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ALDOL REACTIONS OF THE DIANION OF β-KETO ESTERS

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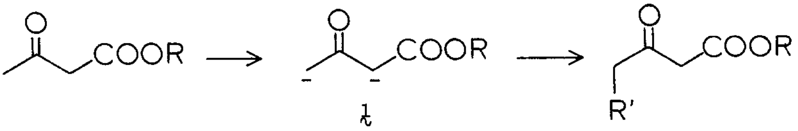
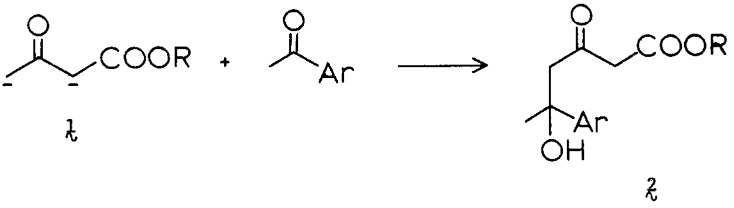
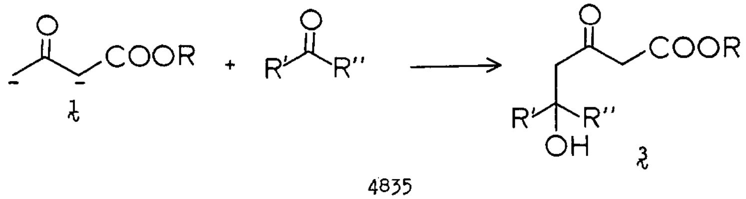
Recently we developed an efficient proceedure to alkylate β-keto esters at the γ carbon.[1] This involved treating the starting β-keto ester with one equivalent of sodium hydride, then with one equivalent of n-butyllithium to give the dianion **1**, and finally alkylation at the more nucleophilic terminal carbon (eq. 1). Subsequently we found that reaction



(1)

of the dianion **1** (R = Me) with a substituted acetophenone gave the aldol product **2** in good yield.[2] We have now investigated this reaction with a range of aldehydes and ketones and the results are summarized in the table. In general the yields of condensation product **3** are





Aldol Reaction of the Dianion **1**.

R	R'	R"	Yield of **3**, %[a,b]	Bp of **3**, °C (P, mm)
Me	Me	H	26	42-43 (0.3)
Me	Et	H	73	86-87 (0.5)
Me	n-Bu	H	36	55-56 (0.2)
Me	t-Bu	H	82	68-69 (0.3)
Me	ϕ	H	89	72-73 (0.4)[c]
Me	2-MeOC$_6$H$_4$	H	73	64-65 (0.5)[c]
Me	2,3-(MeO)$_2$C$_6$H$_3$	H	68	89-91 (0.4)[c]
Me	Furyl	H	68	82-83 (0.1)
Me	Me	Me	70	51-52 (14)
Me	Et	Me	56	88-89 (14)
Me	(CH$_2$)$_5$		63	95-96 (0.3)
Me	(CH$_2$)$_4$		25	67-68 (0.3)
Me	ϕ	Me	77	83 (0.3)[c,d]
Me	2-MeOC$_6$H$_4$	Me	79	83-85 (0.3)[c]
Me	ϕ	ϕ	93	mp 77-79°
Et	ϕ	ϕ	81	mp 68-69°[5]

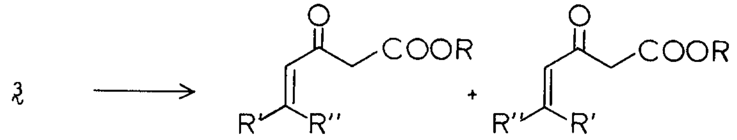
[a] Isolated yield. [b] All compounds exhibited spectral data in accord with the assigned structures. In addition all distillable liquids and crystalline solids gave satisfactory analytical data. [c] Aldol product **3** decomposed to some extent on distillation and bp refers to trimethylsilyl ethers.[b] [d] Bath temperature for distillation of TMS ether.

good. In some instances where the yields are low, proton transfer may be a competing reaction. We were not able to obtain any identifiable products from the reaction of **1** (R = Me) with formaldehyde. Many of the products from aromatic aldehydes and ketones underwent some decomposition, for example, retro-aldol and decarboxymethylation, on distillation. To overcome this difficulty, these products **3** (R' = aromatic, R" = H or Me) were converted to the corresponding trimethylsilyl ethers which could be readily distilled.

The aldol reaction of the dianion **1** was found to be very temperature dependent as was the alkylation reaction of **1**.[1] The reaction of **1** (R = Me) and propionaldehyde at 25°

gave **3** (R = Me, R' = Et, R" = H) in 57% yield after one-half hour. At -78° the yield of **3** was 11% after one-half hour. However, at 0° the yield of **3** was 73% after 10 min. We also investigated the generation of the dianion **1** using other bases. With two equivalents of lithium hexamethyldisilylamide[3] and methyl acetoacetate we were not able to detect any terminal aldol product **3** and we suspect that this base may not be strong enough to generate the dianion. However, two equivalents of lithium diisopropylamide[4] with ethyl acetoacetate gave the dianion **1** (R = Et) and subsequent reaction with benzophenone at 0° gave **3** (R = Et, R' = R" = ϕ) in 76% yield. It would appear that lithium diisopropylamide method is of comparable efficiency to the sodium hydride - n-butyllithium method (cf. table) in generating the dianion **1**. Wolfe, et al., had previously generated the dianion **1** (R = Et) using two equivalents of potassium amide in liquid ammonia. Reaction of this dianion with benzophenone in ether at -33° for two hours gave **3** (R = Et, R' = R" = ϕ) in 50% yield;[5] the sodium hydride - n-butyllithium proceedure gave 81% yield of the same product.

The aldol products **3** can be dehydrated to the α,β-unsaturated ketones **4** by stirring **3** in chloroform saturated with HCl at room temperature. In this way **2** was dehydrated to a mixture of **4a** and **4b** (R = R' = Me, R" = Ar) which were formed in a ratio of ca. 1:1 in good yield[2] and **3** (R = R' = Me, R" = 2-MeOC$_6$H$_4$) gave **4a** and **4b** (ca. 1:2.3) in 86% yield. Although we have not undertaken extensive variation of reaction conditions to achieve maximum yield, we have found that the dianion **1** undergoes aldol reaction with a range of aldehydes and ketones to give **3** in good yield and these products can be smoothly dehydrated to the enones **4a** and **4b**. A typical reaction is given below.



4a **4b**

Sodium hydride, as a 50% mineral oil dispersion, (0.465g, 11.0 mmol) was weighed into a 50 ml flask into which 25 ml of tetrahydrofuran was directly distilled. The flask was stoppered (serum cap), cooled in ice, and flushed with nitrogen. Methyl acetoacetate

(1.16 g, 10.0 mmol) was added dropwise to the cold, stirred slurry, and after the addition was complete the reaction was stirred at 0° for a further 10 min. n-Butyllithium, a 2.35 M solution in hexane, (4.5 ml, 10.6 mmol) was then added in a dropwise manner and the reaction mixture assumed an orange color. This reaction mixture was stirred for 10 min before the pivaldehyde (0.946 g, 11.0 mmol) was added, in one portion. After a further 10 min the reaction was quenched by the addition of 2 ml of concentrated hydrochloric acid. The reaction was worked up by the addition of 5 ml of water and 35ml of ethyl ether. The aqueous layer was removed and extracted with 2x35 ml of ether. The ethereal extracts were combined, washed with 6x25 ml of saturated brine solution, dried over sodium sulfate, filtered, and the solvents were removed under reduced pressure. The oily residue was distilled under vacuum to yield 1.65 g (82%) of **3** (R = Me, R' = t-Bu, R" = H) , bp 68-69° (0.3 mm).[6]

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