with excess $LiNEt_2$ leads exclusively after methylation to 4, a compound arising apparently from endocyclic deprotonation.

1 4

On the other hand Katzenellenbogen[5] has observed only methyl deprotonation for E or Z α,β unsaturated esters 5.



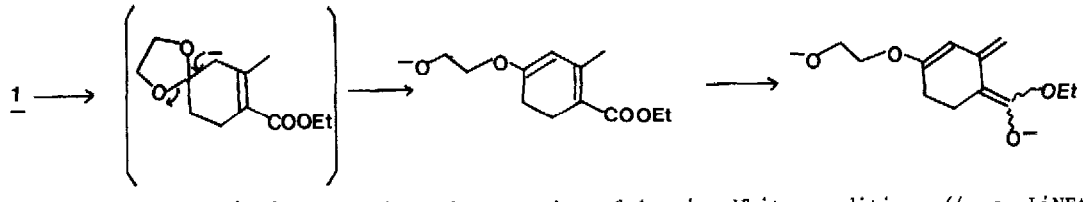
5 E or Z ref. 5

Although an internal base effect of the ketal group may explain the former reaction (1⟶4), the use of excess $LiNEt_2$, a less hindered base than LDA or LiICA, is to be underlined.

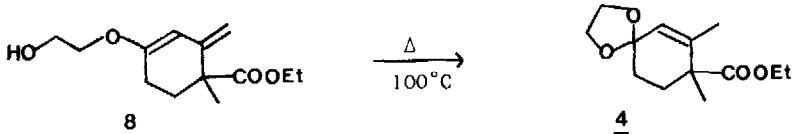
For such reasons we have studied the deprotonation of 1, 2 and 3 with strong bases and the alkylation (CH_3I) of the intermediate anions.

Typically, 1 mmole of ester dissolved in 0.5 ml of dry THF is added dropwise, under N_2, to a cold (-78°C) solution of base (0.5 M in THF-hexane 3/1). The deep red solution is then stirred 10 minutes at -78°C and then at 0°C for 20-30 minutes, excess methyl iodide (0.5 ml) is then added and after 10 minutes the resulting pale yellow solution is extracted with ether. To avoid thermal isomerization (vide infra) the crude mixture is purified by column chromatography over Si gel.

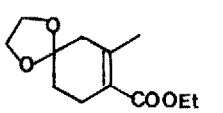
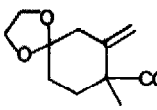
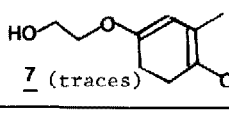
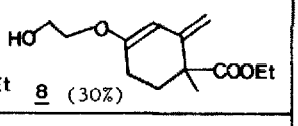
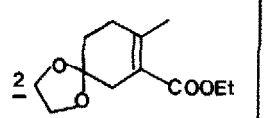
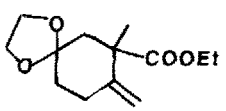
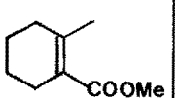
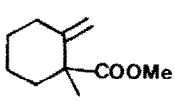
Results summerized in the table show that only exocylic deprotonation is observed for 2 and 3 while both exocyclic (∿ 45%) and endocyclic (∿ 55%) deprotonations are possible for 1. This ratio is changed drastically by addition of 20% HMPA (100% endocyclic deprotonation) but not by the use of other bases (LDA, LiTMP)[7], less polar solvents (hexane) or lower temperatures (-78°C to 0°C). Following endocyclic deprotonation a rapid cleavage of the ethylene ketal group occurs to give a conjugated enol ether (a thick precipitate is observed in THF) which can further react with excess base to give a dianion, precursor of 8.



In fact only 8 is isolated from the reaction of 1 using White conditions (4 eq. $LiNEt_2$, 0°C, 30 mn then CH_3I) but this compound is rapidly isomerized thermally to 4 (Bulb to bulb distillation).

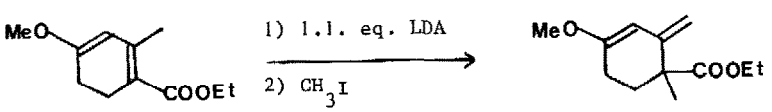


8 4

ESTER	CONDITIONS	PRODUCTS
 1	1) 1.1 eq. LiICA 2) CH_3I	1 (46%) +  + 6 (24%)  7 (traces) +  8 (30%)
	1) 1.6 eq. LiICA 2) CH_3I	6 (45%) + 8 (55%)
	1) 1.1 eq. LDA-HMPA 2) H_2O	7 (> 95%)
 2	1) 1.1. eq. LiICA 2) CH_3I	 9 (≥ 95%)
 3	1) 1.1. eq. LiICA 2) CH_3I	 10 (≥ 95%)

Yields given here are estimated by NMR, 1 and 6, 7 and 8 being respectively difficult to separate by column chromatography. Isolated yields are in the range 75-85%. Structure of compounds 6, 7, 8, 9 and 10 are supported by spectroscopy and analytical data[6].

The clean methyl deprotonation of the intermediate enol ether is also confirmed by the reactivity of the methyl (or trimethylsilyl) ether prepared from Hagemann ester (50%, K_2CO_3, dimethylsulfate, acetone, reflux 24 hr.)[8].



11 12

Finally we have noted that in all cases studied here dienolates are α alkylated with CH_3I, a reactivity which have ample precedent in the litterature[1].

Our results show the preferential methyl deprotonation over the methylene one when this latter position is not activated such as for 1.

Studies on the reactivity of such dienolates with other electrophiles are underway as well as applications in natural product synthesis. Cycloadditions of vinyl ketene acetals derived from such dienolates with various quinones will be reported soon.

A C.N.R.S. grant (M.M.) is greatly acknowledged.

References :

1 R.L. Cargill, D.F. Bushey and J.J. Good, J. Org. Chem., 44, 300 (1979) and references cited therein.

2 For elaboration of anthracycline ring A from β tetralone type intermediates see :
a - A.S. Kende, Y. Tsay and J.E. Mills, J. Amer. Chem. Soc., 98, 1967 (1976).
b - A.S. Kende and Y. Tsay, J. Chem. Soc., Chem. Comm., 140 (1977).

3 1 is prepared from Hagemann ester following the procedure of E. Babbiolini, J.P. Hamlow and K. Schaffner, J. Amer. Chem. Soc., 92, 4906 (1970).
2 is avalaible in four steps from diethyl oxo pimelate and its synthesis will be reported in a forthcoming paper.

4 J.D. White and Wing Lam Sung, J. Org. Chem., 39, 2323 (1974).

5 J.A. Katzenellenbogen and A.L. Crumrine, J. Amer. Chem. Soc., 98, 4925 (1976).

6 All new compounds gave satisfactory mass spectral and/or analytical data. N.M.R. spectra ($CDCl_3$) are given below.

6 : 4.93 (2H, s, $=CH_2$), 4.15 (2H, q, J = 7 Hz, $-OCH_2-$), 3.93 (4H, s, $-O-CH_2-CH_2-O-$), 1.37 (3H, s, $-CH_3$) and 1.25 (3H, t, J = 7 Hz, $-CH_3$).

7 : 4.93 (1H, s, =CH-), 4.15 (2H, q, J = 7 Hz, $-OCH_2-$), 3.87 (4H, s, $-O-CH_2-CH_2-O-$), 2.18 (3H, s, $-CH_3$) and 1.25 (3H, t, J = 7 Hz, $-CH_3$).
I.R. (CCl_4) : 3615, 3490, 1700, 1570, 1260 and 1200 cm^{-1}

8 : 5.32 (1H, s, =CH-), 4.74 and 4.68 (2H, 2s, $=CH_2$), 4.13 (2H, q, J = 7 Hz, $-O-CH_2-$) 3.83 (4H, s, $-O-CH_2-CH_2-O-$), 1.37 (3H, s, $-CH_3$) and 1.2[illegible] (3H, t, J = 7 Hz, $-CH_3$)
I.R. (CCl_4) : 3620, 3530, 1735, 1650, 1610, 1265, 1205, 1190 and 1115 cm^{-1}.

9 : 4.87 and 4.77 (2H, 2s, $=CH_2$), 4.10 and 4.07 (2H, 2q, J = 7 Hz, $-OCH_2-$), 3.88 and 3.85 (4H, 2s, $-O-CH_2-CH_2-O-$), 1.33 (3H, s, $-CH_3-$) and 1.23 (3H, t, J = 7 Hz, $-CH_3$). The same small dedoubling of the methylenes (ester and dioxolane) signals is observed when the exocyclic double bond is replaced by a carbonyl group.

10 : 4.83 and 4.73 (2H, 2s, $=CH_2$), 3.65 (3H, s, $-OCH_3$) and 1.32 (3H, s, $-CH_3$).

7 Ph_3CLi and $LiN(SiMe_3)_2$ gave substantially lower yields of methylated compounds.

8 A similar yield of enol ether is obtained using 2,2 dimethoxy propane, P.T.S.A. and refluxing D.M.F. (3 hr.), however the material is less easily purified.

11 : 4.92 (1H, s, =CH-), 4.15 (2H, q, J = 7 Hz, $-OCH_2-$), 3.62 (3H, s, $-O-CH_3$), 2.21 (3H, s, $-CH_3$) and 1.28 (3H, t, J = 7 Hz, $-CH_3$).

9 12 : 5.30 (1H, s, =CH-), 4.75 and 4.66 (2H, 2s, $=CH_2$), 4.13 (2H, q, J = 7 Hz, $-OCH_2-$), 3.56 (3H, s, $-O-CH_3$), 1.34 (3H, s, $-CH_3$) and 1.23 (3H, t, J = 7 Hz, $-CH_3$).

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