Polyketide Syntheses: Condensations of Keto Esters with Anionic Electrophiles

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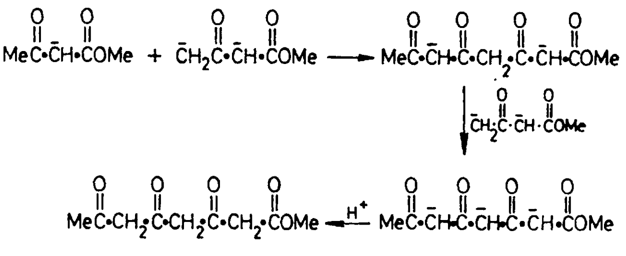
Summary Condensation of multiple anions of acetoacetic and 3,5-dioxohexanoic esters with monoanions of β-keto-esters and β-keto-aldehydes provide a new approach to β-polyketo-esters and related products having biosynthetic significance.

We recently described the reaction of monoanions of β-keto-esters with the dianions of β-diketones and the multiple anions of higher polyketones.[1,2] These anion–anion condensations represent a novel and convergent approach to linear β-polyketones containing as many as eight keto-groups. We now report an extension of this approach to the synthesis of polyketide esters. Polycarbonyl compounds, especially β-polyketo-esters, are of interest in relationship to the biosynthesis of acetate-derived, phenolic natural products.[3]

3,5,7-Trioxo-octanoate is a key intermediate in the formation of orsellinic acid and many other metabolites. Previous syntheses of the acid and methyl ester (I) have involved carboxylation of the trianion of heptane-2,4,6-trione.[4] We have synthesised (I) by self-condensation of methyl acetoacetate *via* the mono- and the di-anion[5] of the keto-ester. The stoicheiometry of the reaction is complex with the condensation giving initially the dianion of (I). Proton abstraction from (I) by the dianion of methyl acetoacetate gives the trianion of (I) plus an equivalent of keto-ester monoanion. The result is that two moles of keto-ester dianion and only a catalytic amount of monoanion are required to form (I). A 59% yield of (I) was obtained from the reaction of a 10:1 mixture of the di- and mono-lithium salts of methyl acetoacetate in tetrahydrofuran at room temperature. Ester (I) cyclized on activated silica gel to give 81% of methyl orsellinate.

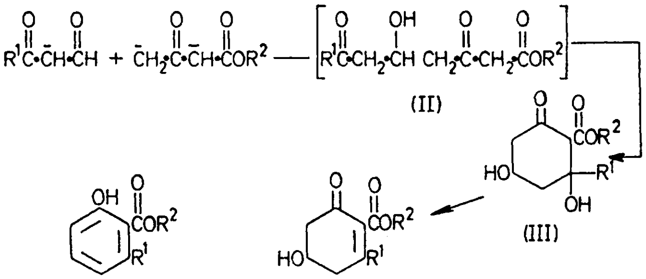
6-Methylsalicylic acid (Vc) and related metabolites apparently arise from partially reduced triketo-esters (*i.e.*, II). The hitherto unexplored condensation of ionized β-keto-aldehydes with strong nucleophiles was explored in an attempt to prepare hydroxydiketo-esters of this type. The reaction of the dilithium salt of methyl acetoacetate with the sodium salt of formylacetophenone (3:1 mole ratio) gave a complex mixture from which the aldol product (II, R^1 = Ph, R^2 = Me) could not be isolated. Nevertheless, treatment of the unresolved mixture with sodium acetate gave cyclohexenone (IVa) and salicylic ester (Va) in yields of 15 and 17%, respectively. In acid, (IVa) dehydrated quantitatively to give (Va).



(I)

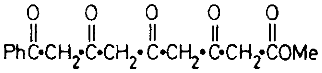
A similar condensation of sodioformylacetone gave only a trace (2·5%) of methyl 6-methylsalicylate after cyclization of the crude product mixture; self-condensation predominated and cyclization conditions produced predominantly methyl orsellinate.† This problem was minimised by use of the dilithium salt of t-butyl acetoacetate; the condensation gave 64% of a mixture of stereoisomers of (III; R^1 = Me, R^2 = Bu^t) from which the major form (m.p. 118—119°) could be isolated by chromatography and crystallization. Treatment of this stereoisomer with methanolic acetic acid gave cyclohexenone (IVb) (72%), with aqueous potassium hydroxide gave t-butyl 6-methylsalicylate (Vb) (56%), and with hydrochloric acid in dioxan gave 6-methylsalicylic acid (Vc) (50%). Acid (Vc) can be prepared in 40% overall yield without isolation of intermediates. This synthesis of (Vc) would appear to mimic the later stages of the biosynthetic process.‡

The trianion of methyl 3,5-dioxoheptanoate, which can be formed by treatment of the diketo-ester with three equivalents of lithium di-isopropylamide, is also an effective nucleophile in the β-ketoacylation reaction. Treatment of the trilithium salt with the sodium salt of ethyl benzoylacetate (2:1 mole ratio) gave 60% of tetraketo-ester (VI). This compound has been synthesised previously in a much lower overall yield by a linear route [triketone → tetraketone → tetraketo acid → (VI)].[7]



(Va) R^1 = Ph, R^2 = Me
(Vb) R^1 = Me, R^2 = Bu^t
(Vc) R^1 = Me, R^2 = H

(IVa) R^1 = Ph, R^2 = Me
(IVb) R^1 = Me, R^2 = Bu^t



$\mathrm{Ph\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}OMe}$

(VI)

The ready availability of starting materials and relatively good yields make the above reactions of anions of di- and tri-keto-esters with negatively charged electrophiles an attractive addition to the field of polyketide synthesis. Work is in progress to extend these reactions to polyketo-ester precursors of polycyclic aromatic compounds.

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† Methyl orsellinate presumably arises by proton abstraction from sodioformylacetone by methyl dilithioacetoacetate. The resulting monoanion of keto-ester catalyses formation of (I), which subsequently cyclizes. The t-butyl group inhibits self-condensation of the keto-ester.

‡ Scott and his co-workers have also described a biogenetically modelled synthesis of 6-methylsalicylic acid.[6]

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[4] T. T. Howarth, G. P. Murphy, and T. M. Harris, *J. Amer. Chem. Soc.*, 1969, **91**, 517.
[5] See S. N. Huckin and L. Weiler, *Tetrahedron Letters*, 1972, **2405** and references therein.
[6] A. I. Scott, H. Guilford, and D. Skingle, *Tetrahedron*, 1971, **27**, 3039.
[7] T. M. Harris and G. P. Murphy, *J. Amer. Chem. Soc.*, 1971, **93**, 6708.