Alkylation of β-Keto-ester Dianions with α-Chloroethers

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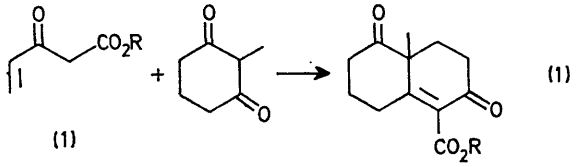
Summary The dianion of β-keto-esters reacts with α-chloroethers to yield δ-alkoxy-β-keto-esters which are useful intermediates in annelation reactions.

Since the work of Nazarov and Zavyalov,[1] the usefulness of esters of 3-oxopent-4-enoic acid, such as (**1**), in Robinson-type annelation reactions with cyclic β-diketones [equation

(1)[1] and cyclic ketones,[2] and in Mannich reactions for the construction of piperidone rings,[3] is well known. However, the tediousness and low overall yield of the classical synthesis of (**1**) were major deterrents to its general utility. More recently, alternative, and in some cases rather better,



(1) (1)

routes to (**1**) and related compounds have been reported, some of which involved the dianion of methyl acetoacetate.[4,5] Subsequently, Heathcock and his co-workers found that ethyl 5-ethoxy-3-oxopentanoate (**2**), which is a precursor of (**1**), could be used directly in the annelation [equation (1)].[6]

We report a simple one-step synthesis of (**2**) and its methyl substituted derivatives which involves the alkylation of the dianion of β-keto-esters (**3**)[5] with the α-chloroethers (**4**) [equation (2)]. The yields of the alkylated products (**5**) are given in the Table. This simple route to (**5**) gives

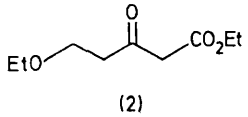
TABLE. Alkylation of the dianion (**3**) with the α-chloroethers (**4**).

(3)	(4)		Yield of (5) (%)[a,b]			
R^1	R^2	R^3	R^1	R^2	R^3	
H	Me	H	H	Me	H	(65)
Me	Me	H	Me	Me	H	(87)
H	Me	Me	H	Me	Me	(89)
H	Et	Me	H	Et	Me	(73)

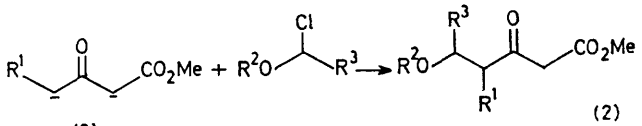
[a] Yields shown are of isolated material. No attempt has been made yet to maximize yields. [b] New compounds were identified by spectroscopic data and, in some cases, by elemental analysis.

good yields and thus provides a range of δ-alkoxy-β-keto-esters for use in the Nazarov–Zavyalov annelation. In addition, the ether derivatives (**5**) can be readily transformed in good yield into the corresponding δ-chloro-β-keto-esters on treatment with HCl in chloroform. These chlorides may also prove valuable in annelation reactions.[7] Finally the ethers (**5**) are readily converted into the corresponding enones by acid-catalysed elimination of alcohol.

In a typical experiment, the dianion of methyl acetoacetate was generated as reported earlier[5] using 0·27 g of a 57% mineral oil dispersion of sodium hydride [washed with tetrahydrofuran (THF) to remove the mineral oil], 0·58 g of methyl acetoacetate, and 2·4 ml of 2·2 M Bu^nLi, all in *ca.* 25 ml of dry THF at 0 °C. 0·54 g of α-chloroethyl ethyl



(2)



(3) (4) (5) (2)

ether, prepared by passing HCl gas into a mixture of acetyldehyde and absolute ethanol,[8] was added to the solution of the dianion and the mixture was stirred at −15 °C for 30 min. The mixture was then washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and the solvents were removed under reduced pressure to yield 0·685 g (73%) of methyl 5-ethoxy-3-oxohexanoate.

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