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CLAISEN CONDENSATION OF THE DIANION OF β-KETO ESTERS

Stuart N. Huckin and Larry Weiler*

Department of Chemistry, University of British Columbia
Vancouver 8, British Columbia, Canada

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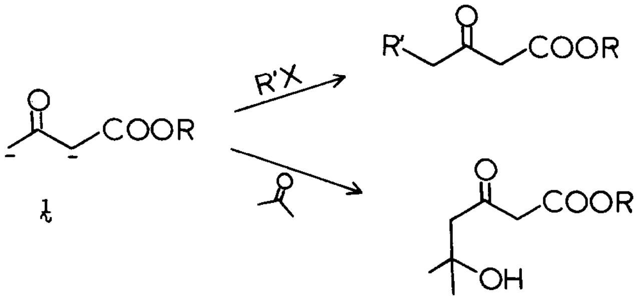
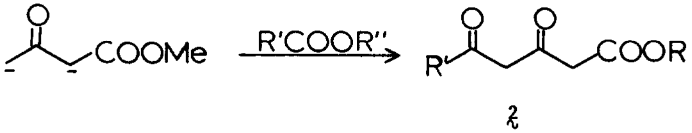
Previously we have reported that the dianions of β-keto esters undergo alkylation[1] and Aldol reaction[2] at the γ-carbon (eq. 1). We have now modified and extended these procedures to produce β,δ-diketo esters 2 from the Claisen condensation of the dianion 1 with a series of esters (eq. 2). Wolfe, et al.,[3] have reported the only previous example of this type of reaction. In their case the dianion of ethyl acetoacetate 1 (R = Et) was treated with ethyl benzoate to give 5-phenyl-3,5-dioxopentanoic acid (2, R = H, R' = C_6H_5) in about 40% yield. Since the monoanion of 2 which is the initial product in reaction 2 has a more acidic



(1)



(2)

proton than the monoanion of the starting β-keto ester, proton transfer from the monoanion of **2** to the dianion **1** should occur.[4] Consequently the maximum conversion of β-keto ester to product would be 50% in this reaction. We have attempted to obviate this difficulty by adding one extra equivalent of base at the start of the reaction.[4] However, this was not successful, as any base which was strong enough to form the dianion **1** also attacked the unreacted ester. For instance, when the dianion **1** was generated by the addition of methyl acetoacetate to three equivalents of lithium N-diisopropylamide and methyl benzoate subsequently added, the major product was N,N-diisopropylbenzamide.[4,5] A similar result was obtained using lithium N-isopropylcyclohexylamide[6] as the base in the above reaction.

Then we envisaged adding only one half of an equivalent of the ester to the dianion **1** and regenerating the quenched dianion **1** by the addition of more base before adding further ester. In this way, we found that the yield of **2** was in excess of 50%. Employing a procedure in which the dianion **1** was generated at 0°, as previously reported,[1,2] to this one half equivalent of ester was added, and the dianion was regenerated by addition of one more equivalent of n-butyllithium followed by addition of a further one half equivalent of ester, the desired product was obtained in reasonable yield with a variety of esters (cf. Table). It was found that under these reaction conditions some transesterification occurred; thus when ethyl butanoate was condensed with the dianion of methyl acetoacetate, the product was a mixture of the ethyl and methyl esters. To avoid this complication all subsequent investigations were performed using methyl esters.

In the previously reported benzoylation of ethyl acetoacetate[3] only the hydrolysed product **2** (R = H, R' = C_6H_5) was isolated. However, in our condensation of methyl acetoacetate and methyl benzoate, using the n-butyllithium procedure, we were able to isolate both the ester **2** (R = Me, R' = C_6H_5) and the acid **2** (R = H, R' = C_6H_5). The hydrolysis of the ester **2** to acid during the reaction appears to be limited to only those condensations involving aryl esters. We believe that this is related to the nature of the monoanion formed in the reaction. Hence we have found that the dianion of β-keto esters can be acylated at the γ-carbon to give β,δ-diketo esters in good yields and this reaction is useful in the synthesis of these compounds. The chemistry of these intermediates awaits developement; however, the applications of this type of intermediate to biogenetic type syntheses of acetogens has been widely recognized.[4,7]

Claisen Condensation of the Dianion of Methyl Acetoacetate With Esters (eq. 2).

R	R'	R"	Yield of **2**, %[a,b]	Bp of **2**, °C (P, mm)
Me	H	Me	69	-[c]
Me	Me	Me	71	44-46 (0.3)
Me	n-Pr	Me	67	83-85 (0.1)
Me	n-Pr	Et	61[d]	
Et	n-Pr	Et	11[d]	94-96 (0.1)
Me	C_6H_5	Me	37[d]	127-129 (0.1)
H	C_6H_5	Me	30[d]	mp 93-97[e]
Me	4-MeOC_6H_4	Me	42[d]	142-143 (0.1)
H	4-MeOC_6H_4	Me	29[d]	mp 103-105

[a] Isolated yield, not corrected for small amount of recovered methyl acetoacetate. [b] All products exhibited spectral data in accord with their assigned structures and all compounds, except where noted, gave satisfactory elemental analyses. [c] Product **2** in this case was isolated by preparative tlc and it decomposed on all attempts to distill it, hence it was not obtained in analytical purity. [d] Both of these products were obtained in this reaction. [e] Lit. mp 94-96°.[3]

The following is a typical procedure. Sodium hydride, as a 57% mineral oil dispersion, (0.465 g, 11.0 mmol) was weighed into a dry 50-ml flask, and approximately 25 ml of tetrahydrofuran was distilled directly into the flask from lithium aluminium hydride. The flask was fitted with a magnetic stirrer, stoppered (serum cap), cooled in ice and flushed with nitrogen. Methyl acetoacetate (1.161 g, 10.0 mmol) was added dropwise to the cooled slurry and the reaction was stirred for 10 minutes after the addition was complete. A solution of n-butyllithium (5 ml of 2.1 M in hexane, 10.5 mmol) was added dropwise to the reaction and this was stirred for a further 10 minutes. Methyl n-butyrate (0.501 g, 5.0 mmol) was then added in one portion. After approximately 15 minutes additional n-butyllithium (5 ml of 2.1 M, 10.5 mmol) was added very slowly and a further 15-20 minutes allowed to elapse before more methyl n-butyrate (0.501 g, 5.0 mmol) was added. The reaction was allowed to stand for a final 15 minutes before being quenched with concentrated hydrochloric acid (*ca.* 3.5 ml). The reaction was worked up by the addition of 10 ml of water and 30 ml of diethyl ether. The aqueous layer was separated and further extracted with 2x30 ml of ether. The extracts were combined, washed with saturated sodium bicarbonate solution (4x15 ml) and with saturated brine (6x15 ml), dried over sodium sulfate and filtered. The solvents were removed under reduced pressure and the oily residue was distilled under vacuum to give 1.25 g (67%) of methyl 3,5-dioxooctanoate (**2**, R = Me, R' = n-Pr), bp 83-85° (0.1 mm).[8]

* Address correspondence to this author.

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