Studies on the Intramolecular Claisen Condensation. Stereospecific Ring-closure of β-Acetyloxy Esters

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On treatment with lithium bis(trimethylsilyl)amide, α-alkyl-β-acetyloxy esters (**2**) and (**3**) undergo stereospecific ring-closure to the 5,6-dihydro-4-hydroxy-2*H*-pyran-2-ones (2,4-dioxotetrahydropyrans) (**4**) and (**5**).

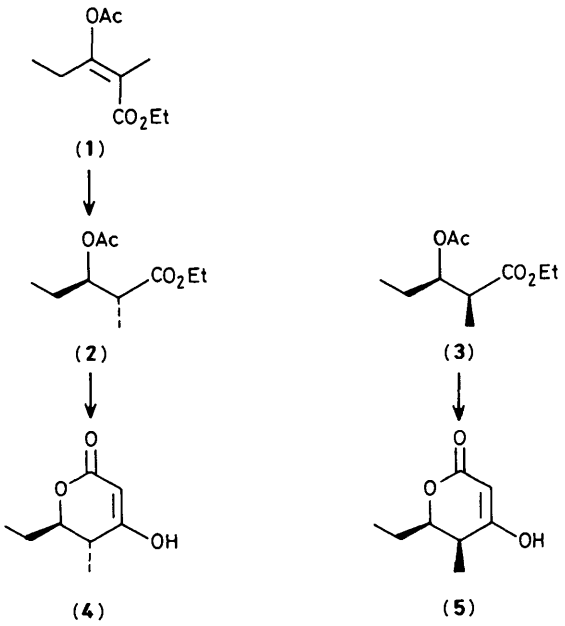
In a previous study of the intramolecular Claisen diester condensation we found that α-acetyloxy esters could be transformed into tetronic acids by treatment with lithium bis(trimethylsilyl)amide and that two β-acetyloxy esters gave α,β-unsaturated esters under the same conditions.[1] The two β-acetyloxy esters studied had no α-substituents. We now report that the presence of an α-methyl group in the β-acetyloxy ester causes the reaction to take a different course, *viz.* ring-closure instead of elimination.

(*E*)-Enol acetate (**1**) was prepared from ethyl 2-methyl-3-oxopentanoate in 45% yield and 98% stereochemical purity (capillary column g.l.c.) by adding acetyl chloride (2 equiv.) in CH_2Cl_2 to a vigorously stirred mixture of the keto ester in CH_2Cl_2 and an aqueous solution of $Bu_4N^+HSO_4^-$ (1 equiv.) and NaOH (3 equiv.). The reaction temperature was kept in the range 16—18 °C by cooling in an ice bath. This is a modification of the technique previously used for the *O*-acetylation of ethyl acetoacetate which leads to a 93 : 7 mixture of (*E*)- and (*Z*)-isomers.[2] Hydrogenation[3] of (**1**) over Rh–C (0.01 equiv., 240 kPa, 2 h) afforded (**2**) in 93% stereochemical purity. Hydrogenolysis leading to ethyl 2-methylpentanoate lowered the yield to 65%. Hydrogenation in EtOH (instead of tetrahydrofuran) is less capricious and shows a higher stereospecificity, but gives somewhat more hydrogenolysis.

The stereoisomeric ester (**3**) was prepared in 95% stereochemical purity starting with a reaction[4] between *N*-propionylphenothiazine and propanal. Oxidation of the condensation product and cleavage with sodium ethoxide[4] gave a β-hydroxy ester, which on acetylation with Ac_2O–pyridine gave (**3**).

To induce ring-closure of (**2**) or (**3**), a solution of 2.5 equiv. of lithium bis(trimethylsilyl)amide in tetrahydrofuran (THF) was added dropwise to a stirred and cooled (*ca.* −75 °C, N_2 atmosphere) THF solution of the ester. After 1—2 h at this temperature, the mixture was poured into dilute hydrochloric acid. Extractions with diethyl ether, drying of the combined organic phases (Na_2SO_4), and analysis by g.l.c. indicated that (**2**) yielded a negligible amount of elimination products (<3%) whereas (**3**) yielded *ca.* 12% of ethyl (*E*)-2-methylpent-2-enoate and <0.5% of the (*Z*)-isomer: *ca.* 10% of the starting ester was left in both reactions. The main products (**4**) and (**5**) showed some decomposition on g.l.c. and on chromatography on silica gel. Concentration, flash chromatography on silica gel (toluene–ethyl acetate, 2 : 1), and crystallisation afforded (**4**) (from diethyl ether), m.p. 56—59 °C; 65% yield and (**5**) (from chloroform–light petroleum), m.p. 97—100 °C; 59% yield. The i.r., n.m.r., and u.v. spectra of (**4**)† and (**5**)† show that these compounds, like some analogues,[5—8] are in the enol form in the crystalline state and in protic solvents, *e.g.* water, and that appreciable amounts of the keto form appear in nonpolar solvents such as chloroform. In the latter solvent, the percentage of enol increased with increasing concentration.

† *Spectroscopic data:* (**4**): ^{1}H n.m.r. ($CDCl_3$) shows only keto form: δ 4.29 (ddd, H-6, *J* 10.7, 6.8, 3.4 Hz), 3.55 and 3.45 (AB spectrum, H-3, J_{AB} 19.0 Hz), 2.43 (dq, H-5, *J* 10.3, 6.8 Hz), 2.2—1.5 (m, CH_2CH_3), 1.18 (d, CH_3–CH, *J* 6.8 Hz), 1.10 (t, CH_3CH_2, *J* 7.3 Hz); ^{13}C n.m.r. ($CDCl_3$) shows *ca.* 90% keto form: δ 203.1 (s), 167.7 (s), 81.1 (d), 46.2 (d), 46.0 (t), 25.3 (t), 10.6 (q), 8.5 (q); i.r. (KBr): broad enol bands around 3000 cm^{-1}, 1660, 1590 cm^{-1}; i.r. ($CHCl_3$): 1760 and 1730 cm^{-1}; u.v. (H_2O) $\lambda_{max.}$ 270 nm, ε 22000. (**5**): ^{1}H n.m.r. ($CDCl_3$) shows only keto form: δ 4.55 (m, H-6), 3.57 and 3.40 (AB spectrum, H-3, J_{AB} 19.5 Hz), 2.70 (dq, H-5, *J* 7.3, 2.9 Hz), 2.0—1.5 (m, CH_2CH_3), 1.14 (d, CH_3CH, *J* 7.3 Hz), 1.08 (t, CH_3CH_2, *J* 7.0 Hz); ^{13}C n.m.r. ($CDCl_3$) shows keto (K) and enol (E) forms in the approximate ratio 1 : 1 : δ 203.6 (s, K), 179.8 (s, E), 170.7 (s, E), 167.9 (s, K), 90.1 (d, E), 80.5 (d), 80.1 (d), 45.6 (t, K), 44.9 (d, K), 35.6 (d, E), 23.8 (t, K, E), 10.3, 9.8, 9.5, 9.1 (calibrated against solvent signal at δ 77.17); i.r. (KBr): broad enol bands around 3000 cm^{-1}, 1660, 1595 cm^{-1}; i.r. ($CHCl_3$): 1760 and 1732 cm^{-1}; u.v. (H_2O): $\lambda_{max.}$ 268 nm, ε 22000.



Scheme 1. Reactions were carried out in the optically inactive series; only one enantiomer is drawn.

Our choice of lithium bis(trimethylsilyl)amide as condensing agent was based on Rathke and Lindert's finding that this base smoothly deprotonates esters of acetic acid in THF at −78 °C but reacts markedly more slowly with esters of the higher carboxylic acids.[9]

Treatment of β-acetyloxy esters with Bu^{t}OK in Bu^{t}OH leads to α,β-unsaturated esters[10] but the stereochemistry of this elimination reaction when applied to α-alkylated β-acetyloxy esters is unknown. A 57 : 43 mixture of (**2**) and (**3**) yielded a 3 : 97 mixture of (*Z*)- and (*E*)-ethyl 2-methylpent-2-enoate when treated with 0.7 equiv. of Bu^{t}OK. No (**4**) or (**5**) could be detected (g.l.c.). The ratio (**2**) : (**3**) changed from 57 : 43 to 17 : 83 and, since side reactions appeared negligible, it must be concluded that both (**2**) and (**3**) yielded mainly (*E*)-alkene. By proper choice of base, it is thus possible to perform either an elimination or a ring-closure of the α-alkylated β-acetyloxy esters.

The synthetic sequence described here represents a two-carbon chain elongation which starts and ends with derivatives of β-keto or β-hydroxy carboxylic acids and should therefore be synthetically useful. In particular, the preparation of optically pure compounds should be facilitated by the variety of routes that lead to β-hydroxy esters in optically pure or enriched form. Further, the cyclic nature of the products (**4**) and (**5**) should permit stereo-controlled reactions at C-3 and C-4 leading to compounds having four contiguous asymmetric carbons.

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